Chapter 6.10 Nickel

General description

Nickel (Ni) is a silvery-white, hard metal. Although it forms compounds in several oxidation states, the divalent ion seems to be the most important for both organic and inorganic substances, but the trivalent form may be generated by redox reactions in the cell *(1)*. Nickel compounds that are practically insoluble in water include carbonate, sulfides (the main forms being amorphous or crystalline monosulfide, NiS, and subsulfide Ni_3S_2) and oxides (NiO, Ni_2O_3). Water-insoluble nickel compounds may dissolve in biological fluids *(2)*. Particles of the same chemical entity (oxides and sulfides) have different biological activity depending on crystalline structure and surface properties *(3,4)*.

Soluble nickel salts include chloride, sulfate and nitrate. Nickel carbonyl ($Ni(CO)_4$) is a volatile, colourless liquid with a boiling-point of 43 ^oC; it decomposes at temperatures above 50 ^oC. In biological systems, nickel forms complexes with adenosine triphosphate, amino acids, peptides, proteins and deoxyribonucleic acid.

Sources

Nickel is widely distributed in nature, forming about 0.008% of the earth's crust. The core of the earth contains 8.5% nickel, deep-sea nodules 1.5%; meteorites have been found to contain 5–50% nickel *(5)*.

The natural background levels of nickel in water are relatively low, in open ocean water 0.228–0.693 µg/litre, in fresh water systems generally less than 2

Agricultural soils contain nickel at levels of 3–1000 mg/kg; in 78 forest floor samples from the north-eastern United States of America, concentrations of 8.5–15 mg/kg were reported *(6)*.

The nickel content is enriched in coal and crude oil. Nickel in coals ranges up to 300 mg/kg; most samples contain less than 100 mg/kg but there is a large variation by region *(7)*. The nickel content of crude oils is in the range <1–80 mg/kg *(6,8)*.

Production and use

There are two commercial classes of nickel ore, the sulfide ores (pentlandite and pyrrhotite) and the silicate-oxide. Most nickel is produced from the sulfide ores, and the two largest producers, Canada and the Russian Federation, account for 20–25% each of total annual production, which was 784.82 thousand tonnes in 1988 *(5)*.

Intermediate uses of nickel include 42% in steel production and 36% in the production of other alloys. Electroplating in the form of nickel sulfate accounts for about 18%. The most important end-uses are transportation 23%, chemical industry 15%, electrical equipment 12%, and construction

10% *(6)*. Nickel in coinage, other manufactured products and household appliances may be important for some health effects (dermatitis).
The burning of residual and fuel oils, nickel mining and refining, and municipal waste incineration are the main anthropogenic sources of nickel emissions to the atmosphere *(6)*. These sources account for about 90% of the total global emission, estimated to be 42.85×10^6 kg/year.

The major nickel species in ambient air is nickel sulfate. This soluble ("leachable") form is estimated to comprise 60–100% *(9)*, or 15–93% (average 54%) *(10)* of the nickel components emitted by fly ash from oil-fired utility boilers. The corresponding value for nickel sulfate emission arising from coal combustion is 20–80%. The insoluble fraction of fly ash emitted from both oil and coal combustion exists as nickel oxides and complex metal oxides (ferrites, aluminates, vanadates). Estimates of emission from natural sources vary in the range $8.5–160 \times 10^6$ kg/year *(6)*.

