Université de Montréal

Methodological considerations of the Canadian job-exposure matrix and the evaluation of the risk of brain cancer in relation to occupational exposure to metallic compounds

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Résumé

Le cancer du cerveau est associé à une morbidité importante et à un fardeau économique considérable pour les systèmes de santé, les patients et leur famille. Malheureusement, on en sait toujours très peu sur l'étiologie de cette maladie. Les métaux, les métalloïdes et les fumées de soudures constituent une grande famille de cancérogènes professionnels potentiels à laquelle des millions de travailleurs sont exposés. La littérature scientifique fournit certains éléments de preuve que l'exposition professionnelle à quelques composés métalliques pourrait augmenter le risque de cancer du cerveau, mais la plupart des études publiées étaient limitées dans leur taille d'échantillons et en leurs capacités de mesurer efficacement l'exposition professionnelle à vie. Cette thèse a pour objectif de fournir de nouveaux éléments de preuve concernant l'association entre l'exposition professionnelle à certains composés métalliques et les deux principaux sous-types histologiques du cancer du cerveau, le gliome et le méningiome.

Deux projets existants constituent la base de cette thèse: INTEROCC, une grande étude internationale cas-témoins sur l'association entre l'exposition professionnelle et le cancer du cerveau, incluant 2 054 cas de gliome, 1 924 cas de méningiome et 5 601 témoins, ainsi que CANJEM, une nouvelle matrice emplois-exposition basée sur plus de 30 000 emplois. CANJEM est un tableau croisé de trois axes: un axe de codes professionnels, un axe de périodes de temps et un axe d'agents chimiques. CANJEM fournit diverses mesures d'exposition à des agents professionnels sélectionnés en fonction d'un titre occupationnel et d'une période de temps. CANJEM étant un outil complexe conçu pour offrir une flexibilité considérable à l'utilisateur, les deux premiers volets de cette thèse ont été consacrés à l'examen de certaines des considérations méthodologiques associées à l'utilisation de CANJEM dans le cadre d'une étude épidémiologique.

Premièrement, nous avons examiné comment la modification de la résolution des axes de codes professionnels et de périodes de temps influençait la proportion d'emplois pouvant être liés à CANJEM dans l'étude INTEROCC. Nous avons ensuite comparé l'accord de paires de versions de CANJEM pour la probabilité d'exposition et la concentration pondérée par la fréquence d'exposition de 19 composés métalliques en utilisant le coefficient d'accord de Gwet (AC2). Nous avons observé que, selon la résolution utilisée, CANJEM pouvait lier entre 70,7% et 98,1% de l'ensemble des emplois disponibles dans l'étude INTEROCC. De plus, la modification de l'axe de code professionnel avait un impact plus important que la modification de l'axe de période de temps sur les mesures d'expositions.

Deuxièmement, l'évaluation par des experts est généralement considérée comme l'étalon-or dans l'évaluation rétrospective de l'exposition professionnelle. Différents seuils peuvent être appliqués à la probabilité d'exposition fournie par CANJEM afin de distinguer «exposé» de «non exposé». Nous avons comparé les rapports de cotes (RC) obtenus à l'aide de plusieurs versions de variables d'exposition binaire et cumulative pour neuf cancérogènes potentiels du poumon avec des RC obtenus à l'aide de l'évaluation par des experts. Des modèles de régression logistique inconditionnels ont été utilisés pour examiner l'association entre chaque variable d'exposition et le cancer du poumon chez 1 200 cas de cancer du poumon et 1 505 témoin issus d'une étude cas-témoin basée à Montréal. La sensibilité de l'évaluation dérivée de CANJEM par rapport à l'évaluation par experts variait de 0,12 à 0,78, tandis que la spécificité variait de 0,84 à 0,99. Dans l'ensemble, CANJEM a été capable reproduire les associations obtenues avec l’évaluation par experts, l’utilisation de seuils de probabilité de 25% ou 50% fournissant généralement les meilleurs résultats.

Finalement, nous avons examiné le lien entre l’exposition professionnelle à 21 composés métalliques et le gliome ainsi que le méningiome dans l’étude INTEROCC à l’aide de régressions logistiques conditionnelles. La stratégie analytique était basée sur les observations faites dans les deux premiers volets. Nous n’avons observé aucune preuve de la présence d’association entre les agents sélectionnés et le gliome, mais la présence d’associations positives entre ces agents et le méningiome a été suggérée. Des associations statistiquement significatives ont également été observées entre le méningiome et une exposition inférieure à 15 ans aux fumées de plomb (RC (intervalle de confiance de 95%)) (1,67 (1,02-2,74)), aux composés du zinc (2,14 (1,02-3,89)), aux fumées de soudure (1,80 (1,17-2,77)), aux fumées d’oxydes métalliques (1,51 (1,03-2,21)) et entre une faible exposition cumulée au chrome VI (1,99 (1,03-3,84)) et aux fumées de brasage (1,83 (1,17-2,87)).

L’évaluation rétrospective de l’exposition constitue l’un des principaux défis de l’épidémiologie professionnelle. Dans cette thèse, nous avons constaté que CANJEM, bien qu’imparfaite, était une approche appropriée pour l’évaluation de l’exposition professionnelle dans les études épidémiologiques. Bien qu’il soit difficile de déterminer le rôle exact joué par chacun des agents examinés, nos résultats supportent la présence d’une association positive entre les composés métalliques et plus particulièrement les fumées métalliques et le méningiome.

Mot-clés: Cancer du cerveau, gliome, méningiome, matrice exposition-emplois, exposition professionnelle, composées métalliques

Abstract

Brain cancer is associated with substantial lifelong morbidity and considerable economic burden for public health systems, patients, and their families. Very little is known regarding the etiology of this disease. Metals, metalloids, and welding fumes are a large family of potential occupational carcinogens to which millions of workers are exposed. The literature provides some evidence that occupational exposure to a few metallic compounds could increase the risk of brain cancer, but most published studies were limited in sample size and ability to effectively measure lifetime occupational exposure. In this thesis, we aimed to provide new evidence concerning the association between occupational exposure to selected metallic compounds and glioma and meningioma, the two major histological subtypes of brain cancer.

Two existing projects provided the basis for the thesis: INTEROCC, a large international pooled case-control study on the association between occupational exposures and brain cancer, including 2,054 glioma cases, 1,924 meningioma cases, and 5,601 controls; CANJEM a new job exposure matrix based on the expert assessment of > 30,000 jobs. CANJEM is a cross-tabulation of three axes: an occupation code axis, a time period axis, and a chemical agent axis that provides various metrics of exposure to selected occupational agents based on a job title and a time period. However, CANJEM is also a complex tool designed to offer considerable flexibility to the user. The first two components of this thesis focused on the examination of some of the methodological considerations associated with the use of CANJEM in the context of an epidemiological study.

First we examined how changing the resolution of the occupational code and time period axes, affected the proportion of jobs in the INTEROCC study that could be linked to CANJEM. We

then compared the agreement among pairs of versions of CANJEM for the probability and frequency weighted concentration of exposure to 19 metallic compounds using Gwet's agreement coefficient (AC2). We observed that, depending on the resolution used, CANJEM could be linked to 70.7% to 98.1% of all jobs available in the INTEROCC study. Furthermore, we observed that varying the occupation code axis had a greater impact than varying the time period axis. Neither the metrics of exposure nor the linkage rate were strongly affected by other aspects of CANJEM examined.

Second, expert assessment is usually considered the gold standard in retrospective occupational exposure assessment. Different cutpoints can be applied to the probability of exposure provided by CANJEM to distinguish "exposed" from "unexposed". We compared odds ratios (ORs) obtained using multiple versions of a binary ever and a cumulative exposure variable for nine potential and known lung carcinogens with ORs obtained using expert assessment. Unconditional logistic regression models adjusted for potential confounders were used to examine the association between each exposure variable and lung cancer in 1,200 lung cancer cases and 1,505 controls from a Montreal based case-control study. Sensitivity of the CANJEM-derived assessment vs. the expert assessment ranged from 0.12 to 0.78 while Specificity ranged from 0.84 to 0.99. Overall, CANJEM was fairly successful in reproducing the associations obtained with the expert assessment method, with the use of probability thresholds of 25% or 50% generally providing the best results for both exposure variables.

Finally, we examined the association between occupational exposure to 21 metallic compound and glioma and meningioma in the INTEROCC study using conditional logistic regression adjusted for potential confounders. The analytical strategy was based on the observations made in the two previous components. We observed no evidence of association between the selected

agents and glioma, but there was evidence of positive associations between some of the agents and meningioma. Statistically significant associations with OR (95% confidence interval) were also observed between < 15 years of exposure to lead fumes (1.67 (1.02-2.74)), zinc compounds (2.14 (1.02-3.89)), soldering fumes (1.80 (1.17-2.77)), and metal oxide fumes (1.51 (1.03-2.21)) and low cumulative exposure to chromium VI (1.99 (1.03-3.84)) and soldering fumes (1.83 (1.17-2.87)) and meningioma.

One of the main challenges in occupational cancer epidemiology is retrospective exposure assessment. In this thesis we found that, while imperfect, CANJEM was a cost-efficient approach to occupational exposure in epidemiological studies. Although it is difficult to determine the exact role played by individual agents examined, our results provide some support for the presence of a positive association between metallic compounds, and more particularly metallic fumes, and meningioma.

Keywords: Brain cancer, glioma, meningioma, job-exposure matrix, occupational exposure, metallic compounds

Table of contents

List of tables

Chapter 2

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Appendix

List of figures

Chapter 2

List of abbreviations

95%CI	95% confidence interval
AC1	Agreement coefficient 1
AC2	Agreement coefficient 2
BC	British Columbia
C	Concentration
CANJEM	Canadian job-exposure-matrix
CAPI	Computer-Assisted Personal Interview
CCDO	Canadian Classification and Dictionary of Occupations
CCDO71	Canadian Classification and Dictionary of Occupations 1971
CNS	Central nervous system
D	Dose
DEE	Diesel engine emission
DNA	Deoxyribonucleic acid
Dr	Duration
F	Weekly frequency in hours
FINJEM	Finnish job-exposure-matrix
FR	Daily frequency in hours
FWC	Frequency weighted concentration

IARC	International Agency for Research on Cancer
ICD-O	International Classification of Diseases for Oncology
ISCO	International Standard Classification
ISCO68	International Standard Classification 1968
ISIC	International Standard Industrial Classification
JEM	Job-exposure-matrix
K	Cohen’s kappa coefficient
NAICS	North American Industry Classification System
NOC	Canadian National Occupational Classification
NZ	New Zealand
OR	Odd ratio
P	Number of days exposed
P_e	Expected agreement
P_o	Observed agreement
Pr	Probability
R	Confidence of exposure
RR	Risk ratio
SES	Socioeconomic characteristics
SIC	Canadian Standard Industrial Classification

SIOPS	Standard International Occupational Prestige Scale
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
SOC	United States Standard Occupational Classification
UK	United Kingdom
USA	United States of America
WDE	Weekly duration of exposure
WHO	World Health Organization

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Chapter 1: Context of the thesis

1.1 General introduction

Central nervous system (CNS) tumors, are the 18th most common cause of cancer worldwide, accounting for around 2% of all cancers (1). However, they are the 13th cause of cancer death worldwide, being responsible for an estimated 241,000 deaths in 2018 (1) and are associated with substantial lifelong morbidity and considerable economic burden for public health systems, patients, and their families (2-5). Prevention of brain cancer is especially important as most CNS tumors originate in the brain (6) and treatments are often ineffective, particularly for the more aggressive histologic types. However, with the exception of the role played by some genetic predispositions and ionizing radiation, very little is known regarding the etiology of this disease (7-10).

Metals, metalloids and welding fumes are a large family of occupational agents to which millions of individuals worldwide, working in a wide range of industries, are exposed to on a daily basis (7, 9, 11). These agents may play a role in the development of brain cancer: they are able to cross the blood-brain barrier (12-16) and some have been shown to act as cancer initiators and promoters *in vivo* and *in vitro* (15-25). Epidemiological studies have provided some evidence that occupational exposure to metals and metalloids, such as lead, cadmium, zinc, mercury or arsenic, and welding fumes can increase the risk of brain cancer (26-43). Most published studies, however, have suffered from methodological weaknesses, particularly in regard to their ability to effectively measure lifetime occupational exposure and/or their small sample sizes.

Indeed, a key challenge in occupational epidemiology, particularly in the case-control design often used when examining cancer etiology, is the retrospective assessment of the subjects' lifetime exposure to potential workplace hazards. While many methods have been developed none are perfect and cost and feasibility often prohibit their use. Thus, a job-exposure matrix (JEM), which allows the estimation of lifetime occupational exposure based on the occupation titles of the jobs held, has become an attractive alternative to other costlier and more time-consuming assessment methods. Recently, a new general JEM for use in epidemiological studies has been developed: the Canadian job-exposure matrix (CANJEM) (44, 45). CANJEM is based on the expert assessment of over 30,000 jobs from four Canadian case-control studies conducted between 1979 and 2004 (46-49) and allows for the estimation of individual lifetime occupational exposure to a list of 258 agents. As CANJEM only recently became available for use, there still remains several methodological questions regarding its application.

Within this context, this thesis aimed to achieve two goals. First, to provide new evidence in regard to the association between occupational exposure to metals, metalloids, and welding fumes with both glioma and meningioma, the two major histological subtypes of brain cancer. To do this, we used the unique opportunity offered by the combination of CANJEM and the INTEROCC study (47), a large population-based multi-national case-control study containing, among other things, the complete lifetime occupational history of 3,978 brain cancer cases and 5,601 controls. Second, to examine selected methodological considerations associated with the use of CANJEM in an epidemiological study and the impact of the choice of methodological approaches on assessment of risk of cancer. In particular, we intended to determine the best method to link CANJEM to a study population and to create lifetime exposure variables based on the information provided by CANJEM.

1.2 Organization of this thesis

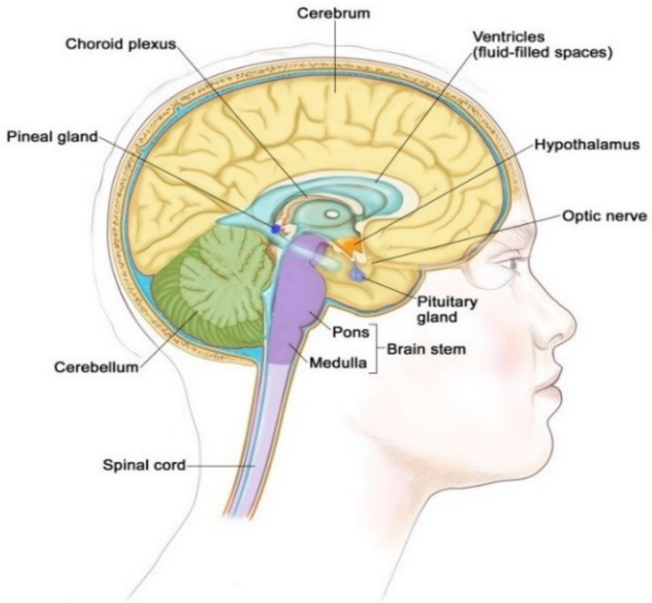
The following chapter summarizes current knowledge regarding brain cancer and its etiology, particularly in relation to metals, metalloids, and welding fumes. A review of past studies examining those occupational agents and brain cancer is included. This chapter also summarizes the strength and weaknesses of different occupational exposure assessment methods. Chapters 3 and 4 describe the objectives and method of this thesis, including a detailed description of the INTEROCC study and CANJEM. Chapters 5 to 7 present three manuscripts and a discussion of the results obtained. Specifically, chapter 5 describes how modifying some aspects of CANJEM affects both the proportion of jobs that could be linked to CANJEM and the metrics of exposure; chapter 6 compares risk estimates obtained when using different approaches to assess occupational exposure (i.e. CANJEM vs. the expert assessment method (50, 51); and chapter 7 examines the association between 21 metallic occupational agents with both glioma and meningioma within the INTEROCC study. Finally, chapter 8 provides a general discussion of the main findings of this thesis

Chapter 2: Overview of the literature

2.1 Brain cancer: diagnosis, trends in incidence and mortality, and risk factors for the disease

Brain cancer is a complex and unique disease which occurs in an organ controlling all of our daily functions; including our thought processes, sense, movement, and our life functions. Brain cancer survival is generally low and its treatment extremely expensive. Moreover, due to the limited amount of space within the skull, even benign tumours can have important life-threatening and life-long consequences. While much progress has been made in regard to its treatment, we still know very little regarding the etiology of this disease.

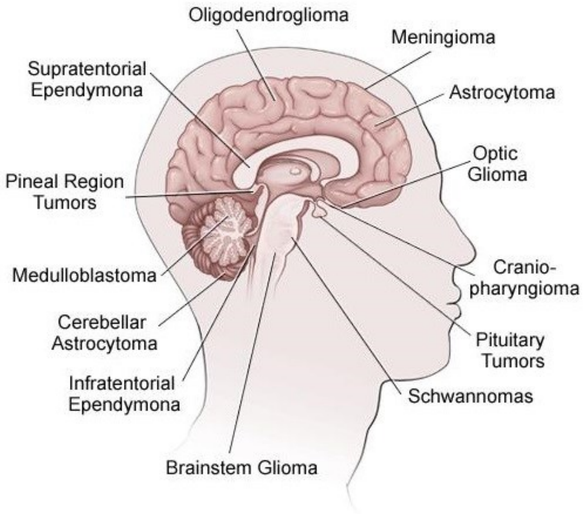
Figure 1. Anatomy of the brain[1]



1. Modified from the National Cancer Institute (52).

2.1.1 Histology

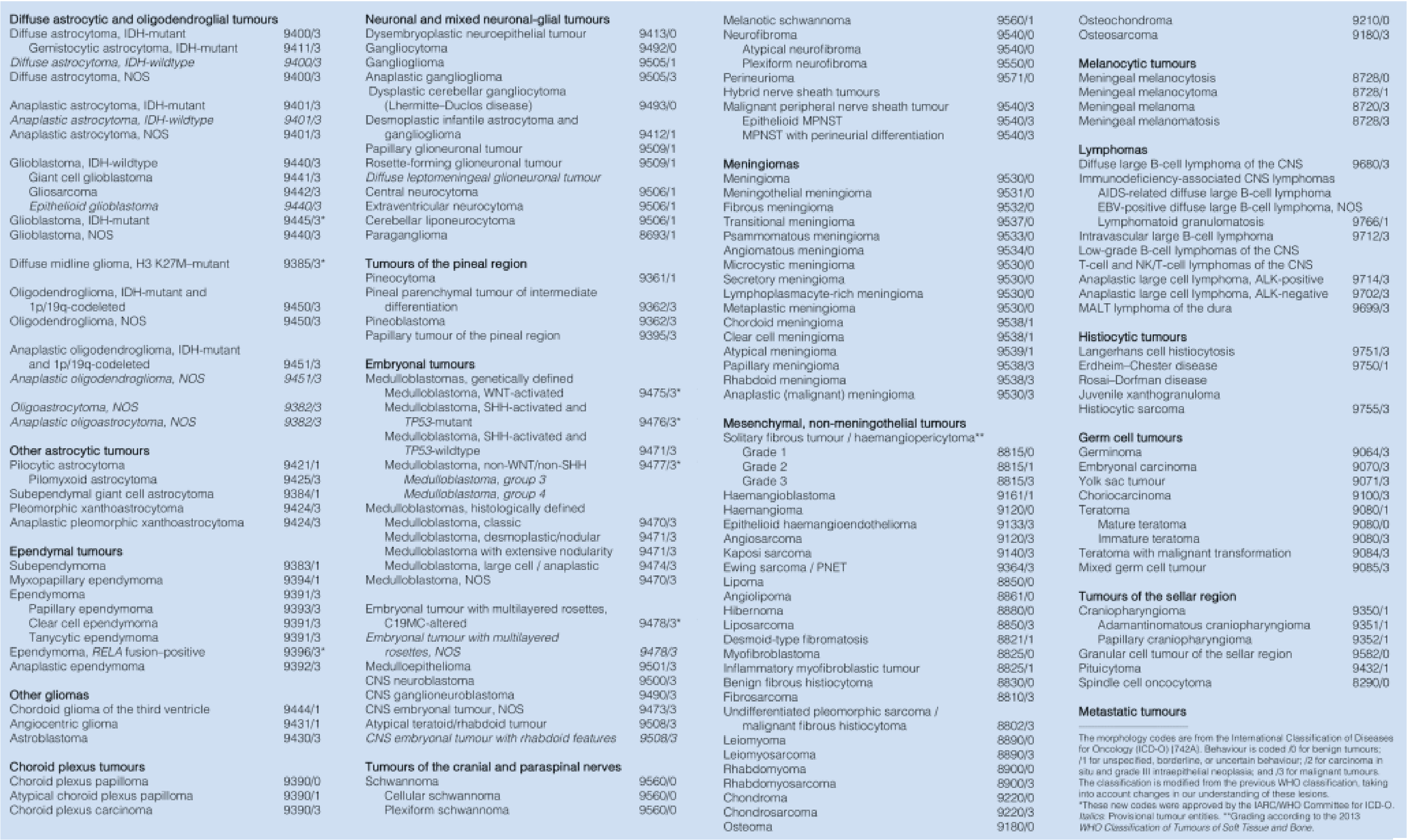
Figure 2. Brain cancer histology by location in the brain[1]



1. Modified from Medbullet (53).

Brain tumors are defined as tumors that form in brain tissues; including brain cells, meninges, nerves or glands. The term CNS tumor is sometimes used to describe brain tumors; however, CNS also encompasses spinal column tumors, which represent around 10-15% of all CNS tumors (6). Brain tumors were historically classified in over a hundred different histological subtypes based on light microscopy of Hematoxylin and Eosin-stained slides, radiological finding, ultra-structural characterization, and immunochemistry (54, 55). Since 2016, however, the World Health Organization (WHO) added molecular parameters to the classification of brain tumors (54). A detailed description of the current International Classification of Diseases for Oncology (ICD-O) for CNS tumors can be found in table I.

Table I: 2016 WHO ICD-O classification of CNS[1]



Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

*These new codes were approved by the IARC/WHO Committee for ICD-O. *Italics*: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone.*

1. Modified from Louis DN et al (54).

Overall, adult brain tumors can be broadly classified into one of two categories: gliomas, which originate from glial cells, accounting for approximately 27% of all brain tumors and 81% of all malignant brain tumors, and non-gliomas, accounting for the rest (56). Gliomas can be further categorised into ependymoma, oligodendroglioma, astrocytoma, glioblastoma, and a number of rare histological subtypes (56). Glioblastoma accounts for approximately 47% of all malignant brain tumors (56). Non-gliomas originate from other types of brain cells and include: lymphoma, meningioma, schwannoma, pineal gland tumor, pituitary gland tumor and medulloblastoma. Meningiomas are the most common benign brain tumors, accounting for as much as 53% of all benign tumors (56). While they rarely become malignant, they are often classified as brain cancer for research purposes and are generally considered to represent as much as 37% of all brain cancers (56). Glioma is more common in men while meningioma is more common in women (56). Brain cancer is the second cause of cancer death in patients aged under 19 years old, with astrocytomas and medulloblastoma being the most common types of brain tumors in this age group (56, 57).

2.1.2 Trends

The worldwide age-adjusted incidence of primary CNS cancers was estimated by the International Agency for Research on Cancer (IARC) in 2018 to be 3.9 per 100,000 person-years in men and 3.1 per 100,000 person-years in women (3.5 per 100,000 person-years in both sexes combined). Mortality rates were estimated to be 3.2 per 100,000 person-years in men and 2.3 per 100,000 person-years in women (2.8 per 100,000 person-years in both sexes combined) (1) . Both the incidence and the mortality are higher in more developed countries compared to less developed ones (1). In the United States of America (USA), for example, the age adjusted incidence of CNS was estimated in 2015 to be 7.5 per 100,000 person-years in men and 5.4 per 100,000 person-years in women, with the mortality ranging from 5.3 per 100,000 person-years in men to 3.6 per 100,000 person-years in women (58). The incidence and mortality rates were also found to be the highest in white Americans and lowest in first nations Americans (58). A meta-analysis that included 38 studies principally conducted in developed countries and published between 1985 and 2010 (59) reported a much higher incidence of primary brain cancer of 13.33 (95% confidence interval (95%CI): 10.07- 20.38) per 100,000 person-years in men and 15.8 (95%CI: 10.30-24.24) per 100,000 person-years in women.

2.1.3 Symptoms and treatment of brain cancer

Because of the role played by the brain in all of our daily functions and the limited space available in the skull, brain tumors, even benign ones, can result in brain injury with lifelong consequences if left untreated (6, 10). Symptoms of brain cancer vary widely and depend on the tumor location. They include: headaches, nausea, vomiting, loss of awareness, fatigue, loss of body function, loss of cognitive ability, personality and memory changes, spasm, seizure, and language, motor, auditory or visual deficits (6, 10). A dull headache that is more perceptible in the morning is the most common symptom of brain cancer, being observed in approximately 50% of all patients, while seizure is extremely common in specific subtypes of brain cancer such as low-grade glioma where it can be observed in as many as 90% of all patients (10).

Treatment of brain cancer has considerably evolved since the use of often lethal neurosurgery in the late 19th century (60). The advent of computer tomography, and magnetic resonance imaging, in the late 20th century made surgery, when possible, the optimal treatment for brain cancer (6, 60). When resection is impossible, surgical debulking can still improve patients' survival and improve their functional status (6, 60). Surgery is, however, increasingly costly and can lead to lifelong neurological consequences or death. When surgery is impossible, whole brain radiation therapy can be used, although it is generally used as an adjunctive therapy to surgery (6, 60). Chemotherapy is more complex to administer due to the blood brain barrier, and it has been found to offer little benefit when used alone (6, 60). Thus, like radiotherapy, chemotherapy is used as an adjunctive therapy, with Temozolomide being the most often used drug to treat malignant brain tumors (6, 60). Both radiation and chemotherapy can result in a number of detrimental side-effects including: irreversible neurocognitive deficit, exacerbation of cerebral edema, hormonal problems, hearing loss, and other side-effects generally associated with chemotherapy (6, 60). Usual treatments consist of surgery followed by radiotherapy and chemotherapy, but gamma-knife stereotactic radiosurgery is becoming a preferable alternative to surgery with fewer side effects, albeit it can only be conducted on tumors < 3 cm in diameter (6, 60).

2.1.4 Cost and survival of brain cancer

Primary brain cancer is among the cancers with the highest pre- and post-diagnosis costs (direct and indirect), particularly in younger patients (2-5). In the USA, it was estimated that in 2010 primary brain cancer had the highest net cost of care during the first year after cancer diagnosis and last year of life before cancer death in patients aged ≥ 65 years old (3), In 2014, the mean cost of healthcare during the 12 months post-surgery in a USA insured population of primary malignant glioma patients was estimated to range from 88,827$ in patients receiving neither Temozolomide chemotherapy nor radiation therapy to 184,107$ in patients receiving both (5). In 2017, in Ontario and British-Columbia, primary brain cancer was one of the cancers with the highest healthcare cost in the periods three months pre-diagnosis, six months post-diagnosis surveillance phase, and 12 month terminal phase, with estimated per person cost ranging from 3,956$ in the pre-diagnosis phase to 86,153$ in the terminal phase (4).

While the effectiveness of treatments has improved, survival of brain cancer is still relatively low, particularly for glioblastoma (56, 61). In the USA, analysis of CNS cancer patient survival between 2000 and 2014 indicated an overall 5-year survival rate of 34.9% for primary CNS cancer, ranging from 94.1% for the low-grade pilocytric astrocytoma to 5.5% for glioblastomas (56). Survival decreased as age increased, ranging from an overall 5-year survival rate of 73.9% in patients aged < 19 years old to < 20% in patients aged ≥ 55 years. In Canada, analysis of survival in patients with primary malignant brain tumor between 1992 and 2008 indicated an overall 5-year survival rate of 26.9%, ranging from 65% for oligodendroglioma to 4% for glioblastoma (61). A strong decrease in survival rate as age of patients increased was also observed.

2.1.5 Risk factors

To date little is known about the etiology of brain cancer. As of 2018, IARC has classified two types of radiation (x- and gamma-radiation) as having sufficient evidence of brain carcinogenicity in humans (62). Another major group of risk factors is genetic predisposition, including certain syndromes (neurofibromatosis 1/2, retinoblastomas, Li-Freumeni syndrome, von Hippel-Lindau syndrome, Turcot syndrome, and Gorlin syndrome) and gene polymorphisms (*ERCC1, ERCC2, GLTCR1*) (7-10). Other factors, including non-ionizing radiation (from cell phones and other sources), acute and chronic infections (simian virus 40, John Cunningham virus, human herpes virus 6, varicella-zoster virus), allergies, nutritional habits (antioxidant, alcohol), head trauma, and socioeconomic characteristics (SES) are also hypothesized to be associated with this disease, although there is still no conclusive evidence that these factors play an etiologic role (7-10, 63). The INTERPHONE study, from which the INTEROCC study used in this thesis was derived, was a large multisite case-control study that specifically examined cell phone use and brain cancer, but the results were inconclusive.

Occupational agents have also been hypothesized to play a role in the pathogenesis of this disease. Specific occupations that have been associated with an increased risk of brain cancer in one or more studies include pathologist, embalmer, firefighter, farmer, miner, smelter, welder and glass worker (7-9). Furthermore, some specific occupational agents, including polycyclic aromatic hydrocarbons, non-arsenic insecticides, organic solvents, metals, metalloids, and welding fumes have also been suggested as playing a role in the development of brain cancer (7-9, 26-43, 64-84).

2.2 Metals, metalloids, and welding fumes: their composition, where they occur in the workplace, changing patterns of use, and possible carcinogenic mechanisms

2.2.1 Descriptive characteristics of metals, metalloids and welding fumes

Metals are solids commonly found in the earth's crust and are characterized by their shiny appearance, high density, malleability and ability to conduct electricity (85). Metalloids are the elements which are on the border between metals and non-metals in the periodic table (85). They possess properties of both metals and non-metals, and are often used with metals to form alloys (85). Small amounts of some metals and metalloids, such as iron, zinc, chromium, nickel, and silicon act as enzyme cofactors and are essential or beneficial for human health, while others, such as mercury, are toxic even in small quantities and can lead to neuro-degeneration or neuronal death (85, 86). Welding fumes result from the cutting or joining of two metals, generally with the help of a third "filler" metal, using different welding techniques (87, 88). Welding occurs principally in metal manufacturing or construction industries (87, 88). The most common welding techniques are arc welding, where an electric arc is used as the source of heat, and gas welding, where a gas such as acetylene is mixed with oxygen and used to produce a flame (87, 88). Soldering, which is often used in plumbing, jewelry making, and in circuit board assembly, can be considered as a subtype of welding where two metals are joined without melting the pieces being joined. Only the filler used to join the pieces is melted (89). Welding is a complex process involving exposure to extreme heat, electro-magnetic fields (both extremely low and radio frequencies), gases and particulate matter. The size of the particles can be an important factor in the development of neurological problems or damage to the lung, liver, kidneys and CNS (90, 91). In this thesis, we will use the term metallic compounds when referring to metals or metalloids in any form, and welding fumes.

2.2.2 Patterns of exposure

Metals and metalloids can be found in varying but generally small concentrations in water, air, and food or drink products. Sometimes, metals and metalloids are present in high concentrations in the environment due to natural or human activities. Well-known examples include the contamination of water wells or underground water sources by arsenic-rich bedrock or mining operations (92), the contamination of tap water by lead from water pipes or lead soldered joints (93), and the contamination of fish and rice by mercury pollution resulting from mining, smelting or coal burning (94, 95). Occupational exposures are the principal sources of exposure to high concentrations of metals and metalloids, with workers in a wide range of industries, including mining, smelting, wood processing, battery manufacturing, weapon manufacturing, metal processing, the glass industry, and electric equipment manufacturing, being exposed to these agents on a daily basis (7, 9, 11). The number of exposed workers and the level of exposure varies greatly by country, based on their industrialization level, major industries, and their safety regulations. In Canada for example, the number of workers exposed to various metallic compounds ranges from an estimated 25,000 for arsenic to 277,000 for lead (11) . More detailed information on the major industries with occupational exposure to selected occupational agents, as well as estimates of the number of workers exposed to them in Canada can be found in table II.

Table II: Selected occupational agents profile table

Occupational agent	IARC classification[1]	Major industries with occupational exposure to the agent in Canada	Estimated number of workers exposed in Canada[2]
Arsenic	1	Wood processing, glass manufacturing, semi-conductor manufacturing, metallurgy, ammunition manufacturing, construction, farming	25,000 (2018)
Cadmium	1	Electric equipment manufacturing, pigment coating, plastic manufacturing , wood processing, automotive repair and maintenance, commercial and industrial machinery manufacturing, machine shop and turned product manufacturing	31,000 (2018)
Chromium VI	1	Printing and support activities, commercial and industrial machinery manufacturing, commercial	104,000 (2018)

Occupational agent	IARC classification[1]	Major industries with occupational exposure to the agent in Canada	Estimated number of workers exposed in Canada[2]
		and industrial machinery equipment repair and maintenance, automotive repair and maintenance, architectural and structural metals manufacturing, wood processing, leather processing, dental technologist and technician	
Iron (occupations in iron and steel founding)	1	Metal manufacturing, construction, commercial and industrial machinery manufacturing, commercial and industrial machinery equipment repair and maintenance, automotive repair and maintenance	15,782[3] (2018)
Nickel	1	Commercial and industrial machinery manufacturing, commercial and industrial machinery equipment repair and maintenance, motor vehicle part manufacturing, automotive repair and maintenance, architectural and structural metals manufacturing, machine shops and turned product manufacturing, screw/nut, and bolt manufacturing	117,000 (2018)
Welding fumes	1	Metal manufacturing, construction, maintenance	103,000[4] (2015)
Lead (inorganic lead)	2A	Public administration, building equipment contractors, automotive repair and maintenance, commercial and industrial machinery repair and maintenance, architectural and structural metal manufacturing, electric equipment manufacturing, painting, ammunition manufacturing	277,000 (2018)
Silicon carbide (fibrous silicon carbide)	2B	Glass manufacturing, metal manufacturing, electric equipment manufacturing, ceramic manufacturing	Unavailable

Occupational agent	IARC classification[1]	Major industries with occupational exposure to the agent in Canada	Estimated number of workers exposed in Canada[2]
Silicon carbide whiskers	2A	Acheson process in manufacture of silicon carbide	Unavailable
Mercury	3	Electric equipment manufacturing, metal processing, pesticide, slimicide or fungicide manufacturing, automotive part manufacturing	Unavailable
Calcium	-	Metal manufacturing, construction, glass manufacturing, wood processing	Unavailable
Zinc	-	Metal manufacturing, construction, maintenance, machine or automotive part manufacturing , electric equipment manufacturing	Unavailable

1. IARC classifications: (1) carcinogenic to humans; (2A) probably carcinogenic to humans; (2B) possibly carcinogenic to humans; (3) unclassifiable as to its carcinogenicity in humans (96).

2. Estimated from data provided by CAREX Canada (11), Statistic Canada (97), and Industry Canada (98).

3. Only includes blue collar workers in the iron and steel manufacturing industry. The number of workers exposed to iron is probably much higher.

4. Estimated from a 2006 Canadian census, do not includes workers who weld as part of their job or that are indirectly exposed to welding fumes.

2.2.3 Possible mechanisms that might account for an association with brain cancer

Metals and metalloids, such as cadmium, calcium, chromium, iron, lead, mercury, nickel, zinc, arsenic, and silicon, are potential human carcinogens which have been shown *in vitro* and *in vivo* animal studies to act as cancer initiators and promoters through many mechanisms including: the generation of reactive oxygen species leading to direct DNA damage, the promotion of inflammation leading to indirect DNA damage, the inhibition of the DNA repair mechanism by binding to the sulfhydryl group of DNA repair proteins such as the zinc-finger family of proteins, and by causing mitochondrial DNA damage (15-25). They are also able to cross the blood brain barrier and accumulate in the brain (12-16). Some (cadmium, zinc, calcium, iron, silicon) have been shown to be present in statistically significantly higher concentrations in blood and tumor samples of brain cancer patients, when compared to those of controls (99, 100). Welding fumes are composed of small airborne metal oxide particles including: iron, nickel, chromium and cadmium, which vary in concentration based on the welding technique and metals used (101, 102). Once inhaled, the metal particles can enter the circulatory system (102), and access the brain.

2.3 Methods for assessment of occupational exposure to agents occurring in the workplace

Identifying occupational hazards and estimating risks quantitatively is heavily dependent on the ability to characterize workplace exposures by type and amount (103). Depending on the study design and disease endpoint, exposure can be assessed for one specific point in time, usually for acute toxicity effects, or prospectively which allows for active ongoing monitoring or measurement, or retrospectively for exposures that occurred in the past. Classic occupational epidemiology in relation to diseases with long latency, such as cancer or heart disease, has used both the industrial cohort and case-control designs, most often involving retrospective exposure assessment. The approaches discussed in this chapter can be used with either the cohort or the case-control design. The main drawback to the industrial cohort design is the lack of lifetime occupational history and information on potential confounding factors for members of the cohort. The case-control design attempts to overcome some of these drawbacks. A population-based case-control study design allows for collection of complete work histories as well as information on potential confounding factors for each individual in the study. The case-control study design generally requires retrospective assessment of occupational exposure which is one of the most challenging aspects of occupational epidemiology, particularly when examining diseases with long latency periods. While many methods have been developed over the years, none are perfect and cost and feasibility often prohibit the use of the most valid method. A good understanding of the limitations and impact of the selected method on the statistical analysis is required to conduct an informative study. The following sections describe the retrospective occupational assessment methods most commonly used in the context of population-based case-control studies.

2.3.1 Self-reported exposure and work history

One of the simplest methods available to retrospectively assess occupational exposure is the use of subject's self-assessment (104, 105). This method is particularly suited for case-control studies where questionnaires and interviews are already employed to collect data on subjects' demographic characteristics and exposure to other risk factors. However, while relatively cheap and easily applicable, this method is generally not considered to be the best way of obtaining valid exposure estimates (104, 105). Indeed, it can be difficult for subjects to provide accurate and reliable estimates of their occupational exposures as they may not have been aware of or remember the presence of specific exposures in their workplaces, particularly if the exposures occurred decades in the past. In addition, this method has also been shown to suffer from differential recall between cases and controls and according to socio-demographic characteristics, age, gender, and time since exposure (104, 105). When compared to the expert assessment method (see section 2.3.3), which is generally considered the gold standard in retrospective occupational exposure assessment in population based studies, despite its shortcomings, a review of six studies published in 2002 reported widely varying agreements with Kappa coefficients ranging from -0.05 to 0.94 and a median of 0.60 (104). More recent studies comparing self-assessment to expert assessment for exposure to solvents and pesticides (106), and formaldehyde, bleach, chlorine, alcohol, quaternary ammonium, ammonia, sprays, and latex gloves (107) reported similarly varying Kappa coefficients. The validity of self-assessment is improved when examining agents that impact strongly one of the five senses (i.e. malodorous gas, strong sound or vibration, visible dust), by interviewing subjects that had to select or purchase agents for a workplace, by providing subjects with a list of agents rather than using open ended question, by using more familiar names when describing agents (e.g. paint stripper rather than methylene chloride), and by providing subjects with an objective or relative benchmark to which they can compare their exposure levels (104, 105). Alternatively, the validity could be improved by gathering subjects' occupational exposure data directly from their past employers. However, this is rarely feasible as subjects may not be willing to provide the name of their previous employers due to privacy concerns and even when they do, the workplace may no longer exist, or employers may not have the relevant hygiene expertise or may not be willing to provide this information to researchers (108). Consequently, the use of self-assessment of occupational exposure should be limited to the development of new research hypotheses or be used to complement other methods such as expert assessment or JEMs.

A more feasible alternative to the use of self-assessment of occupational exposure is the use of self-reported job history. Subjects' self-reported job history has been shown to be more valid and reliable than self-assessment of occupational exposure, with 11 studies that compared self-reported job history to company, pension, or union records and at different points in time reporting agreement percentages ranging from 70% to 90% and Kappa coefficients ranging from of 0.65 to 0.82 (104). Lower agreement was observed for more complex job histories covering a longer time period and containing shorter jobs (104). The analysis of occupations, vs. occupational exposures, has been historically used with some success to identify at risk occupations. However, their main weakness is that when employed by themselves, they do not allow for the evaluation of specific risk factors as subjects may have been exposed to dozens of unique occupational agents within one job or industry; thus making it impossible to identify which agent(s) contributed to the increase in risk and limiting the ability to develop interventions to limit exposure within those occupations (104, 105). It is, however, an essential part of the expert assessment and JEM methods and can still be useful for hypothesis generating, particularly for occupations with highly correlated exposures.

2.3.2 Direct exposure measurement: workplace measurement and biological sampling

When done correctly, the direct measurement of subjects' exposure, either through the use of fixed or personal measurement tools in the workplace or through the use of biological sampling, where exposure is determined from the examination of specific biomarkers in a subject's blood, urine or in other types of biological sample, is the most valid, reliable, and precise occupational assessment method currently available. Its application in the context of retrospective studies of chronic diseases is, however, very limited (104, 105). The cost and logistical challenges associated with the use of this method to assess exposure in the wide range of jobs that can be expected to be observed in most population-based studies by itself limits its application to smaller studies examining only a few types of industries and/or occupational agents. Even with sufficient funding, measurements taken around the time of interview will rarely be representative of the long-term exposures that are more relevant to the examination of chronic diseases for which the case-control design is particularly well suited (104, 105). Biomarkers of exposure to some substances with long half-lives, such as cadmium, may be detected in blood or urine; however, very few of those biomarkers are currently available (105) and the feasibility within the context of a retrospective case-control study is extremely doubtful. Thus, direct measurement will only be truly feasible for well-funded studies examining a limited number of industries, occupational agents, and diseases with a short latency period.

A potentially more feasible alternative to the use of direct measurement is the use of pre-existing measurement databases such as industry or union records. However, few historical measurement databases exist and it is unlikely that measurement data for all the jobs present in a study can be obtained (104, 105). Furthermore, those databases often contain measurements taken from compliance or evaluation testing and they may not be representative of the general level of exposure found under normal circumstances (105). Even if they are, the measurements taken at a specific workplace may not be representative of the average exposure found in all similar workplaces. Thus, while more feasible, the use of pre-existing measurement databases is still not ideal in the context of a case-control study.

While direct exposure measurement methods alone may not be applicable, they can provide critical information when assessing exposure using the expert assessment method, for the development of a JEM, or for the creation of predictive exposure models where these direct exposure measurements can be used to predict exposure levels in other contexts were direct measures are unavailable (104, 105).

2.3.3 Expert assessment

Since its introduction into the field of occupational epidemiology in the early 1980's (50, 51), the expert assessment of subjects' occupational history, where one or more chemists, industrial hygienists, and other professionals assess the occupational exposure to one or more agents for each individual job ever held by a subject, has come to be considered the gold standard in retrospective occupational exposure assessment (104, 105). Indeed, contrary to the direct measurement method, experts are able to assess jobs having occurred decades in the past and, drawing on their training and experience, they have a better understanding than most workers of the processes and conditions of exposures present in a workplace (104, 105). In addition, as mentioned previously, external data from various sources including the subjects themselves, measurement databases, and information from technical literature, can be used by the experts to improve the quality of their assessment.

A major difficulty facing researchers is that subjects may have held dozens of different jobs in a lifetime and examining all of them individually is a very long and costly process that can take decades to accomplish in a large study population (44, 109). Furthermore, as the expertise to accomplish this task is not readily available, the quality of the assessment will vary greatly depending on the experts' experience, their familiarity with a specific job or industry, and on the amount and quality of relevant data available (104, 105). Their assessment is also dependent on the quality of the job history used and to some extent, on the ability of subjects to correctly recall the unique work environment of each of their previous workplaces (104, 105). Thus, while the reliability of the expert assessment method is generally considered to be good, some concerns have been raised in regard to its validity, particularly in the context of population-based studies where large numbers of jobs from various industries need to be assessed (104, 105). Determining the validity of the expert assessment is, however, no easy task and only three studies have examined the validity of the expert assessment compared to direct measurement in a limited number of agents in this context (110-112). Reported sensitivity varied widely, ranging from 0.21 to 0.79, but specificity was consistently ≥ 0.90. While the potentially low sensitivity may seem to raise questions regarding the validity of the expert assessment, there are a few points to keep in mind while interpreting those results. First, although apparently precise, direct measurement is also prone to human error, equipment error and to error due to spatial and temporal variations in exposure (110). Consequently, a measurement taken at one point in time is not necessarily representative of the average exposure experienced by a worker over a longer period of time and thus, the true sensitivity of the expert assessment may be higher than reported. Second, sensitivity can be increased by modifying the assessment method (110-112). For example, including specialized questionnaires (questionnaires developed for specific jobs such as welders to obtain more detailed information specific to that occupation), employing a group of experts rather than only one, and employing more experienced experts resulted in higher sensitivity. Third, in the context of a population-based study, occupational exposure will generally be low and consequently, specificity will have a much bigger impact on the validity of the exposure assessment method than sensitivity. That is, lower specificity will result in the misclassification of exposure of a greater number of jobs than lower sensitivity.

Another criticism of the expert-assessment method is its lack of transparency or “black box” approach to assessment (105, 113, 114). Indeed, experts will often follow no precise set rules to determine the presence or level of exposure within one specific job and while the rationale behind a decision may vary between experts, it is rarely well described, making the evaluation or reproduction of those decisions difficult and reducing the efficiency of this assessment method (105, 113, 114). In order to improve the transparency of the expert assessment, new tools and approaches including fixed decision rules linking questionnaire questions to exposure decisions, and web-based and machine learning software that simplify the process of developing and applying decision rules have been developed (105, 113, 114). However, the ability of these systems to apply nuanced assessment taking into account variations reported in the tasks and work environment from one job to another has not been evaluated.

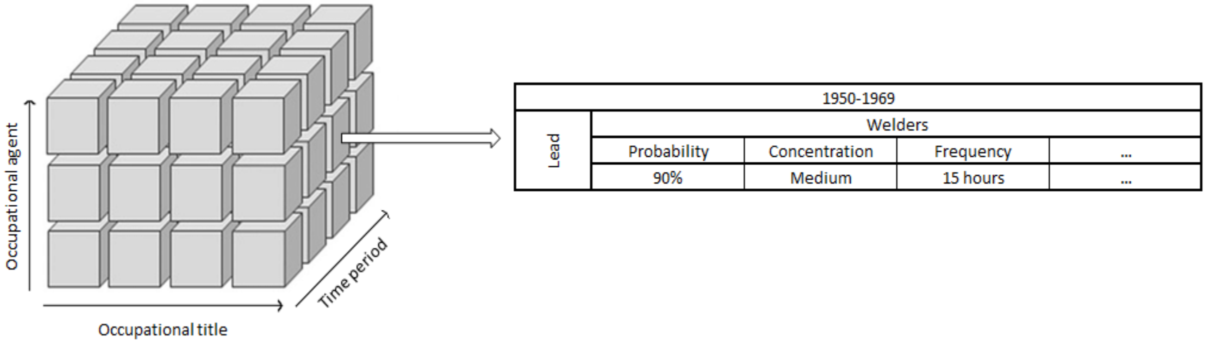
Overall, while not perfect, expert assessment is currently the best available method to assess occupational exposure in retrospective population-based studies and it has been successfully used to help identify many different occupational risk factors over the past three decades. However, the funds and time needed for its implementation are major impediments in the current funding climate and has led to the development of a newer method: JEMs.

2.3.4 Job exposure matrices - JEMs

Since their introduction in the 1980's, JEMs, more specifically generic JEMs, have become an attractive alternative to the costly and time-consuming expert assessment methods (104, 105). JEMs are essentially cross-tabulations providing estimates of exposure to selected occupational agents based on the data gathered from one or more sources, including all of the exposure assessment methods presented previously. At their most basic, JEMs are composed of 2 axes: an occupational title axis and an occupational agent axis, but more complex JEMs that include a time axis also exist (see figure 3). For selected values in each of those axes (i.e. an occupational agent, an occupational title, and a time period) a cell containing the relevant exposure information can be obtained. JEMs can be broadly categorised into two categories;

study- or industry-specific JEMs and generic JEMs. Specific JEMs are created for the sole purpose of examining occupational exposure in a specific setting. Since they are generally built to examine a limited number of occupational titles and/or occupational agents, they can provide as good or better estimates of exposure at a lower cost than generic JEMs (104, 105). However, this limited scope also means that they are not easily transferable to other settings and thus, they are rarely used in a broader research context. By comparison, generic JEMs are created to be applicable to different settings and will generally provide estimates of exposure to a wide range of occupational titles, industries and/or occupational agents. Thus, while they are more time consuming and more expensive to create than specific JEMs, once they are made available to the scientific community, they can be quickly and cheaply used by researchers to estimate occupational exposure in a study population, albeit some care must be taken to ensure that the study population is compatible with the selected JEM. Current examples of generic JEMs include the Finnish job-exposure matrix (FINJEM) (115, 116), MATGENE, developed in France (117), and CANJEM, developed in Canada (44).

Figure 3. Example of a three axis JEM



	1950-1969			
	Welders			
Lead	Probability	Concentration	Frequency	...
	90%	Medium	15 hours	...

Because there are no guidelines for the creation of generic JEMs, they can vary greatly in terms of their structure and complexity. As mentioned above, a JEM may or may not contain a time axis and depending on how each axis is categorised, it can contain anything from a few hundreds to millions of cells. For example, the first recorded generic JEM, developed by Hoar et al (118), contained exposure estimates for 376 occupational agents in 500 occupational/industrial titles without a specified time period. By comparison, FINJEM (115, 116), one of the most popular generic JEMs currently available, contains exposure estimates for 47 occupational agents and around a dozen psychosocial and lifestyle factors in 311 occupational titles and 8 time periods, while CANJEM contains exposure estimates for 258 occupational agents in nearly 1000 occupational titles and 4 time periods (44). In addition to differences in their axes, JEMs can differ in the estimates of exposure they provide, which can be as simple as the binary ever vs. never exposure variable based on the probability of exposure found in Hoar's JEM to the various indices of exposure provided in CANJEM (i.e. probability of exposure, concentration of exposure, frequency of exposure, and expert assessment confidence level).

JEMs can also vary in terms of their quality. Determining the quality of a JEM is difficult as it depends on a multitude of factors, including the source, quality and quantity of data used to create the JEM, the method used to create it and the types of estimates of exposure provided, the occupational agent of interest, and the characteristics of the study population the JEM will be used for. Thus, while a JEM built from the self-assessments of exposure of a few thousand workers will probably have an overall lower quality than one built from the expert assessments of tens of thousands of jobs, it may be more valid to use a JEM based on self-assessment in certain settings. For example, to assess occupational exposure in a Chinese population of young workers, a JEM based on self-assessment of Chinese workers may be more valid than a JEM based on expert assessment of Canadian jobs.

Due to their relatively low cost of use, generic JEMs are considered an attractive alternative to expert assessment in retrospective studies. However, no matter how well they are built, all JEMs suffer from one major common limitation when compared to most other occupational exposure assessment methods; their inability to account for exposure variability within an occupation class (104, 105). Because JEMs only provide one (set) of estimates of exposure for each combination of an occupational title, occupational agent, and when available, time period, it cannot account for the unique exposure characteristics found within a specific occupation, which can result in exposure misclassification. The extent to which exposure misclassification will be present is again hard to predict and will be specific to the occupational agent, occupation, and JEM. However, some amount of misclassification can always be expected to be present when using a JEM. Consequently, JEMs, particularly generic JEMs, are not a perfect replacement for expert assessment; 10 studies comparing the two methods have reported low agreements, with Kappa coefficients generally being under 0.5, ranging from as low as 0.1 for organic solvents to as high as 0.9 for welding fumes (39, 104, 119). Sensitivity was similarly low, being generally around 0.5, but specificity was high, being generally around 0.9; with newer studies reporting better agreements when compared to older studies (39, 104, 119). In terms of its application to an epidemiological study, the major impact that can be expected from this misclassification is a bias of the estimates of association toward the null (39, 120), but bias away from the null can also occur (121). Nonetheless, JEMs have been used to correctly detect the positive association between known and suspected lung carcinogens and lung cancer (122).

As funding for occupational epidemiology is currently scarce, there is a growing need for the development of high quality generic JEMs and of methods to better understand how best to use those JEMs: this would also include an evaluation of the possible extent of misclassification and possible ways to adjust for this in obtaining risk estimates.

2.4 Current evidence on the association between occupational exposures to metallic compounds and brain cancer

A review of the epidemiological literature on the association between brain cancer and occupational exposure to metals (mercury, lead, cadmium, zinc, chromium, iron, nickel, calcium), metalloids (arsenic, silicon), and welding fumes was conducted using a combination of keywords (cancer, brain, glioma, meningioma, central nervous system, occupation, occupational exposure, worker, metal, metalloid, mercury, lead, cadmium, zinc, chromium, iron, nickel, calcium, arsenic, silicon, welding, welder, soldering, solderer, fumes, dust) in Pubmed and Google Scholar search engines. 46 cohort studies (26-33, 64, 68-71, 74-76, 78, 80-84, 123-146), 21 case-control studies (34-43, 65, 66, 77, 79, 147-153), two nested case-control studies (67, 138), and one meta-analysis (154) were identified. Ten cohort studies (78, 129-132, 138-140, 142, 143), three case-control studies (149, 152, 153), and one nested case-control study (138) were excluded from the review because the publication was either only available in Japanese (140), in Norwegian (139) or because updated results had been published (78, 129-132, 138, 142, 143, 149, 152, 153). A detailed summary of the studies included in this review can be found in tables I to XII of the appendix.

