

EPIDEMIOLOGICAL AND PATHOGENETIC ASPECTS OF NICKEL POISONING

Vladimir Ilic¹, Vladmila Bojanic² and Biljana Jovic³

Nickel is widely distributed in the environment. High consumption of nickel containing products inevitably leads to environmental pollution by nickel and its derivatives at all stages of production, utilization, and disposal.

Human exposure to nickel occurs primarily via inhalation and ingestion and is particularly high among nickel metallurgy workers. In addition, implantation of nickel-containing endoprostheses and iatrogenic administration of nickel-contaminated medications leads to significant parenteral exposures. Exposure to nickel compounds can produce a variety of adverse effects on human health. Nickel allergy in the form of contact dermatitis is the most common reaction.

A frontal headache, vertigo, nausea, vomiting, insomnia, and irritability are the most common signs of acute poisoning with nickel compounds. The respiratory tract, kidneys and liver suffer the most significant changes like nickel pneumoconiosis, chronic rhinitis and sinonasal tumors and transitory nephropathy. Although the accumulation of nickel in the body through chronic exposure can lead to lung fibrosis, cardiovascular and kidney diseases, the most serious concerns relate to nickel's carcinogenic activity. Nickel compounds are carcinogenic to humans and metallic nickel is possibly carcinogenic to humans. *Acta Medica Mediana* 2007;46(2):37-44.

Key words: poisoning, toxicity, nickel, epidemiology, cancerogenesis

Bonifar Novi Beograd¹
Institute of Pathophysiology, Faculty of Medicine in Nis²

Correspondence to: Vladimir Ilic
59 Majakovskoi Street
18000 Nis, Serbia
Phone: 065/5555376
E-mail: drtroad@gmail.com

Introduction

Nickel, discovered and named by Cronstedt in 1751, is the 24th element in order of natural abundance in the earth's crust. It is widely distributed in the environment. Natural sources of atmospheric nickel include dusts from volcanic emissions and the weathering of rocks and soils. Natural sources of aqueous nickel derive from biological cycles and solubilization of nickel compounds from soils. Global input of nickel into the human environment is approximately 150,000 metric tones per year from natural sources and 180,000 metric tones per year from anthropogenic sources, including emissions from fossil fuel consumption, and the industrial production, use, and disposal of nickel compounds and alloys. (1)

Major deposits of nickel ores, either oxides or sulfides are located in Australia, Canada, Cuba, Indonesia, New Caledonia, and Russia. Readers are referred to monographs and reviews for detailed discussions of the metallurgy, chemistry, environmental chemistry, biochemistry, toxicology, and biological monitoring of nickel (2-9).

High consumption of nickel-containing products inevitably leads to environmental pollution by nickel and its derivatives at all stages of production, utilization, and disposal. Human exposure to nickel occurs primarily via inhalation and ingestion and is particularly high among nickel metallurgy workers. In addition, implantation of nickel-containing endoprostheses and iatrogenic administration of nickel-contaminated medications (e.g., albumin, radiocontrast media, hemodialysis fluids) leads to significant parenteral exposures (10-14) and wearing or handling of jewelry, coins, or utensils that are fabricated from nickel alloys or that have nickel-plated coatings may result in cutaneous nickel absorption (15).

In industrialized regions and large cities, atmospheric nickel concentrations are related to fly ash from burning fossil fuels in power plants and automobiles and may reach 120-170 ng/m³ as compared to 6-17 ng/m³ in suburban areas (16). Cigarette smoking can further increase inhaled nickel (17,18). Another source of human nickel exposure is dietary where some foods, especially plant foods, may contain well over 1 mg Ni/kg. Occupational exposure to nickel occurs predominantly in mining, refining, alloy production, electroplating, and welding.

In 1990, the International Committee on Nickel Carcinogenesis in Man suggested that respiratory cancer risks are primarily related to exposure to soluble nickel concentrations above 1 mg/m³ and to exposure to less soluble forms at concentrations above 10 mg/m³. The Committee

was unable, however, to determine with confidence the level at which nickel exposure becomes a substantial hazard. Approximately 2% of the work force in nickel-related industries is exposed to airborne nickel-containing particles in concentrations ranging from 0.1 to 1 mg/m³. Exposure to nickel compounds can produce a variety of adverse effects on human health. Nickel allergy in the form of contact dermatitis is the most common reaction.

