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DISCUSSION

The main purpose of this study was to gain a better understanding of the human health risks associated with exposure to different forms of nickel. Although some progress is being made in understanding the mechanisms of nickel carcinogenesis, the clearest picture of nickel-related human health risks can be obtained from studies of human populations known to be exposed to these substances. There are, of course, problems in using these data to assess human health risks. The random variation inherent in the epidemiologic data from a single cohort of these people may be sufficient to prevent the detection of risks or to suggest the existence of risks that are not there. People exposed to different forms of nickel may also vary in other ways from the people they are compared with, particularly if these people live in widely different places, and therefore real differences in health can be missed or attributed to what is actually an irrelevant factor. One of the primary objectives of this study was to combine epidemiologic data from workers exposed to similar levels of nickel compounds in order to increase the ability to detect risk and to use the weight of evidence from the collection of the data to assess the risks associated with exposure to these compounds. Table 83 summarizes the collected data with respect to lung and nasal cancer mortality. Each of the four

Table 83. Summary of lung and nasal cancer mortality in the studied cohorts 15 or more years since first exposure. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval)

Cohort	Lung cancer				Nasal cancer			
	O	E	SMR	95 % CI	O	E	SMR	95 % CI
Mond/INCO (Clydach)[a]	166	42.30	393***	335—457	72	0.32	22513***	17615—28352
Falconbridge (Ontario)	98	76.63	128*	104—157	1	0.65	154	4—858
Hanna Nickel Mining Company	18	12.38	145	86—229	—	0.09	0	0—5953
Huntington Alloys, Inc								
Cohort 1 (Hired before 1947)	72	72.64	99	78—125	2	0.86	233	28—843
Cohort 2 (Hired in 1947 or later)	18	17.74	101	60—160	—	0.28	0	0—1376
INCO								
Sudbury sinter								
Copper Cliff	63	20.51	307***	238—396	6	0.17	3617***	1327—7885
Coniston	8	2.67	292**	126—576	—	0.02	0	0—28375
Sudbury nonsinter Port Colborne	493	444.68	111**	101—121	4	3.50	114	31—293
Leaching, calcining, sintering	72	30.04	239***	187—302	19	0.24	7776***	4681—12144
Non leaching, calcining, sintering	30	32.32	93	63—133	—	0.25	0	0—1472
Falconbridge (Kristiansand)	67	22.38	299***	233—382	3[b]	0.45	669*	138—1953
Oak Ridge Gaseous Diffusion Plant	9	15.10	60	27—113	—	0.18	0	0—2943
Outokumpu Oy (Finland)	1	..[c]	.	.	1	..[c]	.	.
Societé le Nickel (New Caledonia)	.	.	90[d]	.	—	.	.	.
Henry Wiggin Company	19	20.06	95	57—148	—	0.11	0	0—4816

[a] Workers hired before 1930.
[b] Four other nasal cancers occurred in men who are alive and have 15 or more years since first exposure.
[c] 129 men.
[d] Relative risk x 100 based on ratio of cumulative incidences of the nickel-exposed workers and the New Caledonia population.
* P<0.05, ** P<0.01, *** P<0.001.

general forms of nickel examined in this study and its associated respiratory cancer risks are discussed in the following text.

Soluble nickel

There was strong evidence, primarily based on the large excesses observed for the electrolysis workers of the Kristiansand, Norway, refinery (table 43), that exposure to soluble nickel was associated with increased respiratory cancer risk. The electrolysis department at Kristiansand had estimated ambient concentrations of soluble nickel in the 1—5 mg Ni/m³ range, with some concentrations in excess of 5 mg Ni/m³, and small (<1 mg Ni/m³) airborne concentrations of oxidic nickel and sulfidic nickel. The lung cancer risks were strongly associated with increasing duration of exposure to soluble nickel in these amounts at Kristiansand, and the men with more than 10 years' exposure had nearly three times the lung cancer risk of the men with no nickel exposure.

