# 4. Summary of Data Reported and Evaluation

## 4.1 Exposure data

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin contact occur in nickel and nickel alloy production plants as well as in welding, electroplating, grinding and cutting operations. Airborne nickel levels in excess of 1 mg/m$^3$ have been found in nickel refining, in the production of nickel alloys and nickel salts, and in grinding and cutting of stainless-steel. In these industries, modern control technologies have markedly reduced exposures in recent years. Few data are available to estimate the levels of past exposures to total airborne nickel, and the concentrations of individual nickel compounds were not measured.

Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake. Non-occupational sources of nickel exposure include food, air and water, but the levels found are usually several orders of magnitude lower than those typically found in occupational situations.

**Table 26. INCO Ontario (Canada) nickel refinery facilities – average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a]**

| Plant | Department | Estimated airborne concentration ($mg/m^3$ Ni) | | | | | Duration in department | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Ever | | | | ≥5 years | | | |
| | | | | | | | Lung cancer | | Nasal cancer | | Lung cancer | | Nasal cancer | |
| | | Metallic nickel | Oxidic nickel | Sulfidic nickel | Soluble nickel | Total nickel | Obs | SMR (95% CI) | Obs | SMR (95% CI) | Obs | SMR (95% CI) | Obs | SMR (95% CI) |
| Coniston | Sinter | Negl.[b] | 0.1–0.5 | 1–5 | Negl. | 1–5 | 8 | 292 (126–576) | 0 | – | 6 | 492 (181–1073) | 0 | – |
| Copper Cliff | Sinter | | | | | | | | | | | | | |
| 1948–54 | | Negl. | 25–60 | 15–35 | <4 | 40–100 | 63 | 307 (238–396) | 6 | 3617 (1327–7885) | 33 | 789 (543–1109) | 4 | 13 146 (3576–33 654) |
| 1955–63 | | Negl. | 5–25 | 3–15 | <2 | 8–40 | | | | | | | | |
| Port Colborne | Leaching, calcining, | | | | | | | | | | | | | |
| 1926–35 | sintering | Negl. | 20–40 | 10–20 | <3 | 30–80 | 72 | 239 (187–302) | 19 | 7776 (4681–12 144) | 38 | 366 (259–502) | 15 | 18 750 (10 500–30 537) |
| 1936–45 | | Negl. | 3–15 | 2–10 | <3 | 5–25 | | | | | | | | |
| 1946–58 | | Negl. | 5–25 | 3–15 | <3 | 8–40 | | | | | | | | |
| | Electrolysis | <0.5 | <0.2 | <0.5 | <0.3 | <1 | 19 | 88[d] (53–137) | 0[c,d] | – | 10[d,e] | 89 | 0[c,d] | – |

[a]From ICNCM (1990), estimated average airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department; standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]Negl., negligible exposure

[c]Two nasal cancer deaths occurred in men with >20 years in electrolysis and only short exposure (three months and seven months) in leaching, calcining and sintering

[d]Never worked in leaching, calcining and sintering

[e]Workers with ≥10 years in electrolysis

**Table 27. MOND/INCO (Clydach, South Wales, UK) nickel refinery – average nickel exposure levels and cancer risks in 'high-risk' departments in workers with 15 or more years since first exposure[a]**

