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Lung cancer risk associated with occupational exposure to nickel, chromium VI, and cadmium in two population-based case-control studies in Montreal.

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présenté par
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a été évalué par un jury composé des personnes suivantes :

Président-rapporteur :	**André Dufresne**
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Résumé

Cancer du poumon associé à l'exposition au nickel, au chrome VI et au cadmium dans le milieu de travail utilisant deux études populationnelles cas-témoins à Montréal

Au début des années 1990, le nickel, le chrome VI et le cadmium ont été classés en tant qu'agents cancérigènes de classe 1 par le CIRC (Centre International de Recherche sur le Cancer). Cependant, les résultats des études ayant permis la classification de ces métaux n'ont pas toujours été reproduits, et d'importantes questions demeurent quant aux effets de ces métaux à de faibles niveaux d'exposition. Un plus grand nombre de recherches empiriques est donc nécessaire afin de réaffirmer la cancérogénicité de ces agents, et d'identifier les circonstances dans lesquelles ils peuvent être néfastes.

L'objectif de cette étude était d'explorer la relation entre l'exposition à un des métaux (soit le nickel, le chrome VI, ou le cadmium) et les risques subséquents de développer un cancer du poumon chez des travailleurs provenant de différents milieux de travail qui sont exposés à ces métaux à de différents degrés. Deux études cas-témoins de base populationnelle menées à Montréal ont fourni les données nécessaires pour examiner la cancérogénicité de ces métaux. La première étude était menée entre 1979 et 1986 chez des hommes âgés de 35 à 70 ans ayant un cancer dans l'un de 19 sites anatomiques de cancer sélectionnés. La seconde étude était menée entre 1996 et 2001 chez des hommes et des femmes âgés de 35 à 75 ans, avec un diagnostic de tumeur maligne au poumon. Dans ces deux études, les cas ont été recensés dans tous les hôpitaux de l'île de Montréal, tandis que les contrôles populationnels appariés par âge et stratifiés par sexe, ont été sélectionnés des listes électorales. Une entrevue avec chaque sujet a permis d'obtenir un historique d'emploi détaillé ainsi que des informations précises sur les facteurs de risques socio-économiques et personnels. Les descriptions de poste ont été évaluées par une équipe d'experts chimistes et hygiénistes afin de déterminer si le sujet a été exposé à chaque agent, et pour mesurer à la fois la concentration et la durée de chaque exposition, ainsi que l'exposition cumulative tout au long de la vie de chaque participant.

Pour déterminer si une exposition à l'un des trois métaux en cause était associée à une augmentation de l'incidence du cancer du poumon, des données ont été analysées par régression logistique : des ajustements ont été effectués pour des facteurs de confusion pertinents incluant un historique détaillé du tabagisme. Des mesures catégoriques d'exposition cumulée ont été également analysées, ainsi que la modification des effets par le tabagisme. Les deux études ont été analysées séparément, puis par la suite combinées afin d'augmenter la puissance statistique.

Les niveaux d'exposition mesurés dans cette population ne semblaient pas poser un excès de risque de cancer du poumon pour les travailleurs exposés au chrome VI. Cependant, ceux qui ont été exposés au nickel ont subi une augmentation significative du risque, et ce, quel que soit leur niveau d'exposition. Le risque de développer un cancer du poumon suite à une exposition au cadmium était élevé, mais pas de manière significative. Pour chacun des trois métaux, le risque de cancer du poumon était très élevé parmi les non-fumeurs, mais pas parmi les fumeurs. L'effet combiné du tabagisme et de l'exposition aux métaux était compatible avec un excès de risque additif. Cependant, les intervalles de confiance dans cette étude tendaient à être larges, et une faiblesse de puissance statistique peut limiter l'interprétation de certains résultats.

Cette étude est unique dans la mesure où elle a fourni des preuves empiriques sur les risques de développer le cancer du poumon liés aux faibles niveaux d'exposition au nickel, au chrome VI, ou au cadmium provenant de divers contextes de travail. Dans la plupart des autres études, la majorité des expositions pertinentes n'ont pas été bien contrôlées. À l'inverse, cette étude a bénéficié de la collecte et de la disponibilité d'information détaillée concernant le tabagisme et d'autres facteurs de risque.

Les résultats de cette étude ont d'importantes conséquences pour la santé publique, tant au niveau de la détermination des risques pour les travailleurs actuellement exposés à ces métaux, qu'au niveau de l'évaluation des risques pour la population en général, elle-même exposée à ces métaux par le biais de la pollution et de la fumée de cigarette. Cette analyse contribuera fort probablement à une réévaluation par le CIRC de la cancérogénicité de ces métaux. L'exploration

de la relation entre les risques de cancer du poumon et l'exposition au nickel, au chrome VI et au cadmium est donc opportune et pertinente.

MOTS CLÉS: cancer, épidémiologie, cancer du poumon, santé du travail, expositions au milieu de travail, étude cas-témoin, métaux, cadmium, chrome, nickel.

Summary

Nickel, chromium VI and cadmium were designated as IARC class 1 lung carcinogens in the early 1990s. However, the study results informing this designation have not been consistently replicated in the past two decades, and there remain some important questions about these metals' effects at low levels of exposure. Further empiric research is therefore required to confidently reaffirm the carcinogenicity of these agents and to understand the circumstances in which they may be harmful.

The objective of this study was to investigate the relationship between exposure to either nickel, chromium VI or cadmium and subsequent risk of lung cancer among workers exposed to these substances at a variety of levels and in a wide range of occupations. Two large population-based case-control studies conducted in Montreal provided the data to investigate the carcinogenicity of these substances. Study I was conducted from 1979 to 1986, and included males aged 35 to 70 diagnosed with cancer at any of 19 selected cancer sites. Study II was conducted from 1996 to 2001 and included men and women aged 35 to 75 diagnosed with lung malignancies. In both studies, cases were ascertained in all hospitals on the island of Montreal, while age- and sex-stratified population controls were selected from electoral lists. Detailed job histories, as well as lifestyle and socioeconomic measures, were elicited by interviewers with each subject. Job descriptions were then evaluated by an expert team of chemists and hygienists in order to determine whether the subject was exposed to each agent, and if so, to create measures of concentration, duration, and cumulative exposure over the course of each participant's lifetime.

In order to determine whether lifetime exposure to any of the metals of interest was associated with increased incidence of lung cancer, exposure data were analysed by logistic regression, adjusting for relevant confounders including detailed smoking history. Categorical measures of cumulative exposure were analysed, and effect modification by smoking was also explored. Study I and II were first analysed separately, and then combined when appropriate to increase statistical power.

At the exposure levels experienced by this population, subjects exposed to nickel incurred a small but significantly increased risk of cancer compared to those unexposed. Meanwhile, there did not appear to be any excess risk of lung cancer among workers exposed to chromium VI. Lung cancer risk was somewhat elevated, albeit not significantly so, after cadmium exposure. For each of the three metals, lung cancer risk was significantly elevated among non smokers, but not among smokers. The joint effect of smoking and exposure to each of the metals was compatible with an additive excess risk. However, confidence limits in this study tended to be wide, and lack of statistical power may limit interpretation of some of the results.

This study is unique in providing empiric evidence on lung cancer risks associated with low levels of exposure to nickel, chromium VI, or cadmium originating from a variety of occupational contexts. While many studies have failed to control for important co-exposures, this study benefited from the collection and availability of detailed histories of exposure to tobacco and other potential confounders. The results of this study have important public health implications, both in terms of determining ongoing risk experienced by exposed workers, and in terms of assessing risk to the general population exposed to these metals by means of pollution and cigarette smoke. This analysis will likely contribute to an upcoming IARC re-evaluation of the carcinogenicity of these metals. Examination of the relationship between exposure to cadmium, chromium VI and nickel and subsequent risk of lung cancer is therefore timely and pertinent.

KEYWORDS: cancer, epidemiology, lung neoplasms, occupational exposure, case-control study, metals, cadmium, chromium, nickel.

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List of acronyms and abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
Cd	Cadmium
CI	Confidence interval (95% CI = 95% confidence interval)
Cr III	Chromium III, trivalent chromium
Cr VI	Chromium VI, hexavalent chromium
EC	European Commission
IARC	International Agency for Research on Cancer
ICNCM	International Committee on Nickel Carcinogenesis in Man
Ni	Nickel
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program (U.S.A)
OSHA	Occupational Safety and Health Administration
SEP	Socioeconomic position
SMR	Standard mortality rate
TERA	Toxicology Excellence for Risk Assessment
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization
m^3	cubic metres
µg	a microgram, one millionth of a gram
ng	a nanogram, one billionth of a gram

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Note concernant la structure de ce mémoire

Bien que j'ai obtenu permission de rédiger mon mémoire par article, le corps du mémoire et l'article son indépendants dans leur structure courante: les résultats sont présentés d'une façon plus élaboré dans le texte du mémoire mais sont répétés dans l'article, et le contenu de l'introduction et de la discussion sont similaires dans l'article et le corps du mémoire. L'article est donc un complément au mémoire.

Disclaimer regarding the structure of this thesis

Although I received permission to write my master's thesis by article, this work is currently structured such that the thesis body and article are entirely independent : the results are presented in more detail in the thesis body but are repeated in the article, and the introduction and discussion sections share many elements. The article at the end of this thesis should therefore be considered a complement to the main thesis body.

INTRODUCTION

Lung cancer is the most common cause of cancer mortality, with 1.2 million deaths worldwide each year (1). Although smoking is the main cause of lung cancer in most industrialized countries, and increasingly in developing countries, most smokers do not get lung cancer and some non-smokers do. It is therefore clear that multiple etiological factors affect lung cancer development, including occupational and environmental exposure to lung carcinogens other than tobacco (2). Although the carcinogenicity of some substances has been clearly demonstrated, it is questionable or unknown for many others. Identification and confirmation of modifiable risk factors, and estimation of the magnitude of their effect, is essential for lung cancer prevention.

In modern industrial societies, humans are exposed to thousands of products and chemicals. Exposure to metal compounds is common because of their wide use in industry and their environmental persistence. Nickel, cadmium, and chromium VI are three metals that were categorised as Class 1 IARC carcinogens in the early 1990s, based on sufficient evidence from experimental and epidemiological studies (3, 4). Notwithstanding these classifications, evidence of increased lung cancer risk after exposure to these three metals has been inconsistent in recent decades. Epidemiological studies have been limited in their capacity to assess exposure and confounding; they have often suffered from inadequate or incomplete exposure assessment and follow-up data, and have had inadequate statistical power to identify small levels of risk or risk at low exposure levels (5). Many results and updates to early studies have been called into question because of methodological limitations (6, 7), as summarized in *Box 1*.

Although most metal exposures of high concentration occur in occupational settings, low level exposures in the workplace and in the general population are also common. Nickel, chromium

VI and cadmium are also important constituents of tobacco, and may play a role in smoking-associated carcinogenesis (8). While health effects at low exposure levels may be difficult to detect, the attributable risk due to these widespread agents could be significant. Further empiric research is therefore required to confirm their carcinogenic effects, particularly at low exposure levels.

In this study, lung cancer etiology was explored by way of two similarly-designed population-based case-control studies of occupational exposures in Montreal. Reliable estimates of a variety of occupational exposures, as well as socioeconomic and lifestyle factors and detailed smoking histories, were available for analysis. Nickel, cadmium and chromium VI all had sufficiently high prevalences in our data set to allow analysis of their effect on lung cancer incidence. The objective of this study was thus to examine the risk of lung cancer in people exposed to these purportedly carcinogenic metals in a variety of occupations and at a range of exposure levels.

Box 1.

Methodological considerations and limitations concerning the assessment of lung cancer risk after metal exposure

- Exposure levels change over time
- Some substances require a minimum latency period to exert their effects
- Risk may decrease with time since last exposure
- Important exposures may be neglected or misclassified
- The importance of individual dimensions of exposure, such as duration or concentration, varies between agents
- Risk estimates may be confounded
    - By other occupational agents
    - By smoking

SUBSTANTIVE BACKGROUND

In order to assess the carcinogenicity of metal compounds in humans, it is essential to consider information from a variety of fields and sources. This requires careful consideration of epidemiological evidence as well as animal evidence and *in vitro* experiments on genotoxicity and mutagenicity. However, epidemiological and experimental results are sometime divergent. Exposure heterogeneity, concentration and intensity, vary greatly between human and experimental studies, as does the existence of defense or clearance mechanisms (9, 10). Valid extrapolation of experimental models is therefore difficult to achieve, and does not necessarily offer a simple or congruent solution to discrepancies in epidemiological data. Modeling and extrapolation may nonetheless help address the limitations of epidemiological studies at low exposure levels (11).

Risk assessments consider numerous factors in determining whether a substance is carcinogenic, and in setting permissible exposure levels. In order to cause lung cancer, an agent has to enter the lung; cellular uptake of a hazardous substance then depends on its biological half-life and rate of clearance from the lung, where sustained presence may engender a higher risk (12-14). Uptake is also affected by deposition and absorption rates, which vary with particle size and chemical solubility, respectively (15, 16). Small particles are more easily absorbed than larger particles because they have higher deposition rates, penetrate deeper into the lung, and are less easily eliminated. Soluble particles are likely to be absorbed by biological mechanisms, while insoluble particles tend to produce oxidative irritation outside the cell, or to use active transport to enter the cell. The presence of cancer promoters and factors that affect a cell's ability to repair damage further affect the probability that an altered cell will transmit precancerous changes (17).

The following section presents a substantive overview of nickel, chromium VI, and cadmium, summarising the experimental and epidemiological evidence surrounding each metal's status as a carcinogen. Evidence regarding the association between respiratory exposure and lung cancer is emphasized. However, some background is also provided regarding carcinogenic potential in other sites and by other routes of exposure. In the review of epidemiological evidence of the carcinogenicity of these metals, only studies with metal exposure assessments are included, and leaving aside studies assessing occupational risk alone.

NICKEL BACKGROUND

Nickel production and uses

Nickel is the 24th most abundant element on earth, and over one million tonnes of nickel are produced annually worldwide. Nickel mining, refining and smelting are an important primary industries in Canada, the fourth largest nickel producer in the world (13). This metal is used in the production of stainless steel (60%) electroplating (11%), battery production (10%) and nickel alloy production (5%) (18). Nickel imparts corrosion resistance and strength to alloys and plated materials, which are used to create products including catalytic converters for automobiles, electronic components, coins, and other metal items including armaments, tools and utensils (11, 13, 19).

Human exposure to nickel

Food and water are the sources of the majority of human environmental nickel exposure. Plants such as spinach, legumes, and nuts particularly concentrate nickel, which can also be leached by acidic materials from cooking ware, utensils and pipes. Nickel is also an important constituent of industrial and urban air pollution. The primary anthropogenic sources of nickel emissions are fossil fuel combustion and municipal incineration, primary nickel production, and stainless steel or alloy manufacturing (11). Concentrations between 5 and 170 ng/m3 can be found in urban environments (20), leading to an average exposure of 0.25ng/kg/day (15). On average, less than 1% of nickel exposures occur by respiration, as compared to 90% by ingestion of food and water. Exposure to nickel is augmented by approximately 10% by cigarette smoking (11, 15, 16, 21). Approximate doses due to ingestion, respiration, and occupational exposure are detailed in Table 1.

Occupational exposure to nickel

Occupational exposures to nickel occur in the form of airborne dust and particles during mining, refining and smelting, as well as during work in factories and chemical plants (13). Nickel fumes are also produced during stainless steel and alloy welding and soldering (22). Miners have historically been exposed to concentrations of up to 5mg/m^3, and refiners up to 1mg/m^3, leading to absorption of about 100ug per day. However, changes in industrial processes and use of protective equipment have considerably reduced these exposures. A recent evaluation of a Norweigian nickel refinery found average respirable concentrations of 0.7mg/m^3, which is well below most occupational limits (23).

Nickel speciation

A variety of nickel species are found in the occupational and urban environment. Nickel may occur as a soluble species, such as nickel sulphate and nickel chloride, or an insoluble species, such as nickel sulphide and nickel oxide. The dominant nickel species in urban air pollution is nickel sulphate, followed by nickel oxide. Some nickel species produced during refining and smelting, such as nickel subsulphide, are not usually found in the urban environment (11), but occupational exposures are composed of both soluble and insoluble components.

Nickel metabolism and toxicity

Although human nickel intake can amount to 1 mg per day, cellular absorption by the digestive system and skin is minimal. Conversely, approximately 20% of inhaled nickel is absorbed by the respiratory tract, depending on the species involved. Soluble nickel species have relatively low cellular uptake and are rapidly cleared from the lungs, while insoluble forms have a slower

clearance from the lungs, and may be actively transported into nearby cells (11, 14). Nickel subsulfide, generally believed to be the most hazardous of all nickel species, shares biophysical properties of both soluble and insoluble species (24). Once absorbed, only a small amount of nickel is retained in the body, while the majority is efficiently excreted in days to weeks (13).

Acute toxic effects of nickel exposure include vertigo, nausea, vomiting, and pulmonary fibrosis. Nickel carbonyl, produced during nickel purification, is extremely toxic and can lead to lethal systemic poisoning (13). Generalised effects of chronic exposure have been observed in the respiratory tract, kidneys, immune system, reproductive system, endocrine regulation and skin (11). Chronic effects of respiratory exposure among highly exposed workers rhinitis, sinusitis, septum perforation, and asthma, as well as a reduced sense of smell. Sensitivity to skin contact can lead to dermatitis or allergy in up to 30% of the population (13). Nickel is known to cause oxidative stress (25, 26) and is also hepatotoxic. While nickel ingestion is not known to cause any form of cancer, nickel inhalation has been associated with lung, sino-nasal, and pharyngeal cancer (13).

Experimental Evidence

Animal study evidence

In animal models, different forms of nickel invoke different degrees of carcinogenicity and toxicity. Soluble nickel appears to be responsible for the acute toxic responses to nickel, but not for carcinogenic effects (27-29). Meanwhile, insoluble nickel may be genotoxic without associated toxicity. In a series of animal inhalation studies, U.S. NTP found clear evidence of carcinogenicity after exposure to insoluble nickel species (nickel subsulfide and high-

temperature nickel oxide) but did not confirm carcinogenic activity by soluble nickel species (nickel sulfate) (14). Although there were marked differences in effects between rodent species, the responses found in these inhalation studies generally mirrored early injection studies (3, 13, 17). However, some recent inhalation studies have found evidence of carcinogenicity for soluble nickel after inhalation (30). Cytotoxic effects by soluble species in previous studies may have prevented administration of higher doses in animal experiments, thereby leading underestimation their carcinogenic potential (17).

In vitro evidence and potential mechanisms

The molecular and genotoxic aspects of nickel carcinogenicity have recently been reviewed in detail (31-33), and as expected depend on the nickel species of interest. In general, nickel has been found to be a weakly active mutagen in eukaryotic organisms, and an inactive mutagen in bacterial assays (13, 15). *In vitro* evidence mirrors most *in vivo* studies indicating that insoluble nickel species are most likely to be genotoxic. Insoluble nickel has been found to be phagocytosed into mammalian cells, where its ions may induce inflammation, apoptosis, morphological transformations, chromosomal instability and chromosomal deletions (13, 31-33). Genotoxic activity by insoluble nickel is likely mediated by oxidative stress and the production of reactive oxygen species (13, 25). Conversely, evidence for soluble nickel's genotoxicity is mixed; *in vitro* responses are usually weak and occur only at toxic doses (17).

Several reviews of possible mechanisms of nickel carcinogenesis have also recently been published (25, 33, 34). Based on evidence from *in vitro* and *in vivo* experiments, a mechanistic theory of differential nickel carcinogenesis has been developed, proposing that soluble nickel is a

cancer promoter, and insoluble nickel a cancer initiator (11, 14, 17, 19, 35, 36). It is suggested that soluble nickel species exert largely cytotoxic effects, while their physicochemical properties prevent them from direct access to the cell nucleus. This would imply that soluble nickel is not a complete carcinogen, although inflammation caused by toxicity could foster a cancer-promoting environment, enhancing cell proliferation and creating reactive oxygen species (11, 19). Conversely, insoluble nickel species directly enter the cell by phagocytosis (37), which delivers them in higher concentrations to the cell nucleus. Direct access to and interaction with the nucleus could greatly enhance insoluble nickel's carcinogenic potential (17).

The disparities in lung cancer risk between nickel types in experimental studies largely support this mechanistic theory (17, 24, 35). However, recent experimental studies attempting to mimic environmentally relevant exposures to chronic, low doses of soluble nickel show that soluble nickel chloride may in fact be mutagenic and genotoxic, especially after long durations of exposure (38, 39). Numerous mechanisms have been proposed to explain this activity (13, 17, 40, 41).

Regardless of the mechanisms involved, the particular properties and biological effects of different nickel species indicate that separate risk assessments should be conducted for each (24). Epidemiological studies should therefore take these differences into account.

Epidemiological Evidence

Excess risk of lung cancer in nickel-exposed workers was first observed in a Welsh nickel refinery in the 1930s. Since then, a number of occupational cohort studies have confirmed excess risk in workers compared to local or national reference populations (35, 42). However, the exact form of nickel that produces increased risk of lung cancer remains contested.

In 1990, both IARC and the ICNCM published complete reviews of available information from cohorts with a total of over 80,000 workers (3, 43). Both reviews concluded that several forms of nickel give rise to lung cancer. Increased respiratory cancer risk was observed among workers exposed to a mixture of oxidic and sulfidic nickel at high concentrations, as well as to high concentrations of oxidic nickel and soluble nickel species alone. No evidence of carcinogenicity was found outside of the respiratory system.

Updates to several of the cohorts examined by IARC and ICNCM have since been published, extending follow-up and improving methodology and exposure assessment. In particular, cohorts from the Clydach refinery in South Wales (44, 45), the Falconbridge refinery in Norway (10, 46-48), and a large smelter and refinery in Finland (49) calculated semi-quantitative estimates of exposure not available in previous studies. Risk of lung cancer after having ever been exposed to any level of nickel continued to be elevated but insignificant (42, 50), with most recent risk estimates consistently hovering between 130 and 150 (10, 44, 49).

Many recent studies included risk estimates for both high and low concentrations of exposure. High-concentration exposures to nickel were consistently associated with elevated lung cancer

risk (11, 19, 43, 47, 49, 50). People hired before process and employment standard changes in the mid-1900s were subjected to very high concentrations of nickel, and suffered from higher rates of lung cancer than those employed after process changes (10, 45, 46). Although reductions in risk have largely been attributed to decreased levels of nickel exposure, some have suggested that they may have also resulted from concurrent cessation of certain high-risk co-exposures such as arsenic (51).

Many groups exposed at relatively low concentrations have also continued to demonstrate increased risk of lung cancer (43-45, 52). Significantly elevated risks were reported in the Finish cohort after exposure to concentrations lower than the ICNCM estimates of risk cutoff (49). Conversely, in a recent study examining respiratory cancer risk after exposure to low concentrations of nickel, Sorahan and Williams (2005) found that lung cancer risk was barely elevated. However, workers employed for at least five years in environments with the highest concentration of nickel dust had significantly increased risk (SMR=231) (44). A subsequent analysis of workers employed for at least 5 years showed that risk of respiratory cancer persisted despite exposure reductions (SMR=133; 95%CI=103–172). As such, although current exposures are likely substantially lower than those in most historical cohort studies, there is evidence that lower exposure levels continue to be an occupational hazard (52).

Risk of lung cancer has also tended to increase with duration of exposure; risk estimates are consistently significant after exposure durations of at least 15 years (46), particularly in high-concentration environments (11, 19, 44). Similarly, a minimum of ten to twenty years' elapsed time since exposure tends to increase risk estimates (10, 43, 44, 49). Sorahan and Williams

(2005) observed an SMR of 165 (108-243) for those employed over 20 years previously (44), while Grimsrud *et al* (2002) found their data was best fit with a 10-year lag after adjustment for smoking (OR=2.2; 95%CI=1.0-4.6) (10). Similarly, Anttila *et al*. found that exposure to either sulfides (smelter workers) or sulfates (refinery workers) significantly increased incidence of lung cancer after 20 years' latency (49).

Species-specific risk

Metallic nickel

Experimental and epidemiological evidence indicate that exposure to metallic nickel does not increase lung cancer risk (3, 53). Many occupational cohort studies have found no increased risk of lung cancer after exposure to metallic nickel (10, 43, 45, 54-56), and its presence does not seem to alter risk estimates for other species or exposures. Although some activity has been observed in animals, no specific action has been consistently observed in vivo or in vitro (53). As such, the majority of regulatory bodies have excluded metallic nickel as a potential carcinogen (3).

Soluble and insoluble nickel

There is a perplexing contradiction between epidemiological and experimental evidence with regards to the carcinogenicity of soluble and insoluble nickel species: while evidence from recent epidemiological studies supports a leading role for soluble nickel species such as nickel sulfate, evidence from animal studies is strongest where exposure to insoluble nickel species, such as nickel oxide and nickel subsulphite, are concerned. Increased incidence of lung cancer was first found in workers exposed primarily to insoluble nickel species (57, 58), which were assumed to

be responsible for its effect. However, early evidence of elevated lung cancer risk was also found in workers exposed to soluble nickel (59).