The increased lung cancer risks determined for the hydrometallurgy workers at Clydach (table 19) would appear to support the evidence of lung cancer induced by soluble nickel among the Kristiansand electrolysis workers, as the men in both operations were believed to have been exposed to similar concentrations of soluble nickel. However, the association between duration of exposure and lung cancer mortality among Clydach's hydrometallurgy workers who worked for less than a year in other areas in which men exhibited excess lung cancer risks was weaker than that of the Kristiansand workers, especially when exposures to other areas of the refinery and their associated nickel forms were considered. In particular, the cross-classification analysis for Clydach indicated that the men who were exposed to the highest cumulative levels of soluble nickel in the refinery but to relatively low levels of oxidic or metallic nickel elsewhere in the refinery gave no evidence of the increased risks found for the Kristiansand workers (table 33). The reason for the difference in lung cancer risk between these two groups of men, who were believed to have had similar soluble nickel exposures, may be the result of an overestimation of the soluble nickel exposure in the hydrometallurgy department. There were two activities in the hydrometallurgy department in which the men were exposed to differing levels of soluble nickel. In one, exposure was similar to that of Kristiansand, and in the other it was far less intense. The frequency with which the men were engaged in these activities could not be ascertained from their work histories. Consequently, the level of soluble nickel exposure experienced by the hydrometallurgy workers may well have been less than that of the electrolysis workers at Kristiansand.

Although the association between soluble nickel exposure and lung cancer risk among the hydrometallurgy workers at Clydach was weak, there was a good indication that soluble nickel at Clydach in some way played a role in accentuating risk associated with exposure to other nickel compounds. The copper plant workers, for example, were exposed to high levels of oxidic nickel in conjunction with average soluble nickel concentrations estimated to be in excess of 1 mg Ni/m^3, and the men in this department (with less than a year in other "high-risk" areas) experienced high lung and nasal cancer risks (table 23). This increase in risk appeared to be related to either soluble nickel or an interaction between soluble and oxidic nickel. Men with a combination of oxidic and soluble nickel exposures had lung (and nasal) cancer risks in excess of those of workers with a similar level of oxidic nickel, but a smaller amount of soluble nickel, exposure (tables 33 and 37). There was also some evidence of this interaction between soluble and oxidic nickel for lung cancer risks among the Kristiansand workers (figure 4). A similar interaction appeared to occur between soluble and sulfidic nickel at Clydach. The men with high levels of cumulative exposure to sulfidic nickel and soluble nickel had higher lung cancer risks than those exposed to similar amounts of sulfidic nickel but lower levels of soluble nickel (table 33).

Such an interaction may explain the absence of increased lung cancer risks in the main group of Port Colborne electrolysis workers (tables 55 and 57). Although the exposures at Port Colborne were estimated to have been somewhat lower than those at Kristiansand, the major difference in the lung and nasal cancer risks of the two facilities may be related to differences in the amount of insoluble nickel substances in these workplaces. The amount of insoluble material handled in the electrolysis department at Kristiansand was believed to have been seven times as great as that at Port Colborne, while the soluble nickel levels were likely to have been similar. Thus it is conceivable that the difference in cancer response was related to a reduced potential for an interaction between the soluble and insoluble nickel forms at Port Colborne. It is interesting to note that the men at Port Colborne who were engaged in activities such as pumping anode slimes and washing anode scrap that resulted in exposures to soluble and insoluble nickel that were similar to those at Kristiansand gave an indication of increased lung cancer risk (table 56). However, the evidence was weak due to the small number of men engaged in these activities.

The men working at Clydach and Kristiansand also gave evidence that soluble nickel exposure results in increased nasal cancer risk. Two of the seven nasal cancer cases at Kristiansand occurred in individuals who had worked exclusively, and for long periods of time, in electrolysis jobs which produce high levels of soluble nickel (table 47). Similarly, four of the nasal cancer cases at Clydach occurred in workers with long periods of service in the hydrometallurgy department and no time in other departments with high levels of other compounds (table 20). In addition, although no excess lung cancer risk was found for the INCO electrolysis workers in Ontario, there were two nasal cancers in individuals with more than 20 years of service in the electrolysis department and less than a year spent in sintering operations (table 55). There was also a nasal cancer in a man suspected of having exposure to soluble nickel in the Outokumpu refinery in Finland. All of these men with nasal cancer also had low-level (<1 mg Ni/m^3) average exposures to other nickel species such as oxidic and sulfidic nickel. Attribution of the nasal cancer risk to exposure to these forms of nickel instead of to the soluble nickel is difficult given the absence of increased nasal cancer risk among the men with similar low-level exposures to insoluble forms of nickel and much lower levels of soluble nickel exposure (eg, Sudbury nonsinter workers and Port Colborne nickel anode workers).

Sulfidic nickel

The role that sulfidic nickel exposure played in inducing the high lung cancer and nasal cancer risks found in the refineries was somewhat unclear, primarily because high concentrations of sulfidic nickel were found in association with high levels of other nickel species, including oxidic and soluble nickel. There was no doubt that some of the highest lung and nasal cancer risks occurred among the men with experience at the Copper Cliff sinter plant (table 51), the workers in the Port Colborne leaching, calcining, and sintering department (table 53), and those who worked in linear calcining at Clydach (table 27), where exposures to sulfidic nickel were extraordinarily high. However, oxidic nickel levels were also at their highest in these workplaces, and soluble nickel may also have been present at high (>5 mg Ni/m^3) concentrations.