Although the accumulation of nickel in the body through chronic exposure can lead to lung fibrosis, cardiovascular and kidney diseases, the most serious concerns relate to nickel's carcinogenic activity.

Nickel in the environment and in organisms

Special features of nickel chemistry

Nickel is a metallic element, (relative atomic mass 58.69) is found in the first transition series group VIIIb of the periodic table. Five natural isotopes are known, of which ⁵⁸Ni (68.27%) and ⁶⁰Ni (26.10%) are the most abundant. In addition, seven artificial isotopes are known with half-lives ranging from milliseconds to hundreds of years (19). An important isotope for biophysical studies is ⁶¹Ni which has a nuclear spin of 3/2. ⁶¹Ni labeling has been used to determine the presence of nickel in the active sites of several microbial enzymes. In addition, ⁶³Ni, a beta emitter with a half-life of 100.1 years, has proved useful in biological tracer studies. Nickel is found in one of several oxidation states, ranging from ⁻¹ to ⁺⁴. However, the ⁺² oxidation state is the most prevalent form of nickel in biosystems.

Solubilized Ni²⁺ ions in aqueous media at neutral pH are hydrated to the greenish hexahydrated [Ni(H₂O)₆]²⁺. Other Ni²⁺ coordination complexes are also known. Pure nickel can be polished, forged, welded, rolled and drawn and is inert against corrosion by air, water, non-oxidizing acids, alkalis and many organic solvents (20). Nickel dissolves in dilute nitric acid but not in concentrated nitric acid due to passivity of the metal surface. A remarkable property of nickel is its ability to absorb carbon monoxide. Hundred grams of nickel can occlude 500–800 ml carbon monoxide (e.g. nickel tetracarbonyl, Ni(CO)₄). The classical test for detection of nickel represents the reaction with alcoholic dimethyl glyoxime solution that causes formation of a scarlet chelate.

Various methods of nickel mining processes are used depending on the type of ore being mined. Nickel is generated predominantly from the sulfides Ni/Cu-ores in the Canadian Sudbury district. Other countries that mine nickel are Russia, Australia, France and New Caledonia. It is interesting to note that Japan does not mine nickel, but is third after Russia and Canada in processing and production of nickel.

In Sudbury, Canada, nickel ore is processed by the Orford process (21) that involves fusing

the ore with sodium bisulfate and coke, thereby converting it into a mixture of metal sulfides and sodium sulfide. After that, nickel subsulfide (Ni₃S₂) is roasted in air to produce nickel oxide. Nickel oxide (NiO) is reduced with carbon to metallic nickel. The crude nickel is purified by an electrolytic procedure to 99.5% purity or by the Mond process (22) generating nickel tetracarbonyl followed by heating to 200 °C during which decomposition to 99.8–99.9% pure nickel and carbon monoxide occurs.

Environmental exposure

Nickel compounds are important in modern industry and are used in electroplating, electroforming, and for production of nickel-cadmium batteries and electronic equipment. Nickel alloys, like stainless steel, are used in the production of tools, machinery, armaments, and appliances. They are also used to cast coins, and to produce jewelry and medical prostheses. The sources of environmental nickel contamination include the production and processing of nickel and its by-products, the recycling of nickel-containing products and nickel-containing waste disposal.

Nickel compounds are also found in soils and are present in both insoluble forms, such as sulfides and silicates, and in a number of soluble forms. Nickel is also present in the atmosphere and the species of nickel present is dependent on the source of contamination. From anthropogenic sources nickel is emitted as oxides, sulfides, silicates soluble compounds, and to a lesser extent, as metallic nickel. Combustion of fossil fuels produces the greatest contribution of nickel compounds in ambient air (23). Thus, the atmospheric concentration of nickel in industrialized areas has been estimated to be in the range 120–170 ng/m³, and 6–17 ng/m³ in suburban areas. Direct leaching from rocks and sediments can produce significant concentrations of nickel in water where it is present in dissolved forms as well as suspended insoluble particles. Nickel concentration in deep-sea water usually range from 0.1 to 0.5 ppb Ni, whereas surface water contains 15–20 ppb Ni (24). Divalent nickel is the predominant form of nickel in aquatic sources (25). The existence of other nickel compounds depends on the pH and the organic or inorganic binding-partners. Another source of nickel exposure in human populations is dietary where some vegetables (spinach), cocoa and nuts contain high amounts of nickel (26). Occupational exposure occurs in mining, refining, alloy production, electroplating and welding. Epidemiological studies have noted an increased risk of respiratory tract and nasal cancers in miners and workers in nickel refineries. Since the Mond process was used to refine nickel it was originally suggested that the toxic intermediate product Ni(CO)₄ was the sole carcinogen. However, the increased risk of respiratory cancers was observed in refineries where the Mond process was not used.