2.4.1 Metals and metalloids

Of the 55 studies included, eight cohort studies (26-33) and 10 case-control studies (34-43) reported statistically significant positive associations between at least one of the selected metals or metalloids and brain cancer.

Five case-control studies (34-38) reported statistically significant positive associations (34, 35, 37, 38) or borderline statistically significant positive associations (35, 36) with odds ratios (ORs) ranging from 1.6 to 4.2, between occupations involving possible exposure to some metals and glioma (35, 36), meningioma (38), or brain cancer (34). It is important to note that most studies (35-38) also reported wide 95% confidence intervals (95%CIs), with lower confidence limits often close to unity. One case-control study (43) reported borderline statistically significant positive associations between occupational exposure to iron and meningioma in both sexes combined (OR=1.26) and among women (OR=1.70), but not among men. One case-control study (40) reported a statistically significant positive association between occupational exposure to cadmium and meningioma in women, but the observed association in men (ORs ≈ 9.0) was of only borderline significance and based on five exposed male cases. One cohort study (29) reported a statistically significant positive association, with a standardized mortality ratio (SMR) of 6.19 between exposure to nickel fumes and brain cancer; however, the study included only 4 cases also exposed to welding and chromium fumes, and thus, the observed association may not have been due to nickel alone. One cohort study (26) reported a statistically significant positive association (risk ratio (RR)= 1.61) between potential occupational exposure to arsenic and glioma, but a close to null association for meningioma, based on only seven exposed cases. Three cohort studies (27-29) and one case-control study (43) reported positive associations between exposure to chromium and brain cancer (27-29) or meningioma (43) with SMRs/ standardized incidence ratios (SIRs)/ORs ranging from 1.60 to 9.14; however, in one cohort study (29) subjects were also exposed to welding and nickel fumes, another (28) only included 3 exposed cases, while one case-control study (43) reported a statistically significant positive association in both sexes combined and in women, but not in men. Two cohort studies (30, 31) using a similar source population and methodology reported statistically significant positive associations (SIRs= 2.1) between male dentists (30) or male and female dentists/dental nurses (31) potentially exposed to mercury and glioma (30) or glioblastoma (31). Four cohort studies (26, 27, 32, 33) and three case-control studies (40-42) reported statistically significant positive associations (26, 32, 33, 40, 41) or borderline statistically significant associations (27, 40, 42) with relative risks ranging from 1.1 to 7.2, between occupational exposure to lead and brain cancer. However, for one study (26), the association was statistically significant for meningioma, but not glioma, while for another (40), which only included 6 exposed meningioma cases among men and 10 exposed meningioma cases among women, a statistically significant association was reported in women, but only a borderline statistically significant association was reported in men. One study (33) reported statistically significant associations for brain cancer in both sexes combined and in women, but not in men, albeit all analyses included ≤ 10 exposed cases. Another study (27) reported a borderline statistically significant positive association for low probability of occupational exposure to lead, but no statistically significant association at higher probability of occupational exposure. One case-control study (39) reported a statistically significant inverse association at lower level of cumulative exposure to lead and glioma (OR=0.6), but a borderline positive association (OR=2.7) when examining the same category of exposure in relation to meningioma. Two other case-control studies (43, 79) examining the same study population reported borderline (ORs ranging from 0.7 to 0.8) (79) or close to borderline (OR = 0.29) (43) statistically significant inverse associations between occupational exposure to lead and either glioma (79) or meningioma (43).

The remaining studies reported no statistically significant associations, with estimates often too imprecise to be informative. Still, there was a tendency for statistically non-significant positive associations to be reported between the selected occupational agents and brain cancer (26, 27, 37, 40, 43, 64-71, 74-77, 80-82, 84, 128, 141, 145, 150). One meta-analysis (154) of six cohort studies (81, 82, 134, 137, 138, 155) including only 69 brain cancer cases reported a close to null association between occupational exposure to lead and brain cancer, with a pooled OR (95%CI) of 1.06 (0.81-1.40).

2.4.2 Welding and soldering fumes

Three cohort studies (29, 30, 83) reported statistically significant positive associations between welding and brain cancer, with SIRs ranging from 1.4 to 6.2. However, for one study, (83) which examined brain cancer, glioma, and glioblastoma separately, the association was only statistically significant for glioblastoma. Of the remaining studies (27, 37, 40, 43, 67, 71, 79, 84, 136, 145, 146, 150, 151), all but four (79, 136, 146, 151), which reported either close to null associations (136, 146) or weak statistically non-significant inverse associations (79, 151), reported statistically non-significant positive associations between welding or exposure to welding fumes and brain cancer (27, 37, 40, 43, 67, 71, 84, 145, 150). Only one case-control study (150) examined the association between potential exposure to soldering fumes and brain cancer and reported a statistically non-significant positive association.

2.4.3 Limitations of past research

Few studies examined the association between occupational exposure to the selected occupational agents and brain cancer, with the exception of lead, mercury, and welding fumes. In particular, only four studies examined the association between occupational exposure to iron (27, 43, 79, 83), zinc (68-70, 123), or arsenic (26, 27, 37, 123) and brain cancer, one examined silicon (127) or soldering fumes (150), and there has been no study of calcium in relation to brain cancer. The literature suffered from several limitations which may explain the lack of statistically significant results reported by the majority of published studies. First, the statistical power of most studies was very low. Twenty six studies (28, 29, 31, 64, 68-71, 74-76, 80-82, 123-128, 133-137, 144) included ≤ 30 cases, while only 19 studies (26, 27, 30, 34, 36, 37, 38 , 39, 41-43, 65, 77, 79, 84, 146, 148, 150, 151) included > 300 cases. Furthermore, among studies including > 30 cases, nine studies (34, 35, 40, 41, 65, 66, 147, 148, 151) included < 20 cases exposed to at least one of the selected occupational agents, while only nine studies included > 100 exposed cases (26, 36, 37, 39, 42, 43, 79, 145, 146). Another limitation is that a majority of studies used flawed exposure assessment methods. 27 studies (28-31, 34, 38, 64, 65, 69-71, 74, 77, 80, 81, 83, 84, 123-127, 136, 145-147, 151) were primarily limited to analyses of occupation or industry title, which could lead to exposure misclassification and potentially bias the result toward the null. Furthermore, 14 studies (27, 30-32, 34, 41, 42, 65, 83, 84, 145, 146, 148, 150) only gathered or used information on occupation held by subjects in the year before the start of the study (27, 30-32, 83, 84, 145, 146), the time of death (34, 41, 42, 148, 150), or on the usual job held by subjects (65). In addition, one study (26) only gathered information on occupations held at the beginning and end of a 10-year period, while another (151) only examined the longest-held occupation. Thus, for these studies the exposure reported might not have been representative of the exposure during the etiologically relevant time period. This limitation also holds for five studies (64, 68, 125, 127, 134) which gathered information on subjects' lifetime employment in specific industries/plants, but had an overall median of employment of < 10 years (64, 68, 127, 134) or only included subjects employed for < 10 years (125).

Chapter 3: Objectives

3.1 Objective of the thesis

3.1.1 General objectives

The primary general objective of this PhD thesis is to examine the associations between occupational exposure to selected metallic compounds and glioma and meningioma, the two major histological subtypes of brain cancer. The secondary general objective is to explore how to optimize the use of a job-exposure-matrix in occupational cancer epidemiology

3.1.2 Specific objectives

The specific objectives related to the two general objectives are: 1) to examine the associations between occupational exposure to selected metallic compounds, including metals, metalloids, and types of welding fumes and glioma, 2) to examine the associations between occupational exposure to the same agents and meningioma, 3) to describe how the choice of levels of resolution of the occupational classification and the resolution of the time period in CANJEM may affect CANJEM linkage rate and the resulting exposure metrics, 4) to determine the relative validity of the exposure assessment provided by CANJEM by comparing the relative risk results estimated when examining occupational exposures with CANJEM to results estimated using the individualized expert exposure assessment method used to create CANJEM, and 5) to describe how using different strategies of treating the probability of exposure (provided by CANJEM) when assessing occupational exposure with CANJEM affect relative risk estimates.

Chapter 4: Methods

4.1 Context of this PhD thesis

Before presenting the methods of my dissertation research, it is important to explain the context in which these methods were developed. This study builds on the unique opportunity offered by the availability of data from two previous projects: CANJEM, a newly developed generic JEM containing exposure information on over 250 occupational agents, including a large number of metals, metalloids, and types of welding fumes; and the INTEROCC study, a large international pooled case-control study on the association between occupational exposures and brain cancer.

4.2 The Canadian Job Exposure Matrix (CANJEM)

CANJEM is the culmination of over three decades of work that began with the development of an expert assessment method in the early 1980's (51, 156), and the application of this method to examine occupational exposure in four Canadian case-control studies conducted between 1979 and 2004 (46-49), allowing for the development of CANJEM. It is one of the largest and most flexible JEM in the world, in terms of the number of agents, the number of occupational and industry classifications available for use, the multiple time periods of exposure, and the number of metrics of exposure available for each combination of agent, occupation title and time period. An introductory description of the development process and of selected characteristics of CANJEM can be found in two recent publications (44, 45). However, as of now, CANJEM has only been used in one other epidemiological study (157) and little is known in regard to the impact of the flexibility of its structure. This doctoral project will be the first to explore issues related to some of the questions that can be raised regarding the use of such a JEM in an epidemiological study

4.2.1 CANJEM: source data

As mentioned previously, CANJEM was developed from the expert assessment of exposure conducted in four Canadian case-control studies (46-49). Study 1 (49), conducted between 1979 and 1986, examined 19 cancer sites in 3,726 male cancer patients and 533 male population controls aged 35 to 70 years old living in the greater-Montreal area. Study 2 (46), conducted between 1996 and 2001, examined lung cancer in 1,205 cases (739 men and 466 women) and 1,541 controls (925 men and 616 women) aged 35 to 75 years old living in the greater-Montreal area. Study 3 (48), conducted between 1996 to 1997, examined breast cancer in post-menopausal women: 608 cases and 667 controls aged 50 to 75 years old living in the greater Montreal area. Study 4 (47), conducted between 2000 and 2004, examined brain cancer in 264 cases and 653 controls aged 30 to 59 years old living in the greater Montreal, Ottawa, and Vancouver areas. Study 4 represents the Canadian section of the INTEROCC study used in this project. As the expert assessment method was only used in the Montreal and Ottawa centers, only the 245 cases (124 men and 121 women) and 414 controls (198 men and 216 women) from those centers were included in developing CANJEM. All four studies used the same approach to obtaining occupational history (in-depth personal interviews with specially trained interviewers) and the same exposure assessment approach (in fact, there were members of the original team involved in all four studies). In total, CANJEM is composed of the expert assessment of 31,673 unique jobs held by 8,760 subjects. Table I shows the number of jobs coming from each study.

Table I: Numbers of jobs from each of the four studies included in the CANJEM database

Study	Number of jobs
Study 1 (multi-site cancer)	15,067 (men only)
Study 2 (lung cancer)	10,371 (6,877 men; 3,494 women)
Study 3 (breast cancer)	3,510 (women only)
Study 4 (brain cancer)	2,725 (1,461 men; 1,264 women)

4.2.2 Expert assessment of exposure

The expert method employed in those four studies was developed by the team directed by Jack Siemiatycki and included Michel Gérin and Lesley Richardson. It has been described previously (51, 156). Briefly, each study gathered a complete detailed lifetime occupational history for each subject; the information gathered included job titles, tasks performed, employment duration, work environment, products, and equipment used for any jobs ever held by a subject for more than six months, during face-to-face or telephone interview. Each job was then coded according to standardized occupation and industrial codes and reviewed to determine exposure to a predefined list of up to 294 biological, physical, and chemical occupational agents by a team of trained experts in chemistry and industrial hygiene that were blinded to case-control status. The team varied in time between two and five experts, with more involved in the first study than in the later studies. Two of the experts were involved in all four studies which helped ensure consistency in the approach. In total, a dozen experts participated in the exposure assessment process. To ensure consistency in the assessment over time, multiple periodic reviews were conducted.

A consensus approach was used for the coding. Each file was reviewed by two experts: the first would conduct the in-depth assessment, the second would review the estimates. If there was a discrepancy of more than one exposure level (category) for any parameter for any agent, the experts would discuss the case in order to arrive at a consensus. The team of experts assessed each combination of job and agent according to three dimensions: confidence, concentration, and frequency of exposure. The confidence of exposure represented the level of confidence the experts had in their assessment; categorised as possible, probable, or definite. It was not based on any fixed guideline, rather it relied entirely on the assessor's level of certainty that an exposure really occurred. Concentration of exposure was defined as low, medium, or high, with each level established in reference to certain *a priori* benchmarks developed by identifying workplace situations in the study population. Low concentration represented a concentration of exposure above what one would expect to find in the general environment during the relevant time period. High concentration represented the highest concentration of a selected agent that might be found in the work environment during the same time period. Medium concentration represented concentrations in between low and high, loosely based on the agent threshold limit value (upper limit of the acceptable concentration of a substance in the workplace) when available. Experts would assign a level of exposure to a selected agent in a specific job by comparing the concentration of exposure assessed to have been present in that job to the benchmarks created for that agent. Thus, while the concentration of exposure level is not comparable between agents, it is comparable between jobs held during the same time period for the same agent. There were differences in the assessment of frequency of exposure between the studies. For the first study, frequency was categorised into 3 categories low (<5% of the time) medium (5–30%) and high (≥30%). For a subject working a 40-hour work week, this translates into <2 hours per week for low, 2-12 hours per week for medium, and ≥ 12 hours for high. For the other three studies, the number of hours a subject was exposed at each of the three concentrations was assigned. Thus, for each job and agent combination, up to three frequency values could be provided (e.g. 3 hours at high intensity, 5 hours at medium intensity, and 15 hours at low intensity). In studies 2 to 4, experts could also subdivide jobs into different non-exclusive sub-periods when it was judged that exposure levels for a specific agent varied over time, for example when a worker performed a specific task only during part of the job. In addition, in some situations where exposure to one agent would necessarily result in exposure to other agents (e.g. pre-1980's exposure to gasoline would result in exposure to lead), algorithms (automatics) were used to automatically assign exposure to those agents. In total, this approach took close to 50 expert-years to complete for the four studies.

4.2.3 Configuring the original data to create the CANJEM database

The CANJEM database was created from the 31,673 job assessments conducted by the team of experts. In order to make a job exposure matrix that would be useful to researchers from different countries and to harmonise slight differences in the exposure metrics across the four studies, some modifications to the original data had to be made. Exposure data on 36 of the 294 agents also had to be excluded from the database as these agents had not been assessed in all four studies. A description of the 258 agents included in CANJEM can be found at http://www.canjem.ca/, selected descriptive statistics can be found at http://expostats.ca/chems/.

4.2.4 Assigning multiple occupational and industry classifications

Each job was coded by a team of experts using the original job description, occupational code, and official documentation, into four occupation classification systems and three industry classification systems used in Canada and internationally. Table II shows the level of resolution for each classification and numbers of groups in each level of resolution.

Table II: Occupational and industrial classifications available in CANJEM[1]

Classification	Resolution	Level	Number of groups in classification
(A) Occupation			
International Standard Classification (ISCO) 1968	1 digit	Major group	8
	2 digits	Minor group	81
	3 digits	Unit group	282
	5 digits	Occupation	1,504
Canadian Classification and Dictionary of Occupations (CCDO) 1971	2 digits	Major group	23
	3 digits	Minor group	81
	4 digits	Unit group	500
	7 digits	Occupation	7,907
Canadian National Occupational Classification (NOC) 2011	1 digit	Division	10
	2 digits	Major group	40
	3 digits	Minor group	140
	4 digits	Unit group	500
United States Standard Occupational Classification (SOC) 2010	2 digits	Major group	23
	3 digits	Minor group	97
	5 digits	Broad occupation	461
	6 digits	Detailed occupation	840
(B) Industries			
International Standard Industrial Classification (ISIC) revision 2, 1968	1 digit	Major division	9
	2 digits	Division	33
	3 digits	Major group	71
	4 digits	Group	159
	1 digit	Division	18

Classification	Resolution	Level	Number of groups in classification
Canadian Standard Industrial Classification (SIC) 1980	2 digits	Major group	76
	3 digits	Minor group	318
	4 digits	Unit group	860
North American Industry Classification System (NAICS) 2012	2 digits	Sector	20
	3 digits	Subsector	102
	4 digits	Group	323
	5 digits	Industry	711
	6 digits	Canadian industry	922

1. Modified from Sauvé et al (45).

4.2.5 Harmonising exposure metrics across studies

Exposure data had to be standardized for the creation of the CANJEM database. In studies 2 to 4 the experts assigned a quantitative value for the frequency of exposure (hours per week) to each concentration level. In study 1 overall frequency of exposure in the given job was assigned to one of 4 categories (0%, <5%, 5–30%, and ≥30% of workweek exposed). In studies 2 to 4 the assessment of exposure to a given agent in a given job could entail several lines for different combinations of concentration and frequency: for example, 2 hours per week at high concentration and 38 hours at low concentration. The operative concern being a description of the number of hours spent at each of the three possible concentration levels. Thus, a quantitative frequency of exposure metric had to be created for study 1. To do this, the frequency data for each agent obtained in Study 2 (the largest of studies 2 to 4 and most similar in being predominantly male) was reconfigured to correspond to one of the four categories used in study 1, based on an assumption of a 40-hour week. For each combination of agent and frequency category the median of the original values was calculated. The next step was to configure a single average frequency and concentration of exposure for studies 2 to 4. This was done by first calculating the average weekly duration of exposure using the formula:

$$WDE = WDE_1 + WDE_2 + WDE_3, \text{ with } WDE_i = FR_i * ND / 20$$

Where WDE is the weekly duration of exposure, WDE_i is the WDE at a specific concentration level (low (1), medium (2), or high (3)), FR_i is the number of hours per day exposed at a specific concentration level, and ND represents the number of workdays exposed, which is based on the percentage where 0% equals 0 days and 100% equals 5 days. Thus, as each workday equals 20% of the workweek, the percentages were divided by 20 so that ND was in units of days exposed. Average concentration of exposure was then calculated using the formula:

$$Avg\_Conc = \left(\sum_{i=1}^{3} WDE_i * C^{(i-1)}\right)/WDE$$

Where C is a weighted constant equal to 5 (due to the use of a 1:5:25 ratio for the concentration of exposure as explained below) and i is the concentration of exposure. To be used in this formula, the concentration of exposure had to be given a quantitative value. However, the experts followed no fixed guideline when assigning the concentration level and the relative difference between each concentration level may vary by agent. For example, for one agent it is possible that the concentration followed a ratio of 1:3:9, meaning that the concentration of exposure found at a high concentration of exposure was approximately three time higher than the medium concentration, and nine time higher than the low concentration. However, for another agent this ratio may be 1:5:25 or 1:10:100. Because it would have been too time consuming to select a ratio for each agent individually, the average concentration was first calculated using a ratio of 1:5:25, which was considered by the experts as providing the best estimate of the relative difference between each concentration level in most situations. Once this was done, a "year" database which provided exposure by year rather than by job was created for all four studies. Because of the use of automatics and because experts could assign exposure to specific sub-periods in study 2 to 4, multiple "lines" of exposure to a specific agent and year could exist. Thus, those lines needed to be aggregated so that only one value for the concentration, frequency, and confidence of exposure was provided for each year of a job. The calculation of the new frequency of exposure was achieved using the formula:

$$F = min(40, F1+F2/2+F3/4+F4/8....), \text{ with } F1 \geq F2 \geq F3 \geq F4 \geq \ldots$$

Where F represents the weekly hours of exposure and F1 to $F_{\ldots}$ represent different lines of exposure in a selected year. This formula was created to represent an intermediate between considering each frequency of exposure as completely independent (having occurred at different times) or redundant (having occurred at the same time). The concentration of exposure was aggregated using the formula:

$$C = \frac{D1+\frac{D2}{2}+\frac{D3}{4}+\frac{D4}{8}}{F}$$, with $Di=Fi*Ci$, and $D1 \geq D2 \geq D3 \geq D4 \geq \ldots$

Where F_i and C_i are respectively the frequency and concentration of exposure for a selected line of a year. As for the aggregated frequency of exposure, this formula represents an intermediate between cumulating the concentrations (consider them as independent) and using the maximum concentration (consider them as redundant). Finally, confidence was taken as the maximum of all confidence values within a selected year. The last step needed for the creation of the CANJEM database was the recreation of the "job" databases that provided overall exposure estimates for each job. This was accomplished by aggregating the yearly exposure of a job using the following formulas:

$$Concentration = \frac{F1 * C1 + F2 * C2 + F3 * C3 + F \ldots * C \ldots}{F1 + F2 + F3 + F \ldots}$$

$$Freqency = \frac{F1 + F2 + F3 + F \ldots}{number\ of\ F}$$

$$Confidence = max(R1, R2, R3, R \ldots)$$

Where F1 to F…, C1 to C…, and R1 to R… represent respectively the frequency, concentration, and confidence of exposure for each year of the job. The four job databases thus created were than merged to form the CANJEM database.

4.2.6 Structure of CANJEM

CANJEM has three axes: occupational code axis, time period axis, and occupational agent axis. The exposure metrics are provided in cells, each of which relates to a specific combination of occupation code, time period and agent. It is important to note that for a cell to be created, there needed to be jobs in the CANJEM source database fulfilling the occupational code and time period requirement. Consequently, CANJEM does not necessarily contain cells for all potential combinations of an occupational code and time period and may not be able to provide exposure metrics for all jobs present in a study population.

<u>Occupational code axis</u>

CANJEM's occupational code axis is available in four occupational and three industrial classification systems (table II page 43). It is important to understand that each of these classification systems has its own unique hierarchical structure which differs in terms of resolution (number of digits used within a coding system) and in the number of occupational codes contained within each of those resolutions. For example, ISCO68 (International Standard Classification of Occupations 1968) contains four resolutions ranging from one digit (seven occupational codes) to five digits (1,506 occupational codes). By comparison, the Canadian Classification and Dictionary of Occupations 1971 (CCDO71) also contains four resolutions, but those resolutions range from two digits (23 occupational codes) to seven digits (>7,700 occupational codes). Because of the hierarchical structure, occupational codes at a lower resolution (fewer digits) aggregate occupational codes from higher resolutions (more digits). For example, the 2-digit major group CCDO code 11 (managerial, administrative and related occupations) aggregates three minor group 3-digit codes: 111 (official and administrator unique to government), 113/114 (other managers and administrators), and 117 (occupations related to management and administration). Those codes in turn aggregate dozens of 4-digit occupational codes, which themselves can aggregate hundreds of 7-digit codes. Thus, the higher resolution codes will more precisely define each occupation. On the one hand, this may mean that using CANJEM with a coding system containing fewer occupational codes per resolution may not provide exposure estimates that are as accurate as when other coding systems are used. The methodological considerations that are born from this unique characteristic of CANJEM are further discussed in sections 4.2.8, 4.2.9, and chapter 5.

Time period axis

The database upon which CANJEM was built contained jobs covering the period 1930 to 2005, a long period covering a great deal of change in technology and workplace regulation. Thus, CANJEM was designed to allow users to select one of three resolutions in time period: resolution 1) includes the entire time period: 1930-2005; resolution 2) two time periods: 1930-1969 and 1970-2005; and resolution 3) four time periods: 1930-1949, 1950-1969, 1970-1984, and 1985-2005. These latter four time periods were created to take into account most major technological or regulatory changes in the work environment occurring in developed countries. As with the occupational code axis, using a higher resolution of time period may allow for more accurate metrics of exposure to the extent that exposure levels changed over time. The methodological implications associated with the availability of multiple resolutions in the time period axis of CANJEM are also discussed in section 4.2.8, 4.2.9, and chapter 5.

Occupational agent axis

CANJEM contains information on 258 occupational agents. This list of agents includes specific chemicals (e.g. formaldehyde), broader mixtures (e.g. gasoline), physical agents (e.g. ionizing radiation), and groups based on use (e.g. pesticide) or chemical class (e.g. lead compounds). Those last two types of agents will, in some situations, aggregate together other agents available in CANJEM. For example, lead compound aggregates lead chromate, lead oxide, lead dusts, etc.

4.2.7 Metrics available within the CANJEM cells

CANJEM is composed of cells defined by a combination of a specific occupational code, time period, and occupational agent. Each cell provides various metrics of exposure derived from a set of relevant jobs abstracted from the 31,673 jobs that composed the CANJEM database. For example, configuring CANJEM using the CCDO71 occupational classification at a resolution of seven digits, a resolution of one time period (1930 to 2005), and all 258 agents, results in 778,897 unique cells. The cell defined by the combination of the 7-digit CCDO71 occupational code 2165-238 (industrial engineering technician), time period 1930 to 2005, and the agent gas welding fumes, provides estimates of occupational exposure to gas welding fumes based on the exposure assessment assigned to the 11 jobs in the CANJEM database that fulfilled the time period and occupational code requirement. Each cell contains > 40 variables (table III), including the frequency distribution of the confidence, frequency, and concentration of exposure, as well as the number of jobs assessed by the team of experts as exposed or substantially exposed (exposed for at least five years at a concentration of medium and a frequency of two hours per week) to the selected agent. However, the most important variables in regard to any epidemiological analysis, including this thesis, are the total number of jobs providing exposure estimates in a cell, the probability of exposure, and the mean and median concentration, frequency, and frequency weighted concentration of exposure (FWC).

Table III: List of variables present in each CANJEM agent/occupation/time cell

Variable name	Description
IDCHEM	Occupational agent number
Agent_label	Occupational agent name
ISCO68	ISCO68 code
ISCO_label	ISCO68 job title
P	Probability of exposure
ntot	Number of jobs in the cell
nexp	Number of exposed job in the cell
nsub	Number of substantially exposed job in the cell
nexp_s	Number of exposed subjects
n_R1	Number of jobs with a confidence of possible
n_R2	Number of jobs with a confidence of probable
n_R3	Number of jobs with a confidence of definite
n_C1	Number of jobs with a concentration of exposure of low
n_C2	Number of jobs with a concentration of exposure of medium
n_C3	Number of jobs with a concentration of exposure of high
n_F1	Number of jobs with a frequency of exposure of < 2 hours per week
n_F2	Number of jobs with a frequency of exposure of 2 to < 15 hours per week
n_F3	Number of jobs with a frequency of exposure of 15 to < 40 hours per week
n_F4	Number of jobs with a frequency of exposure of ≥ 40 hours per week
p_R1	Proportion of exposed jobs with a confidence of R1
p_R2	Proportion of exposed jobs with a confidence of R2
p_R3	Proportion of exposed jobs with a confidence of R3

Variable name	Description
p_C1	Proportion of exposed jobs with a concentration of R1
p_C2	Proportion of exposed jobs with a concentration of R2
p_C3	Proportion of exposed jobs with a concentration of R3
p_F1	Proportion of exposed jobs with a Frequency of R1
p_F2	Proportion of exposed jobs with a Frequency of R2
p_F3	Proportion of exposed jobs with a Frequency of R3
p_F4	Proportion of exposed jobs with a Frequency of R4
Cmoy_1	Mean concentration of exposure using a ratio of 1:2:3
Cmoy_3	Mean concentration of exposure using a ratio of 1:3:9
Cmoy_5	Mean concentration of exposure using a ratio of 1:5:25
Cmoy_10	Mean concentration of exposure using a ratio of 1:10:100
Dmoy_1	Mean frequency weighted concentration of exposure using a ratio of 1:2:3
Dmoy_3	Mean frequency weighted concentration of exposure using a ratio of 1:3:9
Dmoy_5	Mean frequency weighted concentration of exposure using a ratio of 1:5:25
Dmoy_10	Mean frequency weighted concentration of exposure using a ratio of 1:10:100
Cmed_1	Median concentration of exposure using a ratio of 1:2:3
Cmed_3	Median concentration of exposure using a ratio of 1:3:9
Cmed_5	Median concentration of exposure using a ratio of 1:5:25
Cmed_10	Median concentration of exposure using a ratio of 1:10:100
Dmed_1	Median frequency weighted concentration of exposure using a ratio of 1:2:3
Dmed_3	Median frequency weighted concentration of exposure using a ratio of 1:3:9
Dmed_5	Median frequency weighted concentration of exposure using a ratio of 1:5:25
Dmed_10	Median frequency weighted concentration of exposure using a ratio of 1:10:100
Fmoy	Mean frequency of exposure (hours)
Fmed	Median frequency of exposure (hours)
Cell	Cell ID

Probability of exposure

The probability of exposure is based on the proportion of jobs in a selected cell that were considered by the team of experts to be exposed to a selected agent at any level of concentration or frequency. It is arguably the most important exposure metric provided by any JEM and the source of many of the difficulties associated with their use. Indeed, in common with other JEMs, CANJEM provides the same estimate of exposure to all jobs occurring in a specific time period with a specific occupational code. However, unless the probability is 100%, not all of those with a given job title are truly exposed and some exposure misclassification will occur. Thus, before conducting any analysis, users must decide how to use the probability of exposure to differentiate between exposed and unexposed jobs. One prominent approach is to create a binary exposed/unexposed variable by establishing a cutpoint on the probability of exposure scale. Below the cutpoint, jobs are considered as "unexposed" and above the cutpoint they are considered as "exposed". Lower thresholds will increase the sensitivity of the assessment, but at the cost of also misclassifying a greater number of unexposed individuals as exposed; while selecting higher thresholds will result in the opposite. The probability of exposure can also be used as a weight in the calculation of a cumulative metric of exposure; however, unless the probability of exposure is 0% or 100%, this will often result in the misclassification of truly unexposed subjects as exposed and in the underestimation of cumulative exposure in exposed subjects. In most situations, the probability of exposure provided in a cell of CANJEM can be interpreted as an indication of the potential for misclassification. The extent of misclassification will theoretically be maximized when the probability of exposure is 50%, and be reduced as it gets closer to 0% or 100%. Thus, an ideal or informative cell in CANJEM is one for which the probability of exposure is around 0% or 100%. The more informative cells there are for an agent, the better the exposure assessment will be when using CANJEM. The impact of using different approaches for the probability of exposure in the context of an epidemiological study is examined in chapter 6.

Mean or median concentration of exposure

As the name implies these metrics represent the mean or median concentration of exposure of all exposed jobs that were used to create a selected cell. CANJEM provides the mean concentrations as well as the median concentrations calculated using one of four ratios for the 3-level range from low to high (1:2:3, 1:3:9, 1:5:25, and 1:10:100). Unless there is an indication to the contrary, it is recommended to use the median concentration of exposure with a 1:5:25 ratio in the context of an epidemiological study, as the median is less affected by extreme values than the mean, and the 1:5:25 ratio is the best estimate of the low, medium, and high concentration for the majority of agents.

Mean or median frequency of exposure

The mean or median frequency is based on the number of hours per week of exposure of all exposed jobs that were used to create a selected cell. While it is possible for the mean or median cell frequency to be > 40 hours per week, most cells in CANJEM have a mean or median frequency of exposure < 40 hours per week. For example, among the 778,897 cells present in the CANJEM example presented at the beginning of this section, less than a hundred had a mean or median frequency greater than 40 hours per week, with only 2 cells having a mean or median frequency of over 80 hours per week. Use of the median frequency of exposure rather than the mean is recommended in the context of an epidemiological study since the median will be less affected by unconventionally short or long frequency of exposure values.

Mean or median frequency weighted concentration (FWC)

The mean or median FWC of exposure provides a measure of exposure that combines both the concentration and frequency of exposure. It is calculated using the mean or median frequency and concentration (with any of the 4 ratios) of exposure provided by CANJEM using the formula:

*FWC = Concentration * (frequency/40)*

By dividing the frequency by 40 hours, the usual maximum number of work hours per week, the FWC is not affected by the ratio used for the concentration of exposure. That is, although the FWC will be higher when using larger ratios, this difference will be the consequence of truly stronger expected concentrations of exposure at higher concentration levels rather than being due to a shift of the relative weight of the concentration and frequency terms of the FWC formula. As for the mean or median concentration of exposure, using the median FWC with a ratio of 1:5:25 would be preferable in most situations.

Table IV provides a partial CANJEM output for the cell defined by the CCDO71 code 2165-238 (industrial-engineering technician), the agent gas welding fumes, and the time period 1930-2005. From this output we can see that the cell is based on 11 jobs, five of which were exposed to gas welding fumes, resulting in a probability of exposure of 45%. Because the probability is so close to 50%, this cell is not very informative. The median and mean concentration of exposure is 1 when using a 1:5:25 ratio, while the mean and median frequency are 19 hours and five hours respectively. Finally, the mean and median FWC are 0.475 and

0.125 respectively. In this specific example, the mean and median concentration and FWC would have stayed the same for all four ratios available in CANJEM.

Table IV: Partial CANJEM output for a cell defined by the CCDO71 code 2165-238, the agent gas welding fumes, and the time period 1930-2005

Variable	Value
Occupational agent number	2165-238
Occupational agent name	Gas welding fumes
Number of jobs underlying the cell	11
Number of exposed job in the cell	5
Probability of exposure	45.5%
Mean concentration of exposure using a ratio of 1:5:25	1
Median concentration of exposure using a ratio of 1:5:25	1
Mean frequency of exposure (hours)	19
Median frequency of exposure (hours)	5
Mean frequency weighted concentration of exposure using a ratio of 1:5:25	0.475
Median frequency weighted concentration of exposure using a ratio of 1:5:25	0.125

4.2.8 Versions of CANJEM

Until now in this thesis, CANJEM has been referred to as a single distinct JEM; however, it would be more accurate to refer to CANJEM as a set of distinct JEMs, henceforth defined as "versions" of CANJEM, differentiated by the characteristics of their occupational code classification and time period axes. Indeed, changing the classification of the occupational code axis or the resolution of either axis requires the creation of a new version of CANJEM containing its own sets of cells, each aggregating a unique group of jobs.

These versions of CANJEM can then be further modified based on other factors. In addition to the specific combination of occupation title, time period and agent, some of the available exposure metrics can be used to further refine the information provided in a cell. Two examples of versions of CANJEM that are currently offered to users are based on 1) variations in handling the experts' level of confidence in each assessment of exposure to a given agent in a given occupation and time period, and 2) the minimum acceptable number of jobs providing information in the given cell. As explained previously, whenever the team of experts assigned an exposure to a specific agent and job combination, they also indicated how certain they were that the exposure truly occurred in that job (i.e. their confidence level, rated as "possible", "probable", or "definite"). Because agents assigned with a confidence of possible and, to a lesser extent, probable exposure are more prone to misclassification, it is possible to use versions of CANJEM that only include job/agent/time period combinations with exposure rated above a selected confidence threshold. Thus, CANJEM can include all exposed jobs, only include jobs with probable and definite exposure, or only consider jobs with definite exposure as exposed. In addition, there are two ways to deal with jobs not fulfilling the confidence requirement: to consider them as unexposed or to exclude them from CANJEM. Altogether, there is a total of five versions of CANJEM that vary based on how each deal with the confidence of exposure.

Furthermore, the precision of the metrics of exposure provided in a cell of CANJEM is strongly associated with the number of jobs used to create the cell for which the agent was assessed as exposed. The fewer the number of jobs, the more likely that the metrics of exposure will be affected by jobs with more unique exposure profiles (outliers) and thus, the less likely they are to be representative of the average exposure found in the CANJEM population. This is not only true in regard to the absolute number of jobs in a cell, but also in regard to the number of workers that held those jobs. Indeed, it is more likely that the exposure profile of 10 jobs held by a single worker will not be representative of a typical exposure profile for those employed with that occupation title, than if the profile came from 10 different workers. Thus, to avoid using unnecessarily imprecise cells, versions of CANJEM that only provide metrics of exposure for cells containing a preselected minimum number of jobs from a minimum number of workers can be created. While thousands of possible versions of CANJEM could be created this way, the team behind CANJEM elected to provide two specific versions to users: one with no job count restriction, and one, considered as the main version of CANJEM, that only includes cells based on at least 10 jobs from at least three workers. The decision to provide the version of CANJEM with those job and worker restrictions was not based on any specific scientific evidence, rather it was based on the opinion of experts familiar with the data and methods used to create those metrics. Therefore, using the version of CANJEM with restrictions does not ensure that all cells will provide accurate metrics of exposure and users can decide to exclude cells as they see fit to create alternative versions.

As can be seen, CANJEM comes in many versions and deciding which to use can be a complicated task. Even when the classification system to be used in the occupational code axis is determined by that used in the study population, as is often the case, users still have to decide between more than a hundred versions of CANJEM. When selecting the ISCO68 coding system for example, there are four possible resolutions in the occupational code axis and three possible resolutions in the time period axis, for a total of 12 possible versions of CANJEM. Each of those versions can then be created in five different ways based on how confidence of exposure is dealt with and two different ways based on the minimum number of jobs per cell selected, for a total of 120 versions. Thankfully, the number of useful versions of CANJEM is much lower. Indeed, the 1- and 2-digit ISCO68 resolutions probably aggregate jobs with exposure profiles that are too different to be meaningful. Similarly, obtaining average estimates of exposure from cells containing only 1 job makes little sense. By the same token, considering jobs with "possible" exposure as unexposed will probably exacerbate the level of misclassification. Thus, there are in truth only 18 realistic ISCO68 versions of CANJEM to choose from.

4.2.9 Methodological considerations in relation to the application of a JEM, with a focus on CANJEM

The basic process of linking a JEM to a study population is rather simple and only requires three prerequisites. First, it must be ensured that the selected JEM is applicable to the study population of interest. That is, that the jobs in a given study population can be expected to have exposure profiles similar to the jobs in the population used to create the JEM. Second, the job titles must be coded to a classification system used by the JEM. Lastly, if the JEM contains a time period axis, the duration of all jobs must be recoded so that they do not overlap any time period. This can be accomplished by separating jobs overlapping two or more time periods into smaller jobs contained within each time period. For example, when using CANJEM with four time periods (1930-1949, 1950-1969, 1970-1984, and 1985-2005), a job lasting from 1940 to 1978 would be separated into three jobs with the same job title lasting from 1940 to 1949, 1950 to 1969, and 1970 to 1978 respectively. However, it can be noticed that in doing so, the total duration of the three new jobs (36 years) is smaller than the duration of the original job (38 years). This is due to the fact that the one-year period between two time periods (e.g. the 1949 to 1950 period) is lost when the job is separated and can be easily fixed by adding 0.5 year to the duration or – 0.5 year to the start date and/or 0.5 year to the end date of the newly created jobs whenever they start or end at the beginning or the end of a time period. For example, the duration of each of the three new jobs presented previously would be 9.5 years (9 years + 0.5 year), 20 years (19 years + 0.5 year + 0.5 year), and 8.5 years (8 years + 0.5 year) respectively.

In addition to those three prerequisites, an extra complication is introduced to the linking process in the availability of different resolutions for the occupational code and time period axes in CANJEM. While it can be assumed that linking CANJEM using the highest resolution available in each axis would provide metrics of exposure more representative of the exposure found in a specific job, the CANJEM database may not necessarily contain a sufficient number of jobs needed to produce an informative cell for all possible combinations of occupational code and time period, particularly at higher resolutions where more cells are present. Thus, when linking CANJEM, there is a tradeoff between using the higher resolutions, which can provide more representative metrics of exposure, and using the lower resolutions which may link a larger proportion of jobs in a study population and contain an overall higher proportion of informative cells, but with potentially less representative estimates of exposure for certain cells. As the resolution(s) used for the linkage procedure should be based on the characteristics of the selected agent(s), the optimal linkage procedure for the agents included in this PhD thesis will be examined in chapter 5. There is one final methodological consideration that must be discussed in regard to the linkage of CANJEM to a study population, albeit it is not specific to CANJEM and is more related to the characteristic of a study population itself. Indeed, the average frequency of exposure provided by CANJEM assumes that a job is held full-time; however, job histories often only include the start and end year of a job without indicating whether the job was seasonal or held part-time. While it can be assumed that most jobs are fulltime, it is harder to make this assumption when two or more jobs held by a single subject overlap. If those overlapping jobs are considered as full-time and full-year, we may overestimate a subject's overall occupational exposure, while we may underestimate it when considering them as part-time or seasonal jobs. In the end, there is no single guideline in how to deal with overlapping jobs when no extra information is available. Any decision should be based on a good understanding of a study population's work habits and potentially be made on a subject by subject basis depending on the number of simultaneously overlapping jobs. In any case, as overlapping jobs tend to represent only a small minority of all jobs in a study population, it is unlikely that the method used to deal with them would strongly affect the calculation of risk estimates. The method employed to deal with overlapping jobs in the INTEROCC study will be presented in section 4.4.3.

4.3 The INTEROCC study

INTEROCC is an offspring of the INTERPHONE population-based multi-national case-control study that was designed to assess the possible association between use of cellular phones and risk of primary brain, parotid gland and acoustic nerve cancer (158). INTERPHONE was conducted between 2000 to 2004 in 16 centers from 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand (NZ), Norway, Sweden, United Kingdom (UK)), using a common core protocol. Its main findings on cell phones have been published (159, 160). Seven of the 13 countries that participated in INTERPHONE (Australia, Canada, France, Germany, Israel, NZ, UK) also gathered information on subjects' lifetime job history. These centers banded together to form the INTEROCC consortium, with the objective of studying possible associations between occupational exposures and brain cancer.

4.3.1 Study design

For most centers, the study base included individuals aged 30-59 years old with residency in one of the study regions. However, in Germany, the UK and Israel the age ranges were somewhat different, but all included 30-59. Australia, Canada, France, Germany, and NZ restricted the study base to selected major metropolitan areas, while the UK restricted the study population to certain regions of England and Scotland, and Israel included the entire Jewish population. Some study centers imposed further restrictions, including citizenship and local language proficiency. Table V provides information on study regions and source populations included in INTEROCC.

Table V: Study regions and source populations in INTEROCC by country[1]

Study center	Definition of study regions	Source population
Australia	Sydney Statistical Division, Melbourne Statistical Division	Citizens resident in the study regions, capable of participating in a face-to-face interview in English
Canada	Greater Metropolitan Montreal, Ottawa, Eastern Ontario and Ottawa Valley, Vancouver, Lower BC Mainland, Greater Victoria area of Vancouver Island	Citizens resident in the study regions (Montreal), Residents of the study region (Ottawa, Vancouver)
France	Metropolitan region of Lyon, Metropolitan region of Paris – Ile de France	Citizens resident in the study regions
Germany	Bielefeld 5 “Kreise” (administrative unit similar to a county), Heidelberg 18 “Kreise”, Mainz 10 “Kreise”	Residents of the three study regions with sufficient knowledge of the German language to undertake the interview
Israel	The entire Jewish population within Israel	Jewish citizens of Israel
New Zealand	Greater Auckland; Hamilton, Rotorua, Tauranga; Napier, Hastings; Wellington, Palmerston North; Christchurch	Residents of the study regions for at least 6 months
United Kingdom	Central Scotland (Lothian, Fife, Forth Valley, Greater Glasgow and Lanarkshire, Ayrshire and Arran), West Yorkshire, Trent, West Midlands, containing both densely populated urban city conurbations and sparsely populated rural areas	Residents of the study regions

1. Modified from Cardis E, et al. (164).

Cases included in this thesis were residents of the study region with a primary glioma or meningioma diagnosis from one of the study centers. Cases were either histologically confirmed or confirmed based on unequivocal diagnostic imaging. In total, 2,054 glioma cases (1,251 men, 803 women) and 1,924 meningioma cases (511 men, 1,413 women) were included in this study. The overall response rates for glioma and meningioma cases were 68% and 81% respectively. Table VI provides the response rates for cases and controls by country. Controls in each center were randomly selected from the source population using various sampling frames (table VII) and were either individually (Ottawa, Vancouver, France, Israel, NZ, UK) or frequency (Australia, Montreal, Germany) matched to cases by 5-year age group, sex and study region. For each glioma and meningioma case, one control was selected, with the exception of Germany where two controls were selected. In total, 5,601 controls (2,612 men, 3,191 women) were included in this study. The overall response rate for controls was 50%.

Table VI : Response rates for glioma cases, meningioma cases, and controls in INTEROCC by country

Study center	Glioma		Meningioma		Controls	
	Ascertained (n)	Interviewed (n(%))	Ascertained (n)	Interviewed (n(%))	Ascertained (n)	Interviewed (n(%))
Australia	536	301 (56)	413	254 (62)	1,608	669 (42)
Canada	273	170 (62)	134	94 (70)	2,133	653 (31)
France	155	94 (61)	190	145 (76)	639	472 (74)
Germany	460	366 (80)	431	381 (88)	2,449	1,535 (63)
Israel	515	442 (86)	832	748 (90)	1,442	997 (69)
New Zealand	132	84 (64)	72	52 (72)	350	172 (49)
United Kingdom	946	597 (63)	310	250 (81)	2,491	1,103 (44)
Total	3,017	2,054 (68)	2,382	1,924 (81)	11,112	5,601 (50)

Table VII: Controls sampling frames in INTEROCC by country[1]

Study center	Sampling frame for controls
Australia	Electoral list
Canada	
Montreal	Electoral lists
Ottawa	Random digit dialling
Vancouver	The population-based BC[2] Ministry of Health Client Registry
France	Electoral lists
Germany	Regional population registries
Israel	National population registry
New Zealand	Electoral rolls
United Kingdom	General practice patient lists

1. Modified from Cardis E, et al. (158).
2. British Columbia.

When required by ethics review boards, physician authorization was obtained to contact cases. All eligible subjects were contacted and informed about the study by their treating physician, a nurse or the study research staff. Once informed consent was obtained, subjects or their proxy respondents (generally spouse or offspring) were interviewed in person by trained interviewers using a Computer-Assisted Personal Interview (CAPI) questionnaire. Telephone interviews were used for some hard-to-reach subjects. Proxy response was obtained for 395 (19%) glioma cases, 95 (5%) meningioma cases, and 34 (0.6%) controls. Around 70% of controls were interviewed six months or less after the matched cases. The questionnaire included questions on SES, use of wireless phone and devices, exposure to ionizing radiation, smoking history, and personal and familial medical history. In addition, detailed lifetime job history was gathered using an occupational history questionnaire. The questionnaire gathered data on any job ever held by a subject for more than six months, which included job title, description of tasks and the start and end year of each job. Jobs titles were coded by an industrial hygienist in each country to ISCO68. A common coding guideline was used by each industrial hygienist to ensure homogeneity of coding.

4.3.2 Previous examination of occupational exposure to metals in INTEROCC

Two studies (43, 79), published within the past two years, have already examined the association between occupational exposure to metals and glioma and meningioma in the INTEROCC study, and one may wonder at the necessity of the present PhD thesis project. Those studies were conducted using the INTEROCC-JEM, a slightly modified version of FINJEM. While FINJEM may be the best JEM that has previously been available, it has several limitations. Since it was based on the routine activities of a surveillance and monitoring agency, it does not necessarily contain representative measurements. More likely it represents measurements in situations where there was a need for compliance monitoring. Further, it was built on only 47 chemical agents, only a few of which were metallic compounds. FINJEM uses the Finnish occupational classification for the job axis at a fairly crude and aggregate level (311 distinct occupations). Like CANJEM it does have a time axis, but for each time period the only metrics providing estimates of exposure are an overall probability of exposure and a mean concentration level for the given occupation title and time period. Within the constraints of those limitations, it is valuable, but limited. Thus, examining the association between occupational exposure to metallic compounds and brain cancer in INTEROCC with CANJEM allows, not only the examination of a larger set of metallic compounds not present in FINJEM, but also allows us to compare associations obtained with two JEMs built from different populations that complement each other in regard to their strengths and limitations.

4.4 Organization and complementary information for chapters 5 to 7

When this thesis was first conceptualized, CANJEM had just been finalized and little was known regarding the impact of the application of a JEM of that complexity to the analysis of epidemiological data. Because of this, it was decided early on to take the opportunity offered by this thesis project to explore some of the major methodological considerations associated with the application of CANJEM. More specifically, we decided to focus our attention on two important issues that we and other epidemiologists would have to face when using CANJEM: 1) how should CANJEM be linked to a study population, in our case the INTEROCC study population? 2) Once linkage is satisfactorily achieved, how should we use the metrics of exposure provided by CANJEM, particularly the probability of exposure, to create lifetime exposure variables? The next three chapters are thus organized in the order of the procedure that would generally be followed when using CANJEM to examine the association between an occupational agent and an outcome. The observations made in an earlier chapter are used to develop the methodology of the next. Chapters 5 and 6 focus on linking CANJEM to the INTEROCC study and selection of appropriate methods for analysis, while chapter 7 examines the association between our 21 selected occupational agents and brain cancer.

4.4.1 Complementary information for chapter 5

The manuscript in chapter 5 addresses our third objective: the impact of the choice of levels of resolution of the occupational classification and the resolution of the time period on linkage rate and the resulting exposure metrics. As mentioned, this chapter was envisioned as a way to determine the best approach to link CANJEM to the INTEROCC study while providing some guidance for future users. We used descriptive statistics and agreement analyses to examine these questions. More precisely, we intended to determine whether differences existed in terms of the number of linkable jobs in the INTEROCC study and the values provided by different versions of CANJEM for the probability and FWC of exposure. If important differences existed between two versions, then both would have to be considered during the linkage procedure, but if no or little difference existed, then we would be able to drop one of the versions. Originally, we intended to compare versions of CANJEM varying in one of three possible aspects: 1) the minimum number of jobs per cell required to produce metrics of exposure for that cell, 2) the inclusion criteria for the minimum confidence level of the exposure assessment, and 3) the resolution of the occupational code and time period axes. However, it quickly became obvious that the selected methodology would not be informative for the examination of versions varying in their minimum number of jobs per cell. Indeed, the only consequence of varying the minimum number of jobs per cell is to change the number of cells available in a version of CANJEM. While this will impact the linkage rate, it will not affect the metrics of exposure provided by any of the cells present in both versions of CANJEM. In addition, varying the minimum confidence level of estimates to be included had little impact on the probability and FWC of exposure and the overall results obtained for the FWC of exposure were nearly identical to the ones obtained for the probability of exposure. Therefore, we focused our effort on the comparison of versions of CANJEM that varied in the resolution of their occupational code and time period axes and on the probability of exposure.

While the descriptive statistics employed in chapter 5 are rather straightforward, the method used to examine agreement requires some explanation. The agreement between categorical versions of the probability and FWC of exposure was calculated using the Gwet agreement coefficient (161) rather than the more commonly used Cohen's kappa (162). This decision was made due to the low prevalence of exposure that could be expected to be present for most agents in CANJEM. Indeed, Cohen's kappa provides a chance-adjusted coefficient of the agreement between two raters (two versions of CANJEM in the context of this thesis) for categorical observations, based on the formula:

$$K = \frac{Po - Pe}{1 - Pe}$$

Where P_o is the relative observed agreement and P_e is the expected chance agreement. Based on table VIII, P_o and P_e would be calculated as:

$$Po = \frac{A + D}{N}$$

$$Pe = \left(\frac{AC}{N} x \ \frac{AB}{N}\right) + \left(\frac{BD}{N} x \ \frac{CD}{N}\right)$$

Table VIII: Distribution of exposure assessments between two versions of CANJEM

		Version 1		
		Exposed	Non-exposed	Total
Version 2	Exposed	A	B	AB
	Non-exposed	C	D	CD
	Total	AC	BD	N

While Cohen's kappa generally provides a good measurement of agreement, it has been shown to underestimate agreement in situations where there is a high probability for observations to be classified in one specific category, either because an outcome is extremely rare or prevalent, or because at least one of the factors (i.e. coder or method) compared tends to classify observations in a specific outcome (e.g. one or both methods compared tend to classify most subjects as unexposed to a selected agent). This is often referred to as the Cohen's kappa paradox (163, 164) and in the context of CANJEM where most cells would be categorised as unexposed to a selected agent, using Cohen's kappa will result in abnormally low agreement. For example, when comparing the agreement for the probability of exposure to cadmium in a version of CANJEM using ISCO68 with 5-digits to a version using 3-digits for the time period 1930 to 1949, we obtained a kappa of 0.21, even though both versions classified similarly 1,046 of the 1,156 cells (91%). For other agents, such has mercury, a kappa of 0 could be obtained. This issue can be fixed by using paradox-adjusted measures of agreement such has the Gwet's agreement coefficient (161, 164, 165). The basic Gwet's agreement coefficient (AC1) can be calculated using the formula:

$$AC1 = \frac{Pa - Pe}{1 - Pe}$$

Where P_a, the relative observed agreement, is calculated similarly to Cohen's kappa P_o and where P_e, the expected chance agreement, is calculated using the formula:

$$Pe = 2q(1-q), \text{ with } q = \frac{AC + AB}{2N}$$

This change in how the expected chance agreement is calculated allows Gwet`s AC1 to provide an accurate measure of agreement even in situations where exposure prevalence is low. For example, using our previous cadmium example, we obtained a much more probable agreement of 0.89. In chapter 5 we used Gwet's AC2, a version of Gwet's AC1 that includes weights.

