Gold, Nickel and Copper Mining and Processing

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Ore mining occurs in all Canadian provinces and territories except Prince Edward Island. Ores include bauxite, copper, gold, iron, lead and zinc. Workers in metal mining and processing are exposed, not only to the metal of interest, but also to various other substances prevalent in the industry, such as diesel emissions, oil mists, blasting agents, silica, radon, and arsenic. This chapter examines cancer risk related to the mining of gold, nickel and copper.

The human carcinogenicity of nickel depends upon the species of nickel, its concentration and the route of exposure. Exposure to nickel or nickel compounds via routes other than inhalation has not been shown to increase cancer risk in humans. As such, cancer sites of concern include the lung, and the nasal sinus. Evidence comes from studies of nickel refinery and leaching, calcining, and sintering workers in the early half of the 20th century. There appears to be little or no detectable risk in most sectors of the nickel industry at current exposure levels. The general population risk from the extremely small concentrations detectable in ambient air are negligible. Nevertheless, animal carcinogenesis studies, studies of nickel carcinogenesis mechanisms, and epidemiological studies with quantitative exposure assessment of various nickel species would enhance our understanding of human health risks associated with nickel.

Definitive conclusions linking cancer to exposures in gold and copper mining and processing are not possible at this time. The available results appear to demand additional study of a variety of potential occupational and non-occupational risk factors.

Introduction

Mining occurs in all Canadian provinces and territories except Prince Edward Island. However, it is of most importance in Ontario, Quebec, British Columbia, and Saskatchewan. Canadian mines provide materials for the manufacturing, construction, automotive, and chemical industries, and produce important sources of energy. Canada is a leading mineral-producer and trader of coal, metals, structural materials, and non-metallic or industrial minerals. It is also an important world producer of zinc, uranium, potash, nickel, cadmium, selenium, indium, copper, aluminum, magnesium, titanium, molybdenum, gypsum, and gold.[1] With the recent expansion of diamond mining operations in the north, Canada is now the third largest producer in the world.[2]

This chapter summarizes the history of mining and the types of ores mined in Canada, reviews studies of cancer risk in nickel, gold, and copper mining and processing workers (excluding those in metal and alloy fabrication, engineered products, and metal finishing), and recommends further cancer-related research studies relevant to such workers. Studies of workers are discussed in chronological order of publication. The selection of mining and processing operations discussed is based on metals of high economic value and the prevalence of currently available health literature.[2] Uranium merits separate attention and is therefore excluded from this discussion, as are other types of metals, non-metals, structural materials and fuels. The reader is referred to the Radon section in the present volume for a treatise of the relevance of radiation on the development of cancer.

Canada's metal industry

History, production and economic value

Canada's first prospectors and miners, of First Nations origin, mined copper and shaped it into tools and artifacts. The next epoch in Canadian mining history is documented by evidence of iron mining in ninth century Viking settlements in Newfoundland. Then we skip to the early 1600s, when Samuel de Champlain, with aboriginal assistance, began searching for mineral occurrences. Iron and silver discoveries in Nova Scotia resulted in a few small mining operations subsequently operated by French and English settlers.[1] Farming, forestry, fishing and the fur industry dominated Canada's economic development until 1849 when the discovery of placer (i.e., deposits of sand or gravel that contain valuable metals)[3] gold in California revived mineral exploration interest.[1] The Cariboo gold rush in British Columbia (BC), one of the most colourful periods in Western Canadian history, contributed to the construction of the railway in Canada and launched modern day prospecting, mining and production. Subsequent milestones are summarized in Table 1.

Based on the value of output, the leading types of Canadian metal production in 2004 were nickel, gold, copper, iron ore, zinc, uranium, platinum group, silver, cobalt, and lead (Table 2).[2]

Environmental and health protection strategies

Member companies of The Mining Association of Canada (MAC) are committed to sustainable development that involves, not only a prosperous economy, but also the protection of human health and the natural environment. The MAC is implementing the Towards Sustainable Mining initiative which includes an external verification process and reporting of the industry's releases to the environment. Emission reductions achieved by 2004 compared to the base year 1988 are given in Table 3 for major substances commonly released.[5] The emissions list for the initiative includes arsenic, cadmium, chromium, cobalt, copper, cyanides, hydrogen sulphide, lead, mercury, nickel, silver and zinc, as well as for sulphur dioxide.

The MAC works with governments, local communities, and affected stakeholders to develop, implement, and evaluate the site-specific environmental management plans for each base metal smelter. It monitors levels of, and reports to the Federal-Provincial Task Force about emissions of

dioxins and furans from smelters that have chlorinated plastics and other chlorinated substances in their feeds. Companies also work with other industries, governments, First Nations communities, and citizens' groups to minimize adverse effects upon the environment.[5] The federal/provincial governments retain ultimate oversight.

Toxicology relevant to metal mining and processing

Workers in metal mining and processing are exposed, not only to the metal of interest, but also to various other substances prevalent in the industry and not specific to a particular ore. A wide variety of exposures could be investigated, including diesel emissions, oil mists, blasting agents, silica, radon, and arsenic. The toxicology of some of these will be discussed, followed by gold, nickel and copper. It is important to note that underground and surface exposures can vary substantially, and exposures can vary between underground locations.

Arsenic may be present as organic or inorganic compounds, but inorganic arsenic is the form of primary toxicological concern. Trivalent arsenicals are known human carcinogens.[6] Occupational arsenic exposure occurs mainly in workers involved in the processing of copper, gold, lead, and antimony ores. Other industries with potential occupational exposures include those using or producing arsenicals and arsenic-containing pesticides, burning arsenic-containing coal in power plants, and treating wood with arsenic preservatives.[7,8] Data concerning occupational exposure levels appear limited. The average total daily intake is approximately 90 µg.[7,9] with about 45 µg from food and 10 µg from drinking water.[7,10] Absorption of arsenic compounds can occur through the gastrointestinal tract, lungs and skin. Excretion occurs primarily through urination.[7] In smelter workers inhalation is the primary route of exposure. Whether inorganic arsenic is responsible for cancers other than skin or lung remains unresolved, although there have been reports of bladder, kidney, liver and colon cancers.[6,7,11-13] The possible mechanisms of genotoxicity and carcinogenicity have not been established.[6] Oxidative stress and glutathione depletion may be *in vitro* phenomena evoked by high doses.[6] Inhibition of DNA repair caused by direct enzyme inhibition or enzyme inhibition via arsenic-mediated generation of oxidation products might be more plausible.[6] It has been suggested that arsenic may act as a co-carcinogen or tumour promoter.[7] IARC (International Agency for Research on Cancer) classifies the group of arsenic and arsenic compounds as carcinogenic to humans.[14]

Silica comprises a substantial part of the Earth's crust, is among the most common minerals on Earth, and exists in crystalline (or 'free silica') and amorphous forms.[15] It is the crystalline form that is of concern.[15] Crystalline silica has three main polymorphs, all of the form $(SiO_2)n$, where n represents the various forms of the compound: quartz (the most common form), tridymite, and cristobalite.[15] High exposures are frequent for foundry workers, miners (but highly variable depending upon the silica content of the ore), quarrymen, and sandblasters. Low exposures are possible when mixed dusts are inhaled, but the general population is not exposed to levels sufficient to cause disease.[15] The current American Occupational Safety and Health Administration standard is based on respirable dust and the percent of silica in the dust (i.e., [10 mg/m^3]/[percent crystalline silica + 2]).[15] The concentration of particular metals and silica can vary between deposits of similar type and even within ore bodies in a deposit.

Inhaled silica can cause fibrosis and lung cancer in rats.[16] In mice, however, it causes only fibrosis, and in hamsters it causes neither.[17] Silica can cause progressive granulomatous and fibrotic lung disease in humans.[15] Studies of silica-exposed workers suggest an increased lung cancer risk, but are not consistent, nor are exposure-response analyses.[15] Steenland concluded that the weight of evidence suggests that silica is a human lung carcinogen.[15] Others have proposed that cristobalite and tridymite, which are more fibrogenic than quartz, may be even more carcinogenic.[15,18] Still others claim that the evidence for carcinogenicity of silica is weak in some occupational cohorts, and absent in others. Furthermore, rats can display a propensity for tumour development after exposure to various noncarcinogenic particles. For example, proteases and oxidants generated by inflammatory cells in silicotic and asbestotitic lesions may create a favourable environment for progression and metastases of lung cancer by facilitating tumour cell invasion. Thus the issue of silica carcinogenicity will only be resolved by well-controlled epidemiological studies.[19,20]

In 1997, IARC concluded that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources.[15,16]

Radon is a confirmed occupational carcinogen. It is an inert gas that occurs naturally as a decay product of radium-226 or uranium-238. Radium-226 and uranium-238 are present in most soils and rocks such that radon is continually generated in the Earth and some atoms could enter surrounding air and water. Radon has a half-life of 3.82 days and decays into a series of solid, short-lived radioisotopes referred to as radon daughters, radon progeny, or radon decay products. As inhaled radon progeny decay, they emit alpha particles that can damage the DNA of cells lining airways, and ultimately lung cancer may ensue. Occupational exposure to radon progeny is a concern for uranium and many other types of underground miners and workers. The radon section in the present volume provides further information. Radon progeny also represent an important cause of lung cancer for the general population. Radon and its decay products are invariably present in indoor environments and, in some extreme cases, may reach concentrations equivalent to those in mines.[21]

Cobalt and cobalt compounds are considered by the IARC to be possible human carcinogens.[14] Others have indicated that, although cobalt injection (versus ingestion or inhalation) has proven carcinogenic in mammals,[22-26] the few studies on humans have not demonstrated a significant number of cobalt-induced cancers.[22-24,27] Some recent data suggest that workers exposed to cobalt in the hard-metal industry may be at increased risk of lung cancer development;[22,28-33] however, the problem

TABLE 1
Nineteenth and twentieth century metal discoveries in Canada

Time period	Location	Metal[1]
Late 1800s	Klondike, Yukon gold rush	Placer gold, vein gold, silver, lead
	Sudbury basin, Ontario	Copper, nickel
Late 1890s	Rossland, southern BC	Gold
	Kimberley, southern BC	Lead, zinc, silver
1900s	Cobalt, northern Ontario	Silver
	Porcupine and Kirkland Lake, northern Ontario and Hemlo, northwestern Ontario	Gold
	Cadillac, Rouyn-Noranda, and Val d'Or, Quebec	Copper-gold[4]
	Flin Flon, northern Manitoba	Zinc, copper-nickel
	Yellowknife, southern NWT	Gold
	Great Bear Lake, northern NWT	Uranium, radium
	Gaspé, Québec	Copper
	Québec/Labrador	Iron
	Saskatchewan	Potash (1960), uranium (1970s and 1980s)
	Thompson, northern Manitoba	Copper-nickel
	Bathurst, New Brunswick	Copper-zinc-lead
	Québec and Newfoundland	Asbestos
	Western and eastern Canada	Coal

TABLE 2
Economic value of some Canadian metal production, 2004

Metal[2]	Estimated value (Canadian dollars in billions)
Nickel	$3.3
Gold	$2.2
Copper	$2.0
Iron ore	$1.4
Zinc	$1.0
Uranium	$0.6
Platinum group metals	$0.5
Silver	$0.4
Cobalt	$0.2
Lead	$0.1

TABLE 3
Reductions in environmental emissions achieved to 2004 (from 1988 levels)

Substance	Reduction[5]
Arsenic	57%
Copper	67%
Mercury	93%
Zinc	75%
Hydrogen sulphide	69%
Cadmium	79%
Lead	87%
Nickel	74%
Sulphur dioxide	59%

of co-exposure to other metals (e.g., nickel and arsenic) and small sample sizes[22,24] means there is still insufficient evidence regarding the occupational carcinogenicity of cobalt.

Asbestos is known to cause lung cancer and mesothelioma, and is sometimes present where other minerals are mined. Nonasbestiform amphibole minerals have not been associated with lung cancer, although they are suspect as a result of their similarity to asbestiform fibers.[34]

Sulphur dioxide (SO_2) is listed as unclassifiable regarding carcinogenicity.[14] SO_2 is an emission from mining processes associated with several types of mining. These exposures are experienced by residents in neighbouring communities (or even distant with a bigger smokestack), and not necessarily just by workers alone.