Nickel essentiality and toxicity

Nickel's essentiality in higher organisms is questionable. In order of abundance in the earth's crust, nickel ranks as the 24th element. Thus, humans are constantly exposed to this ubiquitous element although in variable amounts. Due to its abundance, natural nickel deficiency does not occur, moreover a nickel-deficient diet is difficult to maintain because of nickel's abundance in all types of food. The daily dietary intake of nickel is 25–35 g, and it is more than triple the daily requirement (27).

Additionally, no enzymes or cofactors that include nickel are known in higher organisms. All these factors have contributed to the uncertainty in deciding whether nickel is essential to humans. Despite uncertainty, it was suggested in the early 1920s that nickel might have a physiological function in higher organisms. This suggestion resulted from animal experiments with nickel-deficient diets. It was reported that nickel depletion in rats resulted in increased prenatal mortality as well as alterations of grooming behavior, liver development, and decreased growth. The growth dependence on nickel was more significant in the second depleted generation. The second depleted generation also showed anemia that manifested in decreased hemoglobin and hematocrit values (28).

Nickel deficiency impairs the absorption of iron from the intestine. Thus, the concentrations of other metals including iron, copper, and zinc were also decreased in the liver of nickel-depleted animals. Nickel deficiency also results in lowered specific activities of many enzymes involved in carbohydrate and amino-acid metabolism. Nickel-induced alterations in serum and hepatic lipids are similar to those that develop after a moderate iron deficient diet. It was suggested that nickel is involved in CO₂-fixation to propionyl-CoA to form D-methylmalonyl-CoA (29). The depletion of nickel in the diet also indicated that nickel may be involved in lipid metabolism, particularly in the synthesis of phospholipids (30).

Nickel-containing enzymes are well known in the bacterial world (31). Currently, seven microbial nickel-containing enzymes have been identified including urease, hydrogenase, CO-dehydrogenase, methylCoM reductase, Ni-superoxide dismutase, glyoxylase I, and cis-trans isomerase. Bacteria with nickel-containing enzymes represent a good model to study nickel biometabolism, transport systems and nickel-binding proteins. For example, the bacteria *Helicobacter pylorus* is suspected in causing both ulcer and gastric carcinoma because *Helicobacter pylorus* contains a nickel-dependent urease whose activity is correlated with the development of peptic ulcers. Thus, there may be a correlation between nickel intake, growth of *Helicobacter pylori* and cancer development. Several animal species require nickel intake in their diet although they do not contain urease or one of the other nickel enzymes present in bacteria (32). It is conceivable then that nickel, not being essential in the body of humans and animal, is needed for the normal development of the gut's microflora.

Nickel at high doses and in certain forms is toxic to both man and animals. For example, the oral LD50 of nickel acetate was 350 mg/kg in rats and 420 mg/kg in mice, the intraperitoneal LD50 in rats was 23 mg/kg. With nickel chloride intraperitoneal LD50 values in rats were 11 and 48 mg/kg in mice.

Only a small number of reports of acute nickel toxicity caused by inorganic nickel intake are described in the literature. The most acute nickel poisoning is caused by exposure to Ni(CO)₄. Chronic nickel poisoning can affect several organs including the cardiovascular and respiratory systems, skin, and kidney. Experiments with high nickel intake have shown that nickel is teratogenic and has carcinogenic potential. Some authors have systematically investigated the effect of a high nickel diet on metal distribution in different tissues in pigs and hens. They found that nickel exposure resulted in the decrease of the magnesium, manganese and zinc levels in different tissues (33). Also, zinc transfer to eggs was also significantly decreased, which could be harmful for chicken development. They concluded that this effect was mainly based on the antagonistic action of both nickel and zinc. Another study that dealt with reproductive effects in humans reported an increase in spontaneous abortions among females employed in the nickel refinery (34).

