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Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery

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Abstract ***Objectives:*** To assess cancer risk among nickel-exposed workers. ***Methods:*** We updated cancer incidence among 1388 workers employed for at least 3 months at a copper/nickel smelter and nickel refinery in Harjavalta, Finland. There were 1155 workers exposed to nickel during the period 1960–1985 in the smelter (566 workers), repair shop (239 workers), or refinery (418 workers). Cancer incidence was followed through the files of the Finnish Cancer Registry up to 31 December 1995. For overall cancer and for a priori selected specific cancer types the ratio of observed to expected numbers of cases was computed as a standardized incidence ratio (SIR), controlled for age, gender, and calendar period and using the region-specific rates as a reference. ***Results:*** The overall cancer incidence among both nickel-exposed and unexposed subcohorts was at the expected level. A small increase in lung cancer incidence, which reached statistical significance among workers with a latency exceeding 20 years, was observed among the smelter workers exposed to insoluble nickel compounds. Among workers in the refinery, who were exposed primarily to nickel sulfate at levels below 0.5 mg/m^3 as well as to low concentrations of other nickel compounds, there was an increased risk for nasal cancer (SIR 41.1, 95% CI 4.97–148), positively associated with latency and duration of employment, and an excess risk for stomach (SIR 4.98, 95% CI 1.62–11.6) and lung (SIR 2.61, 95% CI 0.96–5.67) cancers. ***Conclusions:*** Since elevated nasal and lung cancer risks were confined to the refinery, where the primary exposure was to nickel sulfate, it is likely that nickel sulfate is mainly responsible for the elevated respiratory cancer risk. We cannot rule out whether the excess stomach cancer risk is a chance finding, or related to the working environment.

Key words Cohort study · Record linkage · Occupational exposure · Nickel sulfate

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Introduction

Although most nickel species induce cancer in experimental animals after local administration (IARC 1990), positive evidence of respiratory cancer induction after inhalation exposure has been obtained for nickel subsulfide and nickel oxide only (Dunnick et al. 1995). In humans the highest nasal and lung cancer rates were originally observed in those sections of nickel refineries where exposures consisted mainly of sparingly soluble nickel compounds, sections where level of exposure were also highest (Morgan 1958; Mastromatteo 1967). Although as early as during the 1970s reports were also published that pointed to an elevated respiratory cancer risk in exposure to mainly soluble nickel compounds (Pedersen et al. 1973), the generally held view was that the greatest hazard involved the sparingly soluble nickel compounds. In 1990, however, after an update of the mortality information and a thorough reinvestigation of the exposure in collaboration with the nickel industry's own expertise, the International Committee on Nickel Carcinogenicity published a report that came to the conclusion that the epidemiology findings on nasal and pulmonary cancer were best explained when both soluble nickel salts and sulfidic nickel compounds were considered causal factors in these cancers (Doll et al. 1990). Other international working groups came to the same conclusion on the basis of the same data (IARC 1990; IPCS 1991). However, the legislation of the European Union and several national regulations continue

to consider the carcinogenicity of soluble nickel species questionable.

An elevated incidence of nasal cancer and a borderline increase in lung cancer incidence was reported among workers in a nickel refinery in Harjavalta, Finland (Karjalainen et al. 1992). The cohort was originally assembled from the company's records in 1987 and was followed for cancer incidence from 1953 (the beginning of the Finnish Cancer Registry) to the end of 1987. To shed further light on the carcinogenicity of different nickel species, we extended the follow-up period of this cohort until December 31, 1995, and report the cancer incidence data herein.

Subjects and methods

Study design

Identification of the cohort members, the levels as well as sources of exposure, and the methods of follow-up have been described elsewhere (Karjalainen et al. 1992). In short, all workers employed at the Harjavalta Works (Outokumpu Oy) for at least 3 months during the period 1945–1985 were identified from the company's employment records. An extensive search of population registers had traced the correct personal identification code and vital status for all but eight (0.6%) of the cohort members. Another seven employees had died before the onset of follow-up and were also excluded. After the exclusions the cohort included a total of 1,388 workers continuously employed at the Harjavalta Works for at least 3 months from 1945 to 1985.