Occurrence in air
Because of the large number of nickel-releasing sources, the nickel concentration in ambient air may show considerable variation. In a remote area (Canadian Arctic) levels of 0.38–0.62 ng/m^3 were recorded *(11)*, as compared to 124 ng/m^3 in the vicinity of a nickel smelter *(12)*. In northern Norway, a level of about 1 ng/m^3 was recorded in an unpolluted area as compared to about 5 ng/m^3 some 5 km distant from a nickel smelter (average values 1990-1991). The highest value recorded was 64 ng/m^3 *(13,14)*. Concentrations of 18–42 ng/m^3 were recorded in 8 United States cities *(15)*. These values correspond to the average value of 37 ng/m^3 for 30 United States Urban Air National Surveillance Network Stations for the period 1957–1968. This average decreased from 47 ng/m^3 for 1957–1960 to 26 ng/m^3 for 1965–1968. The mean (arithmetic) value for 1970–1974 was 13 ng/m^3 *(16)*. Ranges of 10–50 ng/m^3 and 9–60 ng/m^3 have been reported in European cities. Higher values (110–180 ng/m^3) have been reported from heavily industrialized areas *(17)*.

Pentlandite [$(FeNi)_9S_8$] and nickel in the silicate zone (also called the garnierite zone) are two naturally occurring forms of nickel found in rocks. Nickel from man-made sources is probably represented mostly by oxides and sulfates of rather small particle size (mass median diameter (MMD) about 1 µm) and some 15–90% is soluble (leachable). Occupational studies of nickel exposure have not provided dose-specific estimates of risk for individual species, and only rarely total exposure estimates that are comparable between the different plants.

The MMD of nickel in urban air is 0.83–1.67 µm, and less than 1 µm in 28 55% of particles *(18)*. An MMD of 0.98 µm has also been reported *(19)*. The highest concentration of nickel was found in the smallest particles emitted from a coal-fired plant *(20)*. Particles with an MMD of 0.65–1.1 µm contained nickel at a concentration of 1600 mg/kg, while particles of 4.7–11 µm contained 400 mg/kg. Nickel-containing particles released from oil combustion (California, urban area) are in the fine-size fraction, with MMDs of less than 1 µm *(21)*. Nickel carbonyl has never been demonstrated in ambient air.

Analytical methods
Absorption on cellulose ester membrane filters followed by wet digestion and analysis by electrothermal atomic absorption spectrometry (ET-AAS), inductively coupled plasma atomic emission (ICP-AES) or ICP-mass spectrometry are suitable for analysis of nickel in air, with a detection limit of 5 ng/sample *(22)*.

ET-AAS with Zeeman background correction is currently the most common technique for determining nickel in biological materials. Detection limits of 0.4 mg/litre for urine and 0.05 µg/litre for serum have been reported. It is important to exclude sample contact with nickel-containing materials (e.g. steel syringes) *(23,24)*.

Routes of exposure

The main routes of nickel intake for humans are inhalation, ingestion and absorption through the skin.

Air

Assuming a daily respiratory rate of 20 m^3, the amount of airborne nickel entering the respiratory tract is in the range 0.1–0.8 µg/day when concentrations are 5–40 ng/m^3 in ambient air. Owing to the variation in particle size and solubility between nickel compounds, no general statements can be made on the retention or absorption of nickel in the respiratory tract *(25)*. A total deposition of about 50% of the inhaled dose was estimated for particles with an MMD of 2.0 µm, while deposition was about 10% for those of 0.5 µm. For larger particles, more than 50% of the deposited dose was in the nasopharyngeal part of the respiratory tract as against less than 10% for the smaller particles.

In a single experiment, 95% of the nickel in a respirable aerosol of nickel-enriched fly ash was retained in the lung one month after the exposure *(26)*. Following intratracheal administration of nickel chloride, only 0.1% was retained in the lungs of rats at day 21 *(27)*.

About 0.04–0.58 µg of nickel is released with the mainstream smoke of one cigarette *(6)*. Smoking 40 cigarettes per day may thus lead to inhalation of 2–23 µg of nickel. The possibility that nickel occurs in mainstream smoke in part as nickel carbonyl has never been substantiated.

Drinking-water

Nickel concentrations in drinking-water in European countries of 2–13 µg/litre have been reported *(28)*. An average value of 9 µg/litre and a maximum of 34 µg/litre were recorded in Germany *(29)*. Nickel may, however, be leached from nickel-containing plumbing fittings, and levels of up to 500 µg/litre have been recorded in water left overnight in such fittings *(30)*. In areas with nickel mining, levels of up to 200 µg/litre have been recorded in drinking-water. The average level of nickel in drinking-water in public water supply systems in the United States was 4.8 µg/litre in 1969.

