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**Report of the International Committee on Nickel Carcinogenesis in Man.**

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dusty with extremely high levels of oxidic nickel ( $>20$  mg Ni/m<sup>3</sup>) and sulfidic nickel ( $>10$  mg Ni/m<sup>3</sup>), as shown in table 9. In addition, soluble nickel may have been present and, if so, at levels as high as 4 mg Ni/m<sup>3</sup>. Sintering machines were also used at the Coniston sinter plant to agglomerate charge for the blast furnaces in the smelter at Coniston from 1914 until 1972. However, apart from the sinter discharge area, the Coniston sinter plant was believed to have been less dusty than the other two sintering operations were. In addition, the oxidized nickel in the dust, unlike that in the dusts of the Copper Cliff and Port Colborne sinter plants, was greatly diluted by iron oxide.

Until 1984, the Port Colborne nickel refinery smelted the nickel oxide to metal, cast impure nickel anodes, and produced pure nickel by electrolytic refining. The Copper Cliff copper refinery still uses a similar process whereby copper is cast into anodes which are electrolytically refined. Impurities fall to the bottom of the electrolytic tanks as a sludge from which various commercially important metals are recovered in subsequent processing.

The men in most of the electrolytic workplaces at Port Colborne were exposed to average airborne soluble nickel and total nickel concentrations of  $<0.3$  mg Ni/m<sup>3</sup> and  $<1.0$  mg Ni/m<sup>3</sup>, respectively. Electrolysis activities with higher nickel concentrations were the pumping of anode slimes, the washing of anode scrap (1.0–3.0 mg/m<sup>3</sup> soluble nickel), and the handling of reduced nickel oxide ( $<2$  mg Ni/m<sup>3</sup> total nickel). The total airborne nickel concentrations in the nickel anode and foundry additives department were believed to have been as high as 5 mg Ni/m<sup>3</sup>, with less than 0.05 mg Ni/m<sup>3</sup> in soluble form. Men engaged in support ("other") activities at Port Colborne (maintenance and yard personnel) were exposed to relatively low levels of nickel. Recent measurements indicate the total nickel and soluble nickel concentrations to have been  $<1.0$  mg Ni/m<sup>3</sup> and  $<0.20$  mg Ni/m<sup>3</sup>, respectively.

#### *Comparison of the Port Colborne and Kristiansand electrolysis departments*

The estimated concentrations of airborne soluble nickel in the Port Colborne electrolysis department were somewhat less than those at Kristiansand, although the difference was not large. Part of the difference in the estimates related to the classification of nickel carbonate at Port Colborne as an insoluble form, while it was classified as soluble at Kristiansand. These differences in the classification of soluble nickel may, however, have been offset by soluble nickel contamination from the nickel sulfate drier and the copper electrowinning tanks at Kristiansand. Consequently, the airborne soluble nickel concentrations at Port Colborne and Kristiansand were believed to have been of similar magnitude. There were, however, considerable differences in the insoluble nickel exposure. Prior

to 1967, the Kristiansand electrolysis department handled 7.5 times more insoluble nickel per unit of soluble nickel than the Port Colborne electrolysis department. This insoluble nickel in the copper leach was composed mainly of nickel-copper oxide, with smaller amounts of sulfidic nickel, metallic nickel, and nickel arsenide (Ni<sub>3</sub>As<sub>2</sub>).

Thus, prior to 1967, there were considerably higher levels of insoluble nickel materials in the Kristiansand electrolysis department than were found at Port Colborne. The difference in the insoluble nickel levels persisted after 1967 but was reduced, the insoluble to soluble nickel ratio at Kristiansand dropping to 2.5 times that of Port Colborne.

#### **Huntington Alloys, Inc — West Virginia, United States**

The mortality experience of the more than 3000 workers employed for one year or more at a nickel refinery in Huntington, West Virginia, was followed for the period 1 January 1948 through 31 December 1984. The calciners that had been previously in operation were shut down in November 1947, and the cohort was divided into two parts. Cohort 1 consisted of the group of 1855 workers hired prior to 1947, while the 1353 workers hired after 1946 and before 1960 were grouped into cohort 2. (See also reference 19.) The expected numbers of deaths for all cancer sites except nasal sinuses were based on rates from the six-county area surrounding the Huntington plant from which the work force was largely drawn (Cabell, Wayne, Mason, Putnam, and Lincoln counties, West Virginia, and Lawrence County, Ohio). United States (US) mortality rates were the basis for the calculation of the expected number of nasal cancer deaths.

#### *Nickel species exposures*

INCO's high nickel alloy plant at Huntington, West Virginia, was organized into 37 departments. The concentrations of total airborne dust and of total airborne nickel in these departments were estimated in 1979 by plant personnel using current and historic dust measurements. In August 1985 gravimetric samples of airborne dust were collected in six different areas and analyzed chemically to estimate nickel species composition. This information was extrapolated by analogy to 30 other departments. Unfortunately, dust samples were not available for the calcining department, which had been shut down in 1947. Furthermore, the operations carried out in the calcining building were sufficiently different from the rest of the plant to make it impossible to estimate the species mix by analogy. Thus the distribution of nickel among species in the calcining department was estimated with the use of information on the phase composition and relative amounts of -200 mesh material in the feeds, products, and flue dusts

of the calcining department. The estimates for the departments at Huntington are shown in table 10.