Gold is considered the most inert of metals, although it can be sensititizing.[35] Only rarely will the gradual dissolution at very minute levels by thiol-containing molecules yield gold complexes which can generate immunosuppressive and immunostimulative effects, depending upon the dose and duration of exposure.[35,36]

Nickel is ubiquitous and the respiratory system (particularly the nasal cavities and sinuses), the immune system, and the skin are important routes of nickel exposure.[37] The most acutely toxic nickel compound is nickel carbonyl which can result in headache, vertigo, nausea, vomiting, nephrotoxic effect, and severe pneumonia, possibly followed by pulmonary fibrosis.[37,38] Excesses of rhinitis, sinusitis, nasal septum perforations, and bronchial asthma have been observed in nickel refinery and nickel plating workers.[37,39] Nickel contact dermatitis is estimated to affect up to 10% of females and 1% of males in the general population, and has been observed frequently in workers exposed to soluble nickel compounds.[37,39] The IARC classifies nickel compounds as carcinogenic to humans, and metallic nickel as a possible human carcinogen.[38]

Oller et al. noted that the epidemiological literature up to 1990 assumed that all soluble and insoluble (i.e., oxidic, sulphidic, and metallic) nickel compounds had the same carcinogenic mechanism but with different potencies.[40] However, more recent *in vivo* and *in vitro* studies challenge this hypothesis and emphasize the importance of nickel speciation when evaluating the potential carcinogenicity of nickel compounds. Based on epidemiological and animal data, Oller et al. concluded that three examined nickel compounds had very different biological behaviours: (1) nickel subsulphide is likely a human carcinogen; (2) nickel sulphate hexahydrate, alone, is not likely a human carcinogen; however, soluble compounds can cause toxicity and cell proliferation, such that an enhancing effect on carcinogenicity of insoluble nickel compounds is possible and additional animal studies are required to test this effect; and (3) green nickel oxide may be carcinogenic to animals and humans only at doses high enough to induce chronic inflammation/cell proliferation; *in vitro*, concentrations of green nickel oxide must be tenfold higher than concentrations of nickel subsulphide to be equitoxic and to induce some of the same effects. Oller et al. integrated the relevant human and animal data into a general model of lung cancer development: (1) initiation of tumorgenesis from genetic or epigenetic events, as a result of direct or indirect actions of nickel compounds, and (2) promotion of cell proliferation elicited by certain nickel compounds. Snow reported that several studies have indicated that insoluble nickel compounds are strongly carcinogenic *in vitro* and *in vivo*,[41-45] whereas soluble nickel compounds are weaker carcinogens.

Nickel is a mutagen in some mammalian mutagenesis assays[40-42,46] but not in bacterial assays.[41,42,47] Nickel salts, alone, are not generally mutagenic, but act synergistically as co-mutagens. In mammalian cells, *in vitro* cellular transformation by nickel is linked with phagocytic uptake of insoluble nickel species.[41,43,48] Phagocytosis of nickel compounds is also associated with the release of oxygen species by pulmonary alveolar macrophages.[41,49] Snow indicated that the mechanisms of genotoxicity were unclear, likely multifaceted dependent on the mechanism of nickel uptake, and related to alterations in DNA-protein interactions.[41,47]

A Nordic group cited the carcinogenic potency of nickel and relative potency of different nickel compounds as the most important problem in nickel toxicology:

> Metallic nickel and several nickel compounds are carcinogenic in experimental animals after several different exposure regimes. There is a marked discrepancy in the carcinogenic potency of nickel compounds between animals and humans. In humans, soluble nickel salts are carcinogenic but in animals the less soluble nickel compounds seem to be most potent.[50]

Although copper toxicity can occur at elevated exposure levels, copper is an essential trace element for human health, as it is a co-factor for various oxidative enzymes.[51,52] Acute copper poisoning is infrequent in humans and largely the result of ingestion of copper salts.[2] The effects of copper salts in carcinogenesis have not received much attention.[53] In studies of copper and iron effects in Long-Evans Cinnamon rats, a high spontaneous incidence of kidney and liver cancer developed under certain conditions,[53-55] and abnormal copper metabolism was associated with hepatitis and liver cancer.[54] Poirier and Littlefield suggest that this strain of rats could serve as an excellent model to study possible common mechanisms of iron and copper actions, possibly by way of oxidative damage to DNA.[53]

For 2003 threshold limit values (TLVs) for substances associated with the metal mining industry, the reader is referred to the 2003 TLVs and biological exposure indices (BEIs), published by the American Conference of Governmental Industrial Hygienists.[56] The reader is also referred to this publication for other relevant exposures to chemical substances and physical agents that may be of interest. Table 4 presents some of the TLVs that may be relevant to this publication. The threshold limit value-time-weighted average (TLV-TWA) is the time-weighted average concentration for a conventional eight hour work day and 40 hour work week, to which it is thought that nearly all workers may be repeatedly exposed, day after day, without adverse effect.[56]

Gold

Background

Gold is a soft, malleable, lustrous, highly valued yellow metal that resists corrosion. It may represent possibly the most ancient as well as the most modern pharmaceutical therapies.[35] Since ancient times, gold has been used to make jewelry and decorations and as a cosmetic ingredient.[35] Given that the pure metal is soft, alloys are needed to make jewelry, utensils and coins.[57]

In Canada, gold is found in a variety of geological settings and ore deposit types. Most (60%) is found in gold-only bedrock sources, which are referred to as lode gold deposits. These are classified by depth or temperature (i.e., epithermal, mesothermal, or hypothermal), by associated mineral formations (i.e., quartz-carbonate vein or iron-formation-hosted strata-bound), or by the composition of the geological matrix (i.e., disseminated or replacement).[58]

In 2003, Canada was the world's eighth largest global gold producer, trailing South Africa, Australia, the United States, China, Peru, Russia and Indonesia. In 2004, gold

mining was carried out in all provinces and territories with the exception of Prince Edward Island. In addition, there were gold refineries in Quebec and Ontario. While higher before 1966, employment in Canada's gold mines peaked in 1989 at 12,631 workers and subsequently declined.[2]

Studies of gold workers

The South Dakotan Homestake Gold Mine has operated almost continuously since 1876.[59] The gold-bearing rock consists of metamorphosed siderite-quartz and cummingtonite-quartz schists. The gold ore, therefore, contains large quartz masses and many quartz veins, along with chlorite, amphibole, siderite and lesser amounts of sulfides (pyrrhotite, pyrite, arsenopyrite, galena, sphalerite and chalcopyrite), calcite, ankerite, biotite, garnet, fluorite, iron oxides and gypsum.[59,60] Gillam et al. examined mortality for a cohort of 440 Homestake South Dakotan underground gold miners who were employed in underground mining for at least 60 months and who had never mined elsewhere.[61] Follow-up extended from April 1960 to December 1973. Of 71 deaths observed (O), 52.9 were expected (E). The expected number of deaths is calculated by multiplying the person-years at risk in the cohort for each age group by the disease rate in the reference population for the corresponding age group and summing, which produces a non-integer result. Of the 15 cancer deaths observed, 9.7 were expected. Ten deaths were from lung cancer, with 2.7 expected ($p < 0.01$). The study, based on a limited number of events, was hampered by lack of occupational hygiene data and no consideration of potential confounders, prior exposures and other potential risk factors. The conclusions attributing the observed excess of malignant respiratory disease (8 O, 3.2 E, $p < 0.05$) to asbestos with a possible additive role from low exposure to free silica dust appear premature.

McDonald and colleagues continued work on the South Dakotan gold miner cohort.[62] This study included members of the Homestake Veterans Association (HVA), an organization into which workers with 21 years of service with the mine were automatically enrolled. The cohort included 1321 members enrolled between 1905 and the end of 1973. The study follow-up period was from 1937 to 1973. Overall, 660 deaths were observed. The investigators concluded that past exposures in the mine resulted in substantial excess mortality, primarily from silicosis, tuberculosis, and silico-tuberculosis. Mortality from respiratory cancer was not significantly increased (17 deaths O, 16.5 E) and mortality for neoplasms other than respiratory or gastrointestinal was lower than expected (37 O, 38.9 E). This study incorporated more detailed job histories than the previous study, including dust exposure categories based on cumulative work exposure. However, similar criticisms could be applied to this study as to the study by Gillam et al.

Brown et al. continued to study mortality in 3143 miners from the South Dakota gold miner cohort who had worked full time for at least one year between January 1, 1940 and December 31, 1964 (their employment could have begun before 1940).[59,63] Vital status of each worker was determined as of June 1, 1977. Eight hundred sixty-one deaths were observed, whereas 765 were expected. Total malignant neoplasms, respiratory, gastrointestinal and other malignant neoplasms were considered. There was no evidence of increased risk of lung cancer mortality with either increased dust exposure or increased latency. The authors concluded that there was no evidence that lung cancer incidence was elevated due to quartz, arsenic, amphibole particles, or radon. Once again, the absence of occupational hygiene data and lack of consideration of potential confounders and other potential risk factors weaken the results.

Mortality in 1974 Kalgoorlie, Western Australia gold miners, surveyed for respiratory symptoms in 1961 and 1962, was examined by Armstrong et al.[64] Follow-up extended to 1975, and 500 deaths were observed. Slightly increased respiratory cancer mortality among miners after 13 to 14 years of follow-up (59 O, 40.8 E, $p < 0.01$) was noted; however, no statistically significant dose-response relationship was observed between extent of underground experience and risk of death from respiratory cancer. The authors indicated that cigarette smoking might explain the excess, given a smoking prevalence of 66.3% and the strong association of lung cancer with cigarette use. Sporadic occupational data were used, including undated arsenic levels within the mine and a single radon daughter count observed at the end of the cohort study period. Using these limited data, the authors concluded that there was little evidence to support roles for radon, arsenic, and silica in lung cancer mortality.

Muller et al.[65] studied various causes of mortality between 1955 and 1977 in Ontario uranium miners, non-uranium miners, asbestos workers, and Eldorado uranium miners. Gold miners were non-uranium miners with at least 60 months of mining experience, of which 85% or more was in an Ontario gold mine. Workers with known asbestos exposure were excluded. Miners were further classified as full-time underground if they had spent more than 50% of the total time of their dust exposure in Ontario as underground gold miners. Among the 6972 full-time underground gold miners, cancers under study included digestive (stomach, intestine and rectum, other digestive), respiratory system (nose and nasal cavities etc., trachea, bronchus and lung, larynx, other respiratory), lymphatic and hematopoietic, bone, kidney, bladder, brain, prostate, skin, and all other cancers. One-sided p-values were used.

For stomach cancer, a standardized mortality ratio (SMR%) of 148 (60 O, 40.40 E, $p = .0023$) was observed. For trachea, bronchus and lung cancer, the SMR% was 145 (196 O, 134.90 E, $p < .0001$). A SMR% multiplies the SMR by 100 so that a value of 100 indicates the observed number of deaths equals that expected based on the reference area mortality rates. It is used as an alternative to the SMR for presenting results for some papers. Gold miners who worked part-time underground and part-time on the surface ($n = 570$) displayed no significantly increased cancer mortality. When examined by gold mining camp, cancer mortality was not significantly increased at Kirkland Lake, Sudbury, and mixed mining camps; however, cancer mortality was significantly increased for stomach at Timmins (SMR% 148, 35 O,

TABLE 4
Some 2003 threshold limit values (TLVs)[56]

Substance		TWA (time-weighted average) mg/m³ unless otherwise indicated
Arsenic & inorganic compounds		0.01
Asbestos, all forms		0.1 f/cc (fibres/cubic centimetre)[a]
Cobalt & inorganic compounds		0.02
Copper	Fumes	0.2
	Dusts & mists	1
Diesel	Fuel as total hydrocarbons	100[b]
Gold		Not important
Mineral oil	Poorly, mildly and highly refined	5[c]
Nickel	Elemental	1.5[c]
	Soluble inorganic compounds	0.1[c]
	Insoluble inorganic compounds	0.2[c]
	Carbonyl	0.05 ppm
	Nickel Subsulphide	0.1[c]
Silica, crystalline	Quartz	0.05[d]
	Cristobalite	0.05[d]
	Tridymite	0.05[d]
	Tripoli, as quartz	0.1[d]
Sulphur compounds	Sulphuric acid	0.2[e]
	Sulphur dioxide	2 ppm

[a] Respirable fibres: length > 5µm
[b] Vapour and aerosol
[c] Inhalable fraction
[d] Respirable fraction
[e] Thoracic fraction

23.72 E, p = .018) and for trachea, bronchus and lung at both Timmins (SMR% 154, 119 O, 77.36 E, p < .0001) and Fort William (SMR% 168, 19 O, 11.30 E, p = .022). Additional occupational hygiene data, information on potential confounders and other potential risk factors would have been useful. The inclusion of workers who continued to have regular chest x-ray examinations for miners while no longer actively mining may have introduced a self-selection bias, that may have diluted the results.

Muller et al. continued work on the cohort of Ontario gold miners and incorporated a nested case-control study.[66] They excluded men who had a volunteer miner's chest x-ray examination in or before 1955 but who were no longer working as miners. The period of follow-up was from 1955 to 1977, or until entry into the uranium mines, or until death, whichever occurred first. Men with known asbestos exposure or who had worked in a uranium mine outside Ontario or in a uranium processing plant were a separate excluded group. The two reference populations were the male population of Ontario matched by age group and calendar period, and a cohort of Ontario nickel/copper miners matched by age group. The cancers examined in the cohort study were similar to those in Muller et al.'s previous study.[65] One-sided p-values were calculated for the SMR%s. Using the Ontario male reference population, the SMR% for underground gold miners was 157 (p = .001, 54 O, 34.5 E, 95% Confidence Interval (CI) on the observed deaths 40.6-70.5) for stomach cancer and 140 (p < .0001, 165 O, 117.5 E, 95% CI on the observed deaths 140.8-192.2) for cancer of the trachea, bronchus and lung. SMR%s for all other cancer sites did not significantly exceed unity.