Assuming a concentration of 5–10 µg/litre, a daily consumption of 2 litres of drinking-water would result in a daily nickel intake of 10–20 µg.

Food

In most food products, the nickel content is less than 0.5 mg/kg fresh weight. Cacao products and nuts may, however, contain as much as 10 and 3 mg/kg, respectively *(5)*.

Total diet studies indicate a total average oral intake of 200–300 µg/day *(6)*. Recovery studies indicate an absorption rate of less than 15% from the gastrointestinal tract *(31)*.

Relative significance of different routes of exposure

Percutaneous absorption of nickel is quantitatively minor, but is the most significant for cutaneous manifestations of nickel hypersensitivity *(32)*. Iatrogenic exposure to nickel may occur as a result of dialysis treatment, prostheses and implants, and medication. Such exposure is of minor importance for practical purposes *(33)*. Ear-piercing, however, increases the probability of nickel sensitization *(34)*.

Table 1 summarizes the levels of daily nickel intake by humans from different routes of exposure.

Table 1. Levels of daily nickel intake (µg) by humans from different types/routes of exposure

Type/route of exposure	Daily nickel intake	Absorption
Foodstuffs	<300	45 (<15%)
Drinking-water	<20	3 (<15%)
Ambient air (urban dweller)	<0.8	0.4 (50%)
Ambient air (smoker)	<23	12 (50%)

Both the gastrointestinal and respiratory uptake rates have been estimated on the basis of very limited experimental evidence.

Gastrointestinal uptake is of limited interest for effects other than nickel hypersensitivity. Moreover, even though a low-nickel diet has been reported to improve clinical symptoms in some hypersensitive individuals, other factors seem to be more important.

As the respiratory tract is a major target organ as well as an uptake organ for nickel, inhalation is the most significant route of exposure with regards to lung effects. Retention in the respiratory tract is more important than uptake into the general circulation because respiratory cancer is the critical effect. Given the particle distribution in ambient air, an approximate 50% retention figure seems reasonable for risk estimation. Effects in the lung resulting from oral intake cannot be excluded. Inhibition of 5'-nucleotidase activity and enhanced lipid peroxidation in pulmonary alveolar macrophages have been demonstrated in the respiratory tract following parenteral injection of nickel chloride in rats *(35)*. The relative importance for tumour development of respiratory tract exposure from the general circulation is not known.

Population groups at high probability of exposure

Industrial activity accounts for most of the variability of nickel deposition on the earth's surface, but deposits from meteorites and volcanic eruptions may exceed releases from anthropogenic sources *(36)*. Point-source emission increases nickel exposure, but an impact on health from such emissions has not been convincingly documented *(12,13)*.

Little is known about risk groups in the general population, although smokers and those exposed at work have higher exposures than other groups within the population. Nickel concentrations in workroom air, particularly in the refining industry may be significantly increased compared to those in ambient air. An increased cancer risk has been repeatedly demonstrated in the refining industry,

but not for secondary users of nickel. Workroom air levels of nickel in secondary and end-users of nickel are generally much lower than in the refining industry, often by a factor of 10–100 *(37)*.

Exposure levels in workroom air in the refining industry have been estimated at 1–5 mg/m^3 for soluble nickel, and from less than 2 mg/m^3 to more than 9 mg/m^3 for sulfidic nickel. Exposure to oxidic nickel may have exceeded 10 mg/m^3. In addition, mixed exposures have been the rule rather than the exception. Secondary users of nickel are usually exposed to less than 0.1 mg/m^3 with occasional levels of up to 1 mg/m^3 *(5,33,37)*.

Toxicokinetics

Absorption

At least 50% of a single inhaled dose of nickel carbonyl is absorbed, the agent passing the alveolar wall intact *(6)*.