Recent epidemiology studies confirm the likelihood that more than one form of nickel increases lung cancer risk, but evidence has increasingly been shifting away from insoluble nickel compounds in favour of soluble nickel. Most occupational cohorts with quantitative exposure estimates indicate that soluble nickel is the most important risk factor for lung cancer (10, 47, 49). In a detailed quantitative re-assessment of exposure estimates, a highly consistent exposure-dependent risk was reported for exposure to soluble nickel species (23, 46), with significantly elevated risk estimates at higher doses (OR=3.8, 95%CI=1.6-9.0). After adjustment for soluble nickel exposure and smoking, the effects of insoluble (sulfidic and oxidic) forms of nickel were elevated (between 0.9 and 2.2, depending on exposure level) but always insignificant and without any dose-related trends. Similarly, exposure-dependent risk was found in Norwegian workers exposed to soluble nickel alone or in combination with other species (47). Strong evidence of the effects of soluble nickel species were also found in the Finnish cohort, where workers were exposed to either primarily soluble or insoluble nickel species. While both forms of nickel imposed a significantly increased risk after 20 years' latency, soluble nickel was consistently associated with a higher incidence of lung cancer among exposed workers (49).

A number of cohort studies have refuted any association of lung cancer with soluble forms of nickel (60, 61). Electrolysis workers in a refinery at Port Colborne (Canada) exposed primarily to soluble nickel showed no increased lung cancer risk (43), nor did a small cohort of British electroplaters exposed only to soluble nickel (60). Although informative in that they constituted

workers exposed mainly to soluble nickel, these studies may have suffered from methodological limitations such as small sample size, low exposure concentrations, and underestimation of mortality (46).

Confounding

Occupational co-exposures

Inadequate control for potentially important occupational confounders such as arsenic and sulfuric acid mists has been cited as weakening epidemiologic evidence for the association of nickel and lung cancer (11, 14, 17, 19). However, the majority of studies that have investigated the effect of confounding have found that risk estimates for nickel are not highly confounded by occupational agents (46, 62). In a nested case-control study, Grimsrud *et al* (2005) developed time- and department-specific exposure estimates for a number of common carcinogenic co-exposures including arsenic, sulfuric acid mists, and cobalt. After adjusting for smoking and relevant occupational confounders, they found that exposure to soluble nickel remained the most likely explanation for increased risk among nickel refiners, while the other agents had relatively weaker effects (46). Several others investigating the role of occupational exposures in other lifetime occupations have observed negligible effects on the final risk estimates for nickel (46, 63, 64). However, in a case-control study Moulin et al (2000) found that adjustment for PAHs and silica decreased point estimates by up to 30% (62).

Smoking

Confounding by smoking has been investigated in several cohort studies (44, 62, 65), and data from the Norwegian nickel refinery have included information on smoking status (ever/never) for over two decades (10, 47, 48, 66). Inclusion of continuous variables for total amount

smoked, duration, and time since quit did not significantly affect risk estimates in one case-control study (46). Other studies have similarly found that smoking is only a weak confounder, producing less than 20% changes in risk estimates (10, 62). However, smoking data are rarely available for the whole cohort (44) and some analyses suggest that they have not always been reliable (52). Risk estimates in some studies have been neutralized by controlling for smoking by using local population references (65) or alternative methods to re-estimate confounding (11), indicating that smoking remain a confounder in certain contexts.

Conclusion

Although recent epidemiological evidence most strongly implicates soluble nickel as an important risk factor for lung cancer development (10, 47, 49), its independent role as a cancer initiator or promoter has not been determined (11, 17, 19, 46). Epidemiologic studies have been unable to determine whether co-exposure to other carcinogens such as tobacco smoke or other occupational exposures are necessary for soluble nickel's effect (46). Furthermore, exposure to soluble nickel is almost always accompanied by insoluble nickel, which is more likely to be a strong carcinogen according to experimental evidence. If exposure to insoluble nickel is necessary for the effects of soluble nickel (17), current mechanistic theories based mainly in animal and in vitro models would be supported (11, 17, 19, 24). However, given recent evidence regarding the genotoxic effects of soluble nickel, it is also possible that soluble species have played a role in the effects previously ascribed to insoluble forms (10, 46, 49).

Assessment of the effects of different forms of nickel is such a challenge that conclusions remain highly contentious. Even designations by regulators lack coherence; while IARC classified all

nickel compounds but metallic nickel as Group 1 carcinogens in 1990 (3), a decade later the U.S. TERA (Toxicology Excellence for Risk Assessment) group concluded that the carcinogenicity of soluble nickel compounds could not be determined because of the persistence of conflicting data (17, 36). One aspect of this challenge is to reconcile differences in exposure conditions between epidemiological and animal studies: while the results from occupational studies come from workers exposed to a mixture of nickel species, animal studies involve largely homogenous exposures (10, 17). As such, confirmation of nickel's carcinogenicity is required.

CHROMIUM VI BACKGROUND

Production and uses of chromium VI

Chromium is an essential transition element that naturally occurs in two stable oxidation states: chromium III (trivalent) and chromium VI (hexavalent). Hexavalent chromium exists as a strong anion at physiological pHs, and may form soluble compounds such as chromium oxide, or insoluble compounds, such as calcium or lead chromate (12). It is widely used in the metallurgical and chemical industries. Chromium VI was once widely used in the leather tanning industry, but its most frequent use is currently in the production of metal alloys, particularly stainless steel, to which it imparts heat and corrosion, as well as in chrome plating. It is also used in pigment production for the chemical, ceramics, and automobile industries (3).

Human exposure to chromium VI

In non-occupational contexts, diet is the primary source of human exposure to chromium VI, while only small quantities are taken in by drinking and respiration (12) (see Table 1). Concentrations of chromium in air, soil and water depend on the degree of local and global industrial activity, but tend to be minimal (3).

Occupational exposure

Chromium exposure occurs in multiple occupational environments, and several million workers worldwide are exposed to chromium or its compounds each year (3). Leather tanning was once an important source of chromium exposure but now, the most frequent exposures occur during chrome plating and welding. Welders of stainless and mild steel covered with chromium-containing paints breathe in dusts from the materials being welded and as well as chromium fumes from the welding electrodes. Workers are similarly exposed during chromate and pigment production, spray painting, and during use of chromates in the chemical industry (3, 67).

Metabolism and toxicity of chromium VI

Chromium VI exists as a negative ion similar to sulfate and phosphate ions at physiological pHs, and is therefore actively transported into human cell by an anionic transport system, facilitating its accumulation. Once inside the cell, hexavalent chromium is usually reduced to chromium III, often by ascorbic acid (12). Absorbed chromium is transported throughout the body and may be concentrated in numerous tissues and organs, including the lung, liver, and kidneys, but is predominantly excreted through urine (67). The most common toxic effect of chromium exposure is allergic reaction and ulceration of exposed skin. Inhalation of chromium-containing dust can also cause asthma and erosion of the nasal septum. Exposure to high doses of chromate may also have nephrotoxic effects and induce liver necrosis (67).

Experimental evidence

Animal study evidence

A variety of chromium VI compounds have produced tumours in laboratory animals under different experimental conditions and administration routes. Most positive results with regards to carcinogenesis have been obtained from implantation and injection experiments that bypass normal physiological defense mechanisms (68). For example, injection studies produce tumours in a variety of sites and organs (67), and evidence suggests that hexavalent chromium exposure can have systemic effects that are distant from the site of exposure (12). However, relatively few inhalation studies in animals have demonstrated a link between respiratory chromium VI exposure and lung cancer (67).

In vitro evidence and potential mechanisms

Experimental evidence of the mutagenic, genotoxic and cell-transforming activity of chromium VI have been mixed. Some claim that estimates based on *in vitro* assays may have been underestimated, because the levels of ascorbic acid, the main reducer of chromium VI, have been substantially lower *in vitro* than *in vivo*. Others have proposed that the lung's ability to reduce chromium VI to chromium III could function as a physicochemical defense system against carcinogenic effects at chronic low doses (12). Effects should then occur only at very high exposure levels, which could overload the lung's natural defences, allowing chromium VI to enter the cell and produce cancer (68-70). In this case, many in vitro studies may have failed to take into account the physiological environment of the human lung. Hexavalent chromium and its reduced forms have been shown to interact with cellular molecules and DNA, causing cytotoxic effects, chromosomal aberrations, and DNA damage. Induction of oxidative stress may also activate signaling pathways that inhibit apoptosis (12, 67, 71).

Epidemiological Evidence

A possible association between exposure to hexavalent chromium and lung cancer has been recognised since the 19th century, and the carcinogenic effects of respiratory exposure to chromium VI have been extensively established and reviewed (12, 72, 73). An early study of U.S. chromate plants suggested that exposed workers were up to twenty times more likely to have lung cancer than unexposed workers (74). Following this report, a large number of studies have investigated the association of chromium exposure and respiratory cancer and found increased risk of lung cancer in electroplaters (75, 76), ferrochromium manufacturers (77-79), and pigment manufacturers (80-82), especially after long-term employment (67, 71). A recent

study estimated exposure at current occupational standards could result in an excess lifetime risk as high as 1 in 10 (63). However, evidence in many occupational contexts has been inconsistent, and studies producing both positive and negative results have been methodologically limited and potentially confounded. For example, although stainless steel welding has consistently been associated with increased risk of lung cancer, welders are also exposed to oxides of other metals, particularly nickel (3, 83-85). The attribution of increased risk to chromium in particular is difficult in this context.

Chromate manufacturers

The majority of recent epidemiological studies with quantitative measures of exposure to chromium VI come from cohort studies of chromate manufacturers. Epidemiological reports of excess lung cancer cases in these manufacturers began in the 1940s (74, 86-88) and strong evidence of excess lung cancer in chromate manufacturers exposed to hexavalent chromium in particular was first suggested in the 1960s (89, 90). A twofold lung cancer risk at high levels of exposure was well-established (91-93), and was particularly attributed to workers' exposure to insoluble calcium chromate, largely considered to be the most hazardous of the chromium species (92).

Early studies of chromate manufacturers measured the risks associated with exposure before the 1960s, when chromate production involved a high-lime process. This process produced high concentrations of respirable chromium VI by increasing the amount of dusts and insoluble calcium chromate species in the air (67, 94). Consequently, there was a strong association between chromium exposure and lung cancer in workers exposed before the 1960s. Subsequent

production method changes and industrial hygiene improvements reduced these exposures considerably, and studies spanning process changes consistently demonstrate that workers employed after the 1960s have less risk of lung cancer risk than earlier workers (91, 93, 95-98). However, one study examined workers exposed after exposure reduction measures and found an SMR of 180 (95% CI= 110-279) despite a relatively small sample size (95). Lung cancer risks have persisted to variable degree after process changes, and risk at lower levels remains highly contentious. Most cohort studies published before the IARC review (1990) were impaired by common methodological limitations: small cohort size, absence of smoking data, and absence of quantitative exposure estimates. Further, post-process change risk estimates have not allow sufficient latency periods, as it is generally accepted that 20 years is required between exposure and effect (94).

Four recent cohort studies calculated quantitative measures of hexavalent chromium exposure and introduced other methodological improvements, making them amendable to quantitative risk assessment and dose-response modeling. One set of studies on chromate production workers in Germany and Painesville, Ohio was conducted by a common private company commissioned by an industrial sponsor (92, 94), while another set of studies was associated with the U.S. EPA (72). These quantitative studies showed that lung cancer risks were lower after industrial process changes. However, although their results were relatively similar, their conclusions regarding low-level exposure and interpretation have been the subject of some controversy. A fourth cohort in North Carolina found no significant association between chromium exposure and lung cancer (98). The findings of the first three studies are summarized here.

Chromium producers in Baltimore, MD

In an update of a previously studied cohort (95), Gibb *et al* (2000) found that lung cancer risk in chromate producers persisted after process changes in the 1950s (SMR=180, 95%CI=149-214), particularly in those with high cumulative exposure levels. Strong cumulative exposure-response trends were observed between hexavalent chromium and lung cancer. While those exposed at levels under 5 ug/m^3 did not show excess risk, a ten-fold increase in cumulative exposure was associated with a 1.38 increase in hazard (95%CI=1.20-1.63). In the highest category of cumulative exposure, hazard ratios of 3.32 were found compared to the lowest category (72). However, most of the lung cancer cases occurred among smokers, which may have resulted in an overestimation of risk.

Chromate producers in Germany

In a study of two small cohorts of chromate producers in Germany (n = 593 and 308), Birk et al (2006) used urinary chromium levels collected from workers on a regular basis over decades to create a job exposure matrix and estimate cumulative exposure for all workers. Although this measure could not distinguish between chromium VI and III, it had advantages in the precision with which it was able to measure exposure. This study demonstrated that a reduction in exposure levels after process changes have reduced the risk of lung cancer associated with chromium VI. Urinary chromium concentrations greater than 200 ug/L, indicating very high exposure, continued to be associated with increased risk of lung cancer, even after control for smoking (SMR=209, 95%CI=108–365). In the three categories of exposure below 200ug/L, there was no evidence of increased lung cancer risk regardless of lagtime or exposure duration (94).

Chromate producers in Painesville, OH

The original chromium VI risk assessments conducted by U.S. EPA and Health Canada were largely based on the first quantitative estimates of soluble chromium exposure (72) in studies by Mancuso *et al*, conducted in 1975 (99), and updated in 1997 (100). Standardised mortality rates in this cohort ranged from 80.2 to 998.7 depending on the level of exposure. However, these preliminary studies had many limitations: risk estimates differentiated between soluble and insoluble exposures but not between chromium VI and III; smoking data were unavailable; exposure estimates were based on one survey conducted 10 yrs after exposure began; and mortality rates were based on estimated reference rates and not a standard population (70, 72).

This cohort was recently extended and limited to those with over 12 months of employment after 1940 (92). Using a more robust exposure assessment, Luippold *et al* (2003) found that standardized lung cancer mortality rates for the entire cohort were elevated and highly significant (SMR=241; 95%CI =180-317). Mortality rates were above 250 for workers with high levels of cumulative exposure, over 20 years of exposure or over 20 years since first exposure. However, excess lung cancer found to be limited to workers employed before 1960, when the plant was still using high-lime processing. Workers exposed only to low-lime processes between 1960 and 1971 did not demonstrate any increased risk (SMR =92; 95%CI =34-201). A further update focused on employees hired only after process change also claimed to reflect a favorable environment post-process change (SMR = 84; 95% CI = 17 – 244) (101). Limitations of Luippold *et al*'s analysis of the post-process change workers included small sample size and limited follow-up and latency periods; few workers were followed for the 20 years required for

an increased risk to be detected (6, 92). Some also argue that there is evidence of bias from the healthy worker effect (6), although this type generally has little impact on cancer mortality data (102).

Controversy regarding low exposure level effects

The German and Ohio-based studies reviewed here were originally commissioned by industry sponsors to be analysed together, but were later divided because of the differences in their exposure assessment methods. Critics of the industry-sponsored studies suggest that a private report on the original higher-powered, combined results showed evidence of increased risks at intermediate exposure levels, and that this effect was later purposefully minimised by underpowered sample size and combination of low and intermediate exposure groups in the published studies. In particular, the German study had a sample size far too small to detect the minimal increases in risk that would be expected from low exposure levels (103-105).

The authors of the industry-affiliated Germany- and Ohio-based studies have defended the integrity of their studies, and several other epidemiological and methodological studies appear to support their conclusions, suggesting a weakened association between low-level chromium exposure and lung cancer (68, 70, 106). They suggest that the risks observed by Gibb *et al* at low cumulative exposure levels were confounded by largely acknowledged factors (107) associated with the inclusion of short-term workers (92). Indeed, a large proportion of the Gibb cohort were short-term workers, with 40% of the cohort employed for less than 90 days, such that the cumulative exposure levels at which effects were observed among the Baltimore cohort (72) were lower than those in the Painesville cohort (92), which excluded workers employed for

less than a year. Up to 60% of workers in the Baltimore cohort experienced signs of chromium irritation within the first months of employment, and may have left for health reasons, such that the effects at low exposure levels may be unpredictable in this cohort (108). However, this study is nonetheless highly respected and credible according to US regulators.

Confounding

Occupational co-exposure

Occupational confounding remains a significant and as yet weakly addressed factor in the examination of the relationship between chromium VI and lung cancer (92). Confounding by exposure to asbestos was considered plausible in several studies (63, 72, 100) but was not considered to be significant. Meanwhile, exposure to other potentially carcinogenic agents such as nickel has complicated analysis of the specific effects of chromium VI in several occupational contexts. It is also possible that there is a potential synergism between chromium compounds and other carcinogens such as benz-a-pyrene and constituents of cigarette smoke (12, 72).

Most evidence indicates that trivalent chromium is not carcinogenic (68, 73); indeed, it is used as a nutritional supplement and is believed to play a role in the metabolism of glucose (67, 109). However, because chromium III and VI are strongly collinear in most occupational contexts, the role of chromium III in carcinogenesis cannot be ruled out (7, 72).

Smoking

Most recent studies with information on smoking the habits of some or all of their subjects found that the relationship between quantitative measures of cumulative chromium VI exposure and lung cancer not confounded by smoking status (72, 94, 110). However, in most occupational

studies, the majority of cancer cases occurred in smokers, and control for confounding was therefore limited (92). Further, in a recent meta-analysis of epidemiologic studies, mortality rates were 141 (95%CI=112-279) for all chromium studies, but only 118 among the better-quality, smoking-controlled studies. The authors concluded that three quarters of the excess lung cancer in previously uncontrolled studies may have been due to confounding by smoking, and that the association between chromium and lung cancer is weaker than generally accepted (106).

Carcinogenicity at other sites and by other routes of exposure

In addition to being associated with lung cancer, inhalation of hexavalent chromium is suspected by some to cause other cancers including kidney, prostate, bladder cancers and brain cancers (12). In particular, some concern has been raised that it may be associated with stomach cancer if inhaled particles are swallowed (12, 111). Evidence of stomach cancer after exposure to high concentrations of chromium VI in drinking water is also accumulating (12, 111-113), but remains controversial (67, 114). Concern about such effects was widely popularized in the Hollywood movie *Erin Brockovitch*, where hexavalent chromium in one California town's drinking water led to a $333 million lawsuit (109). Historically, there has been little evidence suggesting that ingestion of chromium VI causes cancer (67, 109, 115, 116). While chromium VI may be easily absorbed, it is quickly reduced to trivalent chromium by digestive mucosa, which is much less easily assimilated (68, 117). As a whole, reports of cancers at sites other than the lung, and by routes other than respiration, have been statistically insignificant and inconsistent compared to studies on respiratory exposure and lung cancer (92). This study focuses on respiratory exposure to chromium VI because it has been most consistently associated with increased risk of lung cancer.

Conclusion

There appears to be little doubt of chromium VI's carcinogenicity at high exposure levels. What remains to be determined is whether the exposure-response relationship between chromium VI exposure and lung cancer is linear, as observed (63) or speculated (72) in some studies, or whether there is an exposure threshold under which there is no increased risk (92, 101). Industry-associated groups have suggested that the absence of effect at low exposure levels may be attributable to an exposure threshold effect (92, 94). Recent mechanistic studies are also compatible with a threshold response for chromium VI, based on the lung's capacity to reduce chromium VI into chromium III (68). Although the existence of an exposure threshold is good news for chromium-exposed workers and regulators alike, premature conclusions about risk at low exposure levels could result in optimistic exposure regulations. The effect of chromium VI at low doses therefore has important implications for risk assessments and for the determination of regulatory limits (108).

CADMIUM BACKGROUND

Production and uses of cadmium

Cadmium is a ubiquitous but sparsely distributed element in the natural environment whose presence is concentrated during non-ferrous metal mining, smelting, and refining. It is used primarily in the production of nickel- or silver-cadmium batteries and red or yellow pigments. It is also used to electroplate iron, steel and alloy products to protect against corrosion and as a stabilizer in paints and plastics (5, 118). Among the most common cadmium compounds are cadmium oxide (used in batteries, catalysts, and electroplating), cadmium sulphide (a pigment) cadmium sulphate (used as a chemical intermediate and in electroplating) and cadmium stearate (a plastics stabiliser) (4).

Canada is the fourth largest global producer of cadmium, producing over 17 000 tonnes of cadmium a year. Consumption of cadmium metals dropped 14% between 2002 and 2006 due to environmental concerns, and North American cadmium production has subsequently decreased in recent years (5).

Human exposure to cadmium

The average person is exposed to small quantities of cadmium in their food, water, and air (15). Most cadmium exposures originate from the industries that produce cadmium or cadmium-containing products, although fossil fuel combustion is also an important source of cadmium exposure. Small amounts of cadmium exist in particulate form in the air we breathe, in concentrations that depend on degree of pollution and proximity to industrial sources, but respiratory exposure constitutes a very small proportion of daily exposure. Ingestion of food and water is cadmium's main route of entry into the human body (119), as plants and animals, and

particularly seafood, tend to bioaccumulate cadmium pollution (5). However, only 5 to 10% of ingested cadmium is absorbed by the digestive tract (120, 121). Approximate absorbed doses that result from ingestion, respiration, and occupational exposure are detailed in Table 1.

It is important to note that cigarette smoking can double an individual's daily dose of cadmium (15). Smokers have four to five times higher blood cadmium concentrations than non-smokers and large amounts of accumulated cadmium in their lungs (122-124). There have been two different estimates of the possible impact of cadmium in cigarettes: Hertz-Picciotto and Hu (1994) estimated that that 0.2% to 1.6% of lung cancer deaths may be attributable to cadmium from cigarettes (125), while Cox (2006) estimated that approximately 10% of lung cancer among smokers is attributable to cadmium content (124).

Occupational exposure

Certain work environments are a significant and important source of cadmium exposure, and approximately 500,000 workers in the USA are exposed to cadmium each year. Workers are exposed to cadmium oxide fumes generated while heating or welding of materials containing cadmium, or by inhaling dust and particles of cadmium metal, oxides, hydroxides, sulphides, or sulphates. Before the potential hazard of cadmium was recognised, workers in mining and refining industries were exposed to aerosol cadmium concentrations of up to 5 mg/m^3. Current occupational standards are a great deal more stringent than a generation ago, and most occupational cohorts with exposures dating from the 1970s to the 1990s report exposure concentrations between 0.005 mg/m^3 (126) to 0.2 mg/m^3 (127, 128).

Metabolism and toxicity of cadmium

Cadmium is a non-essential trace element that has a tendency to mimic other more essential elements when introduced into biological systems. Acute oral intoxication leads to vomiting, nausea, and headache, while acute respiratory cadmium toxicity is very rare, requiring concentrations higher than any occupational exposure (15). Chronic respiratory exposure to high levels of cadmium has been associated with obstructive airway disease, emphysema, renal failure, bone disorders and immunosuppression, particularly in highly exposed workers (129). A rare and extreme example of chronic cadmium poisoning was the epidemic of itai-itai (ouch-ouch) disease in the Toyama prefecture of Japan in the 1950s, so called because ingested cadmium competitively replaced bone calcium, resulting in bone fragility, painful deformation and fracture (chronic osteomalacia). This outbreak was a consequence of pollution of the community's water source by a nearby mine (5).

Between 10 and 90% of inhaled cadmium is absorbed by the lung, depending on the form of cadmium involved. Cadmium chlorides, nitrates, and sulfates tend to exist in the form of soluble dusts, which easily passes through cellular membranes. Conversely, insoluble cadmium hydroxide and cadmium sulfide dusts are poorly absorbed, and are largely cleared by ingestion by alveolar macrophages before entering the cell (16). When heated, cadmium also forms oxide fumes (5) which undergo a chemical transformation in the lung and are easily absorbed.

Cadmium is very slowly eliminated from the body; it has a half-life of 5 to 10 yrs in the liver, 20 years in the lung, and a lifetime in the kidney. Once absorbed into the bloodstream, cadmium is transported to the liver, where it is bound to metallotheionein, which acts to protect the body

from its immediate toxicity. It then is transported in its bound state to the kidney, where it is filtered but minimally eliminated. Its presence can induce renal damage if sufficient metallotheionein cannot be produced to re-bind it. As such, urinary cadmium is a good measure of cumulative exposure in a person with healthy kidneys, while blood cadmium is a better measure of current exposure (15). Susceptibility to the toxic effects of cadmium therefore depends partly on the availability of metallothionein, which may genetically influenced (130).

Experimental evidence

Animal study evidence

The first evidence of the toxicity of cadmium arose from injection experiments conducted in the early 1960s which found that cadmium salts induced cancer at the site of injection. Experimental animal studies have since demonstrated that exposure to cadmium causes benign and malignant tumour formation in several organ sites and by several routes of exposure (131). The respiratory system is the primary target site for carcinogenesis after cadmium inhalation. While injection and ingestion studies in rodents have produced mixed results (132, 133), inhalation studies show consistently positive associations between cadmium exposure and lung cancer. An influential study by Takenaka *et al* in 1983 revealed an unequivocal dose-dependent increase in pulmonary cancer incidence in rats continuously exposed to cadmium chloride aerosol (134). Since that time, positive associations between cadmium exposure and lung cancer have been found by several other inhalation studies (131, 135, 136). However, in extrapolating these results to humans, it is important to acknowledge that animal experiments were conducted at much higher doses than most human exposures.