### **Outokumpu Oy nickel refinery — Finland**

The mortality of 129 employees of a Finnish nickel refinery was followed from the beginning of the refinery's operations in 1960 through 1985. The study population was limited to workers who had been employed at least six months between 1960 and 1979 and whose first exposure had occurred by 31 December 1969. This cohort has not been studied before, but, due to its small size, the small number of cancer cases, and the relatively recent opening of the nickel refinery, a formal statistical analysis studying the relationship between exposure to nickel and cancer risk was not conducted. Some observations on the employees are, however, considered where relevant.

#### *Nickel species exposures*

Outokumpu Oy began continuous production of electrolytic nickel in 1960. The company has a smelting operation which converts nickel-copper ore to a high grade matte consisting of nickel-copper alloy, nickel

sub sulfide, and copper sulfide. The matte is ground and nickel is extracted in a refining process which consists of atmospheric pressure leaching, electrolytic copper removal, cobalt removal, and nickel electro-winning. Workers engaged in the refining process are exposed primarily to soluble nickel in the form of nickel sulfate and nickel chloride, nickel sulfate being the predominant compound. Air samples taken in the tankhouse of the refinery in 1966 and during seven years between 1976 and 1986 indicate that the workers were exposed to low levels of soluble compounds. Annual averages of soluble nickel concentrations (based on 11 to 34 measurements) were between 0.16 and 0.52 mg Ni/m<sup>3</sup>. The highest measurement recorded was 1.1 mg Ni/m<sup>3</sup>. Apart from the year with this measurement, the highest recorded concentration in any other year was 0.7 mg Ni/m<sup>3</sup>.

### **Falconbridge mining and smelting operations — Ontario, Canada**

The mortality of more than 11 000 workers at the Falconbridge Nickel Mines, Ltd, in the Sudbury area of Ontario was followed between January 1950 and De-

**Table 10.** Estimated average airborne concentrations of total nickel and nickel species by departments at Huntington Alloys, Inc.

Department	Code	Total nickel (mg Ni/m <sup>3</sup> )	Metallic nickel (mg Ni/m <sup>3</sup> )	Oxidic nickel (mg Ni/m <sup>3</sup> )	Sulfidic nickel (mg Ni/m <sup>3</sup> )	Soluble nickel (mg Ni/m <sup>3</sup> )
Acid reclaim	01	0.02	0.000	0.004	—	0.016
Blacksmith shop	02	0.02	0.012	0.008	—	0.000
Calciner	03	5.00	0.400	0.500	4.000	0.050
Carpenter shop	04	0.02	0.012	0.006	—	0.002
Chipping and hammering	05	0.75	0.262	0.450	—	0.038
Cold drawing	06	0.10	0.060	0.015	—	0.025
Combustion	07	0.05	0.030	0.008	—	0.012
Electrical	08	0.10	0.060	0.003	—	0.010
Engineering	09	0.01	0.006	0.003	—	0.001
Extrusion	10	0.20	0.120	0.080	—	0.000
General offices	11	0.01	0.006	0.003	—	0.001
Heat treat	12	0.02	0.006	0.006	—	0.008
Machine shop	13	0.03	0.027	0.003	—	0.000
Mechanical maintenance	14	0.01	0.006	0.003	—	0.001
Merchant mill (bar and wire)	15	0.30	0.180	0.120	—	0.000
Night superintendent	16	0.01	0.006	0.003	—	0.001
Pipe shop	17	0.08	0.048	0.024	—	0.008
Polishing	18	0.10	0.035	0.060	—	0.005
Primary mill	19	0.06	0.003	0.057	—	0.000
Reduction pilot plant	20	0.02	0.016	0.003	—	0.001
Refinery (casting)	21	0.25	0.125	0.125	—	0.000
Research and development	22	0.05	0.030	0.015	—	0.005
Roll grinding	23	0.03	0.027	0.003	—	0.000
Roll turning	24	0.03	0.027	0.003	—	0.000
Sheet mill	25	0.20	0.120	0.030	—	0.050
Shipping	26	0.01	0.006	0.001	—	0.002
Standards	27	0.01	0.006	0.003	—	0.001
Steel shop	28	0.12	0.036	0.000	—	0.048
Stocks	29	0.01	0.006	0.001	—	0.002
Stores	30	0.01	0.006	0.001	—	0.002
Strip mill	31	0.20	0.120	0.030	—	0.050
Transportation	32	0.01	0.006	0.003	—	0.001
Vacuum melting	33	0.15	0.120	0.030	—	0.000
Welding products	34	0.02	0.014	0.004	—	0.002
Yard	35	0.10	0.060	0.030	—	0.010
Warehouse	36	0.01	0.006	0.001	—	0.002
Watchman	37	0.01	0.006	0.003	—	0.001

ember 1984. The study population consisted of all men who worked at the company's operations for a total of at least six months and who were employed there at some time between January 1950 and December 1976. This definition includes men who had begun work before 1950, some of whom started employment when the company began operations in 1929. (See also reference 14.) Death rates from the province of Ontario were used to compute the expected number of deaths in all the analyses.