Few data exist on the absorption of nickel from particulate matter deposited in the respiratory tract. The upper limit for particle retention may be calculated from respiratory deposition and retention models, but such calculations are of limited practical value because of the different biological availability of nickel compounds. Absorption of nickel into the blood may be of limited significance as particles retained in the cells of the respiratory tract are more important.

Soluble nickel compounds are rapidly removed from the lung. For example, Carvalho & Ziemer *(27)* demonstrated that only 0.1% of the dose was found in the lungs 21 days after tracheal instillation of nickel chloride in rats. Menzel *(38)* demonstrated a saturable clearance mechanism of soluble nickel compounds from rat lungs. A steady-state lung burden was observed at a concentration of 90 µg/m^3, as predicted from computer modelling, while the lung burden continued to increase with repeated exposure to 400 µg/m^3. A maximum clearance velocity of 34.6 ng/g of lung tissue per hour was calculated.

Oxidic nickel remains in the lungs following exposure. In golden hamsters exposed to artificial nickel oxide aerosols (unspecified; MMD 1.0–2.5 µm), 20% of inhaled nickel oxide remained after the initial elimination, and 45% of this was still present after 45 days *(39)*. Continuous inhalation (for 6 weeks) of nickel oxide (NiO) at a concentration of 50 µg/m^3 gave rise to comparable figures *(40)*. Wehner et al. *(26)* exposed Syrian hamsters to nickel-enriched fly ash aerosols. Nickel leaching from the nickel-enriched fly ash did not seem to occur to any extent.

Sulfidic nickel takes an intermediate position. In mice, about 10% of an intratracheally administered dose of nickel subsulfide was retained 35 days after the exposure *(41)*.

Oberdörster has considered lung dosimetry at length, using animal–human extrapolation modelling *(25)*. Equivalent human exposure concentrations were calculated on the basis of results in rats *(25,42)*. The model depends heavily on particle size and solubility; further knowledge of the kinetics of inhaled nickel compounds and on mechanisms of clearance and tumorigenicity is needed for reliable modelling and risk estimation.

Humans absorb 15-50% of nickel in drinking-water after an overnight fast compared to less than 15% of that in foods *(31)*.

Distribution

The main carrier protein of nickel in serum is albumin, but nickel is also bound to α-2 macroglobulin and histidine *(24)*.

The body burden of nickel in adult humans averages about 0.5 mg per 70 kg. The highest concentrations of nickel are found in the lung and in the thyroid and adrenal glands (about 20-25 µg/kg wet weight). Most other organs (e.g. kidney, liver, brain) contain about 8-10 µg/kg wet weight *(43)*. Following parenteral administration to experimental animals, the kidney invariably showed the highest concentrations of nickel followed by either the lung or the pituitary glands *(32)*.

Reference values for nickel concentrations in serum and urine from healthy persons without occupational exposure to nickel compounds have recently been compiled *(23,24)*. Values for serum/plasma are in the range 0.14-0.65 µg/litre; values of around 0.2 µg/litre seem to be the most reliable. Corresponding values for urine are 0.9-4.1 µg/litre, with values of 1-2 µg/litre the most reliable. For whole blood, values of 0.34-1.4 µg/litre are given. These values are substantially lower than those reported prior to 1980 because of better analytical methods and improved control of contamination. The metal concentrations in the different samples were not influenced by age or sex. Various diseases (myocardial infarction, acute stroke, thermal burns, hepatic cirrhosis) influence the kinetics of nickel metabolism.

Metabolism and elimination

Nickel may undergo redox metabolism generating the trivalent form thus forming reactive oxygen species. The intracellular release of nickel ion following phagocytosis of particles of oxidic and/or sulfidic nickel is an important metabolic pathway. Minute particles containing nickel have been demonstrated close to the nuclear membrane. Nickel ions may also enter the cell directly, although possible transport mechanisms are unclear.