In vitro evidence and potential mechanisms

Mechanistic and genotoxic aspects of cadmium carcinogenesis have been reviewed extensively over the past several years (129, 131, 136, 137). Most reviews conclude that cadmium is only weakly genotoxic (131, 136, 137), and corroborate conclusions from animals studies that cadmium's mechanisms of carcinogenesis or co-carcinogenesis are likely multiple (131). *In vitro* models suggest several plausible mechanisms by which cadmium could exert its effects, from initiation to apoptosis. The carcinogenic effects of cadmium likely stem from its mimicry of other essential nutrient metals, as it competes for binding at sites involved in gene regulation, enzyme activity, and other means of maintenance of genomic stability (5, 137). Cadmium may weakly bind to DNA and act through an epigenetic mechanism (131), or may mediate carcinogenesis by production of oxidative stress (131, 137), modification of transcription factors (138), or reduction of antioxidant defenses (41, 137, 139). There is particularly strong evidence that cadmium inhibits the mismatch repair mechanism of DNA repair (140, 141) by preferentially binding zinc-finger motif sites (131). Indeed, the presence of zinc has been observed to reduce the carcinogenic effect of cadmium in the lung. *In vitro* evidence and genotoxicity studies also that indicate that cadmium may be a co-carcinogen when combined with other genotoxic agents (41, 131).

Possible mechanisms of cadmium carcinogenesis have also been studied in humans, by correlating environmental exposure with genetic damage. However, most such studies have suffered from methodological limitations such as small sample size, selection bias, insufficient characterization of exposure, and confounding. Additionally, because of a lack of consensus about the mechanisms being explored, cytogenetic endpoints have been inconsistent between

studies. Although some studies have found a positive correlation between cadmium exposure and cytogenetic endpoints (142), the findings with regard to cadmium's mechanism of action in humans remain conflicting and no definite conclusions can be drawn (143, 144).

Epidemiological Evidence

Increased incidence of cancer after cadmium exposure was first observed in nickel-cadmium battery workers in the 1960s (145), and was subsequently studied in numerous occupational cohorts. In 1993, evaluations by IARC concluded that the evidence presented by these initial studies, in combination with animal and experimental studies, provided sufficient proof that cadmium is a human carcinogen. Their evaluations were largely based on increased risk of lung cancer observed in occupational cohort studies of nickel-cadmium battery manufacturers (146-148), cadmium processing workers (149-153), and smelter or recovery plant workers (154-156). In the majority of these studies, risk was increased by 10 to 50%, but in some highly exposed groups, standardised mortality rates were as high as 200.

The preliminary occupational cohort studies that formed the basis of IARC's evaluation had important and widely acknowledged limitations, such that the carcinogenicity of cadmium alone continued to be questioned. The cohorts studied tended to have small numbers of long-term, highly-exposed workers and only rough exposure assessment data. They were also subject to potential confounding by cigarette smoking and other occupational carcinogens, particularly arsenic (in smelting crude ore) and nickel (in nickel-cadmium battery workers) (5, 119, 157). These limitations have since been addressed in updates to several of the cohorts, which include

improved assessment and quantification of exposure data, extended cohorts, updated mortality statistics (9) and better control of confounding variables.

Results from the most significant cohorts that contributed to the IARC decision, as well as conclusions from subsequent updates, are briefly presented here.

Nickel-cadmium battery cohorts

Reports on occupational health in the first nickel-cadmium battery cohort in the UK began as early as the mid-1960s (145, 158). Early evaluations of cumulative exposure to cadmium hydroxide dust revealed positive associations between exposure and respiratory cancer in small subgroups of moderate- to highly-exposed workers in the UK (SMR=130; 95%CI=107-157) (146, 147). A nickel-cadmium battery factory in Sweden equally found that exposure to long-term, high level exposure to cadmium was associated with increased risk of cancer (SMR=133, 95%CI=60-260), particularly after a latency period of over 20 years (159). However, the roles of nickel and other confounders were not sufficiently addressed in either of these cohorts. Subsequent methodological improvements and updates to the UK cohort reduced the observed association between cumulative cadmium hydroxide exposure and lung cancer (SMR = 111, 95%CI = 81-148) (9). Conversely, after extension of the Swedish cohort and quantification of cumulative cadmium oxide and nickel exposure, risk of cadmium-associated lung cancer remained elevated but barely significant as compared to regional death rates (SMR = 176 95%CI=101-287) after controlling for arsenic and smoking (123). Despite improvements in methodology and measurement, there was no evidence of dose-response relationship in either of these cohorts.

Cadmium recovery workers cohort

The NIOSH-associated GLOBE study involved a cohort of US cadmium recovery workers exposed to several species of cadmium including cadmium oxide, sulphide, sulphate, and metals. Studies conducted in the 70s and 80s consistently found a positive relationship between cadmium exposure and risk of lung cancer (154, 156). Neither confounding by arsenic, an impurity in the feedstock and a previous product of the same plant, nor smoking was considered to account for the excess mortality. Dose-dependent associations were retained in an update to the study cohort using more accurate, quantitative estimates of cumulative exposure (156). However, a matched case-control conducted using the same dataset firmly contradicted these results and found that the effect of cadmium was greatly reduced after careful consideration of the effects of arsenic and smoking (160). Nonetheless, the GLOBE study was the only study with quantitative measures before 1993, and therefore likely played an influential role in the 1993 IARC evaluation of cadmium's carcinogenicity (119).

After the contradictory results regarding confounding by arsenic were reported for the GLOBE cohort, a portion of the exposure estimates were re-evaluated using more specific job environments, which highlighted important misclassification errors in the exposure estimations for this cohort (127). A subsequent update of the cohort found a positive relationship between quantitative measures of cumulative cadmium exposure and lung cancer. However, the observed dose-dependent relationship was not confirmed in the absence of arsenic, which was highly correlated with cadmium exposure (161).

Cadmium processing plant cohorts

Beginning in the 1980s, a series of studies by Kazantzis and colleagues examined the association between exposure to a variety of cadmium products, including stabilizers and pigments, in cadmium processing plants in the UK. Arsenic was present in some factories, while nickel and chromium were present in others. Increased mortality of only borderline significance was observed after low, medium and high intensity cadmium exposures at various durations. No clear dose-dependent relationships were observed, and if those unexposed to arsenic were analysed separately, no association was found (149-153).

Potential confounding by arsenic was further demonstrated in a cohort of copper-cadmium alloy workers, where no association was found between cumulative exposure to cadmium oxide fumes and lung cancer, despite consideration of time since exposure. An updated analysis of this cohort using and quantitative measure of cumulative exposure to cadmium oxide fumes also failed to find increased risk in exposed workers as compared to the national population. However, a third category of workers also employed in the vicinity showed increased cadmium-associated risk; these workers were particularly likely to have been co-exposed to arsenic while working in nearby shipyards (128). Another investigation of workers in a large zinc-lead-cadmium smelter did not produce a positive association between lung cancer and cumulative cadmium exposure. When co-exposure to asbestos and arsenic were controlled, there was no association between cadmium exposure and lung cancer (149). Similarly, a new cohort of tin smelter workers with quantitative measures of both arsenic and cadmium exposure found little evidence of an effect of cadmium in the absence of arsenic. However, the two substances were highly correlated (126).

Confounding

Occupational co-exposures

Although recent updates to a number of occupational cohorts have attempted to address occupational confounding, it is widely acknowledged that the observed inconsistencies between studies may well be due to the presence of other occupational carcinogens such as arsenic and nickel (9, 119). Arsenic is the main occupational co-exposure that has interfered with interpretation of cohort study results and prevented definitive conclusions regarding the carcinogenicity of cadmium. In cohorts where co-exposure exists, cadmium and arsenic are so closely correlated that removing or controlling for arsenic negates any potential for observation of an effect of cadmium (126, 152, 161), while cohorts relatively free of arsenic exposure tend to have equivocal or negative results. Similarly, most studies of nickel-cadmium battery plants have not been successful in distinguishing between the effect of nickel and cadmium (9, 123). These observations suggest that cadmium may simply me a marker for stronger carcinogenic agents such as arsenic (119). It is also possible that cadmium is a cancer promoter that requires the presence of an initiator to exert its effects.

While much attention in the literature has been given to arsenic and nickel, other more prevalent and powerful occupational confounders such as asbestos insulation, silica from refractory brick, and PAHs have been entirely neglected in most analyses.

Smoking

Lifestyle factors such as diet and smoking may be at once sources of unmeasured cadmium exposure and a potential independent risk factor for lung cancer (162). Due to the design of occupational cohort studies, control of smoking has been poor or non-existent in the majority of

the studies conducted to date. Many authors have surmised that smoking history is unlikely to vary between exposed and unexposed individuals (9), while studies adjusting for confounding by smoking for those with available histories have found that it has changed risk estimates only marginally (123).

Carcinogenicity at other sites and by other routes of exposure

Ingestion of high levels of cadmium has been associated with several types of cancer in animal studies, including the testicles and prostate as well as the liver, pancreas, adrenal, pituitary, and hematopoeitic systems (131). In humans, cadmium has also been associated with several cancer sites, including kidney, pancreas, breast, and prostate (5, 119). However, there is mixed evidence that exposure to ingested or environmental cadmium is a lung carcinogen in particular. Ecological studies provide an interesting alternative to the use of occupational cohorts in the examination of the relationship between cadmium exposure and lung cancer. They necessarily (but inaccurately) take into account all potential lifelong sources of cadmium exposure, including those in water, food and air, and therefore automatically control for diet and smoking. While many studies of environmental exposure have not found dose-dependent relationships between cadmium ingestion and lung cancer (119, 122, 163, 164), recent studies using sensitive biological indicators of cumulative exposure observed an increased risk of lung cancer at high cadmium exposure levels after adjustment for age, sex, and smoking (165-167). One prospective population-based study recorded a hazard ratio of 1.7 (95%CI=1.01-2.45), an association that remained after adjustment for arsenic exposure for the 26% of the population for whom data were available (HR = 1.60; 95%CI 1.04 – 2.45) (165). Another environmental study similarly found that overall lung cancer risk was elevated in those highly exposed to environmental cadmium (166).

Conclusion

In recent years, improved study design has not strengthened the evidence of an effect of cadmium on lung cancer. Associations observed in early occupational cohorts have not been consistently replicated in later investigations and updates. Although elevated mortality rates in cadmium-exposed cohorts have been maintained in several settings, they have always been under 200 and of borderline significance (119). Few consistent or specific dose-dependent relationships have been observed, and consideration of exposure to confounders, particularly arsenic, has tended to weaken observed associations. Indeed, when both dose-response relationship and arsenic exposure are taken into account, none of the studies support the hypothesis of a carcinogenic effect of cadmium (9, 119). However, experimental evidence suggests that at the very least, cadmium could be an important cancer promoter or co-carcinogen, likely operating through non-genotoxic mechanisms. Thus, while cadmium may remain an important factor in the development of lung cancer, it seems that a definitive, independent association between cadmium and lung cancer is far from being proven from an occupational epidemiology perspective.

STUDY METHODOLOGY

This study was conducted using data from two population-based case-control studies of occupational exposures and lung cancer. Both studies were conducted in greater Montreal, the population of which was 2.7 and 3.1 in 1979 and 1996 respectively (168). The first study, labeled here as Study I was conducted from 1979 to 1986, and included males aged 35 to 70 diagnosed with cancer at any of 19 sites (169)(170, 171). The second study, labeled here as Study II, was conducted from 1996 to 2001 and included men and women aged 35 to 75 diagnosed with a lung malignancy. In both studies, cases and controls were restricted to Canadian citizens. Because of the very small numbers of women professionally exposed to chromium, cadmium, and nickel, the present analyses were restricted to male subjects.

Case ascertainment

Both studies included patients with incident, histologically confirmed cancers identified across all major Montreal-area hospitals, and living in the Montreal area, assuring a virtually complete population-based ascertainment of cancer cases. Details of subject ascertainment and data collection have been presented in detail previously (169, 172, 173).

Selection of controls

Both studies included a series of population controls randomly selected from electoral lists. In Quebec, electoral lists were maintained by means of active enumeration of households until 1994; they have since been continually updated and are thought to represent nearly complete listings of Canadian citizens residing in the province. In Study I, population controls were frequency matched to all cancer cases by age, and area of residence, based on electoral districts of about 40,000 individuals. In Study II, controls were similarly recruited according to the

distributions of age, sex, and area of residence of lung cancer cases. In Study I, a second group of controls comprising 1,349 patients with cancer at 18 other sites was ascertained in the same years and hospitals as the lung cancer cases. A cancer control set was then created so that none of the individual cancer sites represented more than 20 percent of the overall pool of cancer controls.

Response rates

In Study I, 1,082 lung cancer cases and 740 population controls were approached. Of these, 857 (79 percent) cases and 533 (72 percent) population controls completed the interview. In Study II, 858 eligible male cases and 1,024 eligible male controls were approached, and 86 percent and 70 percent of these, respectively, agreed to participate and completed the interview. In Study I and Study II, interviews were completed by the targeted subjects in over 82 percent and 76 percent of individuals, respectively, whereas surrogate respondents (proxies) provided information for the other participants.

Data Collection

After giving informed consent, each study subject or proxy was individually interviewed by a trained interviewer at the time and place of the subject's choice. Interviews were divided into two sections: a structured section requested information on socio-demographic and lifestyle characteristics, and a semi-structured section elicited a detailed description of each job held by the subject in his working lifetime. Occupations were coded according to the CCDO classification system (174). For each job held, the subject was asked about the nature of the work environment, the subject's main and subsidiary tasks, and any additional information that

could provide clues about work exposures and their intensity (e.g., equipment maintenance, use of protective equipment, activities of coworkers). For some occupations, supplementary questionnaires were used to assist interviewers with detailed technical probing (175).

Exposure assessment

The methodology for exposure assessment has previously been presented in detail (169, 173). A team of chemists and industrial hygienists examined each completed questionnaire and translated each job into a list of potential exposures using a checklist of 294 common occupational agents. Non-exposure was interpreted as exposure up to the level found in the general environment and population. For each substance considered present in each job, the duration of exposure was considered to be the duration of the job. The coders also noted information on three dimensions of exposure: their degree of confidence (reliability) that the exposure had actually occurred (possible, probable, definite), the relative concentration level of the agent (low, medium, high), and the frequency of exposure in a normal work week. In Study I, frequency was estimated as a percent of a 40-hour work week spent exposed to the substance (<5 percent, 5–30 percent, >30 percent); in Study II an estimation of the approximate number of hours/week was recorded. The exposure assessments were based not only on the worker's occupation, industry, and job title but also on individual characteristics of the workplace and tasks reported by the subject; there were many examples of subjects with the same job title having different exposure profiles, and conversely, similar exposures were attributed to many subjects with different job titles. An illustrative example can be found in the Appendix of Parent et al. (176).

For each of the metals considered in this paper, coders established reference benchmark occupations to guide their assignment of concentration levels. Similar benchmarks were used for both studies. Low- to medium-concentration exposures for nickel included benchmark occupations such as electroplating, and MIG or TIG welding on stainless steel. For chromium VI, it was understood that low to medium concentrations occurred during welding, tanning, pigment production, spray painting, and electroplating. Cadmium exposures were attributed to electroplaters, PVC producers, ceramists, artists, and painters.

A team of coders spent about 40 person-years on this project, which included methodology development, interview quality monitoring, background research on exposures in different occupations, coding the individual participants' files, and recoding after the initial complete round of coding was finished. The final exposure codings attributed to each participant were based on consensus among the coders, who were blind to the subject's disease status.

Data were also collected on a large number of other variables including ethnicity, family income, selected dietary items, and alcoholic beverage consumption. A detailed smoking history was also collected, including estimates of cumulative tobacco exposure in cigarette-years, pauses in cigarette consumption, quitting behaviour, and second-hand smoke exposure. For inclusion in the present analyses, subjects were required to have completed both the socio-demographic and the job history interviews.

Data analysis

For each study, unconditional logistic regression (177) was used to estimate odds ratios (ORs) of lung cancer and 95 percent confidence intervals (95% CIs) after exposure to nickel, chromium VI, or cadmium. Subjects were categorized as unexposed or ever exposed. Because of a necessary minimum latency period, those exposed only in the 5 years prior to interview were considered unexposed. Individuals classified as having had only possible likelihood of exposure (low reliability) were excluded from most analyses. Ever exposed individuals were further classified into two exposure subcategories: non-substantial and substantial exposure. Subjects with substantial exposure had been exposed to medium or high concentrations of cadmium for more than five percent of their work week, and for five years or more. It may be seen as being analogous to a cumulative exposure measure.

In addition to analyzing a single categorical measure of cumulative exposure, we had the opportunity to explore the effect of several other dimensions of exposure: duration, concentration, frequency, and intensity (concentration x frequency). The impact of each of these dimensions on lung cancer risk was examined individually, both as continuous variables and after categorization with a variety of cutpoints. Cross-tabulations were also performed to examine risk as a function of different combinations of these dimensions; for example, risk with low, medium or high exposure duration at low, medium or high concentrations was explored.

A variety of potential confounders were routinely included in analysis, including socioeconomic status measured by family income, schooling level, ethno-cultural background, and respondent status (self, proxy). In order to control for smoking, we used an optimized approach to

parameterization of smoking based on a risk model derived from our study subjects (178, 179), which consisted of a three-variable model that provided the best fit for analysis of the effect of smoking: ever smoking, the natural logarithm of the number of pack-years, and number of years since quitting smoking. Potential effect modification by smoking was also explored, where non-smokers were defined as having smoked fewer than 100 cigarettes in their lifetimes or having quit over 20 years previously.

The effect of co-exposure to other common and *a priori* occupational confounders was also considered using a change-in-estimate criterion (180). Those that changed the estimate of association by over 5% were retained. Occupational co-exposures retained in the complete model for nickel and chromium VI were asbestos, silica, benz-a-pyrene, and nickel or chromium VI. The final model for cadmium included asbestos, silica, benz-a-pyrene, lead, and nickel. Other potentially important confounders, such as cadmium in the case of nickel, and arsenic in the case of cadmium, were not present in sufficient quantities to affect point estimates and were not retained in the final model.

Pooling control groups and studies

In Study I, population and cancer control groups were first analysed individually, and then pooled together if individual results were of the same magnitude and direction. Given that it was difficult to ascertain which group gave more accurate results in this context, cancer controls were weighted such that population and cancer controls contributed equally to the combined control set. Similarly, when the results from Study I and Study II showed parallel trends and largely overlapping confidence intervals, a pooled analysis was also conducted. Cases and controls from

each study were simply added together, and a binary study adjustment term was added to logistic regression models.

Ethics approval was obtained for both studies from each participating hospital and university. All participating subjects provided informed consent.

RESULTS

Study Population Characteristics

The distribution of subjects according to selected socio-demographic characteristics is shown in Table 2. As expected, cases were more likely to be current smokers and had smoked more than controls. Interviews were more likely to have been conducted with a proxy for cases than controls. Cases had a lower median family income and fewer years of education than controls.

Exposure and co-exposure prevalence

Table 3 shows the lifetime prevalence of occupational exposure to nickel, chromium VI, or cadmium in each study. Prevalence of any exposure to nickel or chromium VI in this sample of Montreal men was between 6 and 11%; cadmium exposure was somewhat lower. There was substantial exposure to each metal in between 1 to 2% of the population, except for cadmium in Study I, where substantial exposure was less than 0.5%. There was little difference in exposure prevalence between cases and controls, though cases were more likely have been substantially exposed than controls in Study II.

The degree of co-occurrence between the three metals is illustrated in Figure 1. Overall, nickel and chromium VI co-occurred in about 50% of subjects, more frequently in controls than cases, and were often associated with similar occupations (results not shown). As expected, each was found to moderately affect risk estimates for the other. However, investigation of their combined effects revealed no interaction between their effects (results not shown). Co-exposure to chromium VI was also common among those exposed to cadmium, but analyses of the effects of co-exposure were not conducted due to small sample size.

For each metal in question, co-exposure to other common occupational agents was explored. In the pooled dataset, exposure to all three metals heavily coincided with PAHs, particularly benz-a-pyrene. Occupational co-exposure to strong lung carcinogens such as asbestos and silica was also common in those exposed to nickel and chromium VI. Arsenic, a common confounder of cadmium risk estimates in many occupational cohorts, did not co-occur with cadmium in this dataset; as such cadmium risk estimates may be considered unconfounded by arsenic.

Occupational profiles

Table 4 shows the occupations in which these metals were attributed in our study subjects. For the most part, occupational profiles within metals were consistent between Study I and Study II; given the small number of jobs in each study, some variation was expected. The majority of nickel exposures occurred in sheet metal workers, metal machinists, and metal product fabricators; chromium VI exposures occurred in construction painters, sheet meal workers, and mechanics; and cadmium exposures occurred in metal machinists, sheet metal workers, metal product fabricators, and graphic artists. Overall, metal exposures occurred in similar occupations but in different proportions. Those exposed to nickel were more likely to have held jobs related to metal work, while those exposed to chromium VI were more likely to have held jobs in plastics processing, painting, printing, and vehicle maintenance. Because many subjects were exposed to several agents at some point in their lives, these exposures may have occurred in the same jobs; however, this is certainly not necessarily the case.

Risk estimates

Study I: population and cancer controls

Table 5 shows odds ratios derived from separate use of population and cancer controls in Study I, and compares them to results pooling both control sets. Similar trends were observed in population and cancer controls, and results for each metal were of the same magnitude and direction. Risk estimates using cancer controls were consistently higher than those using population controls, but were well within the bounds of their common confidence intervals. As such, pooling of population and cancer controls was deemed justified; pooled results provided a good summary of the results obtained using separate controls, and slightly decreased confidence intervals.

Study I and II: pooled results

Table 6 details the average concentrations of exposure to nickel, chromium VI, and cadmium attributed to the participants of Study II. The majority of exposures were categorized as being of low to medium concentration, while very few participants were exposed to these metals at concentrations over 2. Measures of intensity for Study I were similarly low (data not shown).

Table 7 presents a summary of the odds of being diagnosed with lung cancer after exposure to nickel, chromium VI, or cadmium, adjusted for age, respondent status, years of education, and smoking. Risk estimates for ever having been exposed to nickel or chromium VI were higher in Study I than Study II, but overall, similar trends were observed in both studies. As such, pooled results are mainly summarised here. The pooled data indicated that a small but significant

increase in lung cancer risk was observed in subjects exposed to nickel (OR = 1.27; 95% CI = 1.1 – 1.7). At the exposure levels experienced by this population, there was no increased risk of lung cancer after exposure to any level of chromium VI (OR=1.12, 95%CI = 0.9-1.5). The risk estimate for cadmium was elevated but of borderline significance, with large confidence intervals (OR = 1.54 95% CI = 0.9 – 2.7).

Exposure dimension estimates

Odds ratios were computed separately for each available dimension of exposure, including duration, intensity, frequency, and concentration. None of these showed clear trends for any of the agents (data not shown), except possibly the analyses of duration. Table 8 shows the ORs by duration in the pooled study analysis. Odds of lung cancer tended to increase with duration of nickel exposure in both Study I and Study II, with a significantly elevated risk observed with over 20 years of exposure at any level of exposure (pooled OR=1.56 95%CI = 1.1-2.3). Greater risk was also observed in those exposed to cadmium for over 20 years, while no duration-dependent effect was observed after chromium VI exposure.

Cumulative exposure estimates

Risk estimates for two levels of cumulative exposure, categorised as substantial and non-substantial, are also presented in Table 7. Very few subjects were exposed at the substantial level, and as such risk estimates for this category were somewhat unstable. For all three metals, substantial exposure increased risk in Study II, but not in Study I. Overall, those with substantial exposure to nickel or cadmium had increased risk of lung cancer, while those exposed to chromium VI were not at increased risk regardless of exposure level. Most exposures in this

study were categorized as non-substantial, because the number of jobs with high estimated concentrations was low.

Adjustment for confounding by smoking and occupational co-exposures

Smoking did not appear to be a strong confounder of the relationship between metal exposure and lung cancer in this study. After adjusting for age, respondent status, and SEP, the marginal effect of adding smoking as a covariate reduced the ORs for each metal by less than 7%. Adjusting for occupational confounders also tended to slightly weaken observed associations, but did not affect conclusions.