In Ontario, major ventilation and dust-suppression methods introduced in the mid-1940s substantially altered the occupational environment of underground miners. In Muller et al.'s second study, no association was found between risk of lung cancer mortality and years of underground exposure. However, risk from lung cancer death increased significantly with both the number of years worked and dust exposure in mines prior to 1945; exposures post-1945 contributed very little to risk. This difference led Muller, et al. to conclude that an occupational hypothesis for the observed increase in lung cancer risk was supported.

Using the nickel-copper miner reference population, the relative risk (%) for stomach cancer mortality among underground gold miners under the age of 70 was 238 (p = .001). The relative risk (%) for lung cancer in the same group was

190 ($p < .0001$), with the greatest excess risk in the 55 to 64 year age group. No significant differences were found between underground gold miners and nickel-copper miners for those over age 70. The higher risk of lung cancer mortality in gold miners was not explained by the age difference between the two populations.

The nested case-control study examined men who died from lung cancer matched randomly to a control of similar age who survived the case and who had mined gold but never uranium. Smoking histories were obtained from men, next of kin were traced, and hospital records were examined. Smoking information was difficult to obtain for gold miners born before 1938; therefore, only those with known smoking histories were included in the study (119 of 165 pairs). The final model included smoking history, months in underground gold mining, high dust, high dust/high arsenic, high dust/high sulphides, high dust/high fibres, and high dust/high silica. An increased risk of lung cancer mortality was found for workers with a greater number of months worked in high dust environments. Statistically significant increases in risk was also found for smoking ($p < .0001$), high dust exposure ($p = 0.04$), and high dust/high sulphides ($p = 0.04$). Smokers were seven times as likely as non-smokers to die from lung cancer. The increase in relative risk for high dust exposure prior to 1945 was 2.5 for the average 6.6 years in exposure for cases (3.1 per 100 months).

Aluminum dust used to be added to mines to protect miners from the harmful effects of more serious dusts such as silica. No association between aluminum dust and lung cancer mortality was found. X-ray rating, a standardized method of determining silica exposure among miners, was found to be significantly associated with lung cancer mortality; however, once smoking was controlled for, the association largely disappeared, indicating a possible additive role. Exposure to radon-222 was not related to lung cancer mortality; however, radon data were not derived from occupational readings, but rather were imputed from existing geological data. No causative agents or hypotheses were suggested by the authors for the observed excess stomach cancer deaths, although it must be noted that their emphasis was on lung cancer mortality.

Wyndham et al. examined mortality among 3971 white South African gold miners who had spent 85% of their service in gold mines.[67] The authors conducted both a cohort study of lung cancer mortality, with follow-up to 1978, and a case-control study. The cohort consisted of miners born between 1916 and 1930 who attended compulsory Medical Bureau of Occupational Diseases examinations in 1969, were alive on January 1, 1970, and who worked for mines registered with the national Chamber of Mines. All gold miners worked in the East, Central and West Rand mining areas. Five hundred thirty deaths were observed (450.6 E) for the 3956 individuals whose vital statistics could be determined. The resulting SMR% for all causes was 117.6. Much of this was attributed to excess lung cancer (SMR% 161.2, 95% CI 114.6-220.3, 39 O, 24.2 E), chronic respiratory disease (SMR% 165.6, 95% CI 108.2-242.7, 26 O, 15.7 E), and acute and chronic nephritis (SMR% 381.0, 95% CI 164.4-750.9, 8 O, 2.1 E).

In the case-control study, controls were randomly selected from miners who survived the cases and who were born in the same year.[67] For each lung cancer case, four controls were selected. Cumulative dust exposure and years of underground service were assessed in separate study components, incorporating the effect of amount smoked. Risk ratios (RR) for smoking were statistically significant and similar in both the dust exposure (RR 3.90 [per 20 cigarettes a day], 95% CI 1.85-8.21) and underground service components (RR 3.74, 95% CI 1.71-8.20). Dust exposure, while not significant, was nearly so; the authors found that the additional effect on relative risk was 1.77 per 10 particle-years ($p = 0.06$). Underground experience in years, however, was not significantly associated with lung cancer mortality.

Stomach cancer mortality among Ontario miners was examined by Kusiak et al. in a 1993 cohort study.[68] The cohort was composed of miners who had worked for at least 60 months in the mining industry, with at least two weeks of that time spent in Ontario mines after 1954 and who were exposed to dust. Miners who worked in an asbestos or uranium mine outside Ontario were excluded. Workers older than 74 were excluded because of underascertainment of deaths. Follow-up occurred from 1955 to 1986. Person-years at risk were calculated up to the time of death, age 75, or the end of the study period, whichever came first. Stomach cancer mortality was significantly elevated among gold miners both with and without uranium mining experience (Table 5).

Kusiak et al.'s study considered a number of suspected occupational agents, including chromium, diesel emissions, aluminum powder, arsenic and mineral fibre. Of these, only the time-weighted index of chromium exposure displayed an association with stomach cancer mortality. However, exposure values were not based on regularly collected hygiene data, but rather on sporadic samples. The authors postulated that two mechanisms affected stomach cancer mortality; the first occurs five to 19 years after the miner begins work in a gold mine. The authors stated that this may result from dust, which may contain chromium or an agent closely associated with it. The second mechanism affected only men born overseas, and may result in an excess of stomach cancer mortality after age 60. The authors suggested that smoking and alcohol consumption were not likely explanations for these excesses, although other lifestyle factors (notably diet) which may be associated with stomach cancer were not explored.

Simonato et al. examined mortality in a cohort of gold mine and refinery workers in France.[69] The cohort included males born in France or abroad, employed after 1954, with at least one year of employment in non-administrative jobs, and alive in 1972 ($n = 1330$). Follow-up extended from January 1972 to the end of August 1987. Mortality was notably below expected; 201 deaths were observed, while 248.40 were expected, yielding an SMR% of 81. A wide range of cancer sites was studied, with mortality again comparatively low. For all sites, the SMR% was 93, with 70 observed and 75.0 expected. Notably high rates of cancer mortality in the cohort were observed for rectal cancer (SMR%

280, 95% CI 113-577, 7 O, 2.50 E) and cancer of the trachea, bronchus and lung (SMR% 213, 95% CI 148-296, 35 O, 16.44 E). Workers who had ever been miners displayed higher mortality rates than non-miners for cancer of the trachea, bronchus and lung (SMR% 217, 95% CI 131-339, 19 O, 8.75 E) and Hodgkin's disease (SMR% 1176, 95% CI 142-4250, 2 O, 0.17 E). Refinery workers displayed elevated rates of mortality from rectal cancer (SMR% 483, 95% CI 194-995, 7 O, 1.45 E) and cancer of the trachea, bronchus and lung (SMR% 229, 95% CI 144-347, 22 O, 9.59 E). Duration of employment was slightly related to SMR% amongst miners, but not significantly. However, lung cancer SMR%s were related to period of employment, with a pooling of excess in those employed prior to 1955. The authors noted that there were major decreases in arsenic and dust contamination within the mine in 1954. They concluded that overall mortality risk from lung cancer was similar in magnitude for mine and refinery workers. While no smoking histories were obtained, the authors felt that the magnitude of risk excluded smoking as the sole explanation of lung cancer mortality excess, and suggested that increased cancer risk may be due to insoluble arsenic along with other exposures, such as radon and silica. The results of this study are somewhat tempered by the inability to determine the cause of death in 20.4% of the cohort. Small samples for some of the mortality sub-groups and lack of occupational exposure data, noted by the authors, also preclude definite conclusions. The study's contribution was also minimized by inadequate consideration of other potential risk factors.

Steenland, et al. performed a cohort and nested case-control analysis of lung cancer among South Dakotan gold miners.[34] This study used the cohort examined by Brown et al.,[63] and extended the follow-up to 1990. There were 1551 deaths among 3328 gold miners who worked underground in South Dakota for at least one year between 1940 and 1965. Cancer sites examined were digestive system, peritoneum, respiratory, larynx, lung, other respiratory, urinary, hematopoietic, lymphosarcoma/reticulosarcoma, Hodgkin's disease, leukemia/aleukemia, and other. The case-control study focussed on mortality for these sites, with silica and non-asbestiform amphibole minerals as the primary exposures of concern. Using United States mortality reference rates, the cohort analysis found no statistically significant SMRs. In comparison to local counties, however, rates of lung cancer were slightly elevated among all miners (SMR 1.25, 95% CI 1.03-1.51, 112 O) and for those with 30 or more years since first exposure (SMR 1.27, 95% CI 1.02-1.57, 88 O). With all South Dakota counties as the referent, lung cancer was again significantly elevated, with rates higher than those using local counties as the referent (SMR 1.59, 95% CI 1.31-1.92). Importantly, no positive exposure-response trend was found between lung cancer mortality and cumulative dust exposure, even when time since last employment was considered. Unlike other studies reviewed here, lung cancer mortality was not elevated by period of hire. However, a significant trend was observed for non-Hodgkin's lymphoma, with a significantly elevated SMR in the highest dust category (SMR 3.29, for 48,000+ dust days; dust day = one day with exposure of one million particles per cubic foot [mppcf] dust).

In the case-control portion of the study, Steenland et al. selected 115 lung cancer deaths.[34] Each case was matched to five controls, who were the same age as the case when death occurred, and whose cumulative exposures were truncated at the time of death of the case. Smoking data were historical, extracted from a 1960 survey of the miners. A non-significant trend in risk of death from lung cancer was observed in relation to the transformed log of estimated cumulative exposure, as well as to duration of estimated exposure. In the authors' view, exposure to non-asbestiform amphiboles or silica were not likely responsible for lung cancer excesses. In light of the discrepancies between their findings and other studies demonstrating a link between silica and lung cancer, the authors suggested that all silica may not be alike, or that studies demonstrating positive dose-responses to dust may be partially confounded by radon or arsenic exposures. Additional potential risk factors may have proved important as well, although they were not included in this study.

Gold miners in Kalgoorlie, Western Australia were studied using a proportional mortality analysis.[70] Follow-up was from 1961 to 1991. De Klerk et al. defined cases as all deaths from lung cancer (n = 98) and referents as all deaths from other causes (n = 744) excluding tuberculosis, other respiratory diseases, and cancers of the larynx and of unknown sites. Using logistic regression, risks for a range of variables were determined, including age, smoking, duration of underground employment, and presence of bronchitis at the time of survey. Only smoking displayed a strong effect on lung cancer risk. Forty years or more of underground experience also displayed some effect. The authors stressed that the results were preliminary, but did indicate a role for smoking on the relative risk of lung cancer, and a possible effect of duration of employment for those with 40 years or more of underground experience. Other potential risk factors were not considered.

Another cohort of South African gold miners in the East/Central/West Rand gold mines was examined by Reid and Sluis-Cremer.[71] The cohort included all white gold miners with birth dates between January, 1916 and December, 1930 who had attended compulsory Medical Bureau of Occupational Diseases examinations in 1969 (n = 4925). The miners' ages ranged from 39 to 54 at that time. Two thousand, eight hundred ninety-two miners survived to 1990. Mortality was higher than expected (2032 O, 1568 E), with lung cancer mortality significantly elevated (SMR% 139.8, 95% CI 117.8-164.6, $p < 0.0005$, 143 O, 102.32 E). A nested case-control study included subjects who had at least 85% of their service in gold mines, with at least 15% of that time spent underground. Two surviving controls for each case were matched for age. The case-control study examined a range of smoking and potential occupational risk factors. Smoking behaviour considered the amount smoked, and pipe and cigar smoking was converted to the equivalent cigarette consumption. Smoking habits were recorded for five year intervals from 1960 to 1990, and this average was recorded as a quantitative variable. Additionally,

blood pressure, Quetelet index, and mining service (including duration of underground service and duration of cumulative dust exposure) were included in the model. Smoking was the only significant risk factor (RR 2.41, 95% CI 1.4-4.2); 86% of the miners had smoked at some time, averaging 16 to 17 cigarettes per day. Radon daughter exposure, assessed by number of underground shifts as a surrogate, was not related to lung cancer risk. The authors proposed that more detailed data on exposure to radiation be part of future studies. Consideration of other potential risk factors would also be helpful.

De Klerk and Musk examined silica, silicosis, and lung cancer mortality in a cohort of 2297 Kalgoorlie, Western Australia gold miners.[72] This cohort was derived from surveys in 1961, 1974, and 1975, and follow-up was from 1961 to 1993. Two separate estimates of expected deaths were calculated. The first (SMR1) assumed that all workers lost to follow-up were alive on December 31, 1993 or at age 85, whichever was earlier. The second estimate (SMR2) was calculated by censoring subjects by the date that they were last known to be alive. Semiquantitative estimates of average and cumulative exposure to silica were derived for underground and surface exposure by combining assigned exposure scores and employment records. Additionally, a panel of experts estimated silica exposure for each occupation. At the time of study, 654 members of the cohort were still alive, 1386 had died and 257 could not be traced. All-cause mortality in the cohort was similar to an age, sex and period matched referent group of Western Australians, but lung cancer mortality was elevated (SMR1 1.26, 95% CI 1.07-1.59). Censoring the subjects at date last known alive increased the significance of the lung cancer ratio (SMR2 1.49, 95% CI 1.26-1.76).