Nickel allergy in the form of contact dermatitis is the most common reaction. Nickel directly stimulated the proliferative response and the production of cytokines of T lymphocytes of nickel-sensitive subjects *in vitro*. This stimulation was not restricted by major histocompatibility complex-encoded molecules, since the antibodies against HLA class I and II molecules did not block nickel-induced proliferation. The results of *in vivo* studies suggest that nickel activates the immune response of both non-allergic and Ni-sensitized humans (35).

Nickel homeostasis

The estimated body burden of a healthy non-exposed adult is about 7.3 g Ni/kg body weight. Nickel intake occurs via inhalation, ingestion and dermal absorption and is a function of bioavailability. The chemical form of nickel dictates how nickel enters the vertebrate cell. Insoluble, particulate nickel enters the vertebrate cell by phagocytosis, whereas nickel carbonyl is lipid soluble and can easily cross the cell membrane. Indeed facile absorption of nickel carbonyl during inhalation has been reported in numerous experiments. Soluble nickel is transported into normal vertebrate cells by diffusion or possibly through calcium channels.

After intake via inhalation, inhaled nickel was selectively concentrated in the lung, followed by heart, diaphragm, brain, and spinal cord tissues. In general, the lung has the tendency to retain significant amounts of nickel independently of the route of exposure. When the inhaled insoluble nickel particles are deposited in lungs, the absorption of nickel into the peripheral blood

stream occurs slowly so that the nickel concentration in whole blood of slightly exposed individuals is not significantly higher than those of non-exposed controls.

The quantity of nickel absorbed by the gastrointestinal tract depends on the nickel species in the food, the total nickel content in the food, and the individual capacity for absorption. Under normal dietary conditions 1–2% of ingested nickel is absorbed, and unabsorbed nickel is excreted with the feces. In rats, intravenously injected with nickel chloride 90% is eliminated in the urine within four days postinjection, whereas only 3% is excreted by fecal discharge. The kidney, in addition to the lung, brain, pancreas, and other tissues is considered a target organ for nickel retention following high levels of nickel exposure. In pregnant rats, nickel crossed the placenta, and appeared in the fetal blood and amniotic fluid. Nickel concentration in the fetus was found to be similar to the level of nickel in adults and depended on the dose given to the pregnant animal.

Some authors have estimated that about 10% of the nickel in a normal diet is absorbed, and the others determined that an average nickel resorption from a normal diet is between 20% and 25%. The nickel intake of adults was tested over 3 years in eastern Germany, where the volunteers consumed, on an average, 170 g Ni/day (women) and 192 g Ni/day (men), respectively, and excreted approximately 80% of this nickel amount. In addition, nickel balance was found to be positive and unequal between genders. Thus, women retained 14% and men retained 26% of consumed nickel. It is obvious then that adults store considerable amounts of nickel in the body gradually filling a 'nickel pool'. Nickel concentration in the milk of lactating mothers was on average 172 g Ni/kg, and therefore, breastfed infants consume 5–15 g nickel daily. In general, human nickel intake greatly exceeds the requirement of nickel daily consumption.

Oral provocation tests, which are usually used to investigate nickel contact dermatitis, with provocation doses between 0.4 and 5.6 mg soluble nickel (in most cases nickel sulfate, NiSO₄) showed rapid (1–2 h) nickel absorption with a bioavailability ranging from 1 to 5%. Parallel ingestion of food significantly affects the bioavailability of nickel salts. The urinary excretion of nickel is rapid and elimination appears to follow first-order kinetics without evidence of dose-dependent excretion of nickel. Estimates of the half-life of urinary removal of nickel range from 20 to 60 h. These relatively short half-lives do not exclude the storage of insoluble nickel deposits in the body with much longer biological half-lives. In contrast to nickel absorption via inhalation and ingestion dermal nickel absorption is negligible because ionized nickel compounds do not penetrate intact skin. Soluble nickel salts produced as the result of corrosion of metallic nickel and nickel-containing alloys can cause contact dermatitis by percutaneous absorption. The local or systemic allergic reactions that

resulted from corrosion of nickel-containing alloys in orthopedic prostheses have been described.