Effect modification by smoking

The effects of exposure to nickel, chromium VI, and cadmium were also explored separately in smokers and non-smokers. 752 men in this study were non-smokers, of 90 whom were cases. Table 9 shows the odds ratios for exposure to each agent, stratified by smoking history. For all three metal compounds, significantly increased risk of lung cancer was found among those exposed in non-smokers but not in smokers. This trend was observed in both studies independently, with particularly strong (but imprecise) effects observed in Study I. Pooled data showed that exposed non-smokers had approximately 2.5 the odds of having lung cancer compared to unexposed non-smokers in those exposed to nickel or chromium VI, and over four times the odds in those exposed to cadmium. Meanwhile, odds ratios among smokers hovered around 1.1 for nickel and cadmium, and 1.0 for chromium VI. Interaction terms between smoking status and each metal entered into the logistic regression function were significant for each metal, indicating a departure from a multiplicative joint effect. Figure 2 presents odds

ratios and confidence limits for each metal, stratified by smoking history. It illustrates that ORs were consistently higher among non-smokers than among smokers, and that confidence intervals barely overlapped for nickel and chromium VI.

Figure 3 presents the additional risk incurred by those exposed to each metal, stratified by smoking history. [The additional risk associated with exposure to each metal was calculated based on 2x2 OR tables for subjects exposed to a metal only, tobacco only, or both.] The additional absolute risk attributable to exposure to cadmium and nickel was almost identical in smokers and non-smokers. Exposure to nickel and cadmium therefore appeared to have an approximately additive effect on lung cancer risk. Such a distinct trend was less clear in those exposed to chromium, as no excess risk was detected among smokers.

Non-smokers did not appear to have different co-exposures than smokers, and did not have a greater tendency to be proxy responders. Adjustment for occupational confounders further increased the distinction between smoking categories, but decreased estimate precision.

Because of the small number of non-smokers in the study population, there was a relatively small difference between risk estimates for the metals among smokers and in the entire study population. We therefore chose to retain adjusted, unstratified results in Table 5, as it would allow more easy comparison with previous works.

Factors affecting data quality

Exposure reliability

For each substance considered present in each job for each subject, coders estimated their degree of confidence that the exposure had actually occurred as being possible, probable, or definite, which may be translated into low or uncertain, medium, and high estimate reliabilities. The effects of exclusion of low reliability estimates were different for each substance, as detailed in Table 10. Results are presented from the pooled dataset, but represent trends observed in both independent studies. Only 29 nickel-exposed individuals were attributed exposures at low reliability, but those with low reliability exposures had an OR of 3.1. The 95% confidence interval for this estimate (1.1 to 9.1) was much higher than that obtained for the majority of risk estimates with medium to high reliability (OR = 1.28, 95% CI = 1.0 – 1.7). However, because so few individuals were concerned, exclusion of low reliability estimates did not affect the point estimate or confidence intervals for nickel-associated risk. In subjects exposed to chromium VI, very little difference was observed between high and low reliability exposure estimates; no effect was observed regardless of reliability. For subjects exposed to cadmium, a much larger proportion of exposures were estimated at low reliability. In this case, their removal served to increase the point estimate of the association between cadmium and lung cancer. While by definition more reliable, the estimate excluding low reliability estimates was less precise, due to the absolute decrease in the remaining number of exposed individuals.

Because their exclusion had little effect on point estimates for nickel and chromium, and increased point estimates for cadmium, low reliability estimates were excluded from the final analyses of all three metals.

Non-response bias

The characteristics of non-respondents were not collected in either Study I or Study II, so it is difficult to quantify the extent or direction of non-response bias. There is no reason to believe that occupational exposure among cases would have varied between respondents and non-respondents, particularly given that proxy interviews were conducted for deceased or extremely ill cases. Conversely, a number of factors conceivably associated with metals exposure, including education and socio-economic status, may have affected response rates among controls. For example, given that controls tended to be more educated and richer than cases, they may have been less likely to occupy blue-collar positions where metals exposures occurred. If this was the case, odds ratios may have been slightly underestimated in our analysis.

Proxy response

Interviews were completed by proxy respondents for 18 percent of subjects in Study I and 24 percent of subjects in Study II. Interviews were more likely to have been conducted with a proxy for cases than controls, and metal exposures were more likely to have been attributed in interviews with self than proxy responders (data not shown). Table 11 separately details the odds ratios obtained through interviews with proxy and self respondents. For nickel and chromium VI, odds ratios for proxy respondents were lower than those for self respondents, indicating that data quality may have been compromised for proxy respondents. For cadmium, no exposures were assigned to proxy controls, precluding interpretation. In order to evaluate whether the inclusion of proxy respondents may have biased the findings, we conducted a sensitivity analysis excluding proxy response. There was very little difference in risk estimates between odds ratios obtained with and without proxy respondents (data not shown). As such, we included proxy respondents in our analysis.

DISCUSSION

Substantive findings

Most epidemiological studies on heavy metals have been conducted in cohorts of highly exposed workers, but workers across the entire occupational spectrum are exposed to these agents at much lower levels. While it is initially useful to focus the search for potential carcinogens on high exposure conditions, which are more likely to produce detectable effects, it is just as important to evaluate them in conditions that are more widely experienced by workers.

Indeed, the effects of nickel, chromium VI, and cadmium at lower exposure levels are the subject of ongoing debate. Some argue that mechanistic evidence points to the existence of a threshold effect for nickel and chromium VI (19, 24, 68, 92), but this is not universally accepted (52, 108). The determination of low exposure effects has important regulatory implications: for example, the existence of thresholds could be used to justify the maintenance of current occupational exposure limits, while linear exposure-relations would indicate their reduction.

In this study, the potential effect of exposure to nickel, chromium VI, or cadmium was examined in a variety of occupations and industries and in a range of intensities and durations of exposure. Although the nature of our exposure estimates did not allow us to make direct comparison with the quantitative exposure levels of other studies, it is likely that even those with the greatest exposure concentrations in this study fell into the lower exposure categories in most high-risk occupational cohorts of metal refiners, miners, processors and recovery workers. Thus, this study represents an evaluation of risks among workers in conditions that have not previously been evaluated.

Nickel

This study's results were compatible with previous findings that small increases in lung cancer risk may exist even at low levels of nickel exposure (43-45, 49, 52). The odds ratio estimate for lifetime nickel exposure in this study (1.27) was compatible with most other recent risk estimates, which have consistently hovered between 1.3 and 1.5 (10, 44, 47, 49). Consistent trends for cumulative exposure and exposure duration were also observed, which should further increase confidence in these results. This implies that men employed in occupations such as sheet metal work, metal machining, and metal product fabrication may continue to experience a small but elevated risk of lung cancer as a result of moderate levels of nickel exposure.

The observed overall risk related to exposure to nickel compounds was particularly evident in the stratum of non-smokers, where a significantly elevated odds ratio was observed. The combined effect of nickel and smoking was compatible with an additive joint effect. Only a few studies have examined the joint effects of nickel and smoking. Andersen *et al* (1996) reported that while risk among smokers almost doubled after exposure to nickel, exposure to nickel had little effect in non-smokers (47). This was based on very few cases in categories other than exposed smokers, such that risk estimates in the other categories may have been unreliable. Examination of an interaction between smoking and soluble nickel in two other investigations similarly suggested a sub-multiplicative interaction, although the interaction terms were not always significant. However, there were no cases among never-smokers, so a completely unexposed reference group was not available for analysis. (10, 44, 181).

Chromium VI

Workers exposed to chromium VI in this study included construction painters, sheet metal workers, and mechanics. Lung cancer risk was not elevated in this study's workers, regardless of exposure level, concentration, or duration of exposure. Given that increased risk has only previously been observed at high levels of chromium VI exposure (70, 72, 92, 182), it is likely that the exposure levels experienced by these workers were insufficient to produce observable effects. It is difficult to determine whether this lack of effect was due to exposure below a threshold concentration, or whether this study was simply too underpowered to detect a small but existent effect. While no overall risk related to exposure to chromium VI compounds was observed, there was significantly elevated risk in the stratum of non-smokers. The joint effect of chromium VI and smoking was compatible with an additive joint effect, though it was also compatible with the somewhat implausible hypothesis that there only is a chromium risk in non-smokers. There has been no previous evidence on joint effects between chromium and smoking.

Cadmium

Increased risk of lung cancer was consistently observed among workers with "substantial" exposure to cadmium in this study. Definitive interpretation of these results is difficult; the number of substantially exposed subjects was small and resulting confidence intervals were wide. Recent updates of several previously studied cadmium cohorts, often incorporating methodological improvements and quantification of exposure, have been similarly equivocal (9, 123, 126, 161, 183). As such, the weight of evidence for a carcinogenic role of cadmium in occupational cohorts is largely seen to be less compelling than it was 20 years ago (9, 119). However, risk associated with exposure to cadmium compounds was again observed in the

stratum of non-smokers, where a significant odds ratio was observed. The combined effect of cadmium and smoking was compatible with an additive joint effect. There has been no previous evidence on the joint effects of cadmium and smoking.

Effect modification by smoking

Perhaps the most compelling evidence of carcinogenic effects of all three metals in this study came from the analysis of metal-cancer associations in the stratum of non-smokers. Whereas there was little evidence of increases in risk due to these metals in the stratum of smokers, there were clear statistically significant increases in the stratum of non-smokers for all three metals. This phenomenon was independently observed in both studies, and was assessed using reliable estimates of lifetime smoking history.

These results could be due to chance fluctuations, to unidentified systematic bias, or to a real effect. However, it is unlikely that these results were due to chance, and there were no obvious differences in occupational profiles or co-exposures between non-smokers and smokers. If these agents indeed exert a real effect on lung cancer, then the observed pattern of results could reflect the greater ease in detecting risk among non-smokers. This hypothesis is supported by the observation that the absolute excess of risk associated with nickel and cadmium was similar in smokers and non-smokers. Such a trend was less clear in those exposed to chromium VI, as only non-smoking chromium-exposed workers were observed to experience any increased risk.

These findings appear to indicate that all three metals increase lung cancer risk, even at low levels of exposure, and have additive effect when combined with exposure to tobacco. This

implies that risk at low levels of exposure may have been previously underestimated or even undetected in cohorts composed mainly of smokers. It could also provide part of an explanation for apparently conflicting results between cohorts, which may have different proportions of non-smokers.

Methodological considerations

The results of this study – both the positive ones and the negative or null ones – must be interpreted in light of methodological strengths, weaknesses and characteristics of this study. The following study characteristics are briefly addressed below: exposure assessment, exposure parameterisation and categorisation, statistical power, confounding, and effect modification by smoking.

Control groups

Thoughtful choice of control group is essential to any case-control study. In Study I, data were analysed using two types of controls: cancer controls and population controls. It is difficult to ascertain which control group gave more valid results; each type of control has its own advantages and disadvantages in terms of selection, response, and information bias introduced (184), and may be more or less effective depending on context. While population controls may more accurately represent the state of the population as a whole, cancer controls are less prone to differential information and recall bias. In Study I, odds ratios obtained using separate cancer and population controls tended to be of the same magnitude and direction. By pooling equally weighted cancer and population controls in Study I, any control-specific bias was partly neutralized, while sample size and power were increased.

Pooling studies

The similarities in study design and crude results between Study I and Study II also justified their pooling. Final results using data pooled from Study I and Study II, adjusted for study, represent a weighted average of the two studies' results with improved statistical power.

Exposure assessment

The exposure assessment method employed in this study is widely considered to be the reference method for community-based case-control studies (185, 186). Similar methods have also been used by other research teams exploring occupational exposures and lung cancer (187, 188). There are advantages and disadvantages to this exposure assessment approach compared to cohort study methods. Most cohort studies have "more reliable" exposure assessment measures, as it is much easier to quantify exposure within one industry than across many work environments. However, workers in a particular cohort share many co-exposures, such that it may be difficult to ascribe possible effects to one particular agent. The assessment method used in this study addresses some weaknesses of the traditional cohort-study approach by including information on non-occupational confounders and exposures to a wide range of substances based on complete lifetime job histories for each subject. This approach has the advantage of reducing confounding by occupation-specific co-exposures, and is likely to more accurately represent lifetime exposure. As compared with most other community-based case-control studies, this exposure assessment procedure has the advantage that it does not rely solely on workers' job or industry codes, which can lead to misclassification. Previous analysis of data from this study has revealed that subjects with the same job title have been assigned different exposure profiles; an illustrative example can be found in the Appendix of Parent et al (176). Previous investigations

have also shown that the interview-based job histories used in this study were valid (189) and that the exposure coding was reliable (190, 191).

Notwithstanding the considerable resources devoted to exposure assessment in this study, this expert-based approach was not based on direct measurements in the workplaces under consideration, which undoubtedly led to error and misclassification. Many factors may have influenced the accuracy of exposure assessment, such as the type of occupation, the era of exposure, and the quality of the job description elicited from the respondent. Further, exposure identification was limited to broad classes of metal compounds, which were not specific in terms of speciation or solubility. Some of the determinants of the validity of this exposure assessment are summarised below.

Proxy response

Interview and data quality may have varied between self and proxy respondents in this study. Indeed, metal exposures were somewhat less likely to be attributed in interviews with proxy respondents. However, given that analyses using only self-respondents produced virtually the same risk estimates as those using all respondents, this information bias was likely to have been minimal.

Era of exposure

Even in the best circumstances, it is difficult to take timing of exposure into account. In this study, our exposure assessment experts used all available information to consider variations in exposure over time. However, it is certain that their estimates were imperfect, and that such fluctuations caused a certain degree of exposure imprecision or misclassification.

Speciation

Metals exist in several different forms or species, and the chemical nature and solubility of each species may greatly affect its initial absorption and subsequent behaviour. Therefore, it cannot be assumed that all metal species have the same carcinogenic potential (17, 19, 35). Unfortunately, speciation and solubility could not be estimated in either Study I or Study II. Given the range of occupational contexts at play, it would have been difficult to accurately identify or distinguish them. Grouping all nickel, cadmium or chromium VI species together may therefore have masked the species-specific effects that have been observed in other studies (3, 10, 23, 46, 47, 49, 70).

Impact of exposure misclassification

In the absence of objective measures of exposure, it is certain that a degree of measurement imprecision due to exposure misclassification was present in this study. However, given that coders were blind to subject status, it is likely that misclassification was non-differential, and therefore more likely to lead to attenuation rather than exaggeration of risk estimates.

Parameterisation of exposure dimensions

For each putative carcinogen, risk may be associated to different degrees with different dimensions of exposure; the effects of average intensity or duration of exposure, peak exposure, age at exposure, or time since exposure may vary between agents depending on their deposition, clearance, metabolism, and mechanisms of action. There are therefore as many ideal parameterisations of exposure as there are compounds and mechanisms of action. Without *a priori* knowledge of a particular agent's characteristics, it is impossible to develop the perfect

agent-specific combination of different exposure dimensions. Most epidemiologic studies of environmental or lifestyle factors, when confronted with analogous dilemmas, have chosen to use a cumulative exposure variable as the prime exposure index. While it may not be optimal in every context, it is generally robust enough to detect important effects (192). In order to estimate cumulative exposure, this study used a combination of concentration and duration variables, dichotomised into substantial and non-substantial levels. The cutpoints used in this categorisation were chosen after detailed examination of multiple possible combinations of exposure dimensions.

Statistical power

Statistical power is a function of several parameters, including the numbers of cases and controls, the prevalence of the exposure, and the relative risk induced by the exposure (193). In this study, there were a relatively large number of cases and controls, but low metal exposure prevalence. In order to maximise the power to detect effects, the number of subject subgroups and exposure sub-categories was therefore limited. Subdividing the study sample into yet smaller subgroups would have had the effect of further reducing power. Our capacity to detect effect may also have been limited by a lack of contrast between categories. Given that the majority of the exposures in this population were of low to medium concentration, the contrast between substantial and non-substantial exposures was mostly influenced by exposure duration, which may or may not have been an important determinant of risk. While statistical power was a genuine limitation in this study, it is one that could not generate false positive associations. However, a lack of power might explain why some associations were not detected, and certainly explains the width of confidence intervals for most OR estimates.

Confounding

It is possible that observed risk estimates were affected by other unmeasured carcinogenic exposures related to occupation or lifestyle. Those associated with the exposure of interest may have artificially elevated risk estimates. Confounding by smoking and occupational co-exposures has been insufficiently addressed in the epidemiological literature on metal carcinogenesis, mainly because complete and reliable data are rarely available in the context of most retrospective cohort studies. In this study, there was unlikely to have been significant confounding by smoking or by occupational co-exposures. With regard to smoking, information on lifetime smoking histories were collected and modeled in study analyses. The fact that this study included subjects exposed in a variety of occupations meant that it was unlikely that there would be a standard set of co-exposures associated with the three metals, and thus less likelihood of confounding by occupational exposures. Further, detailed information was collected on co-exposures, and important co-exposures were adjusted for.

Although an effect stratified by smoking history was found in this population, unstratified results adjusted for smoking were retained in the original regression model for ease of comparison with other studies, and to demonstrate the overall impact of adjustment with multiple smoking parameters. In this study, as for others, the smoking-adjusted odds ratios constituted weighted averages of potentially differential risk in smokers and non-smokers.

Exclusion of women

An important limitation of this study is the exclusion of women. In Study I, women were excluded by design, while in Study II, very few women were exposed to any of the metals of interest. Few other studies have investigated the risk of lung cancer after metal exposure in women; those that have tended to find relatively low exposure levels, and consequently, low mortality rates (123, 194). Although it has been suggested that there may be sex differences in susceptibility to metals (195) mirroring suggestions regarding tobacco smoke, such differences are widely contested (196, 197). Nonetheless, specific proof of equivalent effects in women should be obtained before definitive generalisations of these results can be made.

Summary

This study measured the risk of lung cancer in men having ever been exposed to nickel, chromium VI, or cadmium at levels higher than those expected in the general population, but lower than those experienced in most cohort studies of workers with these exposures. Study subjects showed increased incidence of lung cancer after exposure to any level of nickel, while exposure to chromium VI did not appear to significantly increase risk. Data suggested an association between lung cancer risk and cadmium, but estimates tended to be unstable and lacked precision. Risk estimates were minimally confounded, and based on reliable exposure assessments. Most importantly, significantly increased risks of lung cancer were observed in small subgroups of non-smokers exposed to any of the three metals. If these findings are a true reflection of these metals' effect in non-smokers, they demonstrate that in the absence of other major lung cancer determinants, low levels of exposure to nickel, cadmium, or chromium VI remain weak but significant risk factors for lung cancer.

PUBLIC HEALTH IMPLICATIONS

Millions of workers worldwide are regularly exposed to compounds of nickel, chromium VI and cadmium. In North America and Europe, the number of workers exposed and their exposure levels have decreased in recent years, but cancer cases continue to be concentrated in those with particularly hazardous jobs (198). Further, lung cancer is on the rise in the developing world (199), and although this rise has primarily been attributed to an increase in cigarette consumption (200), it may also be due to the fact that the hazards of production in North America and Europe have also largely been exported to countries where occupational environments are less regulated. In fact, on a global scale, the risk of cancer associated with producing a given raw material or product may not have changed a great deal since the 1960s (201). Therefore, continued research into the long-term consequences of occupational exposure to these metals remains important.

Further, many more people are exposed to these compounds at much lower levels than occupational exposure, from sources such as cigarette smoke, urban pollution, food and water. Indeed, it has been proposed that accumulation of cadmium, nickel, and chromium VI from tobacco smoke could play a key role in smoking-related carcinogenesis (8, 202). Thus, clarification and characterization of the cancer risks associated with these compounds are of major public health concern (103, 105, 108) as well as being pertinent to our understanding of lung cancer development and etiology.

While it has long been suspected or recognized that nickel, chromium VI, and cadmium are human lung carcinogens, there remain some major questions about the bodies of evidence on which these inferences have been made, particularly at low levels of exposure. In the past two decades, many published studies have failed to replicate the results of earlier studies. There are

many possible reasons for such apparent inconsistencies; subjects were exposed over different time periods, and varied in their exposure levels, in the types of metal species to which they were exposed, and in the presence of other occupational co-exposures. Further empiric research is required to confidently reaffirm the carcinogenicity of these agents, and to understand the conditions in which they are carcinogenic.

Almost all previous research has been based in industries where workers have been exposed to these agents at high concentrations, and in a narrow range of conditions. The majority of workers are exposed to these agents across all occupational and industrial sectors at relatively lower concentrations and in more heterogeneous conditions. Our study is unique in providing empirical evidence on risks related to such conditions. While many studies have failed to control for important co-exposures, our study also had the benefit of being able to collect and control for smoking and other potential confounders. As such, the findings of this study stand to contribute to the evidence base concerning these important potential carcinogens.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. Ca: a Cancer Journal for Clinicians. 2005;55(2):74-108.

2. Subramanian J, Govindan R. Lung cancer in never smokers: A review [Review]. Journal of Clinical Oncology. 2007;25(5):561-70.

3. Iarc. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 49. Chromium, nickel and welding. Lyon: IARC (International Agency for Research on Cancer); 1990.

4. Iarc. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 58. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. Lyon: IARC (International Agency for Research on Cancer); 1993.

5. Huff J, Lunn RM, Waalkes MP, Tomatis L, Infante PF. Cadmium-induced cancers in animals and in humans [Review]. International Journal of Occupational & Environmental Health. 2007;13(2):202-12.

6. Dweck A, Lurie P, Michaels D, Wolfe S. Hexavalent chromium study's conclusions unjustified. Journal of Occupational & Environmental Medicine. 2005 Oct;47(10):980-1; author reply 1.

7. Nurminen M. On the carcinogenicity risk assessment of chromium compounds. American Journal of Industrial Medicine. 2004;45(3):308-9.

8. Stavrides JC. Lung carcinogenesis: pivotal role of metals in tobacco smoke. Free Radical Biology & Medicine. 2006 Oct 1;41(7):1017-30.

9. Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000. Occupational & Environmental Medicine. 2004;61(2):108-16.

10. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Exposure to different forms of nickel and risk of lung cancer. American Journal of Epidemiology. 2002;156(12):1123-32.

11. Ontario Ministry of the Environment. Information draft on the development of Ontario air standards for nickel and its compounds. Standards Development Branch, Ontario Ministry of the Environment; 2004 [updated 2004 14 August 2008; cited]; Available from:

http://www.ene.gov.on.ca/envision/env_reg/er/documents/2004/air%20standards/information%20drafts/PA04E0029-i.pdf.

12. Costa M, Klein CB. Toxicity and carcinogenicity of chromium compounds in humans. Critical Reviews In Toxicology. 2006 Feb;36(2):155-63.

13. Klein C, Costa M. Nickel. In: Nordberg G, Fowler B, Nordberg M, Friberg L, editors. Handbook on the Toxicology of Metals, Third Edition. Amsterdam: Elsevier; 2007. p. 743-58.

14. Dunnick JK, Elwell MR, Radovsky AE, Benson JM, Hahn FF, Nikula KJ, et al. Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. Cancer Research. 1995 Nov 15;55(22):5251-6.

15. European Commission. Ambient air pollution by AS, CD, and NI compounds. Position Paper. Final Version.; 2000. Report No.: ISBN 92-894-2054-5 Contract No.: Document Number|.

16. Oberdorster G. Pulmonary deposition, clearance and effects of inhaled soluble and insoluble cadmium compounds. IARC Scientific Publications. 1992(118):189-204.

17. Haber LT, Erdreicht L, Diamond GL, Maier AM, Ratney R, Zhao Q, et al. Hazard identification and dose response of inhaled nickel-soluble salts. Regulatory Toxicology & Pharmacology. 2000 Apr;31(2 Pt 1):210-30.

18. McCutcheon B. Nickel. Canadian Minerals Yearbook 2005. Mineral

and Metal Commodity Reviews: Nickel 2005. Natural Resources Canada, Minerals and Metals sector.; 2005 [updated 2005; cited August 20, 2008]; Available from: http://www.nrcan.gc.ca/mms/cmy/content/2005/42.pdf.

19. Seilkop SK, Oller AR. Respiratory cancer risks associated with low-level nickel exposure: an integrated assessment based on animal, epidemiological, and mechanistic data. Regulatory Toxicology & Pharmacology. 2003;37(2):173-90.

20. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Nickel (Update). Prepared by Sciences International, Inc. under subcontract to Research Triangle Institute. Atlanta: U.S. Department of Health and Human Services; 1997.

21. Working Group on Arsenic C, Nickel C. Ambient Air Pollution by As, Cd and Ni Compounds. Position Paper. Luxembourg: Office for Official Publications of the European Communities; 2001.

22. Antonini JM, Taylor MD, Zimmer AT, Roberts JR. Pulmonary responses to welding fumes: role of metal constituents. Journal of Toxicology and Environmental Health A. 2004;67(3):233-49.

23. Grimsrud TK, Berge SR, Resmann F, Norseth T, Andersen A. Assessment of historical exposures in a nickel refinery in Norway. Scandinavian Journal of Work, Environment & Health. 2000;26(4):338-45.

24. Oller AR. Respiratory carcinogenicity assessment of soluble nickel compounds. [Review] [50 refs]. Environmental Health Perspectives. 2002;110(Suppl 5):841-4.

25. Kasprzak KS, Sunderman FW, Jr., Salnikow K. Nickel carcinogenesis. Mutation Research. 2003 Dec 10;533(1-2):67-97.

26. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Current Medicinal Chemistry. 2005;12(10):1161-208.