4.4.2 Complementary information for chapter 6

In chapter 6 we used logistic regression models to examine and compare the estimated associations between lung cancer and nine occupational agents, assessed using different approaches with CANJEM, to the original expert assessment method to address our fourth and fifth objectives. The manuscript presented in chapter 6 had two complementary objectives; the first was to determine how the probability of exposure affected the creation of a lifetime exposure variable and consequently, the association obtained between an occupational agent and the disease outcome. The second was to compare the associations obtained with CANJEM to the ones obtained with expert assessment and determine 1) Whether CANJEM was able to reproduce the associations obtained for the expert assessment it was trying to emulate, and 2) What method, if such a method existed, allowed for the creation of lifetime exposure variables with CANJEM resulting in associations more consistently similar to the ones obtained with the expert assessment.

In order to achieve these objectives, we used the study population and expert assessment from the Montreal lung cancer study, which was study 2 in the development of CANJEM (46) because it represented a large proportion of all data used to create CANJEM and because CANJEM included a relatively large number of known and potential lung carcinogens. While we could have included in our analysis some of the subjects from study 1 (the Montreal multisite cancer study) (49) we decided to limit our analysis to study 2 due to the slight methodological differences that existed in expert exposure assessment between those two studies.

Although we originally explored the use of a wider set of lifetime exposure variables and occupational agents during our preliminary analyses, there was generally little difference in the results obtained and we restricted our analyses to the association between two commonly used lifetime exposure variables (a binary ever/never exposure variable and a cumulative exposure variable) and nine known or potential occupational lung carcinogens.

4.4.3 Complementary information for chapter 7

We address our first two objectives, in the manuscript presented in chapter 7: an examination of the risk of glioma and meningioma in the INTEROCC study in relation to exposure to 21 metallic compounds, using conditional logistic regression. While the method employed to link and assess occupational exposure was based on the observations made in chapters 5 and 6, some extra assumptions had to be made in regard to the duration of exposure. Most of those assumptions, such as considering that jobs with the same start and end year lasted six months, were made based on a guideline provided by the INTEROCC team. The decision to consider overlapping jobs (jobs held by a subject during the same period of time) as part-time, however, was our own. As mentioned previously, when applying a JEM such as CANJEM which provides a frequency of exposure assuming a full-time week to a study population with no information on full-time status of jobs, we need to decide between considering overlapping jobs as full-time and potentially overestimate exposure or as part-time and potentially underestimate it. While a good understanding of the study population can help us make a reasonable assumption in most studies, it is much more complicated to make such an assumption in a study like INTEROCC which includes subjects from a wide range of countries and industries. Nonetheless, we decided to consider as part-time any overlapping jobs when creating our cumulative exposure variable. This was based on the belief that although it was probable that workers with two or more simultaneous jobs had worked over 40 hours per week, it was very unlikely that all those jobs were fulltime, particularly when more than two jobs overlapped. In the end, however, this assumption should have had only minimal impact on the association obtained as only 13% (1,168) of the subjects included in INTEROCC had at least one overlapping jobs, with less than 1% having more than three simultaneously overlapping jobs.

The substances examined in this chapter differ somewhat from those examined in chapter 5 for two main reasons. The first is that, for metals that could be present in the JEM as compounds, fumes or dusts, we only included compounds in chapter 5 (e.g. lead compounds but not lead fumes). The second is that we excluded from chapter 7 any agents with extremely low prevalence of exposure in the INTEROCC study. Consequently, four agents examined in chapter 5 (mercury compounds, arsenic compounds, cadmium compounds, and metal coatings) and seven of the agents originally considered for chapter 7 (cadmium fumes, lead oxides, basic lead carbonate, lead chromate, zinc fumes, zinc oxides, and iron fumes) were eventually excluded from chapter 7. This means that two of the metals (mercury and cadmium) and one metalloid (arsenic) we originally intended to include in this thesis could not be examined in chapter 7.

Chapter 5: Modifications of user-defined dimensions of the Canadian job-exposure matrix (CANJEM) and their effect on the coverage and quality of the data provided

5.1 Manuscript

Modifications of user-defined dimensions of the Canadian job-exposure matrix (CANJEM) and their effect on the coverage and quality of the data provided

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Contribution details: RP designed the study and it`s analytic strategy, conducted the analysis, and drafted the final manuscript. JS and JL are the PIs of the CANJEM database and provided the CANJEM database for use in this project. JS, LR, JL, AK provided advice in study and analytic design. All authors participated in the writing of the manuscript.

5.1.1 Abstract

OBJECTIVE: To describe how the choice of levels of resolution of different axes of the Canadian Job-Exposure-Matrix (CANJEM) affects the numbers of occupational codes for which CANJEM provides metrics of exposure, the linkage of CANJEM to a study population, and the metrics of exposure provided by CANJEM for the study population. **METHOD:** Six versions of CANJEM were created, varying in resolution of the occupational code and time period axes. For each version, we calculated the proportion of occupational codes with informative cells and the proportion of jobs from the large international case-control study INTEROCC that could be linked to each version of CANJEM. We compared the probability of exposure to 19 metallic compounds obtained across the different CANJEM versions by examining the agreement for pairs of versions, using Gwet's agreement coefficient (AC2) with a linear weight. **RESULTS:** Overall, CANJEM provided estimates of exposure for 10% to 81%, of all possible 5-digit and 3-digit ISCO68 codes which translated into the linkage of 70.7% to 98% of all jobs in the INTEROCC study. Strong agreement over 0.90 was generally observed for the probability of exposure between versions of CANJEM. The agreement was, on average, higher between versions of CANJEM varying by time period axis compared to versions varying by occupational code axis. **CONCLUSION:** Although CANJEM did not provides metrics of exposure for all ISCO68 occupational codes, it could be linked to a large majority of jobs that occurred in the international INTEROCC study. As expected, changing the resolution of the occupational code axis had an impact on both the linkage rate and the probability of exposure provided by CANJEM. It may be preferable to apply CANJEM to a study population with sliding scales of resolution for both axes.

5.1.2 Introduction

Estimating exposure to occupational chemicals is a major challenge in occupational health research and in occupational medicine (1). As it is often impractical or impossible to carry out active environmental measurement in workplaces of workers whose exposure histories are at issue or in relevant biospecimens, alternative approaches have been proposed. Exposure assessment of individual jobs by experts has been used extensively by our team, but is very expensive in manpower. A job-exposure-matrix (JEM) can be an attractive option to use, if an appropriate one is available. A JEM is essentially a tool which can provide metrics of exposure to occupational agents for different occupational titles in a fairly automated way. A JEM is typically laid out with two or three axes: an occupational title axis, a time period axis (optional), and an occupational agent axis. Each cell defined by the axes provides some sort of metric of exposure to the given agent among workers in the given occupation and the given time period (2-6)

Taking advantage of the fact that our team of specially trained experts had, over the past four decades, evaluated occupational exposures in over 30,000 jobs held by subjects in a series of case-control studies, we developed the Canadian Job-Exposure-Matrix (CANJEM) (7). CANJEM has been designed to provide considerable flexibility in the level of resolution of the occupational title classification and time period axes, and in the exposure metrics (e.g. probability of exposure, concentration of exposure). Together, these options can be thought of as creating different versions of CANJEM. Since each cell of CANJEM is based on a pre-existing database of actual exposure assessments in jobs that occurred in the histories of a large but finite number of study subjects, some cells are based on large numbers of jobs and some on few. Further, there were many occupational titles that never appeared in any of the job histories in the database, particularly as the resolution of occupational title code and time period increased. A very practical issue is how different versions of CANJEM will in fact cover the occupational spectrum at different resolutions of its axes so that users will be able to find exposure metrics for study subjects.

The objective of the analyses carried out in this paper was to describe how the choice of levels of resolution of different CANJEM axes may affect: (1) the numbers of occupational code with informative cells in CANJEM, which gives an indication of the number of occupational codes that can be linked to a CANJEM exposure metric; (2) the metrics of exposure to 19 occupational agents , which may vary depending on the heterogeneity of jobs within a cell; and (3) the linkage of CANJEM to a study population , which gives an indication of the practical consequences of choices in the resolutions.

5.1.3 Summary description of CANJEM

The methodology used to create CANJEM has been described previously (7, 8). Briefly, CANJEM was developed using data on 31,673 jobs held from the early 1930's to 2001 by more than 8,760 participants of four population-based case-control studies principally carried out in the Montreal area (9-12). In each study, trained interviewers gathered detailed information on participants' lifetime occupational history during face-to-face interviews using a semi-structured questionnaire. This included questions on tasks, equipment, substances and protective equipment used in the work environment. For some jobs with complex tasks and multiple occupational agents and processes, specialized questionnaires were used to complement the main exposure questionnaire. Using the data collected during those interviews, a team of expert chemists and industrial hygienists, blinded to case/control status of the participants, assessed each job to determine exposure to a list of up to 294 occupational agents. Each assessment was based on the information provided by the participant, relevant data gathered from the literature, and on the experts' experience. Participants' exposure status was reached through consensus between experts.

<u>CANJEM axes</u>

Each cell in CANJEM is defined by a unique combination of three axes, including 1) an occupation code axis, 2) a time period axis, and 3) an occupational agent axis.

Occupation code axis

CANJEM is available with four different occupational classification systems; in this paper, we use the International Standard Classification of Occupations 1968 (ISCO68) *(13)*. Its structure is hierarchical with resolutions of 2-, 3-, and 5-digits indicating increased specificity in the occupational code with increasing number of digits. For example, gas welders are represented by the 5-digit code 8-72.15 in ISCO68. They are, however, also contained within the 3-digit code for gas and electric welders 8-72, and both gas and electrical welders are contained within the 2-digit code 8-7 that includes plumbers, welders, sheet-metal and structural metal preparers and erectors. Thus, a lower resolution (i.e. fewer digits in code) aggregates a larger number of different occupations. When creating a JEM based on existing job-based exposure assessment, a larger number of data points will provide more precise exposure metrics. However, if there is high number of data points because of a low resolution in the job code and exposure heterogeneity among the different jobs within a code is high, the validity of the exposure metrics will be affected. Increasing the resolution will thus increase the validity of the exposure metrics for each higher resolution code, but precision will be lost due to fewer data points, i.e. jobs within a code.

Of the 1,506 5-digit occupation codes in ISCO68, two-thirds are present in CANJEM, while 96% of the 284 3-digit ISCO68 codes and all of the 83 2-digit ISCO68 codes are present. For this manuscript, we principally compare resolutions of 5- and 3-digits, as the 2-digit resolution aggregates very heterogeneous sets of occupations.

Time period axis

As mentioned, the 31,673 jobs on which CANJEM was built were held from the early 1930's to 2005. There may well have been changes in exposures within occupations over that long time period. CANJEM was designed to allow users to select among seven time periods, some of which are embedded in others: 1930-2005; 1930-1969; 1970-2005; 1930-1949; 1950-1969; 1970-1984; 1985-2005. Given that a user will have a particular time period for which the exposure is to be estimated, the user is faced with the following trade-off in choosing between higher and lower resolutions of time. In particular, choosing a narrower time period in CANJEM may provide a more temporally relevant window for exposure assessment, but at the price of fewer data points used to provide the estimate and thus reduced precision.

Occupation agent axis

CANJEM contains information on 258 occupational agents.

Cell entries - metrics of exposure

In addition to rating the presence or absence of agents in the jobs they assessed, the experts in the original studies also indicated their confidence in each exposure assessment ("possible", "probable" and "definite"). These confidence ratings are integrated into CANJEM (see table I). For the present analysis, we considered a job as exposed only when the confidence level was “probable” or “definite” and we omitted from the denominator jobs with “possible” exposure confidence level. For each occupational code, time period, and agent, CANJEM provides an estimate of the probability of exposure to that agent among workers in the selected occupation and time period. Further, for each exposed cell, CANJEM provides some quantitative or semi-quantitative metrics of exposure, including the frequency, the concentration, and the confidence of exposure.

5.1.4 Methods

Numbers of occupational codes with informative cells in CANJEM

Based on the resolutions in the occupation code (3-digit or 5-digit) and time period axes (1, 2, or 4 time periods), there are six possible combinations and thus ‘versions’ of CANJEM. For the present project we considered an informative cell to be one that was based on at least 10 jobs, which we believe avoids excessive imprecision in the exposure metrics due to very small numbers of jobs in a cell. Whether a cell has at least 10 jobs and is thus informative varies according to the resolutions of the occupation and time axes. If there were no informative cells associated with a specific occupational code at a selected resolution of the occupational code as well as time axis, that job code would no longer exist in that version of CANJEM.

For each of the six versions of CANJEM, we counted how many occupational codes had cells in the corresponding version of CANJEM satisfying the criterion of 10 or more underlying jobs. When the resolution of the time period axis included two or four time periods, we calculated the number of ISCO68 occupational codes available in each time period separately.

Comparison of exposure metrics using different resolutions of CANJEM

For 19 metals, metalloids, and types of welding fumes (lead, mercury, cadmium, zinc, chromium, iron, nickel, calcium carbonate, calcium oxide, calcium oxide fumes, calcium sulphate, metallic dusts, metal coating, metal oxide fumes, silicon carbide, arsenic, gas welding fumes, arc welding fumes, and soldering fumes) that are the subject of an on-going analysis on the etiology of brain cancer, we determined the exposure metrics using different resolutions of CANJEM. In particular, the exposure index we used was the probability of exposure, categorised as: 0%, > 0% to <25%, 25% to <50%, 50% to <75%, and ≥ 75%. To compare the probability of exposure across the different CANJEM versions, we examined agreement for pairs of CANJEM versions, calculated using Gwet's agreement coefficient (AC2) with a linear weight (14). This variant of Cohen's Kappa provides a chance-corrected measure of agreement that is not affected by the low prevalence of exposure, which is expected for most occupational agents.

As a sensitivity analysis, to determine if the agreement observed in the main analyses was related to the categorisation of the probability of exposure, we also categorised probability of exposure into quartiles for six of our selected occupational agents that varied in their prevalence and exposure levels (lead, mercury, iron, arc welding fumes, metallic dusts, and arsenic). In order to determine if using different strategies for dealing with the expert confidence level in CANJEM would modify our results, we also reproduced our main analyses in versions of CANJEM with varying confidence level threshold. In addition, we also directly compared the agreement for the probability of exposure between those versions of CANJEM. We also reproduced these analyses using the median frequency weighted concentration, another exposure index from CANJEM which considers both the concentration and frequency of exposure. Finally, we also examined the linkage rate in the INTEROCC study excluding the Canadian data that were also part of the database used to create CANJEM. All analyses were conducted using SAS 9.4.

Linkage of CANJEM to a case-control dataset

INTEROCC (10) is a large population-based multi-national case-control study on the association between occupational agents and brain cancer, conducted between 2000 to 2004 in seven countries (Australia, Canada, France, Germany, Israel, New Zealand, United Kingdom). Information on the lifetime job histories of over 9,500 participants was collected, for a total of 35,758 jobs all coded in ISCO68 (10).

We calculated how many jobs in the INTEROCC study population that could be linked to CANJEM for each of the six versions. For the time period resolution that included four periods, we separated each job held by a participant that overlapped more than one time period into jobs that were contained within each time period, which increased the total number of jobs to 45,249. For example, if a participant held a job from 1935 to 1976, 3 jobs were created: one from 1935 to 1949 (period 1), one from 1950 to 1969 (period 2), and one from 1970 to 1976 (period 3).

5.1.5 Results

Table II shows the number of ISCO68 codes that can be linked to CANJEM at different resolutions in the occupation code and time period axes. As expected, the percentage of linkable occupational codes increases as the resolution of each axis decreases. With respect to the 1,506 possible ISCO68 codes, CANJEM provides a linkable code and exposure metrics for 10% to

31% of all possible 5-digit codes, and 41% to 81% of all 3-digit codes, depending on the time period resolution selected.

Table III shows the number of jobs from the INTEROCC study participants that linked to CANJEM at different resolutions of the occupation axis and the time axis. By contrast with the analysis shown in Table II, the analysis of linkages with INTEROCC is weighted by the number of occurrences of different occupations in real populations. At the highest resolution on both axes, 70.7% of jobs among INTEROCC participants could be linked and the linkage percent increased as the resolution decreased on either axis, reaching 98.1% linkability when both axes were at the lowest resolutions.

Table IV summarizes the agreement in the probability of exposure across the 19 selected occupational agents between versions of CANJEM with different resolutions in the time period axis when fixing the occupational code axis resolution. For instance, when fixing the occupational code resolution at 5-digits, and comparing a resolution of four periods to two periods, the Gwet index across all agents ranged from 0.85 (for lead) to 1.00 (for mercury). The median across the 19 agents was 0.98. Overall, the agreement between the different time period resolutions was very high, with median Gwet index values at or above 0.95 for all comparisons, and only a handful of specific comparisons below 0.90. The prevalence of exposure to the agent had some impact on the level of agreement, which tended to be lower for the more prevalent occupational agents, such as lead (median agreement = 0.94), and higher in less prevalent ones, such as mercury (median agreement = 0.99). Agreements were the lowest when comparing a resolution of four time periods to a resolution of one time period, particularly for the first (1930-1949) and fourth (1985-2003) time period. The agreements did not change noticeably by resolution in the occupation code axis.

Table V is analogous to Table IV, but shows the agreement for different resolutions in the occupational code axis when fixing resolution of the time period axis. Compared to different resolutions in time period while fixing occupational code resolutions, we observed generally lower median agreements across agents, ranging from 0.90 to 0.93. When comparing occupational code resolutions of 5- or 3-digits to a resolution of 2-digit, much lower agreements, going as low as 0.68 were observed (results not shown).

Table VI shows a specific example of the cross-tabulation of probability of exposure for one agent, namely lead compounds, between the 3-digit and 5-digit resolution of the occupational code axis in CANJEM, by resolution of the time periods axis. It can be seen that the agreement was over 0.80 for all time periods, and that while the agreement stayed around 0.85 at resolutions of one and two time periods, it ranged from 0.82 (period 1) to 0.90 (period 4) at a resolution of four time periods.

In sensitivity analyses where the confidence level threshold was varied in the version of CANJEM, only marginal differences were observed in the number of ISCO68 codes that can be linked to CANJEM, in the Gwet index for probability of exposure by resolution of the occupational code or time period axis, and in the number of jobs among INTEROCC participants that could be linked to each CANJEM version (results not shown). Similarly, when comparing directly the probability of exposure between versions of CANJEM that varied in terms of the minimum confidence level, we observed strong agreement generally higher than 0.95, but as low as 0.87 when comparing the versions of CANJEM including all jobs estimates to the one only including definite job estimates (results not shown). When probability of exposure was categorised into quartiles, the estimates of Gwet index was lower but still relatively strong, generally ≥ 0.85 between versions of CANJEM that varied by resolution in their time period axis or in their minimum confidence level (results not shown). However, when comparing the agreements between versions of CANJEM that varied by resolution in their occupation code axis, agreements were generally 0.20 to 0.30 lower than what we reported previously and as low as 0.15 when comparing a resolution of 5-digit to a resolution of 2-digit (results not shown).

We also conducted sensitivity analyses by reproducing all of the main analyses presented in this study using the median frequency weighted concentration of exposure and observed that overall, the agreement for all analyses were similar and often slightly higher than for the probability of exposure (results not shown). When the Canadian data from INTEROCC, which was part of the data used to create CANJEM, was excluded, we observed no difference in the linkage rate.

5.1.6 Discussion

Overall, we observed that CANJEM provided estimates of exposure for up to 31% and 81%, of all possible 5-digit and 3-digit ISCO68 codes, respectively. This translated into the linking of 71% to 98% of all jobs coded in the INTEROCC study. The impact of reducing the resolution of the occupational code axis was greater than reducing the resolution of the time axis and while reducing the resolution of the occupational code axis resulted in an increase in the number of occupation codes providing metrics of exposure, it did not necessarily translate into a similar increase in the number of jobs that could be linked in a study population. Indeed, when linking the INTEROCC study to CANJEM, we noticed that although a higher proportion of ISCO68 codes were available at a resolution of 3-digits and four time periods than at a resolution of 5-digits and one time period, this only translated into the linkage of an extra 7% of jobs.

We observed generally strong agreement in exposure metrics between versions of CANJEM that varied in their time axis, but lower agreement in versions of CANJEM that varied in their occupational code axis. This difference may be explained by the particularities of both axes. For instance, for the time period axis, lowering the resolution entails merging two higher resolution periods (e.g. 1970-1984 and 1985-2005) into one period (e.g. 1970-2005). Unless major technological or regulatory changes occurred between the two higher resolutions time periods, little difference will be observed between resolutions of the time axis. However, a lower resolution in the occupation code axis merges different occupations with similar work characteristics into one group. Considering that a majority of jobs are unexposed to any of our selected occupational agents, the main consequence of this aggregation of jobs is an increase in the denominator when calculating the probability of exposure, thus reducing the probability of exposure for exposed occupational codes, but it will also introduce a low probability of exposure to unexposed occupational codes, as long as one of the jobs merged was considered exposed. The extent to which this aggregation will impact the probability of exposure for a selected occupational agent will be dependent on the number and exposure similarities of merged jobs.

Two major choices are available to CANJEM users in regard to choosing the resolution of the occupation code and time period axis: 1) to use the highest resolution in either axes, or 2) to use a lower resolution in one or both axes. The first option will result in lower linkage rate, but will insure exposure metrics based on less potential heterogeneity across jobs. The second option will do the opposite, ensuring a higher linkage rate and a higher number of jobs per cell, but at the cost of exposure metrics based on potentially higher heterogeneity. A third option exists where resolutions can be varied for subsets of a study population. For instance, a study population can be linked using the highest resolutions in both axes, and for those subjects that could not be linked, the resolutions can then be lowered. This will maximize the linkage rate, and allow for exposure metrics based on low heterogeneity for the greatest number of subjects possible. While the decision to use any of the three options should be based on a good understanding of the occupational agent of interest and of the distribution of jobs in the study population, we believe that it is generally preferable to opt for lower resolutions in the time axis before lowering resolutions in the job axis, based on our observations.

We also examined varying the minimum level of confidence in the job estimates for a given CANJEM version and observed little impact on the number of occupation codes available for linking, on the linkage rate itself, or on the metrics of exposure examined. Those observations may be due to the small proportion of cells related to our occupational agents of interest in CANJEM that included job exposure estimates of possible and probable and/or to the fact that those job estimates generally only represented a small proportion of all job estimates in those cells. Still, even when taking into consideration the small impact of the confidence level on both the linkage rate and the estimates of exposure, it may not be recommended to use versions of CANJEM excluding job estimates with a confidence level of possible and probable, as those estimates are not necessary biased and doing so would reduce the precision of the metrics of exposure provided by CANJEM.

In this study we were able to examine different decisions that can be made when using CANJEM for 19 occupational agents. While our agents varied in terms of prevalence and exposure level, they were all metallic compounds and thus, it is possible that our results do not apply to all agents present in CANJEM. However, we believe that the general recommendations we proposed should apply to most agents. For example, conducting the same analyses with organic solvents resulted in agreements 10% lower overall, but with trends similar to what we presented (unpublished results).

In computing the Gwet index, we created categories for the probability of exposure. The number and cutpoints of these categories were devised in consideration of what we considered to be meaningful in the context of an epidemiological study. However, most of our agents ended up in the low probability categories, which may partly explain the strong agreement we obtained. To test this hypothesis, we conducted sensitivity analyses using the quartiles of the probability of exposure for 6 of our selected occupational agents. While we still observed relatively strong agreement between versions of CANJEM that varied in their confidence level or by resolution in their time period axis, the agreement between versions of CANJEM that varied by resolution in their occupation code axis was generally much lower than what we reported in our main analyses. It is important to note, however, that the majority of quartiles compared had probability of exposure limits under 25%. Thus, it is unclear if the lower agreements would strongly impact the examination of causal associations. Still, this exercise indicates that the general conclusions we reached shouldn't be affected by the selection of categories.

We conducted all of our analyses using the probability of exposure as the exposure index of interest. However, when conducting our analysis with the median dose of exposure we observed similar to slightly higher agreement than for the probability of exposure, indicating that the conclusion reached in this study should probably apply to either the frequency or the concentration of exposure.

Similarly, we conducted all of our analyses using versions of CANJEM that included cells with at least 10 jobs. Consequently, our observations may not necessarily apply to versions of CANJEM that differ in the minimum number of jobs per cell.

5.1.7 Conclusion

Notwithstanding the fact that CANJEM was based on over 30,000 jobs that had been coded and assessed by expert coders, once these are broken down by detailed occupation codes, the numbers of observations per cell can be insufficient to derive reliable metrics of exposure in CANJEM. Still, the cells that are sparse or empty may be for jobs that do not occur frequently in the population. For INTEROCC, CANJEM was informative about a large majority of jobs that occurred in an international collection of jobs, even at the highest degrees of resolution. As expected, the resolution of CANJEM axes does have an impact on the number of occupation codes available for linkage and on the metrics of exposure provided by CANJEM and it is possible and perhaps optimal to use CANJEM with sliding scales of resolution for both axes, so that the user would decide on a job-by-job basis at what level of resolution of the time axis and the occupation code axis to take the metrics of exposure. For users who would prefer to exclude job exposure estimates with lower confidence levels, we would recommend excluding at most job exposure estimates that were made with possible confidence by the original exposure assessors.

5.1.8 References

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5.1.9 Tables

Table I: User defined dimensions of CANJEM

Dimensions of CANJEM	Options	Number of options
Job axis (ISCO 1968)	5-digit; 3-digit	2
Time period axis	4 periods (1930-1949; 1950-1969; 1970-1984; 1985-2005) 2 periods (1930-1969; 1970-2005) 1 period (1930-2005)	3
Confidence level considered as exposed	All levels Probable and definite levels, possible level considered as unexposed Probable and definite levels, possible level excluded Definite level, possible and probable levels considered as unexposed Definite level, possible and probable levels excluded	5

Table II: Number of linkable ISCO68 occupational codes[1] according to varying resolutions of the time period and occupation code axes[2]

Resolution of the time period axis		Resolution of the occupational code axis (ISCO68)	
		5-digit	3-digit
		Total 1,506 codes	Total 284 codes
4 time periods n (%)[3]	Period 1 (1930-1949)	195 (12.9)	148 (52.1)
	Period 2 (1950-1969)	305 (20.3)	193 (68.0)
	Period 3 (1970-1984)	260 (17.3)	162 (57.0)
	Period 4 (1985-2005)	149 (9.9)	116 (40.8)
2 time periods n (%)[3]	Period 1 (1930-1969)	373 (24.8)	211(74.3)
	Period 2 (1970-2005)	303(20.1)	178 (62.7)
1 time period n (%)[3]	Period 1 (1930-2005)	467 (31.0)	229 (80.6)

1. Based on at least 10 jobs per cell in the source database.

2. Using the version of CANJEM that excludes exposure estimates with a confidence level of possible.

3. The percentage is calculated as the number of ISCO68 occupational codes providing metrics of exposure for the selected time period at the selected resolution in the time period and occupation code axes divided by the total number of existing ISCO68 occupational codes at the selected resolution in the occupation code axis.

Table III: Number of jobs from the INTEROCC pooled case-control study that could be linked to CANJEM[1,2] by resolution in the occupation code and time period axes

Resolution of the time period axis	Resolution of the occupational code axis (ISCO68)	
	5-digit	3-digit
4 time periods (n(%[3]))	31,994 (70.7)	41,434 (91.6)
2 time periods (n(%))	35,622 (78.7)	43,172 (95.4)
1 time period (n(%))	38,054 (84.1)	44,402 (98.1)

1. A cell was only created if there were at least 10 jobs with the given occupation code in that time period.

2. Using the version of CANJEM that excludes exposure estimates with a confidence level of possible.

3. This percentage is calculated as the number jobs in INTEROCC linked to CANJEM at the selected resolution in the time and job axis divided by the total number of jobs in INTEROCC (45,249). For the purpose of this exercise, jobs that overlapped 1 or more time periods at the selected resolution of the time axis were divided into new jobs contained within each time period.

Table IV: Agreement[1] between the probability of exposure[2] to the 19 selected agents for different resolutions of the time period axis; presented separately for each level of resolution of the occupation code axis, for the selected version of CANJEM[3,4]

Time period resolutions compared	Median Gwet index[5] (min[6]-max[7])
5-digit ISCO68 code	
4 vs. 2 time periods	0.98 (0.85 – 1.00)
4 vs. 1 time period	0.96 (0.78 – 0.99)
2 vs. 1 time period	0.98 (0.92 – 1.00)
3-digit ISCO68 code	
4 vs. 2 time periods	0.98 (0.87 – 1.00)
4 vs. 1 time period	0.95 (0.80 – 0.99)
2 vs. 1 time period	0.97 (0.93 – 1.00)

1. Calculated using Gwet`s agreement coefficient with a linear weight.

2. Probability of exposure categorised as: 0%, > 0% to < 25%, 25% to < 50%, 50% to < 75%, and ≥ 75%.

3. A cell was only created if there were at least 10 jobs with the given occupation code in that time period.

4. Using the version of CANJEM that excludes exposure estimates with a confidence level of possible.

5. Median agreement for the 19 agents included in the analysis and all time periods at the selected resolution of the time period axis.

6. Minimum agreement between the 19 agents included in the analysis and all time periods at the selected resolution of the time period axis.

7. Maximum agreement between the 19 agents included in the analysis and all time periods at the selected resolution of the time period axis.

Table V: Agreement[1] between the probability of exposure[2] to the 19 selected agents for different resolutions of the occupation code axis; presented separately for each level of resolution of the time period axis for the selected version of CANJEM[3,4]

Occupational code resolutions compared	Median Gwet index[5] (min[6]-max[7])
4 time periods	
5-digit vs. 3-digit ISCO68 code	0.93 (0.82 – 0.99)
2 time periods	
5-digit vs. 3-digit ISCO68 code	0.91 (0.84 – 0.99)
1 time period	
5-digit vs. 3-digit ISCO68 code	0.90 (0.84 – 0.98)

1. Calculated using Gwet`s agreement coefficient with a linear weight.
2. Probability of exposure categorised as: 0%, > 0% to < 25%, 25% to < 50%, 50% to < 75%, and ≥ 75%.
3. A cell was only created if there were at least 10 jobs with the given occupation code in that time period.
4. Using the version of CANJEM that excludes exposure estimates with a confidence level of possible.
5. Median agreement for the 19 agents included in the analysis and all time periods at the selected resolution of the time period axis.
6. Minimum agreement between the 19 agents included in the analysis and all time periods at the selected resolution of the time period axis.
7. Maximum agreement between the 19 agents included in the analysis and all time periods at the selected resolution of the time period axis.

Table VI: Agreement[1] between the probability of exposure[2] to lead for different resolutions of the occupation code axis; presented separately for each level of resolution of the time period axis for the selected version of CANJEM[3,4]

Occupational code resolutions compared	Gwet index			
4 time periods				
5-digit vs. 3-digit ISCO68 code	Period 1	Period 2	Period 3	Period 4
	0.824	0.850	0.848	0.901
2 time periods				
5-digit vs. 3-digit ISCO68 code	Period 1 and 2		Period 3 and 4	
	0.843		0.852	
1 time period				
5-digit vs. 3-digit ISCO68 code	Periods 1 to 4			
	0.842			

1. Calculated using Gwet`s agreement coefficient with a linear weight.

2. Probability of exposure categorised as: 0%, > 0% to < 25%, 25% to < 50%, 50% to <75%, and ≥ 75%.

3. A cell was only created if there were at least 10 jobs with the given occupation code in that time period.

4. Using the version of CANJEM that excludes exposure estimates with a confidence level of possible.

5.2 Discussion of the impact of the results on chapters 6 and 7

From the observations made in the manuscript we were able to make a few important decisions regarding the linkage procedure that would be used for the remainder of this thesis. First, and this was briefly mentioned previously, we observed little difference between versions of CANJEM that varied in how they dealt with the confidence level, particularly between versions that differed in regard to the "possible" confidence level. Consequently, we decided to use versions of CANJEM that excluded jobs with confidence levels of "possible" for the remainder of this thesis. This decision was based on the fact that although including or excluding jobs with possible confidence levels would have little impact on CANJEM, there were still reasons to believe that "possible" exposures may, on average, have not occurred. Indeed, this rating principally represented situations where the experts believed that no exposure had occurred, but exposure was self-reported by subjects during the interview. By comparison, the "probable" rating principally represented situations where the experts believed an exposure was present, but the exposure was not self-reported or was contradicted by a subject during the interview and it made more sense to consider those exposure as having occurred in CANJEM.

Another important finding from this manuscript is that there was less difference between versions of CANJEM that varied based on the resolution of their time period axis than occupational code axis and that a nearly perfect linkage rate was obtained for the INTEROCC study only at a resolution of 3-digit in the occupational code axis and one time period in the time period axis. As we intended to link CANJEM to the INTERROC study using a stepwise approach to maximize both the linkage rate and the overall "quality" of the metrics of exposure provided, this provided us with a path to follow for our linkage procedure: to reduce the resolution of the time period axis first, then reduce the resolution of the occupational code axis, up to a resolution of 3-digit and one time period where the linkage would be maximized.

What remained to be decided was which version of CANJEM should be used as the “main” version that would be linked first to the INTEROCC study. We knew from our understanding of the ISCO68 coding system that a resolution of 5-digits should be used first as a resolution of 3-digits often aggregated jobs with different exposure profiles, but not so different that it should be excluded from the linkage procedure altogether as is the case for a resolution of 2-digits. A perfect example of this can be seen for gas welders, arc welders, and solderers which are represented by their own unique 5-digit ISCO68 code, but that are aggregated together with other professions that can be expected to have broadly similar exposure profiles under a single 3-digit ISCO68 code. They are, however, aggregated with plumbers, sheet-metal preparers and other occupations with widely more varied exposure profiles at a resolution of 2-digit. More complicated was to determine which resolution to use in the time period axis. In the end however, we decided to select a resolution of four time periods as some important regulatory changes had occurred over the time period covered by CANJEM for some agents such as lead and the agreement was generally high enough for the remaining agents that any resolution could have been selected.

Chapter 6: Impact of different approaches to the creation of occupational exposure variables and comparisons with expert assessment, using the Canadian Job-Exposure-Matrix (CANJEM)

6.1 Manuscript

Impact of different approaches to the creation of occupational exposure variables and comparisons with expert assessment, using the Canadian Job-Exposure-Matrix (CANJEM)

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6.1.1 Abstract

OBJECTIVE: To compare the impact of different levels of the probability of exposure provided by the Canadian job-exposure-matrix (CANJEM) on relative risk estimates to the relative risks estimated using an expert assessment method. **METHOD:** We estimated occupational exposure to nine potential lung carcinogen in 1,200 lung cancer cases and 1,505 controls from a Canadian case-control study using CANJEM and an expert assessment method. We created multiple versions of a binary ever and a cumulative exposure variable with CANJEM and an equivalent set of variables with the expert assessment method. Unconditional logistic regression models adjusted for potential confounders was used to examine the association between each exposure variable and lung cancer. **RESULTS:** Sensitivity of the CANJEM-derived assessment vs. the expert assessment ranged from 0.12 to 0.78 while Specificity ranged from 0.84 to 0.99. Overall, CANJEM was fairly successful in reproducing the associations obtained with the expert assessment method, with the use of probability thresholds of 25% or 50% generally providing the best results. **CONCLUSION:** Our results indicate that CANJEM is a valid replacement for the expert assessment approach. As the optimal way to use the probability of exposure provided by CANJEM varied by agent, the strategy employed should be based on the exposure characteristics of the selected agents within the intended study population.

6.1.2 Introduction

One of the main challenges in occupational cancer epidemiology is retrospective exposure assessment, with many possible methods being either prohibitively costly, or subject to extreme recall error or principally reflecting recent exposures (1-3). A job-exposure-Matrix (JEM) is an instrument that provides an automated method to assess occupational exposures associated with each job of a study subject, based on the occupational/industrial title and possibly on the calendar year(s) of the job (1-3). While it may be costly to produce a JEM and its validity depends on the human and documentary resources on which it is based, its great benefit is that it is generally inexpensive to apply to a set of jobs to infer occupational exposures.

Our research team has recently developed such a matrix, the Canadian JEM (CANJEM) (4, 5). It was built from a database of over 30,000 one-by-one expert job assessments, accumulated in the course of four previous Canadian case-control studies.

CANJEM can be understood as a cross-tabulation of three axes: an occupation code axis, a time period axis, and a chemical agent axis. Each cell formed by the three axes contains more than one piece of information about potential exposure, but the most important is a probability of exposure. It indicates for a given occupation code in a certain time period, the probability that a worker in that occupation was exposed to a particular agent. Typically, in environmental epidemiology, the exposure assessment procedure leads to a binary variable of exposed/unexposed and one or more quantitative metrics of exposure such as duration or cumulative amount of exposure. The typical primary statistical objective is to estimate a relative risk of disease among exposed vs. unexposed, and secondarily to assess some notion of dose-response. But when using CANJEM and some other JEMs, the user has to deal with the exposure index being a probability of exposure. There is no generally accepted way to deal with this. Our strategy, as users of CANJEM, and this has been the strategy of some others in using other JEMs, is to transform the continuous probability into a binary exposed/unexposed variable on the basis of a cut-point on the probability scale. For instance, in some analyses using FINJEM (6), the authors created the binary variable by defining unexposed as probability of exposure less than 0.25 and exposed as probability of exposure greater than 0.25. Further, the probability could also be used as part of a continuous variable that integrates concentration and duration of exposure (19) and that provides the basis for analysing a kind of dose-response relationship. In fact, there is a plethora of possible ways of dealing with a probability of exposure variable that comes out of CANJEM and some other JEMs.

The purpose of this paper is two-fold. First we will explore how different strategies compare for using the probability of exposure as part of a metric of exposure to estimate relative risks. There will be two avenues, one transforming the continuous probability of exposure into a binary exposed/unexposed variable, and a second integrating the probability into a continuous cumulative exposure variable. The second purpose is to assess the relative validity of using CANJEM by comparing the relative risk results obtained with results from using an expert exposure assessment procedure where interviews have elicited detailed job descriptions and industrial hygiene experts devoted time and effort to assess each job.

This empirical evaluation will be conducted on data that was generated in a lung cancer case-control study in Montreal. While the findings will be helpful in assessing the usefulness of CANJEM, we believe they may equally inform assessment of usefulness of other JEMs that provide a probability of exposure metric. The focus is on nine occupational agents in the hope that some general tendencies may be evident that can be generalized to other agents.

6.1.3 Methods

The Montreal lung cancer case-control study

This study has been described previously (7). Briefly, study participants were Canadian citizens aged 35-75 years who resided in the greater Montreal area, recruited between 1996 and 2001. Controls were selected from the Quebec voter registration list and frequency matched to the cases by 5-year age group, sex, and electoral district. Cases were identified from one of the 18 major hospitals serving the study region. The current analysis was restricted to 1,200 cases and 1,505 controls with complete information on their smoking habits and occupational histories that included detailed task descriptions for each job held. Data on socio-demographic characteristics and lifestyle were collected for each subject in a face to face interview. Each job was assessed by a group of expert chemists and industrial hygienists to determine exposure to a list of 300 agents. (8, 9). For each job, the experts provided, among other things ordinal scale estimates of the concentration of exposure (low, medium, and high); the frequency of exposure, representing the number of hours per week of exposure at a given concentration; and the level of confidence in the exposure assessment, categorised as possible, probable, and definite.

CANJEM

In addition to the study outlined above, our team had carried out three other cancer case-control studies (10, 11) using the same occupational exposure assessment procedures. Combining the four studies, our experts assessed exposures in over 30,000 jobs. For each of those jobs we had an occupational classification code and a list of agents thought by the experts to have been present. The resulting large database was reconfigured to create CANJEM (4, 5).

CANJEM is comprised of three axes: 1) an occupational code axis; 2) a time period axis); and 3) an occupational exposure axis, including 258 occupational agents. In fact CANJEM can be created in a number of optional versions. The occupation code could be based on any of four different occupation classifications and within each classification at different levels of resolution. The time period axis could consist of a single period (1930-2005) or it could be subdivided into two or four sub-periods. Irrespective of the version used, each cell in CANJEM is defined by a unique combination of occupational code, time period and agent, and each cell consists of metrics of exposure including: probability of exposure, and among those cells with non-zero probability, median or mean concentration and frequency, and the distribution of confidence of exposure (possible, probable, and definite). All of these parameters were derived from the empirical data accumulated over the years in the exposure assessments conducted by the team of expert coders.

While the expert assessment assigns a unique set of metrics of exposure to each job for each subject, CANJEM provides aggregated exposure metrics within each of its cells. For instance, exposure levels assigned by the experts to 2 different arc welding jobs held during the same time period may have differed based on the specific characteristics of each job; by contrast, if the two jobs have the same occupational code, CANJEM would provide the same metrics of exposure for all arc welders within the same time period. Nevertheless, the CANJEM-assigned agents might differ if different resolutions are used for either the occupational code or time period. Generally, higher resolutions in both axes result in aggregated metrics of exposure based on fewer, but more similar jobs, while lower resolutions result in the opposite. Many of the cells in CANJEM are based on sparse data, particularly at higher levels of resolution in both axes.

Design of the present analysis

The intention was to assess the impact of different ways of using the probability of exposure from CANJEM in deriving odds ratio (OR) estimates, and also to assess the impact of using CANJEM vs. using the original one-by-one expert assessment on the "bottom line" odds ratio estimates of these associations.

To achieve these objectives, we used the individual case and control data from the Montreal lung cancer case-control study. We focused attention on associations between lung cancer and each of nine agents. The agents were selected as recognized or suspected lung carcinogens, with reasonably high prevalence. These were: asbestos, silica, diesel engine emissions (DEE), gas welding fumes, chromium compounds, iron compounds, benzene, and wood dust. In addition, formaldehyde was also included as an example of an agent with little evidence of association with lung cancer.

Expert approach

The original expert-based exposure estimates were available and standard procedures were used to estimate ORs. This entailed unconditional logistic regression modelling with the exposure variable parameterized either as a binary exposed/unexposed variable or as a semi-quantitative cumulative exposure variable consisting of the product of concentration x frequency x duration of exposure. When constructing this cumulative exposure variable we had to give numerical values to the original expert-assessed ordinal scale of low, medium, high concentration of exposure, and based on opinions of the experts, we gave these relative weights of 1, 5, and 25, respectively. Frequency of exposure was already on a continuous scale ranging from 1 to 40 hours per week of exposure. Duration of exposure in years was available from the subject's job history. Some analyses were conducted on the cumulative exposure variable as a continuous variable with the unit of presentation of the OR being the standard deviation of the cumulative exposure index among controls. Some were conducted after dichotomizing the cumulative exposure variable at the median of the distribution in controls. For all analyses, exposures classified by the hygienists with a level of confidence of "possible" were considered unexposed.

CANJEM approach

To compare the performance of CANJEM with that of the original exposure assessment, we linked all the job histories among the same set of subjects to CANJEM, and derived exposure estimates, and then conducted OR estimation analyses. For this purpose, we used a version of CANJEM that is based on the Canadian Classification and Dictionary of Occupations 1971 (CCDO71). Due to the need to incorporate the probability of exposure in their creation, the exposure variables derived from CANJEM are not perfectly congruent in format from those provided by the original expert assessment.

We linked the lung study occupational histories to CANJEM using CCDO71, starting with the highest available resolution in both axes (7-digits and four time periods) proceeding stepwise to link the remaining jobs using first lower resolutions of the time period axis, and then lower resolutions of the occupational code axis, to a minimum of 4-digits and one time period. To avoid the imprecision and uncertainty that might come from basing CANJEM determinations on very few jobs in the parent database, we implemented a restriction that in order for a CANJEM cell to be informative, it had to be based on at least 10 jobs with the same occupational code and time period. If a cell did not satisfy this criterion, it was excluded from CANJEM. As was done for the expert assessment, jobs within cells of CANJEM with possible level of confidence were considered as unexposed. The ensuing three types of exposure variables were:

1) A binary exposure variable (unexposed, exposed), obtained using different cut-points in the probability of exposure to consider jobs as ever exposed: ≥ 25%, ≥ 50%, and ≥ 75%. Thus, for each agent, there are three versions of the binary variable with exposure determined by the

selected cut-point. Any exposure below the selected cut-point is considered unexposed. Duration, frequency or concentration level are not considered in this variable.

2) A 3-category exposure variable (unexposed, uncertain, exposed), obtained using the same cut-points in probability of exposure mentioned above. While one method to deal with exposures under the probability cut-point is to consider them as unexposed, another is to categorise them separately as uncertainly exposed. Thus, within the 3-category exposure variable, exposures with probability of exposure up to 25% lower than the selected cut-point were classified as uncertainly exposed. For example, at a cut-point of 50%, exposure with probability <25% were classified as unexposed, exposure with a probability between ≥ 25% and < 50% were classified as uncertainly exposed, and exposure with probabilities ≥ 50% were classified as ever exposed. To be classified as uncertainly exposed, a subject needed to have ever held an uncertainly exposed job, without ever having held a job with the higher probability of exposure. There are different options for treating the "uncertain" group: they can be excluded from the analysis; or they can be considered as "possibly" exposed. In order to simplify the comparison with the binary exposure variable created using the expert assessment, we excluded subjects classified as uncertainly exposed from our analyses.

3) A lifetime cumulative exposure variable, obtained by summing the cumulative exposure of each individual job held by a subject using the formula: duration of job * probability of exposure (0 to 1) * exposure concentration (1 for low, 5 for medium, and 25 for high) * frequency of exposure (1-40 hours). The probability of exposure is used only with CANJEM estimates. As for the expert assessment, two versions of this variable were created: a continuous version using units of one standard deviation and a categorical version based on the median of exposure. In order to simplify the comparison between the CANJEM and expert assessment

version of the categorical cumulative variable, we only discuss the results obtained for the ≥ median category.

Analyses

We examined differences in the categorisation of subject's occupational exposure between CANJEM and the expert assessment in two ways; first, for the two categorical exposure variables, by calculating the sensitivity and specificity of the CANJEM assessments compared to the expert assessment. Second, for the cumulative exposure variable, by calculating the Pearson's correlation coefficient for the continuous version of the variable.

We calculated the ORs and 95% confidence intervals (95%CIs) for the association between each of the nine occupational agents and lung cancer separately using unconditional logistic regression adjusted for potential cofounders selected a priori: age (continuous), sex (male, female), ethnicity (English, French, other), years of schooling (< 7, 7 - <12, ≥ 12), median census track family income (low, middle, high), proxy status (self, proxy), and smoking, using a comprehensive smoking index (continuous) (10). For one subject with a missing value for his median census tract family income we used the median value among controls. All analyses were conducted in SAS 9.4.

6.1.4 Results

Table I shows selected characteristics of study subjects. The mean age of subjects was 63 years old and 60% were men. Compared to controls, cases were more likely to be French Canadian, have a secondary education, a low income, be smokers, and to have been represented by a proxy respondent during the interview. Table II shows the prevalence of exposure, as assigned by experts, to the nine selected agents. Prevalence varied from 8.5% to 26% in cases and controls, and cases were more likely to be exposed to silica, DEE, benzene, and wood dust.

Table III shows for each of the nine agents, the overall lifetime exposure prevalence, sensitivity, specificity, and corresponding impact on ORs of the different ways of deriving exposure variables from CANJEM, using the original expert-based exposure assessment as the reference. Based on the expert assessment, lifetime exposure to these nine agents for all subjects combined ranged from 9.0% to 24% in our study population. By comparison, exposure prevalence was generally slightly higher when using the lowest threshold of probability (25%) in CANJEM, but as expected, decreased to a fraction of the expert prevalence as the threshold increased. When the uncertainly exposed in CANJEM are excluded, the prevalence in remaining subjects could increase by more than twice that of the simple binary variable at a threshold of 25%, but was only slightly higher at higher thresholds. In addition, as the probability threshold increased, sensitivity decreased while specificity increased. Sensitivity of the CANJEM-derived assessment vs. the expert assessment ranged from 0.12 (benzene at a threshold of 75%) to 0.78 (iron at a threshold of 25%). Specificity ranged from 0.84 (formaldehyde at a threshold of 25%) to around 0.99 (all agents at a threshold of 75%). When the uncertainly exposed in CANJEM were excluded, sensitivity was generally 0.30 higher and specificity was 0.04 to 0.21 lower than the simple binary exposure variable at a threshold of 25%. The magnitude of the difference in sensitivity and particularly specificity decreased as the selected threshold increased.

The estimates of association of lung cancer in relation to each of the nine agents were reasonably similar whether the exposure had been assessed by the experts or derived from CANJEM, with the statistically significant positive association observed for exposure to silica, DEE, and benzene in the expert assessment being replicated when using different thresholds of probability in CANJEM. Except for an overall increase in the width of the 95%CIs, increasing the probability threshold generally did not have much impact on the magnitude or statistical significance of ORs observed for each agent. Still, four broad patterns could be observed when increasing the probability threshold from 25% to 50% and to 75%: 1) for iron, DEE, and wood dust, no meaningful impact on the association albeit the associations were no longer statistically significant for DEE and wood dust, 2) for asbestos, gas welding fumes, and formaldehyde, more null associations 3) for silica, an increase in the strength of the association and 4) for chromium and benzene, a J-shaped change in the strength of the association (more null associations at a threshold of 50% and stronger positive associations at a threshold of 75% when compared to a threshold of 25%). Excluding uncertainly exposed subjects had little impact at thresholds of 50% or 75%, but resulted in stronger and often significant positive associations at a threshold of 25% for all agents, except silica, gas welding fumes, and chromium.

Continuous cumulative exposure variables were created using the expert assessments and using CANJEM. The Pearson's correlation coefficients for the correlation between analogous versions of expert assessment and CANJEM were generally greater than 0.50 and ranged from 0.26 (chromium) to 0.79 (wood dust) (results not shown). Table IV shows for each agent the ORs (95%CIs) for the continuous and categorical version of the cumulative exposure variable separately for the expert assessment and CANJEM. Overall, for the continuous cumulative variable, we observed closer to null associations for all agents but wood dust, when using CANJEM compared to the expert assessment. The statistically significant associations observed when using the expert assessment for silica and DEE were not reproduced with CANJEM, while for wood dust, a weak positive association was observed when using

CANJEM, but not in the expert assessment. For most agents the 95%CIs were narrower when using CANJEM, but still similar to the ones obtained when using the expert assessment.

When transforming the continuous cumulative exposure variables to binary ones at the median, there were varied impacts on the comparisons between expert and CANJEM assessment. For some agents (iron, asbestos, and silica) the positive association was stronger and/or only statistically significant when using CANJEM, while for others the associations were similar to the expert assessment (chromium and benzene) or more null and/or no longer statistically significant (DEE, gas welding fumes, wood dust). For formaldehyde, a borderline statistically significant positive association was observed when using CANJEM, while a weak statistically non-significant inverse association was observed when using the expert assessment. The 95%CIs obtained with CANJEM were again narrower than the ones obtained when using the expert assessment while staying relatively similar to them.

6.1.5 Discussion

In this study we compared the association between known or suspected occupational lung carcinogens and lung cancer using two exposure assessment approaches: expert assessment and a job exposure matrix, CANJEM. Further, several approaches were used in implementing CANJEM. Overall, CANJEM was fairly successful in reproducing the exposure profiles and associations obtained with the expert binary exposure variable, albeit not all approaches had the same success with each agent. CANJEM was, however, somewhat less successful in reproducing the expert assessment when examining cumulative exposure, particularly as a continuous variable.

A few studies (12-18) have compared the associations obtained using JEMs with corresponding results derived using expert assessment. The occupational agents examined included asbestos (12, 13), DEE (12), silica (12), trichloroethylene (14), organic solvents (15, 17), lead (16, 17), pesticide (17, 18), and polycyclic aromatic hydrocarbon (17). All, but two studies, which examined different levels of exposure (15, 16), examined a binary exposure variable. Some created their exposure variable using only the probability of exposure (12, 13, 15, 18), while the rest used different combinations of probability, frequency, and concentration of exposure (12, 14, 15, 17). Similar to our results, most of the JEMs were able to reproduce the associations obtained with the expert assessment fairly well. However, the results are certainly not consistent across studies or agents.

As expected, raising the threshold of probability to define exposed vs. unexposed led to reductions in sensitivity and prevalence of exposure, while increasing slightly the already high specificity. Although raising the threshold also generally increased the width of the 95%CIs; the overall impact on the estimated associations and on their interpretation varied by occupational agent. Thus, there was no single optimal threshold that could be used for all agents, although there was a tendency for CANJEM to produce similar estimates to that of the expert assessment when using lower thresholds for less prevalent agents and higher thresholds for more prevalent agents. For none of our agents was a threshold of 75% decidedly better than other thresholds. It is difficult to determine exactly what caused those variations between our agents, but there was some evidence that agents with a higher prevalence and an overall higher sensitivity were less affected by the thresholds selected compared to other agents. As for the remaining agents, how they were affected by a change in the threshold may be partially explained by the exposure characteristics of exposed subjects misclassified as unexposed. That is, when increasing the threshold resulted in a dilution of the strength of the association, CANJEM tended to misclassify truly exposed subjects with higher levels of exposure (frequency and/or concentration of exposure) based on the expert assessment as unexposed, while the opposite was true when an increase in the strength of the association was observed.