In a lung cancer case-control study nested within this cohort,[72] cases were matched on age to controls who had survived the cases and had not developed lung cancer by the year of the cases' death. Subjects could be controls for more than one case, or controls prior to the onset of a disease which would qualify them for inclusion as a case. Smoking status at the time of survey, duration of underground and surface employment, cumulative silica exposure score, time-weighted average of the cumulative silica exposure divided by duration of employment, time since first exposure, and decade of first employment were considered as predictor variables. Additionally, a worksite variable was included to differentiate between underground employment only, underground and surface, and surface only. Effect of silicosis by different decades of diagnosis was also included. Mortality risk from lung cancer was very strongly elevated for smokers in this study. There was an apparent dose-response effect, with the lowest risk among those who smoked one to 14 cigarettes per day (RR 19.4, 95% CI 2.6-143.7), intermediate risk for smokers of 15 to 24 cigarettes per day (RR 23.0, 95% CI 3.2-167.6), and highest risk among those smoking 25 or more cigarettes per day (RR 32.5, 95% CI 4.4-241.2). Pipe and cigar smokers also showed higher rates of lung cancer mortality (RR 9.1, 95% CI 0.82-101.1). Silicosis (RR 1.59, 95% CI 1.10-2.28) and bronchitis (RR 1.60, 95% CI 1.09-2.33) were associated with slightly increased risk of death from lung cancer. The effect of a diagnosis of silicosis decayed slightly with time from diagnosis, but not significantly. The strongest effect was within one year of workers' compensation for silicosis. Among other considerations, only the log cumulative exposure to silica, in exposure-score years, was significantly related to lung cancer (RR 1.31, 95% CI 1.01-1.70); however, once silicosis was considered, the significance of this finding was eliminated (RR 1.20, 95% CI 0.92-1.56). The authors concluded that the excess in lung cancer mortality was restricted to miners who had received compensation for silicosis. This may indicate that localized immune suppression due to silicosis leads to increased lung cancer risk.

Hnizdo et al. studied a South African cohort of 2260 white gold miners with an expanded set of risk factors.[73] The 78 cases of lung cancer identified during follow-up between 1970 to 1986 were matched with 386 controls. They found the risk of lung cancer to be associated with pack years of cigarette consumption (RR 1.0 for < 6.5 pack years; 3.5, 95% CI 0.7-16.8 for 6.5-20 pack years; 5.7, 95% CI 1.3-25.8 for 21-30 pack years and 13.2, 95% CI 3.1-56.2 for

TABLE 5
Stomach cancer mortality in Ontario gold miners, 1955–1986

		95% CI			
Group	SMR%	Lower	Upper	O	E
Gold with uranium experience	152	125	185	104	68.2
Gold mining only	147	117	184	79	53.6
Gold only, born in North America	133	99	175	51	38.2
Gold only, born elsewhere	177	132	231	53	30.0
Within 20 years of first gold mine employment, born in North America	255	139	428	14	
Within 20 years of first gold mine employment, born elsewhere	270	140	472	12	
Gold miners under age 60	167	122	223	45	
Gold miners aged 60 to 74	143	109	184	59	

(adapted from Kusiak, 1993)[68]

> 30 pack years), cumulative dust exposure (RR 3.19, 95% CI:1.3-7.6 for the highest exposure group lagged 20 years), duration of underground mining (RR 3.36, 95% CI: 1.02-10.7 for > 20 years of work, lagged 20 years), and with silicosis (RR 2.45, 95% CI 1.2-5.2). Since their results could not be interpreted definitively in terms of causal association, the authors suggest possible interpretations for their findings: subjects with high dust exposure who develop silicosis are at increased risk of lung cancer, high levels of exposure to silica dust on its own is important in the pathogenesis of lung cancer and silicosis is coincidental, and high levels of silica dust exposure may be a surrogate for the exposure to radon daughters.

In 2003 McGlachan et. al. reported on cancer incidence using 12.8 million man-years of follow-up of black men who worked in South African Gold mines between 1964 and 1996.[74] Age-standardized incidence ratios and crude incidence rates for various cancers were calculated and compared by ten geographic territories. Although cancer of the respiratory system was the most numerous site of cancer in the cohort, some areas had significantly more cases while other areas had significantly less. For example, when compared to the total mining cohort, the age standardized incidence ratio (ASIR) for one territory (Cape) is 148 ($p < 0.01$) and 22 ($p < 0.01$) for another (Botswana). Commercial cigarettes are not sold or only recently introduced in the areas where respiratory cancers are lower. The authors concluded from this that rates of the major cancers in this cohort are surrogate measures of the same cancers in workers home territories and suggest that future research should focus on aetiological investigations in specific regions.

An in-depth report was produced in 2003 summarizing previously researched health risks of gold miners in different regions of the world.[75] Among numerous health problems, Eisler found evidence to support increased frequency of trachea, bronchus, lung, stomach, and liver cancer in gold miners. Existing health problems, such as HIV, and health behaviours such as smoking and alcohol consumption, were found to worsen mining related diseases. The author calls for continued medical examinations, monitoring and research of occupational hazards in the mining industry and to improve health behaviour educational programs outside the workplace.

Discussion

In August of 1996, the Occupational Disease Panel (ODP) in the Province of Ontario, in a report to the Workers' Compensation Board, concluded that there is a probable connection between work in Ontario gold mining and the occurrence of stomach cancer.[76] The panel noted that: (1) all analyses of the Ontario cohort and two of three international studies reported elevated rates of stomach cancer among gold miners; (2) differences in the cohort age structure before and after 1945 were considered responsible for the observation of highest SMRs in gold miners who commenced work in gold after 1945; (3) underascertainment problems due to missing social insurance numbers for those hired prior to 1945 were considered to account for approximately 10% of the observed differences between pre- and post-1945 SMRs; (4) the stomach cancer increase appeared five to 19 years after first gold mining and peaked between 10 and 19 years, after which there appeared to be a decline; (5) the Ontario studies consistently indicated that gold miners display significantly elevated mortality rates for stomach cancer, with SMR%s between 136 and 157, and a peak of 463 in those with the highest time-weighted index of exposure to chromium and who were less than 60 years old; (6) a dose-response relationship for time weighted duration of employment in gold mines for men under age 60 was not observed in two studies performed in Ontario that used duration of employment; (7) there appeared to be strong evidence that gold miners under age 60 are at greater risk for stomach cancer than are those over age 60; (8) place of birth was likely not an important factor in increased risk of stomach cancer mortality in Ontario gold miners; and (9) an increase in the intestinal type of stomach cancer in younger miners might explain the elevated rates of stomach cancer mortality within five to 19 years since first mining gold.

Dr. James Heller was recruited by the Ontario Mining Association to review the findings of the ODP report. He also solicited reviews from Dr. Pierre Band, Professor Jack Mandel, and Dr. Anthony Miller. In his submission Dr. Heller concluded that there was insufficient and contradictory evidence to support a finding of occupational stomach cancer risk in the Ontario gold mining industry.[77] He indicated that Ontario epidemiological studies had not addressed the likelihood of information bias. In the Ontario cohort, mortality from other digestive tract cancers was consistently below expectation. The higher observed stomach cancer mortality was more than offset by the low rates for these other cancers, leading to the suggestion by Dr. Heller that systematic misclassification of cancers among this cohort inflated the estimates of stomach cancer mortality. In addition, he emphasized that the Ontario studies did not fully address confounding that may have resulted from non-occupational factors such as place of birth, ethnicity, diet, smoking, alcohol consumption, social class, and socio-economic status. He suggested that place of birth for all Ontario miners, both gold and non-gold, might explain most of the observed excess stomach cancer cases. According to Heller, the general absence of dose-response relationships in the Ontario studies, necessary to establish causation, undermines the results. He also reported that exclusion of miners over age 75 and those without social insurance numbers from the most recent Ontario studies calls into question the inferences regarding occupational stomach cancer risk. The ODP excluded these miners because of low mortality compared to Ontario men, assuming that this was due to underascertainment of deaths. Heller stated that these decisions were inappropriate, that inclusion of the older men would have provided a different mortality picture for gold miners in Ontario, and that underascertainment of deaths in this age group would compromise the accuracy of death ascertainment for the entire cohort. Heller indicated that no evidence was presented to support the contention that the lack of social insurance numbers in the early years of the Ontario Mining Master File resulted in underestimation of occupational risk. He concluded that studies of Ontario gold miners failed to demonstrate a causal

association between work in gold mining and stomach cancer mortality, that there is an association between primary stomach cancer and place of birth in all Ontario miners, and that there may be associations with ethnicity, diet, smoking, alcohol consumption, social class, socio-economic status and other non-occupational factors. Heller recommended: (1) a study of the Mining Master File separated into cohorts by year of start of mining (e.g., pre-1945, 1945-1959, 1960-1975, after 1975) to evaluate the relationship within each cohort of stomach cancer risk and age, stratified by place of birth; (2) a separate occupational hygiene study to ascertain whether a new carcinogen really exists in Ontario gold mines; (3) additional study of the Mining Master File to determine the roles of occupational and non-occupational factors; and (4) the adoption of appropriate methods, including case-control studies and/or internal direct standardized comparisons, to account for potential confounding from non-work related factors.

Nickel

Background

Nickel-copper sulphide deposits occur towards the base of mafic and/or ultramafic intrusions or volcanic flows. Usually they are the simple sulphide, pyrrhotite-pentlandite-chalcopyrite, but subtypes vary significantly in their geological-tectonic settings, and in the geometric form and style of differentiation of the host magmatic bodies. Subtypes can occur as massive sulphides, sulphide-matrix breccias, or disseminations of sulphides. The magmatic hosts in most subtypes are intrusions, but in the komatiitic subtype most are volcanic flows. The ores of the various subtypes display some differences in composition, particularly in their nickle to copper (Ni:Cu) ratios.[78]

From the economic perspective, nickel is of primary interest; copper may be a co- or by-product, and platinum-group elements are usual by-products. Gold, silver, cobalt, sulphur, selenium, and tellerium may also be recovered since they are associated with sulphides.[78] Collectively, magmatic nickel-copper sulphide deposits have generated much of the world's past and current nickel production. However, although international reserves are large, they are exceeded by lateritic nickel deposits – the only other significant nickel source.

In 2003 Canada was the world's third leading nickel producer behind Russia and Australia. In 2004, nickel was mined in the provinces of Ontario, Manitoba and Quebec, with smelters in Ontario and Manitoba, and refineries in Ontario and Alberta.[2]

Sudbury, Ontario ores merit some comment as they represent the world's largest single source of nickel and are also an important economic source of copper.[79] Other than INCO's open pit Whistle Mine, all modern operations in Sudbury are underground.[80] The two major nickel mining companies in Ontario's Sudbury Basin are INCO Limited (now Vale Inco) and Falconbridge Limited (now Xstrata Nickel). The historical process of sintering associated with smelting (high-temperature oxidation) occurred at INCO's Copper Cliff and Coniston smelters in the Sudbury regions and in the leaching, calcining, and sintering (L,C & S) area at the Port Colborne, Ontario refinery which opened in 1918.[80,81] Sintering was also undertaken at Falconbridge Limited's smelter in the Sudbury area. The sintering processes were similar at Copper Cliff (which operated from 1948 to 1963), Port Colborne (the 1920s to 1958), Coniston (1914 to 1972), and Falconbridge (approximately 1939 to 1978).[80] INCO refines nickel and copper in Sudbury, nickel, cobalt, and precious metals in Port Colborne (nickel discontinued in 1984), nickel to high purity at Clydach (which has operated since 1902) in Wales,[82] and platinum group metals at Acton in London, England. Falconbridge primarily refines all ores (i.e., nickel, copper, and cobalt) at Kristiansand, Norway (which has operated since 1910).[80,83]

Nickel production has occurred in Sudbury for more than a century. In one period, open bed roasting formed part of the Sudbury smelting process, utilized timber for fuel, and released large quantities of sulphur dioxide pollution at ground level. By the late 1920s, this process was contained within factories, and emissions were vented through chimneys. In the late 1940s, the use of large magnetic separators improved pyrrhotite separation. In the 1960s, processing steps to remove some of the sulphur dioxide were introduced. In 1972, the newly constructed 387 metre INCO 'Superstack' smelter substantially improved the Sudbury area air quality and vegetation. Recent efforts have focussed on clean-up and ore processing technologies to enhance productivity and substantially reduce environmental impact.[80]