| Department | Estimated airborne concentration ($mg/m^3$ Ni)[b] | | | | Duration in department | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Metallic nickel | Oxidic nickel | Sulfidic nickel | Soluble nickel | Ever | | | | ≥5 years | | | |
| | | | | | Lung cancer | | Nasal cancer | | Lung cancer | | Nasal cancer | |
| | | | | | Obs | SMR (95% CI) | Obs | SMR (95% CI) | Obs | SMR (95% CI) | Obs | SMR (95% CI) |
| Furnaces, 1905–63 | 5.6 | 6.4 | 2.6 | 0.4 | 9 | 409 | 3 | 24 781 | 1 | 370 | 3 | 1000 |
| Linear calciners, 1902–30; milling and grinding, 1902–36 | 5.3 | 18.8 | 6.8 | 0.8 | 16 | 725 | 7 | 44 509 | 12 | 1244 | 6 | 78 280 |
| Copper plant, before 1937 | – | 13.1 | 0.4 | 1.1 | 17 | 317 (185–507) | 5 | 13 912 (4507–32 415) | 8 | 541 (233–1066) | 2 | 14 541 (1759–52 493) |
| 1938–60 | – | 0.4 | 0.01 | 0.01 | – | | – | | – | | – | |
| Hydrometallurgy 1902–79 | 0.5 | 0.9 | 0.05 | 1.3 | 7 | 196 (79–404) | 4 | 18 779 (5108–48 074) | 5 | 333 (108–776) | 4 | 36 363 (9891–93 089) |

[a]From ICNCM (1990); estimated average airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department. In each row, observations are restricted to men with < 1 year employment in other high-risk departments. Standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]The Working Group expressed reservations about the accuracy of these estimates, as discussed on p. 391.

**Table 28. Falconbridge (Kristiansand, Norway) nickel refinery – average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a]**

| Department | Estimated airborne concentration ($mg/m^3$ Ni) | | | | Duration in department | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Ever | | | | ≥5 years | | | |
| | | | | | Lung cancer | | Nasal cancer[b] | | Lung cancer | | Nasal cancer[b] | |
| | Metallic nickel | Oxidic nickel | Sulfidic nickel | Soluble nickel | Obs | SMR (95% CI) | Obs | SMR (95% CI) | Obs | SMR (95% CI) | Obs | SMR (95% CI) |
| Calcining, roasting, smelting; never in electrolysis | 0.3–1.3 | 5.0–10.0 | 0.3 | Negl.[c] | 14 | 225 (122–377) | 5 | – | 8 | 254 (109–500) | 5 | – |
| Electrolysis; never in calcining, roasting smelting | 0.3–1.3 | 0.3–1.3 | Negl.–1.3 | 1.3–5.0 | 30 | 385 (259–549) | 2 | – | 19 | 476 (287–744) | 2 | – |

[a]From ICNCM (1990); estimated average airborne concentrations of nickel species and mortality from or incidence of lung cancer and nasal cancer by department; standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]Three deaths and four incident cases

[c]Negl., negligible exposure

## 4.2 Experimental carcinogenicity data

### Metallic nickel and nickel alloys

*Metallic nickel* was tested by inhalation exposure in mice, rats and guinea-pigs, by intratracheal instillation in rats, by intramuscular injection in rats and hamsters, and by intrapleural, subcutaneous, intraperitoneal and intrarenal injection in rats. The studies by inhalation exposure were inadequate for an assessment of carcinogenicity. After intratracheal instillation, it produced significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung. Intrapleural injections induced sarcomas. Subcutaneous administration of metallic nickel pellets induced sarcomas in rats, intramuscular injection of nickel powder induced sarcomas in rats and hamsters, and intraperitoneal injections induced carcinomas and sarcomas. No significant increase in the incidence of local kidney tumours was seen following intrarenal injection.

*Nickel alloys* were tested by intramuscular, intraperitoneal and intrarenal injection and by subcutaneous implantation of pellets in rats. A ferronickel alloy did not induce local tumours after intramuscular or intrarenal injection. Two powdered nickel alloys induced malignant tumours following intraperitoneal injection, and one nickel alloy induced sarcomas following subcutaneous implantation in pellets.

### Nickel oxides and hydroxides

*Nickel monoxide* was tested by inhalation exposure in rats and hamsters, by intratracheal instillation in rats, by intramuscular administration in two strains of mice and two strains of rats, and by intrapleural, intraperitoneal and intrarenal injection in rats. The two studies by inhalation exposure in rats were inadequate for an assessment of carcinogenicity; lung tumours were not induced in the study in hamsters. Intratracheal instillation resulted in a significant incidence of lung carcinomas. Local sarcomas were induced at high incidence after intrapleural, intramuscular and intraperitoneal injection. No renal tumour was seen following intrarenal injection.