#### *Nickel species exposures*

Nickel-bearing ore is mined in the Sudbury area and is smelted in nearby Falconbridge facilities to produce nickel-copper sulfide matte that is sent to Kristiansand, Norway, for further refining. The ore is first crushed and screened (milling in table 11), and then mixed with recycled furnace dust and other materials (feed preparation in table 11). In the smelting process from 1928 to 1978, the resulting material was heated to about 900°C in the sinter plant to fuse the sulfides for the blast furnace. The hot product was screened to remove undersized particles and dust. The screening of these materials and the recycling to the sinter machines resulted in the highest dust levels in the operation.

The sinter material was fed to the blast furnaces in combination with coke to produce a mixture of molten sulfides and iron silicates which was converted to an iron-free copper nickel matte in the settlers and converters, and then cast in the matte room. After the matte cooled, it was crushed and packed in barrels or rail cars. Estimated airborne nickel concentrations for the steps in the process which operated between 1928 and 1978 are shown in table 11. Details concerning the development of these estimates and descriptions of the subprocesses are provided in the appendix.

#### **Hanna mining and smelting operations — Oregon, United States**

A cohort of 1510 workers who worked in a nickel mine and smelter operated by the Hanna Nickel Smelting Company near Riddle, Oregon, was followed during the period January 1954 through 31 December 1983. All the members of the cohort had worked six months or more between the time the operation started in 1953 until December 1977. (See also the unpublished paper "A Study of Mortality in a Population of Nickel Miners and Smelter Workers" prepared for the Hanna Nickel Smelting Company, Riddle, Oregon, by

**Table 11.** Estimated average air concentrations of generic forms of nickel found in the Falconbridge operations in Sudbury, 1933—1978.

Department	Oxidic nickel (mg Ni/m <sup>3</sup> )	Sulfidic <sup>a</sup> nickel (mg Ni/m <sup>3</sup> )	Soluble <sup>b</sup> nickel (mg Ni/m <sup>3</sup> )	Total nickel (mg Ni/m <sup>3</sup> )	Total dust nickel (mg Ni/m <sup>3</sup> )
Mining	—	0.02	—	0.02	2.0
Milling					
Ore dressing	—	0.04	—	0.04	3.8
Concentrator	—	0.03	—	0.03	3.2
Feed preparation					
Concentrate receiving	—	0.16	0.01	0.17	4.9
Pellet plant	—	0.14	0.01	0.15	4.3
Briquetting	—	0.14	0.01	0.15	4.3
Slurry, filtering and drying plant	—	0.03	—	0.03	0.9
Smelter					
Sinter plant	0.02	0.20	—	0.22	6.3
Blast furnace	0.01	0.12	—	0.13	3.7
Settlers	0.01	0.08	—	0.09	3.0
Converters	0.01	0.04	—	0.05	1.0
Matte room	—	0.09	—	0.10 <sup>c</sup>	1.2
Pyrrhotite treatment					
Pyrrhotite plant	—	—	0.01	0.01	0.9
Nickel-iron refinery	0.01	—	—	0.02	0.5
Maintenance					
Miscellaneous	—	0.09	—	0.09	2.5
Repair crew	0.01	0.17	—	0.18	5.0
Welders	0.05	—	—	0.05	3.7
Shops	0.03	—	—	0.03	2.2
Surface					
Unexposed	—	—	—	<0.001	—

<sup>a</sup> Includes pentlandite, pyrrhotite, and nickel subsulfide. The matte room was the only area in which men were exposed to nickel subsulfide.

<sup>b</sup> Some soluble nickel must have been in the smelter, as it handled flue dusts, which always contain nickel sulfate.

<sup>c</sup> Includes 0.01 mg Ni/m<sup>3</sup> as nickel-copper alloy.

Cooper & Wong in 1982.) The expected numbers of deaths were calculated with the use of death rates from the state of Oregon.

#### *Nickel species exposures*

Production of nickel by the Hanna Nickel Smelting Company began in July 1954 and continued until 1985. Open-cut mining methods were utilized to obtain the ore from a 600-acre (121.5-ha) deposit in Riddle County, Oregon. The ore contained several nickel minerals, garnierite, a complex magnesium silicate of nickel, being the most easily recognized. Iron oxides, magnesia, and silica were the major constituents of the ore, but chromium, cobalt, and aluminum occurred in minor amounts. The ore was transported a short distance and smelted to produce a ferronickel product. The process included ore preparation (reclaiming, drying, screening, crushing, sampling, and calcining), melting, and refining.

There are no quantitative data on airborne nickel concentrations prior to 1967, when the US Public Health Service took samples of air in the plant. None of the samples had nickel concentrations greater than 1.0 mg Ni/m<sup>3</sup>. Of the 22 air samples taken, only four (18 %) were above 0.1 mg Ni/m<sup>3</sup>, and 15 (68 %) were below 0.01 mg Ni/m<sup>3</sup>. Another industrial hygiene survey carried out by the National Institute for Occupational Safety and Health in 1976 showed airborne nickel concentrations to be of a similar magnitude. The nickel concentrations ranged from 0.004 to 0.420 mg Ni/m<sup>3</sup>, five (6 %) of the 81 samples taken being above 0.1 mg Ni/m<sup>3</sup> and 53 (78 %) below 0.01 mg Ni/m<sup>3</sup>. The nickel concentrations in the air samples taken in 1978, 1979, and March 1980 through January 1981 were all below 1.0 mg Ni/m<sup>3</sup>.