Studies of nickel workers

Elevated rates of lung and nasal cancers were observed in workers in nickel refining and preparation of nickel and copper salts from 1929 to 1938 at the Clydach refinery in South Wales.[82,84] This refinery began operation in 1902 and refined nickel by the nickel carbonyl process. The increased rates were attributed to dusty occupations, and/or drying and powdering of copper sulphate, and/or exposure to sulphuric acid which, prior to 1921, contained arsenic.[82] Later, risk was associated with process steps prior to nickel carbonyl formation. This risk was reported to have been eliminated by 1930.[85,86] By 1972, 967 men were being followed. The relative risk for nasal sinus cancer deaths increased sharply with increasing age at first exposure and remained fairly constant throughout the follow-up period; however for lung cancer, risk of death was independent of age at first exposure and declined sharply with increasing time since first employment.[87] For those who commenced work at Clydach before 1920, lung cancer mortality was between six and 11 times the national average.[86] This risk declined to 5.2, 2.5, and 1.5, for those who commenced work between 1920 and 1924, 1925 and 1929, and 1930 and 1944, respectively. Nasal cancer deaths, although rare, were between 300 and 700 times the national average for those who commenced work before 1920, about 100 times the national average for those who started work between 1920 and 1925 and absent thereafter. With follow-up to 1981, a large excess of lung cancer deaths was noted in men first exposed prior to 1925, a smaller but significant risk of about two for those first exposed between 1925 and 1929, and no subsequent excess.[88] During this time, a number of changes were made in the refinery; arsenical

impurities were removed and respirator pads were introduced in 1922; calciners were altered to reduce dust emission in 1924, and after 1932, the amount of copper in the raw material was reduced by about 90% and sulphur was almost completely removed. Further changes in process chemistry occurred after 1930, including the installation of new calciners between 1931 and 1936.[87]

A study of 2247 Kristiansand, Norway nickel refinery workers who commenced work prior to 1966, were alive on January 1 1953, had been employed for at least three years, and were followed from 1953 (or the middle of the year of first employment) to 1979, revealed an observed/expected ratio of 26.3 for cancer of the nose and nasal cavities (21 O, 0.8 E) and 3.7 for lung cancer (82 O, 22.0 E).[89] For both cancers, increased risk was observed for those employed in processing versus non-processing departments, using department of longest work to categorize workers. Both lung and nasal cancer risks were elevated for workers first employed before 1960. For both cancers, excess risk declined with each successive cohort, with nasal cancer risk much lower for those first employed near 1960 versus 1930.

A case-control study was conducted on the island of New Caledonia, where a nickel refinery is located.[90] Sixty-eight lung cancer cases (almost all of whom were dead) were identified from a chart review at a hospital, and 109 cancer-free controls were identified through the hospital's laboratory. After controlling for age, nickel occupation (RR 3.0, $p < 0.05$) and smoking (RR 22, $p < 0.05$) were significantly and independently associated with lung cancer.

The incidence of lung, pleural, laryngeal, and pharyngeal cancers was examined from 1978 to 1987 for New Caledonian men (240,082 person-years in the general population of which 87,957 were nickel workers).[91] No increased risk was detected in nickel workers as compared to the general male population. In a nested case-control study (80 lung cancer cases, 12 laryngeal cancers, 20 pharyngeal cancers, and 298 controls), none of the substances examined (i.e., coal dust, raw ore dust, calcined ore dust, total dust, tar, silica, asbestos, miscellaneous refinery gas, wood dust, mine road and site dust, mine diesel exhaust fumes, nickel silicate oxide, mixed or complex nickel oxides, nickel sulphide, metallic nickel, soluble nickel, total nickel, and nickeliferous dust), or any other occupational variable increased respiratory cancer risk; however, laryngeal cancer was related to level and duration of exposure to mining dust and engine exhaust fumes on mining sites, with statistically significant odds ratios from five to 5.4. Potential lack of study power was acknowledged. However, the authors concluded that the results did not support increased occupational risk of respiratory cancer in New Caledonian nickel workers. They speculated that this was due to less airborne nickel than in other studies, and that respiratory cancers in these workers was the likely result of exposure to mineral fibres in the geological strata, and consumption of tobacco and alcohol.

Enterline et al. studied mortality from 1948 to 1977 from a variety of causes and cancers (i.e., all malignant neoplasms, digestive, respiratory and laryngeal cancers, cancer of the trachea, bronchus and lung, and other residual malignant neoplasms) among a cohort of 1855 workers employed for at least a year in a West Virginian nickel refinery.[92] This refinery received nickel matte from Ontario smelters from 1922 to 1947. Also included in the study were 1354 men employed for at least a year between 1948 and 1959 in a nickel alloy production plant that operated in conjunction with the refinery. Other residual neoplasms constituted the only elevated cancer risk in workers hired before 1947 and employed for at least one year, and only after 20 years since the first exposure. This site was significantly elevated (SMR% 1643.9, $p < 0.05$, 2 O, 0.12 E), based on two cases of sinonasal cancer mortality in the cohort. No significant excess of lung cancer was observed. Cancer mortality rates were elevated, but not significantly, in refinery workers when compared to non-refinery employees. A slight, non-significant overall excess of lung, stomach, and prostate cancers with some evidence of a dose-response relationship was observed in all male nickel workers.

Average airborne nickel exposures were estimated by department using some historical and some recent data, and cumulative exposures were calculated for each worker. Inconsistent trends were observed when respiratory cancer mortality was related to exposure. Nickel exposures in this study were considered to be much lower than at Clydach, Port Colborne, or Copper Cliff.[93] The authors suggested the possibility of some causal relation between lung cancer and nickel, given some evidence of a dose-response relationship for lung cancer, even at lower nickel exposure levels.[92]

In another study, researchers examined employees working with various metallic alloys, including nickel, at a factory producing stainless and alloyed steel in France.[94] All workers in the cohort, both male ($n = 4288$) and female ($n = 609$), had at least one year of work experience between 1 January 1968 and 31 December 1991 with follow-up until 31 December 1992. A panel of experts also created a job-exposure matrix to estimate airborne exposure level measurements. A nested case-control study was also conducted to obtain data on job histories and smoking habits of 54 cases and 162 controls. Overall mortality was significantly lower than expected (SMR 0.91, 649 O, 716.9 E, 95% CI: 0.84-0.98), which was suggested to be due to a healthy worker effect. No cause of death, including lung cancer, was significantly increased for the entire cohort. Lung cancer mortality according to duration of employment, age at death, period of death, and periods of first employment did not reveal any trends. There was, however, a significant increase in lung cancer among employees with less than ten years of work experience (SMR 5.37, 95% CI: 1.71-12.53), which was not the case for employees working longer periods of time. The case-control portion of the study confirmed smoking as a major risk factor of lung cancer, comparing current smokers to never smokers (OR 17.0, 95% CI: 2.23-130, $p = 0.0007$). Nickel and/or chromium exposure did not produce any patterns of significant ORs, although

it is unknown which species of nickel the workers were exposed to. The author noted that the statistical power of this study was low due to small sample sizes and there was a lack of historical measurements which could have led to misclassification.

Finnish workers with nickel exposure were studied by Annila et al.[95] One thousand three hundred and thirty-nine men and 49 women working at the copper/nickel smelter and refinery between 1960-1985 in Harjavalta, Finland were included in the study with follow-up to the end of 1995. Workers were divided according to their exposure to nickel (employees working before 1960 would not have been exposed to nickel as there was no nickel smelting before that time), job site, and duration of employment. Overall rates of cancer incidence were at the expected levels for workers unexposed and exposed to nickel with the exception of cancer of the nose and sinuses in nickel exposed workers, which was higher than expected (SIR% 879, 2 O, 0.2 E, 95% CI: 106-3170). When examining a latency of 20 years, nickel exposed workers again had increased incidence of cancer of the nose and sinuses (SIR% 1590, 2 O, 0.1 E, 95% CI: 192-5730) and cancers of the lung and trachea (SIR% 212, 20 O, 9.4 E, 95% CI: 129-327). The only significant increase in cancer incidence in nickel exposed smelter workers was lung and trachea cancer with a 20 year latency (SIR% 200, 13 O, 6.5 E, 95% CI: 107-342). For nickel exposed refinery workers, stomach cancer (SIR% 498, 5 O, 1 E, 95% CI: 162-1160) and cancers of the nose and sinuses (SIR% 411, 2 O, 0.05 E, 95% CI: 497-1480) were elevated and when examining both 5 year and 20 year latency periods, all cancer sites, stomach, and nose and sinus cancer were elevated. The authors state that the refinery workers had exposures to soluble nickel sulfate while the smelter workers had only sparingly exposure to soluble nickel compounds which is the most likely explanation of the increased lung and nasal cancers in the refinery workers. They also suggest that the two groups would have similar smoking habits so tobacco exposure could be ruled out as the reason for the increase in the refinery workers.

In 2001, Egedahl et al. released the results of a study that was done on Sherritt International hydrometallurgical nickel refinery and fertilizer workers from Fort Saskatchewan, Alberta.[96] There were 1649 male workers included in the cohort who worked at least 12 months between 1954 and 1978 with follow-up until the end of 1995. Work done at this facility between 1954-1976 involved nickel-copper-cobalt sulfide ore mined from Manitoba. When compared to the Canadian population, this group of workers experienced a significantly lower that expected mortality (SMR% 66, 183 O, 275.6 E, 95% CI: 57-77) and when examining only the workers who had nickel exposure (nickel concentrate and metallic nickel) results were also significantly lower than the Canadian population (SMR% 57, 59 O, 103.2 E, 95% CI: 43-74). The only cause of death that was significantly increased for all workers was cancer of the pleura (SMR% 1135, 2 O, 0.1E, 95% CI: 127-4097) and no cause of death was significantly higher for workers with nickel exposure. The authors stated that the decrease in mortality could partially be explained by the healthy worker effect and the results from the nickel exposed workers are consistent with other studies which examined similar nickel exposures and workers.

Workers at Clydach nickel refinery were again studied for cancer incidence and mortality by Sorahan and Williams.[97] Detailed work histories of 812 men with at least five years of work experience between 1953-92 were examined by numerous variables, such as the predominant species of nickel exposure. For the entire cohort, there was no significant excess of mortality for all deaths, for any specific cause of death, or for cancer mortality. When period from commencing employment was analysed, there was a significant increase of lung cancer mortality in those workers who had the latest follow-up period of over 30 years (SMR% 186, 16 O, 8.6 E, 95% CI: 106-301). Nickel species exposure analysis revealed that employees in feed handling and nickel extraction (oxide/metalic nickel) had a significantly increased risk of lung cancer, although there was no significant heterogeneity in either set of SMRs and this SMR was not significantly different from the overall SMR for lung cancer of 139 ($p = 0.18$). The smoking status of 417 employees was known and it revealed a significant increase in lung cancer (SMR% 236, 16 O, 6.8 E, 95% CI: 135-383). From their analysis, the authors conclude that patterns of mortality are more likely due to various selection effects, socioeconomic gradients, regional effects, and lifestyle factors than occupational exposures.

A number of studies have been published by of group of researchers working out of the Cancer Registry of Norway and Falconbridge Nikkelverk.[98-100] Grimsrud et. al.[98] conducted a nested case-control study from within a cohort of 5389 men who had been employed at the nickel refinery in Kristiansand, Norway for at least one year between 1910 and 1994. Two hundred and twenty-seven lung cancer cases were identified by the Cancer Registry of Norway between 1952 and 1995 (13 did not participate in the interview) and 525 controls were age-matched from the cohort. The dose-related associations between lung cancer and cumulative exposure to different forms of nickel (soluble, sulfuric, metallic, and oxidic) were examined using a job-exposure matrix. Soluble nickel was found to have the strongest effect, with an odds ratio of 3.8 (95% CI: 1.6-9.0) for the highest cumulative exposure category. When they plotted the log risk by median exposure, it suggested a curvilinear relation for soluble nickel. When adjusting for smoking and water-soluble nickel exposure, other forms of nickel did not produce significant effects or relationships, however, there were elevated odds ratios for sulfidic and oxidic nickel. The authors noted that there was potential for misclassification of the exposure data prior to 1973 as there was no personal monitoring at that point.

Lung cancer risk by duration of employment and by exposure to different nickel forms was again reported by Grimsrud et al. in 2003.[99] A cohort of 5297 men who worked at the Norwegian nickel refinery between 1910 and 1989 and were alive and residing in Norway after January 1953 were included in the study. Work histories were examined for employment in selected groups of departments and for the duration

of work. A job-exposure matrix was used to assign nickel exposures. Overall lung cancer incidence during the period from 1952-2000 was higher than expected (SIR% 260, 267 O, 104 E, 95% CI:230-290), with those employed between 1910 and 1929 having the highest SIR of 480 (17 0, 3.5 E, 95% CI: 280-760). Men who ever worked in either copper or nickel electrolysis departments had an increased SIR% of 350 and 400, workers from the roasting department had a SIR% of 340 (95% CI: 230-480), smelter workers had a SIR% of 270 (95% CI: 210-360), and maintenance workers had a SIR of 240 (95% CI: 180-300). Restricting analysis to 15 years or more of work experience in a department resulted in increased SIRs for lung cancer. Copper and nickel electrolysis workers with 15 years of work experience had an SIR% of 600 combined (95% CI: 420-830), while those with more than 15 years of smelter or roaster employment had a SIR% of 330 (95% CI: 180-560). Increasing cumulative exposure to water-soluble nickel was found to increase risk of lung cancer, as well as increasing cumulative exposure to total nickel.