Effects on human beings

Nickel carbonyl

In terms of human health, the most acutely toxic nickel compound is nickel carbonyl. The acute toxic effects occur in two stages, immediate and delayed. The immediate symptomatology includes frontal headache, vertigo, nausea, vomiting, insomnia, and irritability, followed by an asymptomatic interval before the onset of delayed pulmonary symptoms. These include constrictive chest pains, dry coughing, dyspnoea, cyanosis, tachycardia, occasional gastrointestinal symptoms, sweating, visual disturbances, and weakness. The symptomatology resembles that of a viral pneumonia (36). In men who died, pulmonary hemorrhage and edema or pneumonitis were observed accompanied by derangement of alveolar cells, degeneration of the bronchial epithelium, and the appearance of a fibrinous intraalveolar exudates. The pathology of the pulmonary lesions was similar to that observed in animal studies. Other affected organs included the liver, kidneys, adrenal glands, and spleen, where parenchyma degeneration was observed. Cerebral edema and punctate cerebral hemorrhages were noted in men dying after inhalation of nickel carbonyl. Leukocytosis was found in 25 out of 179 cases. Urinary nickel concentrations were determined in 27 cases and ranged from 0.003 to 0.66 mg/l. Air concentrations were measured and were reported to have exceeded 50 mg nickel carbonyl /m³ with exposure periods ranging from 30 min to more than 2 h. Recovery time was 7–40 days, depending on the severity of exposure. In some cases, symptoms persisted for 3–6 months. In lethal cases, death occurred between the third and thirteenth days following exposure.

Other nickel compounds

Information on poisoning with other nickel compounds is limited. A case of fatal nickel poisoning of a two and a half year old girl was described, she ingested about 15 g of nickel sulfate crystals (37). On admission to hospital, she was somnolent with wide and unresponsive pupils, a high pulse rate, and pulmonary rhonchi. Cardiac arrest occurred after 4 hours. Autopsy findings revealed increased nickel levels 7.5 mg/kg in blood, 50 mg/l in urine, and 25 mg/kg in liver tissue.

Nickel poisoning was reported in a group of 23 dialyzed patients, when leaching from a nickelplated stainless steel water heater tank contaminated the dialysate. Symptoms occurred during and after dialysis, at plasma-nickel concentrations of approximately 3 mg/l. Symptoms included nausea (37 out of 37), vomiting (31 out of 37), weakness (29 out of 37), headache (22 out of 37), and palpitation (2 out of 37). Recovery occurred spontaneously, generally 3–13 h after cessation of dialysis (38).

Thirty-two workers in an electroplating plant accidentally drank water contaminated with nickel sulfate and nickel chloride (1.63 g Ni/l). Twenty workers rapidly developed symptoms: nausea, vomiting, abdominal discomfort, diarrhea, giddiness, lassitude, headache, cough, shortness of breath. That typically lasted a few hours, but persisted for 1-2 days in 7 cases. The nickel doses in workers with symptoms were estimated to range from 0.5 to 2.5 g. In fifteen exposed workers, who were investigated one day after exposure, serum-nickel concentrations ranged from 12.8 to 1340 µg/l (average 286 µg/l) with urinary nickel concentrations ranging from 0.23 to 37.1 mg/l (average 5.8 mg/l) compared with control values for nickel-plating workers of 2.0-6.5 µg/l (average 4.0 µg/l) for serum nickel and 22-70 µg/l (average 50 µg/l) for urinary nickel. Laboratory tests showed transiently elevated levels of blood reticulocytes (7 workers), urine-albumin (3 workers), and serum bilirubin (2 workers) (39).

Respiratory effects

A lot of cases of chronic rhinitis, sinusitis, perforation of nasal septum, asthma have been found and described in workers in the nickel industry. Some authors reported about pulmonary changes with fibrosis in workers inhaling nickel dust or fumes.