27. Sunderman FW, Jr. Recent advances in metal carcinogenesis. Annals of Clinical Laboratory Science. 1984;14(2):93-122.

28. Kasprzak KS, Gabryel P, Jarczewska K. Carcinogenicity of nickel(II)hydroxides and nickel(II)sulfate in Wistar rats and its relation to the in vitro dissolution rates. Carcinogenesis. 1983;4(3):275-9.

29. Benson JM, Burt DG, Cheng YS, Hahan FF, Haley PJ, Henderson RF, et al. Biochemical responses of rat and mouse lung to inhaled nickel compounds. Toxicology. 1989 Aug;57(3):255-66.

30. Verma M. Biomarkers for risk assessment in molecular epidemiology of cancer. Technology in Cancer Research & Treatment. 2004;3(5):505-14.

31. Costa M, Sutherland JE, Peng W, Salnikow K, Broday L, Kluz T. Molecular biology of nickel carcinogenesis. Molecular & Cellular Biochemistry. 2001 Jun;222(1-2):205-11.

32. Costa M, Salnikow K, Sutherland JE, Broday L, Peng W, Zhang Q, et al. The role of oxidative stress in nickel and chromate genotoxicity. Molecular & Cellular Biochemistry. 2002 May-Jun;234-235(1-2):265-75.

33. Lu H, Shi X, Costa M, Huang C. Carcinogenic effect of nickel compounds. Molecular & Cellular Biochemistry. 2005 Nov;279(1-2):45-67.

34. Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. Chemical Research in Toxicology. 2008 Jan;21(1):28-44.

35. Oller AR, Costa M, Oberdorster G. Carcinogenicity assessment of selected nickel compounds. [Review] [120 refs]. Toxicology & Applied Pharmacology. 1997;143(1):152-66.

36. TERA (Toxicology Excellence for Risk Assessment). Toxicological Review of Soluble Nickel Salts. Cincinnati; 1999. Report No.: EPA Contract #68-C7-0011 Contract No.: Document Number|.

37. Costa M, Simmons-Hansen J, Bedrossian CW, Bonura J, Caprioli RM. Phagocytosis, cellular distribution, and carcinogenic activity of particulate nickel compounds in tissue culture. Cancer Research. 1981 Jul;41(7):2868-76.

38. Ke Q, Kluz T, Costa M. Down-regulation of the expression of the FIH-1 and ARD-1 genes at the transcriptional level by nickel and cobalt in the human lung adenocarcinoma A549 cell line. International Journal of Environmental Research & Public Health. 2005 Apr;2(1):10-3.

39. Costa M, Davidson TL, Chen H, Ke Q, Zhang P, Yan Y, et al. Nickel carcinogenesis: epigenetics and hypoxia signaling. Mutation Research. 2005 Dec 30;592(1-2):79-88.

40. Costa M, Zhuang Z, Huang X, Cosentino S, Klein CB, Salnikow K. Molecular mechanisms of nickel carcinogenesis. Science of the Total Environment. 1994 Jun 6;148(2-3):191-9.

41. Hartwig A. Role of DNA repair inhibition in lead- and cadmium-induced genotoxicity: a review. Environmental Health Perspectives. 1994;102 Suppl 3:45-50.

42. Shannon HS, Walsh C, Jadon N, Julian JA, Weglo JK, Thornhill PG, et al. Mortality of 11,500 nickel workers--extended follow up and relationship to environmental conditions. Toxicology & Industrial Health. 1991 Jul;7(4):277-94.

43. Doll R, Andersen A, Cooper WC, Cosmatos I, Cragle DL, Easton D, et al. Report of the International Committee on Nickel Carcinogenesis in Man. Scandinavian Journal of Work, Environment & Health. 1990;16(1):1-84.

44. Sorahan T, Williams SP. Mortality of workers at a nickel carbonyl refinery, 1958-2000. Occupational & Environmental Medicine. 2005;62(2):80-5.

45. Easton DF, Peto J, Morgan LG, Metcalfe LP, Usher V, Doll R. Respiratory cancer in Welsh nickel refiners: which nickel compounds are responsible? In: Nieboer E, Nriagu JO, editors. Nickel and Human Health: Current Perspectives. New York: Wiley; 1992. p. 621-8.

46. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? Epidemiology. 2005;16(2):146-54.

47. Andersen A, Berge SR, Engeland A, Norseth T. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occupational & Environmental Medicine. 1996;53(10):708-13.

48. Grimsrud TK, Berge SR, Martinsen JI, Andersen A. Lung cancer incidence among Norwegian nickel-refinery workers 1953-2000. Journal of Environmental Monitoring. 2003 Apr;5(2):190-7.

49. Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. International Archives of Occupational & Environmental Health. 1998;71(4):245-50.

50. Karjalainen S, Kerttula R, Pukkala E. Cancer risk among workers at a copper/nickel smelter and nickel refinery in Finland. International Archives of Occupational & Environmental Health. 1992;63(8):547-51.

51. Draper MH, Duffus JH, John P, Metcalfe L, Morgan L, Park MV, et al. Characterization of historical samples of nickel refinery dusts from the Clydach refinery. Experimental & Toxicologic Pathology. 1994 Jul;46(2):111-3.

52. Grimsrud TK, Peto J. Persisting risk of nickel related lung cancer and nasal cancer among Clydach refiners. Occupational & Environmental Medicine. 2006;63(5):365-6.

53. Sivulka DJ. Assessment of respiratory carcinogenicity associated with exposure to metallic nickel: A review [Review]. Regulatory Toxicology & Pharmacology. 2005;43(2):117-33.

54. Egedahl R, Carpenter M, Lundell D. Mortality experience among employees at a hydrometallurgical nickel refinery and fertiliser complex in Fort Saskatchewan, Alberta (1954-95). Occupational & Environmental Medicine. 2001;58(11):711-5.

55. Cragle DL, Hollis DR, Newport TH, Shy CM. A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant. IARC Scientific Publications. 1984;53:57-63.

56. Cox JE, Doll R, Scott WA, Smith S. Mortality of nickel workers: experience of men working with metallic nickel. British Journal of Industrial Medicine. 1981;38:235-9.

57. Morgan JG. Some observations on the incidence of respiratory cancer in nickel workers. British Journal of Industrial Medicine. 1958 Oct;15(4):224-34.

58. Mastromatteo E. Nickel: a review of its occupational health aspects. Journal of Occupational Medicine. 1967 Mar;9(3):127-36.

59. Pedersen E, Hogetveit AC, Andersen A. Cancer of respiratory organs among workers at a nickel refinery in Norway. International Journal of Cancer. 1973 Jul 15;12(1):32-41.

60. Pang D, Burges DCL, Sorahan T. Mortality study of nickel platers with special reference to cancers. Occupational & Environmental Medicine. 1996;53(10):714-7.

61. Roberts RS, Julian JA, Muir DCF, Shannon H. A study of mortality in workers engaged in the mining, smelting and refining of nickel. II: Mortality from cancer of the respiratory tract and kidney. Toxicology & Industrial Health. 1989;60:975-93.

62. Moulin JJ, Clavel T, Roy D, Dananche B, Marquis N, Fevotte J, et al. Risk of lung cancer in workers producing stainless steel and metallic alloys. International Archives of Occupational & Environmental Health. 2000;73(3):171-80.

63. Park RM, Bena JF, Stayner LT, Smith RJ, Gibb HJ, Lees PS. Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment. Risk Analysis. 2004 Oct;24(5):1099-108.

64. Sorahan T, Nichols L, Harrington JM. Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-1998. Occupational Medicine (Oxford). 2002;52(6):333-9.

65. Arena VC, Sussman NB, Redmond CK, Costantino JP, Trauth JM. Using alternative comparison populations to assess occupation-related mortality risk - results for the high nickel alloys workers cohort. Journal of Occupational & Environmental Medicine. 1998;40(10):907-16.

66. Magnus K, Andersen A, Hogetveit AC. Cancer of respiratory organs among workers at a nickel refinery in Norway. International Journal of Cancer. 1982;30:681-5.

67. Langard S, Costa M. Chromium. In: Nordberg G, Fowler B, Nordberg M, Friberg L, editors. Handbook on the Toxicology of Metals, Third Edition. Amsterdam: Elsevier; 2007. p. 487-510.

68. De Flora S. Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. Carcinogenesis. 2000;21(4):533-41.

69. Steinhoff D, Gad SC, Hatfield GK, Mohr U. Carcinogenicity study with sodium dichromate in rats. Experimental Pathology. 1986;30(3):129-41.

70. Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, et al. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Analysis. 2003 Dec;23(6):1147-63.

71. Hayes RB. The carcinogenicity of metals in humans. [Review] [164 refs]. Cancer Causes & Control. 1997;8(3):371-85.

72. Gibb HJ, Lees PSJ, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. American Journal of Industrial Medicine. 2000;38(2):115-26.

73. Langard S. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. American Journal of Industrial Medicine. 1990;17(2):189-215.

74. Machle W, Gregorius F. Cancer of the respiratory system in the United States chromate-producing industry. Public Health Reports. 1948;63:1114-27.

75. Sorahan T, Burges DC, Waterhouse JA. A mortality study of nickel/chromium platers. British Journal of Industrial Medicine. 1987 Apr;44(4):250-8.

76. Sorahan T, Harrington JM. Lung cancer in Yorkshire chrome platers, 1972-97. Occupational & Environmental Medicine. 2000;57(6):385-9.

77. Kjuus H, Andersen A, Langard S, Knudsen KE. Cancer incidence among workers in the Norwegian ferroalloy industry. British Journal of Industrial Medicine. 1986;43:227-36.

78. Langard S, Andersen A, Gylseth B. Incidence of cancer among ferrochromium and ferrosilicon workers. British Journal of Industrial Medicine. 1980 May;37(2):114-20.

79. Langard S, Andersen A, Ravnestad J. Incidence of cancer among ferrochromium and ferrosilicon workers: an extended observation period. British Journal of Industrial Medicine. 1990 Jan;47(1):14-9.

80. Langard S, Norseth T. A cohort study of bronchial carcinomas in workers producing chromate pigments. British Journal of Industrial Medicine. 1975 Feb;32(1):62-5.

81. Langard S, Vigander T. Occurrence of lung cancer in workers producing chromium pigments. British Journal of Industrial Medicine. 1983;40:71-4.

82. Davies JM. Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. British Journal of Industrial Medicine. 1984;41:158-69.

83. Sjogren B, Gustavsson A, Hedstrom L. Mortality in two cohorts of welders exposed to high- and low-levels of hexavalent chromium. Scandinavian Journal of Work Environment & Health. 1987 Jun;13(3):247-51.

84. Sjogren B, Hansen KS, Kjuus H, Persson PG. Exposure to stainless steel welding fumes and lung cancer: A meta-analysis. Occupational & Environmental Medicine. 1994;51(5):335-6.

85. Simonato L, Fletcher AC, Andersen A, Anderson K, Becker N, Chang-Claude J, et al. A historical prospective study of European stainless steel, mild steel, and shipyard welders. British Journal of Industrial Medicine. 1991;48(3):145-54.

86. Baetjer AM. Pulmonary carcinoma in chromate workers. 1. A review of the literature and report of cases. A M A Archives of Industrial Hygiene & Occupational Medicine. 1950 Nov;2(5):487-504.

87. Mancuso TF, Hueper WC. Occupational cancer and other health hazards in a chromate plant: a medical appraisal. I. Lung cancers in chromate workers. Industrial Medicine & Surgery. 1951 Aug;20(8):358-63.

88. Gafafer WM. Health of workers in chromate producing industry: a study. Washington, D.C.: U.S. Public Health Service; 1953 Contract No.: Document Number|.

89. Taylor FH. The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. American Journal of Public Health and the Nation's Health. 1966 Feb;56(2):218-29.

90. Enterline PE. Respiratory cancer among chromate workers. Journal of Occupational Medicine. 1974 Aug;16(8):523-6.

91. Korallus U, Ulm K, Steinmannsteinerhaldenstaett W. Bronchial carcinoma mortality in the German chromate-producing industry, the effects of process modification. International Archives of Occupational & Environmental Health. 1993;65(3):171-8.

92. Luippold RS, Mundt KA, Austin RP, Liebig E, Panko J, Crump C, et al. Lung cancer mortality among chromate production workers. Occupational & Environmental Medicine. 2003;60(6):451-7.

93. Davies JM, Easton DF, Bidstrup PL. Mortality from respiratory cancer and other causes in United-Kingdom chromate production workers. British Journal of Industrial Medicine. 1991;48(5):299-313.

94. Birk T, Mundt KA, Dell LD, Luippold RS, Miksche L, Steinmann-Steiner-Haidenstaett W, et al. Lung cancer mortality in the German chromate industry, 1958 to 1998. Journal of Occupational & Environmental Medicine. 2006;48(4):426-33.

95. Hayes RB, Lilienfeld AM, Snell LM. Mortality in chromium chemical production workers: a prospective study. International Journal of Epidemiology. 1979 Dec;8(4):365-74.

96. Alderson MR, Rattan NS, Bidstrup L. Health of workmen in the chromate-producing industry in Britain. British Journal of Industrial Medicine. 1981 May;38(2):117-24.

97. de Marco R, Bernardinelli L, Mangione MP. [Death risk due to tumors of the respiratory system in workers employed in chromate production]. La Medicina del lavoro. 1988 Sep-Oct;79(5):368-76.

98. Pastides H, Austin R, Lemeshow S, Klar J, Mundt KA. A retrospective-cohort study of occupational exposure to hexavalent chromium. American Journal of Industrial Medicine. 1994;25(5):663-75.

99. Mancuso TF. Considerations of chromium as an industrial carcinogen. In: Hutchinson TC, editor. International Conference on Heavy Metals in the Environment; 1975 October 27-31, 1975; Toronto. Institute for Environmental Studies; 1975. p. 343-56.

100. Mancuso TF. Chromium as an industrial carcinogen. Part 1. American Journal of Industrial Medicine. 1997;31(2):129-39.

101. Luippold RS, Mundt KA, Dell LD, Birk T. Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. Journal of Occupational & Environmental Medicine. 2005;47(4):381-5.

102. Mundt K, Luippold R, Dell L, Birk T. Reply to Dweck et al. Journal of Occupational & Environmental Medicine. 2005;47(10):981.

103. Michaels D, Lurie P, Monforton C. Lung cancer mortality in the German chromate industry, 1958 to 1998. Journal of Occupational & Environmental Medicine. 2006;48(10):995-7.

104. Michaels D, Monforton C. The Beryllium Occupational Exposure Limit: Historical Origin and Current Inadequacy. Journal of Occupational & Environmental Medicine. 2006;48(10):998-1000.

105. Michaels D, Monforton C, Lurie P. Selected science: an industry campaign to undermine an OSHA hexavalent chromium standard. Environmental Health. 2006;5:5.

106. Cole P, Rodu B. Epidemiologic studies of chrome and cancer mortality: A series of meta-analyses. Regulatory Toxicology & Pharmacology. 2005;43(3):225-31.

107. Stayner L, Steenland K, Dosemeci M, Hertz-Picciotto I. Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. Scandinavian Journal of Work, Environment & Health. 2003;29(4):317-24.

108. Park RM, Stayner LT. A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Analysis. 2006;26(1):79-88.

109. Fryzek JP, Mumma MT, McLaughlin JK, Henderson BE, Blot WJ. Cancer mortality in relation to environmental chromium exposure. Journal of Occupational & Environmental Medicine. 2001;43(7):635-40.

110. Halasova E, Baska T, Kukura F, Mazurova D, Bukovska E, Dobrota D, et al. Lung cancer in relation to occupational and environmental chromium exposure and smoking. Neoplasma. 2005;52(4):287-91.

111. Beaumont JJ, Sedman RM, Reynolds SD, Sherman CD, Li LH, Howd RA, et al. Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. Epidemiology. 2008;19(1):12-23.

112. Axelsson G, Rylander R. Environmental chromium dust and lung cancer mortality. Environmental Research. 1980 Dec;23(2):469-76.

113. Zhang JD, Li S. Cancer mortality in a Chinese population exposed to hexavalent chromium in water. Journal of Occupational & Environmental Medicine. 1997 Apr;39(4):315-9.

114. Smith AH. Hexavalent chromium, yellow water, and cancer: a convoluted saga. Epidemiology. 2008 Jan;19(1):24-6.

115. Proctor DM, Otani JM, Finley BL, Paustenbach DJ, Bland JA, Speizer N, et al. Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. Journal of Toxicology and Environmental Health Part A. 2002 May 24;65(10):701-46.

116. Kerger BD, Finley BL, Corbett GE, Dodge DG, Paustenbach DJ. Ingestion of chromium(VI) in drinking water by human volunteers: absorption, distribution, and excretion of single and repeated doses. Journal of Toxicology & Environmental Health. 1997 Jan;50(1):67-95.

117. Shrivastava R, Upreti RK, Chaturvedi UC. Various cells of the immune system and intestine differ in their capacity to reduce hexavalent chromium. FEMS Immunology and Medical Microbiology. 2003 Aug 18;38(1):65-70.

118. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S, et al. Listing occupational carcinogens; see errata: 113 (2); A 89. Environmental Health Perspectives. 2004;112(15):1447-59.

119. Verougstraete V, Lison D, Hotz P. Cadmium, lung and prostate cancer: A systematic review of recent epidemiological data. Journal of Toxicology & Environmental Health Part B, Critical Reviews. 2003;6(3):227-55.

120. Chaney RL, Reeves PG, Ryan JA, Simmons RW, Welch RM, Angle JS. An improved understanding of soil Cd risk to humans and low cost methods to phytoextract Cd from contaminated soils to prevent soil Cd risks. Biometals. 2004;17(5):549-53.

121. Andersen O, Nielsen JB, Nordberg GF. Nutritional interactions in intestinal cadmium uptake--possibilities for risk reduction. Biometals. 2004 Oct;17(5):543-7.

122. Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure--a review of the literature and a risk estimate. Scandinavian Journal of Work, Environment and Health. 1998;24 Suppl 1:1-51.

123. Jarup L, Bellander T, Hogstedt C, Spang G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occupational & Environmental Medicine. 1998;55(11):755-9.

124. Cox LA. Quantifying potential health impacts of cadmium in cigarettes on smoker risk of lung cancer: A portfolio-of-mechanisms approach. Risk Analysis. 2006;26(6):1581-99.

125. Hertz-Picciotto I, Hu SW. Contribution of cadmium in cigarettes to lung cancer: An evaluation of risk assessment methodologies. Archives of Environmental Health. 1994;49(4):297-302.

126. Jones SR, Atkin P, Holroyd C, Lutman E, Batlle JVI, Wakeford R, et al. Lung cancer mortality at a UK tin smelter. Occupational Medicine (Oxford). 2007;57(4):238-45.

127. Sorahan T, Lancashire R. Lung Cancer Findings from the NIOSH Study of United-States Cadmium Recovery Workers - A Cautionary Note. Occupational & Environmental Medicine. 1994;51(2):139-40.

128. Sorahan T, Lister A, Gilthorpe MS, Harrington JM. Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92. Occupational & Environmental Medicine. 1995;52(12):804-12.

129. Bertin G, Averbeck D. Cadmium: cellular effects, modifications of biomolecules, modulation of DNA repair and genotoxic consequences (a review). Biochimie. 2006;88(11):1549-59.

130. Nordberg G, Nogawa K, Nordberg M, Friberg LT. Cadmium. In: Nordberg G, Fowler B, Nordberg M, Friberg L, editors. Handbook on the Toxicology of Metals. Amsterdam: Elsevier; 2007. p. 445-86.

131. Waalkes MP. Cadmium carcinogenesis. Mutation Research. 2003;533(1-2):107-20.

132. Loser E. A 2 year oral carcinogenicity study with cadmium on rats. Cancer Letters. 1980;9(3):191-8.

133. Waalkes MP, Rehm S. Cadmium and prostate cancer. Journal of Toxicology & Environmental Health. 1994;43(3):251-69.

134. Takenaka S, Oldiges H, Konig H, Hochrainer D, Oberdorster G. Carcinogenicity of cadmium chloride aerosols in W rats. Journal of the National Cancer Institute. 1983;70(2):367-73.

135. Oberdorster G. Equivalent oral and inhalation exposure to cadmium compounds: risk estimation based on route-to-route extrapolation. In: Gerrity TR, Henry CJ, editors.

Principles of Route-to-Route Extrapolation for Risk Assessment: . New York: Elsevier Science Co.; 1990. p. 217-35.

136. Waalkes MP. Cadmium carcinogenesis in review. [Review] [32 refs]. Journal of Inorganic Biochemistry. 2000;79(1-4):241-4.

137. Waisberg M, Joseph P, Hale B, Beyersmann D. Molecular and cellular mechanisms of cadmium carcinogenesis. Toxicology. 2003;192(2-3):95-117.

138. Watkin RD, Nawrot T, Potts RJ, Hart BA. Mechanisms regulating the cadmium-mediated suppression of Sp1 transcription factor activity in alveolar epithelial cells. Toxicology. 2003 Mar 3;184(2-3):157-78.

139. Hartwig A, Asmuss M, Ehleben I, Herzer U, Kostelac D, Pelzer A, et al. Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. Environmental Health Perspectives. 2002 Oct;110 Suppl 5:797-9.

140. Jin YH, Clark AB, Slebos RJ, Al-Refai H, Taylor JA, Kunkel TA, et al. Cadmium is a mutagen that acts by inhibiting mismatch repair. Nature Genetics. 2003 Jul;34(3):326-9.

141. McMurray CT, Tainer JA. Cancer, cadmium and genome integrity. Nature Genetics. 2003;34(3):239-41.

142. Hengstler JG, Bolm-Audorff U, Faldum A, Janssen K, Reifenrath M, Gotte W, et al. Occupational exposure to heavy metals: DNA damage induction and DNA repair inhibition prove co-exposures to cadmium, cobalt and lead as more dangerous than hitherto expected. Carcinogenesis. 2003 Jan;24(1):63-73.

143. Verougstraete V, Lison D, Hotz P. A systematic review of cytogenetic studies conducted in human populations exposed to cadmium compounds. Mutation Research. 2002;511(1):15-43.

144. Kirsch-Volders M, Lison D. Re: Hengstler, J.G., Bolm-Auorff, U., Faldum, A., Janssen, K., Reifenrath, M., Gotte, W., Jung, D., Mayer-Popken, O., Fuchs, J., Gebhard, S., Bienfait, H.G., Schlink, K., Dietrich, C., Faust, D., Epe, B. and Oesch, F. Occupational exposure to heavy metals: DNA damage induction and DNA repair inhibition prove co-exposures to cadmium, cobalt and lead as more dangerous than hitherto expected.

Carcinogenesis, 2003, 24, 63-73. Carcinogenesis. 2003 Nov;24(11):1853-4; author reply 5-7.

145. Kipling MD, Waterhouse JA. Cadmium and prostatic carcinoma. Lancet. 1967;1:730-1.

146. Sorahan T, Waterhouse JAH. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. British Journal of Industrial Medicine. 1983;40:293-300.

147. Sorahan T. Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946-84. British Journal of Industrial Medicine. 1987;44:803-9.

148. Kjellstrom T, Friberg L, Rahnster B. Mortality and cancer morbidity among cadmium-exposed workers. Environmental Health Perspectives. 1979;28:199-204.

149. Ades AE, Kazantzis G. Lung cancer in a non-ferrous smelter: the role of cadmium. British Journal of Industrial Medicine. 1988;45:435-42.

150. Armstrong BG, Kazantzis G. The mortality of cadmium workers. Lancet. 1983;June 25:1424-7.

151. Armstrong BG, Kazantzis G. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case control study. British Journal of Industrial Medicine. 1985;42(8):540-5.

152. Kazantzis G, Blanks RG, Sullivan KR, Nordberg GF, Herber RFM, Alessio L. Is cadmium a human carcinogen? Cadmium in the Human Environment: Toxicity and Carcinogenicity. Lyon: IARC; 1992. p. 435-46.

153. Kazantzis G, Lam TH, Sullivan KR. Mortality of cadmium-exposed workers. A five-year update. Scandinavian Journal of Work, Environment & Health. 1988;14(4):220-3.

154. Lemen RA, Lee JS, Wagoner JK, Blejer HP. Cancer mortality among cadmium production workers. Annals of the New York Academy of Sciences. 1976;271:273-9.

155. Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of U.S. cadmium production workers - an update. Journal of the National Cancer Institute. 1985;74(2):325-33.

156. Stayner L, Smith R, Thun M, Schnorr T, Lemen R. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. Annals of Epidemiology. 1992;2(3):177-94.

157. Doll R, Nordberg GF, Herber RFM, Alessio L. Cadmium in the human environment: closing remarks. Cadmium in the Human Environment: Toxicity and Carcinogenicity. Lyon: International Agency for Research on Cancer; 1992. p. 459-64.

158. Potts CL. Cadmium proteinuria: the health of battery workers exposed to cadmiium oxide dust. Annals of Occupational Hygiene. 1965;8:55-61.

159. Elinder CG, Kjellstrom T, Hogstedt C, Andersson K, Spang G. Cancer mortality of cadmium workers. British Journal of Industrial Medicine. 1985;42:651-5.