Excluding uncertainly exposed subjects had little impact on the estimate of exposures at thresholds of 50% and 75%, but resulted in stronger and often statistically significant positive associations for six of our nine agents at a threshold of 25%. The results observed at higher thresholds can be explained by the relatively low number of subjects classified as uncertainly exposed at those thresholds; however, the reason behind the results observed at a threshold of 25% is less obvious. Because an increase in OR was observed for two third of our agents, it is unlikely to have been due to chance, rather, it was probably due to the characteristics of excluded subjects. For example, most exposed subjects misclassified as unexposed in the CANJEM binary exposure variable were classified as uncertainly exposed in the categorical variable, and their exclusion from the unexposed category may have reduced the dilution of the associations present in the binary variable analysis. The generally stronger association observed for the CANJEM categorical variable compared to the expert assessment may have been due to the overall higher level of exposure found in subjects classified as exposed by CANJEM. However, the increase in ORs may also have been due to confounding, as excluding subjects categorised as uncertainly exposed also resulted in the exclusion of most subjects exposed to any other selected occupational agents from the unexposed group, but not from the exposed group. Interestingly, exploratory analyses revealed that the associations obtained with the categorical variable were much closer to the ones obtained with the expert assessment when either excluding subjects with lower level of exposure or excluding unexposed subjects who were exposed to any of the other selected occupational agents (results not shown). Thus, whether the observed increase in ORs was due to biases or not, excluding uncertainly exposed subjects resulted in associations more similar to the examination of high vs. never exposure than ever vs. never exposure.

CANJEM was generally less successful in reproducing the association observed with the expert assessment for the cumulative exposure variable, which may be due to a few reasons. First, contrary to the previous variables, the cumulative exposure variable requires the estimation of the frequency and concentration of exposure, which can introduce more exposure misclassification to the analysis. Second, the cumulative exposure formula included a term for the probability of exposure, which can only lead to one of two potential outcomes; the underestimation of cumulative exposure in exposed jobs by a factor of 1-probability of exposure and the overestimation of cumulative exposure in unexposed jobs by a factor equal to the probability of exposure. Consequently, it is possible that the generally more null associations observed with the continuous version of CANJEM cumulative exposure variable when compared to the expert assessment was due to the aggregation of subjects' cumulative exposure toward the average and the resulting much smaller standard deviation. By comparison, for the categorical version of the variable, a majority of misclassified subjects were categorised in the < median of cumulative exposure category and it is possible that the stronger positive associations observed for some agents when using CANJEM compared to the expert assessment was due to the fact that only the most strongly exposed subjects remained in the ≥ median category. However, the stronger ORs observed with CANJEM may also be the result of biases away from the null as it has been shown that such biases can occur when including a term for the probability of exposure in the calculation of exposure (19). In the end, it may be better to use the probability of exposure as a threshold as doing so resulted in associations closer to the expert assessment for both the continuous and categorical versions of the cumulative exposure variable (result not shown).

In this study, we were able to compare CANJEM to the expert assessment method under the “best-case scenario” where both assessment methods were designed for the study population. Thus, our results may not be representative of the ones obtained when applying CANJEM to other study populations and a potential user of CANJEM should critically evaluate its suitability for the local working population. While the expert assessment was considered as the gold standard in this study, it is not a perfect representation of subject’s true exposure. Thus, the ability of CANJEM to reproduce or not the associations obtained with the expert assessment may not necessarily translate in its ability to reproduce the true association between a selected occupational exposure and outcome. However, the expert assessment is generally considered as the best available method for the retrospective assessment of occupational exposure (1, 20) and CANJEM was a tool developed as a cheaper alternative to this assessment method. Consequently, our interest was to only determine how it succeeded in that respect. We conducted our analyses using a common and limited set of potential confounders selected a priori and it is possible that our analyses suffered from confounding. However, this should not have affected the validity of our comparison. We conducted our comparisons using versions of CANJEM that used the CCDO occupational coding system in their occupational code axis, considered as unexposed exposures with level of confidence of “possible”, and only provided estimates of exposure for cells containing at least 10 jobs and our results may not apply to versions of CANJEM varying in those aspects. Similarly, the agents we selected for our analyses were present in broadly similar occupations and with relatively limited variation in their prevalence and it is possible that our observation would not apply to other agents present in CANJEM.

6.1.6 Conclusion

Overall CANJEM was quite successful in recreating the associations obtained with the expert assessment for most of our selected agents, in particular when examining the less complex binary exposure variable. Although our observations were only based on nine agents, they indicated that there was no single optimal way to use the probability of exposure provided by CANJEM to examine the association between an occupational agent and a selected outcome. While it may be preferable to use probability threshold up to 50% for most agents, to use the probability as a threshold for the calculation of cumulative exposure, and to examine cumulative exposure as a categorical variable; the method employed to create exposure variables with CANJEM should be guided by the examination of the exposure characteristics of the selected agents within the intended study population.

6.1.7 References

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6.1.8 Tables

Table I: Characteristics of study participants

		Cases N = 1,200 n (%)	Controls N = 1,505 n (%)
Age (year)	< 50	100 (8.3)	123 (8.2)
	50 to < 60	291 (24.3)	326 (21.7)
	60 to < 70	518 (43.1)	684 (45.4)
	≥ 70	291 (24.3)	372 (24.7)
Sex	Male	736 (61.3)	894 (59.4)
	Female	464 (38.7)	611 (40.6)
Ethnicity	French Canadian	934 (77.8)	996 (66.2)
	English Canadian	78 (6.5)	83 (5.5)
	Other	188 (15.7)	426 (28.3)
Education	Primary	306 (25.5)	321 (21.3)
	Secondary	592 (49.3)	573 (38.1)
	Tertiary	302 (25.2)	611 (40.6)
Income	Low	534 (44.5)	503 (33.4)
	Medium	389 (32.4)	511 (34.0)
	High	277 (23.1)	491 (32.6)
Respondent status	Self	750 (62.5)	1,390 (92.4)
	Proxy	450 (37.5)	115 (7.6)
Smoking	Never	50 (4.2)	467 (31.0)
	Ever	1,150 (95.8)	1,038 (69.0)
Smoking index	0	50 (4.2)	467 (31.0)
	< 1	49 (4.1)	316 (21.0)
	≥ 1 to < 2	369 (30.7)	438 (29.1)
	≥ 2 to < 3	688 (57.3)	273 (18.2)
	≥ 3	44 (3.7)	11 (0.7)

Table II: Occupational exposure prevalence to the selected agents based on the expert assessment

		Cases N = 1,200 n (%)	Controls N = 1,505 n (%)
Asbestos	Never	1,061 (88.4)	1,347 (89.5)
	Ever	139 (11.6)	158 (10.5)
Silica	Never	984 (82.0)	1,285 (85.4)
	Ever	216 (18.0)	220 (14.6)
Diesel engine emissions	Never	886 (73.8)	1,172 (77.9)
	Ever	314 (26.2)	333 (22.1)
Gas welding fumes	Never	1,089 (90.8)	1,345 (89.4)
	Ever	111 (9.2)	160 (10.6)
Chromium compounds	Never	1,087 (90.6)	1,377 (91.5)
	Ever	113 (9.4)	128 (8.5)
Iron compounds	Never	953 (79.4)	1,207 (80.2)
	Ever	247 (20.6)	298 (19.8)
Formaldehyde	Never	950 (79.2)	1,206 (80.1)
	Ever	250 (20.8)	299 (19.9)
Benzene	Never	1,016 (84.7)	1,308 (86.9)
	Ever	184 (15.3)	197 (13.1)
Wood dust	Never	950 (79.2)	1,236 (82.1)
	Ever	250 (20.8)	269 (17.9)

Table III: Comparison of lifetime exposure prevalence and odds ratios between selected occupational agents and lung cancer derived from expert assessment and those derived from using a JEM, based on binary exposure variables

Agent	Exposure assessment approach[1]	Definition of exposure variable[2]		Lifetime exposure prevalence (%) among all subjects	Comparison to expert[3]		Exposed subjects		Association[4]	
		Unexposed	Exposed		Sensitivity	Specificity	Cases (n)	Controls (n)	OR	95%CI
Iron compounds	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**20.2**	**-**	**-**	**247**	**293**	**1.19**	**0.93 - 1.52**
	CANJEM	< 25%	≥ 25%	21.7	0.782	0.926	279	307	1.07	0.85 - 1.36
		0%	≥ 25%	38.4	0.991	0.854			1.46	1.06 - 2.01
		< 50%	≥ 50%	15.6	0.650	0.969	195	226	1.01	0.78 - 1.32
		< 25%	≥ 50%	16.5	0.744	0.968			1.02	0.77 - 1.33
		< 75%	≥ 75%	10.3	0.461	0.988	130	148	1.07	0.79 - 1.46
		< 50%	≥ 75%	10.8	0.553	0.987			1.07	0.78 - 1.46
Asbestos	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**11.0**	**-**	**-**	**139**	**158**	**1.23**	**0.90 - 1.68**
	CANJEM	< 25%	≥ 25%	12.9	0.633	0.933	179	171	1.31	0.98 - 1.75
		0%	≥ 25%	21.1	0.959	0.889			1.77	1.24 - 2.52
		< 50%	≥ 50%	6.5	0.428	0.980	90	85	1.25	0.85 - 1.85
		< 25%	≥ 50%	6.9	0.534	0.979			1.31	0.88 - 1.94
		< 75%	≥ 75%	3.5	0.283	0.996	45	49	1.13	0.68 - 1.88
		< 50%	≥ 75%	3.6	0.322	0.996			1.15	0.69 - 1.91

Agent	Exposure assessment approach[1]	Definition of exposure variable[2]		Lifetime exposure prevalence (%) among all subjects	Comparison to expert[3]		Exposed subjects		Association[4]	
		Unexposed	Exposed		Sensitivity	Specificity	Cases (n)	Controls (n)	OR	95%CI
Silica	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**16.1**	**-**	**-**	**216**	**220**	**1.43**	**1.10 - 1.85**
	CANJEM	< 25%	≥ 25%	19.1	0.677	0.903	248	268	1.18	0.92 - 1.52
		0%	≥ 25%	35.1	0.974	0.811			1.30	0.92 - 1.83
		< 50%	≥ 50%	12.9	0.532	0.948	180	169	1.46	1.09 - 1.96
		< 25%	≥ 50%	13.7	0.619	0.946			1.42	1.06 - 1.92
		< 75%	≥ 75%	5.5	0.280	0.988	86	63	1.95	1.28 - 2.98
		< 50%	≥ 75%	5.9	0.368	0.988			1.97	1.29 - 3.02
Diesel engine exhaust	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**23.9**	**-**	**-**	**314**	**333**	**1.43**	**1.12 - 1.83**
	CANJEM	< 25%	≥ 25%	24.8	0.714	0.898	343	328	1.30	1.02 - 1.66
		0%	≥ 25%	54.2	0.985	0.728			1.65	1.09 - 2.49
		< 50%	≥ 50%	12.5	0.405	0.963	182	157	1.29	0.96 - 1.73
		< 25%	≥ 50%	14.2	0.577	0.960			1.39	1.02 - 1.90
		< 75%	≥ 75%	9.5	0.322	0.977	144	112	1.26	0.90 - 1.75
		< 50%	≥ 75%	9.7	0.346	0.976			1.27	0.91 - 1.78
Gas welding fumes	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**10.0**	**-**	**-**	**111**	**160**	**0.94**	**0.68 - 1.30**
	CANJEM	< 25%	≥ 25%	11.6	0.646	0.943	138	176	0.83	0.62 - 1.12
		0%	≥ 25%	19.5	0.967	0.903			0.94	0.66 - 1.33
		< 50%	≥ 50%	4.7	0.362	0.989	59	67	0.93	0.59 - 1.44
		< 25%	≥ 50%	5.0	0.493	0.988			0.90	0.58 - 1.41
		< 75%	≥ 75%	1.9	0.170	0.998	23	27	1.01	0.52 - 1.97
		< 50%	≥ 75%	1.9	0.210	0.998			1.02	0.52 - 1.99

Agent	Exposure assessment approach[1]	Definition of exposure variable[2]		Lifetime exposure prevalence (%) among all subjects	Comparison to expert[3]		Exposed subjects		Association[4]	
		Unexposed	Exposed		Sensitivity	Specificity	Cases (n)	Controls (n)	OR	95%CI
Chromium compounds	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**8.9**	**-**	**-**	**113**	**128**	**1.22**	**0.88 - 1.69**
	CANJEM	< 25%	≥ 25%	10.5	0.660	0.950	137	146	1.17	0.86 - 1.59
		0%	≥ 25%	16.7	0.976	0.919			1.18	0.84 - 1.67
		< 50%	≥ 50%	4.5	0.373	0.987	59	63	1.02	0.66 - 1.58
		< 25%	≥ 50%	4.8	0.503	0.987			1.02	0.66 - 1.59
		< 75%	≥ 75%	2.6	0.241	0.996	39	30	1.58	0.88 - 2.84
		< 50%	≥ 75%	2.6	0.271	0.996			1.56	0.87 - 2.81
Formaldehyde	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**20.3**	**-**	**-**	**250**	**299**	**1.04**	**0.82 - 1.31**
	CANJEM	< 25%	≥ 25%	28.3	0.763	0.839	379	387	1.24	1.00 - 1.54
		0%	≥ 25%	56.3	0.979	0.628			1.46	1.08 - 1.97
		< 50%	≥ 50%	15.1	0.514	0.942	182	226	0.97	0.73 - 1.27
		< 25%	≥ 50%	17.3	0.681	0.935			1.00	0.75 - 1.32
		< 75%	≥ 75%	4.5	0.193	0.993	59	63	1.04	0.66 - 1.64
		< 50%	≥ 75%	5.0	0.275	0.992			1.03	0.65 - 1.63
Benzene	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**14.1**	**-**	**-**	**184**	**197**	**1.37**	**1.04 - 1.81**
	CANJEM	< 25%	≥ 25%	14.5	0.633	0.935	209	184	1.42	1.08 - 1.88
		0%	≥ 25%	31.3	0.988	0.850			1.72	1.19 - 2.48
		< 50%	≥ 50%	7.4	0.362	0.973	105	96	1.33	0.93 - 1.91
		< 25%	≥ 50%	8.3	0.488	0.972			1.38	0.96 - 2.00
		< 75%	≥ 75%	2.2	0.123	0.995	34	25	1.90	1.00 - 3.61
		< 50%	≥ 75%	2.3	0.154	0.995			1.91	1.01 - 3.61

Agent	Exposure assessment approach[1]	Definition of exposure variable[2]		Lifetime exposure prevalence (%) among all subjects	Comparison to expert[3]		Exposed subjects		Association[4]	
		Unexposed	Exposed		Sensitivity	Specificity	Cases (n)	Controls (n)	OR	95%CI
Wood dust	**Expert opinion**	**“Unexposed”**	**“Exposed”**	**19.2**	**-**	**-**	**250**	**269**	**1.17**	**0.91 - 1.50**
	CANJEM	< 25%	≥ 25%	18.6	0.711	0.939	248	255	1.30	1.01 - 1.68
		0%	≥ 25%	40.1	0.976	0.847			1.85	1.27 - 2.71
		< 50%	≥ 50%	12.2	0.588	0.989	160	170	1.31	0.97 - 1.76
		< 25%	≥ 50%	13.0	0.666	0.988			1.35	1.00 - 1.82
		< 75%	≥ 75%	8.2	0.409	0.995	111	112	1.28	0.91 - 1.81
		< 50%	≥ 75%	8.6	0.495	0.995			1.32	0.93 - 1.86

1. Approach used to assess subjects’ occupational exposure in the selected analysis; the expert assessment (Expert) or the Canadian Job-Exposure-Matrix (CANJEM).

2. Provide the probability of exposure thresholds used to differentiate between exposure and no exposure when using CANJEM.

3. Sensitivity and specificity of JEM exposure dichotomy vs. expert exposure dichotomy.

4. Each model was adjusted for: age (continuous), sex, smoking index (continuous), ethnicity (French Canadian, English Canadian, other), years of education (> 0 to <7 years, 7 to 12 years, ≥ 12 years), census track median income (low, medium, high), proxy respondent (self, other).

Table IV: Comparison of odds ratios between selected occupational agents and lung cancer derived from expert assessment and those derived from using a JEM, based on a continuous and categorical cumulative exposure variable

Agent	Exposure assessment[1]	Metric[2]	Unit	OR[3]	95%CI
Iron compounds	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.13**	**0.95 - 1.34**
	JEM	CxFxDrxPr	1 standard deviation	1.04	0.94 - 1.16
	Expert opinion	**CxFxDr**	**> Median**	**1.30**	**0.95 - 1.79**
	JEM	CxFxDrxPr	> Median	1.37	1.05 - 1.78
Asbestos	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.16**	**0.94 - 1.43**
	JEM	CxFxDrxPr	1 standard deviation	1.08	0.96 - 1.22
	Expert opinion	**CxFxDr**	**> Median**	**1.39**	**0.93 - 2.10**
	JEM	CxFxDrxPr	> Median	1.61	1.23 - 2.12
Silica	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.30**	**1.05 - 1.63**
	JEM	CxFxDrxPr	1 standard deviation	1.05	0.95 - 1.17
	Expert opinion	**CxFxDr**	**> Median**	**1.42**	**0.99 - 2.04**
	JEM	CxFxDrxPr	> Median	1.32	1.01 - 1.74
Diesel engine exhaust	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.24**	**1.07 - 1.44**
	JEM	CxFxDrxPr	1 standard deviation	1.07	0.96 - 1.18
	Expert opinion	**CxFxDr**	**> Median**	**1.38**	**1.01 - 1.88**
	JEM	CxFxDrxPr	> Median	1.07	0.80 - 1.43
Gas welding fumes	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**0.86**	**0.64 - 1.16**
	JEM	CxFxDrxPr	1 standard deviation	0.87	0.75 - 1.02
	Expert opinion	**CxFxDr**	**> Median**	**0.93**	**0.61 - 1.42**
	JEM	CxFxDrxPr	> Median	1.02	0.79 - 1.32
Chromium compounds	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.01**	**0.80 - 1.29**
	JEM	CxFxDrxPr	1 standard deviation	0.96	0.88 - 1.04
	Expert opinion	**CxFxDr**	**> Median**	**1.05**	**0.67 - 1.64**
	JEM	CxFxDrxPr	> Median	1.05	0.81 - 1.35
Formaldehyde	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**0.98**	**0.82 - 1.16**
	JEM	CxFxDrxPr	1 standard deviation	1.00	0.89 - 1.12
	Expert opinion	**CxFxDr**	**> Median**	**0.89**	**0.63 - 1.46**
	JEM	CxFxDrxPr	> Median	1.30	1.00 - 1.69
Benzene	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.19**	**0.96 - 1.46**
	JEM	CxFxDrxPr	1 standard deviation	1.09	0.99 -1.21
	Expert opinion	**CxFxDr**	**> Median**	**1.59**	**1.10 - 2.30**
	JEM	CxFxDrxPr	> Median	1.46	1.12 - 1.90

Agent	Exposure assessment[1]	Metric[2]	Unit	OR[3]	95%CI
Wood dust	**Expert opinion**	**CxFxDr**	**1 standard deviation**	**1.02**	**0.81 - 1.29**
	JEM	CxFxDrxPr	1 standard deviation	1.10	0.99 - 1.23
	Expert opinion	**CxFxDr**	**> Median**	**1.51**	**1.09 - 2.08**
	JEM	CxFxDrxPr	> Median	1.22	0.93- 1.61

1. Approach used to assess subjects' occupational exposure in the selected analysis; the expert assessment (Expert) or the Canadian Job-Exposure-Matrix (CANJEM).

2. Formula used to calculate cumulative exposure in the selected analysis. The terms are as follow: C (concentration of the exposure quantified as 1 for low, 5 for medium, and 25 for high), F (weekly frequency of the exposure in hours varying from 0 to 40 hours), Dr (duration of the exposure in years), and Pr (probability of the exposure in percentage).

3. Each model was adjusted for: age (continuous), sex, smoking index (continuous), ethnicity (French Canadian, English Canadian, other), years of education (> 0 to <7 years, 7 to 12 years, ≥ 12 years), census track median income (low, medium, high), proxy respondent (self, other).

6.2 Discussion of the impact of the results on the analytic strategy used in chapter 7

In this manuscript we presented many discoveries that helped us develop the method used for the analyses of the associations between selected occupational exposures and the risk of brain cancer which form the basis of chapter 7. Probably the most important finding was that CANJEM, or more precisely the linkage procedure and versions of CANJEM used in this manuscript, appeared to be a valid proxy method for the expert assessment. While it does not necessarily mean that CANJEM is a valid occupational assessment method, as this would require knowing each subject's true lifetime occupational exposure, it does allow us to assume with some confidence that CANJEM can be used to examine occupational exposures in the INTEROCC study, which includes subjects from developed countries with industrial processes and occupational exposures broadly similar to those prevailing in Canada.

Another important finding was that although there was no overall "optimal" way to deal with the probability of exposure when creating exposure variables with CANJEM, there was an indication that thresholds between 25% to 50% generally provided the best results and this stayed true when examining more than the three probability thresholds presented in the manuscript (e.g. 15%, 35%, 85%, etc.). From our results it was, however, difficult to decide whether to use a threshold of 25% or 50% in chapter 7. The optimal threshold varied by agent, and although a threshold of 25% was arguably better for the two metal compounds examined (iron compounds and chromium compounds), a threshold of 50% was arguably better for welding fumes. For some other agents that were examined in chapter 7 but were not included in this manuscript (e.g. lead compound or chromium VI), both thresholds resulted in broadly similar results; while for other agents such as nickel compounds, a threshold of 50% was arguably better. In the end, because it was hard to argue for one threshold over the other, we decided to select a threshold of 50% as the main threshold used in chapter 7 and to also examine the associations obtained when using a threshold of 25% in sensitivity analyses.

Another important finding related to the probability threshold was that using a categorical cumulative exposure variable and using the probability of exposure as a threshold in the creation of the cumulative exposure variable resulted in associations more similar to the expert assessment than the more popular approach of using the probability of exposure as a term in the calculation of cumulative exposure (i.e. calculating cumulative exposure as probability * concentration * frequency * duration). Based on this, we decided to measure the cumulative exposure as a categorical variable and to use the probability of exposure as a threshold when calculating this variable in chapter 7. In order to stay consistent, we employed a similar approach to examine the duration of exposure variable.

Last, an important, but much more difficult to interpret finding was the general increase in the strength of positive associations observed when excluding from the unexposed category those subjects whose probability of exposure to a selected agent fell in the > 0 and < 25% range ("uncertainly" exposed subjects). There are two possible explanations for this observation. The first explanation is that excluding those subjects resulted in potentially confounded associations less similar to those obtained when using the expert assessment method; while the second explanation is that CANJEM classified as exposed subjects with on average higher level of exposure than the expert assessment, which resulted in the stronger positive associations observed. And thus, considering uncertainly exposed subjects as unexposed resulted in a dilution of the association. Although both explanations are plausible, our observation seems to indicate a higher likelihood for the second explanation; we observed that subjects classified as exposed with CANJEM often had higher levels of exposure compared to subjects classified as exposed with the expert assessment; and that most exposed subjects misclassified by CANJEM were misclassified as uncertainly exposed. Thus for manuscript 7, we decided to exclude uncertainly exposed subjects from the unexposed category. To stay consistent and because we had observed that excluding uncertainly exposed subjects from the unexposed category of the cumulative variable resulted in associations similar to the expert's assessment, we also excluded uncertainly exposed subjects from the cumulative and duration exposure analyses in chapter 7.

Chapter 7: Using CANJEM to examine the association between occupational exposure to selected metals, metalloids, and welding fumes and brain cancer in the INTEROCC pooled international case-control study

7.1 Manuscript

Using CANJEM to examine the association between occupational exposure to selected metals, metalloids, and welding fumes and brain cancer in the INTEROCC pooled international case-control study

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Contribution details: RP designed the study and it`s analytic strategy, conducted the analysis, and drafted the final manuscript. EC is the PI of the INTERPHONE and INTEROCC studies. On behalf of the INTEROCC study group she provided the data for analysis. JS and JL are the PIs of the CANJEM database and provided the CANJEM database for use in this project. JS, LR, and AK provided advice in study and analytic design. All authors participated in the writing of the manuscript.

7.1.1 Abstract

PURPOSE: With the exception of ionizing radiation and some genetic factors, little is known regarding the etiology of brain cancer. Metallic compounds are an important family of occupational agents that may play a role in the development of brain cancer. We investigated the association between 21 metallic compounds and two major histological subtypes of brain cancer: glioma and meningioma in the large international case-control study INTEROCC. **METHODS:** For each agent we estimated the adjusted odds ratios (ORs) for the association between three metrics of exposure (ever, duration, and cumulative exposure) and 1,917 glioma cases, 1,827 meningioma cases, and 5,475 controls, using unconditional logistic regression. **RESULTS:** We did not observe evidence of associations between our selected agents and glioma. Positive associations were generally observed between the selected agents and meningioma, with a statistically significant association (OR (95% confidence interval)) observed between < 15 years of exposure to lead fumes (1.67 (1.02-2.74)), zinc compounds (2.14 (1.02-3.89)), soldering fumes (1.80 (1.17-2.77)), and metal oxide fumes (1.51 (1.03-2.21)) and low cumulative exposure to chromium VI (1.99 (1.03-3.84)) and soldering fumes (1.83 (1.17-2.87)) and meningioma. **CONCLUSION:** Our result provides some support for the presence of positive associations between metallic compounds and meningioma, but not glioma.

7.1.2 Introduction

Central nervous system (CNS) tumors are the 13th leading cause of cancer mortality worldwide, being responsible for an estimated 241,000 deaths in 2018 (1) and are associated with substantial lifelong morbidity and considerable economic burden for patients, their families and health care systems (2-5). The most prevalent type of CNS tumors are brain tumors (6). Little is known regarding modifiable risk factors for this disease (7-10).

Metallic compounds are a large family of occupational agents to which millions of individuals worldwide, working in a wide range of industries, are potentially exposed on a daily basis (7, 9, 11). These agents are able to cross the blood-brain barrier (12-16) and have been shown to act as cancer initiators and promoters *in vivo* and *in vitro* (15-25). There have been some inconclusive indications, from occupational epidemiology studies, of associations between brain cancer and certain metallic compounds (lead, cadmium, zinc, mercury, arsenic, and welding fumes) (26-43). Most of these studies, however, were limited by small sample sizes and crude exposure assessment.

The INTEROCC study (44, 45) is a large population-based multi-national case-control study designed to examine the association between lifetime occupational exposures and meningioma and glioma, the two major histological subtypes of brain cancer. Two previous analyses have been conducted on the INTEROCC database investigating possible associations between occupational exposures and brain cancer (43, 46). Those analyses used a job-exposure matrix (JEM), namely a modified version of the Finnish job-exposure matrix (FINJEM) (47, 48) that the investigators called INTEROCC-JEM. Because of the limited number of metallic compounds in FINJEM, those analyses only examined associations with six metallic compounds. They found some evidence of positive association between occupational exposure to iron and chromium and meningioma, but not with glioma.

Our team has recently created a new JEM, CANJEM (49, 50), that embodies exposure information regarding a larger list of agents than FINJEM, and that contains information on > 30 different metallic compounds. In an effort to replicate the earlier analyses of metal-brain cancer associations using a different exposure assessment tool, and to expand the list of agents under scrutiny, we have applied CANJEM to the INTEROCC case-control database and derived estimates of associations between each type of brain cancer (glioma and meningioma) and 21 different metallic compounds.

7.1.3 Methods

The INTEROCC study

The INTEROCC study is an offspring of the INTERPHONE population-based multi-national case-control study which was designed to assess the possible association between use of cellular phones and risk of brain cancer (51). INTERPHONE was conducted between 2000 and 2004 in 16 centers from 13 countries, using a common core protocol. Its main findings on cell phones have been published (44, 45). Seven of the 13 countries that participated in INTERPHONE (Australia, Canada, France, Germany, Israel, New-Zealand, United-Kingdom) also gathered information on subjects' lifetime job history. These centers banded together to form the INTEROCC consortium, with the objective of studying possible associations between occupational exposures and brain cancer.

Study population

The study base included individuals aged ≥ 18 years old with residency in one of the study regions. Cases were residents of the study region with primary incident glioma or meningioma, either histologically confirmed or confirmed based on unequivocal diagnostic imaging. Controls in each center were randomly selected from the source population using various sampling frames and were either individually or frequency matched to cases by 5-year age group, sex and study region. In total, 2,054 glioma cases, 1,924 meningioma cases, and 5,601 controls were included in this study. The overall response rates were: 50% for controls, 68% for glioma cases and 81% for meningioma cases.

Data collection

Subjects or their proxy respondents were interviewed in person by trained interviewers using questionnaires that included questions on socio-demographic characteristics, use of wireless phones and devices, exposure to ionizing radiation, smoking history, and personal and familial medical history. In addition, detailed job title, description of tasks and the start and end year of each job held by subjects for more than six months was gathered, using an occupational history questionnaire.

The Canadian job-exposure matrix

CANJEM has been described elsewhere (49, 50). Briefly, it was developed by our team based on the expert assessment of > 30,000 jobs, held from the early 1930's to 2001 by more than 8,700 participants of four Montreal area case-control studies (52-55). CANJEM is comprised of three axes: 1) an occupation code axis which, for the purpose of this study used the International Standard Classification of Occupations 1968 (ISCO68) with 1,506 unique occupational codes at the 5-digit level, 2) a time period axis that includes four time periods (1930-1949, 1950-1969, 1970-1984, and 1985-2005), and 3) an occupational exposure axis, which includes exposure metrics for 258 substances. Each unique combination of those three axes defines a cell in CANJEM. Further the occupation and time axes can be collapsed to smaller numbers of broader categories (3-digit for occupation, and one or two time periods for the time axis).

Linkage of CANJEM

CANJEM offers considerable flexibility in linking to a study population, with different levels of resolution available for the occupational code (3-digit or 5-digit) and the time period (1, 2, or 4 time periods) axes. For this study, we linked CANJEM to the jobs present in the INTEROCC study in a step-wise fashion linking first to the highest resolution available in both axes, and then progressing through lower resolutions for jobs for which the 5-digit occupation code did not have a reliable estimate in the CANJEM database. The optimal method shown in previous work (chapter 5) is to reduce first the resolution of the time period axis and then that of the occupational code axis, down to a resolution of 3-digits and one time period. Using this methodology, 98% of all jobs present in the INTEROCC study population were linked to CANJEM, 71% of which were linked using the highest resolution in both axes. Jobs that could not be linked to an informative entry in CANJEM were considered as unexposed to all of the examined agents.

Selected occupational agents

For the present analyses, we selected 21 occupational agents which fulfilled the following criteria: 1) they were available in CANJEM, 2) they were compounds of metals, and

3) there were at least 10 exposed cases (meningioma or glioma) and controls in our study population based on the definition of exposure described below. The selected agents were: lead compounds, lead fumes, leaded gasoline (liquid), chromium compounds, chromium fumes, chromium VI, zinc compounds, iron compounds, iron fumes, nickel compounds, nickel fumes, calcium carbonate, calcium oxide, calcium oxide fumes, calcium sulphate, silicon carbide (also considered as a metalloid), gas welding fumes, arc welding fumes, soldering fumes, metallic dusts, and metal oxide fumes. This list of agents contains both more specific groups of compounds (e.g. lead fumes) and larger families of related compounds (e.g. lead compounds).

Information provided by CANJEM

Each cell of CANJEM provides the following information about exposure to a given agent, within a given occupation code and time period:

- Probability of exposure. This is simply the proportion of all jobs that were present in the historic database of our case-control studies in the given occupation code and time period, and that were considered as exposed to the given agent by our team of experts.
- Degree of exposure among those considered exposed. This is a summary of the dimensions of exposure that were coded by our expert coders among those subjects in that occupation who were considered exposed to the agent. This includes: median exposure concentration, classified as low, medium or high, and the frequency of exposure, quantified as the median hours of exposure per week and ranging from > 0 to 40 hours.
- The number of jobs in the original studies on which each cell of CANJEM is based. This can be used as a marker of the statistical reliability of the estimates in each cell, and can

be used, as we have done, to help determine which level of resolution of occupation code and time period to use in establishing exposure estimates from CANJEM.

Establishing exposure variables for INTEROCC subjects

In linking the INTEROCC study subjects to CANJEM, we obtained, for each job held, the estimate of the probability of exposure to each agent as well as the quantitative measures of exposure mentioned above. We used a threshold of 10 jobs in a cell in the underlying studies as the threshold for accepting the cell data as informative. Starting with the highest resolutions on the occupation and time dimensions, we gradually moved to lower resolutions as needed to end up with an informative estimate for the job being evaluated. We first created a binary exposed/ unexposed variable using the probability of exposure; the cutpoint of 50% was used to designate a job as exposed (chapter 6). When the probability was less than 50%, we considered the job as unexposed to the agent. The exposure concentrations of low, medium and high, were quantified by assigning values of 1, 5 and 25, respectively, based on the recommendation of the experts who assigned those exposure levels in our original studies. Furthermore, the experts that conducted the original exposure assessment used in CANJEM, also indicated their confidence in each assessment (“possible”, “probable” and “definite”). For the present analysis, we excluded from each cell jobs with “possible” exposure confidence level. In addition, from the INTEROCC job history we obtained the duration of exposure in the job. Using all of the data derived from linking with CANJEM, we defined three metrics of exposure for statistical analysis:

1) The basic exposure variable was categorized by the following trichotomy: never, uncertain, or ever exposed. Ever exposed was defined as having been exposed for ≥ 2 years at a probability of ≥ 50%. Uncertain exposure was defined as having been

exposed for < 2 years at a probability of ≥ 50%, or ≥ 2 years at a probability of < 50%. Never exposed was defined as having never been exposed to the selected agent at any probability level.

2) 'Duration of exposure' was categorized as never exposed, > 0 to < 15 years, and ≥ 15 years, where the duration of exposure was calculated by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subjects only exposed to the selected agent with a probability <50% were excluded from this analysis.
3) 'Cumulative exposure' was categorized as never, low, and high, where low exposure was defined as having a lifetime cumulative exposure to the selected agent < 70th percentile of cumulative exposure among controls, and high exposure was defined as having a lifetime cumulative exposure ≥ 70th percentile. For each job with an exposure probability ≥ 50%, we calculated the cumulative exposure as: (concentration / 25 * 100) * (frequency / 40 * 100) * duration of exposure. The result was summed across all exposed jobs. This formula was created to ensure that both the concentration and frequency of exposure would have a similar weight in the calculation of cumulative exposure. Subjects only exposed to the selected agent with a probability < 50% were excluded from this analysis.

Statistical analyses

We described selected characteristics of the study population. We examined the association between the 21 agents by calculating the phi correlation coefficient (mean square contingency coefficient) (56) between pairs of agents using our original binary exposure variable (never exposed or exposed with a probability < 50% / ever exposed with a probability

≥ 50%). The phi coefficient is related to the chi square statistic and is equivalent to the Pearson correlation coefficient.

The associations between each of the three exposure metrics for each of the 21 selected occupational agents with glioma and meningioma were examined using conditional logistic regression, conditioned on the matching variables (age (5-year groups), sex, and study center). Covariates were selected *a priori* from the epidemiological literature based on their potential association with the exposure and outcome and included age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), social class based on the Standard International Occupational Prestige Scale (SIOPS) (57) (categorised into quartiles among controls), and respondent status (self/proxy). In addition, as current evidence indicates that atopy may be inversely associated with glioma, atopy (which was measured by whether the subject was never/ever diagnosed with allergy, asthma and/or eczema) was also included as a covariate in the glioma analysis. All analyses were conducted using SAS 9.4.

Sensitivity analyses

We also conducted a number of sensitivity analyses. First, because a threshold of 50% for the probability of exposure may not necessarily be the best for all agents, we conducted all of our main analyses using a threshold of 25%. Second, because brain cancer may take decades to develop, we conducted all of our main analyses excluding exposures having occurred in the 10 years prior to subjects' inclusion in the INTEROCC study. Third, because both the incidence of glioma and meningioma and the occupations generally held by subjects varies considerably by sex, we conducted all of our main analyses separately for men and women. Fourth, we conducted random effects meta-analyses for the ever exposure variable in order to examine the coherence of this approach with the pooled single dataset approach used in our main analyses and to formally evaluate heterogeneity between countries. This was done by first calculating the country specific OR and 95%CI using conditional logistic regressions and estimating the pooled ORs and their 95%CIs by combining the $\log_{(e)}$OR obtained for each country, weighted by the inverse of the variance, using the DerSimonian and Laird random-effects model (58). Heterogeneity was evaluated with the I^2 statistic (59), which is based on Cochran's Q measure of heterogeneity and provides the percentage of variation across studies that is due to heterogeneity rather than chance. Finally, because the information provided by proxy respondents during the interview may not be as accurate as that provided by self-respondents, we conducted all of our main analyses restricted to self-respondents.

7.1.4 Results

Table I shows selected characteristics of cases and controls. Overall, the mean age ranged from 52 to 55 years old and most subjects originated from Germany, Israel, and the United Kingdom. There were more men than women amongst glioma cases and they tended to have a lower socioeconomic status compared to controls. Proxy response was obtained for 17% of glioma cases. There were more women than men amongst meningioma cases and they tended to have a lower education level and socioeconomic status compared to controls. Proxy response was obtained for 4% of meningioma cases.

Table II shows selected exposure characteristics of cases and controls. Prevalence of exposure in subjects ranged from 0.6% to 12.7% and tended to be higher in glioma cases when compared to controls and meningioma cases. The mean concentration of exposure ranged from 1 to 14 and tended to be higher in glioma and meningioma cases when compared to controls.

The mean weekly frequency of exposure ranged from 3.2 to 39 hours and tended to be higher in glioma and particularly meningioma cases when compared to controls. The top 5 most prevalent exposed occupational titles for each agent can be found in complementary table I.

Table III shows the correlation between our agents. For most agent combinations, correlations were low. Very high correlations (> 0.80) were observed between iron compounds and metallic dusts, iron fumes and calcium oxide fumes, and nickel fumes and calcium oxide fumes.

Table IV provides the adjusted ORs (95%CIs) for the association between occupational exposure to the selected agents and glioma. We principally observed close to null associations between occupational exposure to the selected agents and glioma. When considering duration of exposure, elevated risks for ≥ 15 years of exposure vs. never exposed were suggested for leaded gasoline, chromium fumes, nickel fumes, and silicon carbide. Reduced risks were suggested for >15 years of exposure to lead fumes, chromium VI, and soldering fumes, which was marginally significant for lead fumes, though based on only 5 exposed cases. Increased risks of glioma were also suggested for high cumulative exposure vs. never exposed to chromium fumes and nickel fumes.

Table V provides the adjusted ORs (95%CIs) for the association between occupational exposure to the selected agents and meningioma. Overall, we generally observed positive associations between our selected agents and meningioma, particularly when considering duration of exposure and cumulative exposure. Elevated risks were consistently observed for chromium compounds and fumes, nickel fumes, soldering fumes, and metal oxide fumes. When considering duration of exposure, elevated risks were observed for < 15 years of exposure vs.

never exposed for lead fumes, chromium fumes, chromium VI, zinc compounds, nickel fumes, calcium oxide, soldering fumes, and metal oxide fumes, with the association being statistically significant for lead fumes, zinc compounds, soldering fumes, and metal oxide fumes. Elevated risks were also observed for ≥ 15 years of exposure vs. never exposed for chromium compounds, chromium fumes, iron fumes, nickel compounds, nickel fumes, calcium oxide fumes, soldering fumes, silicon carbide and arc welding fumes. When considering cumulative exposure, elevated risks were observed for low cumulative exposure vs. never exposed for lead fumes, chromium compounds, chromium fumes, chromium VI, zinc compounds, nickel fumes, arc welding fumes, soldering fumes, and metal oxide fumes, with the association being statistically significant for chromium VI and soldering fumes and marginally significant for metal oxide fumes. Elevated risks were also observed between high cumulative vs. never exposed for chromium fumes, iron compounds, iron fumes, nickel compounds, nickel fumes, calcium sulphate, silicon carbide, and metal oxide fumes, with the association being marginally significant for nickel compounds.

When conducting the analyses using a probability of exposure threshold of 25% rather than 50%, the associations were generally attenuated (supplementary tables II and III). When conducting the analyses with a 10-year lag, we generally observed results similar to the ones obtained in our main analyses for glioma, but slightly stronger positive associations for meningioma (supplementary tables IV and V). When conducting analyses restricted to men, we also observed similar associations between occupational exposure to the selected agents and glioma, but generally slightly stronger positive associations for meningioma (supplementary tables VI and VII). There were generally too few exposed women to obtain meaningful associations. However, associations similar to what we observed in our main analysis were observed for agents with sufficient prevalence of exposure (results not shown). When conducting random effect meta-analyses, we generally observed similar results to the ones obtained when using the pooled single dataset approach (supplementary table VIII). Heterogeneity between countries was generally low, with most I^2 being $\leq$ 30%, but with somewhat high heterogeneity ($I^2 \geq$ 50%) for uncertain exposure to some agents (leaded gasoline, chromium VI, iron compounds, and iron fumes) in the glioma analysis and for ever exposure to some other agents in the glioma analysis (calcium carbonate and calcium sulphate) and meningioma analysis (nickel compounds and silicon carbide). Excluding proxy respondents from the analyses did not meaningfully change the results (not shown).

7.1.5 Discussion

In this large multi-national case-control study on brain cancer we observed little evidence of associations between occupational exposure to any of the selected agents and glioma; but some evidence of positive associations between occupational exposure to lead fumes, chromium VI, zinc compounds, soldering fumes, and metal oxide fumes and meningioma. While some differences existed, we observed broadly similar results when conducting sensitivity analyses using random-effect meta-analyses or when changing certain parameters: using a threshold of 25% for the probability of exposure; restricting to a 10-year lag period; analyses by sex; exclusion of proxy respondents.

We observed generally positive associations between the selected metallic compounds and meningioma; however, all statistically significant positive associations were observed in the < 15 years of exposure and low cumulative exposure categories and not at higher levels of exposure. It is possible that these results were due to chance considering the large number of analyses conducted, but this is unlikely since although attenuated we also observed positive associations for some of the agents (albeit non-significant and attenuated) at the highest level of exposure. The lower precision of the point estimates and the exposure misclassification inherent in the use of a JEM are more likely to explain our results. Correlation between occupational exposure to some of our agents was relatively high (table III). In particular, there was moderate correlation between lead fumes, zinc compounds, and soldering fumes, which makes it difficult to determine if those agents were independently associated with meningioma in our study.

It is interesting to note that in both our glioma and meningioma analyses there was a tendency for stronger positive associations to be observed for fumes compared to broader compounds. Indeed, we observed statistically significant associations for lead fumes, soldering fumes and metal oxide fumes, which encompass a large number of metallic fumes formed during high temperature treatment of metals in industrial operations. The two remaining agents for which we observed significant associations, zinc compounds and chromium VI, are also principally found in the forms of fumes. Metallic fumes are composed of ultrafine airborne metallic particles which, once inhaled, can enter the lung alveoli and penetrate the circulatory system to reach the brain. By comparison, metallic dusts are composed of larger metallic particles that can less easily penetrate the circulatory system, which may explain the weaker positive associations observed between metallic dusts and meningioma in our study. Thus, our results may point to the importance of examining metallic fumes in relation to brain cancer.

Conducting our analyses using a probability threshold of 25% instead of 50% resulted in similar but slightly more null associations; this is likely due to misclassification of a larger number of unexposed subjects as exposed, an increase in the overestimation of subject's exposure, and/or an overall reduction in the level of exposure of exposed subjects. Nonetheless, evidence of positive associations was still observed between the selected metallic compounds and meningioma, particularly for fumes. Conducting analyses with a 10-year lag period resulted in similar, but generally slightly stronger positive associations for meningioma, which could be due to the exclusion of exposures occurring in potentially less relevant etiological time periods or to chance. Interestingly, restricting analyses to men also resulted in similar yet stronger positive associations for meningioma. Again, the observed differences may be due to chance, but it may also be due to an overall higher level of exposure in men compared to women; although this would be hard to determine with CANJEM. Indeed, the exposure profile of female workers may differ from that of male workers within a specific occupation. Unfortunately, the current version of CANJEM does not allow for sex-specific exposure assignments and since around 75% of all expert assessments used to create CANJEM were derived from male workers, it is possible that CANJEM overestimates female workers' exposure in male-dominated occupations and underestimates it in female-dominated occupations. This does, however, show the need to develop female oriented occupational exposure assessment methods.

Two previous studies (43, 46) based on INTEROCC have examined the association between occupational exposure to five of the metallic compounds included in this study (lead compounds, iron compounds, chromium compounds, nickel compounds, and welding fumes) and glioma (46) or meningioma (43) using a modified version of FINJEM (INTEROCC-JEM). In those studies, no meaningful associations were observed between occupational exposure to the five metallic compounds and glioma, while principally positive associations were observed for meningioma, with statistically significant associations observed between occupational exposure to iron and chromium compounds in both sexes combined and women alone. The prevalence of exposures obtained in those studies using a threshold of 25% tended to be slightly higher than ours, with the exception of lead compounds. Compared to those studies, we observed similar, but often slightly more null associations between occupational exposure to those five agents and glioma, when using a probability threshold of either 50% or 25%. Overall, we also observed broadly similar associations for meningioma, particularly when using a probability threshold of 25%. Thus, our results confirm those obtained previously when using the INTEROCC-JEM, with the difference observed in results (e.g. in prevalence of exposure, point estimates and statistical significances) likely due to methodological differences between the two JEMs (e.g. construction of the exposure variable, source population) or the statistical analyses (e.g. different age cutpoints, different lag period, different exposure variables categorisation)

Excluding the two INTEROCC studies, 31 cohort studies (26-33, 60-81), 16 case-control studies (34-42, 82-88), and one nested case-control study (89) have examined the association between occupational exposure to metals overall or to at least one of the selected metallic compounds and brain cancer, with a few reporting statistically significant positive associations between occupational exposure to metals (34, 35, 37, 38), chromium compounds (27-29), lead compounds (26, 32, 33, 40, 41) or welding fumes (29, 30, 65) and brain cancer. However, only six cohort studies (26, 27, 32, 33 , 77, 78), 10 case-control studies (35-37, 39-42, 83, 86, 87), and one nested case-control study (89) included at least 10 cases or examined exposure to the selected metallic compounds rather than presuming exposure based on occupational titles. Most of the results reported in these studies were close to null or positive. One cohort study (27) examining women reported a positive association between chromium compounds and brain cancer in all subtypes combined. Furthermore, three cohort studies (26, 32, 33) and two case-control studies (40, 41) reported statistically significant positive associations between lead compounds (26, 32, 40, 41) or lead dust and/or fumes (33) and brain cancer. For one study (26), the association was statistically significant for meningioma, but not glioma, while for two other studies (33, 40) that also included few exposed cases, statistically significant associations between lead compounds and meningioma were reported in women only (40) or in both sexes combined and women only (33). Another study (41) reported a statistically significant positive association between lead compounds and all subtypes of brain cancer in men only. One case-control study (39) reported a statistically significant inverse association between occupational exposure to lead compounds and glioma, but not for meningioma. One meta-analysis (90) of six cohort studies (70, 71, 73, 77, 91, 92) including 69 brain cancer cases reported a close to null association between occupational exposure to lead and brain cancer. No statistically significant associations have been reported between any of the remaining agents and brain cancer, albeit few studies, if any, have examined them. Overall, our results are broadly consistent with the literature while providing some new evidence of positive associations between zinc compounds, soldering fumes, and metal oxide fumes and meningioma.

The main strength of this study was that, compared to most previous studies, we were able to examine specific levels (i.e. concentration, frequency, as well as probability) of occupational exposure to a wide range of metallic compounds in a large number of glioma and meningioma cases, the two major histological subtypes of brain cancer. However, exposure prevalence to some of our agents was still relatively low which limited the precision of some of our analyses, particularly when examining higher levels of exposure or exposure in women. Furthermore, correlation between some of our agents was high, which limited our ability to interpret the association observed for individual agents. As subjects' job history was self-reported, there is a potential for differential recall bias if the quality of the reporting depends on both the exposure and outcome status. However, this is unlikely since self-reported occupational history has been shown to be reliable, with no evidence of difference in the validity of jobs reported between cases and controls (93). Another limitation of our assessment method is that CANJEM allocates the same exposure estimate to each individual in any given occupation without considering inter-individual variability in intensity or duration of exposure, which can lead to exposure misclassification. However, this misclassification is non-differential with respect to disease status and is more likely to bias the OR estimates toward the null. Furthermore, we had previously observed (chapter 6) that the associations obtained when using CANJEM were similar to those obtained using the expert assessment method, often considered as the gold standard for retrospective lifetime occupational exposure assessment. Thus, even if present, exposure misclassification should have limited impact on the estimates of exposure. Another source of exposure misclassification is that CANJEM was built on the expert assessment of Canadian occupations; however, the occupational exposures present in one occupation might vary by country. Still, since all countries included in INTEROCC are developed countries with modern industries, there is likely to be broad similarity in the industrial processes used within any given occupation.

7.1.6 Conclusion

In this study we did not observe evidence of associations between occupational exposure to 21 metallic compounds and glioma, but generally observed positive associations between the selected agents and meningioma, which were statistically significant for occupational exposure to lead fumes, chromium VI, zinc compounds, soldering fumes, and metal oxide fumes. While the presence of co-exposure makes it difficult to interpret the individual role played by those agents, our results provide some evidence of the potential role played by metallic fumes in the development of meningioma. Future studies examining occupational exposure to each agent individually with gender specific assessment tools would be required to better understand the role played by those agents. In order to do this, we would need to explore new analytical strategies such as principal component analysis among others, in order to tease out the individual effect of each agent.

7.1.7 References

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7.1.8 Tables

Table I: Selected characteristics of study participants

		Controls N = 5,475 n (%)	Glioma cases N = 1,917 n (%)	Meningioma cases N = 1,827 n (%)
Sex	Male	2,464 (45.0)	1,187 (61.9)	496 (27.1)
	Female	3,011 (55.0)	730 (38.1)	1,331 (72.9)
Age (years)	< 40	866 (15.8)	366 (19.1)	171 (9.3)
	40 to < 50	1,379 (25.2)	451 (23.5)	441 (24.1)
	50 to < 60	2006 (36.7)	662 (34.5)	684 (37.4)
	60 to < 70	948 (17.3)	327 (17.1)	351 (19.2)
	70 to < 80	215 (3.9)	93 (4.9)	142 (7.8)
	≥ 80	61 (1.1)	18 (0.9)	38 (2.1)
Country	Australia	665 (12.2)	274 (14.3)	254 (13.9)
	Canada	651 (11.9)	166 (8.7)	93 (5.1)
	France	470 (8.6)	92 (4.8)	143 (7.8)
	Germany	1,527 (27.9)	363 (18.9)	375 (20.5)
	Israel	939 (17.1)	389 (20.3)	667 (36.5)
	New Zealand	143 (2.6)	64 (3.3)	50 (2.8)
	United Kingdom	1,080 (19.7)	569 (29.7)	245 (13.4)
Education	Primary/secondary	2,417 (44.1)	818 (42.7)	895 (49.0)
	Intermediate college/ professional	1,142 (20.9)	421 (21.9)	398 (21.8)
	Tertiary	1,916 (35.0)	678 (35.4)	534 (29.2)
SIOPS	Q1 (< 35)	1,361 (24.9)	512 (26.7)	546 (29.9)
	Q2 (≥ 35 to < 42.9)	1,376 (25.1)	539 (28.1)	443 (24.3)
	Q3 (≥ 42.9 to < 52.2)	1,369 (25.0)	436 (22.8)	417 (22.8)
	Q4 (≥ 52.2)	1,369 (25.0)	430 (22.4)	421 (23.0)
Respondent status	Self	5,462 (99.8)	1,598 (83.4)	1,752 (95.9)
	Proxy	13 (0.02)	319 (16.6)	75 (4.1)
Atopy	Never	4,033 (73.7)	1,488 (77.6)	1,433 (78.4)
	Ever	1,442 (26.3)	429 (22.4)	394 (21.6)

Table II: Selected exposure[1] characteristics of cases and controls

Agent	Prevalence of exposure (%)			Mean concentration[2] of exposure in exposed jobs			Mean frequency of exposure in exposed jobs (hours)		
	Controls	Glioma cases	Meningioma cases	Controls	Glioma cases	Meningioma cases	Controls	Glioma cases	Meningioma cases
Lead compounds	10.0	11.2	6.8	1.5	1.5	1.3	24.6	26.1	25.1
Lead fumes	1.9	1.4	2.1	1.0	1.0	1.0	6.9	6.5	14.6
Leaded gasoline	2.3	3.1	1.5	5.0	5.0	5.0	9.9	8.3	13.6
Chromium compounds	2.3	3.8	2.0	3.2	4.5	3.3	15.2	14.3	15.7
Chromium fumes	0.7	1.2	1.0	5.0	5.0	5.0	5.8	5.4	5.4
Chromium VI	0.9	1.6	1.0	3.5	5.0	3.9	10.7	11.5	10.3
Zinc compounds	1.5	1.7	1.7	1.0	1.0	1.0	7.1	6.5	14.1
Iron compounds	7.9	10.6	6.5	3.3	3.6	3.9	25.2	27.0	28.7
Iron fumes	1.5	2.4	1.6	4.5	5.6	6.0	35.9	38.2	39.0
Nickel compounds	2.2	2.8	1.9	3.6	3.5	3.5	8.6	7.9	8.4
Nickel fumes	0.7	1.2	1.0	5.0	5.0	5.0	5.8	5.4	5.4
Calcium carbonate	6.2	6.2	6.4	1.3	1.7	1.3	7.3	7.7	6.4
Calcium oxide	1.2	1.6	0.6	5.0	5.0	5.0	3.2	3.5	3.7
Calcium oxide fumes	1.0	1.7	1.2	6.1	5.4	4.2	19.7	19.8	20.0
Calcium sulphate	3.5	5.4	2.4	4.4	4.8	3.9	5.0	5.9	5.7
Silicon carbide	1.6	2.6	1.3	1.0	1.0	1.0	6.2	5.5	5.4
Gas welding fumes	3.3	5.0	2.5	6.6	7.4	7.0	26.5	33.8	31.2
Arc welding fumes	2.3	3.6	2.1	11.8	14.0	12.4	34.1	38.8	36.7
Soldering fumes	2.6	2.4	3.0	4.6	4.5	4.5	9.9	9.6	18.9
Metallic dusts	9.7	12.7	7.4	3.1	3.2	3.4	21.5	22.2	23.3
Metal oxide fumes	4.5	6.0	4.3	4.8	5.3	5.0	17.7	19.7	21.1

1. Jobs with a probability of exposure to a selected agent ≥ 50% were considered exposed to that agent.

2. The concentration of exposure ranged from 1 for low exposure to 25 for high exposure, with medium exposure having a value of 5.