Follow-up of cancer incidence through the files of the Finnish Cancer Registry was done using the personal identification code as the key. Follow-up of cancer started at 3 months after the date of first employment or on January 1, 1953, whichever was later, and ended at death, emigration, or on December 31, 1995, whichever occurred first. Three persons had emigrated during the follow-up period. In the basic analyses made within subcategories (period of employment and type/site of work), the beginning of follow-up was defined on the basis of first employment in the category in question. Some persons had worked at more than one site/task and thus basically produced person-years pertaining to more than one category. We also performed analysis within the subgroups of "smelter only" and "refinery only" so as to check if the overlap between the subcategories would in any way affect the risk estimates. Further division was made by the time that had elapsed since first employment in the working category in question. Relative risks were also calculated as a function of duration of employment, with the follow-up period (person-years at risk) starting at the date when the person had been working the required time at the respective work. The duration of employment in nickel-exposed work was used as a proxy measure of long-term and/or cumulative exposure. In calculations of the duration the periods of employment since 1985 were not known.

We used the population of southwestern Finland around the factory (a population of 1 million) to compute the expected numbers of cancer cases. For overall cancer and specific cancer types the ratio of observed to expected numbers of cases was reported as a standardized incidence ratio (SIR), controlled for age, gender, and 7-year calendar period (from 1953 to 1987, the extension period after the earlier follow-up, 1988–1995, as the last period). The 95% confidence intervals (CI) of the SIRs were calculated on the presumption that the number of observed cases followed a Poisson distribution.

Exposure to nickel among cohort members

Copper smelting started in Harjavalta in 1945; nickel smelting, in January 1960; and refining, in May 1960. Thus, the cohort members who had stopped working in the facilities before 1960 were not exposed to nickel (n = 233, Table 1). The remaining 1,155 cohort members whose employment started or continued after January 1, 1960, were exposed to various nickel species.

Workers in the nickel smelter (566) were exposed to low levels of nickel in various forms (nickel matte, nickel subsulfide, and nickel sulfides), and also to other metals (Cu, Cd, Pb, Co, As), sulfur compounds, and, possibly asbestos. The airborne concentrations of these impurities varied, depending probably on the year and the working area. According to industrial hygienic measurements made in the smelter in 1983, mean personal levels of exposure to nickel varied between 0.02 and 0.2 mg/m^3, with the exception of a single value (0.7 mg/m^3). Mean personal levels of exposure to cadmium were below 0.001 mg/m^3, and those of exposure to Pb were below 0.01 mg/m^3 in the same year. Arsenic was not present in the Finnish copper/nickel ore that was exclusively used until the early 1980s, but was present as an impurity in the imported ore, whose use had increased from the beginning of the 1980s as the Finnish mines were exhausted. In 1988 the proportion of the imported ore was about 85%, and the mean breathing zone levels of arsenic varied between 4–19 μg/m^3 in the smelter (Hakala et al. 1991).

The nickel matte, containing nickel and nickel sulfides and subsulfides, was ground and leached in the grinding and leaching section, which was originally located at one end of the electrolysis hall of the refinery. According to measurements from stationary sampling in 1973, the mean total nickel concentration was approx. 0.2–0.4 mg/m^3 in grinding and 0.06–0.20 mg/m^3 in leaching. In these operations, short-term peak exposures could reach 2 mg/m^3. Until that time these insoluble dusts had also spread to the elec-

Table 1 Number of persons and person-years at risk in the follow-up of the smelter and refinery workers from 1953 to 1995 by period of employment, type (site) of work, and gender

Site of work	Employment ended before January 1, 1960 (unexposed to nickel)		Employment continued or started after January 1, 1960 (exposed to nickel)	
	n[a]	Person-years[a]	n[a]	Person-years[a]
Men:				
Smelter	197	5,757	566	13,973
Repair shop	42	1,357	239	6,203
Refinery	–	–	369	8,794
All men	233	6,972	1,106	27,348
Women:				
Refinery	–	–	49	1,081
Total	233	6,972	1,155	28,429