160. Lamm SH, Parkinson M, Anderson M, Taylor W. Determinants of lung cancer risk among cadmium-exposed workers. Annals of Epidemiology. 1992;2(3):195-211.

161. Sorahan T, Lancashire RJ. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States - an analysis with detailed job histories. Occupational & Environmental Medicine. 1997;54(3):194-201.

162. Boffetta P, Nordberg GF, Herber RFM, Alessio L. Methodological aspects of the epidemiological association between cadmium and cancer in humans. Cadmium in the Human Environment: Toxicity and Carcinogenicity. Lyon: International Agency for Research on Cancer; 1992. p. 425-34.

163. Arisawa K, Nakano A, Saito H, Liu XJ, Yokoo M, Soda M, et al. Mortality and cancer incidence among a population previously exposed to environmental cadmium. International Archives of Occupational & Environmental Health. 2001;74(4):255-62.

164. Elliott P, Arnold R, Cockings S, Eaton N, Jarup L, Jones J, et al. Risk of mortality, cancer incidence, and stroke in a population potentially exposed to cadmium. Occupational & Environmental Medicine. 2000;57(2):94-7.

165. Nawrot T, Plusquin M, Hogervorst J, Roels HA, Celis H, Thijs L, et al. Environmental exposure to cadmium and risk of cancer: a prospective population-based study. Lancet Oncology. 2006;7(2):119-26.

166. Nordberg GF. Lung cancer and exposure to environmental cadmium. Lancet Oncology. 2006;7(2):99-101.

167. Gerhardsson L, Nordberg GF. Lung cancer in smelter workers--interactions of metals as indicated by tissue levels. Scandinavian Journal of Work, Environment and Health. 1993;19 Suppl 1:90-4.

168. Ramanakumar AV, Parent ME, Siemiatycki J. Risk of lung cancer from residential heating and cooking fuels in Montreal, Canada. American Journal of Epidemiology. 2007;165(6):634-42.

169. Gérin M, Siemiatycki J, Kemper H, Bégin D. Obtaining occupational exposure histories in epidemiologic case-control studies. Journal of Occupational Medicine. 1985;27(6):420-6.

170. Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. Discovering carcinogens in the occupational environment: methods of data collection and analysis of a large case-referent monitoring system. Scandinavian Journal of Work, Environment & Health. 1987;13:486-92.

171. Siemiatycki J, Richardson L. Chapter 3. Case-control design and fieldwork methods. Risk Factors for Cancer in the Workplace. Boca Raton: CRC Press; 1991. p. 29-44.

172. Ramanakumar AV, Parent ME, Latreille B, Siemiatycki J. Risk of lung cancer following exposure to carbon black, titanium dioxide and talc: Results from two case-control studies in Montreal. International Journal of Cancer. 2008;122(1):183-9.

173. Siemiatycki J, Nadon L, Lakhani R, Bégin D, Gérin M. Chapter 4. Exposure assessment. Risk Factors for Cancer in the Workplace. Boca Raton: CRC Press; 1991. p. 45-114.

174. Department of M, Immigration. Canadian Classification and Dictionary of Occupations 1971. Vol 1. Classification and Definitions. Ottawa: Information Canada; 1974.

175. Gérin M, Siemiatycki J. The occupational questionnaire in retrospective epidemiologic studies: recent approaches in community-based studies. Applied Occupational and Environmental Hygiene. 1991;6(6):495-501.

176. Parent ME, Rousseau MC, Boffetta P, Cohen A, Siemiatycki J. Exposure to diesel and gasoline engine emissions and the risk of lung cancer. American Journal of Epidemiology. 2007;165(1):53-62.

177. Breslow NE, Day NE. Statistical Methods in Cancer Research Volume 1 - The analysis of case-control studies. Lyon: International Agency for Research on Cancer; 1980.

178. Leffondré K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: A comparison of different approaches. American Journal of Epidemiology. 2002;156(9):813-23.

179. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. A flexible modeling approach to estimating the component effects of smoking behavior on lung cancer. Journal of Clinical Epidemiology. 2004;57(10):1076-85.

180. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. American Journal of Epidemiology. 1989;129(1):125-37.

181. Agency for Toxic Substances and Disease Registry (ATSDR). Study of Disease and Symptom Prevalence in Residents of Yukon and Cokeburg, Pennsylvania. Atlanta: U.S. Department of Health and Human Services; 1990.

182. Matos EL, Vilensky M, Mirabelli D, Boffetta P. Occupational exposures and lung-cancer in Buenos Aires, Argentina. Journal of Occupational & Environmental Medicine. 2000;42(6):653-9.

183. Sorahan T. Mortality of workers at a plant manufacturing nickel alloys, 1958-2000. Occupational Medicine (Oxford). 2004;54(1):28-34.

184. Smith AH, Pearce NE, Callas PW. Cancer case-control studies with other cancers as controls. International Journal of Epidemiology. 1988;17(2):298-306.

185. Bouyer J, Hemon D. Retrospective evaluation of occupational exposures in population-based case-control studies - general overview with special attention to job exposure matrices. International Journal of Epidemiology. 1993;22(Suppl. 2):S57-S64.

186. Tielemans E, Heederik D, Burdorf A, Vermeulen R, Veulemans H, Kromhout H, et al. Assessment of occupational exposures in a general population: comparison of different methods. Occupational & Environmental Medicine. 1999;56(3):145-51.

187. Kjuus H, Skjaerven R, Langard S, Lien JT, Aamodt T. A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. Scandinavian Journal of Work, Environment & Health. 1986;12:193-202.

188. Stewart PA, Stewart WF, Heineman EF, Dosemeci M, Linet M, Inskip PD. A novel approacha to data collection in a case-control study of cancer and occupational exposures. International Journal of Epidemiology. 1996;25(4):744-52.

189. Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. American Journal of Epidemiology. 1983;118(4):583-91.

190. Goldberg MS, Siemiatycki J, Gérin M. Inter-rater agreement in assessing occupational exposure in a case-control study. British Journal of Industrial Medicine. 1986;43:667-76.

191. Siemiatycki J, Fritschi L, Nadon L, Gerin M. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. American Journal of Industrial Medicine. 1997;31(3):280-6.

192. Checkoway H, Pearce N, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. In: MacMahon B, editor. New York: Oxford University Press; 1989.

193. Schlesselman JJ. Case-control studies. New York: Oxford University Press; 1982.

194. Arena VC, Costantino JP, Sussman NB, Redmond CK. Issues and findings in the evaluation of occupational risk among women high nickel alloys workers. American Journal of Industrial Medicine. 1999;36(1):114-21.

195. Vahter M, Akesson A, Liden C, Ceccatelli S, Berglund M. Gender differences in the disposition and toxicity of metals [Review]. Environmental Research. 2007;104(1):85-95.

196. Bain C, Feskanich D, Speizer FE, Thun M, Hertzmark E, Rosner BA, et al. Lung cancer rates in men and women with comparable histories of smoking. Journal of the National Cancer Institute. 2004;96(11):826-34.

197. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: Looking to the future [Review]. Journal of Clinical Oncology. 2005;23(14):3175-85.

198. Clayson DB. Toxicological Carcinogenesis. Boca Raton: Lewis Publishers; 2001.

199. Jones LA, Chilton JA, Hajek RA, Iammarino NK, Laufman L. Between and within: international perspectives on cancer and health disparities. Journal of Clinical Oncology. 2006 May 10;24(14):2204-8.

200. Parkin DM. International variation. Oncogene. 2004;23(38):6329-40.

201. Colditz GA, Sellers TA, Trapido E. Epidemiology - identifying the causes and preventability of cancer? [Review]. Nature Reviews. 2006;Cancer. 6(1):75-83.

202. Stohs SJ, Bagchi D, Bagchi M. Toxicity of trace elements in tobacco smoke. Inhalation Toxicology. 1997;9(9):867-90.

Tables

Table 1. Approximate daily absorbed doses of nickel, chromium VI, and cadmium by different exposure routes and environments #

		Daily exposure per kilogram (ng/kg/d)			
Element	**Level**	*Food + Water*	*Air*	*20 Cigarettes*	*Occupation**
Nickel	L	125	0.17	8.3	167
	M	375	0.83	33	1670
	H	1500	2.5	100	16 700
Chromium VI *	L	25	1.7	NA	83 000
	M	230	4.8	3.9	166 700
	H	1000	8.3	NA	1 700 000
Cadmium	L	4.2	0.08	8.3	8 300
	M	8.5	0.25	25	83 000
	H	50	2.5	42	166 700

Adapted from a European Commission Report [1]; averages assume a 60kg individual with a respiratory volume of 20 m^3 / day. Absorption rates for respiratory exposure were assumed to be 50%, for oral exposure were 5%.

* Rough estimates from our study benchmarks, calculated using the same assumptions

Table 2. Selected socio-demographic characteristics of male subjects in Montreal in two population-based case-control studies

		Study I (1979-1986)			Study II (1996-2001)	
		Pop' Controls	Cancer Controls	Cases	Pop' Controls	Cases
Variable	Categories	N=533	N=1349	N=857	N=899	N=741
Age (%)	<= 55	28.0	32.5	27.4	11.9	13.7
	56-65	45.2	43.7	50.8	28.5	32.8
	66-75	26.8	23.7	21.8	59.6	53.5
Ethnicity (%)	French Canadian	64.2	58.0	69.1	64.4	77.5
	English Canadian	14.1	16.1	13.5	6.3	4.6
	Other	21.8	25.9	17.4	29.3	17.9
Schooling (%)	< 7 years	20.3	22.3	30.3	24.6	27.3
	7-12 years	56.1	55.2	57.1	47.2	51.8
	13+ years	23.6	22.5	12.6	27.3	15.8
Median Family Income *		26627	24761	22386	35250	32951
Smoking status (%)	Never	19.7	17.3	1.5	18.1	3.2
	Quit 2-5 yrs ago	8.8	6.7	7.6	2.9	5.8
	Quit 6-10 yrs ago	7.9	6.2	6.0	6.6	7.6
	Quit > 10 yrs ago	16.7	11.8	5.0	44.6	26.3
	Current†	46.9	58.0	79.9	27.9	57.1
Mean pack-years‡		50.6	53.1	75.9	41.5	75.1
Respondent (%)	Self	87.4	80.8	70.6	90.1	60.0
	Proxy	12.6	19.2	29.4	9.9	40.0

*Median family income for census tract, in Canadian $

†Current smokers and subjects who quit less than two years before recruitment

‡Among ever smokers, based on 20 cigarettes per packet.

Table 3. Distribution of male subjects according to lifetime occupational exposure to nickel, cadmium or chromium VI compounds in two Montreal-based studies

	Study I (1979-1986)						Study II (1996-2001)			
	Pop. Controls		Cancer Controls		Cases		Pop. Controls		Cases	
Occupational Agent	N	%	N	%	N	%	N	%	N	%
Nickel compounds										
Non-exposed	487	91.4	1243	92.1	770	89.8	804	89.4	654	88.6
Non-substantial level	39	7.3	86	6.4	70	8.2	83	9.2	64	8.7
Substantial level	7	1.3	13	1.0	9	1.1	4	0.4	10	1.4
Chromium VI compounds										
Non-exposed	472	88.6	1210	89.7	758	88.4	820	91.2	681	92.3
Non-substantial level	44	8.3	101	7.5	79	9.2	55	6.1	34	4.6
Substantial level	11	2.1	16	1.2	11	1.3	9	1.0	12	1.6
Cadmium compounds										
Unexposed	526	98.7	1334	98.9	845	98.6	848	94.3	694	94.0
Non-substantial level	6	1.1	11	0.8	9	1.0	37	4.1	28	3.8
Substantial level	1	0.2	4	0.3	3	0.4	14	1.6	16	2.2

Table 4. Percentage distribution of occupations held by male subjects exposed to nickel, chromium VI, or cadmium compounds in two Montreal-based studies

	Nickel		Chromium VI		Cadmium	
Occupation category	Study I	Study II	Study I	Study II	Study I	Study II
*# jobs with exposure to each compound**	*333*	*246*	*406*	*164*	*39*	*68*
Sheet metal workers	25%	21%	17%	14%	11%	8%
Metal machinists and metal product fabricators	27%	24%	4%	8%	20%	19%
Metal processors	8%	9%	8%	5%	13%	4%
Mechanics	9%	4%	15%	14%	5%	19%
Construction and other related painters	0%	0%	19%	18%	0%	12%
Construction workers	5%	7%	5%	8%	8%	2%
General machinists	5%	5%	1%	1%	8%	2%
Electrical and electronic workers	0%	0%	0%	0%	8%	10%
Graphic artists	0%	0%	0%	0%	13%	6%
Printers	0%	0%	5%	5%	0%	0%
Chemical processing, rubber, and plastic workers	0%	0%	5%	6%	0%	10%
Materials handlers	2%	6%	1%	2%	0%	0%
Administrators, scientists, teachers, clerks, and salesmen	9%	14%	10%	11%	13%	7%
Other occupations NEC	10%	9%	10%	8%	0%	1%

***** Each subject may have been exposed in one or more jobs

Table 5. Odds ratios between lung cancer and occupational exposure to nickel, cadmium, or chromium VI among Montreal males using population, cancer, and pooled controls from Study I (1979-1986)

	Population Controls					Cancer Controls					Pooled Controls				
	Controls/ Cases		**OR** *	95% CI		Controls/ Cases		**OR** *	95% CI		Controls/ Cases		**OR** *	95% CI	
Nickel compounds															
Unexposed	487	770				1243	770				978	770			
Any level of exposure	46	79	**1.34**	0.9	2.1	99	79	**1.48**	1.0	2.1	85	79	**1.35**	1.0	1.9
Chromium VI compounds															
Unexposed	472	758				1210	758				950	758			
Any level of exposure	55	90	**1.17**	0.8	1.8	117	90	**1.36**	1.0	1.9	101	90	**1.22**	0.9	1.7
Cadmium compounds															
Unexposed	526	845				1334	845				1053	845			
Any level of exposure	5	11	**1.46**	0.5	4.5	12	11	**1.81**	0.7	4.4	10	11	**1.54**	0.9	2.7

*Adjusted for age, respondent status, years of education, and smoking (time since quitting, ever smoked, ln(cigarette years)), as well as study for pooled results. Low reliability estimates are excluded.

Table 6. Number of participants in Study II assigned to three exposure categories of average lifetime concentrations* of chromium VI, nickel, or cadmium.

Metal	*Average exposure concentration, weighted by exposure duration*		
	Low	**Medium**	**High**
Chromium VI	141	18	2
Nickel	77	22	11
Cadmium	40	15	1

* Concentrations were estimated on a qualitative ordinal scale of 1 to 3 for each job, and weighted by duration over the course of each participant's lifetime.

Table 7. Odds ratios between lung cancer and occupational exposure to nickel, chromium VI, or cadmium among Montreal males in two studies and in a pooled analysis

	Study I (1979-1986)					Study II (1996-2001)					Pooled Studies				
	Controls/ Cases		**OR ***	95% CI		Controls/ Cases		**OR ***	95% CI		Controls/ Cases		**OR ***	95% CI	
Nickel compounds															
Unexposed	978	770				804	654				1782	1424			
Any level of exposure	85	79	**1.35**	1.0	1.9	87	74	**1.18**	0.8	1.7	172	153	**1.27**	1.1	1.7
Non-substantial level	73	70	**1.48**	1.0	2.2	83	64	**1.03**	0.7	1.6	156	134	**1.25**	0.9	1.6
Substantial level	12	9	**0.80**	0.3	2.0	4	10	**4.96**	1.3	19.	16	19	**1.46**	0.7	3.1
Chromium VI compounds															
Unexposed	950	758				820	681				1770	1439			
Any level of exposure	101	90	**1.22**	0.9	1.7	64	46	**0.93**	0.6	1.5	165	136	**1.12**	0.9	1.5
Non-substantial level	84	79	**1.33**	0.9	1.9	55	34	**0.81**	0.5	1.4	139	113	**1.11**	0.8	1.5
Substantial level	17	11	**0.75**	0.3	1.8	9	12	**1.74**	0.6	5.2	26	24	**1.06**	0.5	2.0
Cadmium compounds															
Unexposed	1053	845				848	694				1901	1539			
Any level of exposure	10	11	**1.54**	0.6	3.9	20	23	**1.56**	0.7	3.3	37	34	**1.54**	0.9	2.7
Non-substantial level	7	8	**1.53**	0.5	4.5	25	22	**0.98**	0.5	1.9	32	30	**1.09**	0.6	1.9
Substantial level	3	3	**1.57**	0.3	9.7	3	6	**5.67**	0.7	17.	6	9	**2.87**	0.7	11.

*Adjusted for age, respondent status, years of education, and smoking (time since quitting, ever smoked, ln(cigarette years)), as well as study for pooled results. Low reliability estimates are excluded.

Table 8. Odds ratios between lung cancer and occupational exposure to nickel, chromium VI, or cadmium by duration of exposure in a pooled analysis of two Montreal-based studies

Exposure duration (years)	Controls/ Cases		**OR***	95% CI	
Nickel					
0	1782	1424			
< 5	45	29	**0.92**	0.5	1.6
5 - 20	54	45	**1.24**	0.8	2.0
> 20	74	79	**1.56**	1.1	2.3
Chromium VI					
0	1770	1439			
< 5	34	32	**1.28**	0.7	2.2
5 - 20	59	48	**1.06**	0.7	1.7
> 20	72	56	**1.11**	0.7	1.6
Cadmium					
0	1901	1539			
< 5	17	15	**0.96**	0.4	2.1
5 - 20	21	16	**0.77**	0.4	1.7
> 20	26	25	**1.44**	0.7	2.8

* Adjusted for age, proxy, respondent status, socio-economic position (years of education), smoking, and study. Pooled results are presented, and reflect trends from both individual studies.

Table9. Odds ratios between lung cancer and exposure to nickel, cadmium, or chromium VI, stratified by smoking history †

	Non-smokers **			**Smokers**			**P (interaction)**
	Ctls / Cases	**OR***	95%CI	Ctls / Cases	**OR***	95%CI	
Nickel							
Unexposed	605 / 74			1172 / 1348			
Exposed	51 / 15	**2.49**	1.3 – 4.7	121 / 138	**1.11**	0.9 – 1.4	0.017
Chromium VI							
Unexposed	606 / 74			1159 / 1363			
Exposed	46 / 12	**2.39**	1.2 – 4.8	119 / 124	**0.97**	0.7 – 1.3	0.029
Cadmium							
Unexposed	82 / 647			1455 / 1250			
Exposed	5 / 9	**4.67**	1.5 – 14.3	29 / 21	**1.36**	0.8 – 2.4	0.046

† Results are presented for pooled data, and reflect trends observed in both individual studies.

** Non-smokers are those who have never smoked or quit over 20 years prior to study participation.

* Adjusted for age, respondent status, and socioeconomic position (years of education) as well as study for pooled results.

Table 10. Effect of exposure reliabilities on odds ratios between lung cancer and exposure to nickel, chromium VI, or cadmium for Montreal men pooled from Study I and II.

	Pooled Studies				
	Controls/ Cases		**OR ***	95% CI	
Chromium VI compounds					
Unexposed	1770	1439			
Any reliability	195	156	**1.10**	0.9	1.4
Low reliabilty (uncertain)	30	20	**0.95**	0.5	1.8
High reliability	165	136	**1.12**	0.9	1.5
Nickel compounds					
Unexposed					
Any reliability	183	171	**1.35**	1.0	1.7
Low reliabilty (uncertain)	11	18	**3.13**	1.1	9.1
High reliability	172	153	**1.28**	1.0	1.7
Cadmium compounds					
Unexposed	1901	1539			
Any reliability	64	56	**1.11**	0.7	1.7
Low reliabilty (uncertain)	26	17	**0.75**	0.4	1.5
High reliability	38	39	**1.29**	0.8	2.2

*Adjusted for age, respondent status, years of education, and smoking (ever smoked, time since quitting, ln (cigarette years)).

Table 11. Effect of respondent status on odds ratios for lung cancer and exposure to nickel, chromium VI, or cadmium for Montreal men pooled from Study I and II.

		Proxy respondents			Self Respondents		
		Ctls / Cases	**OR***	95%CI	Ctls / Cases	**OR***	95%CI
Chromium VI							
	Unexposed	237 / 523			1533 / 916		
	Exposed	18 / 21	**0.62**	0.3 – 1.2	147 / 115	**1.25**	0.9 – 1.7
Nickel							
	Unexposed	243 / 511			1539 / 913		
	Exposed	13 / 30	**1.11**	0.5 – 2.3	159 / 123	**1.32**	1.0 – 1.7
Cadmium							
	Unexposed	258 / 536			1643 / 1003		
	Exposed	0 / 8	**5.65**	0.2 – 143	37 / 31	**1.20**	0.7 – 2.1

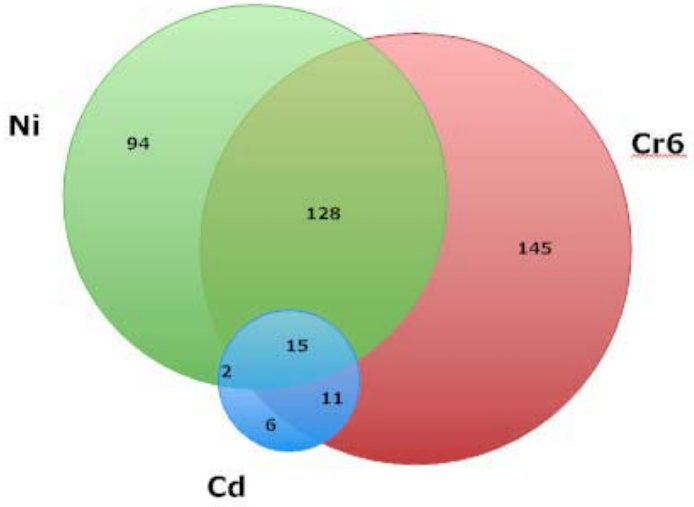
* Adjusted for age, respondent status, and sep (years of education) as well as study for pooled results.

Low reliability estimates are excluded.

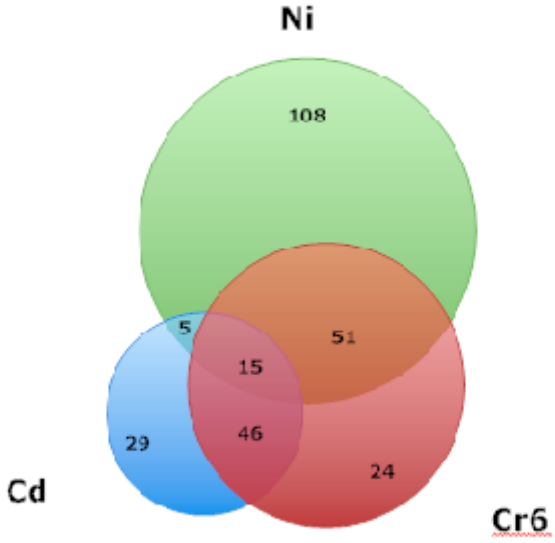
Figures

Figure 1.

Number of subjects exposed to nickel (Ni), chromium VI (CrVI), and cadmium (Cd), in Study I and Study II, and degree of overlap between each.



Study I: Total number of subjects = 2739.
Total number of subjects exposed to nickel, chromium VI, or cadmium = 401.



Study II: Total number of subjects = 1640.
Total number of subjects exposed to nickel, chromium VI, or cadmium = 278.