Table III: Phi correlation coefficients[1] between pair of agents[2]

Agent	Lead compounds	Lead fumes	Leaded gasoline	Chromium compounds	Chromium fumes	Chromium VI	Zinc compounds	Iron compounds	Iron fumes	Nickel compounds	Nickel fumes	Calcium carbonate	Calcium oxide	Calcium oxide fumes	Calcium sulphate	Silicon carbide	Gas welding fumes	Arc welding fumes	Soldering fumes	Metallic dusts	Metal oxide fumes
Lead compounds		0.42	0.39	0.06	0.01	0.05	0.26	0.35	0.08	0.05	0.05	-0.04	0.01	0.04	0.08	0.04	0.31	0.10	0.35	0.34	0.28
Lead fumes			-0.02	0.01	<0.01	-0.01	0.51	0.19	0.02	0.02	0.03	-0.03	-0.01	0.02	0.01	0.02	0.05	0.01	0.56	0.18	0.35
Leaded gasoline				<0.01	<0.01	<0.01	<0.01	0.39	0.02	0.02	0.02	-0.02	<0.01	0.02	0.02	0.01	0.50	0.04	-0.02	0.35	0.04
Chromium compounds					0.38	0.49	0.08	0.39	0.41	0.65	0.37	-0.03	0.02	0.31	0.19	0.63	0.27	0.26	0.01	0.33	0.25
Chromium fumes						0.01	0.01	0.23	0.53	0.46	0.74	-0.02	<0.01	0.64	<0.01	0.45	0.36	0.43	0.01	0.21	0.31
Chromium VI							0.11	0.09	0.06	0.03	0.02	-0.02	<0.01	0.01	0.23	0.05	0.03	0.05	-0.01	0.07	0.03
Zinc compounds								0.28	0.04	0.02	0.03	-0.03	-0.01	0.03	<0.01	0.04	0.08	0.17	0.48	0.32	0.39
Iron compounds									0.44	0.47	0.31	-0.04	0.01	0.36	0.03	0.45	0.56	0.50	0.16	0.87	0.56
Iron fumes										0.55	0.72	-0.03	0.01	0.82	0.01	0.47	0.61	0.69	0.02	0.38	0.59
Nickel compounds											0.62	-0.03	0.02	0.51	0.04	0.74	0.37	0.38	0.02	0.46	0.34
Nickel fumes												-0.02	0.01	0.83	<0.01	0.44	0.48	0.58	0.02	0.28	0.42
Calcium carbonate													0.16	-0.02	0.12	-0.02	-0.04	-0.03	-0.03	-0.05	-0.05
Calcium oxide														0.01	0.10	0.02	<0.01	<0.01	<0.01	<0.01	<0.01
Calcium oxide fumes															<0.01	0.38	0.49	0.65	0.02	0.31	0.48
Calcium sulphate																<0.01	0.02	0.02	0.13	0.05	0.03
Silicon carbide																	0.32	0.32	0.02	0.41	0.30
Gas welding fumes																		0.53	0.05	0.55	0.53
Arc welding fumes																			0.09	0.47	0.70
Soldering fumes																				0.17	0.41
Metallic dusts																					0.54
Metal oxide fumes																					

1. Calculated by comparing pairs of agents using a binary exposure variable (never exposed or exposed with a probability < 50% / exposed with a probability ≥ 50%).
2. As the coefficients repeated themselves in the lower half of the table, only the upper half is provided.

🟩	Correlation coefficient < 0.20.
🟨	Correlation coefficient between 0.20 to < 0.40.
🟧	Correlation coefficient between 0.40 to < 0.60.
🟥	Correlation coefficient between 0.60 to < 0.80.
🟫	Correlation coefficient between 0.80 to 1.00.

Table IV: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and glioma

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	512 / 1,686	1,218 / 3,342	187 / 447	154 / 415	61 / 131	146 / 382	69 / 164
Adjusted OR (95% CI)[5]	1.00 (ref)	1.09 (0.95 - 1.26)	0.93 (0.73 - 1.18)	0.85 (0.64 - 1.13)	1.12 (0.74 - 1.71)	0.85 (0.64 - 1.14)	1.06 (0.71 - 1.59)
Lead fumes							
#cases / #controls	883 / 2,779	1,011 / 2,612	23 / 84	22 / 66	5 / 38	21 / 72	6 / 32
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.86 - 1.11)	0.64 (0.38 - 1.06)	0.87 (0.51 - 1.49)	0.35 (0.12 - 1.01)	0.75 (0.44 - 1.29)	0.54 (0.20 - 1.46)
Leaded gasoline							
#cases / #controls	927 / 2,967	939 / 2,403	51 / 105	41 / 104	18 / 22	45 / 88	14 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.87 - 1.13)	0.97 (0.65 - 1.44)	0.86 (0.56 - 1.32)	1.82 (0.84 - 3.94)	1.05 (0.68 - 1.62)	0.86 (0.42 - 1.79)
Chromium compounds							
#cases / #controls	1,023 / 3,044	830 / 2,320	64 / 111	48 / 87	24 / 38	51 / 87	21 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.86 - 1.09)	1.04 (0.73 - 1.49)	0.99 (0.66 - 1.49)	1.01 (0.54 - 1.87)	1.04 (0.69 - 1.56)	0.89 (0.47 - 1.69)
Chromium fumes							
#cases / #controls	1,409 / 4,226	490 / 1,216	18 / 33	14 / 28	9 / 11	13 / 27	10 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.82 - 1.10)	1.00 (0.54 - 1.85)	0.82 (0.41 - 1.64)	1.34 (0.50 - 3.56)	0.78 (0.38 - 1.58)	1.43 (0.56 - 3.66)
Chromium VI							
#cases / #controls	1,399 / 4,172	490 / 1,260	28 / 43	24 / 33	7 / 18	24 / 34	7 / 17
Adjusted OR (95% CI)[5]	1.00 (ref)	0.86 (0.75 - 1.00)	1.10 (0.64 - 1.91)	1.38 (0.75 - 2.53)	0.41 (0.14 - 1.22)	1.15 (0.63 - 2.12)	0.65 (0.23 - 1.81)
Zinc compounds							
#cases / #controls	1,088 / 3,344	802 / 2,056	27 / 75	21 / 45	12 / 39	29 / 58	4 / 26
Adjusted OR (95% CI)[5]	1.00 (ref)	0.93 (0.82 - 1.06)	0.81 (0.50 - 1.31)	0.97 (0.55 - 1.72)	0.71 (0.33 - 1.53)	1.06 (0.64 - 1.76)	0.35 (0.10 - 1.20)
Iron compounds							
#cases / #controls	616 / 1,908	1,118 / 3,169	183 / 398	130 / 282	74 / 152	142 / 303	62 / 131
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.87 - 1.13)	0.86 (0.68 - 1.08)	0.93 (0.70 - 1.24)	0.95 (0.66 - 1.37)	0.93 (0.70 - 1.23)	0.96 (0.66 - 1.42)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	1,020 / 3,081	862 / 2,320	35 / 74	32 / 61	14 / 21	34 / 57	12 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.87 - 1.11)	0.89 (0.56 - 1.40)	1.00 (0.61 - 1.62)	1.15 (0.53 - 2.49)	1.14 (0.70 - 1.84)	0.78 (0.35 - 1.78)
Nickel compounds							
#cases / #controls	1,145 / 3,440	724 / 1,933	48 / 102	30 / 82	23 / 37	29 / 82	24 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.89 - 1.14)	0.92 (0.62 - 1.35)	0.66 (0.42 - 1.06)	1.22 (0.66 - 2.25)	0.66 (0.41 - 1.06)	1.18 (0.65 - 2.16)
Nickel fumes							
#cases / #controls	1,431 / 4,303	468 / 1,139	18 / 33	14 / 28	9 / 11	13 / 27	10 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.85 - 1.13)	1.01 (0.55 - 1.88)	0.82 (0.41 - 1.63)	1.39 (0.52 - 3.68)	0.77 (0.38 - 1.57)	1.49 (0.58 - 3.79)
Calcium carbonate							
#cases / #controls	996 / 2,914	810 / 2,251	111 / 310	68 / 198	50 / 141	70 / 237	48 / 102
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.13)	1.19 (0.91 - 1.55)	1.09 (0.79 - 1.52)	1.22 (0.82 - 1.81)	1.08 (0.78 - 1.48)	1.27 (0.83 - 1.93)
Calcium oxide							
#cases / #controls	1,300 / 3,767	590 / 1,649	27 / 59	18 / 33	12 / 30	20 / 43	10 / 20
Adjusted OR (95% CI)[5]	1.00 (ref)	0.89 (0.78 - 1.01)	0.95 (0.58 - 1.58)	1.10 (0.59 - 2.08)	0.81 (0.38 - 1.70)	0.87 (0.48 - 1.58)	1.19 (0.52 - 2.72)
Calcium oxide fumes							
#cases / #controls	1,412 / 4,074	481 / 1,354	24 / 47	21 / 40	11 / 13	20 / 37	12 / 16
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.82 - 1.09)	0.95 (0.55 - 1.63)	1.04 (0.59 - 1.83)	1.28 (0.52 - 3.19)	1.07 (0.61 - 1.90)	1.17 (0.48 - 2.82)
Calcium sulphate							
#cases / #controls	1,068 / 3,147	751 / 2,157	98 / 171	63 / 123	41 / 69	65 / 133	39 / 59
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.83 - 1.06)	1.05 (0.78 - 1.41)	0.95 (0.66 - 1.37)	1.04 (0.66 - 1.64)	0.91 (0.64 - 1.30)	1.15 (0.71 - 1.87)
Silicon carbide							
#cases / #controls	1,323 / 4,074	548 / 1,318	46 / 83	29 / 65	21 / 25	31 / 63	19 / 27
Adjusted OR (95% CI)[5]	1.00 (ref)	1.05 (0.91 - 1.20)	1.06 (0.70 - 1.59)	0.84 (0.52 - 1.36)	1.41 (0.72 - 2.76)	0.89 (0.56 - 1.44)	1.25 (0.63 - 2.47)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	907 / 2,770	926 / 2,551	84 / 154	70 / 133	26 / 47	68 / 126	28 / 54
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.86 - 1.10)	1.03 (0.75 - 1.41)	0.88 (0.62 - 1.24)	0.97 (0.55 - 1.72)	0.85 (0.59 - 1.22)	1.02 (0.61 - 1.72)
Arc welding fumes							
#cases / #controls	884 / 2,696	980 / 2,666	53 / 113	47 / 87	22 / 37	49 / 86	20 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.85 - 1.09)	0.88 (0.60 - 1.27)	0.98 (0.64 - 1.48)	0.93 (0.50 - 1.72)	1.01 (0.66 - 1.52)	0.86 (0.46 - 1.62)
Soldering fumes							
#cases / #controls	1,039 / 3,105	836 / 2,244	42 / 126	35 / 99	11 / 45	38 / 100	8 / 44
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.85 - 1.09)	0.74 (0.50 - 1.10)	0.77 (0.50 - 1.19)	0.54 (0.26 - 1.13)	0.79 (0.52 - 1.20)	0.44 (0.18 - 1.05)
Metallic dusts							
#cases / #controls	577 / 1,745	1,120 / 3,244	220 / 486	153 / 334	91 / 196	171 / 371	73 / 159
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.07)	0.88 (0.71 - 1.10)	0.93 (0.71 - 1.22)	0.85 (0.61 - 1.18)	0.90 (0.70 - 1.17)	0.90 (0.63 - 1.29)
Metal oxide fumes							
#cases / #controls	779 / 2,368	1,047 / 2,889	91 / 218	83 / 163	32 / 83	76 / 172	39 / 74
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.84 - 1.09)	0.83 (0.62 - 1.11)	0.97 (0.70 - 1.35)	0.71 (0.44 - 1.16)	0.85 (0.61 - 1.19)	0.98 0.62 - 1.56)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), proxy respondent status (self, proxy), and atopy (allergy, asthma and/or eczema) (never/ever).

Table V: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and meningioma

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	572 / 1,686	1,153 / 3,342	102 / 447	93 / 415	32 / 131	87 / 382	38 / 164
Adjusted OR (95% CI)[5]	1.00 (ref)	1.07 (0.94 - 1.22)	0.90 (0.69 - 1.17)	1.06 (0.77 - 1.45)	0.88 (0.53 - 1.46)	1.12 (0.81 - 1.56)	0.81 (0.52 - 1.28)
Lead fumes							
#cases / #controls	921 / 2,779	875 / 2,612	31 / 84	28 / 66	11 / 38	25 / 72	14 / 32
Adjusted OR (95% CI)[5]	1.00 (ref)	1.05 (0.93 - 1.19)	1.36 (0.86 - 2.15)	1.67 (1.02 - 2.74)	1.08 (0.50 - 2.34)	1.62 (0.96 - 2.72)	1.23 (0.61 - 2.48)
Leaded gasoline							
#cases / #controls	1,024 / 2,967	786 / 2,403	17 / 105	26 / 104	1 / 22	21 / 88	6 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.07)	0.73 (0.42 - 1.27)	1.19 (0.72 - 1.96)	0.17 (0.02 - 1.32)	1.15 (0.67 - 2.00)	0.63 (0.25 - 1.64)
Chromium compounds							
#cases / #controls	1,035 / 3,044	761 / 2,320	31 / 111	26 / 87	11 / 38	25 / 87	12 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.90 - 1.14)	1.31 (0.84 - 2.04)	1.36 (0.82 - 2.25)	1.42 (0.68 - 2.94)	1.42 (0.86 - 2.35)	1.29 (0.63 - 2.65)
Chromium fumes							
#cases / #controls	1,481 / 4,226	331 / 1,216	15 / 33	11 / 28	8 / 11	11 / 27	8 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.86 - 1.17)	1.75 (0.90 - 3.43)	1.57 (0.74 - 3.32)	2.24 (0.83 - 6.08)	1.63 (0.76 - 3.47)	2.06 (0.78 - 5.48)
Chromium VI							
#cases / #controls	1,466 / 4,172	349 / 1,260	12 / 43	15 / 33	4 / 18	16 / 34	3 / 17
Adjusted OR (95% CI)[5]	1.00 (ref)	1.03 (0.89 - 1.21)	1.21 (0.60 - 2.43)	1.92 (0.97 - 3.80)	1.06 (0.34 - 3.33)	1.99 (1.03 - 3.84)	0.85 (0.23 - 3.07)
Zinc compounds							
#cases / #controls	1,192 / 3,344	609 / 2,056	26 / 75	20 / 45	11 / 39	20 / 58	11 / 26
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.85 - 1.09)	1.29 (0.78 - 2.11)	2.14 (1.17 - 3.89)	0.97 (0.46 - 2.05)	1.66 (0.93 - 2.96)	1.34 (0.61 - 2.92)
Iron compounds							
#cases / #controls	672 / 1,908	1,050 / 3,169	105 / 398	80 / 282	39 / 152	75 / 303	44 / 131
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.85 - 1.09)	1.22 (0.93 - 1.60)	1.29 (0.93 - 1.81)	1.16 (0.74 - 1.83)	1.15 (0.82 - 1.62)	1.51 (0.97 - 2.34)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	1,090 / 3,081	715 / 2,320	22 / 74	17 / 61	12 / 21	18 / 57	11 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	1.06 (0.94 - 1.20)	1.19 (0.70 - 2.01)	1.06 (0.59 - 1.93)	1.90 (0.85 - 4.25)	1.20 (0.67 - 2.17)	1.47 (0.66 - 3.29)
Nickel compounds							
#cases / #controls	1,166 / 3,440	631 / 1,933	30 / 102	19 / 82	16 / 37	16 / 82	19 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.90 - 1.16)	1.35 (0.86 - 2.11)	1.08 (0.62 - 1.88)	1.88 (0.97 - 3.66)	1.02 (0.57 - 1.85)	1.87 (1.00 - 3.52)
Nickel fumes							
#cases / #controls	1,500 / 4,303	312 / 1,139	15 / 33	11 / 28	8 / 11	11 / 27	8 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	1.03 (0.88 - 1.21)	1.77 (0.90 - 3.46)	1.69 (0.80 - 3.58)	2.40 (0.88 - 6.52)	1.76 (0.82 - 3.76)	2.20 (0.83 - 5.85)
Calcium carbonate							
#cases / #controls	983 / 2,914	733 / 2,251	111 / 310	63 / 198	54 / 141	87 / 237	30 / 102
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.88 - 1.12)	0.98 (0.76 - 1.26)	0.88 (0.63 - 1.23)	0.92 (0.64 - 1.33)	0.95 (0.71 - 1.27)	0.78 (0.49 - 1.25)
Calcium oxide							
#cases / #controls	1,220 / 3,767	596 / 1,649	11 / 59	8 / 33	3 / 30	7 / 43	4 / 20
Adjusted OR (95% CI)[5]	1.00 (ref)	1.09 (0.96 - 1.24)	0.90 (0.45 - 1.80)	1.79 (0.74 - 4.31)	0.49 (0.15 - 1.67)	1.00 (0.42 - 2.39)	1.08 (0.35 - 3.30)
Calcium oxide fumes							
#cases / #controls	1,383 / 4,074	427 / 1,354	17 / 47	12 / 40	10 / 13	13 / 37	9 / 16
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.87 - 1.14)	1.14 (0.62 - 2.09)	0.99 (0.50 - 1.98)	2.32 (0.93 - 5.75)	1.31 (0.66 - 2.60)	1.34 (0.55 - 3.26)
Calcium sulphate							
#cases / #controls	1,086 / 3,147	702 / 2,157	39 / 171	25 / 123	18 / 69	24 / 133	19 / 59
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.89 - 1.14)	0.98 (0.66 - 1.46)	1.04 (0.63 - 1.71)	1.23 (0.69 - 2.18)	0.93 (0.57 - 1.53)	1.47 (0.82 - 2.65)
Silicon carbide							
#cases / #controls	1,376 / 4,074	429 / 1,318	22 / 83	15 / 65	9 / 25	16 / 63	8 / 27
Adjusted OR (95% CI)[5]	1.00 (ref)	1.11 (0.96 - 1.27)	1.30 (0.78 - 2.19)	0.92 (0.49 - 1.72)	1.61 (0.70 - 3.69)	0.94 (0.51 - 1.72)	1.66 (0.69 - 3.99)

Agent	**Never exposed**[1]	**Ever exposure**[2]		**Duration of exposure**[3]		**Cumulative exposure**[4]	
		Uncertain	**Ever**	**< 15 years**	**≥ 15 years**	**Low**	**High**
Gas welding fumes							
#cases / #controls	985 / 2,770	809 / 2,551	33 / 154	33 / 133	13 / 47	23 / 126	23 / 54
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.90 - 1.15)	0.91 (0.60 - 1.38)	1.25 (0.80 - 1.95)	0.92 (0.45 - 1.84)	1.02 (0.61 - 1.68)	1.34 (0.76 - 2.37)
Arc welding fumes							
#cases / #controls	959 / 2,696	837 / 2,666	31 / 113	23 / 87	15 / 37	23 / 86	15 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.90 - 1.15)	1.21 (0.77 - 1.88)	1.21 (0.72 - 2.06)	1.44 (0.71 - 2.94)	1.43 (0.84 - 2.42)	1.07 (0.53 - 2.16)
Soldering fumes							
#cases / #controls	1,053 / 3,105	731 / 2,244	43 / 126	38 / 99	16 / 45	35 / 100	19 / 44
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.86 - 1.10)	1.28 (0.87 - 1.88)	1.80 (1.17 - 2.77)	1.25 (0.66 - 2.38)	1.83 (1.17 - 2.87)	1.29 (0.71 - 2.33)
Metallic dusts							
#cases / #controls	600 / 1,745	1,107 / 3,244	120 / 486	94 / 334	42 / 196	93 / 371	43 / 159
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.86 - 1.11)	1.12 (0.87 - 1.44)	1.23 (0.90 - 1.69)	1.00 (0.66 - 1.54)	1.10 (0.80 - 1.50)	1.34 (0.86 - 2.07)
Metal oxide fumes							
#cases / #controls	811 / 2,368	951 / 2,889	65 / 218	52 / 163	27 / 83	53 / 172	26 / 74
Adjusted OR (95% CI)[5]	1.00 (ref)	1.10 (0.98 - 1.24)	1.36 (0.98 - 1.88)	1.51 (1.03 - 2.21)	1.34 (0.80 - 2.27)	1.48 (1.00 - 2.17)	1.40 (0.82 - 2.39)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), and proxy respondent status (self, proxy).

Supplementary table I: Most prevalent exposed[1] occupations for each of the 21 selected agents in the INTEROCC study

Agent	Occupation
Lead compounds	Automobile mechanic, lorry and van driver (long-distance transport), plumber , other motor-vehicle drivers
Lead fumes	Plumber, refrigeration and air-conditioning plant installer and mechanic, solderer (hand)
Leaded gasoline	Automobile mechanic, other salesmen, shop assistants and demonstrators
Chromium compounds	Automobile painter, vehicle sheet-metal worker, fabric dyer, electroplater, buffing- and polishing-machine operator
Chromium fumes	Gas and electric welder, other welders and flame-cutters, other metal melters and reheaters
Chromium VI	Automobile painter, vehicle sheet-metal worker, fabric dyer, electroplater, other welders and flame-cutters
Zinc compounds	Plumber, dentist, solderer (hand)
Iron compounds	Automobile mechanic, gas and electric welder, tool and die maker, plumber , machinery mechanic
Iron fumes	Gas and electric welder, electric arc welder (hand), vehicle sheet-metal worker, bench moulder (metal), other welders and flame-cutters
Nickel compounds	Gas and electric welder, dental prosthesis maker and repairer, electroplater, buffing- and polishing-machine operator, other welders and flame-cutters
Nickel fumes	Gas and electric welder, other welders and flame-cutters, other metal melters and reheaters
Calcium carbonate	First-level education teacher, other primary education teachers, housebuilder languages and literature teacher (second level), natural science teacher (second level)
Calcium oxide	Bricklayer (construction), farm worker , farm manager, plasterer, dairy farm worker
Calcium oxide fumes	Gas and electric welder, electric arc welder (hand), bench moulder (metal), furnaceman, metal-melting, except cupola, other metal moulders and coremakers
Calcium sulphate	Electrician, building painter, housebuilder , building electrician, fire-fighter
Silicon carbide	Machine-tool operator, vehicle sheet-metal worker
Gas welding fumes	Gas and electric welder, refrigeration and air-conditioning plant installer and mechanic, jeweller , motor-truck mechanic, vehicle sheet-metal worker
Arc welding fumes	Gas and electric welder, constructional steel erector, electric arc welder (hand), motor-truck mechanic, metal shipwright
Soldering fumes	Plumber, electronic equipment assembler, building electrician, maintenance electrician, radio and television mechanic
Metal oxide fumes	Gas and electric welder, plumber , machinery mechanic , sheet-metal worker, radio and television mechanic
Metallic dusts	Automobile mechanic, gas and electric welder , machinery fitter-assembler , tool and die maker, plumber

1. Exposed with a probability of exposure ≥ 50%

Supplementary table II: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and glioma using a probability threshold of 25%

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	512 / 1686	973 / 2848	432 / 941	306 / 715	174 / 349	341 / 744	139 / 320
Adjusted OR (95% CI)[5]	1.00 (ref)	1.08 (0.93 - 1.25)	1.08 (0.89 - 1.30)	1.02 (0.82 - 1.27)	1.07 (0.80 - 1.41)	1.05 (0.85 - 1.31)	0.96 (0.71 - 1.30)
Lead fumes							
#cases / #controls	883 / 2779	856 / 2307	178 / 389	124 / 291	69 / 153	135 / 309	58 / 135
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.85 - 1.11)	0.89 (0.71 - 1.12)	0.83 (0.63 - 1.08)	0.90 (0.63 - 1.28)	0.86 (0.66 - 1.11)	0.84 (0.57 - 1.22)
Leaded gasoline							
#cases / #controls	927 / 2967	894 / 2296	96 / 212	79 / 192	30 / 55	74 / 172	35 / 75
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.14)	0.90 (0.67 - 1.21)	0.87 (0.63 - 1.20)	1.03 (0.60 - 1.77)	0.90 (0.65 - 1.26)	0.91 (0.56 - 1.48)
Chromium compounds							
#cases / #controls	1023 / 3044	759 / 2154	135 / 277	92 / 209	60 / 101	109 / 217	43 / 93
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.85 - 1.09)	1.02 (0.79 - 1.30)	0.96 (0.72 - 1.28)	1.07 (0.72 - 1.58)	1.06 (0.80 - 1.39)	0.84 (0.54 - 1.30)
Chromium fumes							
#cases / #controls	1409 / 4226	468 / 1167	40 / 82	33 / 67	17 / 25	31 / 64	19 / 28
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.82 - 1.10)	0.99 (0.66 - 1.49)	0.95 (0.61 - 1.49)	1.24 (0.64 - 2.42)	0.99 (0.62 - 1.57)	1.11 (0.59 - 2.10)
Chromium VI							
#cases / #controls	1399 / 4172	463 / 1197	55 / 106	41 / 79	21 / 44	41 / 86	21 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	0.86 (0.74 - 0.99)	1.03 (0.71 - 1.49)	1.05 (0.68 - 1.60)	0.80 (0.44 - 1.46)	0.99 (0.65 - 1.50)	0.89 (0.48 - 1.66)
Zinc compounds							
#cases / #controls	1088 / 3344	728 / 1910	101 / 221	79 / 159	41 / 89	85 / 173	35 / 75
Adjusted OR (95% CI)[5]	1.00 (ref)	0.93 (0.81 - 1.05)	0.92 (0.70 - 1.21)	1.00 (0.73 - 1.37)	0.90 (0.59 - 1.38)	1.02 (0.76 - 1.38)	0.84 (0.53 - 1.33)
Iron compounds							
#cases / #controls	616 / 1908	1040 / 2985	261 / 582	175 / 378	113 / 255	201 / 443	87 / 190
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.87 - 1.14)	0.90 (0.73 - 1.10)	0.98 (0.77 - 1.26)	0.85 (0.63 - 1.16)	0.92 (0.72 - 1.17)	0.98 (0.70 - 1.37)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	1020 / 3081	785 / 2143	112 / 251	95 / 195	39 / 86	89 / 196	45 / 85
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.13)	0.83 (0.64 - 1.09)	0.90 (0.67 - 1.22)	0.84 (0.53 - 1.31)	0.88 (0.65 - 1.19)	0.89 (0.58 - 1.37)
Nickel compounds							
#cases / #controls	1145 / 3440	669 / 1820	103 / 215	74 / 159	45 / 74	84 / 163	35 / 70
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.13)	1.01 (0.77 - 1.33)	1.00 (0.73 - 1.38)	1.11 (0.72 - 1.73)	1.12 (0.82 - 1.52)	0.86 (0.54 - 1.38)
Nickel fumes							
#cases / #controls	1431 / 4303	450 / 1095	36 / 77	29 / 64	16 / 23	26 / 60	19 / 27
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.85 - 1.14)	0.96 (0.63 - 1.47)	0.84 (0.52 - 1.36)	1.39 (0.70 - 2.78)	0.87 (0.53 - 1.43)	1.21 (0.64 - 2.28)
Calcium carbonate							
#cases / #controls	996 / 2914	744 / 2070	177 / 491	109 / 310	85 / 234	122 / 380	72 / 164
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.88 - 1.13)	1.14 (0.92 - 1.40)	1.02 (0.79 - 1.33)	1.18 (0.87 - 1.61)	1.04 (0.81 - 1.34)	1.18 (0.84 - 1.64)
Calcium oxide							
#cases / #controls	1300 / 3767	578 / 1626	39 / 82	26 / 58	17 / 36	30 / 65	13 / 29
Adjusted OR (95% CI)[5]	1.00 (ref)	0.89 (0.78 - 1.01)	0.95 (0.61 - 1.48)	0.88 (0.51 - 1.51)	0.90 (0.46 - 1.77)	0.79 (0.46 - 1.33)	1.12 (0.55 - 2.27)
Calcium oxide fumes							
#cases / #controls	1412 / 4074	472 / 1336	33 / 65	30 / 60	13 / 14	15 / 65	7 / 29
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.82 - 1.09)	0.91 (0.57 - 1.44)	0.93 (0.58 - 1.50)	1.21 (0.51 - 2.90)	0.86 (0.46 - 1.61)	1.18 (0.48 - 2.89)
Calcium sulphate							
#cases / #controls	1068 / 3147	696 / 2037	153 / 291	91 / 197	71 / 131	101 / 229	61 / 99
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.06)	1.01 (0.79 - 1.28)	0.90 (0.67 - 1.22)	1.01 (0.71 - 1.44)	0.88 (0.66 - 1.16)	1.11 (0.75 - 1.65)
Silicon carbide							
#cases / #controls	1323 / 4074	506 / 1220	88 / 181	56 / 139	40 / 63	61 / 140	35 / 62
Adjusted OR (95% CI)[5]	1.00 (ref)	1.05 (0.92 - 1.21)	1.00 (0.75 - 1.34)	0.85 (0.60 - 1.20)	1.17 (0.73 - 1.86)	0.91 (0.65 - 1.27)	1.04 (0.64 - 1.69)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	907 / 2770	875 / 2430	135 / 275	97 / 196	55 / 106	105 / 210	47 / 92
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.86 - 1.11)	0.95 (0.74 - 1.23)	0.92 (0.68 - 1.24)	0.83 (0.55 - 1.24)	0.89 (0.66 - 1.18)	0.89 (0.58 - 1.36)
Arc welding fumes							
#cases / #controls	884 / 2696	845 / 2406	188 / 373	142 / 272	66 / 140	154 / 288	54 / 124
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.84 - 1.08)	0.99 (0.79 - 1.25)	0.97 (0.75 - 1.27)	0.88 (0.62 - 1.27)	1.01 (0.78 - 1.30)	0.79 (0.54 - 1.17)
Soldering fumes							
#cases / #controls	1039 / 3105	750 / 2042	128 / 328	92 / 260	48 / 119	105 / 265	35 / 114
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.86 - 1.10)	0.83 (0.65 - 1.06)	0.76 (0.57 - 1.01)	0.90 (0.61 - 1.33)	0.81 (0.61 - 1.06)	0.79 (0.52 - 1.21)
Metallic dusts							
#cases / #controls	577 / 1745	1045 / 3057	295 / 673	214 / 455	117 / 279	239 / 513	92 / 221
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.07)	0.90 (0.74 - 1.10)	0.99 (0.79 - 1.25)	0.76 (0.56 - 1.03)	0.95 (0.76 - 1.19)	0.80 (0.58 - 1.11)
Metal oxide fumes							
#cases / #controls	779 / 2368	908 / 2582	230 / 525	176 / 404	82 / 192	186 / 417	72 / 179
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.84 - 1.09)	0.91 (0.74 - 1.12)	0.89 (0.70 - 1.12)	0.82 (0.59 - 1.15)	0.90 (0.71 - 1.13)	0.79 (0.56 - 1.11)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 25% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 25%. Subject with only exposure with probability < 25% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 25%. Subject with only exposure with probability < 25% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), proxy respondent status (self, proxy), and atopy (allergy, asthma and/or eczema) (never/ever).

Supplementary table III: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and meningioma using a probability threshold of 25%

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	572 / 1686	1028 / 2848	227 / 941	188 / 715	82 / 349	203 / 744	67 / 320
Adjusted OR (95% CI)[5]	1.00 (ref)	1.06 (0.93 - 1.21)	1.03 (0.84 - 1.27)	1.16 (0.92 - 1.47)	1.01 (0.72 - 1.42)	1.29 (1.02 - 1.64)	0.75 (0.53 - 1.06)
Lead fumes							
#cases / #controls	921 / 2779	806 / 2307	100 / 389	79 / 291	38 / 153	77 / 309	40 / 135
Adjusted OR (95% CI)[5]	1.00 (ref)	1.05 (0.92 - 1.19)	1.15 (0.88 - 1.49)	1.18 (0.87 - 1.60)	1.07 (0.70 - 1.65)	1.16 (0.85 - 1.58)	1.12 (0.74 - 1.69)
Leaded gasoline							
#cases / #controls	1024 / 2967	765 / 2296	38 / 212	45 / 192	6 / 55	38 / 172	13 / 75
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.07)	0.83 (0.57 - 1.22)	1.02 (0.70 - 1.50)	0.50 (0.21 - 1.23)	0.97 (0.64 - 1.46)	0.78 (0.41 - 1.48)
Chromium compounds							
#cases / #controls	1035 / 3044	720 / 2154	72 / 277	61 / 209	26 / 101	63 / 217	24 / 93
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.90 - 1.14)	1.13 (0.84 - 1.52)	1.24 (0.89 - 1.74)	1.23 (0.75 - 2.02)	1.27 (0.91 - 1.77)	1.16 (0.70 - 1.94)
Chromium fumes							
#cases / #controls	1481 / 4226	322 / 1167	24 / 82	18 / 67	13 / 25	17 / 64	14 / 28
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.86 - 1.18)	1.18 (0.72 - 1.94)	1.17 (0.67 - 2.06)	1.69 (0.81 - 3.52)	1.18 (0.66 - 2.09)	1.63 (0.80 - 3.34)
Chromium VI							
#cases / #controls	1466 / 4172	327 / 1197	34 / 106	30 / 79	13 / 44	30 / 86	13 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.03 (0.88 - 1.20)	1.20 (0.78 - 1.85)	1.39 (0.87 - 2.22)	1.17 (0.59 - 2.32)	1.34 (0.84 - 2.14)	1.26 (0.63 - 2.50)
Zinc compounds							
#cases / #controls	1192 / 3344	568 / 1910	67 / 221	54 / 159	29 / 89	57 / 173	26 / 75
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.83 - 1.08)	1.24 (0.91 - 1.71)	1.55 (1.08 - 2.22)	1.19 (0.73 - 1.92)	1.53 (1.07 - 2.18)	1.18 (0.71 - 1.95)
Iron compounds							
#cases / #controls	672 / 1908	1014 / 2985	141 / 582	101 / 378	59 / 255	107 / 443	53 / 190
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.85 - 1.09)	1.09 (0.86 - 1.38)	1.19 (0.89 - 1.59)	1.03 (0.71 - 1.49)	1.09 (0.81 - 1.45)	1.25 (0.84 - 1.84)

Agent	**Never exposed**[1]	**Ever exposure**[2]		**Duration of exposure**[3]		**Cumulative exposure**[4]	
		Uncertain	**Ever**	**< 15 years**	**≥ 15 years**	**Low**	**High**
Iron fumes							
#cases / #controls	1090 / 3081	675 / 2143	62 / 251	48 / 195	25 / 86	43 / 196	30 / 85
Adjusted OR (95% CI)[5]	1.00 (ref)	1.06 (0.93 - 1.19)	1.20 (0.87 - 1.66)	1.27 (0.87 - 1.86)	1.43 (0.85 - 2.41)	1.22 (0.82 - 1.80)	1.54 (0.94 - 2.51)
Nickel compounds							
#cases / #controls	1166 / 3440	603 / 1820	58 / 215	46 / 159	21 / 74	47 / 163	20 / 70
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.90 - 1.15)	1.21 (0.87 - 1.68)	1.30 (0.89 - 1.90)	1.32 (0.76 - 2.29)	1.31 (0.91 - 1.90)	1.28 (0.73 - 2.27)
Nickel fumes							
#cases / #controls	1500 / 4303	303 / 1095	24 / 77	18 / 64	13 / 23	17 / 60	14 / 27
Adjusted OR (95% CI)[5]	1.00 (ref)	1.04 (0.88 - 1.21)	1.27 (0.77 - 2.10)	1.29 (0.73 - 2.28)	1.96 (0.93 - 4.14)	1.32 (0.74 - 2.37)	1.81 (0.89 - 3.72)
Calcium carbonate							
#cases / #controls	983 / 2914	690 / 2070	154 / 491	94 / 310	72 / 234	124 / 380	42 / 164
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.88 - 1.12)	0.99 (0.80 - 1.23)	0.97 (0.74 - 1.27)	0.92 (0.68 - 1.25)	0.95 (0.74 - 1.21)	0.94 (0.64 - 1.39)
Calcium oxide							
#cases / #controls	1220 / 3767	589 / 1626	18 / 82	19 / 58	3 / 36	15 / 65	7 / 29
Adjusted OR (95% CI)[5]	1.00 (ref)	1.10 (0.96 - 1.25)	0.89 (0.51 - 1.55)	1.35 (0.74 - 2.44)	0.36 (0.11 - 1.21)	0.86 (0.46 - 1.61)	1.18 (0.48 - 2.89)
Calcium oxide fumes							
#cases / #controls	1383 / 4074	425 / 1336	19 / 65	15 / 60	11 / 14	16 / 51	10 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.87 - 1.14)	1.08 (0.62 - 1.90)	1.03 (0.56 - 1.90)	2.39 (1.00 - 5.71)	1.43 (0.78 - 2.64)	1.16 (0.51 - 2.63)
Calcium sulphate							
#cases / #controls	1086 / 3147	677 / 2037	64 / 291	37 / 197	34 / 131	44 / 229	27 / 99
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.89 - 1.14)	0.98 (0.72 - 1.35)	1.05 (0.70 - 1.58)	1.25 (0.80 - 1.94)	1.06 (0.73 - 1.56)	1.28 (0.78 - 2.09)
Silicon carbide							
#cases / #controls	1376 / 4074	404 / 1220	47 / 181	37 / 139	19 / 63	43 / 140	13 / 62
Adjusted OR (95% CI)[5]	1.00 (ref)	1.10 (0.95 - 1.27)	1.27 (0.89 - 1.83)	1.20 (0.80 - 1.80)	1.41 (0.79 - 2.52)	1.40 (0.95 - 2.07)	0.92 (0.48 - 1.79)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	985 / 2770	776 / 2430	66 / 275	56 / 196	24 / 106	50 / 210	30 / 92
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.89 - 1.14)	1.15 (0.84 - 1.58)	1.40 (0.97 - 2.01)	1.06 (0.63 - 1.77)	1.28 (0.89 - 1.86)	1.28 (0.78 - 2.09)
Arc welding fumes							
#cases / #controls	959 / 2696	780 / 2406	88 / 373	70 / 272	33 / 140	63 / 288	40 / 124
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.89 - 1.14)	1.17 (0.89 - 1.55)	1.25 (0.90 - 1.74)	1.09 (0.69 - 1.72)	1.13 (0.81 - 1.59)	1.35 (0.88 - 2.09)
Soldering fumes							
#cases / #controls	1053 / 3105	693 / 2042	81 / 328	61 / 260	34 / 119	60 / 265	35 / 114
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.87 - 1.12)	0.94 (0.71 - 1.24)	1.01 (0.74 - 1.39)	1.10 (0.71 - 1.69)	1.05 (0.76 - 1.46)	1.02 (0.67 - 1.55)
Metallic dusts							
#cases / #controls	600 / 1745	1058 / 3057	169 / 673	137 / 455	57 / 279	140 / 513	54 / 221
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.86 - 1.11)	1.03 (0.83 - 1.29)	1.16 (0.89 - 1.52)	0.87 (0.60 - 1.25)	1.04 (0.80 - 1.35)	1.19 (0.81 - 1.75)
Metal oxide fumes							
#cases / #controls	811 / 2368	881 / 2582	135 / 525	111 / 404	45 / 192	110 / 417	46 / 179
Adjusted OR (95% CI)[5]	1.00 (ref)	1.11 (0.98 - 1.25)	1.17 (0.92 - 1.48)	1.25 (0.95 - 1.63)	1.07 (0.72 - 1.60)	1.22 (0.93 - 1.61)	1.13 (0.76 - 1.67)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 25% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 25%. Subject with only exposure with probability < 25% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 25%. Subject with only exposure with probability < 25% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), and proxy respondent status (self, proxy).

Supplementary table IV: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and glioma with a 10-year lag period using a probability threshold of 50%

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	622 / 1932	1118 / 3116	177 / 427	149 / 399	56 / 120	105 / 272	72 / 155
Adjusted OR (95% CI)[5]	1.00 (ref)	1.04 (0.90 - 1.19)	0.88 (0.69 - 1.12)	0.79 (0.60 - 1.04)	1.08 (0.70 - 1.67)	0.76 (0.56 - 1.05)	1.02 (0.68 - 1.52)
Lead fumes							
#cases / #controls	990 / 2993	911 / 2410	16 / 72	16 / 54	4 / 32	9 / 46	7 / 26
Adjusted OR (95% CI)[5]	1.00 (ref)	0.93 (0.82 - 1.06)	0.52 (0.29 - 0.95)	0.74 (0.40 - 1.35)	0.30 (0.09 - 1.01)	0.44 (0.20 - 0.95)	0.82 (0.32 - 2.12)
Leaded gasoline							
#cases / #controls	1023 / 3114	843 / 2256	51 / 105	41 / 104	18 / 22	37 / 67	14 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	0.90 (0.78 - 1.02)	0.91 (0.61 - 1.35)	0.82 (0.53 - 1.25)	1.74 (0.81 - 3.74)	1.03 (0.64 - 1.67)	0.86 (0.42 - 1.79)
Chromium compounds							
#cases / #controls	1096 / 3212	766 / 2172	55 / 91	60 / 97	3 / 12	41 / 60	14 / 31
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.84 - 1.08)	1.05 (0.71 - 1.55)	1.05 (0.71 - 1.55)	0.43 (0.09 - 1.97)	1.04 (0.64 - 1.69)	0.91 (0.45 - 1.83)
Chromium fumes							
#cases / #controls	1476 / 4354	424 / 1090	17 / 31	11 / 30	7 / 7	8 / 19	9 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	0.89 (0.77 - 1.04)	1.00 (0.53 - 1.88)	0.65 (0.31 - 1.37)	1.46 (0.48 - 4.47)	0.81 (0.34 - 1.93)	1.18 (0.45 - 3.09)
Chromium VI							
#cases / #controls	1436 / 4267	456 / 1171	25 / 37	26 / 37	2 / 7	20 / 21	5 / 16
Adjusted OR (95% CI)[5]	1.00 (ref)	0.88 (0.76 - 1.02)	1.07 (0.59 - 1.92)	1.15 (0.64 - 2.09)	0.56 (0.11 - 2.76)	1.45 (0.71 - 2.98)	0.53 (0.17 - 1.62)
Zinc compounds							
#cases / #controls	1163 / 3535	731 / 1868	23 / 72	21 / 48	9 / 33	15 / 47	8 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.07)	0.71 (0.42 - 1.20)	0.94 (0.53 - 1.65)	0.61 (0.26 - 1.42)	0.73 (0.38 - 1.39)	0.70 (0.28 - 1.73)
Iron compounds							
#cases / #controls	747 / 2200	1001 / 2909	169 / 366	137 / 284	52 / 125	99 / 243	70 / 123
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.82 - 1.07)	0.83 (0.66 - 1.06)	0.93 (0.71 - 1.22)	0.72 (0.47 - 1.10)	0.75 (0.55 - 1.02)	1.06 (0.73 - 1.55)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	1125 / 3281	762 / 2131	30 / 63	27 / 61	9 / 13	18 / 40	12 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	0.93 (0.82 - 1.05)	0.89 (0.55 - 1.46)	0.80 (0.48 - 1.34)	1.06 (0.40 - 2.79)	0.87 (0.47 - 1.62)	0.80 (0.35 - 1.83)
Nickel compounds							
#cases / #controls	1227 / 3608	645 / 1777	45 / 90	33 / 84	13 / 27	26 / 56	19 / 34
Adjusted OR (95% CI)[5]	1.00 (ref)	0.96 (0.85 - 1.10)	0.98 (0.65 - 1.47)	0.76 (0.49 - 1.20)	0.81 (0.36 - 1.83)	0.87 (0.52 - 1.48)	1.15 (0.61 - 2.18)
Nickel fumes							
#cases / #controls	1500 / 4430	400 / 1014	17 / 31	11 / 30	7 / 7	8 / 19	9 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	0.92 (0.79 - 1.07)	1.01 (0.53 - 1.91)	0.66 (0.31 - 1.38)	1.55 (0.51 - 4.74)	0.80 (0.34 - 1.89)	1.26 (0.48 - 3.30)
Calcium carbonate							
#cases / #controls	1117 / 3215	709 / 2001	91 / 259	75 / 193	30 / 98	54 / 171	37 / 88
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.87 - 1.12)	1.22 (0.92 - 1.63)	1.25 (0.91 - 1.72)	1.12 (0.67 - 1.87)	1.24 (0.86 - 1.79)	1.18 (0.75 - 1.88)
Calcium oxide							
#cases / #controls	1401 / 3986	490 / 1432	26 / 57	19 / 37	10 / 25	18 / 38	8 / 19
Adjusted OR (95% CI)[5]	1.00 (ref)	0.84 (0.73 - 0.96)	0.93 (0.56 - 1.56)	1.01 (0.55 - 1.86)	0.81 (0.36 - 1.83)	0.86 (0.46 - 1.62)	1.06 (0.43 - 2.60)
Calcium oxide fumes							
#cases / #controls	1436 / 4097	458 / 1334	23 / 44	19 / 41	8 / 9	13 / 29	10 / 15
Adjusted OR (95% CI)[5]	1.00 (ref)	0.91 (0.79 - 1.05)	0.97 (0.55 - 1.69)	0.89 (0.49 - 1.62)	1.33 (0.46 - 3.86)	0.93 (0.46 - 1.87)	0.98 (0.39 - 2.49)
Calcium sulphate							
#cases / #controls	1170 / 3385	663 / 1941	84 / 149	68 / 121	26 / 51	51 / 99	33 / 50
Adjusted OR (95% CI)[5]	1.00 (ref)	0.92 (0.81 - 1.04)	1.04 (0.76 - 1.42)	1.07 (0.75 - 1.52)	0.77 (0.44 - 1.35)	1.04 (0.70 - 1.53)	0.96 (0.57 - 1.63)
Silicon carbide							
#cases / #controls	1397 / 4197	480 / 1209	40 / 69	36 / 68	7 / 14	25 / 44	15 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.85 - 1.13)	1.09 (0.70 - 1.69)	1.03 (0.65 - 1.61)	0.55 (0.16 - 1.90)	1.22 (0.71 - 2.08)	0.86 (0.40 - 1.85)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	1009 / 2965	831 / 2366	77 / 144	68 / 134	19 / 36	52 / 94	25 / 50
Adjusted OR (95% CI)[5]	1.00 (ref)	0.92 (0.81 - 1.04)	0.98 (0.71 - 1.35)	0.83 (0.59 - 1.18)	0.86 (0.44 - 1.67)	0.82 (0.54 - 1.24)	0.95 (0.55 - 1.65)
Arc welding fumes							
#cases / #controls	982 / 2875	889 / 2497	46 / 103	44 / 89	14 / 27	28 / 68	18 / 35
Adjusted OR (95% CI)[5]	1.00 (ref)	0.90 (0.79 - 1.02)	0.80 (0.54 - 1.18)	0.84 (0.55 - 1.29)	0.65 (0.31 - 1.38)	0.72 (0.44 - 1.19)	0.78 (0.40 - 1.52)
Soldering fumes							
#cases / #controls	1123 / 3290	757 / 2071	37 / 114	31 / 96	11 / 37	25 / 73	12 / 41
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.83 - 1.07)	0.70 (0.46 - 1.07)	0.66 (0.42 - 1.04)	0.67 (0.32 - 1.43)	0.67 (0.40 - 1.13)	0.74 (0.36 - 1.51)
Metallic dusts							
#cases / #controls	709 / 2073	1004 / 2950	204 / 452	161 / 342	62 / 160	137 / 301	67 / 151
Adjusted OR (95% CI)[5]	1.00 (ref)	0.91 (0.80 - 1.04)	0.88 (0.70 - 1.09)	0.95 (0.74 - 1.22)	0.66 (0.45 - 0.97)	0.88 (0.67 - 1.15)	0.85 (0.59 - 1.23)
Metal oxide fumes							
#cases / #controls	896 / 2616	942 / 2660	79 / 199	79 / 167	21 / 62	42 / 128	37 / 71
Adjusted OR (95% CI)[5]	1.00 (ref)	0.92 (0.81 - 1.04)	0.78 (0.57 - 1.06)	0.89 (0.64 - 1.23)	0.53 (0.29 - 0.97)	0.62 (0.41 - 0.94)	0.97 (0.61 - 1.55)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), proxy respondent status (self, proxy), and atopy (allergy, asthma and/or eczema) (never/ever).