On the basis of a comparison of the risks of men with similar levels of cumulative exposure to soluble, metallic, and oxidic nickel, the Clydach data gave evidence to suggest that sulfidic nickel was a lung and nasal cancer hazard (tables 34 and 38). There was, however, no corroborative evidence of a relationship between cumulative sulfidic nickel exposure and increased lung cancer risk among the men from Kristiansand (figure 3) or Huntington Alloys (tables 61 and 62). This result may be explained by lower sulfidic nickel concentrations in the Kristiansand and Huntington operations. For example, linear calcining and nickel plant cleaning were two jobs associated with high lung cancer risk at Clydach (tables 27 and 30). These areas had estimated average sulfidic nickel concentrations at Clydach of over 9 mg Ni/m^3, while the highest estimated concentrations were less than 2 mg Ni/m^3 at Kristiansand and less than 4 mg Ni/m^3 at Huntington. These differences in exposure intensity

were in part responsible for the lower levels of cumulative exposure at Kristiansand and Huntington and may therefore explain the absence of evidence for an association between sulfidic nickel exposure and lung cancer risk in these cohorts. An alternative explanation might be that there was an opportunity for exposure to both high levels of sulfidic nickel and soluble nickel in some high-risk areas at Clydach (eg, linear calcining) that did not occur at Kristiansand or Huntington.

The Clydach cohort also gave evidence, on the basis of a cross-classification analysis of cumulative exposure to different forms of nickel (table 38), that sulfidic nickel was a strong nasal cancer hazard. The evidence of the other cohorts was, however, unclear. For example, although some of the highest nasal cancer risks observed for the refinery workers occurred among the men with exposure in the Port Colborne leaching, calcining, and sintering department (table 53), the mixture of sulfidic, oxidic, and (possibly) soluble nickel exposures precludes identification of a risk related to a specific nickel form. No definitive relationship between sulfidic nickel exposure and nasal cancer risk was seen in any of the other cohorts either. Of the four nasal cancers occurring at Huntington, only one was in a man believed to have had sulfidic nickel exposure (table 64). Although five of the seven nasal cancer cases at Kristiansand had some of the highest cumulative sulfidic nickel exposures in the refinery, they also had the highest oxidic nickel concentrations. These oxidic nickel exposures were estimated to have exceeded the sulfidic exposures by a factor of 20.

Oxidic nickel

There was some evidence to suggest that exposure to oxidic nickel may result in increased lung and nasal cancer risks. The men in Kristiansand's roasting, smelting, and calcining department, who were believed to have been exposed primarily to oxidic nickel, showed some evidence of increased lung cancer risk although the magnitude of the excess and association between duration of exposure and risk was not strong (table 44). There was also some evidence that the lung cancer risks of the Kristiansand workers in roasting, smelting, and calcining diminished with reductions in the atmospheric oxidic nickel levels related to changes in refinery processes. In addition, the men at Clydach with cumulative exposure to oxidic nickel in excess of 50 (mg Ni/m^3) · years exhibited lung cancer risks that were elevated relative to those of men with lower cumulative exposures (table 35). The men who worked in the copper plant at Clydach, with its large concentrations of oxidic nickel (>10 mg/m^3), exhibited strongly increased lung and nasal cancer risks (table 23). However, it was uncertain whether this excess was related to oxidic nickel, soluble nickel, or the combination of these two species to which these men were exposed.

There was also some evidence of an association between oxidic nickel exposure and nasal cancer risks. At Clydach, nasal cancer occurred in men with more than 15 years' exposure to high levels of oxidic nickel in furnace operations and less than a year in other areas with high levels of sulfidic nickel or soluble nickel (table 29). Cumulative exposure analyses also showed a systematic (but statistically nonsignificant trend) in nasal cancer risk with increasing oxidic exposure at Clydach (table 39). Supportive evidence that oxidic nickel is a nasal cancer hazard was also found in the Kristiansand cohort. Five of the seven nasal cancer cases at Kristiansand occurred in the long-term roasting, smelting, and calcining workers with the highest (>90th percentile) cumulative exposures to oxidic nickel at the Kristiansand refinery (table 47). These men also received some of the highest sulfidic exposures in the refinery, but the level of sulfidic exposure was estimated to be comparable to that found in Clydach workplaces with a low nasal cancer risk, eg, in the "general" nickel plant (table 31) and rotary calciner (table 28).