Many studies have been performed on nickel workers employed at Sudbury in northeastern Ontario and at Port Colborne in southwestern Ontario. Our summary of this work emphasizes the findings for the underground component of the workforce, and where multiple analyses have been conducted we highlight the most recent results.

Shannon et al. examined multiple causes of death in a cohort 11,567 nickel workers who had worked at least six months at Falconbridge's Sudbury operations between 1950 and 1976.[101] The follow-up of the cohort extended from 1950 to 1984. Limited occupational hygiene data were used. Konimeter counts (measuring dust in particles per cubic centimetre) were used sporadically before 1960 and semi-annually from 1960 to 1984. Some gravimetric sampling data that measured total dust in milligrams per cubic metre were available from 1978 onwards. Some side-by-side sampling was conducted for comparison purposes. Regression was used to convert konimeter counts to gravimetric measures. During periods of limited or absent data, a best estimate was obtained by considering work practices, ventilation, and production. It was assumed that nickel species occurred in respirable dust in the same proportions as in the material being handled in the various work areas. Average nickel concentrations in the mines from 1933 to 1978 by department (worksite) were very low (0.02 mg/m^3); they averaged 0.03 to 0.04 mg/m^3 in the mills and 0.22 mg/m^3 in the sinter plant. Estimated levels of various nickel species and work history data were used to calculate cumulative exposures by multiplying the number of years at a given exposure level of a nickel compound by the estimated concentration. Changes in job or concentration were taken into account by summing the cumulative exposures for each worker in the different jobs.

The cancers studied included: lip, oral cavity and pharynx; respiratory system; nasal, etc; larynx; trachea, bronchus and lung; bone and articular cartilage; male genitourinary organs; prostate; kidney; lymphatic and hematopoietic; leukemia; and cancers of other sites. There were 1398 deaths in the cohort with 1289.3 expected (SMR% 108, 95% CI 103-114, $p < 0.001$). When accidental and violent deaths were excluded, there were 1053 observed deaths, with 1073.0 expected (SMR% 98, 95% CI 92-104). An SMR% of 128 was observed for both respiratory system cancers (95% CI 105-155, $p < 0.05$, 104 O, 81.3 E) and cancer of the trachea, bronchus and lung (95% CI 104-156, $p < 0.05$, 98 O, 76.6 E), but no consistent or statistically significant trend with increasing exposure to either all forms of nickel or to dust was observed. When mortality was considered by sector (i.e., mines, mill, smelter, service, and administration) and beyond 15 years from first exposure in that sector, SMR%s for all cancer deaths were 123 (95% CI 104-145, $p < 0.05$, 150 O, 121.7 E) in miners, and 55 in administration workers (95% CI 33-86, $p < 0.01$, 19 O, 34.5 E). Similarly, for lung cancer, the values were 153 (95% CI 118-196, $p < 0.001$, 63 O, 41.1 E) in miners and 9 (95% CI 1-49, $p < 0.01$, 1 O, 11.4 E) in administrative workers. Shannon et al. emphasized the existence of sample size limitations, the dearth of occupational hygiene data, and the absence of smoking histories. However, they indicated that the results by era of first mining and duration of mining, and their assessment of cumulative exposure to different nickel species did not appear consistent with an occupational etiology.

Roberts and his colleagues studied various types of mortality in a very large cohort of male nickel workers who had worked for INCO Ltd. in Ontario for at least six months (apart from sinter plant workers for whom any length of experience was considered acceptable) and who were known to be alive some time during the follow-up period of 1950 to 1984 ($n = 54,509$ of which 50,222 worked in Sudbury and 4287 in Port Colborne).[102,103] Non-production office workers were excluded. One-sided p values were used for statistical testing. There were 8387 deaths in the cohort (7382 deaths occurred and 7138.3 were expected in 50,222 Sudbury workers; 1005 deaths occurred and 1044.7 were expected in 4287 workers at Port Colborne). A strong healthy-worker effect was evident in terms of cancer mortality, with lower than expected mortality persisting for about 15 years post-hiring. For sinter plant workers time since first exposure was based on the earliest employment date in the sinter plant and for non-sinter plant workers this was calculated from the date of first hire.

The cohort of men with 15 or more years since first exposure was subdivided into men who did and did not work in one of three high nickel dust areas – the sinter plants at Copper Cliff and Coniston, and the LC&S department at Port Colborne.[103] At the Copper Cliff sinter plant: (1) workers displayed a lung cancer SMR% of 311 (95% CI 243-398, $p < 10^{-7}$, 63 O, 20.27 E); (2) workers with five or more years exposure in this area displayed an SMR% of 790 (95% CI 538-1114, $p < 0.001$, 32 O, 4.1 E); and (3) a steeply increasing SMR% with increasing duration of service was observed. The smaller Coniston sinter plant staff displayed a similar excess risk of lung cancer mortality (SMR% 298, 95% CI 127-590, $p = .0016$, 8 O, 2.68 E). In the LC&S department at Port Colborne: (1) lung cancer mortality was higher than expected (SMR% 241, 95% CI 191-303, $p < 10^{-7}$, 72 O, 29.93 E); and (2) workers with five or more years exposure in this area had an SMR% of 366 (95% CI 258-503, $p < 0.001$, 38 O, 10.4 E).[102]

Non-sinter plant workers in the Sudbury area who had worked 15 or more years since first exposure displayed a lung cancer SMR% of 112 (95% CI 103-123, p = .006, 485 O, 433.27 E); the authors considered this excess to be largely attributable to mining (SMR% 111, $p < 0.05$, 298 O, 268.9 E; at 25 or more years of exposure the figures were: 130, $p < 0.05$, 111 O, 85.6 E) or work in the copper refinery (SMR% 138, $p < 0.05$, 50 O, 36.3 E; at 25 or more years of exposure, the values were: 196, $p < 0.0001$, 26 O, 13.3 E). Additional analyses of the copper refinery cohort suggested that much of this excess risk arose from a small group of lead welders who repaired lead-lined electrolytic tanks and tankhouse cranemen, most of whom worked above the electrolytic tanks where fumes may concentrate.

Nasal cancer deaths were significantly increased for those with 15 or more years since first exposure at the Copper Cliff sinter plant (SMR% 3704, 95% CI 1380-8190, $p < 10^{-7}$, 6 O, 0.16 E) and in the LC&S department at Port Colborne (SMR% 7755, 95% CI 4600-11,800, $p < 10^{-7}$, 19 O, 0.25 E). No excess of laryngeal cancer deaths was observed in either the three high nickel dust areas or elsewhere. There was little evidence of excess kidney cancer mortality in areas with high nickel dust or in other parts of the process. Although a statistically significant excess of kidney cancer mortality was seen in non-sinter Sudbury workers with 15 years since first exposure and 15 to 24.9 years duration of exposure (SMR% 197, $p < 0.01$, 16 O, 8.13 E), there was no suggestion of increasing risk with duration of exposure in miners with 15 or more years since first exposure (SMR% 141, p = .036, 30 O, 21.2 E).

To summarize this study: (1) large excess risks of lung cancer were detected in the Copper Cliff and Coniston sinter plants and in the Port Colborne LC&S department; (2) the risk gradient of lung cancer with duration of employment was shallow for non-sinter workers. Most of the excess in lung cancer mortality in non-sinter workers appeared to be associated with mining. The authors suggested that this may have been hard-rock mining rather than nickel, as airborne concentrations of respirable nickel were estimated to be in the microgram range. Quartz in underground airborne dust was mentioned as one possible explanation. The excess lung cancer mortality in Port Colborne LC&S workers, coupled with a rate quite close to that anticipated for Ontario in non-LC&S workers, led Roberts et al. to attribute the excess to exposure in areas of high airborne nickel oxide/subsulphide; (3) nasal cancer risks were detected at the Copper Cliff sinter plant and the Port Colborne LC&S department. In this study, nasal cancers incorporated nasal, nasopharyngeal, and ethmoid bone cancers. The cases were scattered and occurred in men with no apparent employment in high nickel areas. However, the authors believed that slight excesses could have been due to unrecorded employment in high nickel oxide or nickel subsulphide areas. Also, the SMR for this cancer may have been underestimated as a result of an overestimation of the expected number of cases; because this is a rare cancer, the excess deaths at INCO would have increased Ontario's mortality rate appreciably, inflating the expected number of deaths; (4) neither lung cancer nor nasal cancer mortality appeared in excess in other parts of the process (except for lead welders and cranemen in the copper refinery); and (5) cancer of the larynx and kidney were not associated with INCO's operations. Finally, the occupational hygiene data in the study were sparse and influences of potential confounders were not considered.[103]

Julian and Muir studied cancer incidence in the combined INCO and Falconbridge Ontario nickel cohorts.[46] Follow-up was from 1964 to 1989. Workers had to have accumulated six months or more of non-office service and to have worked or been on active pension between January 1950 and December 1976 to have been included in the original cohort that was later updated to 1989. All workers with any sinter exposure were included. Because the Ontario Cancer Registry data commenced in 1964, the definition of the cohort was further updated to include anyone alive on January 1, 1964; thus deaths prior to 1964 were excluded. The information was presented for those aged 20 to 85 years of age. Of 61,964 men, 4199 had a cancer diagnosis. The cancers studied included: lung, larynx, nasal sinuses, oral, esophageal, colorectal, prostate, bladder, kidney, brain and central nervous system, lymphoma, and leukemia. Both one-sided tests of statistical significance and two-sided 95% confidence limits were provided. The results were usually displayed for those with 15 or more years since first exposure and are described here for such workers unless otherwise noted. Julian and Muir emphasized that: (1) exposure information was limited to department and job category and did not incorporate occupational hygiene measurements or information about non-occupational factors, and (2) the list of job categories was very complex, changed with time, and was not identical between the two companies.

A significantly elevated risk of laryngeal cancer was observed in millers with more than 25 years exposure (SIR% 400, 95% CI 147-871, 6 O, 1.5 E). There was also a trend of increasing risk with duration of exposure in underground miners, commencing in the 25 to 29 year duration category.

A significantly increased risk of lung cancer was detected in sinter workers; the SIR% for Copper Cliff sinter workers with 10 or more years since first exposure was 250 (95% CI 205-302); for Port Colborne LC&S workers with 15 or more years since first exposure the SIR% was 178 (95% CI 139-224); and for Falconbridge workers with 15 or more years since first exposure the SIR% was 141 (95% CI 103-189). A significantly increased risk of lung cancer was noted in underground miners with more than 25 years exposure. The significant increases were concentrated in underground miners at INCO who were initially exposed before and during the 1930s and at Falconbridge in underground miners first exposed between 1940 and 1949; the odd statistically significant result was observed in those first exposed during the 1960s or later, but there was no trend with increasing duration of exposure. For underground miners, the SIR% was 102 (95% CI 94-111) overall, 142 (95% CI 114-174) for those with 25 to 29 years duration of employment, 139 (95% CI 110-173) for those with 30 to 34 years duration of

employment, and 171 (95% CI 122-233) for those with 35 or more years duration of employment.

A sizeable risk of nasal and sinus cancer was detected in Copper Cliff sinter plant workers who were first exposed before 1952 and in Port Colborne's LC&S department. The overall nasal and sinus SIR% for the Copper Cliff sinter plant was 2004 (95% CI 1067-3427, 13 O, 0.649 E) and for Port Colborne's LC&S department was 2656 (95% CI 1518-4312, 16 O, 0.603 E). Statistically significant but less dramatic risks for nasal and sinus cancer were seen in INCO smelter workers (SIR% 217, 95% CI 116-371, 13 O, 5.99 E). Risk among transportation and maintenance subgroups was elevated, but not significantly (SIR% 213, 95% CI 92-420, 8 O, 3.75 E), although this may have resulted from inappropriate job classification for some workers.

Julian and Muir suggested that additional research was warranted to provide an explanation for several excess risks observed in exploratory analyses. An SIR% of 157 (95% CI 88-259, 15 O, 9.55 E) was observed for oral cancer in the Port Colborne LC&S department. The SIR% for esophageal cancer risk in the INCO Copper Cliff copper refinery was 263 (95% CI 136-460, 12 O, 4.56 E). INCO underground miners with 30 to 34 years duration of employment had an SIR% of 161 (95% CI 120-213, 50 O) for colorectal cancer. The broadly-defined group of hourly-rated workers and foremen in INCO mining transportation and maintenance (including electrical) displayed an unusual prostate cancer finding (SIR% 114, 95% CI 89-144, 70 O, 61.61 E); the value was 253 (95% CI 142-417, 15 O, 5.93 E) for those with 25 to 29 years of exposure, and 201 (95% CI 130-296, 25 O, 12.45 E) for those with at least 25 years of exposure. In the Falconbridge and Coniston sinter plants, an SIR% of 164 (95% CI 97-259, 18 O, 10.97 E) was detected for bladder cancer; workers with 10 or more years of exposure had an SIR% of 389 (95% CI 106-995, 4 O, 1.03 E). In the INCO copper refinery tankhouse, the SIR% for brain cancer was 366 (95% CI 158-721, 8 O, 2.19 E) for workers with 10 or more years since first exposure, and 472 (95% CI 173-1028, 6 O, 1.27 E) for those exposed for more than one year.