***Figure 2*:**
Risk of lung cancer after occupational exposure
to cadmium, nickel, and chromium VI in smokers and non-smokers

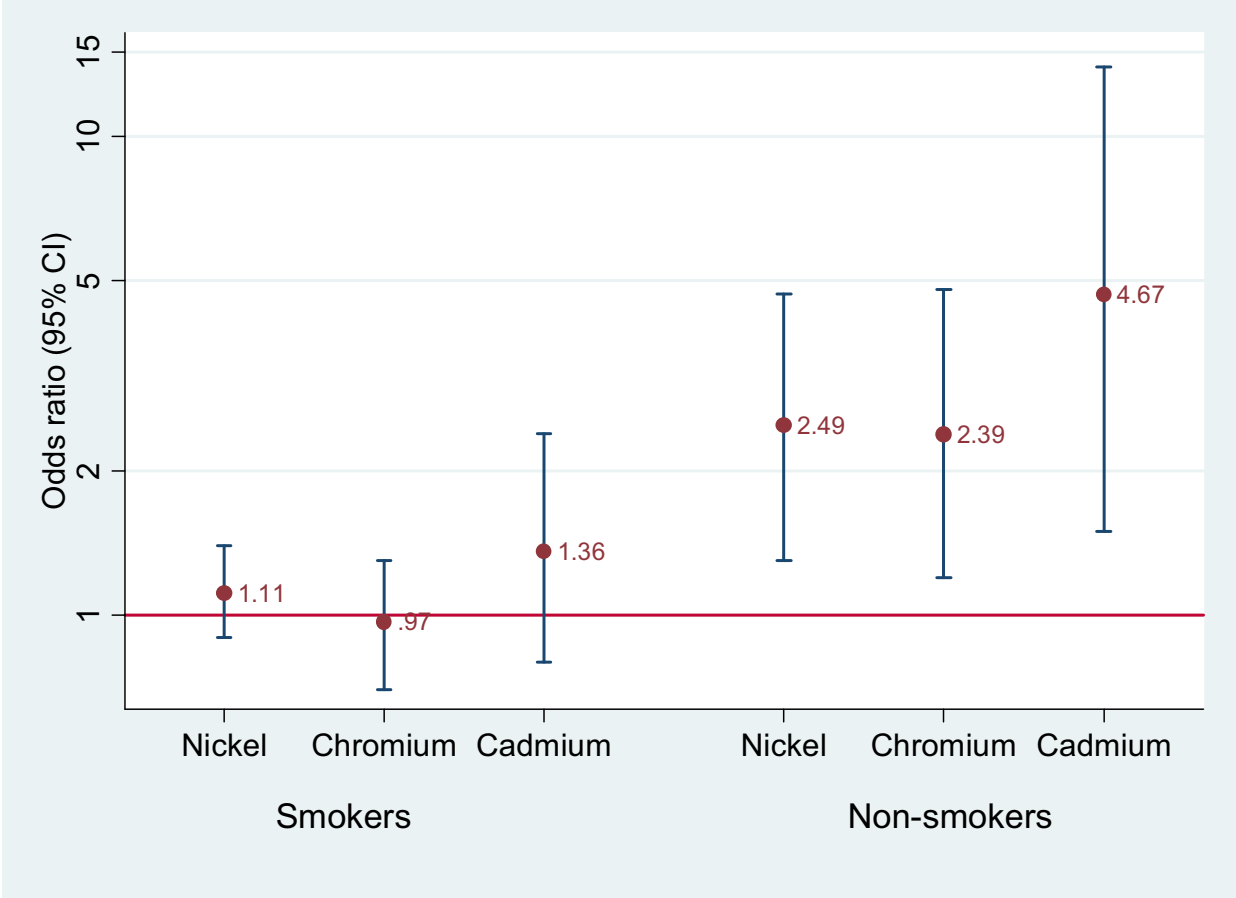
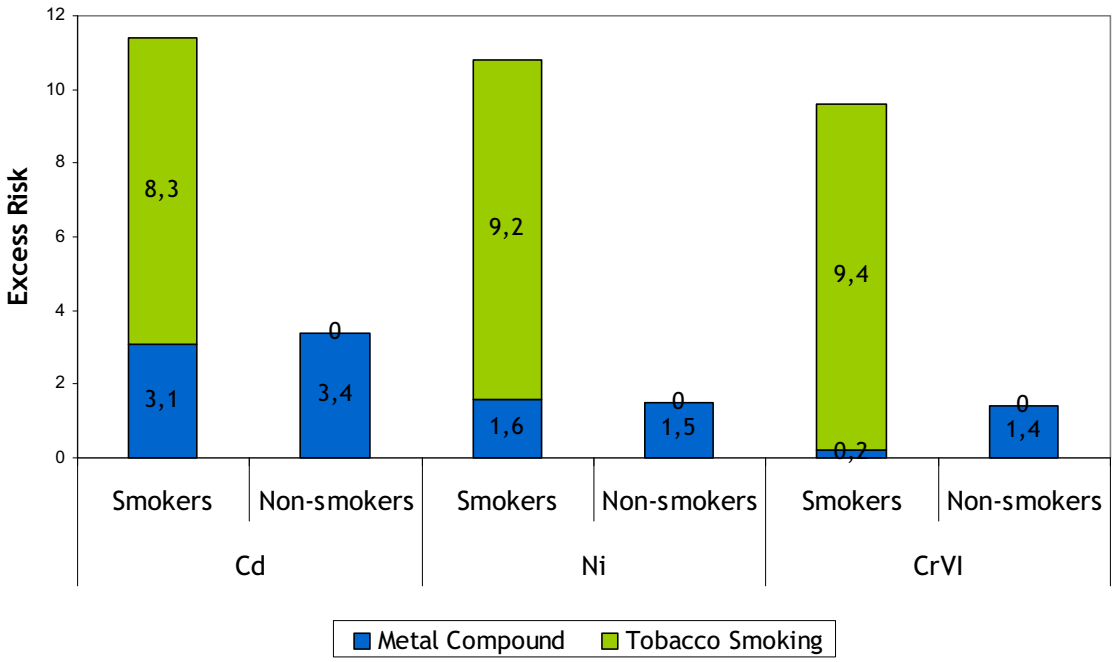


Figure 3.
Excess risk of lung cancer resulting from exposure to 3 metal compounds and tobacco in smokers and non-smokers.



ARTICLE

ABSTRACT

Lung cancer risk associated with occupational exposure to nickel, chromium VI, and cadmium in two population-based case-control studies in Montreal.

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Objective: To investigate the risk of lung cancer associated with occupational exposure to nickel, chromium VI, or cadmium, among workers exposed to these agents at a variety of levels and in a wide range of occupations.

Methods: Two population-based case-control studies were conducted in Montreal (1979-1981 and 1996-2001). In both studies, cases were ascertained in all hospitals on the island of Montreal, while age-matched and sex-stratified population controls were selected from electoral lists. Detailed job histories were obtained by interview, and evaluated by an expert team of chemist-hygienists in order to estimate intensity, duration, and cumulative exposure to multiple substances over the course of each participant's lifetime. Odds ratios (ORs) and 95% confidence intervals (CIs) for lung cancer were estimated using logistic regression, adjusting for confounders including detailed smoking history, education, and respondent status.

Results: At the exposure levels experienced by this population, no increase in risk of lung cancer was associated with exposure to chromium VI (OR=1.12, 95% CI = 0.9-1.5). A small but significant increase in lung cancer risk was observed in subjects exposed to nickel (OR = 1.27; 95% CI = 1.1 – 1.7), while among subjects exposed to cadmium, risk was elevated but of borderline significance, with large confidence intervals (OR = 1.54 95% CI = 0.9 – 2.7). Neither smoking nor occupational co-exposures were found to be strong confounders of the relationship between metals exposure and lung cancer. Further, lung cancer risk was significantly elevated after exposure to any of the metals of interest in non-smokers.

Discussion: This study is unique in providing empiric evidence on lung cancer risks associated with low levels of exposure to nickel, chromium VI, or cadmium originating from a variety of occupational contexts. The results of this study have important public health implications, both in terms of determining ongoing risk to exposed workers, and in terms of assessing risk to the general population exposed to these metals through pollution and cigarette smoke. This analysis will likely contribute to an upcoming IARC evaluation of the carcinogenicity of these metals. Examination of the relationship between exposure to cadmium, chromium VI and nickel and subsequent risk of lung cancer is therefore timely and pertinent.

INTRODUCTION

Lung cancer is the most common cause of cancer mortality, responsible for over 1 million deaths worldwide each year. Although tobacco smoking is its most important determinant**,** several lesser factors are recognised or suspected to contribute to development of lung cancer. These are important because in aggregate they account for large numbers of lung cancers, and because lung cancer is a multi-factorial disease which can be prevented by eliminating one or other of the contributing factors.

Nickel, chromium VI, and cadmium have long been recognised as lung carcinogens (1, 2). Human exposure to these metals is common because of their industrial concentration and environmental persistence. Although the highest levels of exposure occur in certain workplaces, lesser levels of exposure are also common in the general population. All three metals are also constituents of tobacco smoke, and have been implicated in tobacco-induced carcinogenesis (3, 4). However, while it seems that the book has been closed on lung carcinogenicity related to these agents, there remain some lingering doubts about the respective bodies of evidence that have accumulated, and there remain open questions about the nature of the relations between each of these agents and lung cancer.

Most of the evidence regarding cancer risks due to these agents comes from cohort studies in a narrow range of industries in which exposures have been relatively high and in which it has been difficult to rule out confounding by smoking or other exposures as a possible explanation for the associations. The present study stems from a unique opportunity to provide additional evidence on the effect of exposure to occupational nickel, chromium VI, and cadmium, at levels of

exposure found in the entire range of industries in which these exposures occur. In the early 1980s, we carried out a population-based case-control study in Montreal, Canada, exploring possible associations between hundreds of occupational substances and multiple cancer sites, including lung cancer. In the late 1990s we carried out a similar study in the same region, this time focusing on respiratory cancers. These two investigations offer the potential to examine the effect of occupational exposure from a variety of sources, in a wide range of occupations, and at exposure levels lower than those found in historical cohorts. Further, because detailed lifetime smoking histories were collected, it is possible to adjust for possible confounding by smoking and to examine effect modification in relation to smoking. The objective of the present study was therefore to examine the link between occupational exposure to nickel, chromium VI or cadmium and lung cancer in these conditions.

METHODOLOGY

Two large population-based case-control studies of occupational exposures and lung cancer have been conducted in Montreal, Canada since the 1980s. In brief, the first study, labeled here as Study I, was conducted from 1979 to 1986, and included men aged 35 to 70 diagnosed with cancer at any of 19 sites (5, 6). The second study, labeled here as Study II, was conducted from 1996 to 2001 and included men and women aged 35 to 75 diagnosed with a lung malignancy. Both studies included patients with incident, histologically confirmed cancers identified across all major Montreal-area hospitals, and living in the Montreal area, assuring a virtually complete population-based ascertainment of cancer cases. Both studies included a series of population controls randomly selected from electoral lists. In Quebec, electoral lists were maintained by means of active enumeration of households until 1994; they have since been continually updated

and are thought to represent nearly complete listings of Canadian citizens residing in the province. In Study I, population controls were frequency matched by age and area of residence (electoral district of about 40,000 individuals) to all cancer cases. In Study II, controls were recruited according to the distributions of age, sex, and area of residence of lung cancer cases. Details of subject ascertainment and data collection have been presented in detail previously (7-10).

In study I, 1,082 lung cancer cases and 740 population controls were approached. Of these, 857 (79 percent) cases and 533 (72 percent) controls completed the interview. In addition to population controls, a second set of controls was used, comprising 1,349 cancer patients who had been ascertained in the same years and hospitals as the lung cancer cases, and selected so that none of the 19 individual cancer sites represented more than 20 percent of the overall pool of cancer controls. In Study II, 858 eligible male cases and 1,024 eligible male controls were approached, and 86 percent and 70 percent of these, respectively, agreed to participate and completed the interview. Since the prevalence of occupational exposure to all three metals among females was very low (1%) in Study II, and unavailable for Study I, results are presented for males only.

DATA COLLECTION AND EXPOSURE ASSESSMENT

In Study I and Study II, interviews were completed by the targeted subjects in over 82 percent and 76 percent of eligible individuals, respectively. Most interviews were completed with self-respondents, while surrogate respondents (proxies) provided information for 29% of cases in Study I and 40% of cases in Study II. For controls, the fraction of interviews conducted with

surrogates was under 20%. The methodology for exposure assessment has been presented previously (5, 9, 11, 12). Briefly, interviews were divided into two sections: a structured section requested information on socio-demographic and lifestyle characteristics, and a semi-structured section elicited detailed descriptions of each job held by the subject in his working lifetime. Occupations were coded according to the CCDO classification system (13). For each job held, a trained interviewer asked the subject about the nature of the work environment, the subject's main and subsidiary tasks, and any additional information (e.g., equipment maintenance, use of protective equipment, activities of coworkers) that could provide clues about work exposures and their intensities. For certain occupations, supplementary questionnaires were used to assist interviewers with detailed technical probing (14).

A team of chemists and industrial hygienists examined each completed questionnaire and translated each job into a list of potential exposures using a checklist of 294 agents. In both studies, exposures assessed included nickel, chromium VI, and cadmium compounds as well as many common occupational co-exposures. The coders spent about 40 person-years on this project, which included developing methodology, monitoring interview quality, conducting background research on exposures in different occupations, coding and recoding the individual participants' files. The final exposure codes attributed to each participant were based on consensus among the coders, who were blind to the subject's disease status. For each substance considered present in each job, the coders noted three dimensions of information: their degree of confidence (reliability) that the exposure had actually occurred (possible, probable, definite), the frequency of exposure in a normal work week (<5 percent, 5–30 percent, >30 percent of the time in Study I; an estimation of the number of hours/week exposed in Study II), and the relative level

of concentration of the agent (low, medium, high). Non-exposure was interpreted as exposure up to the level found in the general environment. Exposure assessment was based not only on the worker's occupation, industry, and job title but also on individual characteristics of the workplace and tasks reported by the subject. Data were also collected regarding a large number of other variables including ethnicity, family income, detailed smoking history, dietary intake, and alcoholic beverage consumption. For inclusion in the present analyses, subjects were required to have completed both the socio-demographic and the job history interviews.

DATA ANALYSIS

Unconditional logistic regression (15) was used to estimate odds ratios (ORs) of disease and 95 percent confidence intervals (95% CIs) of lung cancer associated with exposure to nickel, chromium VI, or cadmium for each study.

Subjects were categorized as unexposed or ever exposed to each metal of interest, where those exposed only in the 5 years prior to interview were considered unexposed. Individuals classified as having had only possible likelihood of exposure were excluded from most analyses. Ever-exposed individuals were further classified into non-substantial and substantial exposure subcategories. Subjects with substantial exposure had been exposed to medium or high metal concentrations for more than five percent of their work week, for five years or more. This delineation was based on best goodness of fit results of a set of analyses using different combinations of weights given to various dimensions of exposure (frequency, concentration, and duration) for Study I, and replicated in Study II (data not shown). In addition to analyzing this categorical approximation of cumulative exposure, we also examined the effects of several

related dimensions of exposure, including duration, intensity, concentration, and frequency. For individuals exposed in more than one job, duration-weighted averages were calculated.

A variety of potential confounders were explored for inclusion in analysis, including ethno-cultural background, and respondent status (self, proxy). Investigated socio-economic indicators included median household income, years and level of education, and family class. Both median household income and years of education had noticeable impacts on the point estimates. However, they were highly correlated. Years of education was therefore chosen to be included as a proxy for socioeconomic position it was less likely to have been inflated between studies.

In order to evaluate the extent of confounding by other common occupational exposures, the effects of *a priori* occupational confounders on the crude risk estimate were assessed using a change-in-estimate approach (6, 16). Those whose inclusion changed the estimate of association by over 5% were retained. Occupational co-exposures retained in the complete model for chromium VI and nickel were asbestos, silica, benz(a)pyrene, and nickel or chromium VI. The final model for cadmium included asbestos, silica, benz(a)pyrene, lead, and nickel. Other potentially important confounders, such as cadmium in the case of nickel, and arsenic in the case of cadmium, were not present in sufficient quantities to affect point estimates or had a neutral effect, and were not retained in the final model.

Smoking was modeled as a combination of three variables (cigarette years, time since quitting, and ever smoker status) based on a risk model derived from our study subjects proven to most accurately fit this data set (17, 18). Potential effect modification by smoking was also explored,

where non-smokers were defined as having smoked fewer than 100 cigarettes in their lifetimes or having quit over 20 years previously.

In Study I, analyses using population and cancer controls were initially conducted separately. When the point estimates were consistent and of the same magnitude and direction, controls were then pooled and weighted such that population and cancer controls contributed equally to a combined data set. Results are presented from this pooled analysis, and summarise results from both separate control groups. Similarly, if results from Study I and Study II showed parallel trends and largely overlapping confidence intervals, pooled study analyses were conducted. Cases and controls from each study were simply added together, and a binary study adjustment term was added to logistic regression models.

Ethics approval was obtained for both studies from each participating hospital and university. All participating subjects provided informed consent.

RESULTS

Study Population Characteristics

Table 1 shows the distribution of subjects according to selected socio-demographic characteristics. As expected, cases were more likely to be current smokers and had smoked more than controls. Cases had a lower median family income and fewer years of education than controls, and interviews were more likely to have been conducted with a proxy for cases than controls.

Table 2 shows the lifetime prevalence of occupational exposure to nickel, cadmium, or chromium VI in each study. Prevalence of any exposure to nickel or chromium VI in this sample of Montreal men was between 6 and 11%; cadmium exposure was somewhat lower. There was substantial exposure to each metal in between 1 to 2% of the population, except for cadmium in Study I, where substantial exposure was less than 0.5%. There was little difference in exposure prevalence between cases and controls, though cases were more likely have been substantially exposed than controls in Study II.

Overall, lifetime exposure to nickel and chromium VI co-occurred in about 50% of exposed subjects, more frequently in controls than cases. Co-exposure to chromium VI was also common among those exposed to cadmium.

Occupational profiles

Table 3 shows the occupations in which these metals were attributed in our study subjects. For the most part, occupational profiles within metals were consistent between Study I and Study II. The majority of nickel exposures in our study population occurred in sheet metal workers, metal machinists, and metal product fabricators; chromium VI exposures occurred in construction painters, sheet meal workers, and mechanics; and cadmium exposures occurred in metal machinists, sheet metal workers, metal product fabricators, and graphic artists.

Overall, exposures to the three metals occurred in similar occupations but in different proportions. Those exposed to nickel were more likely to have held jobs related to metal work, while those exposed to chromium VI were more likely to have held jobs in plastics processing,

painting, printing, and vehicle maintenance. Because many subjects were exposed to several agents at some point in their lives, exposures may have occurred in the same jobs; however, this is not necessarily the case.

Lung cancer risk estimates

Table 4 presents a summary of the odds ratios of lung cancer diagnosis associated with exposure to nickel, chromium VI, or cadmium, adjusted for age, respondent status, years of education, and smoking history. Risk estimates for ever having been exposed to nickel or chromium VI were higher in Study I than Study II, but overall, similar trends were observed in both studies. The pooled data indicated that at the exposure levels experienced by this population, there was no increased risk of lung cancer after exposure to any level of chromium VI (OR=1.12; 95%CI = 0.9-1.5). A small but significant increase in lung cancer risk was observed in subjects exposed to nickel (OR=1.27; 95%CI=1.1–1.7). The risk estimate for cadmium was elevated but of borderline significance, with large confidence intervals (OR = 1.54; 95%CI = 0.9 – 2.7). Investigation of the independent and combined effects of nickel and chromium VI revealed that risk estimates were similar regardless of co-exposure (results not shown). Analyses of the effects of co-exposure to cadmium were not conducted due to low co-exposure prevalence.

Risk estimates at two cumulative exposure levels, categorised as substantial and non-substantial, are also presented in Table 4. Very few subjects were exposed at the substantial level, and as such risk estimates for this category were somewhat unstable. Overall, those with substantial exposure to nickel or cadmium had increased risk of lung cancer compared to those with only

non-substantial exposure, while those exposed to chromium VI were not at increased risk regardless of exposure level.

Odds ratios were also computed separately for each available dimension of exposure, including duration, intensity, frequency, and concentration. None of these showed clear trends for any of the agents (data not shown), with the possible exception of duration. Table 5 details the ORs by duration in the pooled study analysis. Odds of lung cancer tended to increase with duration of nickel exposure in both Study I and Study II, with a significantly elevated risk observed with over 20 years of exposure at any level (pooled OR=1.56 95%CI = 1.1-2.3). Greater risk was also observed in those exposed to cadmium for over 20 years, while no duration-dependent effect was observed after chromium VI exposure.

Control for confounding by smoking and occupational co-exposures

Smoking did not appear to be a strong confounder of the relationship between metal exposure and lung cancer in this study. After adjusting for age, respondent status, and socio-economic position, the marginal effect of adding smoking as a covariate reduced the ORs by less than 7%. Adjusting for occupational confounders tended to slightly weaken observed associations, but did not affect conclusions.

Effect modification by smoking

The effects of metals exposure were also explored separately in smokers and non-smokers. 752 men in this study were non-smokers. Table 6 shows the odds ratios for exposure to each agent, stratified by smoking history. For all three metal compounds, significantly increased risk of lung

cancer was found among exposed non-smokers but not among smokers. This trend was observed in both studies independently, with particularly strong (but imprecise) effects observed in Study I. Pooled data showed that non-smokers exposed to nickel or chromium VI had approximately 2.5 the odds of being diagnosed with lung cancer compared to unexposed non-smokers, while non-smokers exposed to cadmium had over four times the odds of lung cancer compared to unexposed non-smokers. Meanwhile, odds ratios among smokers hovered around 1.1 for nickel and cadmium, and 1.0 for chromium VI. The confidence intervals of the estimates for smokers and non-smokers barely overlapped and interaction terms between smoking status and each metal entered into the logistic regression function were significant for each compound, indicating a departure from a multiplicative joint effect.

The additional absolute risk attributable to cadmium or nickel exposure was almost identical among smokers and non-smokers (data not shown). Exposure to nickel and cadmium therefore appeared to have an approximately additive effect on lung cancer risk. Such a distinct trend was less clear in those exposed to chromium, as no excess risk was detected in smokers. Non-smokers did not appear to have different co-exposures than smokers, and did not tend to be proxy responders. Adjustment for occupational confounders further increased the distinction between smoking categories, but decreased estimate precision.

Because of the small number of non-smokers in the study population, there was a relatively small difference between risk estimates for the metals among smokers and in entire study population. We therefore chose to retain adjusted, unstratified results in Table 4, as it would allow more easy comparison with previous works.

Proxy response

Interview quality may have varied between self and proxy respondents. For example, proxy respondents may have been less likely to provide detailed job history information, causing underestimation of certain exposures. Indeed, metal exposures were somewhat less likely to be attributed to proxy respondents (data not shown). Thus, we conducted an analysis restricted to self-respondents only. These results (also not shown) were virtually identical to the risk analyses shown in Tables 4 to 6.

DISCUSSION

ADDED VALUE OF THIS RESEARCH

While it has long been suspected or recognized that nickel, chromium VI, and cadmium are human lung carcinogens, there remain some major questions about the bodies of evidence on which these inferences have been made. First, in the past two decades some published studies have failed to replicate results of earlier studies. There are many possible reasons for such apparent inconsistencies, but they indicate that further empiric research is required to reaffirm the carcinogenicity of these agents. Second, almost all previous research has been based within industries with workers exposed to these agents at relatively high concentrations, and in a narrow range of conditions. The majority of workers in most occupations are exposed to these agents at much lower concentrations and in more heterogeneous conditions. Our study is unique in providing empirical evidence on risks related to such conditions. Third, our study had the benefit of having collected and controlled for detailed smoking history and other potential confounders.

SUBSTANTIVE FINDINGS

Nickel

Our risk estimate for the association between any nickel exposure and lung cancer (OR=1.27) was compatible with most other recent estimates, which have consistently hovered between 1.3 and 1.5 (19-22). However, no strong exposure-dependent trend was observed. Given that the majority of our subjects were exposed at relatively low levels, our results support previous findings that small increases in lung cancer risk may be detected even at low levels of nickel exposure (19, 22-25). Our study is also consistent with previous observations of elevated risk after over 20 years of nickel exposure (22, 26, 27).

Chromium VI

Overall, we found no increased risk of lung cancer at the levels of chromium VI exposure experienced by this population, and no cumulative exposure- or duration-dependent trends were observed. Given that increased risks have almost exclusively been observed at high levels of exposure to chromium VI (28-31), it is likely that the exposure levels of the workers in this population were insufficient to produce observable effects. It is difficult to tell whether this was due to exposure below a threshold level, or whether the effect at these exposure levels were simply too small to detect.

Cadmium

Increased risk of lung cancer was consistently observed among workers with “substantial” exposure to cadmium in this study. However, definitive interpretation of these results is

difficult; the number of substantially exposed subjects was small and resulting confidence intervals were wide. Recent updates of several previously studied cadmium cohorts, often incorporating methodological improvements and quantification of exposure, have been similarly equivocal (32-36). As such, the weight of evidence for a carcinogenic role of cadmium in occupational cohorts appears to be less compelling than it was 20 years ago (33, 37).

Effect modification by smoking

We found that exposure to either nickel, cadmium, or chromium VI significantly increased the risk of lung cancer in a subgroup of non-smokers, while it had virtually no effect among smokers. This phenomenon was independently observed in both studies, and was based on reliable estimates of lifetime smoking histories.

There are several potential interpretations of the strong metal-associated risk observed in non-smokers: it could be due to chance fluctuations, to unidentified systematic bias, or to a real effect. However, it is unlikely that these results were due to chance, and there were no obvious differences in occupational profiles or co-exposures between non-smokers and smokers. This pattern could also result from a greater ability to detect risk in non-smokers; the observed effect could be a cleaner, albeit imprecise, indication of these metals' actual effects. This hypothesis is supported by the observation that the absolute increase in risk associated with these metals was similar in smokers and non-smokers exposed to nickel or cadmium. This trend was less clear in those exposed to chromium VI, as only non-smokers were observed to experience increased risk. This possibility is particularly important in that it suggests that risk at low levels of exposure may have been previously undetected in cohorts composed mainly of smokers. The observed

phenomenon of increased risk among non-smokers could therefore provide part of an explanation for apparently conflicting results in different cohorts, which may have different proportions of non-smokers.

If these results reflect a true association, they suggest that nickel, cadmium, and potentially chromium VI had independent, additive effects with respects to smoking. Our data demonstrate that in specific circumstances, even low exposures to all three metals can increase risk of lung cancer.