The lack of air measurements prior to 1967 makes it impossible to estimate with any degree of certainty the levels of nickel to which workers were exposed during that period. However, dust control measures undertaken between the opening of the plant in 1954 and the first measurements of airborne nickel in 1967 imply that the airborne nickel concentrations were probably higher than those measured from 1967 to 1981. Reductions in nickel exposure over time are suspected to have been greatest for those men with the highest potential exposures, such as crane operators and men in the upper levels of the smelter.

Although available assays did not identify the actual nickel compounds in the air, the composition of the ore and the process used suggested that oxidized nickel and possibly some ferronickel were the most likely species. There would be no sulfidic nickels and little, if any, soluble nickel. On the basis of the exposure data obtained since 1967 and discussions with plant personnel, each work area in the operation was classified as to probable exposure to oxidized nickel over the history of the plant as shown in table 12.

#### **Société le Nickel mining and smelting operations — New Caledonia**

The study of workers in the Société le Nickel mining and smelting operations in New Caledonia was carried out independently of the joint effort, but it was included because of its importance in providing information concerning health risks associated with exposure to oxidic nickel. The study population was examined differently from any of the others that were included in the investigation because of the unavailability of age- and time-specific reference rates of the cancer mortality of the New Caledonian population. The main objectives of the study were (i) to compare the incidence rate of respiratory cancer among the population of nickel workers with the rate in the general population and (ii) to look for a possible association between the occurrence of respiratory cancer and certain exposures specific to the nickel mining and refining industries. (See also reference 20.) With respect to these objectives, respiratory cancer incidence during the period 1978—1984 was examined. Only nickel workers with 10 or more years of exposure from the onset of employment in the nickel industry were included. Respiratory cancers were identified through several cancer registries, and cumulative incidence rates were computed as described by Waterhouse et al (27). Details concerning the identification of cancer cases and the calculation of person-years for the New Caledonian and nickel-exposed populations can be found in the report of Goldberg et al (21).

A nested case-referent analysis was used to examine the incidence of respiratory cancer in relation to exposure to five nickel compounds (silicate oxides, complex oxides, sulfides, metallic iron-nickel alloy, and soluble nickel) and other potential occupational hazards. Cumulative nickel exposure to the five nickel species was computed for the 79 cases and 233 referents matched for age and year of hire at Société le Nickel. The accumulation of exposure for the referents was truncated at the diagnosis date of the matching cases.

**Table 12.** Estimated maximum nickel oxide exposure by work area in the Hanna Nickel Smelting Company.

Area	Estimated maximum oxidic nickel exposure (mg Ni/m <sup>3</sup> )
Mining	0.01
Ore preparation and crushing and calcining	0.10
Laboratory and warehouse	0.01
Yard	0.10
Smelter	1.00
Pig deck and skull plant	1.00
Refining furnaces	1.00
Ferrosilicon plant	1.00
Maintenance	0.10

### *Nickel species exposures*

Nickel has been mined in New Caledonia since 1866 and smelted there since 1885. Ore in New Caledonia is of silicate form (garnierite/laterite) and is mined in open pits. The smelting and refining operations include, in succession, ore preparation (homogenization), drying, calcining, smelting, and refining. The two products that are produced are ferronickel (20–25 % nickel) and high-grade nickel matte (75 % nickel). There are two production lines, one for matte and one for ferronickel.

The matte line in the first decades of operations used a calcining operation on sintering machines followed by smelting with coke and gypsum in blast furnaces to produce a crude iron-nickel matte that was further upgraded in converters into high-grade nickel matte. In more recent years, the introduction of sulfur to the process was modified, first by the direct introduction of gypsum to the electric furnace of the ferronickel line and second by the direct introduction of molten sulfur into molten ferronickel. The ferronickel line consists of a calcining operation in rotary kilns, followed by smelting in electric furnaces. After the converting and refining operations, the ferronickel is cast into ingots.

Estimates of the concentrations of nickel species in Société le Nickel's Doniambo smelter during the period 1926–1982 suggest low-level exposure to nickel. Added across all species, the highest estimated nickel exposure was less than 2 mg Ni/m<sup>3</sup>. In many workplaces in which airborne nickel was estimated to attain its highest levels, the predominant nickel form was believed to be a fairly equal mixture of the silicate oxide ore itself and oxidic nickel. None of the workplaces had significant levels of sulfidic or soluble nickel; the highest estimated concentration of either of these compounds was 0.1 mg Ni/m<sup>3</sup>.

### **Oak Ridge Gaseous Diffusion Plant — Tennessee, United States**

The Oak Ridge Gaseous Diffusion Plant, located in Oak Ridge, Tennessee, employed 813 workers between 1 January 1948 and 31 December 1953 in the production of barrier material for use in the gaseous diffusion process of uranium enrichment. All of the workers had at least 1 d of service in the barrier manufacturing department before 31 January 1953. (See also reference 17.) The mortality of these workers was followed for the period 1 January 1948 through 31 December 1982.<sup>1</sup> The expected numbers of deaths were based on US mortality rates.