Parenteral administration of nickel induces changes in the tissue distribution of other metals, and several physiological divalent cations influence nickel metabolism. Specifically, manganese inhibits the dissolution of nickel subsulfide in rat serum, and inhibits phagocytosis of nickel subsulfide particles *(5)*.

Unabsorbed nickel in the gastrointestinal tract is lost in the faeces (reflecting the daily dietary intake). Figures of 180–250 µg/day should be expected on the basis of an estimated daily intake of 200-300 µg and absorption of less than 15%. Excretion of 258 µg/day has been reported *(44)*.

Absorbed nickel is eliminated in the urine. Excretion via sweat, secretion via saliva and deposition in hair have been reported. However, urinary excretion is the main clearance route. The biological half-time of nickel depends on the nickel species tested. For soluble compounds, the half-time of plasma nickel is 11–39 hours in humans; for particulate compounds, half-times of 30–54 hours have been recorded *(33)*. A urinary elimination half-time of 17–48 hours has been reported for the absorbed dose following experimental oral exposure in humans *(31)*. Protracted retention and

gradual elimination from body pools (respiratory organs) take place following exposure to nickel particulates of low solubility *(45)*.

Biomarkers of exposure

Both plasma and urine concentrations of nickel are useful biomarkers of nickel inhalation exposure on a group basis *(33)*. The correlation between exposure and biological values on an individual basis is low and significant only in some investigations involving exposure to soluble compounds.

The levels in plasma and urine are highly dependent on the nickel species in air. High air levels of oxidic and sulfidic nickel give relatively lower plasma and urine values than a corresponding level of soluble chlorides or sulfates, but higher values in the nasal mucosa and probably also in the lungs (possible target organs) *(45,46)*.

Physiologically-based pharmacokinetic modelling

A two-compartment model describing mathematically the whole-body kinetics of the nickel ion has been formulated by Onkelinx & Sunderman *(47)*. Results based on single-injection, continuous-infusion and multiple-dosing experiments using nickel chloride in rats and rabbits revealed a typical two-compartment distribution and an elimination pattern comprising a rapid and a slow clearance phase. The model has been extended to humans with an excellent fit *(31)*. Estimated urinary elimination half-time for absorbed nickel was 28 ± 9 hours.

Menzel *(38,48)* has developed a complete integrated physiologically-based pharmacokinetic model for nickel metabolism based on his inhalation study. In addition to information on lung dosimetry, data pertaining to the kidneys are important because nickel is predominantly excreted in the urine. At a steady state situation with continued intravenous injection, the highest nickel concentration was found in the kidney followed by the lung (ratio about 17:1). The lung value was about two times that of most other organs investigated. For risk assessment, Oberdörster *(25)* has modelled the human lung burden using animal exposure data from Ottolenghi et al. *(42)* as a basis. Inhalation of nickel subsulfide at a concentration of 970 $\mu g/m^3$ in rats was found to be equivalent to inhalation of 4400 $\mu g/m^3$ in humans.

Health effects

There is evidence that nickel is an essential trace element in several animal species, plants and prokaryotic organisms. Nickel appears to be essential for humans, although no data are available concerning nickel deficiency.

Effects on experimental animals and *in vitro* test systems

Toxicological effects

Inhalation of all types of nickel compounds induces respiratory tract irritation, chemical pneumonia, emphysema and varying degrees of hyperplasia of pulmonary cells, and fibrosis (pneumoconiosis) *(5)*. Nickel may precipitate autoimmune phenomena and induce immunosuppression *in vitro*; the clinical importance of such effects has not been reported *(49)*.

Nickel can cross the placental barrier, thus being able to influence prenatal development by direct action on the embryo. Fetal death and malformations have been reported following injection of various species of nickel compounds in experimental animals *(5)*.