[a] Some of the male employees had worked at two or three sites. They were included in all these categories in this table

trowinning part of the hall. In 1973 this section was separated from the electrolysis all and thereafter, workers in the electrolysis hall were thus almost exclusively exposed to nickel sulfate. In a study performed in 1991 the proportion of soluble nickel in the air exceeded 90% in all sampling locations in the electrolysis hall. At this time, in the leaching process as well, more than 90% of the airborne nickel was water soluble. For the period 1960–1966, measured data on the exposure were not available, but thereafter the exposure was rather well documented (Karjalainen et al. 1992; Kiilunen et al. 1997) and remained stable at 0.2–0.8 mg/m^3 (stationary samplers) until 1988 in the electrolysis hall. The highest nickel concentration measured at stationary sites in the electrowinning hall has been 1.2 mg/m^3. The range of nickel concentrations detected in the breathing-zone samples obtained during 1979–1981 was 0.1–0.4 mg/m^3. The yearly personal mean levels of exposure were estimated to be at most on the order of 0.25 mg Ni/m^3 (Kiilunen et al. 1997). Nickel oxides, nitrates, and carbonyl have not been present; very limited exposure to nickel hydroxide may have taken place in the cobalt-removal stage in the oxidation tanks. Extremely low-level exposure to metallic nickel may have taken place in the cutting and packing department.

Nickel chloride has not been a component of the refining process but has apparently occasionally occured as a contaminant in raw materials because the smell of chlorine gas has been reported in the electrowinning hall a couple of times (personal communication, Matti Koponen, Outokumpu Harjavalta Works, 1997).

In 1966, the concentration of total air-borne sulphates was measured in 11 stationary locations in the tankhouse during 2 days. The mean concentration of total sulphates was 1.5 mg/m^3 (range 0.5–2.3 mg/m^3). Since it is likely that the ratio of sulphuric acid and total sulphates was the same in the electrolysis fluid (H_2SO_4, 40 g/L, $NiSO_4$, 120 g/L, Na_2SO_4, 200 g/L) and in the mist generated by the oxygen bubbles formed in the electrolysis, the average concentration of free sulphuric acid in the air was not higher than 0.1–0.2 mg/m^3.

Repair shop workers (239) were not continuously exposed to nickel compounds but certainly experienced short-term exposure to various nickel compounds in different locations in the works.

Results

There were 1,339 men and 49 women in the study. The numbers of person-years accumulated during the whole follow-up period (also including those without nickel exposure) were 34,320 and 1,081, respectively. The mean duration of follow-up of a person was 25.5 years. The number of person-years recorded following potential nickel exposure was 28,429 person-years (Table 1). In the nickel cohort, 24% of the follow-up years applied to workers aged less than 30 years; 68%, to those aged 30–59 years; and 8%, to those aged 60 years or more. There were 7,393 person-years (26%) with a latency of 20 years within the nickel cohort. The number of follow-up years in the nickel cohort increased by 8,025 after the previous report (Karjalainen et al. 1992).

Table 2 shows the results with regard to cancer incidence for the whole study cohort as defined by the exposure status to nickel. The extension of follow-up since the earlier study added 9 new cancer cases among the nonexposed group and 35 among the nickel-exposed group. The increases in the expected numbers were 11.3 and 31.3, respectively. The overall incidence of cancer was at the expected level among both the unexposed (SIR 1.00) and exposed (SIR 1.02) workers (Table 2).