<sup>1</sup> These data are part of the Health and Mortality Study of the Department of Energy Workers being conducted by the Oak Ridge Associated Universities under contract DEAC0576OR0033 between the US Department of Energy, the Office of Energy Research, and the Oak Ridge Associated Universities. Permission was granted by the Department of Energy for use of these data, collected by Union Carbide, in this report.

### *Nickel species exposures*

In one department of the Oak Ridge Gaseous Diffusion Plant, high purity nickel powder was used to manufacture "barrier," a special porous material used in the enrichment of uranium by gaseous diffusion. Routine air sampling was conducted in various areas of the barrier plant from 1948 to 1963. The median nickel concentration from 3044 air samples reported in the original study (22) was 0.13 mg Ni/m<sup>3</sup>. The upper quartiles for air samples in two manufacturing areas where about 70 % of the work force was assigned were 0.56 and 0.70 mg Ni/m<sup>3</sup>. The 90th percentiles of the nickel concentrations for these areas were 1.8 and 1.4 mg Ni/m<sup>3</sup>. The detection limit for the instrumentation used for the monitoring was 0.1 mg Ni/m<sup>3</sup>, and it was stated that "under considerably improved working conditions, current levels of nickel collected by industrial hygiene personnel are higher than historical data. Therefore, it is reasonable to assume that the reported median of 0.13 mg Ni/m<sup>3</sup> is biased toward the low side [p 801]." This bias would also seem to apply to the other percentiles in the distribution of nickel concentrations, and it lends uncertainty to the average metallic nickel exposures to which the barrier plant workers were exposed. However, the average concentrations of airborne metallic nickel at the plant were believed to have been below 1 mg Ni/m<sup>3</sup>.

### **Henry Wiggin Alloy Company — Hereford, England**

The Henry Wiggin Alloy Company in Hereford, England, manufactures nickel alloys from metallic nickel, iron, copper, cobalt, chrome, and molybdenum. The plant opened in May 1953 and continues operation to the present day. A cohort of men employed at Wiggin was followed from the time the plant began its operation in May 1953 until April 1985. The cohort was limited to 1907 workers who had been employed in the operating area of the plant, other than as members of the staff, for five or more years prior to April 1978. (See also reference 23.) The numbers of deaths expected at national rates were calculated with the use of England and Wales mortality rates. For the expected number of deaths based on local mortality, the expected numbers of deaths based on national rates were multiplied by the standardized mortality ratio (SMR) values divided by 100 for men aged 15–64 years for the period 1969–1973 in the urban areas of the county in which the factory was located.

### *Nickel species exposures*

The workplace categories and the averages of environmental measurements from the plant during the period 1975–1980 shown in table 13 have been taken from the report of Cox et al (23). Samples were obtained during this period and during the years after 1980 with Casella personal samplers. The measure-

ments of dust and nickel concentrations in the samples indicate that men at the Wiggin plant were exposed to small amounts of nickel in both time periods. Most of this exposure was to metallic and oxidic nickel. The consensus of opinion among plant personnel was that ventilation improvements through the history of the plant had reduced the airborne concentrations of dust and nickel. Thus the measurements taken since 1975 are likely to underestimate the level of oxidic and metallic nickel exposure experienced by workers in earlier periods.

### Summary of nickel species exposures

By means of the environmental estimates that have already been presented, subgroups of the cohorts with common exposures can be characterized as shown in table 14. From the table it is clear that, for workers included in this study, exposure to very high ( $>10 \text{ mg Ni/m}^3$ ) average concentrations of oxidic and/or sulfidic nickel species was confined to refining operations at Mond/INCO (Clydach) and to the Copper Cliff and Port Colborne sinter plants of INCO, Ontario. Some

**Table 13.** Total dust and nickel concentrations in air samples by department and time period in the Henry Wiggin Alloy Company.

Category	Department	Total dust ( $\text{mg/m}^3$ )				Nickel ( $\text{mg/m}^3$ )			
		1981–1985		1975–1980		1981–1985		1975–1980	
		Mean	Median	Mean		Mean	Median	Mean	
1	Melting, fettling, pickling	9.61	1.30	9.57		0.73	0.14	0.84	
2	Extrusion and forge, hot strip and rolling, engineering, melting stores	1.74	1.56	4.49		0.07	0.03	0.53	
3	Machining, hot rolling, nimonic finishing, craft apprentice	3.72	1.8	3.29		0.42	0.20	0.55	
4	Roll turning and grinding, cold rolling, cold drawing, wire drawing, inspection	3.70	1.4	1.01		0.31	0.15	0.40	
5	Process stock handling, distribution and warehouse	—	—	1.05		—	—	0.04	

**Table 14.** Estimated average air concentrations<sup>a</sup> of nickel species in exposure groups within the cohorts studied.