Carcinogenic effects

Cancer in experimental animals can be induced by the injection or implantation of nickel compounds in a variety of organs. Nickel subsulfide and ß-nickel monosulfide seem to be the most potent carcinogens in these experiments *(5)*. The production of localized tumours at the site of injection is of limited relevance to occupational or environmental exposure, although some important information on potency has been obtained from such studies. Great differences in carcinogenic potency have been demonstrated, depending on the nickel compound. Some correlations exist between the carcinogenic potency of a given compound and its solubility in biological fluids, its surface oxidation-reduction state, its ability to be phagocytized, and its ability to stimulate erythropoiesis by intravenous injection *(3)*.

Inhalation and ingestion studies are the most relevant for the assessment of potential human risk from environmental exposure to nickel. No ingestion studies are reported and only a few inhalation studies. Ottolenghi et al. *(42)* described a significant increase in the number of lung tumours in rats following inhalation exposure to nickel subsulfide for about 2 years.

Nickel sulfate hexahydrate, green nickel oxide and nickel subsulfide have been tested in 2-year inhalation studies in mice and rats under the United States National Toxicology Program *(50–52)*. No tumorigenic activity was found with any of the compounds in mice or with nickel sulfate in rats. Increases in lung adenomas and carcinomas were found in rats for both the oxide and the subsulfide. The increase was related to the exposure dose but not to the retained dose and subsulfide was the most potent tumorigen, while nickel was retained in the lung to a considerably higher degree after oxide exposure. Both the oxide and the subsulfide also caused an increase in adrenal pheochromocytomas in rats.

Nickel monoxide (not further specified) and metallic nickel dust induced tumours in hamsters following intratracheal instillation. Soluble nickel seems to have a low tumorigenic potential in experimental animals as indicated by the National Toxicology Program study. Inhalation of nickel carbonyl in rats has produced only one lung tumour in three reported experiments compared to none in corresponding control groups *(5)*.

There is no experimental evidence that nickel compounds are carcinogenic when administered orally or cutaneously.

Mutagenic effects and effects identified by other in vitro assays

Negative mutagenicity data were obtained in most bacterial test systems owing to lack of absorption, but many nickel compounds can induce *in vitro* mammalian cell transformation and are clastogenic to various degrees *(5)*.

Critical organs, tissues and effects

The critical organ following inhalation exposure is the respiratory tract. After short-term high-dose inhalation exposure, lung irritation and pneumonia are critical effects. Increased mortality of non-malignant respiratory disease has been reported in nickel refinery workers with more than 5 years of

exposure, and pneumoconiosis has been reported following 12–20 years of exposure. No details on nickel compounds or exposure levels was given, but nickel oxide (Ni_2O_3)was found to be fibrogenic when instilled intratracheally *(6)*. Tumour induction must, however, be regarded as the critical effect.

Ingestion of high doses of nickel salts causes gastric irritation and the skin can be considered as a target organ with dermatitis as a critical effect *(6)*.

The lung is the critical organ following nickel carbonyl inhalation, the effect being pulmonary oedema.

Effects on humans

Toxicological effects
Severe lung damage has been recorded following acute inhalation exposure to nickel carbonyl. Reversible renal effects (in workers), allergic dermatitis (most prevalent in women), and mucosal irritation and asthma (in workers) have been reported following exposure to inorganic nickel compounds *(5)*. Renal effects and dermatitis presumably relate both to nickel uptake by both inhalation and ingestion, in addition to cutaneous contact for dermatitis.

Allergic skin reactions to nickel (dermatitis) have been documented both in nickel workers and in the general population. However, the significance of nickel as a cause of occupationally-induced skin reaction is decreasing. In contrast, there is evidence that nickel is increasingly a major allergen in the general population, especially in women. About 2% of males and 11% of females show a positive skin reaction to patch testing with nickel sulfate. Ear-piercing considerably increases the risk of nickel sensitization *(34)*.

The respiratory tract is also a target organ for allergic manifestations of nickel exposure. Allergic asthma has been reported among workers in the plating industry following exposure to nickel sulfate.