Table 2 Observed and expected numbers and SIRs of selected cancer types at Harjavalta Works in Finland as determined from 1953 to 1995 by exposure status to nickel (*Obs* observed, *Exp* expected)

Primary site (ICD 7 code)	Unexposed to nickel				Exposed to nickel			
	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
All sites (140–204)	40	40.1	1.00	0.71–1.35	71	69.5	1.02	0.80–1.28
Stomach (151)	7	4.6	1.51	0.61–3.11	9	5.7	1.57	0.72–2.97
Colon (153)	0	1.6	0.00	0.00–2.35	2	3.2	0.63	0.08–2.27
Rectum (154)	2	1.5	1.32	0.16–4.75	2	2.6	0.76	0.09–2.74
Nose, sinuses (160)	0	0.1	0.00	0.00–26.2	2	0.2	8.79	1.06–31.7*
Latency 20+ years	*0*	*0.1*	*0.00*	*0.00–37.8*	*2*	*0.1*	*15.9*	*1.92–57.3**
Larynx (161)	1	0.9	1.14	0.03–6.36	1	1.3	0.79	0.02–4.40
Lung, trachea (162.0–1)	13	10.7	1.22	0.65–2.08	21	15.1	1.39	0.86–2.13
Latency 20+ years	*13*	*8.8*	*1.48*	*0.79–2.53*	*20*	*9.4*	*2.12*	*1.29–3.27***
Mesothelioma[a]	0	0.1	0.00	0.00–40.1	0	0.3	0.00	0.00–13.0
Prostate (177)	3	5.2	0.58	0.12–1.68	6	7.1	0.85	0.31–1.84
Testis (178)	0	0.1	0.00	0.00–35.7	0	0.9	0.00	0.00–4.17
Kidney (180)	0	1.4	0.00	0.00–2.56	3	3.0	1.00	0.21–2.90
Bladder (181)	3	2.0	1.50	0.31–4.38	2	3.5	0.57	0.07–2.04
Skin melanoma (190)	0	0.7	0.00	0.00–5.21	3	2.5	1.22	0.25–5.36
Nervous system (193)	0	1.0	0.00	0.00–3.89	3	2.9	1.02	0.21–2.98

* $P < 0.05$; ** $P < 0.01$

[a] Includes mesothelioma cases, after histological verification, of the pleura (ICD-7 162.2) and peritoneum (ICD-7 158)

None of the SIRs noted for specific primary sites was in statistically significant excess except that recorded for nasal cancer in the nickel-exposed cohort. When a latency time of 20 years from the first date of employment in nickel work was considered, the risk of nasal and lung cancers were increased significantly among the exposed cohort members. No case of mesothelioma was observed; the expected number for the whole cohort was 0.4.

Among nickel-exposed smelter workers the overall and stomach cancer incidences were at the expected levels, but the incidence of lung cancer was in slight excess (Table 3). There was a 2-fold significant increase among the smelter workers in terms of the risk for lung cancer when a latency time of 20 years was allowed. The risk was not associated with the duration of employment, the SIR approaching unity among workers with an employment period of 5 or more years in the smelter since 1960.

Among refinery workers the overall cancer incidence was slightly increased (Table 4). The risks for stomach (SIR 4.98) and nasal (SIR 41.1) cancers were significantly increased. In all, 19 of 21 cancer cases in the refinery population had been observed after 20 years since the first exposure to nickel. Assuming such a latency interval, the risks for overall cancer as well as for stomach, nasal, and lung cancers were in statistically significant excess. There were 16 cases (8.6 expected) of cancer among employees with a duration of employment in the refinery of at least 5 years. Risks for overall (SIR

Table 3 Observed and expected numbers and SIRs of selected cancer types among nickel-exposed smelter workers at Harjavalta Works in Finland as determined from 1960 to 1995 by latency time and duration of employment in the exposed work (*Obs* observed, *Exp* expected)

Primary site (ICD 7 code)	Obs	Exp	SIR	95% CI
All sites (140–204)	46	45.0	1.02	0.75–1.36
Stomach (151)	4	4.0	1.01	0.27–2.57
Nose, sinuses (160)	0	0.2	0.00	0.00–24.8
Lung, trachea (162.0–1)	15	10.8	1.39	0.78–2.28
Prostate (177)	5	5.3	0.94	0.31–2.20
Latency 20+ years:				
All sites (140–204)	31	27.8	1.12	0.76–1.58
Stomach (151)	2	2.0	1.00	0.12–3.59
Nose, sinuses (160)	0	0.08	0.00	0.00–46.1
Lung, trachea (162.0–1)	13	6.5	2.00	1.07–3.42*
Prostate (177)	2	4.3	0.46	0.06–1.67
Duration of employment 5+ years:				
All sites (140–204)	25	32.7	0.76	0.50–1.12
Stomach (151)	1	2.8	0.36	0.01–1.99
Nose, sinuses (160)	0	0.1	0.00	0.00–34.9
Lung, trachea (162.0–1)	8	8.0	1.01	0.43–1.98
Prostate (177)	1	4.1	0.24	0.01–1.35