Study	Number of exposure groups <sup>b</sup>	Metallic nickel <sup>c</sup>				Oxidic nickel <sup>c</sup>				Sulfidic nickel <sup>c,d</sup>				Soluble nickel <sup>c</sup>			
		L	M	H	VH	L	M	H	VH	L	M	H	VH	L	M	H	VH
Mond/INCO (Clydach)	30	18	7	4	1	9	7	6	8	19	8	3	—	28	2	—	—
Falconbridge (Ontario)	20	None				20	—	—	—	19	1	—	—	20	—	—	—
Hanna Nickel Smelting Company	9	None				5	4 <sup>e</sup>	—	—	None				None			
Huntington Alloys																	
Cohort 1	37	37	—	—	—	37	—	—	—	36	1	—	—	37	—	—	—
Cohort 2	36	36	—	—	—	36	—	—	—	36	—	—	—	36	—	—	—
INCO (Ontario)																	
Copper Cliff sinter	1	None				All H or VH				All H or VH				All L or M			
Coniston sinter	1	None				All				None to L				None to L			
Port Colborne leaching, calcining, sintering <sup>f</sup>	1	None				All H or VH				All H or VH				All L to M			
Port Colborne electrolysis	11	10	1			None to L				All L or M				9	2		
Port Colborne other	2	All L to M				All L to M				All Low				All Low			
Sudbury nonsinter	5	All L to M				All L to M				All Low				All Low			
Falconbridge (Kristiansand)	22	20	2	—	—	14	5	1	2 <sup>g</sup>	17	5	—	—	15	7	—	—
Oak Ridge Gaseous Diffusion Plant	1	1	—	—	—	None				None				None			
Société Le Nickel	1	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—	—
Henry Wiggin Alloy Company	5	5	—	—	—	5	—	—	—	None				5	—	—	—

<sup>a</sup> Average level based on personal gravimetric sampling methods.

<sup>b</sup> An exposure group is a group of departments, processes, or work areas that have comparable species and levels of nickel. See the environmental data sections of the individual cohorts for a description of the environmental estimates for each exposure group.

<sup>c</sup> L = low ( $<1 \text{ mg Ni/m}^3$ ), M = medium (1–4  $\text{mg Ni/m}^3$ ); H = high (5–9  $\text{mg Ni/m}^3$ ); VH = very high ( $\geq 10 \text{ mg Ni/m}^3$ ).

<sup>d</sup> Primarily nickel subsulfide.

<sup>e</sup> These four departments drop to low after 1967.

<sup>f</sup> Estimates are only for the sinter plant, not the entire department.

<sup>g</sup> These two departments drop to medium after 1955.

men in these cohorts, as well as those in the Falconbridge refinery in Kristiansand, were also exposed to more than 1 mg Ni/m<sup>3</sup> in soluble form. In contrast, men working at Huntington Alloys in West Virginia, at Société le Nickel's New Caledonia facilities, and in mining and smelting operations at Hanna Mining in Oregon and the Falconbridge mines in Ontario had much lower (<2 mg Ni/m<sup>3</sup>) average nickel species exposures, although some of the men at Huntington Alloys were exposed to fairly high average levels (4 mg Ni/m<sup>3</sup>) of sulfidic nickel. The men at Huntington Alloys and in the mining and smelting operations also had extremely low exposure to soluble nickel compounds. The workers involved in the use (as opposed to the production) of nickel were exposed to comparatively low airborne nickel concentrations. Oak Ridge barrier plant workers, for example, were exposed to less than 1 mg Ni/m<sup>3</sup> in the form of metallic nickel, and men at Wiggin Alloy were exposed to metallic and

oxidic nickel concentrations that were less than 1 mg Ni/m<sup>3</sup>.

For a sense of the magnitude of these occupational exposures, it is of interest to compare them with background ambient air levels of nickel in the United States. The national air monitoring filter site and inhalable particulate networks of the US Environmental Protection Agency collect such samples from both urban and nonurban sites. In every year between 1977 and 1982, the median concentration of nickel in the ambient air for sites in this network was below 0.01 µg Ni/m<sup>3</sup> (28). The 70th percentiles of measurements at these sites for each of these years were all less than 0.025 µg Ni/m<sup>3</sup>, and the 99th percentiles were below 2 µg Ni/m<sup>3</sup>. Thus the lowest occupational nickel exposures (100—500 µg Ni/m<sup>3</sup>) of the men studied in this investigation were several orders of magnitude greater than those experienced by the general US population through inhalation of the ambient air.

## METHODS OF EPIDEMIOLOGIC ANALYSIS

The primary objective of the epidemiologic analysis was to investigate relationships between cancer risk and exposure to different forms of nickel. This objective required a characterization of exposure to these forms of nickel through the merging of individual mortality and work history data with estimated concentrations of nickel forms in the workplaces. Both the length of time spent in specific workplaces and the quantitative exposure estimates were used to examine cancer response relative to exposure to the different forms of nickel. The results of the analyses were reported separately for each of the cohorts and then collectively interpreted or pooled to increase statistical power.

The separate analysis of cancer mortality in each cohort (as opposed to an overall pooled analysis) was desirable for two reasons. First, the results of the analyses could be compared with those that had been previously published. This information was of interest since all of the cohorts had been updated with additional follow-up for this study. More importantly, separate cohort analyses facilitated comparisons of cancer risks in groups of men with similar levels of exposure. This information was desirable since systematic discrepancies in dose-related response to a nickel form could then be considered in assessments of causality, and a "weight of evidence" approach could be used in interpreting the results. If analyses using data pooled across cohorts had been employed in the absence of separate cohort analyses, this approach would not have been possible. Nonetheless, some pooling of data was used to explore relationships between cancer risks and exposure to specific nickel forms. In particular, non-respiratory cancer mortality was examined with a

pooled approach in an effort to increase statistical power.