Cytogenic studies have been conducted in workers in the nickel-refining industry (crushing, roasting, smelting and electrolysis), in nickel carbonyl production, and in electroplating. Elevated levels of sister chromatid exchanges and chromosomal aberrations have been demonstrated in workers in nickel refining plants and in nickel platers; the main effect was chromosomal gaps *(5)*. No effects were found in workers exposed to nickel carbonyl *(5)*.

Torjussen et al. *(53)* suggested the use of histopathological changes in the nasal mucosa as a biomarker of effect in refinery workers, but Boysen et al. *(54)* later concluded that such results at best could indicate groups of persons at increased risk for nasal carcinoma.

Carcinogenic effects
Studies linking nickel uptake from the environment and cancer incidence in the general population are not available. There is agreement that nickel refinery workers exposed by inhalation to various nickel compounds in the past are at a significantly higher risk for cancer of the lungs and the nasal cavity than the non-occupationally exposed population *(5,37)*. Laryngeal cancer, kidney cancer, and cancer of the prostate or bone have also been found in nickel workers, but the epidemiological evidence does not indicate a relationship to nickel exposure or to any other occupational origin *(37)*.

At the Clydach refinery, Wales, a high relative risk of nasal and lung cancer has been associated with inhalation exposure in the calcining, roasting and leaching departments before 1920. Much of the risk was related to work at the linear calciner where nickel exposure levels were 10–100 mg/m^3 with a composition of about 60% oxidic, 20% sulfidic, 20% metallic and 3% soluble nickel. Even if the exposure to soluble nickel compounds is low compared to that to the particulate form, analysis indicates that exposure to soluble forms together with the oxidic or sulfidic forms increases the risk. The decrease in nickel air concentrations to a maximum of 20 mg/m^3 in the workplace after 1930 seems to explain the decrease in risk, even if other changes (lower copper and sulfur in the feed) in the production technology also took place *(37)*.

Very high relative risks of nasal and lung cancer have also existed in the calcining, roasting and leaching departments of refineries in Canada (INCO, Ontario) and Norway, (Falconbridge, Kristiansand). Exposure levels in the same range as in Clydach were recorded in Canada, somewhat lower (>10 mg/m^3) in Norway *(37)*. In Norway, oxidic nickel was reduced to concentrations of less than 5 mg/m^3 after 1955, but an increased risk of lung cancer was still recorded in a cohort with first job entry after 1956 *(55)*. In a recent follow-up, the highest risk was found among those with the highest estimated dose of soluble nickel. There appeared to be a multiplicative effect for smoking and exposure to total nickel *(56)*.

Studies of industrial secondary and end-users of nickel have generally not shown carcinogenic effects, but the exposure levels have been less than 1 mg/m^3 both for particulate and for soluble nickel compounds.

Evaluation of human health risks

Exposure evaluation

Nickel is present throughout nature and is released into air and water both from natural sources and as a result of human activity.

In nonsmokers, about 99% of the estimated daily nickel absorption stems from food and water; for smokers the figure is about 75%. Nickel levels in the ambient air are in the range 1–10 ng/m^3 in urban areas, although much higher levels (110–180 ng/m^3) have been recorded in heavily industrialized areas and larger cities. There is, however, limited information on the species of nickel in ambient air.

Consumer products made from nickel alloys and nickel-plated items lead to cutaneous contact exposure.

Exposure to nickel levels of 10–100 mg/m^3 have been recorded for occupational groups, with documented increased cancer risk. Exposure levels in the refining industry are currently usually less than 1–2 mg/m^3, often less than 0.5 mg/m^3. Experimental and epidemiological data indicate that the nickel species in question is important for risk estimation.

Health risk evaluation

Allergic skin reactions are the most common health effect of nickel, affecting about 2% of the male and 11% of the female population. Nickel content in consumer products and possibly in food and

water are critical for the dermatological effect. The respiratory tract is also a target organ for allergic manifestations of occupational nickel exposure.