A chemical engineer, who had been exposed for a long period to low levels of nickel carbonyl, developed asthma and Löffler's syndrome. In addition to pulmonary infiltrations and eosinophilia, which are markers in Löffler's syndrome, the patient had an eczematous dermatitis of the hands (40).

Examining of 486 workers from nickel-refining plants, exposed mainly to nickel sulfate during electro refining operations showed that rhinitis was observed in 10-16%, chronic rhinitis in 5.3%, nasal septal erosions in 13%, perforations in 6.1%, and ulceration in 1.4%. Exposure levels were not given. The frequencies of hyposmia and anosmia were 30.6 and 32.9% (41).

Data are available on the development of pulmonary changes with fibrosis in workers inhaling nickel dust or fumes. Some authors studied respiratory function in 13 workers, who had been exposed to nickel dust for periods of 12.9-21.7 years. Exposure levels were not given. There was a decreased pulmonary residual capacity, increased respiratory frequency, and radiography showed a diffuse fibrosis, considered to be nickel pneumoconiosis (42).

Respiratory symptoms, chest X-rays, and lung ventilation capacities in 12 steelworkers, who had been employed as desteamers of steel ingots for periods of up to 16 years have been studied. Total fume concentration at the workplace ranged from 1.3 to 294.1 mg/m³, either from iron oxide, chromium oxide, and nickel oxide in proportions of 6:1:1 (stainless steel fume) or 98.8% iron oxide (special steel fume). Airborne nickel oxide concentrations of 0.15-34 mg/m³ were calculated from these values. Two of

the workers had measurable loss of pulmonary function. In five men, definite signs of pneumoconiosis were detected radiographically (43).

Five stainless steel welders, suffering from respiratory distress, developed asthmatic symptoms during provocation tests with stainless steel fumes (44).

Renal effects

Nephrotoxic effects, like edema followed by hyperemia and parenchyma degeneration, have been found in male workers who accidentally ingested drinking-water contaminated with nickel sulfate and chloride. Also, there was elevation of urine-albumin concentrations (68, 40, and 27 mg/g creatinine), which returned to normal on the fifth day after exposure. The findings suggested a mild transient nephrotoxicity.

There are some works about different parameters for kidney dysfunction in urine samples from electrolytic nickel refinery workers (45).

Cardiovascular effects

Patients with acute myocardial infarction and unstable angina pectoris develop high serum-nickel levels, which may be followed by coronary vasoconstriction (46). The mechanism and source of nickel release are not yet known, but it was recommended that the amount of nickel in intravenous solutions should not exceed 5 µg/kg per day.

It was reported the elevation of the cerebrovascular mortality (16 deaths, 8.5 expected) among nickel refinery workers who had worked for 5 years in the process area, where lung and nasal cancer rates were highest. Mortality from all other cardiovascular causes was similar to local population rates (47).

Other effects

Nickel carbonyl refinery workers were compared with a control group. Exposure ranged from 0.007 to 0.52 mg Ni(CO)₄/m³. A decrease in the MAO (serum monoamine oxidase) activity, and EEG abnormalities were observed in the most severely exposed. A number of non-specific symptoms in persons exposed for long periods to low concentrations (unspecified) were reported, but no details were given.

Immune reactions elicited in the serial of individuals exposed to nickel and cobalt were assessed according to changes in the concentrations of the serum immunoglobulins, IgG, IgA, and IgM, and the serum proteins, alpha₂ macroglobulin (A₂M), transferrin (TRF), alpha₁-antitrypsin (A₁AT), ceruloplasmin (CPL), and lysozyme (LYS). Examinations were carried out on workers occupationally exposed to nickel (38 individuals) or cobalt (35 individuals) and in groups of non-occupationally exposed children living in areas with different levels of air pollution from a nearby source of nickel and cobalt emissions. Non-exposed controls were represented by a group of 42 male adults, matched by age, and by a group

of 48 children from a non-polluted area. Significantly increased average values were obtained for IgG, IgA, and IgM, in the group of workers exposed to nickel, for IgA, in workers exposed to cobalt, and for A₁AT, A₂M,

CPL and LYS, in both groups of occupationally exposed adults ($P > 0.001$ and $P > 0.005$). Among non-occupationally exposed children, the most highly exposed group had significantly elevated average values for A₂M and A₁AT, which were higher than those recorded in the groups of "less exposed" and control children ($p > 0.02$ and $p > 0.05$, respectively) (48).