Collective examination of the separate cohort results and pooled data analyses required standardization of the treatment of different sets of epidemiologic data. For example, a standard measure of risk was adopted, and cancer risks were examined at consistent points of time from the onset of exposure. These and other methods used to standardize the analyses and the reporting of their results are described in the following discussion.

### Coding of causes of death

Most of the studies had deaths coded to a single revision of the International Classification of Diseases (ICD). The seventh revision was used for the Clydach, Huntington, and Kristiansand studies, and the eighth was employed for the Hanna, Oak Ridge, and Wiggin Alloy cohorts. In the INCO, Ontario, and Falconbridge, Ontario, studies deaths were coded to the ICD revision in effect at the time of death (seventh, eighth, or ninth) and converted to the ninth revision. The ICD codes that were used to classify the cancer mortality in this study are presented in table 15.

### Follow-up treatment of unknown vital status

In most of the cohorts, workers with an unknown vital status as of the last day of follow-up were considered to have been under observation until the last day they were known to be alive (generally the employment ter-

mination date) to avoid an overestimation of the person-years. There were two cohorts (Falconbridge and INCO, Ontario) in which a worker for whom no record of death was available was assumed to be still alive until the last day of follow-up. In these populations the infrequency of emigration and the absence of any recording of death was considered sufficient proof that the worker had not died (because of a highly reliable death certificate registry) and could therefore justifiably contribute person-years to the analysis to the end of the follow-up period.

### Measures of risk

The SMR was the principal measure of risk used in the analyses. The SMR values were calculated by expressing the observed number of deaths attributed to a particular cause as the percentage of the number expected in a reference population of the same age distribution during the same calendar period. The occupational cohort mortality analysis program (OCMAP), developed by Marsh & Preininger (29), was used to calculate the SMR values based on expected numbers of deaths in five-year calendar periods and five-year age groupings. The 95 % confidence intervals were estimated for the SMR values, and the significance of the difference of an SMR from 100 was tested on the assumption that the observed number of deaths followed a Poisson distribution with the mean equal to the expected number of deaths. All reported P-values were from one-tailed tests. Therefore an observed SMR at the limit of a 95 % confidence interval had a P-value of 0.025. The SMR values were compared with the use of a chi-square based test (30).

### Reference rates

The expected numbers of deaths in the analysis of mortality risk were based on the mortality rates in the reference populations given in table 1. Where possible, local rates (or, in one case, adjustment factors to national rates) were used in the assessment of lung cancer risks. When local rates were unavailable (or considered inappropriate), provincial or national rates were used. Analyses of the risks associated with nasal cancer, a disease that is very rare in the general population, used national or provincial rates because they were more stable than rates from smaller, local populations.

### Lagged exposures

Exposure during the last five years prior to death was omitted from all the analyses associated with duration of exposure. This omission was made to preclude exposures that were unrelated to the development of disease from biasing the assessments of the relationships between exposure and risk.

### Latency

The analyses of the lung and nasal cancer mortality of each cohort were initially subdivided by duration of employment and time since first employment. In evaluations of risks associated with exposure to specific work areas only men observed 15 or more years since first exposure in the workplace being studied were included. For cancers in sites other than those of the lung and nose, the risks for all the cohorts were estimated without regard for latency. Observed and expected deaths from these cancers were pooled across the cohorts and subsequently examined relative to duration of exposure and time since first exposure.

### Approach to identifying risks associated with exposure to specific forms of nickel

The simplest approach to gaining insight into whether exposure to a specific chemical form of nickel results in increased cancer risk would be to examine cancer mortality in groups of workers with exposure to only one form of nickel. Ideally, exposure in these groups would be at a relatively constant concentration, and the strength of the relationship between risk and increasing years of exposure could be used to assess whether exposure to that form of nickel was hazardous. However, in most workplaces the workers were exposed to more than a single form of nickel, and some workers were exposed to different forms of nickel as a result of moving between jobs.

The identification of risks associated with exposure to specific forms of nickel was approached in the following two ways: (i) comparisons of risks associated with workplaces in which men were exposed to different forms of nickel and (ii) examination of dose-response relationships based on quantitative estimates of each individual's exposure to different forms of nickel. Inherent in both of these analytical approaches was the need to isolate the risk associated with a specific nickel form through an examination of the dose-

**Table 15.** Codes of the International Classification of Diseases (ICD) used in the analysis of cancer mortality.

Cancer site	ICD (revision 7)	ICD (revisions 8 & 9)
Lung	162—163	162
Nasal	160	160
Buccal cavity and pharynx	140—148	140—149
Nasopharynx	146	147
Pharynx (other)	145, 147—148	146, 148—149
Larynx	150	150
Esophagus	151	151
Large Intestine	153	153
Kidney	180	189
Prostate	177	185
Bladder	181	188
Bone	196	170
Soft-tissue sarcoma	197	171

related response to that form of nickel at constant levels of the remaining forms. To accomplish this step with workplace-related risks, it was necessary to identify two workplaces with different airborne concentrations of one form of nickel (species A), but with similar concentrations of the remaining forms of nickel. If groups of men who had worked in one or the other of these workplaces (but nowhere else) could be found, one could compare the risks of the two groups to obtain information concerning species A. Suppose, for example, that one workplace had "high" levels of nickel species A and "low" levels of the remaining nickel species, while another workplace had "low" levels of all nickel species. If men who worked in the workplace with the higher concentrations of species A had significantly higher risks than the group exposed to the lower levels, species A could be considered responsible for the increased risk.