Two studies in rats in which *nickel trioxide* was injected intramuscularly or intracerebrally were inadequate for evaluation.

In a study in which *nickel hydroxide* was tested in three physical states by intramuscular injection in rats, local sarcomas were induced by dry gel and crystalline forms. Local sarcomas were induced in one study in which nickel hydroxide was tested by intramuscular injection in rats.

### Nickel sulfides

*Nickel subsulfide* was tested by inhalation exposure and by intratracheal instillation in rats, by subcutaneous injection to mice and rats, by intramuscular admin-

istration to mice, rats, hamsters and rabbits, by intrapleural, intraperitoneal, intrarenal, intratesticular, intraocular and intra-articular administration in rats, by injection into retroperitoneal fat in rats, by implantation into rat heterotopic tracheal transplants and by administration to pregnant rats.

After exposure by inhalation, rats showed a significant increase in the incidence of benign and malignant lung tumours. Multiple intratracheal instillations resulted in malignant lung tumours (adenocarcinomas, squamous-cell carcinomas and mixed tumours).

A high incidence of local sarcomas was observed in rats after intrapleural administration. Subcutaneous injection induced sarcomas in mice and rhabdomyosarcomas and fibrous histiocytomas in rats. Nickel subsulfide has been shown consistently to induce local sarcomas following intramuscular administration, and dose-response relationships were demonstrated in rats and hamsters. The majority of the sarcomas induced were of myogenic origin, and the incidences of metastases were generally high. In rats, strain differences in tumour incidence and local tissue responses were seen. After intramuscular implantation of millipore diffusion chambers containing nickel subsulfide, a high incidence of local sarcomas was induced.

Mesotheliomas were included among the malignancies induced by intraperitoneal administration. Intrarenal injections resulted in a dose-related increase in the incidence of renal-cell neoplasms. A high incidence of sarcomas (including some rhabdomyosarcomas) was seen after intratesticular injection, and a high incidence of eye neoplasms (including retinoblastomas, melanomas and gliomas) after intraocular injection. Intra-articular injection induced sarcomas (including rhabdomyosarcomas and fibrous histiocytomas), and injection into retroperitoneal fat induced mainly fibrous histiocytomas. Implantation of pellets containing nickel subsulfide into rat heterotopic tracheal transplants induced both carcinomas and sarcomas; in the group given the highest dose, sarcomas predominated. The study in which pregnant rats were injected with nickel subsulfide early in gestation was inadequate for evaluation.

*Nickel disulfide* was tested by intramuscular and intrarenal injection in rats. High incidences of local tumours were induced.

*Nickel monosulfide* was tested by intramuscular and intrarenal injection in rats. The crystalline form induced local tumours, but the amorphous form did not.

*Nickel ferrosulfide matte* induced local sarcomas after administration by intramuscular injection in rats.

**Nickel salts**

*Nickel sulfate* was tested for carcinogenicity by intramuscular and intraperitoneal injection in rats. Repeated intramuscular injections did not induce local

tumours; however, intraperitoneal injections induced malignant tumours in the peritoneal cavity.

*Nickel chloride* was tested by repeated intraperitoneal injections in rats, inducing malignant tumours in the peritoneal cavity.

*Nickel acetate* was tested by intraperitoneal injection in mice and rats. After repeated intraperitoneal injections in rats, malignant tumours were induced in the peritoneal cavity. In strain A mice, lung adenocarcinomas were induced in one study and an increased incidence of pulmonary adenomas in two studies.

Studies in rats in which *nickel carbonate* was tested for carcinogenicity by intraperitoneal administration and *nickel fluoride* and *nickel chromate* by intramuscular injection could not be evaluated.

### Other forms of nickel

*Nickel carbonyl* was tested for carcinogenicity by inhalation exposure and intravenous injection in rats. After inhalation exposure, a few lung carcinomas were observed two years after the initial treatment. Intravenous injection induced an increase in the overall incidence of neoplasms, which were located in several organs.