Supplementary table V: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and meningioma with a 10-year lag period using a probability threshold of 50%

Agent	**Never exposed**[1]	**Ever exposure**[2]		**Duration of exposure**[3]		**Cumulative exposure**[4]	
		Uncertain	**Ever**	**< 15 years**	**≥ 15 years**	**Low**	**High**
Lead compounds							
#cases / #controls	639 / 1932	1088 / 3116	100 / 427	95 / 399	27 / 120	60 / 272	40 / 155
Adjusted OR (95% CI)[5]	1.00 (ref)	1.07 (0.94 - 1.21)	0.92 (0.70 - 1.21)	1.13 (0.83 - 1.54)	0.79 (0.46 - 1.36)	1.17 (0.80 - 1.70)	0.91 (0.58 - 1.43)
Lead fumes							
#cases / #controls	979 / 2993	819 / 2410	29 / 72	28 / 54	7 / 32	16 / 46	13 / 26
Adjusted OR (95% CI)[5]	1.00 (ref)	1.05 (0.92 - 1.19)	1.42 (0.88 - 2.30)	1.93 (1.15 - 3.25)	0.77 (0.30 - 1.94)	1.59 (0.83 - 3.06)	1.47 (0.69 - 3.12)
Leaded gasoline							
#cases / #controls	1074 / 3114	736 / 2256	17 / 105	26 / 104	1 / 22	11 / 67	6 / 38
Adjusted OR (95% CI)[5]	1.00 (ref)	0.91 (0.80 - 1.04)	0.72 (0.42 - 1.25)	1.23 (0.75 - 2.03)	0.17 (0.02 - 1.29)	0.92 (0.45 - 1.85)	0.63 (0.24 - 1.62)
Chromium compounds							
#cases / #controls	1076 / 3212	722 / 2172	29 / 91	33 / 97	3 / 12	17 / 60	12 / 31
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.13)	1.47 (0.92 - 2.34)	1.53 (0.97 - 2.42)	1.04 (0.28 - 3.91)	1.51 (0.82 - 2.77)	1.45 (0.69 - 3.05)
Chromium fumes							
#cases / #controls	1507 / 4354	306 / 1090	14 / 31	12 / 30	6 / 7	7 / 19	7 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.87 - 1.20)	1.79 (0.89 - 3.60)	1.78 (0.87 - 3.64)	2.14 (0.64 - 7.12)	1.69 (0.66 - 4.29)	1.61 (0.58 - 4.49)
Chromium VI							
#cases / #controls	1479 / 4267	337 / 1171	11 / 37	17 / 37	1 / 7	9 / 21	2 / 16
Adjusted OR (95% CI)[5]	1.00 (ref)	1.08 (0.92 - 1.26)	1.38 (0.66 - 2.88)	2.25 (1.19 - 4.26)	0.42 (0.05 - 3.53)	1.94 (0.81 - 4.63)	0.62 (0.14 - 2.82)
Zinc compounds							
#cases / #controls	1239 / 3535	562 / 1868	26 / 72	24 / 48	6 / 33	16 / 47	10 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.83 - 1.08)	1.35 (0.82 - 2.22)	2.41 (1.36 - 4.25)	0.57 (0.22 - 1.48)	1.68 (0.88 - 3.19)	1.09 (0.50 - 2.41)
Iron compounds							
#cases / #controls	755 / 2200	973 / 2909	99 / 366	83 / 284	31 / 125	56 / 243	43 / 123
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.83 - 1.07)	1.23 (0.94 - 1.62)	1.33 (0.96 - 1.84)	1.05 (0.64 - 1.70)	1.12 (0.77 - 1.63)	1.47 (0.95 - 2.28)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	1136 / 3281	670 / 2131	21 / 63	18 / 61	10 / 13	10 / 40	11 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	1.06 (0.93 - 1.20)	1.34 (0.78 - 2.31)	1.24 (0.70 - 2.20)	2.19 (0.85 - 5.67)	1.03 (0.49 - 2.19)	1.56 (0.69 - 3.51)
Nickel compounds							
#cases / #controls	1209 / 3608	591 / 1777	27 / 90	21 / 84	12 / 27	13 / 56	14 / 34
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.14)	1.32 (0.82 - 2.12)	1.15 (0.68 - 1.94)	1.73 (0.80 - 3.72)	1.27 (0.65 - 2.46)	1.46 (0.73 - 2.93)
Nickel fumes							
#cases / #controls	1525 / 4430	288 / 1014	14 / 31	12 / 30	6 / 7	7 / 19	7 / 12
Adjusted OR (95% CI)[5]	1.00 (ref)	1.06 (0.90 - 1.25)	1.82 (0.90 - 3.64)	1.92 (0.94 - 3.94)	2.37 (0.70 - 7.95)	1.77 (0.70 - 4.51)	1.71 (0.61 - 4.77)
Calcium carbonate							
#cases / #controls	1052 / 3215	676 / 2001	99 / 259	70 / 193	35 / 98	74 / 171	25 / 88
Adjusted OR (95% CI)[5]	1.00 (ref)	1.03 (0.91 - 1.17)	1.05 (0.81 - 1.38)	1.07 (0.78 - 1.47)	0.77 (0.50 - 1.20)	1.03 (0.74 - 1.41)	0.89 (0.54 - 1.48)
Calcium oxide							
#cases / #controls	1294 / 3986	524 / 1432	9 / 57	7 / 37	2 / 25	5 / 38	4 / 19
Adjusted OR (95% CI)[5]	1.00 (ref)	1.08 (0.95 - 1.24)	0.84 (0.40 - 1.75)	1.48 (0.62 - 3.54)	0.35 (0.08 - 1.51)	0.87 (0.33 - 2.35)	1.00 (0.33 - 3.04)
Calcium oxide fumes							
#cases / #controls	1388 / 4097	423 / 1334	16 / 44	12 / 41	9 / 9	7 / 29	9 / 15
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.87 - 1.14)	1.18 (0.63 - 2.20)	1.10 (0.55 - 2.20)	2.50 (0.91 - 6.84)	0.95 (0.40 - 2.28)	1.43 (0.58 - 3.55)
Calcium sulphate							
#cases / #controls	1149 / 3385	643 / 1941	35 / 149	27 / 121	13 / 51	21 / 99	14 / 50
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.88 - 1.13)	1.05 (0.69 - 1.59)	1.12 (0.69 - 1.81)	1.08 (0.55 - 2.11)	1.04 (0.61 - 1.77)	1.22 (0.62 - 2.39)
Silicon carbide							
#cases / #controls	1402 / 4197	404 / 1209	21 / 69	19 / 68	5 / 14	14 / 44	7 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	1.11 (0.96 - 1.28)	1.42 (0.83 - 2.43)	1.09 (0.62 - 1.92)	1.71 (0.56 - 5.19)	1.21 (0.63 - 2.35)	1.40 (0.56 - 3.49)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	1030 / 2965	766 / 2366	31 / 144	33 / 134	11 / 36	14 / 94	17 / 50
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.89 - 1.14)	0.92 (0.60 - 1.41)	1.26 (0.81 - 1.95)	0.90 (0.42 - 1.94)	0.85 (0.46 - 1.59)	1.11 (0.59 - 2.08)
Arc welding fumes							
#cases / #controls	997 / 2875	800 / 2497	30 / 103	24 / 89	13 / 27	18 / 68	12 / 35
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.90 - 1.15)	1.31 (0.83 - 2.06)	1.33 (0.79 - 2.23)	1.45 (0.66 - 3.16)	1.37 (0.75 - 2.49)	0.98 (0.46 - 2.08)
Soldering fumes							
#cases / #controls	1100 / 3290	687 / 2071	40 / 114	41 / 96	9 / 37	22 / 73	18 / 41
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.86 - 1.11)	1.29 (0.86 - 1.93)	1.90 (1.24 - 2.92)	0.80 (0.36 - 1.78)	1.49 (0.86 - 2.58)	1.19 (0.65 - 2.18)
Metallic dusts							
#cases / #controls	689 / 2073	1026 / 2950	112 / 452	95 / 342	34 / 160	64 / 301	48 / 151
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.86 - 1.11)	1.13 (0.87 - 1.46)	1.29 (0.95 - 1.75)	0.93 (0.59 - 1.47)	1.02 (0.72 - 1.44)	1.53 (1.00 - 2.33)
Metal oxide fumes							
#cases / #controls	878 / 2616	886 / 2660	63 / 199	57 / 167	21 / 62	39 / 128	24 / 71
Adjusted OR (95% CI)[5]	1.00 (ref)	1.08 (0.96 - 1.22)	1.45 (1.04 - 2.02)	1.67 (1.16 - 2.41)	1.25 (0.69 - 2.24)	1.56 (1.01 - 2.41)	1.38 (0.80 - 2.36)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), and proxy respondent status (self, proxy).

Supplementary table VI: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and glioma in men using a probability threshold of 50%

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	240 / 533	770 / 1540	177 / 391	144 / 350	59 / 126	137 / 332	66 / 144
Adjusted OR (95% CI)[5]	1.00 (ref)	1.13 (0.92 - 1.38)	0.95 (0.72 - 1.25)	0.87 (0.64 - 1.20)	1.08 (0.69 - 1.69)	0.87 (0.63 - 1.19)	1.09 (0.70 - 1.67)
Lead fumes							
#cases / #controls	437 / 943	733 / 1459	17 / 62	17 / 41	4 / 35	17 / 53	4 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.84 - 1.19)	0.52 (0.28 - 0.94)	0.89 (0.47 - 1.69)	0.28 (0.08 - 0.95)	0.75 (0.40 - 1.40)	0.37 (0.11 - 1.33)
Leaded gasoline							
#cases / #controls	470 / 1032	669 / 1336	48 / 96	36 / 89	18 / 21	38 / 77	16 / 33
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.86 - 1.21)	0.94 (0.62 - 1.43)	0.77 (0.48 - 1.23)	1.76 (0.81 - 3.85)	0.93 (0.58 - 1.49)	0.93 (0.45 - 1.92)
Chromium compounds							
#cases / #controls	560 / 1148	564 / 1214	63 / 102	46 / 77	24 / 36	51 / 80	19 / 33
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.82 - 1.13)	1.06 (0.73 - 1.54)	0.98 (0.64 - 1.51)	0.98 (0.52 - 1.85)	1.05 (0.68 - 1.60)	0.83 (0.43 - 1.62)
Chromium fumes							
#cases / #controls	743 / 1524	426 / 909	18 / 31	12 / 25	9 / 11	11 / 25	10 / 11
Adjusted OR (95% CI)[5]	1.00 (ref)	0.99 (0.84 - 1.16)	1.05 (0.56 - 1.96)	0.80 (0.39 - 1.64)	1.32 (0.49 - 3.53)	0.74 (0.35 - 1.56)	1.45 (0.56 - 3.75)
Chromium VI							
#cases / #controls	732 / 1456	428 / 967	27 / 41	22 / 29	7 / 17	22 / 30	7 / 16
Adjusted OR (95% CI)[5]	1.00 (ref)	0.88 (0.74 - 1.03)	1.05 (0.60 - 1.85)	1.41 (0.74 - 2.68)	0.39 (0.13 - 1.19)	1.18 (0.62 - 2.24)	0.61 (0.22 - 1.74)
Zinc compounds							
#cases / #controls	547 / 1136	618 / 1260	22 / 68	19 / 40	9 / 36	25 / 53	3 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.81 - 1.12)	0.65 (0.38 - 1.10)	0.90 (0.49 - 1.63)	0.45 (0.18 - 1.12)	0.88 (0.51 - 1.52)	0.24 (0.06 - 1.04)
Iron compounds							
#cases / #controls	312 / 689	693 / 1398	182 / 377	125 / 254	74 / 151	137 / 284	62 / 121
Adjusted OR (95% CI)[5]	1.00 (ref)	1.09 (0.91 - 1.31)	0.94 (0.73 - 1.22)	0.95 (0.70 - 1.29)	0.93 (0.63 - 1.36)	0.92 (0.69 - 1.24)	0.99 (0.66 - 1.48)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	524 / 1087	628 / 1309	35 / 68	29 / 54	14 / 21	31 / 52	12 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.87 - 1.20)	0.97 (0.61 - 1.55)	0.96 (0.57 - 1.62)	1.11 (0.51 - 2.44)	1.09 (0.66 - 1.82)	0.78 (0.34 - 1.82)
Nickel compounds							
#cases / #controls	627 / 1308	513 / 1066	47 / 90	27 / 73	23 / 32	26 / 73	24 / 32
Adjusted OR (95% CI)[5]	1.00 (ref)	1.02 (0.87 - 1.19)	0.98 (0.65 - 1.46)	0.64 (0.39 - 1.04)	1.32 (0.70 - 2.50)	0.64 (0.39 - 1.05)	1.26 (0.68 - 2.34)
Nickel fumes							
#cases / #controls	763 / 1578	406 / 855	18 / 31	12 / 25	9 / 11	11 / 25	10 / 11
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.86 - 1.19)	1.06 (0.57 - 1.98)	0.79 (0.39 - 1.63)	1.39 (0.52 - 3.71)	0.74 (0.35 - 1.55)	1.53 (0.59 - 3.94)
Calcium carbonate							
#cases / #controls	559 / 1199	559 / 1156	69 / 109	41 / 74	32 / 49	45 / 86	28 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.06 (0.90 - 1.24)	1.44 (1.00 - 2.06)	1.31 (0.84 - 2.06)	1.40 (0.82 - 2.40)	1.21 (0.78 - 1.87)	1.64 (0.93 - 2.90)
Calcium oxide							
#cases / #controls	766 / 1564	398 / 843	23 / 57	15 / 33	11 / 28	16 / 41	10 / 20
Adjusted OR (95% CI)[5]	1.00 (ref)	0.89 (0.75 - 1.05)	0.82 (0.48 - 1.40)	0.91 (0.47 - 1.77)	0.75 (0.34 - 1.65)	0.70 (0.37 - 1.32)	1.20 (0.52 - 2.74)
Calcium oxide fumes							
#cases / #controls	822 / 1670	341 / 750	24 / 44	19 / 36	11 / 13	18 / 34	12 / 15
Adjusted OR (95% CI)[5]	1.00 (ref)	0.91 (0.76 - 1.08)	0.96 (0.55 - 1.67)	1.00 (0.55 - 1.81)	1.27 (0.51 - 3.16)	1.01 (0.55 - 1.84)	1.22 (0.49 - 2.99)
Calcium sulphate							
#cases / #controls	589 / 1198	505 / 1104	93 / 162	58 / 115	41 / 65	62 / 126	37 / 54
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.80 - 1.10)	1.01 (0.74 - 1.37)	0.91 (0.62 - 1.33)	1.07 (0.68 - 1.70)	0.89 (0.62 - 1.28)	1.16 (0.70 - 1.92)
Silicon carbide							
#cases / #controls	708 / 1531	433 / 858	46 / 75	28 / 58	21 / 24	30 / 57	19 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	1.04 (0.89 - 1.23)	1.13 (0.75 - 1.72)	0.86 (0.52 - 1.42)	1.37 (0.70 - 2.70)	0.89 (0.54 - 1.46)	1.30 (0.64 - 2.64)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	458 / 944	645 / 1374	84 / 146	67 / 124	26 / 46	65 / 119	28 / 51
Adjusted OR (95% CI)[5]	1.00 (ref)	0.94 (0.80 - 1.11)	1.05 (0.76 - 1.46)	0.88 (0.61 - 1.27)	0.98 (0.55 - 1.75)	0.85 (0.58 - 1.24)	1.05 (0.62 - 1.78)
Arc welding fumes							
#cases / #controls	434 / 898	700 / 1455	53 / 111	44 / 84	22 / 37	46 / 84	20 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.82 - 1.15)	0.89 (0.60 - 1.30)	0.93 (0.60 - 1.43)	0.90 (0.48 - 1.68)	0.95 (0.62 - 1.46)	0.84 (0.44 - 1.60)
Soldering fumes							
#cases / #controls	595 / 1280	555 / 1080	37 / 104	32 / 74	9 / 44	33 / 81	8 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.85 - 1.17)	0.72 (0.47 - 1.10)	0.86 (0.53 - 1.38)	0.42 (0.19 - 0.96)	0.82 (0.51 - 1.30)	0.43 (0.18 - 1.05)
Metallic dusts							
#cases / #controls	305 / 652	671 / 1365	211 / 447	142 / 291	89 / 188	165 / 335	66 / 144
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.84 - 1.21)	0.92 (0.72 - 1.18)	0.95 (0.71 - 1.27)	0.83 (0.59 - 1.18)	0.93 (0.70 - 1.22)	0.85 (0.58 - 1.25)
Metal oxide fumes							
#cases / #controls	386 / 805	714 / 1458	87 / 201	77 / 142	31 / 82	74 / 156	34 / 68
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.85 - 1.19)	0.84 (0.61 - 1.15)	0.99 (0.70 - 1.41)	0.67 (0.40 - 1.11)	0.89 (0.62 - 1.26)	0.87 (0.53 - 1.45)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), proxy respondent status (self, proxy), and atopy (allergy, asthma and/or eczema) (never/ever).

Supplementary table VII: Odds ratio estimates for the association between occupational exposure to the 21 selected agents and meningioma in men using a probability threshold of 50%

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Lead compounds							
#cases / #controls	83 / 533	344 / 1540	69 / 391	60 / 350	24 / 126	60 / 332	24 / 144
Adjusted OR (95% CI)[5]	1.00 (ref)	1.19 (0.89 - 1.59)	0.89 (0.60 - 1.30)	1.14 (0.73 - 1.78)	0.91 (0.48 - 1.70)	1.21 (0.77 - 1.89)	0.80 (0.43 - 1.48)
Lead fumes							
#cases / #controls	168 / 943	311 / 1459	17 / 62	12 / 41	8 / 35	14 / 53	6 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.77 - 1.23)	1.36 (0.74 - 2.50)	1.98 (0.94 - 4.16)	1.15 (0.46 - 2.88)	1.71 (0.84 - 3.49)	1.35 (0.49 - 3.71)
Leaded gasoline							
#cases / #controls	188 / 1032	295 / 1336	13 / 96	18 / 89	1 / 21	17 / 77	2 / 33
Adjusted OR (95% CI)[5]	1.00 (ref)	0.98 (0.78 - 1.24)	0.66 (0.35 - 1.24)	1.19 (0.65 - 2.18)	0.20 (0.03 - 1.59)	1.23 (0.66 - 2.29)	0.32 (0.07 - 1.46)
Chromium compounds							
#cases / #controls	210 / 1148	259 / 1214	27 / 102	22 / 77	10 / 36	22 / 80	10 / 33
Adjusted OR (95% CI)[5]	1.00 (ref)	1.05 (0.85 - 1.31)	1.45 (0.88 - 2.37)	1.55 (0.88 - 2.74)	1.69 (0.78 - 3.68)	1.63 (0.93 - 2.85)	1.52 (0.68 - 3.39)
Chromium fumes							
#cases / #controls	305 / 1524	177 / 909	14 / 31	10 / 25	8 / 11	10 / 25	8 / 11
Adjusted OR (95% CI)[5]	1.00 (ref)	0.91 (0.73 - 1.13)	1.76 (0.87 - 3.58)	1.79 (0.80 - 3.99)	2.59 (0.94 - 7.12)	1.79 (0.80 - 3.99)	2.59 (0.94 - 7.12)
Chromium VI							
#cases / #controls	291 / 1456	197 / 967	8 / 41	12 / 29	3 / 17	13 / 30	2 / 16
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.78 - 1.20)	0.94 (0.41 - 2.17)	2.05 (0.95 - 4.39)	1.04 (0.28 - 3.83)	2.12 (1.01 - 4.41)	0.77 (0.17 - 3.59)
Zinc compounds							
#cases / #controls	216 / 1136	261 / 1260	19 / 68	16 / 40	8 / 36	19 / 53	5 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.80 - 1.25)	1.32 (0.75 - 2.34)	2.58 (1.32 - 5.04)	0.91 (0.38 - 2.17)	2.06 (1.12 - 3.80)	0.96 (0.33 - 2.75)
Iron compounds							
#cases / #controls	122 / 689	289 / 1398	85 / 377	59 / 254	37 / 151	58 / 284	38 / 121
Adjusted OR (95% CI)[5]	1.00 (ref)	0.93 (0.72 - 1.21)	1.06 (0.76 - 1.50)	1.10 (0.73 - 1.64)	1.07 (0.65 - 1.75)	0.95 (0.63 - 1.43)	1.42 (0.86 - 2.34)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Iron fumes							
#cases / #controls	209 / 1087	267 / 1309	20 / 68	14 / 54	12 / 21	16 / 52	10 / 23
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.81 - 1.26)	1.19 (0.67 - 2.11)	1.14 (0.59 - 2.20)	2.17 (0.95 - 4.96)	1.38 (0.73 - 2.61)	1.55 (0.64 - 3.72)
Nickel compounds							
#cases / #controls	245 / 1308	225 / 1066	26 / 90	14 / 73	16 / 32	12 / 73	18 / 32
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.80 - 1.24)	1.46 (0.89 - 2.42)	1.05 (0.55 - 2.00)	2.61 (1.29 - 5.29)	1.00 (0.50 - 1.98)	2.52 (1.27 - 4.98)
Nickel fumes							
#cases / #controls	306 / 1578	176 / 855	14 / 31	10 / 25	8 / 11	10 / 25	8 / 11
Adjusted OR (95% CI)[5]	1.00 (ref)	1.00 (0.80 - 1.25)	1.84 (0.90 - 3.73)	1.98 (0.88 - 4.43)	2.79 (1.01 - 7.69)	1.98 (0.88 - 4.43)	2.79 (1.01 - 7.69)
Calcium carbonate							
#cases / #controls	212 / 1199	254 / 1156	30 / 109	18 / 74	13 / 49	19 / 86	12 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.15 (0.92 - 1.43)	1.27 (0.78 - 2.06)	1.19 (0.62 - 2.27)	1.30 (0.63 - 2.69)	1.14 (0.62 - 2.09)	1.45 (0.64 - 3.25)
Calcium oxide							
#cases / #controls	285 / 1564	200 / 843	11 / 57	8 / 33	3 / 28	7 / 41	4 / 20
Adjusted OR (95% CI)[5]	1.00 (ref)	1.23 (0.98 - 1.53)	1.02 (0.50 - 2.06)	1.76 (0.72 - 4.33)	0.57 (0.17 - 1.97)	1.07 (0.43 - 2.63)	1.17 (0.38 - 3.63)
Calcium oxide fumes							
#cases / #controls	329 / 1670	151 / 750	16 / 44	10 / 36	10 / 13	11 / 34	9 / 15
Adjusted OR (95% CI)[5]	1.00 (ref)	0.88 (0.70 - 1.11)	1.15 (0.61 - 2.17)	1.01 (0.47 - 2.15)	2.51 (1.00 - 6.33)	1.40 (0.66 - 2.95)	1.43 (0.56 - 3.61)
Calcium sulphate							
#cases / #controls	213 / 1198	247 / 1104	36 / 162	23 / 115	17 / 65	21 / 126	19 / 54
Adjusted OR (95% CI)[5]	1.00 (ref)	1.15 (0.93 - 1.44)	1.06 (0.69 - 1.63)	0.99 (0.58 - 1.71)	1.31 (0.72 - 2.38)	0.85 (0.49 - 1.47)	1.69 (0.91 - 3.12)
Silicon carbide							
#cases / #controls	292 / 1531	183 / 858	21 / 75	13 / 58	9 / 24	14 / 57	8 / 25
Adjusted OR (95% CI)[5]	1.00 (ref)	1.04 (0.83 - 1.30)	1.51 (0.87 - 2.63)	1.01 (0.51 - 2.00)	1.94 (0.82 - 4.55)	1.07 (0.55 - 2.09)	1.81 (0.74 - 4.44)

Agent	Never exposed[1]	Ever exposure[2]		Duration of exposure[3]		Cumulative exposure[4]	
		Uncertain	Ever	< 15 years	≥ 15 years	Low	High
Gas welding fumes							
#cases / #controls	174 / 944	291 / 1374	31 / 146	29 / 124	13 / 46	22 / 119	20 / 51
Adjusted OR (95% CI)[5]	1.00 (ref)	0.97 (0.77 - 1.22)	0.90 (0.57 - 1.42)	1.30 (0.80 - 2.11)	1.07 (0.51 - 2.21)	1.10 (0.65 - 1.87)	1.45 (0.78 - 2.72)
Arc welding fumes							
#cases / #controls	167 / 898	301 / 1455	28 / 111	19 / 84	15 / 37	19 / 84	15 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	0.95 (0.75 - 1.20)	1.08 (0.66 - 1.76)	1.12 (0.63 - 2.00)	1.64 (0.77 - 3.48)	1.31 (0.74 - 2.34)	1.21 (0.58 - 2.54)
Soldering fumes							
#cases / #controls	227 / 1280	242 / 1080	27 / 104	27 / 74	10 / 44	30 / 81	7 / 37
Adjusted OR (95% CI)[5]	1.00 (ref)	1.09 (0.87 - 1.36)	1.38 (0.86 - 2.21)	2.89 (1.72 - 4.84)	1.06 (0.49 - 2.28)	2.64 (1.60 - 4.34)	1.04 (0.44 - 2.48)
Metallic dusts							
#cases / #controls	113 / 652	285 / 1365	98 / 447	70 / 291	40 / 188	77 / 335	33 / 144
Adjusted OR (95% CI)[5]	1.00 (ref)	1.01 (0.78 - 1.32)	1.11 (0.80 - 1.54)	1.20 (0.82 - 1.76)	1.09 (0.68 - 1.74)	1.14 (0.79 - 1.65)	1.23 (0.74 - 2.04)
Metal oxide fumes							
#cases / #controls	146 / 805	297 / 1458	53 / 201	36 / 142	26 / 82	39 / 156	23 / 68
Adjusted OR (95% CI)[5]	1.00 (ref)	1.07 (0.84 - 1.36)	1.33 (0.90 - 1.96)	1.42 (0.90 - 2.25)	1.39 (0.79 - 2.43)	1.39 (0.88 - 2.20)	1.43 (0.80 - 2.57)

1. Reference category for all analyses.

2. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

3. Subjects duration of exposure was obtained by summing the number of years a subject was exposed to the selected agent with a probability of exposure ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

4. Subjects were classified as having low exposure to the selected agent if their lifetime cumulative exposure was < 70th percentile of lifetime cumulative exposure to that agent within controls and as high if their lifetime cumulative exposure was ≥ 70th percentile. Lifetime cumulative exposure was obtained by summing the cumulative exposure of each exposed job held by a subject, which was obtained using the formula: (concentration / 3 * 100) * (frequency / 40 * 100) * duration) when the probability was ≥ 50%. Subject with only exposure with probability < 50% were excluded from the analysis.

5. Conditioned on age groups (5-year), sex, and study center, adjusted for age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), Standard International Occupational Prestige Scale (SIOPS) (quartile), and proxy respondent status (self, proxy).

Supplementary table VIII: Odds ratio estimates for the association between ever occupational exposure to the 21 selected agents and glioma and meningioma using random effect meta-analyses and a probability threshold of 50%

Agent	Exposure[1]	Glioma		Meningioma	
		Adjusted[2] OR (95% CI)	I^2	Adjusted[3] OR (95% CI)	I^2
Lead compounds	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	1.04 (0.91-1.20)	0.00	1.10 (0.94-1.31)	28.63
	Ever	0.89 (0.70-1.12)	0.00	0.97 (0.73-1.28)	3.89
Lead fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.96 (0.84-1.08)	0.00	1.08 (0.92-1.26)	29.74
	Ever	0.69 (0.33-1.44)	36.08	1.43 (0.90-2.29)	0.00
Leaded gasoline	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.99 (0.80-1.23)	59.32	0.94 (0.81-1.09)	15.76
	Ever	1.00 (0.65-1.55)	14.45	0.87 (0.50-1.50)	0.00
Chromium compounds	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.95 (0.81-1.12)	37.42	1.03 (0.91-1.16)	0.00
	Ever	1.04 (0.74-1.48)	0.00	1.57 (0.84-2.93)	34.24
Chromium fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.91 (0.78-1.06)	10.62	1.02 (0.85-1.23)	21.67
	Ever	1.00 (0.53-1.87)	0.00	3.01 (0.88-10.29)	42.38
Chromium VI	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.84 (0.65-1.08)	60.90	1.04 (0.89-1.22)	0.00
	Ever	1.53 (0.86-2.72)	0.21	2.08 (0.96-4.48)	9.04
Zinc compounds	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.90 (0.78-1.04)	22.82	0.97 (0.85-1.10)	0.00
	Ever	1.32 (0.77-2.26)	0.00	1.36 (0.82-2.25)	0.00
Iron compounds	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.94 (0.76-1.17)	60.00	0.97 (0.86-1.10)	0.00
	Ever	0.86 (0.67-1.08)	4.35	1.29 (0.98-1.69)	0.00

Agent	**Exposure**[1]	**Glioma**		**Meningioma**	
		Adjusted[2] **OR (95% CI)**	**I**^{2}	**Adjusted**[3] **OR (95% CI)**	**I**^{2}
Iron fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.96 (0.80-1.15)	50.28	1.06 (0.94-1.20)	0.00
	Ever	0.88 (0.54-1.45)	12.40	1.40 (0.73-2.67)	14.32
Nickel compounds	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.97 (0.85-1.09)	0.00	1.03 (0.91-1.17)	0.00
	Ever	1.00 (0.60-1.68)	30.85	1.57 (0.59-4.13)	65.96
Nickel fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.93 (0.81-1.08)	0.00	1.04 (0.89-1.22)	0.00
	Ever	1.01 (0.54-1.90)	0.00	3.06 (0.88-10.67)	44.17
Calcium carbonate	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.99 (0.85-1.15)	26.40	1.00 (0.87-1.16)	21.17
	Ever	1.06 (0.67-1.68)	60.39	0.98 (0.70-1.37)	26.74
Calcium oxide	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.89 (0.76-1.03)	19.64	1.08 (0.92-1.25)	19.40
	Ever	0.89 (0.54-1.47)	0.00	1.16 (0.59-2.30)	0.00
Calcium oxide fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.92 (0.80-1.05)	3.85	0.98 (0.80-1.20)	42.92
	Ever	0.85 (0.49-1.48)	0.00	1.77 (0.90-3.47)	0.00
Calcium sulphate	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.93 (0.82-1.05)	0.00	1.02 (0.90-1.16)	6.07
	Ever	1.01 (0.61-1.67)	55.88	0.98 (0.60-1.61)	21.38
Silicon carbide	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	1.01 (0.84-1.22)	42.03	1.12 (0.97-1.29)	0.00
	Ever	1.04 (0.69-1.58)	3.17	1.48 (0.64-3.44)	55.10
Gas welding fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.94 (0.78-1.12)	46.12	1.02 (0.90-1.15)	2.55
	Ever	1.13 (0.73-1.74)	43.04	1.00 (0.54-1.84)	41.50

Agent	Exposure[1]	Glioma		Meningioma	
		Adjusted[2] OR (95% CI)	I^2	Adjusted[3] OR (95% CI)	I^2
Arc welding fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.92 (0.78-1.07)	32.67	1.02 (0.90-1.15)	0.00
	Ever	0.81 (0.55-1.17)	0.00	1.33 (0.84-2.11)	0.00
Soldering fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.95 (0.84-1.07)	0.00	0.97 (0.86-1.10)	0.00
	Ever	0.76 (0.52-1.12)	0.00	1.34 (0.87-2.05)	7.59
Metallic dusts	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.91 (0.75-1.12)	49.43	0.99 (0.84-1.16)	24.47
	Ever	0.86 (0.70-1.07)	0.00	1.16 (0.90-1.50)	0.00
Metal oxide fumes	**Never**	**1.00 (ref)**	**-**	**1.00 (ref)**	**-**
	Uncertain	0.92 (0.77-1.11)	46.60	1.10 (0.98-1.25)	0.00
	Ever	0.78 (0.53-1.16)	36.07	1.44 (1.04-2.01)	0.00

1. Subjects were classified as having ever exposure if they were exposed to the selected agent with a probability of ≥ 50% for ≥ 2 years. Exposed subjects not fulfilling those requirements were classified as having uncertain exposure.

2. For countries using individual matching, analyses were conditioned on age (5-year groups), sex, and study center and adjusted on age (continuous), education (primary/secondary, intermediate college/ professional, tertiary), social class based on the Standard International Occupational Prestige Scale (SIOPS) (56) (categorised into quartiles among controls), respondent status (self/proxy), and atopy (never/ever diagnosed with allergy, asthma and/or eczema). Analyses for countries using frequency matching were in addition adjusted for sex and study center.

3. Conditioned and adjusted for the same variables as glioma, excluding atopy.

Chapter 8: General discussion

8.1 Addition to current knowledge

The contribution of this thesis to current knowledge is twofold: first, it provides new evidence regarding the role played by metallic compounds in the development of glioma and meningioma, using the largest study to date addressing occupational exposures and brain cancer as well as a rich high-quality JEM. Second, it provides new evidence regarding the performance of CANJEM as an occupational exposure assessment method in the context of epidemiological studies. As the evaluation of the performance of CANJEM as a tool for exposure assessment influenced strongly the analytic strategy used in the assessment of risk of glioma and meningioma in relation to exposure to the 21 metallic compounds of interest, we will address the value of the work done in relation to CANJEM before discussing the results of the risk analysis.

8.1.1 Applicability of CANJEM in epidemiological studies

As a newly developed assessment tool, very little was known regarding the functionality of CANJEM in the context of an epidemiological study. In this thesis, we filled some of this knowledge gap by proposing a linkage procedure for CANJEM, a method for creating lifetime occupational exposure variables based on the metrics of exposure available in CANJEM, and by providing evidence of the validity of CANJEM as a proxy for expert assessment in the context of an epidemiological study.

While it is true that the recommendations and observations made in chapters 5 and 6 may not apply to all potential datasets for which CANJEM may be used, as this would have required taking into consideration all potential decisions related to the creation of CANJEM and examining all potential versions of CANJEM, all occupational agents and metrics of exposure available in CANJEM, and all potential lifetime exposure variables that could be created based on CANJEM; we believe that the general recommendations we made can be expected to apply to most situations commonly faced by CANJEM users. Furthermore, the method we employed to develop our linkage procedure can be easily reproduced and modified by CANJEM users to develop their own personalized linkage procedure. The exposure variables evaluated in chapter 6 and used in the risk analysis presented in chapter 7 provide robust examples for future users of CANJEM.

8.1.2 Association between metals, metalloids, and welding fumes and brain cancer

In chapter 7 we observed no meaningful association between any of the selected agents and glioma, with most associations being close to null and/or imprecise. However, while also often imprecise, we generally observed positive associations between the selected agents and meningioma, which were statistically significant for lead fumes, chromium VI, zinc compounds, soldering fumes, and metal oxide fumes, which encompass a wide range of metallic fumes. While our observations do not provide strong evidence of the role played by each individual agent due to both the lack of consistency in the strength and significance of the associations observed when examining increasing levels of duration and cumulative exposure to many of our included agents, and to exposure correlation between agents, it does nonetheless provide some evidence of the role played by metallic fumes in general, in the development of meningioma. While there is overall little evidence regarding the role played by metallic fumes in the development of meningioma in the current scientific literature, our results are not completely unexpected. Indeed, the main mechanism by which metallic substances may reach the brain is through the circulatory system. As skin permeation of metals is generally limited and only small amounts of ingested metals can reach the circulatory system, inhalation is thus the principal pathway by which metals can enter the circulatory system. Somewhat more unexpected was the lack of association between metallic dusts and meningioma. While this may have been due to chance or exposure misclassification, it may also indicate that most metallic particles present in dusts are too large to reach the lung alveoli and effectively penetrate the circulatory system.

It is difficult to determine why positive associations were primarily observed for meningioma. The current epidemiological literature does not provide any strong evidence that the risk of occupational exposure to metallic compounds is limited to meningioma; however, the literature on this subject is either rather poor or lacking entirely. Many studies evaluated risk for brain tumors as a whole rather than evaluating evidence for the histologic sub-types. Still, we cannot completely exclude the possibility that our results were due to chance or to characteristics of the INTEROCC study population. For example, around 40% of all meningioma cases present in the INTEROCC study were from Israel, where a large proportion of meningioma cases may have been due to treatment for mass ringworm infection of Israeli children with x-ray irradiation of the head and neck between 1948 and 1960 (166). Although unlikely, it is possible that the associations we observed were due to some form of interaction between irradiation during childhood and exposure to metals later in life; however, we were unable to examine this possibility in this thesis. More likely is that the differences in results were due to differences between the two brain cancer subtypes. For example, many metals are known to affect hormone production (167) and thus, may more strongly affect the development of meningioma, a potentially hormone dependent tumor (168), than glioma. This may be particularly true for female meningioma cases, although it may also apply to men as we still observed strong positive associations when examining men alone.

8.2 Validity of the thesis

8.2.1 Validity of CANJEM

Determining the true validity of CANJEM, that is, determining the ability of CANJEM to correctly estimate the true average occupational exposure in jobs present in a study population, is a potentially impossible and futile endeavour. Indeed, obtaining data on the true average occupational exposure in all jobs present in a given study population would not only require knowing the level of exposure observed in the target organ (or knowing the relationship between the level of exposure in the target organ and the level of exposure in a subject's blood or direct work environment), but also requires knowing and having exposure data on the smallest meaningful unit of time for the whole duration of each job, which potentially includes jobs held in the 1930's. Even if such data were available, our observations would not be easily generalizable as they would be specific to the intended study population, linkage procedure, versions of CANJEM employed, definition of exposure used, and exposure variables and occupational agents examined. Consequently, it is better to discuss the validity of CANJEM as a cheaper and more convenient alternative to the expert assessment method that is often considered as the gold standard in retrospective assessment of lifetime occupational exposure in epidemiological studies, and which CANJEM is intending to approximate. In that regard, we found that when using the most appropriate approach to create lifetime exposure variables with CANJEM for each of the agents examined, CANJEM was a reasonable, albeit imperfect, replacement for the expert assessment method. While it could be argued that the small number of agents examined in chapter 6 limited our ability to generalize the relative validity of CANJEM to all available agents, we believe that the selected agents varied sufficiently in terms of their chemical and exposure circumstances to be broadly representative of the majority of agents available in CANJEM and minimally of all agents included in chapter 7. Given our assumption that the exposure profile of jobs in the INTEROCC study population is broadly similar to the exposure profile of jobs used to create CANJEM, at least in terms of the agents examined, it is reasonable to consider CANJEM as a valid exposure assessment tool for the purpose of this thesis. Nonetheless, it must be acknowledged that this may not necessarily be true in other contexts where job exposure profiles would differ more greatly from the ones found in CANJEM. Even within the Canadian population, CANJEM may be less valid when examining younger workers with occupations occurring after 2005, particularly in industries that saw large regulatory or technological change within the past 15 years. But while this is currently true, CANJEM is a constantly evolving tool and future versions may include new jobs allowing us to better estimate exposure in more current occupations.

8.2.2 Information bias

A discussion of information bias is most pertinent to the epidemiologic analyses carried out in chapter 7. Any error in exposure measurement in chapter 6 would have affected the CANJEM and the expert assessment analyses similarly and thus, would not have impacted our comparison. Regarding chapter 7, occupational exposures were assessed based on subject’s self-reported job history which, as mentioned in section 2.3.1, has been shown to be generally valid and reliable in both cases and controls. Furthermore, while subjects in the INTERPHONE study, the original study from which INTEROCC was created, were aware of the main objective to examine the association between cell phone use and brain cancer, they were not told of the objective to analyse occupational exposures as a main variable. Since occupations were not commonly associated with brain cancer, it is unlikely that cases (or their proxies) tried harder to remember or associated their illness with their occupations, thus the possibility for recall bias is limited. While it is also true that some subjects in the INTERPHONE study were interviewed by phone rather than in person, which could have affected the quality of the information provided, the proportion of subjects interviewed by phone was similar between cases and controls and only represented a very small percentage of subjects included in INTEROCC. Some of the interviews were conducted with proxy respondents rather than the subjects themselves, which again may have affected the quality of the information provided. However, excluding proxy respondents from our chapter 7 analysis did not meaningfully change the results. While INTEROCC contains data from multiple countries, interviews were conducted by centrally trained interviewers using a common questionnaire which should limit differences in the quality of the interviews by country. Interviewers were not blinded to case and control status of subjects which may result in interviewer bias. However, it is unlikely that interviewers tried harder to gather data on subject's job history for cases than for controls as they were trained to ensure cases and controls would be treated equally and as occupations were not commonly associated with brain cancer. Finally, as mentioned before, while some misclassification of subject's occupational exposure can be expected due to the use of CANJEM, this exposure misclassification is non-differential with respect to case/control status and is more likely to bias the OR estimates toward the null. Furthermore, based on our observations in chapter 6, this misclassification could be expected to have little overall impact on the OR estimates calculated in chapter 7.

8.2.3 Selection bias

The overall response rate in the INTEROCC study (table VI of chapter 4 page 63) was 68% (ranging from 56% to 86% by country) in glioma cases, 81% (ranging from 62% to 90% by country) in meningioma cases and 50% (ranging from 31% to 74% by country) in controls. The overall low response rate among controls warrants the consideration of potential selection bias. Response rates in the INTERPHONE study were associated with mobile phone ownership. The extent to which the differential response rates present in INTERPHONE could have biased the OR estimates of the association between mobile phone use and brain cancer was described (158, 169) and estimated to have potentially biased the estimates by at most 15% in simulations (169). Because in the INTERPHONE study, and consequently the INTEROCC study, cell phone ownership was positively associated with SES, response rates could be suspected to be lower in those potential controls with lower SES occupations and thus, those that were potentially more exposed to metallic compounds, which could have biased the association observed between our selected agents and brain cancer away from the null. However, it is likely that that the observed bias would be at most as strong as the one estimated in the INTERPHONE study and thus, it would not have affected our overall conclusions.

8.2.4 Confounding

Confounding is an issue that may only have affected our results in chapter 7. Although we adjusted our analyses for most known potential risk factors of glioma or meningioma that may have acted as confounders in our study, we were unable to adjust for all of them, which could have resulted in confounding. For example, irradiation of the brain by ionizing radiation, such as the one that occurred in Israeli children, is a known risk factor for both glioma and meningioma; it can also affect cognitive ability of individuals and limit their employment opportunity. Consequently, our lack of adjustment for exposure to ionizing radiation may have biased our results if exposed subjects were more or less likely to work in occupations exposed to our agents, although it is difficult to determine exactly how this confounding would have affected our results. While the evidence is not as strong, the same may be true for non-ionizing radiation such has that by cell phones, another potential confounder we were unable to adjust for. In addition, as the etiology of brain cancer is relatively unknown we cannot exclude the possibility of confounding due to unknown confounders. However, it is unlikely that a large number of risk factors for glioma or meningioma also associated with subject's occupational exposure to our selected agents exist. Finally, residual confounding may also have been an issue in our analyses. Although we adjusted for subject's education and SIOPS, those may not be sufficient proxies for SES, reducing the validity of our SES measurement. Similarly, although we adjusted our glioma analysis for diagnosis of allergy, asthma and/or eczema, we had no information on the severity of those diseases which may have reduced the validity of our assessment for atopies.

8.3 Originality of the thesis

In this thesis we examined the association between occupational exposure to a set of metallic compounds and the two major histological subtypes of brain cancer; glioma and meningioma, in the large multi-national case-control study INTEROCC, using CANJEM to assess occupational exposure. The examination of occupational exposure to metallic compounds in relation to brain cancer is not in itself a novel concept and neither is the use of a JEM to examine this association in the INTEROCC study. However, very few studies have examined the association between all our selected metallic compounds and brain cancer and most suffered from limitations of size or exposure assessment. It is important to replicate findings and the INTEROCC study provides an excellent opportunity to do this, given the size of the study population. Previous analyses of the INTEROCC study population in relation to occupational exposure were based on use of FINJEM to assess exposure. There are several drawbacks to the use of FINJEM discussed in chapter 4.3.2 which justify the reexamination of some occupational agents with CANJEM.

In addition, CANJEM is unique in the range of options it offers users in regard to its compilation, the axes, and the metrics of exposure it provides. This wider range of options translates into the need to make a larger set of complex decisions when applying CANJEM, which are not generally needed with other JEMs or assessment methods. Consequently, the main originality of this thesis is in the methods we developed to determine the best answer to some of those decisions and the overall approach we proposed to examine lifetime occupational exposure in a study population based on CANJEM.

8.4 Future perspectives

There is much that remains to be understood both in terms of the use of CANJEM as an exposure assessment method and in terms of the etiology of brain cancer. In regard to CANJEM, there is the obvious need to examine agents not included in chapters 5 and 6 and to examine a larger set of metrics of exposure and lifetime occupational exposure variables. In addition, it would also be important to improve on the methodology employed in those chapters and examine some of the other decisions that must be made when using CANJEM, such as the minimum number of jobs required for metrics of exposure to be provided in a cell.

Another important aspect of CANJEM we were unable to examine in this thesis is how the distribution of the probability of exposure to a selected agent in exposed cells could affect the usability of CANJEM as an exposure assessment tool for that agent. Ideally, the probability of exposure for a given cell in a JEM should be as close as possible to 0% or 100% in order to minimize the potential for exposure misclassification. If a JEM only contains cells with a probability of exposure of 50% to a selected agent, then the JEM will not be a good assessment tool for that agent, while the opposite will be true if the JEM only contains cells close to 0% and/or 100%. Thus, by examining for each individual agent available in CANJEM the distribution of the probability of exposure in exposed cells and determining if an association exists between the shape of the distribution and the relative validity of CANJEM compared to the expert assessment approach, we may be able to efficiently exclude from CANJEM, agents that are not well suited to this approach to exposure assessment. It is important not to confuse the optimal probability of exposure discussed here with the optimal thresholds for the probability of exposure presented in chapter 6. The first defines the optimal probability of exposure to a selected agent that we would want to see in each individual cell of CANJEM to reduce exposure misclassification, while the latter represents the optimal threshold to define exposed and unexposed in a group of occupations with a wide range of probability of exposures to a selected agent. Clearly, both are interrelated and no optimal threshold can exist for an agent unless at least some meaningful cells exist in the JEM for that agent. Nonetheless, it is important to understand that the observation that thresholds of 50% were optimal when examining lifetime occupational exposure to some agents does not contradict the fact that cells with probability of exposure of 50% have the highest risk of exposure misclassification. For example, if a threshold of 50% is used in a population where all jobs have probability of exposures between 45% and 60%, then most jobs would be classified as exposed even though close to half are in truth unexposed. In that situation there exists no optimal probability threshold. However, if all jobs have probability of exposure around 90% to 100%, then while the same threshold of 50% would classify all jobs as exposed, misclassification would be minimal (at most 10%) and this threshold or any thresholds under 90% for that matter could be considered as optimal. In reality most study populations will be composed of jobs with a wide range of probability of exposures and the optimal probability threshold will be the threshold that allows the overall minimization of exposure misclassification within all included jobs. Nonetheless, no matter what is the true distribution of exposure in a study population, if all cells in CANJEM for a selected agent have probability of exposure around 50%, then using CANJEM to assess exposure to that agent would be meaningless and the agent should be removed from the list of agents available in CANJEM.

It may also be interesting to examine the use of non-frequentist approaches to assess occupational exposure with CANJEM. The use of Bayesian probability for example, where new data (e.g. the probability of exposure of each job held by each subject, the number of potentially exposed jobs held by each subject, the expert's confidence level in their exposure assessment, the occupational code or time period resolutions used to link each job to CANJEM) is used to "update" prior knowledge or belief regarding the data (e.g. the exposure status of a subject based on a threshold of probability of exposure) may provide an efficient way to examine occupational exposure with CANJEM. As can be seen, there is still much to learn about CANJEM and its application.

In regard to the etiology of brain cancer, there is a need to both replicate our results in hypothesis testing studies and to expand our understanding of the role played by other occupational agents that may accumulate in the brain in hypothesis generating studies, both of which could be achieved with the help of CANJEM. Of particular interest would be the examination of occupational exposure in women, in particular in relation to meningioma. Lastly, the potential interaction between exposure to electromagnetic fields (EMF) and occupational exposure to metallic compound in regard to brain cancer in the INTEROCC study would also deserve future examination. Indeed. It has been suggested that EMF may act as an effect modifier of the possible association between metallic compounds and brain cancer (170), with a few potential mechanisms, including an increase in the accumulation of metallic compounds in the brain due to an increase in the permeability of the blood brain barrier (171-175) resulting from EMF exposure, an increase in brain cell absorption of EMF due to the micro antenna properties of metallic compounds (85), and the promotion of DNA damage through oxidative stress created by the formation of free radicals created from direct interaction between EMF and metallic compounds (176-179). While a previously published study has examined the potential interaction between EMF and the agents available in the INTEROCC-JEM, including metallic compounds, and reported no clear evidence of interaction, CANJEM would offer us the opportunity to examine a wider and potentially more relevant set of metallic compounds.

8.5 General conclusion

Brain cancer is a complex disease that occurs in an enclosed organ controlling all of our daily functions. This particularity of brain cancer makes even benign tumors potentially debilitating and life-threatening and treatment complex and expensive. Under those circumstances, prevention of brain cancer remains our best option to reduce the public health burden of this disease. However, whether due to its lower overall mortality or to its complexity, we still know very little regarding the etiology of brain cancer. Metallic compounds are elements which, in small quantity, are necessary for life. However, millions of workers are potentially exposed to high concentration of those compounds which may accumulate in the brain and initiate or promote brain tumour formation. While some studies have tried to examine the association between metallic compounds and brain cancer, most were limited in their statistical power or exposure assessment method. Thus, new studies not suffering from those limitations are required to better understand this association.

In this thesis, we used the unique opportunity offered by the newly developed CANJEM and the availability of the INTEROCC study to provide new evidence regarding the role played by 21 metallic compounds in the development of the two major histological subtypes of brain cancer: glioma and meningioma. To ensure the quality of our exposure assessment, we examined some of the methodological considerations associated with CANJEM and developed a method for its application in the context of an epidemiological case-control study. While our examination of CANJEM is not, in itself, sufficient to fully demonstrate its validity, it provides nonetheless some strong evidence of its potential value in the field of occupational epidemiology, a field consistently in need of new and accurate assessment tools.

We observed no evidence of association between any of the selected agents and glioma, but some evidence of positive association between metallic fumes and meningioma. While the body of scientific knowledge is currently insufficient to reach any strong conclusion regarding the role played by metallic compounds in the development of brain cancer, our results do highlight the importance of examining glioma and meningioma separately and of the use of assessment tools able to differentiate between the different physical forms (i.e. dusts, fumes) of metallic compounds. Through the continued evaluation of metallic compounds and other occupational agents in different study populations with varied exposure profiles and with special consideration of the role played by sex in the development of brain cancer, we may be able to better understand the etiology of this unique disease.