A major disadvantage of using workplace analyses to isolate individual nickel species risks was that the data might be underutilized. For example, there might be only a few workplaces with appropriate nickel species concentration profiles, and these areas may have employed small numbers of men. A fuller use of the data required quantitative characterizations of exposure to different forms of nickel. Cumulative exposure to individual nickel forms was used to quantify the amount of each nickel form to which the men were exposed. It was calculated as the sum of the products of duration of exposure in each occupation held and the estimated mean concentration to that form of nickel for that occupation.

Relationships between cumulative exposure and observed cancer risk were examined in two ways. The first approach was to examine the association between risk and cumulative exposure to each nickel form, disregarding the other nickel forms. If this analysis gave evidence that more than one nickel species may be related to increased risk, a more comprehensive examination based on cross-classified nickel exposures was carried out. A man's exposure to nickel could, for example, be classified as being "low" for sulfidic nickel, "high" for oxidic nickel, and "medium" for metallic and soluble nickel. With all the men categorized according to exposure to individual forms of nickel, the strength of the dose-responses for a nickel species could be assessed at each level of exposure to the remaining species. For example, cancer risks of men with "high" exposure to soluble nickel and "low" exposure to insoluble nickel forms could be compared to those of men with "low" exposure to both soluble and insoluble nickel forms. An increased risk in the group of men with "high" soluble nickel exposure relative to those with "low" exposure to all of the nickel forms would provide evidence that soluble nickel exposure was related to increased risk.

Cross-classification analyses based on categorized cumulative exposure were performed for the Clydach

and Kristiansand cohorts. The value of these analyses is that they examine the dose-response to a specific nickel species independent of variations in other species. A similar stratification technique was used to separate risks associated with exposure to nickel species in several workplaces. Through previously published work, high risk workplaces within some cohorts had been identified (eg, calcining at Clydach and sinter plants at INCO, Ontario). In evaluating the risks in a group with a specific type of nickel exposure, mortality was stratified by duration of exposure in the known high-risk workplaces. Latency and person-years were computed (allowing for a five-year lag) from the time that an individual first worked in the group with the specific nickel exposure of interest.

In some cohorts, there were no known high-risk groups, and the men had worked in several different departments with different nickel exposures. When this happened (eg, in the Falconbridge mining and smelting cohort), the men were included in each department in which they had worked. Latency and person-years were computed relative to first exposure in each of these departments. As a result, deaths and the corresponding expected numbers could be double- and triple-counted, and the sum of the deaths in the analyses of individual departments could exceed the total number of deaths observed in the cohort.

Analyses of respiratory cancer risk associated with duration of exposure to specific workplaces (eg, the linear calcining area in Clydach, the electrolysis department in Kristiansand, etc) were carried out for all the cohorts, even when more quantitative cross-classification analyses had been performed. One reason for this procedure was to allow comparisons to previously published work. More importantly, these "workplace" analyses provided a means with which to understand the origin of risks that may have been identified in the cumulative exposure analyses. In addition, they provided a means to allow the uncertainty in the environmental estimates to be part of the interpretive process. For example, men who worked in linear calcining at Clydach were known to be exposed to some of the highest airborne nickel concentrations in the refinery. However, the concentrations of oxidic nickel in this and other areas was uncertain (table 3) since no measurements were available. The breadth of the estimated exposure range for total nickel in linear calcining ( $10-100 \text{ mg Ni/m}^3$ ) reflected this uncertainty. Estimated levels of specific forms of nickel were even more uncertain because of the uncertainty of the nickel species composition. However, there was no question that the airborne concentrations of metallic, oxidic, and sulfidic nickel in linear calcining were some of the highest in the refinery. Similarly, there was little question that the levels of these three insoluble nickel forms were much lower in the hydrometallurgy department. There was, however, some question as to the amounts of soluble nickel that were present in the linear calcining area and in the two areas of the hydrometallurgy

department. If one applies the limits of the estimated percentage of soluble nickel to the limits of the range for total nickel, the estimated level of soluble nickel is 0.3—5.0 mg Ni/m<sup>3</sup> for the hydrometallurgy department and 0—5 mg Ni/m<sup>3</sup> for the linear calcining area. Thus the average estimated exposure in each of the these two workplaces would be similar. However, the ranges of the estimates suggested that the two areas may have had considerably different soluble nickel concentrations. This finding had an important bearing on the interpretation of the results. For example, suppose that a group of men that worked predominately in linear calcining could be identified, and this group's cancer risks were clearly greater than those of a group

of men who worked mainly in the hydrometallurgy department. On the basis of the nearly equivalent estimated averages of the soluble nickel concentrations for the two areas (as used in an analysis based on cumulative exposure), we would be inclined to believe that the observed risk may have been attributable to the insoluble compounds. However, if one bears in mind the uncertainty associated with the soluble nickel estimates, it would be conceivable that the soluble nickel levels estimated for linear calcining were considerably higher than those of the hydrometallurgy department and that soluble nickel exposure could also be related to, if not totally responsible for, the observed risks.