NICKEL AND NICKEL COMPOUNDS (Group 1*)

A. Evidence for carcinogenicity to humans (*sufficient*)

Early epidemiological studies of populations of workers in nickel refineries in different countries clearly demonstrate excess incidences of cancers of the nasal cavity and lung and, possibly, excesses of cancer of the larynx. Although the carcinogen(s) could not be specified, the cancer hazards seemed to be associated primarily with the early stage of nickel refining. Nickel carbonyl was considered unlikely to be involved, while nickel subsulphide and nickel oxide emerged as the strongest candidates[1].

Later reports from Canada and the USA confirmed the increased risks for lung and sinonasal cancers carried by exposure during nickel refining operations, where the primary exposure was to nickel sulphides (including subsulphide) and nickel oxides[2-4]. The early studies of nickel refinery workers in Wales (UK) and Norway were extended and updated. Among workers in South Wales, the elevated risks for cancers of the lung and nasal sinuses persisted until 1930[5]. For both lung cancer (137 cases before 1925) and nasal cancer (56 cases before 1925), the increased risk was significantly associated with employment in calcining and at furnaces and with copper sulphate and nickel sulphate production[6,7]. In Norway, the highest incidence rates for cancers of the respiratory organs occurred among workers employed in roasting, smelting and electrolysis departments. The increased incidence of nasal cancers (21 cases; relative risk, 26.3) exhibited a very steep decrease with more recent

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38). After the meeting of the Working Group, the Secretariat became aware of epidemiological and experimental studies in progress on the carcinogenicity of nickel and nickel compounds.

year of first employment; the incidence of lung cancer (82 cases; relative risk, 3.7) gave no indication of a consistent decrease during the period 1916-1959. A slight, statistically nonsignificant excess of laryngeal cancer (5 cases observed, 2.4 expected) was also reported[8,9].

Reports of an increased occurrence of lung cancer among nickel smelting workers have also come from New Caledonia, Slovakia and the USSR[10-16].

There have been three case reports of cancers of the respiratory tract in workers who were involved in nickel plating and grinding operations[1].

Three investigations that examined the possible cancer risk associated with exposure to nickel and nickel compounds in nickel alloy plants showed no significant increase in mortality from cancer[17-19]. In one of these, excess mortality from lung cancer was noted in maintenance workers; however, it was unclear whether the risk was directly associated with nickel exposures[18]. Workers at a gaseous diffusion plant who were exposed to high-purity metallic nickel powder did not exhibit any increase in mortality from respiratory-tract cancers[20,21]. An incidence study at a hydrometallurgical nickel refining plant in Canada did not indicate an increased risk of cancer. Exposure was to metallic nickel and nickel concentrate dust[22].

Other investigations have addressed more complex and mixed exposure conditions and thus provide little evidence to evaluate the specific role of nickel and nickel compounds[23-30].

The association of specific types of cancer with nickel exposure has also been examined by means of case-control investigations. One study of cancer of the larynx supported an association with nickel exposure[31], but another did not[32]. Studies of sinonasal cancer and lung cancer yielded contradictory results; all suffered from inadequate description of the exposure to nickel[33-36]. In one of these[35], the risk was high in welders with nickel exposure (relative risk, 3.3, 95% confidence interval, 1.2-9.2); however, exposure to nickel compounds was so highly correlated with the presence of chromium that the observed exposure to nickel could have reflected a confounding effect of chromium (see p. 165). A study at an aircraft-engine factory showed no association between lung cancer deaths and exposure to nickel oxides, sulphate, chloride or alloys[37].

It is still not possible to state with certainty which specific nickel compounds are human carcinogens, and which are not. A large amount of evidence has accrued that nickel refining carries a carcinogenic risk to workers. The risk is particularly high in those exposed during certain processes, mainly entailing exposure to nickel (sub)sulphides and oxides. The lung and nasal sinuses are the most clearly established target organs.

B. Evidence for carcinogenicity to animals (*sufficient*)

Nickel subsulphide produced malignant tumours in rats after its inhalation[1] or intramuscular[1,38,39], intrarenal[40,41], intratesticular[42] or intraocular[43] administration and after its insertion into heterotransplanted tracheas[44]; it also produced local sarcomas in mice and rabbits after intramuscular administration[1,45-47]. Nickel powder, nickel oxide, hydroxide and carbonate, nickelocene and nickel-iron sulphide matte produced local sarcomas in mice, rats, hamsters and rabbits when given intramuscularly[1,38,48]. Intravenous

administration of nickel carbonyl increased the incidences of various tumours in rats[1], and inhalation of nickel carbonyl produced a low incidence of lung tumours in rats[1]. Nickelous acetate administered intraperitoneally to mice produced an excess of lung adenomas and carcinomas[49]. Nickel sulphide produced renal tumours in rats when injected intrarenally[50].

With few exceptions, the nickel compounds tested produced sarcomas and/or carcinomas at the tissue sites where they were deposited. Bioavailability and persistence in the tissues appear to be important in nickel carcinogenesis.

C. Other relevant data

Studies of the uptake, content and release of nickel in nasal mucosa indicate that workers exposed to water-insoluble nickel salts (e.g., roasting and smelting workers) retain more nickel than those exposed to soluble compounds (e.g., electrolysis workers). Nickel accumulated during active work is retained in the mucous membrane for years after retirement[51-53].

Workers exposed to nickel in one refinery had slight excesses of chromosomal aberrations (mainly gaps) in their peripheral lymphocytes, but no increase in the incidence of sister chromatid exchanges was seen[54].

Nickel compounds did not induce dominant lethal mutations in mice. Soluble nickel compounds caused DNA strand breaks and cross-links in rats treated *in vivo*, and particles of crystalline nickel sulphide bound to DNA in Chinese hamster cells *in vitro*. Nickel compounds were weakly active in inducing chromosomal aberrations and sister chromatid exchanges in human lymphocytes and rodent cells *in vitro*. They induced transformation in several rodent cell systems *in vitro*. Particles of crystalline nickel sulphides induced mutation in a protozoan. In general, negative results were obtained in bacterial mutation assays; nickel compounds induced prophage in bacteria. Insoluble nickel compounds bound to isolated DNA[54].

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