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Appendix: Summaries of the studies identified in the literature review

Table I: Overview of the literature on the association between metals and brain cancer

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Navas-Acien A **(2002)** **Cohort** **(26)**	Swedish men and women employed in 1970, aged 24-65 years old	2,465 incident glioma cases, 848 incident meningioma cases	Exposure to occupational agents from occupation in 1960 and 1970, and a JEM	Age, calendar period, geographical risk area, town size, solvents, asbestos, chromium/nickel, oil mist, polycyclic aromatic hydrocarbons and petroleum products	Glioma	(reference category: no exposure) **possible exposure to metallic compounds** (29 cases) RR (95%CI): 1.28 (0.84-1.94), **probable exposure to metallic compounds** (74 cases) RR (95%CI): 1.06 (0.77-1.45)	
					Meningioma	**possible exposure to metallic compounds** (14 cases) RR (95%CI): 1.38 (0.73-2.61), **probable exposure to metallic compounds** (16 cases) RR (95%CI): 0.73 (0.40-1.33)	
Danielsen TE **(2000)** **Cohort** **(64)**	Finnish women born between 1906-1945, who reported occupation in a 1970 national census	18 incident cases	Occupation from company registry	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from national rate) **shipyard workers** (18 cases) SIR: 1.25 (0.74-1.97)	Air measurements indicate presence of metals in the air at workplace
McLaughlin JK **(1987)** **Cohort** **(30)**	Swedish men employed in 1960	3,394 incident cases	Occupation from 1960 census	5-year birth cohort, region	Glioma	(expected cases calculated in the general Swedish population) **metal making and metal treating workers** (63 cases) SIR: 1.0, p-value: >0.05, **fabricated metal products** (190 cases) SIR:1.0, p-value: >0.05, **toolmakers and machinists** (106 cases) SIR:1.1, p-value: >0.05	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Sadetzki S (2016) **Case-control** **(43)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged ≥ 18 years old	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary)	Meningioma	**For all subjects:** (reference category: never exposed to any metals or welding fumes) **ever exposed to metals** (210 cases) OR (95%CI): 1.16 (0.96-1.40)	Using data from the INTEROCC study. Metals included: cadmium, chromium, iron, nickel, and lead. Similar results observed when also adjusting for occupational exposure to oil mist. All analyses were conducted with a 5-year lag period
						For men: (reference category: never exposed to any metals or welding fumes) **ever exposed to metals** (148 cases) OR (95%CI):1.19 (0.94-1.51)	
						For women: (reference category: never exposed to any metals or welding fumes) **ever exposed to metals** (62 cases) OR (95%CI):1.11 (0.80-1.55)	
Ruder AM (2012) **Case-control** **(151)**	Adults aged 18 to 80 years old and non-metropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin	798 incident glioma cases	Self-reported occupation from questionnaire coded by experts	Age (10-year age groups + continuous), sex, education (< 12 years, high school graduate, college graduate)	Glioma	(reference category: all other ever employed subjects) **sheetmetal workers, etc.** (16 cases) OR (95%CI): 0.73 (0.39-1.36), **vehicle manufacturing workers** (12 cases) OR (95%CI): 1.98 (0.90-4.73)	Only used the longest job held by subjects in the analyses. Similar results were observed when only considering jobs that lasted ≥ 5 years, only considering jobs that started by either 1985 or 1975, and when using a lower occupational coding system resolution

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Samkange-Zeeb F **(2010)** **Case-control** **(38)**	Inhabitants of Germany, aged 30-69 years old and living in one of 4 German cities	366 incident glioma cases, 381 incident meningioma cases	Self-reported occupations from questionnaire	Conditional on sex and study center, adjusted for age (linear), education, area of residence, smoking status (never, ex, current)	Glioma	(reference category: never worked in occupation) **ever worked in metal sector** (49 cases) OR (95%CI): 1.02 (0.68-1.53), **1-4 years of work** (7 cases) OR (95%CI): 0.97 (0.38-2.51), ≥ **5 years of work** (42 cases) OR (95%CI):1.03 (0.66-1.59)	
					Meningioma	**ever worked in metal sector** (35 cases) OR (95%CI): 1.51 (0.92-2.48), **1-4 years of work** (11 cases) OR (95%CI): 2.62 (1.05-6.53), **≥ 5 years** (24 cases) OR (95%CI):1.18 (0.66-2.11)	
Speers MA **(1988)** **Case-control** **(148)**	Men residents in one of 40 east Texas counties, aged 35-79 years old	382 deaths	Exposure to occupational agents from occupation in death certificate and exposure linkage system	Age	Glioma	**(reference category: no exposure) exposed to metals** (6 cases) OR (95%CI): 0.45 (0.15-1.41)	Clusters used for the analysis, clusters included exposure to dust, aromatic/ aliphatic hydrocarbons, minerals, and ionizing radiation
Pan SY **(2005)** **Case-control** **(37)**	Individuals aged 20-76 years old, living in one of 8 Canadian provinces	1,009 incident cases	Occupations from questionnaire	Age (continuous), province of residence, sex, education level (years), alcohol consumption (serving/week), smoking pack-years (continuous), total energy intake (kcal/week)	Brain cancer (only malignant tumors)	**(reference category: never held occupation) ever held occupation in metal** production (16 cases) OR (95%CI): 0.97 (0.56-1.67)**, usual occupation in metal production** (6 cases) OR (95%CI): 1.19 (0.48-2.95), **ever held occupation in motor vehicle fabricating and assembling** (7 cases) OR (95%CI): 2.79 (1.10-7.10)**, usual occupation in motor vehicle fabricating and assembling** (3 cases) OR (95%CI): 1.92 (0.51-7.23), **ever held occupation in metal shaping and** forming (35 cases) OR (95%CI): 1.24 (0.82-1.86)**, usual occupation in metal shaping and forming** (16 cases) OR	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						(95%CI): 1.26 (0.65-2.08), **ever held occupation in metal** machining (12 cases) OR (95%CI): 0.69 (0.37-1.28), **usual occupation in metal** machining (3 cases) OR (95%CI): 0.46 (0.14-1.51), **ever held occupation in metal processing and related occupations** (14 cases) OR (95%CI): 1.00 (0.55-1.82),**usual occupation in metal processing and related occupations** (8 cases) OR (95%CI): 2.04 (0.85-4.88)	
Schlehofer B (2005) **Case-control** **(36)**	Individuals aged 20-80 years old, residing in area of study centers	1,169 incident cases (638 men, 531 women)	Self-reported occupation and exposure to occupational agent from questionnaire	Conditional on age (5-year group) and center, adjusted for years of schooling	Glioma	**<u>For men:</u>** (reference category: subjects with ≤ 5 years in occupation) **working > 5 years in metal industry, for all glioma** (148 cases) OR (95%CI): 1.24 (0.96-1.62), **for low grade glioma** (45 cases) OR (95%CI): 1.59 (1.00-2.52), **for high grade glioma** (101 cases) OR (95%CI): 1.12 (0.82-1.53), (reference category: subjects with ≤ 48 hours of cumulative exposure) **> 48 hours of cumulative exposure to metal and metal compounds, for all glioma** (122 cases) OR (95%CI): 0.70 (0.54-0.91), **for low grade glioma** (42 cases) OR (95%CI): 0.74 (0.47-1.15), **for high grade glioma** (80 cases) OR (95%CI): 0.70 (0.51- 0.96) **<u>For women:</u>** (reference category: subjects with ≤ 5 years in occupation) **working > 5 years in metal industry, for all glioma** (6 cases) OR (95%CI): 0.79 (0.28-2.20), **for low grade glioma** (1 case) OR (95%CI): 0.41 (0.04-4.02), **for high grade glioma** (5 cases) OR (95%CI): 0.89 (0.29-2.72). (reference category: subjects with ≤ 48 hours of cumulative exposure) **> 48 hours of cumulative exposure to metal and**	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						metal compounds, for all glioma (30 cases) OR (95%CI): 1.05 (0.64-1.72), **for low grade glioma** (12 cases) OR (95%CI): 0.98 (0.46-2.13), **for high grade glioma** (18 cases) OR (95%CI): 1.06 (0.57-1.96)	
Carozza SE (2000) Case-control (77)	Individuals aged at least 20 years old living in the San Francisco bay area	476 incident cases	Self-reported occupation from questionnaire	Age (20-54, ≥55), sex, years of education (<16, ≥16), race (White, non-White)	Glioma	(reference category: subjects not employed in industry) **ever employed in sheet metal, iron, other metal industries** (27 cases) OR (95%CI): 0.6 (0.4-1.1), **< 10 years employment** OR (95%CI): 0.5 (0.3-1.1), **≥ 10 years employment** OR (95%CI): 1.2 (0.4-3.5), **with a 10-year lag period**, **ever employed in sheet metal, iron, other metal industries** OR (95%CI): 0.7 (4-1.2), **< 10 years employment** OR (95%CI): 0.6 (0.3-1.2), **≥ 10 years employment** OR (95%CI): 1.2 (0.4-4.0). **ever employed in foundry and smelting industries** (6 cases) OR (95%CI):2.6 (0.5-13.1), **<10 years employment** OR (95%CI): 2.2 (0.4-11.4), **with a 10-year lag period ever employed in foundry and smelting industries** OR (95%CI): 1.7 (0.3-9.6), **<10 years employment** OR (95%CI): 0.4 (0.1-1.3)	
Santana VS. (1999) Case-control (147)	Brazilian Navy men (active and inactive)	40 deaths	Occupations from division record	Age (Mantel-Haensze)	Brain cancer	(reference category: subjects working in other occupations) **metal/machine workers** (6 cases) OR (95%CI) :0.63 (0.26-1.55), **workers with < 20 years of enlistment** (unadjusted) (3 cases) OR (95%CI): 0.73 (0.19-2.75), **workers with ≥ 20 years of enlistment** (3 cases) OR (95%CI): 0.52 (0.16-1.72)	Metal/machine occupations include: motor operator, aircraft repairmen, machine operator, steel and welding craftsmen, boiler

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
							operator, signalmen
Rodvall Y **(1996)** **Case-control** **(35)**	Individuals aged 25 -74 years old, living in catchment area of the Neurosurgery department at Uppsala university hospital	151 incident cases	Self-reported occupations and exposure to occupational agent from questionnaire	Age (5 categories), population density	Glioma	**Men:** (reference category: subjects working in other occupations) **working in basic metal industry** (19 cases) OR (95%CI): 2.0 (1.0-4.0), **blacksmith, toolmakers, machine tool operators** (15 cases) OR (95%CI):1.8 (0.8-3.8), (reference category: no exposure), **exposure to metals and metal compounds** (15 cases) OR (95%CI): 0.7 (0.4-1.5).	Conditional analyses stratified on age and parish produced similar results
						Women: (reference category: subjects working in other occupations) **working in basic metal industry** (1 case) OR (95%CI): 0.4 95%CI: (0.1-3.6), (reference category: no exposure) **exposure to metals and metal compounds** (4 cases) OR (95%CI): 1.8 (0.5-5.8)	
Brownson RC **(1990)** **Case-control** **(65)**	White men from Missouri	312 incident cases	Longest held job reported to the Missouri cancer registry	Age, smoking	Brain cancer	(reference category: subjects working in other occupations) **working in metal manufacturing** (7 cases) OR (95%CI): 1.3 (0.5-3.2)	
Mallin K **(1989)** **Case-control** **(34)**	Illinois men aged 35-74 years old	1,212 deaths (1,130 white men, 82 black men)	Occupation from death certificate	Age (35-54 years old, 55-74 years old)	Brain cancer	(reference category: subjects working in other occupations) **blue collar sheet-metal workers** (6 cases) OR:4.2, p-value: <0.05, **white collar metal industry workers** (19 cases) OR: 2.2, p-value <0.05	No black men cases in occupations of interest. Further adjustment for rural/urban residence and ethnicity produced similar results

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Preston-Martin S (1989) **Case-control** **(66)**	Men aged 25-69 years old and residents of Los Angeles county	202 incident glioma cases, 70 incident meningioma cases	Self-reported exposure to occupational agents from questionnaire	Conditional on neighborhood, race, age (5-year group)	Meningioma	(reference category: no exposure) **exposed at least weekly to metal dust or fumes** (19 cases) OR (95%CI): 2.6 (0.9-9.3)	Exposed to metals other than aluminum, arsenic, beryllium, cadmium, lead, mercury, nickel

RR: Risk ratio, SIR: Standardized incidence ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table II: Overview of the literature on the association between zinc and brain cancer

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Cocco P **(1994)** **Cohort** **(70)**	Men working in two metal mines located in Sardinia, with more than 1 year of employment between 1932-1971	8 deaths	Occupation from company registry	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from regional rate) **workers in lead and zinc mines** (8 cases) SMR (95%CI): 1.17 (0.50-2.30), **surface workers only** (2 cases) SMR (95%CI): 0.91 (0.11-3.27), **underground workers only** (6 cases) SMR (95%CI):1.33 (0.49-2.90), **underground workers mine A only** (2 cases) SMR (95%CI): 1.15 (0.14-4.15), **underground workers mine B only** (4 cases) SMR (95%CI): 1.43 (0.39-3.66), **surface worker mine A only** (1 case) SMR (95%CI): 0.70 (0.02-3.88), **surface worker mine B only** (1 case) SMR (95%CI): 1.29 (0.03-7.21)	Workers in mine A also exposed to high level of radon and low level of silica, workers in mine B also exposed to high level of silica and low level of radon
Sankila R **(1990)** **Cohort** **(123)**	Workers in two glass factories, with at least 3 months of continuous employment between 1953-1971	6 incident cases (5 men, 1 woman)	Occupation from factory's employment record	Sex, age, time period	Brain cancer	(expected cases calculated from general Finnish population) **All glass factory workers** (6 cases) SIR (95%CI): 0.60 (0.22-1.31)	Subjects potentially exposed to chromium, arsenic, cadmium, lead, nickel oxide, and zinc selenite
Guberan E **(1989)** **Cohort** **(69)**	Men working as painters who resided in the canton of Geneva in 1970	1 incident cases and 3 deaths	Occupation from 1970 census and numerous registries	Age, calendar year	Brain cancer	(expected cases calculated from regional rate) **for painters** (1 case) SMR (95%CI) 0.52 (0.03-2.50), (3 cases) SIR (95%CI): 1.43 (0.39-3.69),	Subjects potentially exposed to zinc chromate
Dalager NA **(1980)** **Cohort** **(68)**	White men working in two large government owned aircraft maintenance bases	3 deaths	Exposure to occupational agent estimated from occupation in service record card	Age (5-year groups), time interval (5-year group)	Brain cancer	(expected cases calculated from USA white male population) **workers exposed to zinc**, (3 cases) PMR: 2.5, PCMR: 1.88	P-value or 95%CI not provided

SMR: Standardized mortality ratio, SIR: Standardized incidence ratio, PMR: Proportionate mortality ratio, PCMR: Proportionate cancer mortality ratio, 95%CI: 95% confidence interval.

Table III: Overview of the literature on the association between iron and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Wesseling C (2002) Cohort (27)	Finnish women, born between 1906-1945, who reported their occupation in a 1970 national census	693 incident cases	Exposure to occupational agent from 1970 census occupation and a JEM	Year of birth , period of diagnosis, turnover rate	Brain cancer	(expected cases calculated from unexposed subjects) l**ow exposure to iron and its compounds** SIR (95%CI): 1.05 (0.68-1.61), **medium/high exposure to iron and its compounds** SIR (95%CI): 2.15 (0.96-4.80)	
Tornqvis S (1991) Cohort (83)	Swedish working men, aged 20-64 years old, working in electrically related occupations	250 incident cases	Occupation from 1960 census	Age (5-year group), social class (based on employment in three groups), population density (four groups), county	Brain cancer	(expected cases calculated from a population of 1 905 660 Swedish working men born between 1896-1940) **miners in iron/ore mine** (3 cases) SIR (95%CI): 0.7 (0.1-2.0), **furnace men/metal converters in iron/steel industry** (7 cases) SIR (95%CI): 0.8 (0.3-1.6)	
					Glioblastoma	(expected cases calculated from a population of 1 905 660 Swedish working men born between 1896 - 1940) **miners in iron/ore mine** (2 cases) SIR (95%CI): 0.8 (0.1-2.9), **furnace men/metal converters in iron/steel industry** (4 cases) SIR (95%CI): 0.7 (0.2-1.8)	
Parent ME (2017) Case-control (79)	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged 30 to 69 years old	1,800 incident cases	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary), time-weighted average International Occupational Prestige Scale (SIOPS) (continuous), atopy	Glioma	(reference category: non-exposed) **subjects ever exposed to iron** (244 cases) OR (95%CI): 0.9 (0.7-1.1), **≤ 70 mg/m^3 blood iron level** (64 cases) OR (95%CI):0.7 (0.5-1.0), **> 70 to ≤ 254.3 mg/m^3 blood iron level** (81 cases) OR (95%CI): 0.9 (0.7-1.2), **> 254.3 mg/m^3 blood iron level** (99 cases) OR (95%CI): 1.1 (0.8-1.5), **1-4 years of exposure to iron** (52 cases) OR (95%CI): 0.8 (0.6-1.2), **5-9 years of exposure to iron** (57 cases) OR (95%CI): 0.9 (0.6-1.3), **≥ 10 years of**	Using data from the INTERROC study. Assessed exposure using a modified version of FINJEM. All analyses conducted using a 5-year lag period. No difference observed when conducting the analyses using different thresholds for the probability of

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
				(never, ever asthma, allergy, and/or eczema), respondent status (self, proxy)		**exposure to iron** (135 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to iron in males** (237 cases) OR (95%CI): 0.9 (0.7-1.1), **ever exposure to iron in high grade glioma cases** (181 cases) OR (95%CI): 1.0 (0.8-1.2), **ever exposure to iron in glioblastoma cases** (125 cases) OR (95%CI): 1.2 (0.4-3.2), **ever exposure to iron in self-respondents** (211 cases) OR (95%CI): 0.9 (0.7-1.1)	exposure, using different lag time, or when conducting the analysis in women.
Sadetzki S (2016) Case-control (43)	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged ≥ 18 years old	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary)	Meningioma	**For all subjects:** (reference category: never exposed) **ever exposed to iron** (139 cases) OR (95%CI): 1.26 (1.00-1.58), **< 48.1 mg/m^3 blood iron level** (27 cases) OR (95%CI): 1.00 (0.64-1.57), **48.1 to < 140.8 mg/m^3 blood iron level** (33 cases) OR (95%CI): 1.35 (0.89-2.06), **140.8 to < 374.6 mg/m^3 blood iron level** (34 cases) OR (95%CI): 1.29 (0.85-1.95)), **≥ 374.6 mg/m^3 blood iron level** (45 cases) OR (95%CI): 1.38 (0.94-2.02), **p-value for linear trend**: 0.03 , **1 to 4 years exposed to iron** (38 cases) OR (95%CI): 1.16 (0.78-1.71), **5 to 14 years exposed to iron** (50 cases) OR (95%CI): 1.47 (1.03-2.09), **≥ 15 years exposed to iron** (51 cases) OR (95%CI): 1.16 (0.82-1.65), **p-value for linear trend**: 0.08 , **age at first iron exposure < 18 years old** (58 cases) OR (95%CI): 1.18 (0.85-1.64), **age at first iron exposure ≥ 18 years old** (81 cases) OR (95%CI): 1.32 (0.99-1.76), **p-value for linear trend**: 0.04	Using data from the INTERROC study. Similar results observed when also adjusting for the Standard International Occupation Prestige Scale (SIOPS), marital status, cigarette smoking, respondent status, allergy history, age of first exposure, and occupational exposure to oil mist or when using different probability of exposure thresholds. Significant positive trends observed when conducting analyses 5-14 and 15-24 years before reference.

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						For men: (reference category: never exposed) **ever exposed to iron** (113 cases) OR (95%CI): 1.19 (0.91-1.54), **< 48.1 mg/m^3 blood iron level** (25 cases) OR (95%CI): 1.11 (0.69-1.79), **48.1 to < 140.8 mg/m^3 blood iron level** (27 cases) OR (95%CI): 1.26 (0.80-2.00), **140.8 to < 374.6 mg/m^3 blood iron level** (26 cases) OR (95%CI): 1.10 (0.69-1.74)), **≥ 374.6 mg/m^3 blood iron level** (35 cases) OR (95%CI): 1.27 (0.83-1.94), **p-value for linear trend**: 0.20, **1 to 4 years exposed to iron** (26 cases) OR (95%CI): 1.07 (0.67-1.71), **5 to 14 years exposed to iron** (40 cases) OR (95%CI): 1.38 (0.94-2.05), **≥ 15 years exposed to iron** (47 cases) OR (95%CI): 1.11 (0.77-1.60), **p-value for linear trend**: 0.24 , **age at first iron exposure < 18 years old** (49 cases) OR (95%CI): 1.06 (0.74-1.51), **age at first iron exposure ≥ 18 years old** (64 cases) OR (95%CI): 1.30 (0.94-1.81), **p-value for linear trend**: 0.12	When stratifying by menopause status, the results were only significant in the postmenopausal group. When conducting analyses on iron, chromium, and nickel combined, no statistically significant results observed. All analyses were conducted with a 5-year lag period.
						For women: (reference category: never exposed) **ever exposed to iron** (26 cases) OR (95%CI): 1.70 (1.00-2.89), **< 48.1 mg/m^3 blood iron level** (2 cases) OR (95%CI): 0.41 (0.09-1.84), **48.1 to < 140.8 mg/m^3 blood iron level** (6 cases) OR (95%CI): 2.08 (0.63-6.93), **140.8 to < 374.6 mg/m^3 blood iron level** (8 cases) OR (95%CI): 3.08 (1.12-8.42), **≥ 374.6 mg/m^3 blood iron level** (10 cases) OR (95%CI): 2.10 (0.82-5.34), **p-value for linear trend**: 0.01, **1 to 4 years**	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						exposed to iron (12 cases) OR (95%CI): 1.40 (0.67-2.92), **5 to 14 years exposed to iron** (10 cases) OR (95%CI): 1.95 (0.82-4.64), **≥ 15 years exposed to iron** (4 cases) OR (95%CI): 2.97 (0.52-17.07), **p-value for linear trend**: 0.03, **age at first iron exposure < 18 years old** (9 cases) OR (95%CI): 3.06 (1.15-8.17), **age at first iron exposure ≥ 18 years old** (17 cases) OR (95%CI): 1.34 (0.71-2.53), **p-value for linear trend**: 0.13	

SIR: Standardized incidence ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table IV: Overview of the literature on the association between cadmium and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Wesseling C **(2002)** **Cohort** **(27)**	Finnish women, born between 1906-1945, who reported their occupation in a 1970 national census	693 incident cases	Exposure to occupational agent from self-reported occupation in a 1970 census and a JEM	Year of birth , period of diagnosis, turnover rate	Brain cancer	(expected cases calculated from unexposed subjects) **low exposure to cadmium and its compounds** SIR (95%CI): 1.30 (0.91-1.86), **medium/high exposure to cadmium and its compounds** SIR (95%CI): 1.47 (0.93-2.31).	associations were close or closer to null when further adjusting models for exposure to chromium and lead or for exposure to nickel and lead
Sankila R **(1990)** **Cohort** **(123)**	Workers in two glass factories, with at least 3 months of continuous employment between 1953-1971	6 incident cases (5 men, 1 woman)	Occupation from factory's employment record	Sex, age, time period	Brain cancer	(expected cases calculated from general Finnish population) **glass factory workers** (6 cases) SIR (95%CI): 0.60 (0.22-1.31)	Subjects potentially exposed to chromium, arsenic, cadmium, lead, nickel oxide, and zinc selenite
Parent ME **(2017)** **Case-control** **(79)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged 30 to 69 years old	1,800 incident cases	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary), time-weighted average International Occupational Prestige Scale (SIOPS) (continuous), atopy (never, ever asthma, allergy, and/or eczema), respondent status (self, proxy)	Glioma	(reference category: non-exposed) **subjects ever exposed to cadmium** (40 cases) OR (95%CI): 1.1 (0.7-1.6), **≤ 111.4 ug/m^3 blood cadmium level** (12 cases) OR (95%CI): 1.0 (0.5-1.9), **> 111.4 to ≤ 343.8 ug/m^3 blood cadmium level** (19 cases) OR (95%CI): 1.6 (0.9-2.8), **> 343.8 ug/m^3 blood cadmium level** (9 cases) OR (95%CI): 0.7 (0.3-1.5), **1-4 years of exposure to cadmium** (20 cases) OR (95%CI): 1.1 (0.6-1.8), **5-9 years of exposure to cadmium** (10 cases) OR (95%CI): 1.4 (0.6-3.3), ≥ **10 years of exposure to cadmium** (10 cases) OR (95%CI): 0.8 (0.4-1.8), **ever exposure to cadmium in males** (31 cases) OR (95%CI): 1.1 (0.7-1.8), **ever exposure to cadmium in high grade glioma cases** (25 cases) OR (95%CI): 0.9 (0.6-1.5), **ever**	Using data from the INTERROC study. Assessed exposure using a modified version of FINJEM. All analyses conducted using a 5-year lag period. No difference observed when conducting the analyses using different thresholds for the probability of exposure, using different lag time, or when conducting the analysis in women.

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						exposure to cadmium in glioblastoma cases (18 cases) OR (95%CI): 0.9 (0.5-1.5), **ever exposure to cadmium in self-respondents** (38 cases) OR (95%CI): 1.1 (0.7-1.7)	
Sadetzki S **(2016)** **Case-control** **(43)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged ≥ 18 years old	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary)	Meningioma	**<u>For all subjects:</u>** (reference category: never exposed) **ever exposed to cadmium** (30 cases) OR (95%CI): 0.94 (0.6-1.46), **< 92.6 ug/m^3 blood cadmium level** (13 cases) OR (95%CI): 1.95 (0.91-4.16), **92.6 to < 184.1 ug/m^3 blood cadmium level** (3 cases) OR (95%CI): 0.46 (0.14-1.58), **184.1 to < 394.9 ug/m^3 blood cadmium level** (4 cases) OR (95%CI): 0.49 (0.16-1.46), **≥ 394.9 ug/m^3 blood cadmium level** (10 cases) OR (95%CI): 0.97 (0.44-2.13), **p-value for linear trend**: 0.42, **1 to 4 years exposed to cadmium** (14 cases) OR (95%CI): 1.01 (0.53-1.91), **5 to 14 years exposed to cadmium** (10 cases) OR (95%CI): 1.04 (0.49-2.22), **≥ 15 years exposed to cadmium** (6 cases) OR (95%CI): 0.68 (0.26-1.79), **p-value for linear trend**: 0.61, **age at first cadmium exposure < 18 years old** (4 cases) OR (95%CI): 0.86 (0.27-2.73), **age at first cadmium exposure ≥ 18 years old** (26 cases) OR (95%CI): 0.95 (0.59-1.53), **p-value for linear trend**: 0.8	Using data from the INTERROC study. Similar results observed when also adjusting for occupational exposure to oil mist. All analyses were conducted with a 5-year lag period.
						<u>For men:</u> (reference category: never exposed) **ever exposed to cadmium** (14 cases) OR (95%CI): 0.88 (0.46-1.66), **< 92.6 ug/m^3 blood cadmium level** (5 cases) OR (95%CI): 1.77	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						(0.57-5.47), **92.6 to < 184.1 ug/m^3 blood cadmium level** (1 case) OR (95%CI): 0.35 (0.04-2.77), **184.1 to < 394.9 ug/m^3 blood cadmium level** (2 cases) OR (95%CI): 0.63 (0.13-3.07), **≥ 394.9 ug/m^3 blood cadmium level** (6 cases) OR (95%CI): 0.85 (0.32-2.29), **p-value for linear trend**: 0.51 , **1 to 4 years exposed to cadmium** (5 cases) OR (95%CI): 0.85 (0.31-2.33), **5 to 14 years exposed to cadmium** (5 cases) OR (95%CI): 1.02 (0.35-3.00), **≥ 15 years exposed to cadmium** (4 cases) OR (95%CI): 0.77 (0.24-2.53), **p-value for linear trend**: 0.68 , **age at first cadmium exposure < 18 years old** (1 case) OR (95%CI): 0.38 (0.04-3.29), **age at first cadmium exposure ≥ 18 years old** (13 cases) OR (95%CI): 0.97 (0.50-1.89), **p-value for linear trend**: 0.8	
						For women: (reference category: never exposed) **ever exposed to cadmium** (16 cases) OR (95%CI): 1.01 (0.54-1.87), **< 92.6 ug/m^3 blood cadmium level** (8 cases) OR (95%CI): 2.15 (0.76-6.03), **92.6 to < 184.1 ug/m^3 blood cadmium level** (2 cases) OR (95%CI): 0.56 (0.12-2.63), **184.1 to < 394.9 ug/m^3 blood cadmium level** (2 cases) OR (95%CI): 0.39 (0.09-1.81), **≥ 394.9 ug/m^3 blood cadmium level** (4 cases) OR (95%CI): 1.26 (0.33-4.85), **p-value for linear trend**: 0.65, **1 to 4 years exposed to cadmium** (9 cases) OR (95%CI): 1.16 (0.50-2.69), **5 to 14 years exposed to cadmium** (5 cases) OR (95%CI): 1.06 (0.36-3.10),	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						≥ 15 years exposed to cadmium (2 cases) OR (95%CI): 0.54 (0.10-2.87), **p-value for linear trend**: 0.77, **age at first cadmium exposure < 18 years old** (3 cases) OR (95%CI): 1.44 (0.34-6.02), **age at first cadmium exposure ≥ 18 years old** (13 cases) OR (95%CI): 0.93 (0.47-1.85), **p-value for linear trend**: 0.93	
Pan SY **(2005)** **Case-control** **(37)**	Individuals aged 20 -76 years old, living in one of 8 Canadian provinces	1,009 incident cases	Exposure to occupational agent in occupation from questionnaire	Age (continuous), province of residence, sex, education level (years), alcohol consumption (serving/week), smoking pack-years (continuous), total energy intake (kcal/week)	Brain cancer (only malignant tumors)	**Men:** (reference category: never exposed) **ever exposed to cadmium salts** (13 cases) OR (95%CI): 1.44 (0.75-2.77), **1 to < 10 years of exposure to cadmium salts** (9 cases) OR (95%CI): 1.69 (0.75-3.81), **≥ 10 years of exposure to cadmium salts** (4 cases) OR (95%CI): 1.14 (0.37-3.50)	No exposed cases in women
Hu J **(1999)** **Case-control** **(40)**	Adults admitted to department of neural surgery in Heilongjiang province	183 incident cases (70 men, 113 women)	Self-reported exposure to occupational agent from questionnaire	Conditional on sex, age (5-year group), area of residence. For men adjusted for family income (low, medium, high), education (primary school, middle school, university), fruits/veggies consumption (quartiles among all subjects), also adjusted for smoking (pack-years) for women	Meningioma	**Men:**(reference category: never exposed) **ever exposed to cadmium** (5 cases) OR (95%CI): 9.35 (1.00-87.85) **Women:**(reference category: never exposed) **ever exposed to cadmium** (9 cases) OR (95%CI): 8.53 (1.62-44.96)	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Magnani C **(1986)** **Case-control** **(150)**	Men aged 18-54 residing in the counties of Cleveland, Humberside, and Cheschire, and in the Wirral district of Merseyside, UK	432 death	Exposure to occupational agents from a JEM	Conditional on county of residence or local authority and 5-year age groups	Brain Cancer	(reference category: no exposure) **potential exposure to cadmium and cadmium compounds** OR (95%CI): 0.9 (0.6-1.2)	Generally only the most recent fulltime job available from death certificate, occupational data more often available for cases than controls

SIR: Standardized incidence ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table V: Overview of the literature on the association between nickel and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Lightfoot N **(2010)** **Cohort** **(126)**	Men employed in Xstrata Nickel Sudbury, Ontario for 6 months or more between 1928 -2001 and who were alive as of 1 January 1964	23 incident cases, 21 deaths	Occupation from company payrolls	Age (5-year group), calendar period (5-year group)	Brain cancer	(expected cases calculated from rate in Ontario men) **workers in nickel cohort first hired at least 15 years ago** (23 cases) SIR (95%CI): 0.97 (0.61-1.45), (21 cases) SMR (95%CI): 1.20 (0.74-1.83)	
Navas-Acien A **(2002)** **Cohort** **(26)**	Swedish men and women employed in 1970, aged 24-65 years old	2,465 incident glioma cases, 848 incident meningioma cases	Exposure to occupational agent from 1960 and 1970 census and a JEM	Age, calendar period, geographical risk area and town size, solvents, metallic compounds, oil mist	Glioma	(reference category: no exposure) **possible/probable exposure** to nickel (83 cases) RR (95%CI): 1.17 (0.86-1.60),	Subjects exposed to nickel and subjects exposed to chromium were analysed jointly
					Meningioma	(reference category: no exposure) **possible/probable exposure to nickel** (23 cases) RR (95%CI): 0.96 (0.55-1.70)	
Becker N **(1999)** **Cohort** **(29)**	Turners and welders who had worked at least 6 months from 1950-1970 at one of 25 metal processing factories	4 deaths	Occupation from questionnaire answered by foreman and/or superior	Age, calendar period in 4 categories (1950-1967, 1968-1973, 1974-1978, and 1979-1985)	Brain cancer	(expected cases calculated from rate in German population) **welders using coated electrodes exposed to nickel fumes** (4 cases) SMR (95%CI): 6.19 (1.68-15.85), **welders with ≤ 25% effective welding period per day** (2 cases) SMR (95%CI): 1.96 (0.23-7.11), **welders with > 25% effective welding period per day** (2 cases) SMR (95%CI): 2.09 (0.25-7.55)	All subjects also exposed to welding and chromium fumes
Sankila R **(1990)** **Cohort** **(123)**	Workers in two glass factories, with at least 3 months of continuous employment between 1953-1971	6 incident cases (5 men, 1 woman)	Occupation from factory's employment record	Sex, age, time period	Brain cancer	(expected cases calculated from rate in general Finnish population) **glass factory workers** (6 cases) SIR (95%CI): (0.60 (0.22-1.31)	Subjects potentially exposed to chromium, arsenic, cadmium, lead, nickel oxide, and zinc selenite

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Polednak AO **(1981)** **Cohort** **(71)**	White men welders working in Oak ridge nuclear facilities between 1943-1977	3 deaths	Occupation from employment record	age (5-year group), calendar period (5-year group)	Brain cancer	(expected cases calculated from rate in the USA white men population) **welders exposed to nickel oxide** (3 cases) SMR (95%CI): 3.82 (0.79-13.79)	Also exposed to welding fumes
Carpenter AV **(1988)** **Nested case-control** **(67)**	Workers employed between 1943-1977 at two nuclear facilities located in Oak Ridge, Tennessee	89 deaths (72 men, 17 women)	Exposure to occupational agent from self-reported occupation assessed by industrial hygienist	Conditional on race, sex, place of employment, year of birth, year of hire	Brain cancer	(reference category: probably no exposure) **ever exposed to nickel** (60 cases) OR: 1.10, p-value: 0.74, **with 10-year lag period** (44 cases) OR:0.88, p-value: 0.67. **low potential for exposure to nickel** (32 cases) OR: 1.38, p-value:0.30, **with 10-year lag period** (28 cases) OR: 1.12, p-value: 0.73, **moderate potential for exposure to nickel** (14 cases) OR: 0.60, p-value: 0.17, **with 10-year lag period (**9 cases) OR: 0.43, p-value: 0.06, **high potential for exposure to nickel** (14 case) OR: 2.46, p-value: 0.06, **with 10-year lag period** (7 cases) OR: 1.70, p-value: 0.38. (reference category: < 1 year of high/moderate potential exposure) **exposed (high/moderate potential) to nickel for 1-3 years** (5 cases) OR: 0.54, p-value: 0.22, **with 10-year lag period** (5 cases) OR: 0.71 p-value: 0.52, **exposed (high/moderate potential) to nickel for >3 to 10 years** (2 cases) OR: 0.46, p-value: 0.32, **with 10-year lag period** (2 cases) OR: 0.46, p-value: 0.32, **exposed (high/moderate potential) to nickel for >10 to 20 years** (3 cases) OR: 0.87, p-value: 0.84, **with 10-year lag period** (2 cases) OR: 1.28, p-value: 0.80, **exposed**	Analyses included subjects exposed to nickel and subjects exposed to chromium. Similar results were obtained when adjusting for socioeconomic status (pay code and job classification), duration of employment, external radiation exposure, and internal radiation exposure or with a 5-year lag period

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						(high/moderate potential) to nickel for >20 years (2 cases) OR: 2.19, p-value: 0.40, **with 10-year lag period** (1 case) OR: 1.27, p-value: 0.84	
Parent ME **(2017)** **Case-control** **(79)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged 30 to 69 years old	1,800 incident cases	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary), time-weighted average International Occupational Prestige Scale (SIOPS) (continuous), atopy (never, ever asthma, allergy, and/or eczema), respondent status (self, proxy)	Glioma	(reference category: non-exposed) **subjects ever exposed to nickel** (215 cases) OR (95%CI): 0.9 (0.8-1.1), **≤ 317.2 ug/m^3 blood nickel level** (55 cases) OR (95%CI): 0.8 (0.5-1.1), **> 317.2 to ≤ 951.3 ug/m^3 blood nickel level** (72 cases) OR (95%CI): 0.9 (0.7-1.3), **> 951.3 ug/m^3 blood nickel level** (88 cases) OR (95%CI): 1.1 (0.8-1.5), **1-4 years of exposure to nickel** (46 cases) OR (95%CI): 0.8 (0.5-1.1), **5-9 years of exposure to nickel** (51 cases) OR (95%CI): 0.9 (0.6-1.3), **≥ 10 years of exposure to nickel** (118 cases) OR (95%CI): 1.0 (0.8-1.3), **ever exposure to nickel in males** (209 cases) OR (95%CI): 0.9 (0.8-1.2), **ever exposure to nickel in high grade glioma cases** (155 cases) OR (95%CI): 1.0 (0.8-1.2), **ever exposure to nickel in glioblastoma cases** (107 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to nickel in self-respondents** (184 cases) OR (95%CI): 0.9 (0.8-1.1)	Using data from the INTERROC study. Assessed exposure using a modified version of FINJEM. All analyses conducted using a 5-year lag period. No difference observed when conducting the analyses using different thresholds for the probability of exposure, using different lag time, or when conducting the analysis in women.
Sadetzki S **(2016)** **Case-control** **(43)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary)	Meningioma	<u>**For all subjects:**</u> (reference category: never exposed) **ever exposed to nickel** (106 cases) OR (95%CI): 1.14 (0.88-1.47), **< 225 ug/m^3 blood nickel level** (23 cases) OR (95%CI): 0.92 (0.57-1.48), **225 to < 600 ug/m^3 blood nickel level** (26 cases) OR (95%CI): 1.29 (0.81-2.05), **600 to < 1309.3 ug/m^3 blood nickel level** (19	Using data from the INTERROC study. Similar results observed when also adjusting for occupational exposure to oil mist. When conducting analyses on iron, chromium,

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
	2000 and 2004 aged ≥ 18 years old					cases) OR (95%CI): 0.90 (0.53-1.53), **≥ 1309.3 ug/m^3 blood nickel level** (38 cases) OR (95%CI): 1.44 (0.95-2.17), **p-value for linear trend**: 0.16, **1 to 4 years exposed to nickel** (27 cases) OR (95%CI): 0.87 (0.55-1.36), **5 to 14 years exposed to nickel** (41 cases) OR (95%CI): 1.35 (0.91-1.98), **≥ 15 years exposed to nickel** (38 cases) OR (95%CI): 1.21 (0.80-1.79), **p-value for linear trend**: 0.17 , **age at first nickel exposure < 18 years old** (38 cases) OR (95%CI): 1.04 (0.71-1.53), **age at first nickel exposure ≥ 18 years old** (68 cases) OR (95%CI): 1.21 (0.89-1.64), **p-value for linear trend**: 0.25	and nickel combined, no statistically significant results observed. All analyses were conducted with a 5-year lag period.
						For men: (reference category: never exposed) **ever exposed to nickel** (86 cases) OR (95%CI): 1.11 (0.83-1.47), **< 225 ug/m^3 blood nickel level** (18 cases) OR (95%CI): 0.91 (0.53-1.56), **225 to < 600 ug/m^3 blood nickel level** (22 cases) OR (95%CI): 1.31 (0.80-2.17), **600 to < 1309.3 ug/m^3 blood nickel level** (15 cases) OR (95%CI): 0.83 (0.47-1.50), **≥ 1309.3 ug/m^3 blood nickel level** (31 cases) OR (95%CI): 1.34 (0.86-2.10), **p-value for linear trend**: 0.38, **1 to 4 years exposed to nickel** (20 cases) OR (95%CI): 0.88 (0.53-1.48), **5 to 14 years exposed to nickel** (31 cases) OR (95%CI): 1.24 (0.80-1.90), **≥ 15 years exposed to nickel** (35 cases) OR (95%CI): 1.17 (0.77-1.77), **p-value for linear trend**: 0.33, **age at first nickel exposure < 18 years old**	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						(33 cases) OR (95%CI): 1.00 (0.66-1.52), **age at first nickel exposure ≥ 18 years old** (53 cases) OR (95%CI): 1.19 (0.84-1.68), **p-value for linear trend**: 0.38	
						<u>For women:</u> (reference category: never exposed) **ever exposed to nickel** (20 cases) OR (95%CI): 1.37 (0.76-2.46), **< 225 ug/m^3 blood nickel level** (5 cases) OR (95%CI): 0.95 (0.33-2.74), **225 to < 600 ug/m^3 blood nickel level** (4 cases) OR (95%CI): 1.11 (0.32-3.83), **600 to < 1309.3 ug/m^3 blood nickel level** (4 cases) OR (95%CI): 1.50 (0.39-5.69), **≥ 1309.3 ug/m^3 blood nickel level** (7 cases) OR (95%CI): 2.55 (0.77-8.47), **p-value for linear trend**: 0.13 , **1 to 4 years exposed to nickel** (7 cases) OR (95%CI): 0.82 (0.34-2.02), **5 to 14 years exposed to nickel** (10 cases) OR (95%CI): 2.03 (0.85-4.88)), **≥ 15 years exposed to nickel** (3 cases) OR (95%CI): 3.17 (0.32-30.95), **p-value for linear trend**: 0.12, **age at first nickel exposure < 18 years old** (5 cases) OR (95%CI): 1.45 (0.48-4.36), **age at first nickel exposure ≥ 18 years old** (15 cases) OR (95%CI): 1.34 (0.68-2.66), **p-value for linear trend**: 0.32	

SMR: Standardized mortality ratio, SIR: Standardized incidence ratio, RR: Risk ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table VI: Overview of the literature on the association between arsenic and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Wesseling C **2002)** **Cohort** **(27)**	Finnish women, born between 1906-1945, who reported their occupation in a 1970 national census	693 incident cases	Exposure to occupational agent from self-reported occupation in a 1970 census and a JEM	Year of birth , period of diagnosis, turnover rate	Brain cancer	(expected cases calculated from unexposed subjects) **low exposure to arsenic and its compounds** SIR (95%CI): 0.76 (0.50-1.17), **medium/high exposure to arsenic and its compounds** SIR (95%CI): 0.86 (0.51-1.46)	
Navas-Acien A **(2002)** **Cohort** **(26)**	Swedish men and women employed in 1970, aged 24-65 years old	2,465 incident glioma cases, 848 incident meningioma cases	Exposure to occupational agent from 1960 and 1970 census and a JEM	Age, calendar period, geographical risk area, town size, pesticides/herbicides	Glioma	(reference category: no exposure) **possible exposure to arsenic** (34 cases) RR (95%CI): 1.61 (1.12-2.32)	
					Meningioma	(reference category: no exposure) **possible exposure to arsenic** (7 cases) RR (95%CI): 1.07 (0.49-2.33)	
Sankila R **(1990)** **Cohort** **(123)**	Workers in two glass factories, with at least 3 months of continuous employment between 1953-1971	6 incident cases (5 men, 1 woman)	Occupation from factory's employment record	Sex, age, time period	Brain cancer	(expected cases calculated from rate in general Finnish population) **glass factory workers** (6 cases) SIR (95%CI):0.60 (0.22-1.31)	Subjects potentially exposed to chromium, arsenic, cadmium, lead, nickel oxide, and zinc selenite
Pan SY **(2005)** **Case-control** **(37)**	Individuals aged 20-76 years old, living in one of 8 Canadian provinces	1,009 incident cases	Exposure to occupational agent in occupation from questionnaire	Age (continuous), province of residence, sex (when both sexes included in analyses), education level (years), alcohol consumption (serving/week), smoking pack-years (continuous), total energy intake (kcal/week)	Brain cancer (only malignant tumors)	(reference category: never exposed) **ever exposed to arsenic salts** (12 cases) OR (95%CI): 1.25 (0.64-2.45), **1 to < 10 years of exposure to arsenic salts** (9 cases) OR (95%CI): 1.35 (0.61-2.99), **≥ 10 years of exposure to arsenic salts** (3 cases) OR (95%CI): 1.08 (0.30-3.90)	.
						Men: (reference category: never exposed) **ever exposed to arsenic salts** (11 cases) OR (95%CI): 1.44 (0.70-2.95)	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						Women: (reference category: never exposed) **ever exposed to arsenic salts** (1 case) OR (95%CI): 0.52 (0.06-4.34)	

SIR: Standardized incidence ratio, RR: Risk Ratio, OR: Odds ratio. 95%CI: 95% confidence interval.

Table VII: Overview of the literature on the association between silicon and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Hobbesland A **(1999)** **Cohort** **(127)**	Men employed between 1933-1991 for at least 6 months at one of 8 plants producing ferrosilicon and silicon metal	16 incident cases	Occupation from employment record	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from national men rate) **furnace workers** (5 cases) SIR (95%CI): 0.72 (0.23-1.76), **non-furnace workers** (11 cases) SIR (95%CI): 1.07 (0.53-1.91)	Furnace workers are exposed to higher level of ferrosilicon and silicon metal. Subjects also exposed to silica

SIR: Standardized incidence ratio, 95%CI: 95% confidence interval.

Table VIII: Overview of the literature on the association between chromium and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Hara T **(2010)** **Cohort** **(28)**	Men working as platers, alive and aged ≥ 35 years old with ≥ 5 years of employment	4 deaths	Occupation from questionnaire sent to employers	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from national men rate) **chromium platers** (3 cases) SMR (95%CI): 9.14 (1.81-22.09), **only including the follow-up period from 1976-1989** (1 case) SMR (95%CI): 7.85 (0.01-30.16), **only including the follow-up period 1990-2003** (2 cases) SMR (95%CI): 9.96 (1.03-28.09), **working as chromium plater for 1-10 years** (1 case) SMR (95%CI): 5.61 (0.01-21.57), **working as chromium plater for 11-20 years** (2 cases) SMR (95%CI): 25.22 (2.60-71.11), **first year of work between 1960-1969** (2 cases) SMR (95%CI): 16.00 (1.65-45.11), **first year of work between 1970-1976** (1 case) SMR (95%CI): 11.80 (0.02-45.35)	
Navas-Acien A **(2002)** **Cohort** **(26)**	Swedish men and women employed in 1970, aged 24-65 years old	2,465 incident glioma cases, 848 incident meningioma cases	Exposure to occupational agent from 1960 and 1970 census and a JEM	Age, calendar period, geographical risk area, town size, solvents, metallic compounds, oil mist	Glioma	(reference category: no exposure) **possible/probable exposure to chromium** (83 cases) RR (95%CI): 1.17 (0.86-1.60)	Subjects exposed to nickel and subjects exposed to chromium were analysed jointly
					Meningioma	(reference category: no exposure) **possible/probable exposure to chromium** (23 cases) RR (95%CI): 0.96 (0.55-1.70)	
Wesseling C **(2002)** **Cohort** **(27)**	Finnish women, born between 1906-1945, who reported their occupation in a 1970 national census	693 incident cases	Exposure to occupational agent from self-reported occupation in a 1970 census and a JEM	Year of birth , period of diagnosis, turnover rate	Brain cancer	(expected cases calculated from unexposed subjects) **low exposure to chromium and its compounds** SIR (95%CI): 0.77 (0.58-1.03), **medium/high exposure to chromium and its compounds** SIR (95%CI): 1.88 (1.17-3.04).	Associations were similar (low exposure) or closer to null (medium/high exposure) when further adjusting models for exposure to cadmium and lead

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Becker N **(1999)** **Cohort** **(29)**	Turners and welders who had worked at least 6 months from 1950-1970 at one of 25 metal processing factories	4 deaths	Occupation from questionnaire answered by foreman and/or superior	Age, calendar period in 4 categories (1950-1967, 1968-1973, 1974-1978, and 1979-1985)	Brain cancer	(expected cases calculated from rate in German population) **welders using coated electrodes exposed to chromium fumes** (4 cases) SMR (95%CI): 6.19 (1.68-15.85), **welders with ≤ 25% effective welding period per day** (2 cases) SMR (95%CI): 1.96 (0.23-7.11), **welders with > 25% effective welding period per day** (2 cases) SMR(95%CI): 2.09 (0.25-7.55)	All subjects also exposed to welding and nickel fumes
Sankila R **(1990)** **Cohort** **(123)**	Workers in two glass factories, with at least 3 months of continuous employment between 1953-1971	6 incident cases (5 men, 1 woman)	Occupation from factory's employment record	Sex, age, time period	Brain cancer	(expected cases calculated from rate in general Finnish population) **glass factory workers** (6 cases) SIR (95%CI): 0.60 (0.22-1.31)	Subjects potentially exposed to chromium, arsenic, cadmium, lead, nickel oxide, and zinc selenite
Carpenter AV **(1988)** **Nested case-control** **(67)**	Workers employed between 1943-1977 at two nuclear facilities located in Oak Ridge, Tennessee	89 deaths (72 men, 17 women)	Exposure to occupational agent from self-reported occupation assessed by industrial hygienist	Conditional on race, sex, place of employment, year of birth, year of hire	Brain cancer	(reference category: probably no exposure) **ever exposed to chromium** (60 cases) OR: 1.10, p-value: 0.74,**with 10-year lag period** (44 cases) OR:0.88, p-value: 0.67. **low potential for exposure to chromium** (32 cases) OR:1.38, p-value:0.30, **with 10-year lag period** (28 cases) OR:1.12, p-value: 0.73, **moderate potential for exposure to chromium** (14 cases) OR: 0.60, p-value: 0.17, **with 10-year lag period (**9 cases) OR: 0.43, p-value: 0.06, **high potential for exposure to chromium** (14 cases) OR:2.46, p-value: 0.06, **with 10-year lag period** (7 cases) OR:1.70, p-value: 0.38. (reference category: < 1 year of high/moderate potential exposure) **exposed (high/moderate potential) to chromium for 1-3 years** (5 cases) OR:0.54, p-value: 0.22, **with 10-year lag period** (5 cases) OR:0.71, p-value: 0.52,	Analyses included subjects exposed to nickel and subjects exposed to chromium. Similar results were obtained when adjusting for socioeconomic status (pay code and job classification), duration of employment, external radiation exposure, and internal radiation exposure or with a 5-year lag period

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						exposed (high/moderate potential) to chromium for >3 to 10 years (2 cases) OR:0.46, p-value: 0.32, **with 10-year lag period** (2 cases) OR:0.46, p-value: 0.32, **exposed (high/moderate potential) to chromium for >10 to 20 years** (3 cases) OR:0.87, p-value: 0.84, **with 10-year lag period** (2 cases) OR:1.28, p-value: 0.80, **exposed (high/moderate potential) to chromium for >20 years** (2 cases) OR: 2.19, p-value: 0.40, **with 10-year lag period** (1 case) OR: 1.27, p-value: 0.84	
Parent ME **(2017)** **Case-control** **(79)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged 30 to 69 years old	1,800 incident cases	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary), time-weighted average International Occupational Prestige Scale (SIOPS) (continuous), atopy (never, ever asthma, allergy, and/or eczema), respondent status (self, proxy)	Glioma	(reference category: non-exposed) **subjects ever exposed to chromium** (178 cases) OR (95%CI): 0.9 (0.7-1.1), **≤ 445.5 ug/m^3 blood chromium level** (61 cases) OR (95%CI):0.9 (0.6-1.3), **> 445.5 to ≤ 3000 ug/m^3 blood chromium level** (57 cases) OR (95%CI): 0.9 (0.6-1.3), **> 3000 ug/m^3 blood chromium level** (60 cases) OR (95%CI): 0.9 (0.6-1.3), **1-4 years of exposure to chromium** (41 cases) OR (95%CI): 0.9 (0.6-1.3), **5-9 years of exposure to chromium** (36 cases) OR (95%CI): 0.8 (0.5-1.2), **≥ 10 years of exposure to chromium** (101 cases) OR (95%CI): 1.0 (0.8-1.4), **ever exposure to chromium in males** (175 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to chromium in high grade glioma cases** (124 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to chromium in glioblastoma cases** (83 cases) OR (95%CI): 0.8 (0.6-1.1), **ever exposure to chromium in self-respondents** (150 cases) OR (95%CI): 0.9 (0.7-1.1)	Using data from the INTERROC study. Assessed exposure using a modified version of FINJEM. All analyses conducted using a 5-year lag period. No difference observed when conducting the analyses using different thresholds for the probability of exposure, using different lag time, or when conducting the analysis in women.