* $P < 0.05$

Table 4 Observed and expected numbers and SIRs of selected cancer types among nickel refinery workers at Harjavalta Works in Finland as determined from 1960 to 1995 by latency time and duration of employment in the exposed work (*Obs* observed, *Exp* expected)

Primary site (ICD 7 code)	Obs	Exp	SIR	95% CI
All sites (140–204)	21	15.4	1.36	0.84–2.08
Stomach (151)	5	1.0	4.98	1.62–11.6**
Nose, sinuses (160)	2	0.05	41.1	4.97–148**
Lung, trachea (162.0–1)	6	2.3	2.61	0.96–5.67
Prostate (177)	2	0.8	2.45	0.30–8.85
Latency 20+ years:				
All sites (140–204)	19	9.6	1.98	1.19–3.08**
Stomach (151)	3	0.6	4.97	1.02–14.5*
Nose, sinuses (160)	2	0.03	67.1	8.12–242***
Lung, trachea (162.0–1)	6	1.8	3.38	1.24–7.36*
Prostate (177)	2	0.8	2.62	0.32–9.47
Duration of employment 5+ years:				
All sites (140–204)	16	8.6	1.86	1.07–3.02*
Stomach (151)	4	0.6	6.75	1.84–17.3**
Nose, sinuses (160)	2	0.03	75.2	9.10–271***
Lung, trachea (162.0–1)	3	1.5	1.99	0.41–5.80
Prostate (177)	2	0.6	3.20	0.39–11.6

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

1.85), stomach (SIR 6.75), and nasal cancers (SIR 75.2) increased with the duration of employment. A similar pattern was not seen for lung cancer. There was also a nonsignificant excess of prostate cancer among the refinery workers.

The analysis of the subgroups of "smelter only" and "refinery only" did not essentially change the risk estimates obtained in the basic analysis. None of the workers with nasal or stomach cancer had worked in both the smelter and the refinery, whereas two workers with lung cancer had done so. We did not detect any marked increase in the cancer risk among repair shop workers (SIR of overall cancer 0.88, 12 cases observed; SIR of lung cancer 0.67, 2 cases observed).

Discussion

Thus far, our study evaluating the cancer risk among 1,155 workers with exposures to mixed amounts and forms of nickel at a Cu/Ni smelter and Ni refinery has yielded 28,000 person-years at follow-up, one-fourth of these with a latency period of 20 years or more. Although the size of the present cohort is not large, this study has some advantages in comparison with some earlier studies on nickel workers. The tracing of the cohort members was almost complete. The cancer registration system in Finland is virtually complete (Teppo et al. 1994), and the computerized record-linkage procedure is precise (Pukkala 1992). Therefore, technical incompleteness does not cause underestimation in the results. Observed and expected cases share the same base; therefore, they are strictly comparable. In the Outokumpu Harjavalta electrolytic nickel refinery, where nickel production commenced in 1960, industrial hygienic measurements are available from 1966 onward. Exposure to nickel is thus documented unusually well during the whole production time.

In this update we have corroborated the earlier finding (Karjalainen et al. 1992) of an increased risk for nasal cancer among the 418 refinery workers. The risk was positively associated with the latency and with the duration of employment in the refinery. Refinery workers was the only group exposed to soluble nickel sulfate. The lung cancer risk was also increased, particularly when a long latency period was assumed. However, the lung cancer risk did not clearly increase with increasing duration of employment in the refinery.