Julian and Muir indicated that some of the associations detected in their study were likely work-related (e.g., in workers with over 25 years of exposure, the fourfold risk of laryngeal cancer in millers, and laryngeal and lung cancer in underground miners). However, their criteria for determining work-relatedness were unclear. The authors acknowledged that, since historical exposure intensities of specific contaminants were not used, they could only speculate as to the specific causes of increased risks that they considered to be work-related. In their summary, they also highlighted the very high risk of nasal and sinus cancer in the Copper Cliff sinter plant for workers first exposed before 1952, and in Port Colborne's LC&S department. Some have expressed genuine concern regarding the combination of the INCO and Falconbridge cohorts, given the necessary assumptions made about the similarity of exposures and working conditions for similar job titles, departments, and time periods in the two companies.

Discussion

The International Committee on Nickel Carcinogenesis in Man, chaired by Sir Richard Doll, first met in 1985 to clarify the cancer risk associated with nickel. In 1989 the Committee prepared a report summarizing the results from ten nickel cohorts, of which the Ontario cohorts were the largest.[104]

The committee concluded that, given the large respiratory cancer excesses primarily detected in electrolysis workers in the Kristiansand refinery in Norway, there was strong evidence that exposure to **soluble nickel** was associated with increased respiratory cancer risk. For the electrolysis workers, estimated ambient concentrations of soluble nickel ranged from 1 to 5 mg Ni/m^3, with some concentrations exceeding 5 mg Ni/m^3, and small (< 1 mg Ni/m^3) airborne concentrations of oxidic and sulphidic nickel. Lung cancer risks in nickel refinery workers were strongly associated with increasing duration of exposure to soluble nickel; men with greater than ten years exposure displayed nearly three times the lung cancer risk of those without nickel exposure. At the Clydach refinery, the association between soluble nickel exposure and lung cancer risk in hydrometallurgy workers was weaker, but it was felt that soluble nickel at Clydach had some role in enhancing risk associated with exposure to other nickel compounds. Men with high levels of cumulative exposure to sulphidic nickel and soluble nickel had higher lung cancer risks than those exposed to similar amounts of sulphidic nickel but lower levels of soluble nickel. The amounts of insoluble material encountered in the Kristiansand electrolysis department was considered to have been seven times greater than at the Port Colborne refinery, although soluble nickel levels were probably similar. Results from men working at the Clydach and Kristiansand refineries provided evidence that soluble nickel exposure can lead to increased nasal cancer risk.

The role of **sulphidic nickel** exposure in lung and nasal cancer risk observed in the refineries was unclear, as high concentrations of sulphidic nickel were found in association with high levels of other nickel species, including oxidic and soluble nickel. Some of the highest lung and nasal cancer risks were observed in Copper Cliff sinter plant workers, Port Colborne LC& S workers, and Clydach linear calcining workers, where exposures to sulphidic nickel were extremely high, but oxidic nickel levels were also highest and soluble nickel may also have been present at high (> 5 mg Ni/m^3) concentrations.

The committee indicated that:

> Although the miners exposed to low levels of sulphidic nickel in mineral form (pentlandite and pyrrhotite) at the INCO and Falconbridge mines in Ontario had an increased lung cancer risk...evidence of increased lung cancer among other Canadian hardrock miners with no exposure to nickel suggests that the risks may not be attributable to nickel exposure.

Some evidence was presented to indicate that exposure to oxidic nickel might result in increased lung and nasal cancer risks. Kristiansand roasting, smelting, and calcining workers, thought to have been exposed mainly to oxidic nickel, displayed some evidence of increased lung cancer

risk, but the magnitude of the excess and association between duration of exposure and risk was not strong. There was some evidence that lung cancer risks in the Kristiansand roasting, smelting, and calcining workers decreased with reductions in atmospheric oxidic nickel levels related to refinery process changes. Men at Clydach with cumulative exposure to oxidic nickel of > 50 mg/m^3 displayed elevated lung cancer risks when compared to those with lower exposures; and those who worked in the Clydach copper plant, where oxidic nickel concentrations were over 10 mg/m^3, displayed strongly increased lung and nasal cancer risks. Whether this was due to oxidic or soluble nickel, or their combination was unclear. In addition, there was some evidence of an association between oxidic nickel exposure and nasal cancer risks. At Clydach, nasal cancer occurred in men with greater than 15 years exposure to high levels of oxidic nickel in furnace operations and less than one year in other areas with high levels of sulphidic or soluble nickel. At Kristiansand, five of seven nasal cancer cases occurred in long-term roasting, smelting, and calcining workers with highest (> 90th percentile) cumulative exposures to oxidic nickel. The data did not permit separate risk estimation for nickel-copper-oxide versus oxidic nickel forms that were copper-free.

Of the studies examined, only the Oak Ridge Gaseous Diffusion Plant workers were exposed to **metallic nickel** alone at low levels (< one mg Ni/m^3) and did not provide evidence of increased respiratory cancer risk. In the refinery cohorts, exposure to metallic nickel was mixed with exposure to other forms of nickel, but analyses of lung and nasal cancer mortality cross-classified by cumulative exposure to metallic nickel at Clydach and Kristiansand yielded no evidence of increased lung or nasal cancer risk with exposure to metallic nickel.

The International Committee observed that more than one form of nickel may result in the development of lung and nasal cancers. Most of the excess risk of respiratory cancer observed in refinery workers was attributed to exposure to a mixture of oxidic and sulphidic nickel at very high concentrations, although increased risk was also associated with exposure to large concentrations of oxidic nickel without sulphidic nickel. Soluble nickel exposure increased the risk of lung and nasal cancers and might enhance the risk associated with exposure to less soluble types of nickel. There was no evidence that metallic nickel was associated with increased lung and nasal cancer risk and no substantial evidence that occupational exposure to nickel or any of its compounds was likely to produce cancers other than lung and nasal cancers. No excesses of any type of cancer were observed in cohorts that did not display an excess of lung and nasal cancers. The preponderance of evidence for increased lung and nasal cancer risks in refinery workers exposed to large amounts of nickel species in processes used in the past was noted.

The Committee concluded that respiratory cancer risks are primarily related to exposure to soluble nickel at concentrations exceeding 1 mg Ni/m^3 and to exposure to less soluble forms at concentrations over 10 mg Ni/m^3. Examination of men exposed to a variety of nickel species provided no definitive evidence of increased cancer risk associated with exposure to metallic nickel, oxidic nickel or sulphidic nickel (i.e., insoluble nickel) at concentrations under 1 mg Ni/m^3. Soluble nickel concentrations close to 1 mg Ni/m^3 resulted in increased lung and possibly increased nasal cancer risks. Additional research was recommended to generate quantitative dose-specific estimates of risk.

The committee also concluded that, as excess risks were confined to high levels of exposure coupled with the absence of hazard from metallic nickel, the general population risk that would occur at extremely small concentrations in ambient air (under 1 µg Ni/m^3) would be minute, if any. The Committee recognized the value of obtaining additional information, such as animal carcinogenesis studies and studies of nickel carcinogenesis mechanisms to enhance our understanding of human health risks associated with nickel.

Two other groups have drawn conclusions from the evidence at hand. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals concluded that:

> Inhalation exposure to soluble nickel and nickel oxides/sulphides has caused nasal and pulmonary cancer in workers in nickel refineries. . . . In nickel refineries, exposure to approximately 0.1 mg/m^3 soluble nickel salts, and approximately 1 mg/m^3 nickel oxides/sulphides seem to involve cancer hazard, whereas for metallic nickel dust, there are no convincing data on carcinogenicity in humans. Exposure to nickel or nickel compounds via routes other than inhalation has not been shown to increase the cancer risk in humans.[50]

This group also recommended further research, in particular, epidemiological studies on population groups with defined qualitative and quantitative exposures, and basic research into the mechanisms of nickel carcinogenesis (using experimental systems of relevance for human carcinogenesis) at levels of nickel that human cells may have experienced during occupational exposure.

The World Health Organization concluded that although some, and possibly all, forms of nickel may be carcinogenic, there is little or no detectable risk in most sectors of the nickel industry at current exposure levels.[39] Some past processes were associated with very high lung and nasal cancer risks. Long-term exposure to soluble nickel at concentrations around 1 mg/m^3 may cause a marked increase in lung cancer risk, but the relative risk among workers exposed to average metallic nickel levels at about 0.5 mg/m^3 is about unity. The cancer risk at a particular exposure level may be higher for soluble nickel compounds than for metallic nickel and perhaps other forms. The IARC classifies nickel compounds as carcinogenic to humans, and metallic nickel as a possible human carcinogen.[38]

Copper

Background

The Sudbury nickel-copper ores and numerous volcanogenic massive sulphide deposits across the country represent important sources of Canadian copper. Some aspects

of nickel-copper-sulphide deposits have been addressed in the nickel section, above. Porphyry copper deposits (i.e., deposits of disseminated copper minerals in or around a sizeable body of intrusive rock)[3] represent the world's most important source of copper, but less than 50% of Canadian copper production and about 60% of copper reserves.[105] Skarn (i.e., metamorphic rocks surrounding an intrusive where it contacts a limestone or dolostone formation)[3] and vein (i.e., a fissure, fault or crack in a rock filled by minerals that have travelled up from a deep source) deposits also represent significant production sources.[105]

In 2003, Canada was ranked as the world's eighth leading producer of copper, trailing Chile, the United States, Indonesia, Peru, Australia, Russia and China. Copper was mined in New Brunswick, Quebec, Ontario, Manitoba, Saskatchewan and British Columbia, with primary smelters located in Quebec, Ontario and Manitoba, and with refineries in Quebec, Ontario and British Columbia.[2]

Studies of copper workers

Tokudone and Kuratsune examined cancer risk in 839 copper smelter workers who were part of a larger cohort of 2675 Japanese male smelter workers (both retirees and current workers employed for at least one year as of August 1, 1971).[106] Men who lived outside the study area and those with less than one year of service before the end of 1971 were excluded from the study. The copper smelter workers had belonged to the copper smelting section for at least one year, and some also had lead smelting experience. One hundred fifty-seven deaths occurred among the copper smelter workers. Lack of quantitative data on arsenic and other smelting exposures led to an approximate categorization of exposure, which was then used to subdivide this cohort into a number of sub-groups. Sub-groups were also defined by length of employment in the smelter. Comparison cohorts were ferro-nickel smelting workers (n = 268; six deaths), maintenance and transportation workers (n = 821; 108 deaths), copper or lead electrolysis or sulphuric acid production workers (n = 389; 22 deaths) and clerical workers (n = 358; 32 deaths).

Fifty-five deaths from malignant neoplasms were observed among the copper smelter workers, whereas 28.82 were expected (SMR% 191, p = .01). Excess mortality in this cohort was seen for large intestine cancer (except rectum) (SMR% 508, p = .05, 3 O, 0.59 E), liver (primary, secondary and unspecified) and biliary passage cancer (SMR% 337, p = .01, 11 O, 3.26 E), and cancer of the trachea, bronchus and lung (SMR% 1189, p = .01, 29 O, 2.44 E). Significantly elevated lung cancer SMR%s were also observed in all of the copper smelter sub-cohorts, with a distinct positive gradient for exposure level, length of employment and time period of exposure. Workers exposed for 15 years or more before 1949 had a much higher mortality risk than others (SMR% 2048, p = .01, 17 O, 0.83 E). Bearing in mind the small observed numbers in the sub-groups, mortality risk among pre-1949 workers was also found to be closely associated with exposure level, with risk ratios of 25, 28 and 14 in heavy, moderate and lightly exposed categories. The latency period for lung cancer was 37.6 years on average.

After World War II, copper production dropped, production methods changed, and the ore came from a source containing far less arsenic. In the post-1949 group, mortality was higher for workers with 15 or more years of exposure than for those with less experience, but did not display the same mortality gradient with exposure level. Of the 29 copper smelter workers who died from lung cancer, 28 began smelting work before 1949.

The authors concluded that arsenic compounds and sulphur dioxide were probably responsible for the excess lung cancer mortality in copper smelter workers, although they also noted that polycyclic aromatic hydrocarbons may have been involved. The liver and biliary passage cancers were mainly unspecified, and without diagnostic validity. Tokudone and Kuratsune also noted, with some surprise, the lack of skin cancer deaths, expected to be higher due to arsenic exposure. They postulated that the favourable prognosis for this cancer may have minimized mortality.