*Nickelocene* induced some local tumours in rats and hamsters following intramuscular injection.

One sample of *dust collected in nickel refineries*, containing nickel subsulfide and various proportions of nickel monoxide and nickel sulfate, induced sarcomas in mice and rats following intramuscular injection. Intraperitoneal administration of two samples of dust, containing unspecified nickel sulfides and various proportions of nickel oxide, soluble nickel and metallic nickel, induced sarcomas in rats. In a study in which hamsters were given prolonged exposure to a *nickel-enriched fly ash* by inhalation, the incidence of tumours was not increased.

Intramuscular administration to rats of *nickel sulfarsenide*, two *nickel arsenides*, *nickel antimonide*, *nickel telluride* and two *nickel selenides* induced significant increases in the incidence of local sarcomas, whereas administration of *nickel monoarsenide* and *nickel titanate* did not. None of these compounds increased the incidence of renal-cell tumours in rats after intrarenal injection.

## 4.3 Human carcinogenicity data

Increased risks for lung and nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand) and the UK (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant) and extraction of nickel salts from concentrated solution (hydrometallurgy) in the UK (see Table 26).

The substantial excess risk for lung and nasal cancer among Clydach hydrometallurgy workers seems likely to be due, at least partly, to their exposure to 'soluble nickel'. Their estimated exposures to other types of nickel (metallic, sulfidic and oxidic) were up to an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. Similarly, high risks for lung and nasal cancers were observed among electrolysis workers at Kristiansand. These men were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate was the only or predominant soluble nickel species present in these areas.

The highest risks for lung and nasal cancers were observed among calcining workers, who were heavily exposed to both sulfidic and oxidic nickel. A high lung cancer rate was also seen among nickel plant cleaners at Clydach, who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides cannot be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in calcining furnaces and nickel plant cleaners were also exposed to high levels of metallic nickel.

Among hard-rock sulfide nickel ore miners in Canada, there was some increase in lung cancer risk, but exposure to other substances could not be excluded. In studies of open-cast miners of silicate-oxide nickel ores in the USA and in New Caledonia, no significant increase in risk was seen, but the numbers of persons studied were small and the levels of exposure were reported to be low.

No significant excess of respiratory tract cancer was observed in three studies of workers in high-nickel alloy manufacture or in a small study of users of metallic nickel powder. No increase in risk for lung cancer was observed in one small group of nickel electroplaters in the UK with no exposure to chromium.

In a case-control study, an elevated risk for lung cancer was found among persons exposed to nickel together with chromium-containing materials.

The results of epidemiological studies of stainless-steel welders are consistent with the finding of excess mortality from lung cancer among other workers exposed to nickel compounds, but they do not contribute independently to the evaluation of nickel since welders are also exposed to other compounds. (See also the monograph on welding.)

### 4.4 Other relevant data

Nickel and nickel compounds are absorbed from the respiratory tract, and to a smaller extent from the gastrointestinal tract, depending on dissolution and cellular uptake. Absorbed nickel is excreted predominantly in the urine. Nickel tends to persist in the lungs of humans and of experimental animals, and increased concen-

trations are seen notably in workers after inhalation of nickel. The nasal mucosa may retain nickel for many years.

Nickel carbonyl is the most acutely toxic nickel compound and causes severe damage to the respiratory system in experimental animals and in humans. Nickel causes contact dermatitis in humans. In experimental animals, adverse effects have also been documented in the respiratory system and in the kidney.

In four studies, the frequency of sister chromatid exchange did not appear to be increased in peripheral blood lymphocytes of nickel workers exposed during various processes. Enhanced frequencies of chromosomal gaps and/or anomalies were observed in single studies in peripheral blood lymphocytes of employees engaged in: (i) crushing, roasting and smelting (exposure mainly to nickel oxide and nickel subusulfide); (ii) electrolysis (exposure mainly to nickel chloride and nickel sulfate); and (iii) electroplating (exposure to nickel and chromium compounds). Enhanced frequencies were also seen in lymphocytes from retired workers who had previously been exposed in crushing, roasting and smelting and/or electrolysis.