From the available data it was not possible to separate definitively the risks associated with exposure to nickel-copper oxide from that of oxidic nickel forms free of copper. At Clydach and Kristiansand, where respiratory risks were high, the feed contained a large amount of copper. At the Hanna mining and smelting plant and at the Societé le Nickel's New Caledonia facility, the oxidic nickel contained no copper, and there was no evidence of increased respiratory cancer risk (tables 72 and 74). An argument could thus be made that it was the nickel-copper oxide that was largely responsible for the cancer risks seen at Clydach and Kristiansand, while nickel oxide was not a hazard. This possibility cannot be totally rejected, since the nickel oxides at Clydach and Kristiansand did indeed contain substantial amounts of copper while those at Hanna mining and in New Caledonia did not. However, the absence of evidence of respiratory cancer risks at Hanna and Societé le Nickel does not convincingly dismiss nickel oxide (as opposed to nickel-copper oxide) as a respiratory hazard because of the vast differences in the intensity of exposure and cumulative dose. Men in several workplaces at Clydach were exposed to 10—100 mg Ni/m^3 nickel-copper oxide, and those in Kristiansand's roasting, smelting, and calcining department were exposed to more than 8 mg Ni/m^3, while men at Hanna mining and Societé le Nickel were exposed to less than 1 mg Ni/m^3.

Metallic nickel

In the cohorts that were studied, only the workers of the Oak Ridge Gaseous Diffusion Plant were exposed to metallic nickel alone. These men, with low-level exposure to metallic nickel (concentrations of less than

1 mg Ni/m³), gave no evidence of increased respiratory cancer risks (tables 75 and 76).

In the refinery cohorts, exposure to metallic nickel occurred in combination with exposure to other forms of nickel. However, analyses of lung and nasal cancer mortality cross-classified by cumulative exposure to metallic nickel at Clydach and Kristiansand gave no evidence of a relationship between exposure to metallic nickel and increased lung cancer risk (table 32, figure 1, table 46, and figure 3) or increased nasal cancer risks (table 36 and figure 2).

Low-level nickel exposure

Using the epidemiologic data to provide dose-specific estimates of risk will require further research. The environmental measures used to provide dose-specific estimates of risk are for the most part unreliable, and the statistical power achievable for demonstrating an absence of risk is low, particularly in light of the nature of the nickel exposures experienced by those men studied in the present investigation. The men had either very intense exposures or comparatively modest ones. It was therefore difficult to estimate the levels of risk associated with exposures between these extremes. Nonetheless, the examination of groups of men exposed to a variety of nickel species gave no definitive evidence of increased cancer risk associated with exposure to metallic nickel, oxidic nickel, or sulfidic nickel at concentrations of less than 1 mg Ni/m³. There was, however, evidence that soluble nickel concentrations close to 1 mg Ni/m³ resulted in increased lung and possibly increased nasal cancer risks.

Evidence of an absence of respiratory cancer risks associated with oxidic nickel exposure at low concentrations (< 1 mg Ni/m³) came from both the Wiggin Alloy and Hanna mining cohorts. Men working at Wiggin Alloy showed no evidence of increased cancer risk (tables 78). The only excess in respiratory cancer for the men at Hanna mining was found for the short-term (< 1 year) workers (table 72). As there was no evidence of a relationship between risk and duration of exposure at Hanna mining, the excess observed for the short-term workers could be plausibly attributed to hazards unrelated to the specific occupation. The absence of evidence for an increased respiratory cancer risk among the men engaged in nonrefinery work at INCO in Ontario (table 58), with average exposure to less than 5 mg Ni/m³ of oxidic, metallic, or sulfidic nickel, supports this possibility. In addition, there was no evidence of excess respiratory cancer risk among the men who began work at Clydach after 1940, when many of the high-level exposures in high-risk areas were reduced considerably.

Although the miners exposed to low levels of sulfidic nickel in mineral form (pentlandite and pyrrhotite) at the INCO and Falconbridge mines in Ontario had an increased lung cancer risk (tables 59 and 69), evidence of increased lung cancer among other Canadian hard-rock miners with no exposure to nickel suggests that the risks may not be attributable to nickel exposure. The lack of evidence of increased risk among the men involved in open pit mining at the Societé le Nickel operation in New Caledonia supports the belief that the excess mortality in the Ontario mines was not attributable specifically to nickel. However, it should also be noted that the New Caledonia ore is rich in oxidic nickel rather than being a sulfidic form.