Ahlman et al. presented the lung cancer mortality of a male cohort which included a copper mine and a zinc mine in Finland.[107] An excess was reported for each mine, the total was statistically significant compared to Finnish men but not compared to the regional comparison (10 O, 4.3 E, p < 0.05 for Finnish reference; 6.9 E for North Karelia). The smoking prevalence among the miners was similar to surface workers. The authors concluded that the slight excess mortality from lung cancer could be explained by exposure to radon daughters in addition to the silica dust and diesel exhaust gases in the zinc mine.

Mortality among Chinese copper miners was examined by Chen et al.[108] The cohort included Chinese men who mined copper for at least one year between 1969 and 1988 (n = 7088). Emphasis in this study was place on esophageal, stomach, liver and lung cancers. The authors found significantly increased deaths from stomach cancer (SMR% 131, 95% CI 105-161, p < 0.05, 90 O, 68.82 E) and lung cancer (SMR% 147, 95% CI 112-189, p < 0.01, 60 O, 40.75 E). The increased lung cancer risk was confined to men who mined during the 1950s (SMR% 157, p < 0.05, 56 O, 35.75 E). Age at the start of exposure was found to have no effect on risk, but a dose-response relationship was evident in relation to duration of exposure, time since first exposure and degree of exposure determined by job type; SMR%s were 147 (p < 0.01, 60 O, 40.75E) for all miners, 169 (p < 0.01, 57 O, 33.80 E) for underground miners, and 193 (p < 0.01, 48 O, 24.85 E) for drilling miners. The authors indicated that the SMR% for lung cancer in copper miners might be underestimated because copper miners accounted for about 15% of the reference population. When the national male population was used as a reference, the SMR% for lung cancer in copper miners was 423 (p < 0.01, 60 O, 14.2 E). The authors considered the mining of copper to be a true occupational risk for lung cancer.

Changes in Chinese production methods, according to the authors, took place in the early 1960s. Prior to this, copper mining was highly labour-intensive. Dry-drilling was used extensively, generating large amounts of inhaled dust. After 1963, wet drilling

was introduced, and ventilation improved, reducing the amount of ambient dust. The authors noted that this may explain the lower lung cancer risk among those who mined copper after the 1950s.

Chen et al. considered radiation exposure an unlikely contributor to the excess lung cancer mortality in copper miners because radiation in the sites measured (1.29, standard deviation 0.55, x 10^{11} Curies/litre) was below accepted thresholds (3 x 10^{11} Curies/litre). Secondly, the increase in the SMR% for lung cancer was restricted mainly to drilling miners. Given the excess among drilling miners and miners employed in the 1950s who were exposed to more dust, the authors felt that attention should be concentrated on suspected human carcinogenic ore components. Components present in the ore under study, in decreasing quantity, were silica, iron, copper, manganese, arsenic, titanium, and sulphur. Arsenic concentrations were quite low (0.061%), leading the authors to exclude it from consideration as an important lung cancer carcinogen among these workers; silica and iron were not ruled out. The possible role of smoking among these miners was largely discounted, primarily because of the high prevalence of smoking in the male population. A possible interaction between smoking and other occupational risk factors could not be excluded, however, and the authors are considering this in a further case-control study.[108]

Viren and Silvers examined cohort data from various copper smelter cohorts in Washington State, Sweden and Montana to develop unit risk estimates for airborne arsenic exposure.[109] A pooled estimate was obtained by combining cumulative exposure to airborne arsenic and lung cancer mortality data from all of the studies examined. Unit risk was defined as the excess probability of developing lung cancer, given continuous atmospheric exposure to 1 µg/m^3 of arsenic over a lifetime. This value represents the best estimate for projecting excess lung cancer risk in the general population. The unit risk value for chronic lifetime exposure to airborne arsenic determined by Viren and Silvers was 1.43 x 10^{-3}. They emphasized the value of complete and adequate exposure assessment when developing quantitative estimates from epidemiological data. Detailed exposure reconstruction was considered valuable in resolving uncertainties in future analyses. They also advocated clarification of the association between arsenic levels measured in workers' urine and airborne arsenic, in order to evaluate the relationship between inorganic arsenic and cancer of other sites. The roles of other sources of arsenic exposure and possible confounders could be examined in future case-control studies.

Lubin et al. updated the analysis of 8014 white male workers employed at a Montana copper smelter from 1938 to 1989.[110] A significantly increased SMR was observed for respiratory cancer (SMR = 1.55, 95% CI 1.41-1.70). Analyses with an internal reference group revealed a significant, linear increase in the excess relative risk of respiratory cancer with increasing exposure to inhaled airborne arsenic. The estimate of the excess relative risk per mg/m^3-year was 0.21/(mg/m^3-year) (95% CI 0.10, 0.46).

In an update of an earlier study, Enterline et al. examined cancer and other types of mortality in a small cohort of 2802 men in Washington state who had worked in the copper smelter for a year or more between 1940 and 1964.[111] The copper smelter had operated from 1913 to 1984. The follow-up period was from 1941 to 1986 for cancers and from 1960 to 1986 for other causes of death. In total, there were 1583 deaths, 395 of which were from cancer. Arsenic exposure was estimated from departmental measurements of arsenic, mostly from departments where arsenic was thought to be problematic. These data were published in company annual reports from 1938 onwards. Measurements of urinary arsenic, offered to all workers, commenced in 1948. Arsenic air data were derived from spot and tape samples before 1971 and from personal samples from 1971 onwards. An exposure matrix of arsenic in air was developed by department and year from 1938 to 1984. Job histories for each worker were combined with arsenic data to calculate cumulative exposure (µg/m^3/yr) per worker. This exposure matrix included categories of < 750, 750-, 2000-, 4000-, 8000-, 20,000-, and 45,000-µg/m^3/yr.

Significant mortality excesses were found for malignant neoplasms (SMR% 143.1, $p < 0.01$, 395 O, 276.06 E), large intestine cancer (SMR% 161.8, $p < 0.01$, 38 O, 23.48 E), and collective respiratory system cancer (SMR% 209.7, $p < 0.01$, 188 O, 89.65 E). Mortality was also significantly increased for cancer of the trachea, bronchus and lung (SMR% 214.1, $p < 0.01$, 182 O, 85.03 E) and bone cancer (SMR% 455.6, $p < 0.05$, 5 O, 1.10 E). For workers with less than 20 years of exposure, significant mortality increases were observed for respiratory system cancers collectively (SMR% 176.0, $p < 0.05$, 17 O, 9.66 E) and for cancer of the trachea, bronchus and lung (SMR% 188.1, $p < 0.05$, 17 O, 9.04 E). Those with 20 years or more of exposure had mortality excesses for all malignant neoplasms collectively (SMR% 146.7, $p < 0.01$, 352 O, 239.95 E), large intestine cancer (SMR% 172.5, $p < 0.01$, 36 O, 20.87 E), respiratory cancers collectively (SMR% 213.8, $p < 0.01$, 171 O, 79.99 E), cancer of the trachea, bronchus and lung (SMR% 217.1, $p < 0.01$, 165 O, 76.99 E), and bone cancer (SMR% 610.2, $p < 0.01$, 5 O, 0.82 E).

Statistically significant excesses were noted for all but the lowest exposure category and a dose-response relationship was evident. The linear correlation between log dose and respiratory cancer SMR%s was significant ($p < 0.001$). The fitted regression equation between dose and SMR%s was expressed as: SMR% = 100 + 10.5 (cumulative exposure) x 0.279. The largest increments in risk were at the lower exposure levels. Separating the cohort into workers hired before and those hired after 1940, the plots were more irregular, partly due to smaller numbers, yet still displayed the trend seen for the entire cohort.

There did not appear to be any relation between cumulative exposure to arsenic in air and either colorectal or buccal cancer, and there was a weak relation for kidney and bone cancers. Observed numbers of cancers other than respiratory were rather small. Enterline, Day and Marsh concluded that their study provided some support for a relation between exposure to arsenic in air and kidney cancer, but little support for the other cancers, apart from lung cancer. They noted that the dose-response relation

between airborne arsenic and respiratory cancer was unusual. In the authors' estimation, air measurements may not be adequate measures of biological dose. They considered that the relation was not likely due to confounding by factors such as smoking, however this required additional investigation. In addition, they indicated that the bone cancer excess may be important, since arsenic is stored in bone.

Chen studied various forms of mortality among 7031 subjects who had worked at a copper mine in China for at least one year between January 1, 1969 and June 30, 1985. The follow-up period was from 1970 to 1992. There were 1121 deaths in the cohort and 799.81 were expected. All sites, esophogeal, stomach, liver and lung cancer were considered.[112] Statistically significant excesses of cancer mortality were observed for all cancer sites (SMR% 129, $p < 0.01$, 397 O, 307.75 E), stomach cancer (SMR% 141, $p < 0.01$, 114 O, 80.85 E), and lung cancer (SMR% 152, $p < 0.01$, 89 O, 58.55 E). Risk of death from cancer was highest in the 50 to 59 year age group, increased by year and appeared to be associated with younger age at first employment as a copper miner. The SMR%s also increased with duration of exposure and time since first exposure. Risk appeared lower for miners who commenced work after 1960, which the authors thought might be the result of lower levels of ore dust in the copper mines after 1963 when newer wet drilling methods were introduced. When job titles were considered, reflecting occupational and dust exposure levels ranging from heavy to light, the SMR% for all cancer sites was 129 for all miners (397 O, 307.75 E, $p < .05$), 137 (353 O, 257.66 E, $p < 0.05$) for all underground miners, and 138 (251 O, 181.88 E, $p < 0.05$) for drilling miners. Chen suggested that the risk of cancer was more common in underground and drilling miners, and that exposure to silica dust could be considered to have a role in cancer development in these miners. Chen also calculated life expectancy (for all cancers, circulatory system diseases, silicosis, and industrial injuries) by age group and discovered that, in younger age groups, there was a shorter life expectancy for copper miners versus local male residents. Those over age 60 displayed a slightly higher life expectancy. Chen suggested that this indicated that occupational hazards affected the life expectancy of the miners in earlier life.

In addition to studies of workers, other studies have examined health risk in people living near copper smelters. A Swedish case-control study of lung cancer deaths in men reported a relative risk of 2.0 for lung cancer in men who lived within about 20 km of a large copper smelter.[113] The deaths were recorded from 1961 to 1979 and smoking habits and occupational background were considered. The authors suggested that very substantial air emissions from the smelter (e.g., arsenic) may have played a role, but no firm conclusions were possible due to inadequate exposure data.

In Arizona, lung cancer mortality was examined in a case-control study ($n = 142$ cases with two matched controls per case) which examined residents who lived near copper smelters between 1979 and 1990.[114] Lifetime residential, occupational, and smoking histories were obtained. Estimated historical environmental exposures were linked to smelter emissions based on atmospheric diffusion modelling of measured sulphur dioxide concentrations. The study produced little evidence of a positive association between lung cancer and residential exposure to smelter emissions, although a statistically significant positive association between lung cancer and reported employment in copper mines and/or smelters was observed. Odds ratios were 1.73 ($p = .05$) for copper trades and smelter-specific jobs, and 2.24 ($p = .005$) for ever having worked in a copper mine. However, specific exposures and other factors could not be identified.

An American study examined acute and chronic respiratory disease between 1969 and 1975 in white women who lived near copper smelters in eight locations.[115] A statistically significant trend toward elevated acute respiratory mortality associated with increased ambient particulate levels in the presence of sulphur dioxide emissions was observed, but there was no evidence of elevated mortality from chronic respiratory diseases or respiratory tract cancer. This may have been due to confounding factors, which the authors proposed to examine in the future. Smoking was largely undetermined among the study population. The authors speculated that the absence of a respiratory cancer relationship may be because the effect of smelter emissions was small relative to other risk factors. Study limitations included a small population base and incomplete air monitoring data, such that exposures for components other than particulates and sulphur dioxide were limited.

Discussion

Conclusions linking cancer to exposures in copper mining and processing are not possible at this time other than through airborne exposure to arsenic and arsenic compounds which are classified as carcinogenic to humans as a group.[14]

Concluding comments

The clearest evidence for an association between cancer and work in metal mining and processing is in relation to nickel. Studies conducted in various locations have suggested increased lung and nasal cancer risks in early refinery workers, sinter workers and leaching, calcining, and sintering workers. Yet, it is still difficult to determine where best to direct preventive efforts. Definitive conclusions linking cancer to exposures in gold and copper mining and processing are not possible. The available results appear to demand additional study of a variety of potential occupational and non-occupational risk factors.

Occupational epidemiology teams are encouraged to use well designed case-control studies with strong occupational hygiene involvement. Occupational hygiene expertise is particularly valuable in situations where recorded hygiene data are sparse.[116,117] Occupational exposure assessment needs to progress to the use of appropriate quantitative measures based on representative prospective sampling (including the use of personal sampling data), more detailed study of specific work areas, and consideration of intensity and dose-response relationships. Investigative teams could benefit from thorough knowledge of mining and processing methods

from the engineering perspective, as well as how processes and exposures have changed over time.

A large number of studies have been reviewed. The strongest designs are those with adequate measures of exposure and those with suitable control populations or suitable control for smoking and other carcinogens.

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