Some nickel compounds have adverse effects on reproduction and prenatal development in rodents. Decreased fertility, reduction in the number of pups per litter and birth weight per pup, and a pattern of anomalies, including eye malformations, cystic lungs, hydronephrosis, cleft palate and skeletal deformities, have been demonstrated.

In one study, metallic nickel did not induce chromosomal aberrations in cultured human cells, but it transformed animal cells *in vitro*. Nickel oxides induced anchorage-independent growth in human cells *in vitro* and transformed cultured rodent cells; they did not induce chromosomal aberrations in cultured human cells in one study.

Crystalline nickel subsulfide induced anchorage-independent growth and increased the frequency of sister chromatid exchange but did not cause gene mutation in human cells *in vitro*. Crystalline nickel sulfide and subsulfide induced cell transformation, gene mutation and DNA damage in cultured mammalian cells; the sulfide also induced chromosomal aberrations and sister chromatid exchange. Amorphous nickel sulfide did not transform or produce DNA damage in cultured mammalian cells. In one study, crystalline nickel sulfide and crystalline nickel subsulfide produced DNA damage in *Paramoecium*.

Nickel chloride and nickel nitrate were inactive in assays *in vivo* for induction of dominant lethal mutation and micronuclei, and nickel sulfate did not induce chromosomal aberrations in bone-marrow cells; however, nickel chloride induced chromosomal aberrations in Chinese hamster and mouse bone-marrow cells.

Soluble nickel compounds were generally active in the assays of human and animal cells *in vitro* in which they were tested.

Nickel sulfate and nickel acetate induced anchorage-independent growth in human cells *in vitro*. Nickel sulfate increased the frequency of chromosomal aberrations in human cells, and nickel sulfate and nickel chloride increased the frequency of sister chromatid exchange. Nickel sulfate did not induce single-strand DNA breaks in human cells. Nickel sulfate and nickel chloride transformed cultured mammalian cells. Chromosomal aberrations were induced in mammalian cells by nickel chloride, nickel sulfate and nickel acetate, and sister chromatid exchange was induced by nickel chloride and nickel sulfate. Nickel chloride and nickel sulfate also induced gene mutation, and nickel chloride caused DNA damage in mammalian cells. In one study, nickel sulfate inhibited intercellular communication in cultured mammalian cells.

Nickel sulfate induced aneuploidy and gene mutation in a single study in *Drosophila*; nickel chloride and nickel nitrate did not cause gene mutation. Nickel chloride induced gene mutation and recombination in yeast.

In single studies, nickel acetate produced DNA damage in bacteria, while nickel nitrate did not; the results obtained with nickel chloride were inconclusive. In bacteria, neither nickel acetate, sulfate, chloride nor nitrate induced gene mutation.

Nickel carbonate induced DNA damage in rat kidney *in vivo*. Crystalline nickel subselenide transformed cultured mammalian cells, and nickel potassium cyanide increased the frequency of chromosomal aberrations. Nickelocene did not induce bacterial gene mutation. DNA damage was induced in calf thymus nucleohistone by nickel[III]-tetraglycine complexes.

## 4.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry.

There is *inadequate evidence* in humans for the carcinogenicity of metallic nickel and nickel alloys.

There is *sufficient evidence* in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulfides.

There is *limited evidence* in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride.

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[1]For descriptions of the italicized terms, see Preamble, pp. 33–37.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel trioxide, amorphous nickel sulfide and nickel titanate.

The Working Group made the overall evaluation on nickel compounds as a group on the basis of the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data, supported by the underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells.

**Overall evaluation**

Nickel compounds *are carcinogenic to humans* (Group 1).

Metallic nickel *is possibly carcinogenic to humans* (Group 2B).