Much of the evidence of increased lung and nasal cancer risks was seen for refinery workers exposed to large amounts of nickel species through processes used in the past. Improvements in equipment and changes in processes appear to have diminished considerably the respiratory cancer risks associated with nickel refining. In particular, the disappearance of respiratory cancer risks at Clydach appears to have been associated mainly with the reduction in the airborne levels of oxidic and sulfidic nickel dust and soluble nickel mist. The dust reductions were related to improvements in equipment (rotary calciners instead of linear calciners and a centralized grinding plant) and to prior removal of copper from the feed. The reduction in copper content reduced the amount of calcining that was done and eliminated sulfuric acid leaching in the copper plant. These changes resulted in average oxidic nickel concentrations in the calciner being reduced from approximately 20 mg Ni/m³ with intermittent exposures of 100 mg Ni/m³ to an average of 6—8 mg Ni/m³ with intermittent levels of a comparatively modest 20 mg Ni/m³. In conjunction with the decrease in oxidic nickel, the average sulfidic nickel concentrations around the calciner were reduced by more than 50 %, from 6—9 mg Ni/m³ to less than 3 mg Ni/m³. The reduction in copper levels in the refinery feed changed the process used in the Clydach copper plant. Average levels of oxidic nickel were reduced from 10 mg Ni/m³ to 1 mg Ni/m³, and soluble nickel was virtually eliminated from this workplace.

At Kristiansand there was also some evidence that lung and nasal cancer risk was reduced with decreases in the level of oxidic nickel. The introduction of new equipment in the roasting, calcining, and smelting operation in 1956 resulted in a 50 % reduction in the average oxidic nickel levels from 10 mg Ni/m³ to 5 mg Ni/m³, and this change appears to correspond with a reduction in respiratory cancer risk (table 44). The men who started working in the roasting, calcining, and smelting department after the introduction of the new equipment have experienced lung cancer mortality consistent with national rates, and there have been no nasal cancer cases reported among the men hired after 1956. This evidence from Kristiansand should, however, be viewed cautiously because of the small number of person-years on which it is based and the relatively short follow-up of many of the men.

Although the respiratory cancer risks at Clydach appear largely to have disappeared in response to the

removal of processes which produced large amounts of dust, there is good evidence that soluble nickel concentrations in excess of 1 mg Ni/m³ in some electrolysis refining workplaces are still a hazard. In particular, men working in Kristiansand's electrolysis department after 1956 with soluble nickel exposures of this magnitude have continued to exhibit an increased risk of lung cancer (table 43).

With the apparent patterns in the epidemiologic data come a few contradictions. One of the anomalies is the occurrence of four nasal cancers among the Huntington refinery workers (table 64), with no corresponding evidence of increased lung cancer risk (tables 62 and 63). Only one of these men had a cumulative nickel exposure comparable to that of cohorts with increased nasal cancer risks. This man's primary exposure to nickel was in the sulfidic form through work in the calcining department. His cumulative exposure to this nickel form was similar, although somewhat lower, than those found in some of the high-risk areas at Clydach. His nasal cancer would therefore be consistent with the evidence from Clydach that sulfidic nickel is a strong nasal carcinogen. The remaining three nasal cancer cases occurred in men exposed to levels of nickel that were similar to those of nonrefinery cohorts in which no excess nasal cancer risk was observed. One of these cancers could be plausibly related to work in another industry that has been associated with increased nasal cancer risk. Classification of the other two cases as nasal cancers occurred as a result of a reinterpretation of the death certificates. According to the rules in force at the time, the wording used had resulted in the deaths being attributed to cancers of the bone, but subsequent experience has shown that the great majority of tumors so described are in fact tumors of the paranasal sinuses. It must therefore be assumed that they were.

The other inconsistency that was found in this study was the apparent increase in lung cancer risk for workers in the Coniston and Falconbridge sinter plants. These operations were almost identical facilities that are believed to have had much lower concentrations of sulfidic nickel (1—5 mg Ni/m³) than the other workplaces associated with increased lung and nasal cancer risks. The approximately doubled lung cancer risk of the men who worked in these two operations does not seem to be consistent with the risks observed for men with similar exposures elsewhere. In addition, there were no nasal cancers among the men who worked at either Coniston or Falconbridge. The absence of nasal cancers among both the Coniston and Falconbridge workers makes attribution of the observed lung cancer risk to the reported low levels somewhat questionable, given the occurrence of both excess lung and nasal cancers among other refinery workers. Arsenic, which was released from the ore into the workplace by sintering in these facilities, is one possible explanation for the increased lung cancer risk in the absence of nasal cancers. Alternatively, the environmental estimates might be questioned. There were only a few measurements of dust from Coniston, but they varied considerably and were much higher than the environmental estimates reported at Falconbridge, although the two facilities performed similar operations using similar equipment with similar feeds.