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Sadetzki S **(2016)** **Case-control** **(43)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged ≥ 18 years old	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary)	Meningioma	**For all subjects:** (reference category: never exposed) **ever exposed to chromium** (89 cases) OR (95%CI): 1.23 (0.93-1.62), **< 346.5 ug/m^3 blood chromium level** (14 cases) OR (95%CI): 0.88 (0.48-1.63), **346.5 to < 776.4 ug/m^3 blood chromium level** (15 cases) OR (95%CI): 0.90 (0.50-1.62), **776.4to < 5775 ug/m^3 blood chromium level** (29 cases) OR (95%CI): 1.42 (0.90-2.24), **≥ 5775 ug/m^3 blood chromium level** (31 cases) OR (95%CI): 1.60 (1.01-2.53), **p-value for linear trend**: 0.03 , **1 to 4 years exposed to chromium** (21 cases) OR (95%CI): 0.96 (0.58-1.60), **5 to 14 years exposed to chromium** (34 cases) OR (95%CI): 1.29 (0.85-1.96), **≥ 15 years exposed to chromium** (34 cases) OR (95%CI): 1.41 (0.92-2.15), **p-value for linear trend**: 0.07, **age at first chromium exposure < 18 years old** (22 cases) OR (95%CI): 1.21 (0.73-1.99), **age at first chromium exposure ≥ 18 years old** (67 cases) OR (95%CI): 1.24 (0.90-1.69), **p-value for linear trend**: 0.15	Using data from the INTERROC study. Similar results observed when also adjusting for the Standard International Occupation Prestige Scale (SIOPS), marital status, cigarette smoking, respondent status, allergy history, age of first exposure, and occupational exposure to oil mist or when using different probability of exposure thresholds. Significant positive trend observed when conducting analyses 5-14 and 15-24 years before reference. When stratifying by menopause status, the results were only significant in the postmenopausal group. When conducting
						For men: (reference category: never exposed) **ever exposed to chromium** (73 cases) OR (95%CI): 1.21 (0.89-1.64), < **346.5 ug/m^3 blood chromium level** (13 cases) OR (95%CI): 0.91 (0.48-1.71), **346.5 to < 776.4 ug/m^3 blood chromium level** (14 cases) OR (95%CI): 1.08 (0.59-2.00), **776.4to < 5775 ug/m^3 blood chromium level** (22 cases) OR (95%CI): 1.40 (0.83-2.34), **≥ 5775 ug/m^3 blood chromium level** (24 cases) OR (95%CI): 1.40 (0.84-2.32), **p-value for linear trend**: 0.10, **1 to 4 years exposed to chromium** (16 cases) OR (95%CI): 1.05	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						(0.59-1.88), **5 to 14 years exposed to chromium** (26 cases) OR (95%CI): 1.19 (0.75-1.91), **≥ 15 years exposed to chromium** (31 cases) OR (95%CI): 1.33 (0.85-2.06), **p-value for linear trend**: 0.17, **age at first chromium exposure < 18 years old** (19 cases) OR (95%CI): 1.16 (0.68-1.97), **age at first chromium exposure ≥ 18 years old** (54 cases) OR (95%CI): 1.23 (0.87-1.75), **p-value for linear trend**: 0.22	analyses on iron, chromium, and nickel combined, no statistically significant results observed. All analyses were conducted with a 5-year lag period.
						<u>For women:</u> (reference category: never exposed) **ever exposed to chromium** (16 cases) OR (95%CI): 1.45 (0.74-2.83), **< 346.5 ug/m^3 blood chromium level** (1 case) OR (95%CI): 0.72 (0.06-8.45), **346.5 to < 776.4 ug/m^3 blood chromium level** (1 case) OR (95%CI): 0.24 (0.03-1.99), **776.4to < 5775 ug/m^3 blood chromium level** (7 cases) OR (95%CI): 1.57 (0.58-4.26), **≥ 5775 ug/m^3 blood chromium level** (7 cases) OR (95%CI): 5.06 (1.25-20.55), **p-value for linear trend**: 0.08, **1 to 4 years exposed to chromium** (5 cases) OR (95%CI): 0.73 (0.25-2.10), **≥ 5 years exposed to chromium** (11 cases) OR (95%CI): 2.58 (1.03-6.47), **p-value for linear trend**:0.11 , **age at first chromium exposure < 18 years old** (3 cases) OR (95%CI): 2.00 (0.42-9.48), **age at first chromium exposure ≥ 18 years old** (13 cases) OR (95%CI): 1.35 (0.64-2.83), **p-value for linear trend**: 0.33	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Pan SY **(2005)** **Case-control** **(37)**	Individuals aged 20-76 years old, living in one of 8 Canadian provinces	1,009 incident cases	Exposure to occupational agent in occupation from questionnaire	Age (continuous), province of residence, sex (when both sexes included in analyses), education level (years), alcohol consumption (serving/week), smoking pack-years (continuous), total energy intake (kcal/week)	Brain cancer (only malignant tumors)	(reference category: never exposed) **ever exposed to chromium salts** (16 cases) OR (95%CI): 1.35 (0.75-2.41), **1 to < 10 years of exposure to chromium salts** (10 cases) OR (95%CI): 1.53 (0.72-3.28), **≥ 10 years of exposure to chromium salts** (6 cases) OR (95%CI): 1.16 (0.47-2.89)	.
						Men: (reference category: never exposed) **ever exposed to chromium salts** (14 cases) OR (95%CI): 1.40 (0.74-2.63)	
						Women: (reference category: never exposed) **ever exposed to chromium salts** (2 cases) OR (95%CI): 1.06 (0.22-5.12)	

SIR: Standardized incidence ratio. SMR: Standardized mortality ratio, RR: Risk ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table IX: Overview of the literature on the association between mercury and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Navas-Acien A **(2002)** **Cohort** **(26)**	Swedish men and women employed in 1970, aged 24-65 years old	2,465 incident glioma cases, 848 incident meningioma cases	Exposure to occupational agent from 1960 and 1970 census and a JEM	Age, calendar period, geographical risk area, town size, solvents	Glioma	(reference category: no exposure) **probable exposure to mercury** (12 cases) RR (95%CI): 1.76 (0.99-3.14)	
					Meningioma	(reference category: no exposure) **probable exposure to mercury** (4 cases) RR (95%CI): 1.39 (0.51-3.77)	
Boffetta P **(1998)** **Cohort** **(124)**	Men employed in four mercury mines in Italy, Spain, Slovenia, and Ukraine	14 deaths	Occupation from employment record	Age, calendar period	Brain cancer	(expected cases calculated from rates in Spain, Slovenia, and Italy population obtained from the WHO) **all mercury mine workers** (14 cases) SMR (95%CI):1.00 (0.55-1.68), **mercury mine workers in Italy** (2 cases) SMR (95%CI): 0.82 (0.10-2.95), **mercury mine workers in Spain** (9 cases) SMR (95%CI): 1.12 (0.51-2.13), **mercury mine workers in Slovenia** (3 cases) SMR (95%CI): 0.85 (0.18-2.48), **workers with longest employment in mine** (10 cases) SMR (95%CI): 1.04 (0.50-1.90), **workers with longest employment in mills** (4 cases) SMR (95%CI): 0.99 (0.27-2.53)	No brain cancer case in Ukraine. Subjects also exposed to silica and radon, information on average concentration of mercury in each mine available
Loomis DP **(1996)** **Cohort** **(74)**	Workers employed at least 30 days at Y-12 nuclear production plant between 1947-1974	20 deaths	Occupation from employment record	Age, calendar time, sex (for analyses of both sexes combined)	Brain cancer	(expected cases calculated from rate in USA population) **all subjects working in nuclear materials production plant** (20 cases) SMR (95%CI): 1.29 (0.79-2.00)	Not all subjects exposed to mercury. Subjects also exposed to relatively low doses of internal alpha radiation and external penetrating radiation, as well as to beryllium, metal dusts, and solvents
						Men: (expected cases calculated from rate in USA population) **all white men working in nuclear materials production plant** (18 cases) SMR (95%CI): 1.28 (0.76-2.02)	
						Women: (expected cases calculated from rate in USA population) **all women working in nuclear materials production plant** (2 cases) SMR (95%CI): 1.82 (0.20-6.59)	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Merler E **(1994)** **Cohort** **(76)**	Individuals receiving compensations because of disabilities due to mercury intoxication, resident in the province of Arezzo, and still being paid in 1974	4 deaths (2 men, 2 women)	Claim of mercury poisoning from pensions award list	Age, calendar period	Brain cancer	**Men:** (expected cases calculated from the national Italian rates) **subjects with mercury poisoning claim** (2 cases) SMR: 2.63 **Women:** (expected cases calculated from the national Italian rates) **subjects with mercury poisoning claim** (2 cases) SMR (95%CI):1.31 (0.15-4.72)	No 95%CI provided for analysis in men
Ellingsen DG **(1993)** **Cohort** **(125)**	Men employed in one of three chloralkali plants for more than a year before 1989	2 incident cases	Occupation from company record	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from rate in Norwegian men population) **chloralkali factory workers first employed before 1980** (2 cases) SIR (95%CI): 0.82 (0.08-2.94)	
Barregard L **(1990)** **Cohort** **(75)**	Swedish men working at one of 8 chloralkali plants and monitored with urine or blood mercury for more than 1 year until 1984	4 incident cases	Occupation with urinary/blood mercury measurements	Age (5-year group), calendar year	Bain cancer	(expected cases calculated from rate in general Swedish men population) **working in chloralkali plant** (4 cases) SMR: 2.2, **with 10-year lag period** (3 cases) SMR (95%CI): 2.7 (0.5-7.7)	95%CI not calculated for analysis without lag period, around 70% of subjects had a cumulative mercury in blood of < 1000 ug/L
McLaughlin JK **(1987)** **Cohort** **(30)**	Swedish men employed in 1960	3,394 incident cases	Occupation from 1960 census	5-year birth cohort, region	Glioma	(expected cases calculated from rate in the general Swedish population) **dentists** (12 cases) SIR: 2.1, p-value: <0.05	Dentists potentially exposed to mercury

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Ahlbom A **(1986)** **Cohort** **(31)**	Men and women dentists, and women dental nurses, aged 24-64 years old, and identified from a national census in 1960	18 glioblastoma incident cases, 4 glioma incident cases, 6 meningioma incident cases	Occupation from 1960 census	Age (5-year group), sex, county (for glioblastoma analyses)	Glioblastoma	(expected cases calculated in the employed population) **all subjects** (18 cases) SIR (95%CI): 2.1 (1.3-3.4), **dentist men only** (9 cases) SIR (95%CI): 2.0 (0.9-3.7), **dentist women only** (3 cases) SIR (95%CI): 2.5 (0.5-7.2), **dental nurse women only** (6 cases) SIR (95%CI): 2.2 (0.8-4.9)	
					Glioma	(expected cases calculated in the employed population) **all subjects** (4 cases) SIR (95%CI): 1.8 (0.5-4.7), **dentist men only** (2 cases) SIR (95%CI): 2.0 (0.2-7.3), **dental nurse women only** (2 cases) SIR (95%CI): 2.1 (0.2-7.4)	
					Meningioma	(expected cases calculated in the employed population) **all subjects** (6 cases) SIR (95%CI): 1.3 (0.5-2.8), **dentist men only** (4 cases) SIR (95%CI): 2.6 (0.7-6.6), **dentist women only** (1 case) SIR (95%CI): 1.0 (0-5.6), **dental nurse women only** (1 case) SIR (95%CI): 0.5 (0-2.7)	
Cragle DL **(1984)** **Cohort** **(128)**	White men employed at the Y-12 Plant at least one day and whom worked for at least 4 months when exposure to mercury were likely to be high	18 deaths	Occupation with urinalyses of mercury from company record	Age (5-year group), time period	Brain cancer	(expected cases calculated from rate in USA men), **workers exposed to mercury** (4 cases) SMR: 1.22, p-value: >0.05, **worked > 1 year only** (3 cases) SMR: 1.12, p-value: >0.05	All subjects had ≤ 0.3 mg of mercury per liter of urine
Carozza SE **(2000)** **Case-control** **(77)**	Individuals aged at least 20 years old living in the San Francisco bay area	476 incident cases	Self-reported occupation from questionnaire	Age (20-54, ≥55), sex, years of education (<16, ≥16), and race (White, non-White)	Glioma	(reference category: subjects not employed in occupation) **ever employed as dentists and dental technicians** (7 cases) OR (95%CI): 1.0 (0.4-3.0), **<10 years employment only** OR (95%CI): 0.6 (0.2-2.0), **with a 10-year lag period, ever**	Dentists might be exposed to mercury

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						employed as dentists and dental technicians OR (95%CI): 1.5 (0.5-4.7), **< 10 years employment only** OR (95%CI): 1.0 (0.3-3.6)	
Carpenter AV **(1988)** **Nested case-control** **(67)**	Workers employed between 1943-1977 at two nuclear facilities located in Oak Ridge, Tennessee	89 deaths (72 men, 17 women)	Exposure to occupational agent from self-reported occupation assessed by industrial hygienist	Conditional on race, sex, place of employment, year of birth, year of hire	Brain cancer	reference category: probably no exposure) **ever exposed to mercury** (29 cases) OR: 1.77, p-value: 0.34,**with 10-year lag period** (21 cases) OR:1.35, p-value: 0.63. **low potential for exposure to mercury** (21 cases) OR:2.01, p-value:0.26, **with 10-year lag period** (16 cases) OR:1.58, p-value: 0.47, **moderate potential for exposure to mercury** (7 cases) OR: 1.33, p-value: 0.69, **with 10-year lag period (**4 cases) OR: 0.77, p-value: 0.74, **high potential for exposure to mercury** (1 case) OR:1.19, p-value: 0.89, **with 10-year lag period** (1 case) OR:1.57, p-value: 0.72. (reference category: < 1 year of high/moderate potential exposure) **exposed (high/moderate potential) to mercury for 1-3 years** (2 cases) OR:1.11, p-value: 0.90, **exposed (high/moderate potential) to mercury for >3 to 10 years** (1 case) OR:0.30, p-value: 0.29, **with 10-year lag period** (1 case) OR:0.96, p-value: 0.96, **exposed (high/moderate potential) to mercury for >10 to 20 years** (1 case) OR:0.30, p-value: 0.28, **exposed (high/moderate potential) to mercury for >20 years** (2 cases) OR: 2.10, p-value: 0.50, **with 10-year lag period** (2 cases) OR: 1.86, p-value: 0.57	Similar results were obtained when adjusting for socioeconomic status (pay code and job classification), duration of employment, external radiation exposure, and internal radiation exposure or with a 5-year lag period
Magnani C **(1986)** **Case-control** **(150)**	Men aged 18-54 residing in the counties of Cleveland, Humberside, and Cheschire, and in	432 death	Exposure to occupational agents from a JEM	Conditional on county of residence or local authority and 5-year age groups	Brain Cancer	(reference category: no exposure) potential exposure to mercury and mercury compounds OR (95%CI): 0.8 (0.4-1.3)	Generally only the most recent fulltime job available from death certificate, occupational data

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
	the Wirral district of Merseyside, UK						more often available for cases than controls

SIR: Standardized incidence ratio, SMR: Standardized mortality ratio, RR: Risk ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table X: Overview of the literature on the association between lead and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Steenland K **(2017)** **Cohort** **(141)**	Workers from three large cohort studies conducted in the USA (143), Finland (130, 138), and UK (142)	111 deaths (from 39 malignant brain cancers and 72 benign brain cancers)	Blood lead level	For HR: birth year decade, gender, country For SMR: stratified by 5-year age groups, gender, calendar time categories	Brain cancer	(reference: < 20 ug/dl maximum blood lead) **20 to < 30 ug/dl maximum blood lead** (26 cases) HR (95%CI): 1.31 (0.79-2.17), **30 to < 40 ug/dl maximum blood lead** (14 cases) HR (95%CI): 1.05 (0.55-1.99), **≥ 40 ug/dl maximum blood lead** (33 cases) HR (95%CI): 1.42 (0.83-2.43), (continuous) **maximum blood lead value** HR: 1.29, p-value: 0.09, (expected rate calculated from each country national mortality rate) **< 20 ug/m^3 maximum blood lead** (39 cases) SMR (95%CI): 0.78 (0.54-1.03), **20 to 39 ug/m^3 maximum blood lead** (40 cases) SMR (95%CI): 0.84 (0.58-1.10), **≥ 40 ug/m^3 maximum blood lead** (33 cases) SMR (95%CI): 0.93 (0.61-1.20)	Half of pooled cohort only had 1 blood lead test. 4 % of pooled cohort were women
Liao LM **(2016)** **Cohort** **(33)**	Women aged 40-70 years old and men aged 40-74 years old residing in Shanghai from 2 cohort studies (180, 181)	77 incident brain cancer cases, 59 meningioma cases	Exposure to occupational agents from a JEM calibrated with exposure measurements	Education (elementary school or less, middle school, high school, professional/college or higher), income level (cohort specific), cigarette pack-years (study specific), and menopausal status for the female cohort	Brain cancer	(reference: never exposed) **ever exposed to lead dusts and fume** (10 cases) RR (95%CI): 1.8 (0.7-4.8), **low exposure to lead dusts and fume** (7 cases) RR (95%CI): 3.1 (1.0-9.1), **high exposure to lead dusts and fume** (3 cases) RR (95%CI): 1.0 (0.3-3.2),**ever exposed to lead dusts** (5 cases) RR (95%CI): 2.3 (0.9-5.8), **low exposure to lead dusts** (2 cases) RR (95%CI): 2.0 (0.5-8.3), **high exposure to lead dusts** (3 cases) RR (95%CI): 2.6 (0.8-8.2), **ever exposed to lead fume** (9 cases) RR (95%CI): 1.8 (0.8-4.1), **low exposure to lead fume** (6 cases) RR (95%CI): 2.9 (1.2-6.7), **high exposure to lead fume** (3 cases) RR (95%CI): 1.1 (0.3-3.5) **cohort of men:** (reference: never exposed) **ever exposed to lead dusts and fume** (2 cases) RR (95%CI): 0.9 (0.2-	Used meta-analysis with random effects for pooled RR. Update of (78)

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						3.8), **low exposure to lead dusts and fume** (1 case) RR (95%CI): 1.2 (0.2-8.5), **high exposure to lead dusts and fume** (1 case) RR (95%CI): 0.7 (0.1-5.4) **<u>cohort of women:</u>** (reference: never exposed) **ever exposed to lead dusts and fume** (8 cases) RR (95%CI): 2.6 (1.2-5.6), **low exposure to lead dusts and fume** (6 case) RR (95%CI): 4.2 (1.8-10.1), **high exposure to lead dusts and fume** (2 case) RR (95%CI): 1.2 (0.3-5.0)	
					Meningioma (women cohort only)	(reference: never exposed) **ever exposed to lead dusts and fume** (9 cases) RR (95%CI): 2.4 (1.1-5.0), **low exposure to lead dusts and fume** (3 cases) RR (95%CI): 1.7 (0.5-5.4), **high exposure to lead dusts and fume** (6 cases) RR (95%CI): 3.1 (1.3-7.4), **ever exposed to lead dusts** (5 cases) RR (95%CI): 2.9 (1.1-7.3), **low exposure to lead dusts** (1 case) RR (95%CI): 1.5 (0.2-10.6), **high exposure to lead dusts** (4 cases) RR (95%CI): 3.8 (1.4-10.7), **ever exposed to lead fume** (9 cases) RR (95%CI): 2.6 (1.2-5.4), **low exposure to lead fume** (4 cases) RR (95%CI): 2.2 (0.8-6.3), **high exposure to lead fume** (5 cases) RR (95%CI): 3.0 (1.2-7.6)	
Gwini S **(2012)** **Cohort** **(144)**	Male workers from Victoria and New South Wales (Australia) in lead exposed occupations with confirmed vital status after 1982	6 incident cases	Having worked in occupations defined by the government as exposed to inorganic lead and from blood lead level	Age (5-year group) sex, calendar year	Brain cancer	(expected cases calculated from the national incidence cancer rate) **male workers exposed to inorganic lead** (6 cases) SIR (95%CI): 105 (47-233), **male workers exposed to inorganic lead with complete date of birth (1 case)** SIR (95%CI) : 63 (9-450), **male workers exposed to inorganic lead with incomplete date of birth (5 cases)** SIR (95%CI) : 120 (50-289), **male workers with at least one blood lead level**	Examined inorganic lead. Blood lead was available for 63.5% of cohort

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						measurement ≤ 30ug/dl (2 cases) SIR (95%CI): 100 (25-402)	
LAM TV **(2007)** **Cohort** **(133)**	Working men resident of New Jersey with blood lead measurement	2 incident cases	Blood lead level > 25 ug/dl (measurement obtained from the New Jersey adult blood lead epidemiology and surveillance system)	Age (5-year groups), calendar year	Brain cancer	(expected cases calculated from the New Jersey State Cancer Registry rate) **workers with blood lead level >25 ug/dl** (2 cases) SIR (95%CI): 0.83 (0.09-3.00)	Subjects could be exposed to cadmium and/or arsenic
Van Wijngaarden E **(2006)** **Cohort** **(32)**	Individuals from USA with occupational or industry code available from the national longitudinal mortality study	119 deaths	Exposure to occupational agent from self-reported occupation in 1980-1981 survey and a JEM	Age (continuous), race (white or non-white), urban status (urban or rural), marital status (ever or never married) and education level (< any high school, some high school or some college).	Brain cancer	(reference category: no exposure) **exposure to lead** (29 cases) HR (95%CI): 1.56 (1.00-2.43), **low probability of exposure to lead only** (3 cases) HR (95%CI): 0.72 (0.23-2.30), **medium probability of exposure to lead only** (13 cases) HR (95%CI): 1.47 (0.81-2.68), **high probability of exposure to lead only** (13 cases) HR (95%CI): 2.35 (1.28-4.32), **low intensity of exposure to lead** (16 cases) HR (95%CI): 1.33 (0.77-2.31), **medium intensity of exposure to lead** (13 cases) HR (95%CI): 1.99 (1.09-3.66), **medium/high intensity of exposure to lead** (10 cases) HR (95%CI): 2.50 (1.27-4.92), **high intensity of exposure to lead** (3 cases) HR (95%CI): 1.19 (0.37-3.80), **only including probability of exposure > low, low intensity of exposure to lead** (13 cases) HR (95%CI): 1.61 (0.88-2.92), **medium/high intensity of exposure to lead** (13 cases) HR (95%CI): 2.05 (1.12-3.76), **only including probability of exposure > medium, medium/high intensity of exposure to lead** (13 cases) HR (95%CI): 2.39 (1.29-4.41)	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Wesseling C **(2002)** **Cohort** **(27)**	Finnish women, born between 1906-1945, who reported their occupation in a 1970 national census	693 incident cases	Exposure to occupational agent from 1970 census occupation and a JEM	Year of birth, period of diagnosis, turnover rate	Brain cancer	(expected cases calculated from unexposed subjects) **low exposure to lead and its compounds** SIR (95%CI): 1.25 (1.00-1.57)**, medium/high exposure to lead and its compounds** SIR (95%CI): 1.33 (0.90-1.96)	Associations were closer to null when further adjusting for exposure to chromium and cadmium or nickel and cadmium
Navas-Acien A **(2002)** **Cohort** **(26)**	Swedish men and women employed in 1970, aged 24-65 years old	2,465 incident glioma cases, 848 incident meningioma cases	Exposure to occupational agent from 1960 and 1970 census and a JEM	Age, calendar period, geographical risk area, and town size	Glioma	(reference category: no exposure) **possible exposure to lead** (10 cases) RR (95%CI): 1.08 (0.58-2.01)	
					Meningioma	**possible exposure to lead** (7 cases) RR (95%CI): 2.36 (1.12-4.96)	
Englyst V **(2001)** **Cohort** **(135)**	Smelter exposed to lead employed for at least 1 year between 1928-1979, and also included in the blood lead register	1 incident case	Occupation and blood lead level from company record	Age (5-year group), sex, calendar year	Brain cancer	(expected cases calculated from rate in county) **workers employed at lead department with a 15-year lag period** (1 case) SIR (95%CI): 0.6 (0.02-3.6)	This study analysed a sub cohort of Lundstrom NG et al. 1997 (82), cohort mean yearly blood lead index = 24 umol/l, subjects might have worked at an arsenic or nickel plant
Wong O **(2000)** **Cohort** **(137)**	Men working in a lead battery plant or as lead smelters, with at least 1 year of employment between 1946-1970	15 deaths (10 deaths in lead battery workers, 5 deaths in lead smelters)	Occupation from company record	Age, calendar time	Brain cancer	(expected cases calculated from rate in USA men) **all subjects** (15 cases) SMR (95%CI): 0.75 (0.42-1.23), with **< 20-year lag period** (4 case) SMR: 8.87, p-value > 0.05,with **20-34-year lag period** (2 cases) SMR: 0.26, p-value < 0.05, **with > 34-year lag period** (4 cases) SMR: 1.15, p-value > 0.05, **subjects hired before 1946** (7 cases) SMR: 0.67, p-value > 0.05**, subjects hired after 1946** (8 cases) SMR: 0.83, p-value > 0.05,	Urinary lead measurements (average = 129.7 ug/l for lead battery workers and 173.2 ug//l for lead smelters) and blood lead measurements (average = 62.7 ug/100g for lead

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						subjects with 1-9 years of employments (2 case) SMR: 0.47, p-value > 0.05, **subjects with 10-19 years of employments** (5 cases) SMR: 1.28, p-value > 0.05, **subjects with ≥ 20 years of employments** (8 cases) SMR: 0.67, p-value > 0.05, **lead battery smelters only** (5 cases) SMR (95%CI): 0.75 (0.36-1.38), **lead battery smelters hired before 1946** SMR: 0.57, p-value > 0.05, **lead battery smelters hired after 1946** (5 cases) SMR: 1.09, p-value > 0.05, **lead battery worker only** (10 cases) SMR (95%CI): 0.75 (0.36-1.38), **lead battery worker hired before 1946** (5 cases) SMR: 0.57, p-value > 0.05, **lead battery worker hired after 1946** (5 cases) SMR: 1.09, p-value > 0.05	battery workers and 79.7 ug/100g for lead smelters) available for some subjects
Lundstrom NG **(1997)** **Cohort** **(82)**	Primary lead smelters employed for at least 3 months between 1928-1979	6 incident cases	Occupation and blood lead level from company record	Age (5-year group), calendar year, sex	Brain cancer	(expected cases calculated from rate in county) **workers exposed to lead** (6 cases) SIR (95%CI): 1.1 (0.4-2.3), **workers with a cumulative blood lead index > 10 umol/l** (4 cases) SIR (95%CI): 1.6 (0.4-4.2), **workers mainly employed in lead exposed department** (2 cases) SIR (95%CI): 1.1 (0.1-3.8), **workers mainly employed in lead exposed department with a cumulative blood lead index > 10 umol/l** (1 case) SIR (95%CI): 1.9 (0.1-10.5)	A 15-year lag period was considered for all analyses. Subjects may have been exposed to arsenic
Cocco P **(1997)** **Cohort** **(81)**	Men employed in a lead smelting plant for at least 12 consecutive months and hired between 1932-1971	4 deaths	Occupation from company registry	Age (5-year group) group, calendar period	Brain cancer	(expected cases calculated from national rate in men) **lead smelters** (4 cases) SMR (95%CI): 1.25 (0.34-3.19), (expected cases calculated from regional rate in men) **lead smelters** (4 cases) SMR (95%CI): 2.17 (0.57-5.57)	All cases worked for less than 10 years in the plant. Subjects are potentially exposed to silica, cadmium and arsenic

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Gerhardsson L **(1995)** **Cohort** **(134)**	Men working in lead battery factories employed for at least 3 months between 1942-1987	1 incident case	Occupation and blood lead level from company database (Only subject with a cumulative or highest intensity of blood lead >3.4 umol/L considered as exposed)	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from men rate in county) **subjects exposed to lead** (1 case) SIR (95%CI): 0.75 (0.02-4.20)	
Cocco P **(1994)** **Cohort** **(70)**	Men working in two metal mines located in Sardinia, with more than 1 year of employment between 1932-1971	8 deaths	Occupation from company registry	Age (5-year group), calendar year	Brain cancer	(expected cases calculated from regional rate) **workers in lead and zinc mines** (8 cases) SMR (95%CI): 1.17 (0.50-2.30), **surface workers only** (2 cases) SMR (95%CI): 0.91 (0.11-3.27), **underground workers only** (6 cases) SMR (95%CI):1.33 (0.49-2.90), **underground workers mine A only** (2 cases) SMR (95%CI): 1.15 (0.14-4.15), **underground workers mine B only** (4 cases) SMR (95%CI): 1.43 (0.39-3.66), **surface worker mine A only** (1 case) SMR (95%CI): 0.70 (0.02-3.88), **surface worker mine B only** (1 case) SMR (95%CI): 1.29 (0.03-7.21)	Workers in mine A also exposed to high level of radon and low level of silica. Miners in mine B also exposed to high level of silica and low level of radon
Sankila R **(1990)** **Cohort** **(123)**	Workers in two glass factories, with at least 3 months of continuous employment between 1953-1971	6 incident cases (5 men, 1 woman)	Occupation from factory's employment record	Sex, age, time period	Brain cancer	(expected cases calculated from rate in general Finnish population**) glass factory workers** (6 cases) SIR (95%CI): 0.60 (0.22-1.31)	Subjects potentially exposed to chromium, arsenic, cadmium, lead, nickel oxide, and zinc selenite

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Sweeney MH **(1986)** **Cohort** **(80)**	Men employed in an east Texas chemical plant	4 deaths	Occupation from company record	Age (5-year group), calendar period (5-year group)	Brain cancer	(expected cases calculated from white men rate in USA) **subjects working in chemical plant with exposure to organic and inorganic lead** (4 cases) SMR (95%CI): 2.13 (0.73-4.87), **subjects with organic lead as the major exposure** (3 cases) SMR (95%CI): 1.86 (0.51-4.82)	No case in non-white
Parent ME **(2017)** **Case-control** **(79)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged 30 to 69 years old	1,800 incident cases	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary), time-weighted average International Occupational Prestige Scale (SIOPS) (continuous), atopy (never, ever asthma, allergy, and/or eczema), respondent status (self, proxy)	Glioma	(reference category: non-exposed) **subjects ever exposed to lead** (159 cases) OR (95%CI): 0.8 (0.7-1.0**), ≤ 128.8 umol/l blood lead level** (45 cases) OR (95%CI): 0.8 (0.6-1.2**), > 128.8 to ≤ 413.2 umol/l blood lead level** (47 cases) OR (95%CI): 0.7 (0.5-1.0), **> 413.2 umol/l blood lead level** (67 cases) OR (95%CI): 1.0 (0.7-1.3), **1-4 years of exposure to lead** (58 cases) OR (95%CI): 1.0 (0.7-1.4), **5-9 years of exposure to lead** (32 cases) OR (95%CI): 0.7 (0.4-1.1**), ≥ 10 years of exposure to lead** (69 cases) OR (95%CI): 0.8 (0.7-1.0), **ever exposure to lead in males** (151 cases) OR (95%CI): 0.9 (0.7-1.1), **ever exposure to lead in high grade glioma cases** (121 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to lead in glioblastoma cases** (85 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to lead in self-respondents** (135 cases) OR (95%CI): 0.8 (0.7-1.0)	Using data from the INTERROC study. Assessed exposure using a modified version of FINJEM. All analyses conducted using a 5-year lag period. No difference observed when conducting the analyses using different thresholds for the probability of exposure, using different lag time, or when conducting the analysis in women.
Sadetzki S **(2016)** **Case-control** **(43)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom)	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary,	Meningioma	For all subjects: (reference category: never exposed**) ever exposed to inorganic lead** (95 cases) OR (95%CI): 1.02 (0.79-1.32**), < 90 umol/l blood inorganic lead level** (27 cases) OR (95%CI): 1.05 (0.66-1.66**), 90 to < 233.6 umol/l blood inorganic lead level** (18 cases) OR (95%CI): 0.73 (0.43-1.25),	Using data from the INTERROC study. Similar results observed when also adjusting for occupational exposure to oil

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
	recruited between 2000 and 2004 aged ≥ 18 years old			intermediate college, tertiary)		**233.6 to < 587.7 umol/l blood inorganic lead level** (28 cases) OR (95%CI): 1.30 (0.82-2.06), **≥ 587.7 umol/l blood inorganic lead level** (22 cases) OR (95%CI): 1.03 (0.62-1.70)**, p-value for linear trend:** 0.75, **1 to 4 years exposed to inorganic lead** (35 cases) OR (95%CI): 0.91 (0.61-1.36), **5 to 14 years exposed to inorganic lead** (29 cases) OR (95%CI): 1.13 (0.73-1.75), **≥ 15 years exposed to inorganic lead** (31 cases) OR (95%CI): 1.07 (0.69-1.65), **p-value for linear trend**: 0.70, **age at first inorganic lead exposure < 18 years old** (24 cases) OR (95%CI): 0.79 (0.50-1.25), **age at first inorganic lead exposure ≥ 18 years old** (71 cases) OR (95%CI): 1.14 (0.85-1.53), **p-value for linear trend:** 0.60	mist. All analyses were conducted with a 5-year lag period.
						<u>For men:</u> (reference category: never exposed) **ever exposed to inorganic lead** (64 cases) OR (95%CI): 1.09 (0.80-1.50), **< 90 umol/l blood inorganic lead level** (14 cases) OR (95%CI): 1.29 (0.69-2.41), **90 to < 233.6 umol/l blood inorganic lead level** (15 cases) OR (95%CI): 1.02 (0.56-1.85), **233.6 to < 587.7 umol/l blood inorganic lead level** (20 cases) OR (95%CI): 1.28 (0.75-2.18), **≥ 587.7 umol/l blood inorganic lead level** (15 cases) OR (95%CI): 0.85 (0.47-1.53), **p-value for linear trend:** 0.86, **1 to 4 years exposed to inorganic lead** (22 cases) OR (95%CI): 1.11 (0.67-1.85), **5 to 14 years exposed to inorganic lead** (20 cases) OR (95%CI): 1.27 (0.76-2.14), **≥ 15 years exposed to inorganic lead** (22 cases) OR (95%CI): 0.95 (0.58-1.55), **p-value for linear trend:** 0.77, **age at first inorganic lead exposure < 18 years old** (19 cases) OR (95%CI): 0.84 (0.50-1.42), **age at**	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						first inorganic lead exposure ≥ 18 years old (45 cases) OR (95%CI): 1.25 (0.86-1.81), **p-value for linear trend**: 0.36	
						For women: (reference category: never exposed) **ever exposed to inorganic lead** (31 cases) OR (95%CI): 0.90 (0.58-1.41), **< 90 umol/l blood inorganic lead level** (13 cases) OR (95%CI): 0.85 (0.44-1.67), **90 to < 233.6 umol/l blood inorganic lead level** (3 cases) OR (95%CI): 0.29 (0.08-0.98), **233.6 to < 587.7 umol/l blood inorganic lead level** (8 cases) OR (95%CI): 1.43 (0.55-3.72), **≥ 587.7 umol/l blood inorganic lead level** (7 cases) OR (95%CI): 3.22 (0.80-13.04), **p-value for linear trend:** 0.68, **1 to 4 years exposed to inorganic lead** (13 cases) OR (95%CI): 0.68 (0.35-1.30), **5 to 14 years exposed to inorganic lead** (9 cases) OR (95%CI): 0.87 (0.39-1.94), **≥ 15 years exposed to inorganic lead** (9 cases) OR (95%CI): 2.11 (0.73-6.10), **p-value for linear trend:** 0.76, **age at first inorganic lead exposure < 18 years old** (5 cases) OR (95%CI): 0.66 (0.24-1.84), **age at first inorganic lead exposure ≥ 18 years old** (26 cases) OR (95%CI): 0.98 (0.59-1.61), **p-value for linear trend:** 0.78	
Bhatthi P **(2011)** **Case-control** **(39)**	Patients diagnosed at one of three hospitals from 1994-1998, and aged ≥18 years old	282 incident glioma cases, 151 incident meningioma cases	Exposure to occupational agent from self-reported occupation from questionnaire and JEM + expert assessment	Age, sex, race, hospital, residential proximity to hospital	Glioma	(reference category: no exposure) **subjects ever exposed to lead** (157 cases) OR (95%CI): 0.8 (0.5-1.1), **subjects with ≤ 80th percentile of cumulative exposure to lead** (77 cases) OR (95%CI): 0.8 (0.5-1.1), **subjects with ≤ 80th to 95th percentile of cumulative exposure to lead** (48 cases) OR (95%CI): 0.6 (0.4-0.9), **subjects with >95th percentile of cumulative exposure to lead** (21 cases) OR (95%CI):1.0 (0.5-2.0)	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
					Meningioma	(reference category: no exposure) **subjects ever exposed to lead** (42 cases) OR (95%CI): 0.9 (0.5-1.5), **subjects with ≤ 80th percentile of cumulative exposure to lead** (17 cases) OR (95%CI): 0.7 (0.4-1.3), **subjects with ≤ 80th to 95th percentile of cumulative exposure to lead** (15 cases) OR (95%CI): 1.0 (0.5-2.1), **subjects with >95th percentile of cumulative exposure to lead** (8 cases) OR (95%CI): 2.7 (1.0-7.8)	
Cocco P **(1999)** **Case-control** **(42)**	Women from 24 USA states aged > 34 years old at their time of death	12,980 brain cancer deaths including 161 meningioma deaths	Exposure to occupational agent from occupation in death certificate and a JEM	Age (continuous), marital status (never married versus ever married), SES (five categories, based on the Green's score for specific occupations)	Brain cancer	(reference category: no exposure) **women exposed to lead** (366 cases) OR (95%CI): 1.1 (1.0-1.2), **women with low probability of exposure to lead** (214 cases) OR (95%CI): 1.1 (0.9-1.3), **women with medium probability of exposure to lead** (94 cases) OR (95%CI): 1.0 (0.8-1.3), **women with high probability of exposure to lead** (58 cases) OR (95%CI): 1.2 (0.9-1.6), **women with low intensity of exposure to lead** (187 cases) OR (95%CI): 1.2 (1.0-1.4), **women with medium intensity of exposure to lead** (138 cases) OR (95%CI): 1.0 (0.8-1.2), **women with high intensity of exposure to lead** (41 cases) OR (95%CI): 1.1 (0.8-1.6)	Similar population as Cocco P et al. 1998 (41)
					Meningioma	(reference category: no exposure) **women exposed to lead** (9 cases) OR (95%CI): 1.9 (1.0-3.9)	
Hu J **(1999)** **Case-control** **(40)**	Adult admitted to the department of neural surgery in Heilongjiang province	183 incident cases (70 men, 113 women)	Self-reported exposure to occupational agent from questionnaire	Conditional on sex, age (5-year group), area of residence. For men adjusted for family income (low, medium, high), education (primary school,	Meningioma	<u>**Men:**</u>(reference category: never exposed) **ever exposed to lead** (6 cases) OR (95%CI): 7.20 (1.00-51.72)	
						<u>**Women:**</u>(reference category: never exposed) **ever exposed to lead** (10 cases) OR (95%CI): 5.69 (1.39-23.39)	

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
				middle school, university), fruits/veggies consumption (quartiles among all subjects), for women also adjusted for smoking (pack-years)			
Coco P **(1998)** **Case-control** **(41)**	Individual from 24 USA states, aged > 34 years old at the their time of death	27,000 deaths (14,655 men, 12,405 women)	Exposure to occupational agent from occupation in death certificate and a JEM	Age (continuous), marital status (never married/ ever married), residence (rural versus urban residence, and socioeconomic status (five categories, based on the Green's score for specific occupations)	Brain cancer	**(reference category: no exposure) white men with high probability and high level exposure to lead (14 cases) OR (95%CI): 2.1 (1.1-4.0)**	Similar associations reported in white men unexposed to solvent or metal dust. No information provided on women. Similar population as Cocco P et al. 1999 (42)
Carpenter AV **(1988)** **Nested case-control** **(67)**	Workers employed between 1943-1977 at two nuclear facilities located in Oak Ridge, Tennessee	89 deaths (72 men, 17 women)	Exposure to occupational agent from self-reported occupation assessed by industrial hygienist	Conditional on race, sex, place of employment, year of birth, year of hire	Brain cancer	(reference category: probably no exposure) **ever exposed to lead** (29cases) OR: 1.08, p-value: 0.90, **with 10-year lag period** (21 cases) OR: 0.83, p-value: 0.78, **low potential for exposure to lead** (10 cases) OR: 0.77, p-value: 0.70, **with 10-year lag period** (10 cases) OR: 0.68, p-value: 0.60, **moderate potential for exposure to lead** (15 cases) OR: 2.72, p-value: 0.19, **with 10-year lag period** (8 cases) OR: 1.93, p-value: 0.44, **high potential for exposure to lead** (4 cases) OR: 0.83, p-value: 0.82, **with 10-year lag period** (3 cases) OR: 0.62, p-value: 0.59, (reference category: < 1 year of high/moderate potential exposure)	Similar results were obtained when adjusting for socioeconomic status (pay code and job classification) , duration of employment, external radiation exposure, and internal radiation exposure or with a 5-year lag period

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
						exposed (high/moderate potential) to lead for 1-3 years (3 cases) OR: 1.55, p-value: 0.55, **with 10-year lag period** (2 cases) OR: 1.05, p-value: 0.95, **exposed (high/moderate potential) to lead for >3 to 10 years** (6 cases) OR: 0.92, p-value: 0.90, **with 10-year lag period** (2 cases) OR: 0.79, p-value: 0.82, **exposed (high/moderate potential) to lead for >10 to 20 years** (3 cases) OR: 1.49, p-value: 0.60, **with 10-year lag period** (3 cases) OR: 2.23, p-value: 0.33, **exposed (high/moderate potential) to lead for >20 years** (3 cases) OR: 2.88, p-value: 0.19, **with 10-year lag period** (2 cases) OR: 2.46, p-value: 0.37	
Magnani C (1986) **Case-control** **(150)**	Men aged 18-54 residing in the counties of Cleveland, Humberside, and Cheschire, and in the Wirral district of Merseyside, UK	432 death	Exposure to occupational agents from a JEM	Conditional on county of residence or local authority and 5-year age groups	Brain Cancer	(reference category: no exposure) **potential exposure to lead and lead compounds** OR (95%CI): 1.1 (0.8-1.5)	Generally only the most recent fulltime job available from death certificate, occupational data more often available for cases than controls

SIR: Standardized incidence ratio, SMR: Standardized mortality ratio, RR: Risk ratio, OR: Odds ratio, HR: Hazard ratio, 95%CI: 95% confidence interval.

Table XI: Overview of the literature on the association between welding fumes and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Macleod JS **Cohort** **(2017)** **(145)**	Canadian workers aged between 25 and 74 years old in 1991	225 incident cases	Occupation at baseline	10-year age group, region, and for the main education level (No high school, high school, postsecondary non-university, university) for the main analysis	Brain cancer	(reference category: non-welders) **welders** (35 cases) HR (95%CI): 1.16 (0.83-1.63), **occasional welders** (190 cases) HR (95%CI): 1.08 (0.93-1.26), **In blue-collars only:** **welders** (35 cases) HR (95%CI): 1.17 (0.83-1.65), **occasional welders** (190 cases) HR (95%CI): 1.09 (0.93-1.27)	Use data from the Canadian Census Health and Environmental Cohort. Because of low number of female welders. Only had information on occupation at baseline (1991).
Pukkala E **(2009)** **Cohort** **(146)**	Individuals born between 1896 and 1960, aged 30 to 64 years old and still alive and living in one of five European countries (Denmark, Finland, Iceland, Norway, and Sweden) 1 year after having participated in any computerized population census ≤ 1990	37,771 incident cases	Occupation	Conditioned on age (5-year age groups), and calendar period (5-year age group)	Brain and CNS	**In men:** (expected cases calculated from national rate from entire population) **all welders** (346 cases) SIR (95%CI): 0.99 (0.90 – 1.11), **Finland welders** (71 cases) SIR: 0.95, **Norway welders** (72 cases) SIR: 1.09, **Sweden welders** (203 cases) SIR: 0.98	
						In women: (expected cases calculated from national rate from entire population) **all welders** (16 cases) SIR (95%CI): 1.39 (0.80 – 2.26), **Finland welders** (6 cases) SIR: 1.51, **Norway welders** (4 cases) SIR: 2.43, **Sweden welders** (6 cases) SIR: 1.03	
Wesseling C **(2002)** **Cohort** **(27)**	Finnish women, born between 1906-1945, who reported their occupation in a 1970 national census	693 incident cases	Occupation from 1970 census	Year of birth , period of diagnosis, turnover rate	Brain cancer	(expected cases calculated from subjects not in occupation) **welders and flame cutters** SIR (95%CI): 2.82, p-value > 0.05	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Becker N **(1999)** **Cohort** **(29)**	Turners and welders who had worked at least 6 months from 1950-1970 at one of 25 metal processing factories	4 deaths	Occupation from questionnaire answered by foreman and/or superior	Age, calendar period in 4 categories (1950-1967, 1968-1973, 1974-1978, and 1979-1985)	Brain cancer	(expected cases calculated from rate in German population) **welders using coated electrodes** (4 cases) SMR (95%CI): 6.19 (1.68-15.85), **welders with ≤ 25% effective welding period per day** (2 cases) SMR (95%CI): 1.96 (0.23-7.11), **welders with > 25% effective welding period per day** (2 cases) SMR (95%CI): 2.09 (0.25-7.55)	All subjects also exposed to nickel and chromium fumes
Danielsen TE **(1996)** **Cohort** **(136)**	Norwegian men registered as boiler electric gas welders	10 incident cases	Occupation from national registry	Age (5-year group) and calendar year	Brain cancer	(expected cases calculated in the Norwegian men population rate) **ever worked as boiler welder** (10 cases) SIR (95%CI): 1.02 (0.49-1.88)	Steel welders may be exposed to nickel and chromium
Tornqvis S **(1991)** **Cohort** **(83)**	Swedish working men aged 20-64 years old, working in electrically related occupations	250 incident cases	Occupation from 1960 census	Age (5-year group) , social class (based on employment in three groups), population density (four groups), county	Brain cancer	(expected cases calculated from a population of 1 905 660 Swedish working men born between 1896 and 1940) **welders and flame cutters** (46 cases) SIR (95%CI): 1.3 (1.0-1.7)	Similar methodology and population as McLaughlin JK et al. 1987 (30)
					Glioma	(expected cases calculated from a population of 1 905 660 Swedish working men born between 1896-1940) **welders and flame cutters** (6 cases) SIR (95%CI): 1.1 (0.4-2.3)	
					Glioblastoma	(expected cases calculated from a population of 1 905 660 Swedish working men born between 1896-1940) **welders and flame cutters** (34 cases) SIR (95%CI): 1.5 (1.1-2.1)	
McLaughlin JK **(1987)** **Cohort** **(30)**	Swedish men employed in 1960	3,394 incident cases	Occupation from 1960 census	5-year birth cohort, region,	Glioma	(expected cases calculated in the general Swedish men population) **welders and metal cutters** (46 cases) SIR: 1.4, p-value < 0.05	Similar methodology and population as Tornqvis S et al. 1987 (83)

Author and design	**Population**	**n cases**	**Exposure variable**	**Covariates**	**Outcome**	**Associations**	**Note**
Englund A **(1982)** **Cohort** **(84)**	Swedish individuals whom answered a 1960 national census	7,359 incident cases	Occupation from 1960 census	Age, sex, period	Brain	(expected cases calculated from the Swedish population rate) **welders** (50 cases) SIR (lower 99%CI): 1.35 (0.91), **welders in metal industry** (44 cases) SIR (lower 99%CI): 1.44 (0.91)	
Polednak AO **(1981)** **Cohort** **(71)**	White male welders working in Oak ridge nuclear facilities between 1943-1977	3 deaths	Occupation employment record	Age (5-year group), calendar period (5-year group)	Brain cancer	(expected cases calculated from rate in the USA white men population) **welders exposed to nickel oxide** (3 cases) SMR (95%CI): 3.82 (0.79-13.79)	Also exposed to nickel
Parent ME **(2017)** **Case-control** **(79)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged 30 to 69 years old	1,800 incident cases	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary), time-weighted average International Occupational Prestige Scale (SIOPS) (continuous), atopy (never, ever asthma, allergy, and/or eczema), respondent status (self, proxy)	Glioma	(reference category: non-exposed) **subjects ever exposed to welding fumes** (182 cases) OR (95%CI): 0.9 (0.7-1.1), **≤ 180 mg/m^3 blood welding fumes level** (63 cases) OR (95%CI):0.9 (0.6-1.2), **> 180 to ≤ 684 mg/m^3 blood welding fumes level** (54 cases) OR (95%CI): 0.8 (0.6-1.2), **> 684 mg/m^3 blood welding fumes level** (65 cases) OR (95%CI): 1.0 (0.7-1.4), **1-4 years of exposure to welding fumes** (44 cases) OR (95%CI): 0.8 (0.6-1.2), **5-9 years of exposure to welding fumes** (39 cases) OR (95%CI): 0.9 (0.6-1.4), **≥ 10 years of exposure to welding fumes** (99 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to welding fumes in males** (178 cases) OR (95%CI): 0.9 (0.7-1.1), **ever exposure to welding fumes in high grade glioma cases** (131 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to welding fumes in glioblastoma cases** (95 cases) OR (95%CI): 0.9 (0.7-1.2), **ever exposure to welding fumes in self-respondents** (157 cases) OR (95%CI): 0.9 (0.7-1.1)	Using data from the INTERROC study. Assessed exposure using a modified version of FINJEM. All analyses conducted using a 5-year lag period. No difference observed when conducting the analyses using different thresholds for the probability of exposure, using different lag time, or when conducting the analysis in women.

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Sadetzki S **(2016)** **Case-control** **(43)**	Individuals from 10 centers in 7 countries (Australia, Canada, France, Germany, Israel, New Zealand, United-kingdom) recruited between 2000 and 2004 aged ≥ 18 years old	1,906 incidence cases (507 men, 1,399 women)	Exposure to occupational agents from a JEM	Conditioned on age (5-year group), sex, study center. Adjusted for age (continuous), maximum education of subject or spouse (primary, intermediate college, tertiary)	Meningioma	**For all subjects:** (reference category: never exposed) **ever exposed to welding fumes** (94 cases) OR (95%CI): 1.19 (0.91-1.56), **< 120 mg/m^3 blood welding fumes level** (23 cases) OR (95%CI): 1.20 (0.73-1.97), **120 to < 324 mg/m^3 blood welding fumes level** (14 cases) OR (95%CI): 0.97 (0.53-1.77), **324 to < 1119.8 mg/m^3 blood welding fumes level** (23 cases) OR (95%CI): 1.20 (0.72-1.97), **≥ 1119.8 mg/m^3 blood welding fumes level** (34 cases) OR (95%CI): 1.32 (0.85-2.03), **p-value for linear trend**: 0.18, **1 to 4 years exposed to welding fumes** (31 cases) OR (95%CI): 1.31 (0.84-2.02), **5 to 14 years exposed to welding fumes** (27 cases) OR (95%CI): 1.16 (0.73-1.84), **≥ 15 years exposed to welding fumes** (36 cases) OR (95%CI): 1.12 (0.75-1.69), **p-value for linear trend**: 0.35, **age at first welding fumes exposure < 18 years old** (40 cases) OR (95%CI): 1.10 (0.75-1.61), **age at first welding fumes exposure ≥ 18 years old** (54 cases) OR (95%CI): 1.28 (0.90-1.81), **p-value for linear trend**: 0.16	Using data from the INTERROC study. Similar results observed when also adjusting for occupational exposure to oil mist. All analyses were conducted with a 5-year lag period.
						For men: (reference category: never exposed) **ever exposed to welding fumes** (82 cases) OR (95%CI): 1.15 (0.86-1.54), **< 120 mg/m^3 blood welding fumes level** (22 cases) OR (95%CI): 1.24 (0.74-2.07), **120 to < 324 mg/m^3 blood welding fumes level** (14 cases) OR (95%CI): 0.97 (0.53-1.77), **324 to < 1119.8 mg/m^3 blood welding fumes level** (21 cases) OR (95%CI): 1.22 (0.72-2.04), **≥ 1119.8 mg/m^3 blood welding fumes level** (25 cases) OR (95%CI): 1.14 (0.70-1.86), **p-**	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
						value for linear trend: 0.43, **1 to 4 years exposed to welding fumes** (26 cases) OR (95%CI): 1.26 (0.78-2.04), **5 to 14 years exposed to welding fumes** (23 cases) OR (95%CI): 1.12 (0.69-1.83), **≥ 15 years exposed to welding fumes** (33 cases) OR (95%CI): 1.08 (0.71-1.66), **p-value for linear trend**: 0.52, **age at first welding fumes exposure < 18 years old** (37 cases) OR (95%CI): 1.06 (0.72-1.58), **age at first welding fumes exposure ≥ 18 years old** (45 cases) OR (95%CI): 1.23 (0.84-1.79), **p-value for linear trend**: 0.29	
						For women: (reference category: never exposed) **ever exposed to welding fumes** (12 cases) OR (95%CI): 1.79 (0.78-4.10), **< 120 mg/m^3 blood welding fumes level** (1 case) OR (95%CI): 0.70 (0.07-6.63), **324 to < 1119.8 mg/m^3 blood welding fumes level** (2 cases) OR (95%CI): 0.97 (0.16-5.83), **≥ 1119.8 mg/m^3 blood welding fumes level** (9 cases) OR (95%CI): 3.05 (0.98-9.48), **p-value for linear trend**: 0.09, **1 to 4 years exposed to welding fumes** (5 cases) OR (95%CI): 1.63 (0.51-5.20), **5 to 14 years exposed to welding fumes** (4 cases) OR (95%CI): 1.61 (0.37-6.88), **≥ 15 years exposed to welding fumes** (3 cases) OR (95%CI): 3.17 (0.33-30.92), **p-value for linear trend**: 0.16, **age at first welding fumes exposure < 18 years old** (3 cases) OR (95%CI): 1.86 (0.42-8.22), **age at first welding fumes exposure ≥ 18 years old** (9 cases) OR (95%CI): 1.76 (0.65-4.75), **p-value for linear trend**: 0.19	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Ruder AM **(2012)** **Case-control (151)**	Adults aged 18 to 80 years old and non-metropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin	798 incident glioma cases	Self-reported occupations from questionnaire coded by experts	Age (10-year age groups + continuous), sex, education (< 12 years, high school graduate, college graduate)	Glioma	(reference category: all other ever employed subjects) **Welders, cutters** (5 cases) OR (95%CI): 0.89 (0.29-2.76)	Only used the longest job held by subjects in the analyses. Similar results were observed when only considering jobs that lasted ≥ 5 years, only considering jobs that started by either 1985 or 1975, and when analysing using a lower occupational coding system resolution
Pan SY **(2005)** **Case-control** **(37)**	Individuals aged 20-76 years old, living in one of 8 Canadian provinces	1,009 incident cases	Exposure to occupational agent in occupation from questionnaire	Age (continuous), province of residence, sex, education level (years), alcohol consumption (serving/week), smoking pack-years (continuous), total energy intake (kcal/week)	Brain cancer (only malignant tumors)	(reference category: never exposed) **ever exposed to welding fumes** (183 cases) OR (95%CI): 1.26 (0.98-1.45), **1 to < 10 years of exposure to welding fumes** (106 cases) OR (95%CI): 1.21 (0.96-1.55), **10 to < 20 years of exposure to welding fumes** (29 cases) OR (95%CI): 0.96 (0.68-1.49), **≥ 20 years of exposure to welding fumes** (54 cases) OR (95%CI): 1.41 (0.97-1.84).	
						<u>Men:</u> (reference category: never exposed) **ever exposed to welding fumes** (173 cases) OR (95%CI): 1.27 (0.97-1.46)	
						<u>Women:</u> (reference category: never exposed) **ever exposed to welding fumes** (10 cases) OR (95%CI): 1.15 (0.57-2.33)	
Hu J **(1999)**	Adults admitted to department of neural surgery in	183 incident cases (70	Self-reported exposure to occupational	Conditional on sex, age (5-year group), area of	Meningioma	**<u>Men:</u>** (reference category: never exposed) **ever exposed to welding rod** (4 cases) OR (95%CI): 1.99 (0.40-9.89)	

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Case-control (40)	Heilongjiang province	men, 113 women)	agent from questionnaire	residence, for men adjusted for family income (low, medium, high), education (primary school, middle school, university), fruits/veggies consumption (quartiles among all subjects), also adjusted for smoking (pack-years) for women		**Women:** (reference category: never exposed) **ever exposed to welding rod** (5 cases) OR (95%CI): 3.05 (0.52-18.03)	
Carpenter AV (1988) **Nested case-control (67)**	Workers employed between 1943-1977 at two nuclear facilities located in Oak Ridge, Tennessee	89 deaths (72 men, 17 women)	Exposure to occupational agent from self-reported occupation assessed by industrial hygienist	Conditional on race, sex, place of employment, year of birth, year of hire	Brain cancer	(reference category: probably no exposure) **ever exposed to welding fumes** (33 cases) OR: 1.23, p-value: 0.54, **with 10-year lag period** (26 cases) OR: 1.21, p-value: 0.60, **low potential for exposure to welding fumes** (19 cases) OR: 1.80, p-value: 0.13, **with 10-year lag period** (17 cases) OR: 1.72, p-value: 0.17, **moderate potential for exposure to welding fumes** (13 cases) OR: 0.79, p-value: 0.57, **with 10-year lag period** (9 cases) OR (95%CI): 0.72, p-value: 0.48, (reference category: < 1 year of high/moderate potential exposure) **exposed (high/moderate potential) to welding fumes for 1-3 years** (4 cases) OR: 0.54, p-value: 0.28, **with 10-year lag period** (4 cases) OR: 0.81, p-value: 0.72, **exposed (high/moderate potential) to welding fumes for >3 to 10 years** (1 case) OR: 0.85, p-value: 0.89, **with 10-year lag period** (1 case) OR: 0.94, p-value: 0.96	Similar results were obtained when adjusting for socioeconomic status (pay code and job classification), duration of employment, external radiation exposure, and internal radiation exposure or with a 5-year lag period

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Magnani C (1986) **Case-control (150)**	Men aged 18-54 residing in the counties of Cleveland, Humberside, and Cheschire, and in the Wirral district of Merseyside, UK	432 death	Exposure to occupational agents from a JEM	Conditional on county of residence or local authority and 5-year age groups	Brain Cancer	(reference category: no exposure) potential exposure to welding fumes OR (95%CI): 1.1 (0.8-1.5)	Generally only the most recent fulltime job available from death certificate, occupational data more often available for cases than controls

SIR: Standardized incidence ratio, SMR: Standardized mortality ratio, OR: Odds ratio, 95%CI: 95% confidence interval.

Table XII: Overview of the literature on the association between soldering fumes and brain cancer

Author and design	Population	n cases	Exposure variable	Covariates	Outcome	Associations	Note
Magnani C **(1986)** **Case-control** **(150)**	Men aged 18-54 residing in the counties of Cleveland, Humberside, and Cheschire, and in the Wirral district of Merseyside, UK	432 death	Exposure to occupational agents from a JEM	Conditional on county of residence or local authority and 5-year age groups	Brain Cancer	(reference category: no exposure) potential exposure to solder fumes OR (95%CI): 1.2 (0.8-1.9)	Generally only the most recent fulltime job available from death certificate, occupational data more often available for cases than controls

OR: Odds ratio, 95%CI: 95% confidence interval.