Among refinery workers, in addition to the two nasal cancer cases (ICD-7 code 160) observed during the follow-up period, a further such case was diagnosed in the summer of 1997. Furthermore, a large tumor, partly located in the nose, was observed in 1990 in a female refinery employee, who had worked in the refinery from 1960 to 1977. The exact anatomical origin (nose or pharynx) of this tumor is not clear, and the tumor was classified as a nasopharyngeal cancer (ICD-7 code 146). The expected number of nasopharyngeal cancers in the refinery cohort was 0.04. The finding of a further case of nasal cancer among refinery workers so soon after the closing date of the follow-up and the fourth case, which could also equally well be of nasal origin, point to the possibility that the relative risk presented for nasal cancer in this report is likely to be an underestimate of the true risk.

According to earlier studies, both nasal and lung cancers have been associated with exposure to nickel compounds (Doll et al. 1990; IARC 1990). The Norwegian studies among Kristiansand refinery workers have given strong evidence of a relationship between exposure to soluble nickel and the incidence of cancer of the lung and nasal sinuses (Pedersen et al. 1973; Magnus et al. 1982, Doll et al. 1990; Andersen et al. 1996). An increase in the mortality of these cancers was observed in the studies in Clydach, whereas the data on Port Colborne electrolysis workers were more equivocal (Doll et al. 1990).

It is not likely that the main finding of an excess in nasal and lung cancer risk among refinery workers – showing such high relative risk point estimates – would be explained by occupational exposures other than those to nickel compounds, by smoking habits, or by other social-class-related habits. There is nothing to suggest that smoking habits or life style were different between the refinery and smelter workers.

Among the smelter workers exposed to low levels of nonsoluble nickel and to other metals and chemicals, the nasal cancer incidence was not elevated and the lung cancer risk estimates were lower. As exposure to arsenic took place during rather late periods, from the 1980s onward, it hardly affects the lung cancer rates in the present update. Nonetheless, only limited data on occupational exposures were available for the smelter population, and it is therefore difficult to attribute any effects solely to nickel among them.

In the present study an increased risk for stomach cancer was also observed among the refinery workers – increasing with the duration of employment – but not among the smelter workers. No relationship between exposure to nickel compounds and gastric cancer has been observed in the most informative studies among refinery workers (Doll 1990; IARC 1990; Andersen et al. 1996; Julian and Muir 1996). Increased risks have been reported only in some early studies (Saknyn and Shabynina 1970, 1973) was and among a small group of nickel platers (Pang et al. 1996). We cannot rule out the possibility that the excess stomach cancer risk was a chance finding or related to factors in the working environment.

A statistically nonsignificant increase was seen in the incidence of prostatic cancer among the refinery workers. Similar small increases were reported in the refinery cohorts with high levels of exposure to nickel compounds (Doll et al. 1990; Julian and Muir 1996; Andersen et al. 1996).

It has previously been suggested that respiratory cancer risks are primarily related to exposure to soluble

nickel at concentrations in excess of 1 mg/m^3 and to exposure to less soluble forms at concentrations of greater than 10 mg/m^3 (Doll et al. 1990). According to the industrial hygienic measurements available, exposure levels within this cohort have been much lower. It was not until the early 1990s that the workers started the systematic use of effective respirators and protective masks. Importantly, when masks are used in tasks where the concentrations of nickel in air are expected to be high, the present levels of exposure are generally below 10 μg/m^3 (see Kiilunen et al. 1997).

In conclusion, the present study showed little evidence of an elevated risk for respiratory tract cancer among workers in the nickel smelter, where the sources of exposure involved sparingly soluble nickel compounds. In contrast, among employees in the nickel refinery, where the primary source of exposure was nickel sulfate (although workers were also exposed to a smaller extent to some other nickel species and even to other metals and chemicals), there was an elevated risk for nasal cancer and also for lung and stomach cancer. This study strengthens earlier findings on the nasal and lung cancer risk involved in exposure to nickel sulfate. The study indicates that the respiratory cancer risk may be elevated at exposure levels considered safe until now.

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