Work-related exposure in the nickel-refining industry has been documented to cause an increased risk of lung and nasal cancers. Inhalation of a mixture of oxidic, sulfidic and soluble nickel compounds at concentrations higher than 0.5 mg/m^3, often considerably higher, for many years has been reported *(37)*.

Nickel has a strong and prevalent allergenic potency. There is no evidence that airborne nickel causes allergic reactions in the general population, although this reaction is well documented in the working environment. The key criterion for assessing the risk of nickel exposure is its carcinogenic potential.

In general, nickel compounds give negative results in short-term bacterial mutagenicity tests because of limited uptake. However, they show a wide range of transformation potencies in mammalian cell assays, depending mainly on their bioavailability.

Both green nickel oxide and the subsulfide have caused tumours in animal inhalation studies. In addition, nickel monoxide (not further specified) and an alloy with 66.5% nickel and 12.5% chromium caused tumours following tracheal instillation. A corresponding instillation with an alloy of 26.8% nickel and 16.2% chromium had no such effect, indicating that it was nickel and not chromium which caused the tumours. Injection-site tumours in a number of organs are found with many particulate nickel compounds. The tumorigenic potency varies with chemical composition, solubility and particle surface properties *(57,58)*.

Epidemiological evidence from the nickel-refining industry indicates that sulfidic, oxidic and soluble nickel compounds are all carcinogenic. Exposure to metallic nickel has not been demonstrated to cause cancer in workers.

Several theories have been suggested for the mechanisms of nickel tumorigenesis. All of these assume that the nickel ion is the ultimate active agent. On the basis of the underlying concept that all nickel compounds can generate nickel ions which are transported to critical sites in target cells, IARC classified nickel compounds as carcinogenic to humans (group 1) and metallic nickel as possibly carcinogenic to humans (group 2B) *(5)*.

On the basis of one inhalation study *(42)*, the US Environmental Protection Agency (EPA) classified nickel subsulfide as a class A carcinogen and estimated the maximum likelihood incremental unit risk to be $1.8–4.1 \times 10^{-3}$ *(59)*. However, this study involves only exposure to nickel subsulfide. It is not known whether this compound is present in ambient air, but since it is probably one of the most nickel potent compounds, this risk estimate may represent an upper limit, if accepted. WHO estimated an incremental unit risk of 4×10^{-4} $(\mu g/m^3)^{-1}$ calculated from epidemiological results *(60)*.

On the basis of epidemiological studies, EPA classified nickel dust as a class A carcinogen and estimated the lifetime cancer risk from exposure to nickel dust to be 2.4×10^{-4}. This estimate placed nickel in the third quartile of the 55 substances evaluated by the EPA Carcinogen Assessment

Group with regard to their relative carcinogenic potency *(61)*. Assuming a content of 50% of nickel subsulfide in total dust, a unit risk of 4.8×10^{-4} was estimated for this compound.

An estimate of unit risk can be given on the basis of the report of lung cancer in workers with first employment in 1968–1972 followed through to 1987 in Norway *(55,56)*. Using the estimated risk of 1.9 for this group and an exposure of 2.5 mg/m^3, a lifetime exposure of 155 µg/m^3 and a unit risk of 3.8×10^{-4} (µg/m^3)$^{-1}$ can be calculated.

Guidelines

Even if the dermatological effects of nickel are the most common, such effects are not considered to be critically linked to ambient air levels.

Nickel compounds are human carcinogens by inhalation exposure. The present data are derived from studies in occupationally exposed human populations. Assuming a linear dose– response, no safe level for nickel compounds can be recommended.

On the basis of the most recent information of exposure and risk estimated in industrial populations, an incremental risk of 3.8×10^{-4} can be given for a concentration of nickel in air of 1 µg/m^3. The concentrations corresponding to an excess lifetime risk of 1:10 000, 1:100 000 and 1: 1 000 000 are about 250, 25 and 2.5 ng/m^3, respectively.

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