METHODOLOGICAL CONSIDERATIONS

The results of this must be interpreted in light of methodological strengths, weaknesses and characteristics of this study. Some of the methodological considerations that may have influenced our estimates are discussed below, including choice of controls, exposure assessment, exposure parameterisation, statistical power, and confounding.

Choice of controls and pooling

Thoughtful choice of control group is essential to any case-control study. In Study I, we began by analysing data using two types of controls: cancer controls and population controls. Each type of control has its own advantages and disadvantages in terms of selection, response, and information bias introduced (10, 38), and it is difficult to ascertain which control group gave more valid results. By pooling equally weighted cancer and population controls in Study I, we partly neutralized control-specific bias while increasing our sample size and power.

The similarities in study design and crude results for Study I and Study II also justified their pooling. Final results using data pooled from Study I and Study II, adjusted for study, represent a weighted average of the two studies' results with improved statistical power. We have presented results for each study individually in order to illustrate where parallel trends were observed, which should enable other reviewers or investigators to conduct different types of meta-analyses and assessments.

Exposure assessment

The present study estimates the risk of lung cancer associated with exposure to nickel, chromium VI, and cadmium from a wide range of occupations and exposure levels. The exposure assessment method we employed is widely considered to be the reference method for this type of study design (39, 40), and similar methods have been used by other research teams exploring occupational exposures and lung cancer (41, 42). There are tradeoff advantages and disadvantages to our approach compared to cohort study methods. Most cohort studies have "more reliable" exposure assessment measures than our study, as it is much easier to quantify exposure within one industry than across many work environments. However, cohort-based exposure assessments also have limitations (43); exposures from jobs held outside the company under study are unaccounted for, and exposures are often misclassified (37, 44, 45). Our exposure assessment method addresses some weaknesses of the traditional cohort-study approach to identification of occupational carcinogens by including information on non-occupational confounders and exposures to a wide range of substances in different jobs. In our study, complete lifetime job histories and associated exposure estimates were available for each subject. Compared with cohort studies based on a single employer or industry, this approach has

the advantage of reducing confounding by occupation-specific co-exposures, and is likely to more accurately represent lifetime exposures. Previous investigations have shown that the interview-based job histories used in this study were valid (46) and that the exposure coding was reliable (47, 48).

Misclassification

In the absence of objective measures of exposure, it is certain that a degree of exposure misclassification was present. Many factors may have influenced the accuracy of exposure assessment, including the type of occupation, the era of exposure, and the quality of the job description elicited from the respondent. However, given that coders were blind to subject status, it is probable that misclassification was non-differential. Further, exposure identification was limited to broad classes of metal compounds, which were not specific in terms of speciation or solubility. Given that different metal species may have different degrees of carcinogenicity, grouping all nickel, chromium VI, or cadmium species together may have masked species-specific effects observed in other studies (1, 19-21, 27, 29, 49).

Exposure levels

Although the nature of our exposure estimates does not allow us direct comparison to the quantitative exposure levels of other studies, we expect that metal exposure in our study was low compared to most high-risk historical occupational cohorts. While it is initially useful to limit the analysis of potential carcinogens to high exposure conditions, which are more likely to produce detectable effects, we believe it is just as important to evaluate them in conditions that are more widely experienced by workers. This study allows us to examine the potential effects of long-

term, sporadic, and chronic low-concentration exposures from a range of sources and levels. The accumulation of such exposures may have been overlooked in occupational cohort studies, which have by definition been limited to one place of work.

Parameterisation of exposure dimensions

For each putative carcinogen, risk may be associated to different degrees with different dimensions of exposure; the effects of average intensity or duration of exposure, peak exposure, age at exposure, or time since exposure may vary between agents depending on their deposition, clearance, metabolism, and mechanisms of action. There are therefore as many ideal parameterisations of exposure as there are compounds and mechanisms of action. Without *a priori* knowledge of a particular agent's characteristics, it is impossible to develop the perfect agent-specific combination of different exposure dimensions. Most epidemiologic studies of environmental or lifestyle factors, when confronted with analogous dilemmas, have chosen to use a cumulative exposure variable as the prime exposure index. While it may not be optimal in every context, it is generally robust enough to detect important effects (50). In order to estimate cumulative exposure, this study used a combination of concentration and duration variables, dichotomised into substantial and non-substantial levels. The cutpoints used in this categorisation were chosen after detailed examination of multiple possible combinations of exposure dimensions.

Statistical power

Statistical power is a function of several parameters, including numbers of cases and controls, prevalence of the exposure, and relative risk induced by the exposure (51). In this study, there

were large numbers of cases and controls, but relatively low metal exposure prevalence. In order to maximise the power to detect effects, the number of subject subgroups and exposure sub-categories was therefore limited. Subdividing the study sample into yet smaller subgroups in order to investigate more specific features of exposure or study population would have had the effect of further reducing power. Our capacity to detect effect may also have been limited by a lack of contrast between categories. Given that the majority of the exposures in this population were of low to medium concentration, the contrast between substantial and non-substantial exposures was mostly influenced by exposure duration. While statistical power was a genuine limitation in this study, it is one that could not have generated false positive associations. However, a lack of power might explain failure to detect some associations, and certainly explains the width of confidence intervals for most OR estimates.

Confounding

It is possible that observed risk estimates were affected by other unmeasured carcinogenic exposures related to occupation or lifestyle, where those associated with the exposure of interest may have artificially elevated risk estimates. Confounding by smoking and occupational co-exposures has been insufficiently addressed in the epidemiological literature on metal carcinogenesis, mainly because complete and reliable data are rarely available in the context of most retrospective cohort studies. In this study, there was unlikely to have been significant confounding by smoking or by occupational co-exposures. With regard to smoking, information on lifetime smoking histories were collected and modeled in study analyses. With regard to other occupational exposures, the fact that this study included subjects exposed in a variety of occupations meant that it was unlikely that there would be a standard set of co-exposures

associated with the three metals, and thus less likelihood of confounding. Further, detailed information was collected on co-exposures, and important co-exposures were adjusted for.

Although an effect stratified by smoking history was found in this population, unstratified results adjusted for smoking were retained in the original regression model for ease of comparison with other studies, and to demonstrate the overall impact of adjustment with multiple smoking parameters. In this study, as for others, the smoking-adjusted odds rations constitute weighted averages of potentially differential risk in smokers and non-smokers.

CONCLUSION

Increased risk after any nickel exposure was small but significant, and slightly elevated after substantial exposure. For cadmium, risk estimates after substantial exposure were non-significantly but consistently elevated compared to non-substantial exposure. Meanwhile, the levels of occupational chromium VI exposure in this study did not lead to an observable elevated risk of lung cancer. None of the metals were confounded by smoking or other occupational carcinogens. However, for all three metals, a significant association between exposure and lung cancer was observed in small subgroups of non-smokers. If these findings are a true reflection of these metals' effect in non-smokers, they demonstrate that in the absence of other major lung cancer determinants, low levels of exposure to nickel, chromium VI, and cadmium remain weak but significant risk factors for lung cancer.

It is in the areas of low exposure, where evidence is least clear, that the majority of decisions regarding occupational and population-level health limits and regulations are made / required.

While they may be difficult to detect, the minor contribution of individual agents have important repercussions at the population level. It is therefore essential not to prematurely discount the hazard of potentially carcinogenic compounds. As such, our study has important implications, both in terms of cancer risk assessment and elucidation of carcinogenesis mechanisms.

Table 1. Selected socio-demographic characteristics of male subjects in Montreal in two population-based case-control studies

		Study I (1979-1986)			Study II (1996-2001)	
		Pop' Controls	Cancer Controls	Cases	Pop' Controls	Cases
Variable	Categories	N=533	N=1349	N=857	N=899	N=741
Age (%)	<= 55	28.0	32.5	27.4	11.9	13.7
	56-65	45.2	43.7	50.8	28.5	32.8
	66-75	26.8	23.7	21.8	59.6	53.5
Ethnicity (%)	French Canadian	64.2	58.0	69.1	64.4	77.5
	English Canadian	14.1	16.1	13.5	6.3	4.6
	Other	21.8	25.9	17.4	29.3	17.9
Schooling (%)	< 7 years	20.3	22.3	30.3	24.6	27.3
	7-12 years	56.1	55.2	57.1	47.2	51.8
	13+ years	23.6	22.5	12.6	27.3	15.8
Median Family Income *		26627	24761	22386	35250	32951
Smoking status (%)	Never	19.7	17.3	1.5	18.1	3.2
	Quit 2-5 yrs ago	8.8	6.7	7.6	2.9	5.8
	Quit 6-10 yrs ago	7.9	6.2	6.0	6.6	7.6
	Quit > 10 yrs ago	16.7	11.8	5.0	44.6	26.3
	Current†	46.9	58.0	79.9	27.9	57.1
Mean pack-years‡		50.6	53.1	75.9	41.5	75.1
Respondent (%)	Self	87.4	80.8	70.6	90.1	60.0
	Proxy	12.6	19.2	29.4	9.9	40.0

*Median family income for census tract, in Canadian $
†Current smokers and subjects who quit less than two years before recruitment
‡Among ever smokers, based on 20 cigarettes per packet.

Table 2. Distribution of male subjects with lifetime occupational exposure to nickel, cadmium or chromium VI compounds in two Montreal-based studies

	Study I (1979-1986)						Study II (1996-2001)			
	Pop. Controls		Cancer Controls		Cases		Pop. Controls		Cases	
Occupational Agent	N	%	N	%	N	%	N	%	N	%
Nickel compounds										
Non-exposed	487	91.4	1243	92.1	770	89.8	804	89.4	654	88.6
Non substantial exposure	39	7.3	86	6.4	70	8.2	83	9.2	64	8.7
Substantial exposure	7	1.3	13	1.0	9	1.1	4	0.4	10	1.4
Chromium VI compounds										
Non-exposed	472	88.6	1210	89.7	758	88.4	820	91.2	681	92.3
Non substantial exposure	44	8.3	101	7.5	79	9.2	55	6.1	34	4.6
Substantial exposure	11	2.1	16	1.2	11	1.3	9	1.0	12	1.6
Cadmium compounds										
Unexposed	526	98.7	1334	98.9	845	98.6	848	94.3	694	94.0
Non-substantial exposure	6	1.1	11	0.8	9	1.0	37	4.1	28	3.8
Substantial exposure	1	0.2	4	0.3	3	0.4	14	1.6	16	2.2

Table 3. Percentage distribution of occupations held by male subjects exposed to nickel, chromium VI, or cadmium compounds in two Montreal-based studies

	Nickel		Chromium VI		Cadmium	
Occupation category	Study I	Study II	Study I	Study II	Study I	Study II
*Number of jobs with exposure to each compound**	*333*	*246*	*406*	*164*	*39*	*68*
Sheet metal workers	25%	21%	17%	14%	11%	8%
Metal machinists and metal product fabricators	27%	24%	4%	8%	20%	19%
Metal processors	8%	9%	8%	5%	13%	4%
Mechanics	9%	4%	15%	14%	5%	19%
Construction and other related painters	0%	0%	19%	18%	0%	12%
Construction workers	5%	7%	5%	8%	8%	2%
General machinists	5%	5%	1%	1%	8%	2%
Electrical and electronic workers	0%	0%	0%	0%	8%	10%
Graphic artists	0%	0%	0%	0%	13%	6%
Printers	0%	0%	5%	5%	0%	0%
Chemical processing, rubber, and plastic workers	0%	0%	5%	6%	0%	10%
Materials handlers	2%	6%	1%	2%	0%	0%
Administrators, scientists, teachers, clerks, and salesmen	9%	14%	10%	11%	13%	7%
Other occupations NEC	10%	9%	10%	8%	0%	1%

**Each subject may have been exposed in one or more jobs.*

Table 4. Odds ratios between lung cancer and occupational exposure to nickel, chromium VI, or cadmium among Montreal males in two studies and in a pooled analysis

	Study I (1979-1986)					Study II (1996-2001)					Pooled Studies				
	Controls/ Cases		**OR ***	95% CI		Controls/ Cases		**OR ***	95% CI		Controls/ Cases		**OR ***	95% CI	
Nickel compounds															
Unexposed	978	770				804	654				1782	1424			
Any level of exposure	85	79	**1.35**	1.0	1.9	87	74	**1.18**	0.8	1.7	172	153	**1.27**	1.1	1.7
Non-substantial level	73	70	**1.48**	1.0	2.2	83	64	**1.03**	0.7	1.6	156	134	**1.25**	0.9	1.6
Substantial level	12	9	**0.80**	0.3	2.0	4	10	**4.96**	1.3	19.	16	19	**1.46**	0.7	3.1
Chromium VI compounds															
Unexposed	950	758				820	681				1770	1439			
Any level of exposure	101	90	**1.22**	0.9	1.7	64	46	**0.93**	0.6	1.5	165	136	**1.12**	0.9	1.5
Non-substantial level	84	79	**1.33**	0.9	1.9	55	34	**0.81**	0.5	1.4	139	113	**1.11**	0.8	1.5
Substantial level	17	11	**0.75**	0.3	1.8	9	12	**1.74**	0.6	5.2	26	24	**1.06**	0.5	2.0
Cadmium compounds															
Unexposed	1053	845				848	694				1901	1539			
Any level of exposure	10	11	**1.54**	0.6	3.9	20	23	**1.56**	0.7	3.3	37	34	**1.54**	0.9	2.7
Non-substantial level	7	8	**1.53**	0.5	4.5	25	22	**0.98**	0.5	1.9	32	30	**1.09**	0.6	1.9
Substantial level	3	3	**1.57**	0.3	9.7	3	6	**5.67**	0.7	17.	6	9	**2.87**	0.7	11.

*Adjusted for age, respondent status, years of education, and smoking (time since quitting, ever smoked, ln(cigarette-years)), as well as study for pooled results. Low reliability estimates are excluded.

Table 5. Odds ratios between lung cancer and occupational exposure to nickel, chromium VI, or cadmium by duration of exposure in a pooled analysis of two Montreal-based studies

Exposure duration (years)	Controls/ Cases		OR*	95% CI	
Nickel					
0	1782	1424			
< 5	45	29	**0.92**	0.5	1.6
5 - 20	54	45	**1.24**	0.8	2.0
> 20	74	79	**1.56**	1.1	2.3
Chromium VI					
0	1770	1439			
< 5	34	32	**1.28**	0.7	2.2
5 - 20	59	48	**1.06**	0.7	1.7
> 20	72	56	**1.11**	0.7	1.6
Cadmium					
0	1901	1539			
< 5	17	15	**0.96**	0.4	2.1
5 - 20	21	16	**0.77**	0.4	1.7
> 20	26	25	**1.44**	0.7	2.8

* Adjusted for age, proxy, respondent status, years of education, smoking, and study. Pooled results presented reflect trends for both individual studies.

*Table 6.*Odds ratios between lung cancer and exposure to nickel, cadmium, or chromium VI, stratified by smoking history †

	Non-smokers **			**Smokers**			**P (interaction)**
	Ctls / Cases	**OR***	95%CI	Ctls / Cases	**OR***	95%CI	
Nickel							
Unexposed	605 / 74			1172 / 1348			
Exposed	51 / 15	**2.49**	1.3 – 4.7	121 / 138	**1.11**	0.9 – 1.4	0.017
Chromium VI							
Unexposed	606 / 74			1159 / 1363			
Exposed	46 / 12	**2.39**	1.2 – 4.8	119 / 124	**0.97**	0.7 – 1.3	0.029
Cadmium							
Unexposed	82 / 647			1455 / 1250			
Exposed	5 / 9	**4.67**	1.5 – 14.3	29 / 21	**1.36**	0.8 – 2.4	0.046

† Results are presented for pooled data, and reflect trends observed in both individual studies.

** Non-smokers are those who have never smoked or quit over 20 years prior to study participation.

* Adjusted for age, respondent status, and socioeconomic position (years of education) as well as study for pooled results.

References

1. Iarc. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 49. Chromium, nickel and welding. Lyon: IARC (International Agency for Research on Cancer); 1990.

2. Iarc. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 58. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. Lyon: IARC (International Agency for Research on Cancer); 1993.

3. Stavrides JC. Lung carcinogenesis: pivotal role of metals in tobacco smoke. Free Radical Biology & Medicine. 2006 Oct 1;41(7):1017-30.

4. Stohs SJ, Bagchi D, Bagchi M. Toxicity of trace elements in tobacco smoke. Inhalation Toxicology. 1997;9(9):867-90.

5. Gérin M, Siemiatycki J, Kemper H, Bégin D. Obtaining occupational exposure histories in epidemiologic case-control studies. Journal of Occupational Medicine. 1985;27(6):420-6.

6. Siemiatycki J, Wacholder S, Richardson L, Dewar R, Gérin M. Discovering carcinogens in the occupational environment: methods of data collection and analysis of a large case-referent monitoring system. Scandinavian Journal of Work, Environment & Health. 1987;13:486-92.

7. Ramanakumar AV, Parent ME, Menzies D, Siemiatycki J. Risk of lung cancer following nonmalignant respiratory conditions: Evidence from two case-control studies in Montreal, Canada. Lung Cancer. 2006;53(1):5-12.

8. Ramanakumar AV, Parent ME, Siemiatycki J. Exposures in painting related occupations and risk of lung cancer: results from two case-control studies in Montreal. Occupational & Environmental Medicine.

9. Ramanakumar AV, Parent ME, Latreille B, Siemiatycki J. Risk of lung cancer following exposure to carbon black, titanium dioxide and talc: Results from two case-control studies in Montreal. International Journal of Cancer. 2008;122(1):183-9.

10. Siemiatycki J, Richardson L. Chapter 3. Case-control design and fieldwork methods. Risk Factors for Cancer in the Workplace. Boca Raton: CRC Press; 1991. p. 29-44.

11. Siemiatycki J, Nadon L, Lakhani R, Bégin D, Gérin M. Chapter 4. Exposure assessment. Risk Factors for Cancer in the Workplace. Boca Raton: CRC Press; 1991. p. 45-114.

12. Parent ME, Rousseau MC, Boffetta P, Cohen A, Siemiatycki J. Exposure to diesel and gasoline engine emissions and the risk of lung cancer. American Journal of Epidemiology. 2007;165(1):53-62.

13. Department of M, Immigration. Canadian Classification and Dictionary of Occupations 1971. Vol 1. Classification and Definitions. Ottawa: Information Canada; 1974.

14. Gérin M, Siemiatycki J. The occupational questionnaire in retrospective epidemiologic studies: recent approaches in community-based studies. Applied Occupational and Environmental Hygiene. 1991;6(6):495-501.

15. Breslow NE, Day NE. Statistical Methods in Cancer Research Volume 1 - The analysis of case-control studies. Lyon: International Agency for Research on Cancer; 1980.

16. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. American Journal of Epidemiology. 1989;129(1):125-37.

17. Leffondré K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: A comparison of different approaches. American Journal of Epidemiology. 2002;156(9):813-23.

18. Rachet B, Siemiatycki J, Abrahamowicz M, Leffondre K. A flexible modeling approach to estimating the component effects of smoking behavior on lung cancer. Journal of Clinical Epidemiology. 2004;57(10):1076-85.

19. Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. International Archives of Occupational & Environmental Health. 1998;71(4):245-50.

20. Andersen A, Berge SR, Engeland A, Norseth T. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occupational & Environmental Medicine. 1996;53(10):708-13.

21. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Exposure to different forms of nickel and risk of lung cancer. American Journal of Epidemiology. 2002;156(12):1123-32.

22. Sorahan T, Williams SP. Mortality of workers at a nickel carbonyl refinery, 1958-2000. Occupational & Environmental Medicine. 2005;62(2):80-5.

23. Easton DF, Peto J, Morgan LG, Metcalfe LP, Usher V, Doll R. Respiratory cancer in Welsh nickel refiners: which nickel compounds are responsible? In: Nieboer E, Nriagu JO, editors. Nickel and Human Health: Current Perspectives. New York: Wiley; 1992. p. 621-8.

24. Doll R, Andersen A, Cooper WC, Cosmatos I, Cragle DL, Easton D, et al. Report of the International Committee on Nickel Carcinogenesis in Man. Scandinavian Journal of Work, Environment & Health. 1990;16(1):1-84.

25. Grimsrud TK, Peto J. Persisting risk of nickel related lung cancer and nasal cancer among Clydach refiners. Occupational & Environmental Medicine. 2006;63(5):365-6.

26. Seilkop SK, Oller AR. Respiratory cancer risks associated with low-level nickel exposure: an integrated assessment based on animal, epidemiological, and mechanistic data. Regulatory Toxicology & Pharmacology. 2003;37(2):173-90.

27. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? Epidemiology. 2005;16(2):146-54.

28. Gibb HJ, Lees PSJ, Pinsky PF, Rooney BC. Lung cancer among workers in chromium chemical production. American Journal of Industrial Medicine. 2000;38(2):115-26.

29. Crump C, Crump K, Hack E, Luippold R, Mundt K, Liebig E, et al. Dose-response and risk assessment of airborne hexavalent chromium and lung cancer mortality. Risk Analysis. 2003 Dec;23(6):1147-63.

30. Luippold RS, Mundt KA, Austin RP, Liebig E, Panko J, Crump C, et al. Lung cancer mortality among chromate production workers. Occupational & Environmental Medicine. 2003;60(6):451-7.

31. Matos EL, Vilensky M, Mirabelli D, Boffetta P. Occupational exposures and lung-cancer in Buenos Aires, Argentina. Journal of Occupational & Environmental Medicine. 2000;42(6):653-9.

32. Sorahan T, Lancashire RJ. Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States - an analysis with detailed job histories. Occupational & Environmental Medicine. 1997;54(3):194-201.

33. Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000. Occupational & Environmental Medicine. 2004;61(2):108-16.

34. Sorahan T. Mortality of workers at a plant manufacturing nickel alloys, 1958-2000. Occupational Medicine (Oxford). 2004;54(1):28-34.

35. Jones SR, Atkin P, Holroyd C, Lutman E, Batlle JVI, Wakeford R, et al. Lung cancer mortality at a UK tin smelter. Occupational Medicine (Oxford). 2007;57(4):238-45.

36. Jarup L, Bellander T, Hogstedt C, Spang G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occupational & Environmental Medicine. 1998;55(11):755-9.

37. Verougstraete V, Lison D, Hotz P. Cadmium, lung and prostate cancer: A systematic review of recent epidemiological data. Journal of Toxicology & Environmental Health Part B, Critical Reviews. 2003;6(3):227-55.

38. Smith AH, Pearce NE, Callas PW. Cancer case-control studies with other cancers as controls. International Journal of Epidemiology. 1988;17(2):298-306.

39. Bouyer J, Hemon D. Retrospective evaluation of occupational exposures in population-based case-control studies - general overview with special attention to job exposure matrices. International Journal of Epidemiology. 1993;22(Suppl. 2):S57-S64.

40. Tielemans E, Heederik D, Burdorf A, Vermeulen R, Veulemans H, Kromhout H, et al. Assessment of occupational exposures in a general population: comparison of different methods. Occupational & Environmental Medicine. 1999;56(3):145-51.

41. Kjuus H, Skjaerven R, Langard S, Lien JT, Aamodt T. A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information. Scandinavian Journal of Work, Environment & Health. 1986;12:193-202.

42. Stewart PA, Stewart WF, Heineman EF, Dosemeci M, Linet M, Inskip PD. A novel approacha to data collection in a case-control study of cancer and occupational exposures. International Journal of Epidemiology. 1996;25(4):744-52.

43. Siemiatycki J, Day NE, Fabry J, Cooper JA. Discovering carcinogens in the occupational environment: a novel epidemiologic approach. Journal of the National Cancer Institute. 1981;66(2):217-25.

44. Sorahan T, Lancashire R. Lung Cancer Findings from the NIOSH Study of United-States Cadmium Recovery Workers - A Cautionary Note. Occupational & Environmental Medicine. 1994;51(2):139-40.

45. Proctor DM, Otani JM, Finley BL, Paustenbach DJ, Bland JA, Speizer N, et al. Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. Journal of Toxicology and Environmental Health Part A. 2002 May 24;65(10):701-46.

46. Baumgarten M, Siemiatycki J, Gibbs GW. Validity of work histories obtained by interview for epidemiologic purposes. American Journal of Epidemiology. 1983;118(4):583-91.

47. Goldberg MS, Siemiatycki J, Gérin M. Inter-rater agreement in assessing occupational exposure in a case-control study. British Journal of Industrial Medicine. 1986;43:667-76.

48. Siemiatycki J, Fritschi L, Nadon L, Gerin M. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. American Journal of Industrial Medicine. 1997;31(3):280-6.

49. Grimsrud TK, Berge SR, Resmann F, Norseth T, Andersen A. Assessment of historical exposures in a nickel refinery in Norway. Scandinavian Journal of Work, Environment & Health. 2000;26(4):338-45.

50. Checkoway H, Pearce N, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. In: MacMahon B, editor. New York: Oxford University Press; 1989.

51. Schlesselman JJ. Case-control studies. New York: Oxford University Press; 1982.