Distribution, retention, and elimination

The distribution of nickel in the body and its mode of elimination are relevant in view of the occupational and non-occupational exposures to nickel resulting from its wide industrial applications. Studies on the distribution of nickel in the tissues of animals are useful for the understanding of the interaction between nickel and biological materials and, consequently, of its toxic and carcinogenic effects.

Nickel is concentrated in the kidneys, liver, and lungs; it is excreted equally well via urine and feces. Nickel can also be found in the urine of non-occupationally exposed persons. Since the bioavailability of nickel and the rate of elimination depend very much on the nature of the nickel compound, urinary excretion may not always be an appropriate measure of exposure.

Carcinogenic effects in humans

The propensity of nickel workers to develop cancers of the nasal cavities was first reported by Bridge in 1933. In 1937, Baader described 17 nasal and 19 lung cancer cases among workers of the same Welsh refinery. By 1949, these numbers increased to 47 nasal cancers and 82 lung cancers (diagnosed between 1923 and 1948), and cancers at both locations were proclaimed in Great Britain as industrial diseases among some classes of nickel refinery workers. During the decades since these pioneering findings, the carcinogenicity of nickel compounds has been confirmed and corroborated by numerous epidemiological studies in humans and carcinogenesis bioassays in animals (49). The epidemiological studies have demonstrated increased mortality from malignant tumors of the lung and nasal cavities in nickel refinery workers who were chronically exposed to inhalation of nickel-containing dusts and fumes from roasting and smelting. Welding of nickel alloys (stainless steel) also may be a source of such fumes. For many years, it was believed that only water-insoluble nickel components of the dusts (e.g., Ni₃S₂, NiO) were carcinogenic. However, more recent epidemiological data clearly indicate that aerosols of water-soluble nickel compounds, generated in nickel electro-refining plants (e.g., from Ni(II) sulfate), are carcinogenic to the human respiratory tract as well, with a clear dose-related effect (50).

Histopathology of the respiratory tract tu-

mors in nickel refinery workers was like this (51). Among the investigated 100 sinonasal cancers were squamous cell carcinomas (48%), anaplastic and undifferentiated carcinomas (39%), adenocarcinomas (6%), transitional cell carcinomas (3%), and other malignant tumors (4%). The 259 lung tumors examined were diagnosed as squamous cell carcinomas (67%), anaplastic, small cell, and oat cell carcinomas (15%), adenocarcinomas (8%), large cell carcinomas (3%), other malignant tumors (1%), and unspecified cancers (6%). Thus, this study suggests some prevalence of squamous cell carcinomas induction by the occupational nickel inhalation. There is no epidemiological evidence on possible cancer risk from general environmental and dietary nickel exposures. Nonetheless, based on available data on occupational exposure levels and health effects of inhaled metals, including nickel, the Canadian Environmental Health Directorate concluded that the priority for analysis of options to reduce exposure to nickel in the general environment of Canada is considered to be moderate to high (52).

Increased risks of other malignant tumors, such as carcinomas of the larynx, kidney, prostate, stomach, and soft-tissue sarcomas, have occasionally been noted, but the statistical significance of these findings is doubtful.

Besides occupational exposures, nickel released internally from endoprostheses, bone-fixing plates and screws, and other medical devices made of nickel-containing alloys, has been suspected, but not proven, to be the major cause of sporadic local tumors (53).

The carcinogenic effects of nickel and nickel compounds have been critically evaluated by the International Agency for Research on Cancer. The evaluation was based on the combined results of epidemiological studies, carcinogenicity in experimental animals, and other relevant data, supported by the underlying concept that nickel compounds can deliver nickel ions to or generate such ions at critical sites in target cells. The IARC evaluation concluded that 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. Overall evaluation: Nickel compounds are carcinogenic to humans (Group 1) and metallic nickel is possibly carcinogenic to humans (Group 2).

Conclusion

Nickel is widely distributed in the environment. The high consumption of nickel containing products inevitably leads to environmental pollution by nickel and its derivatives at all stages of production, utilization, and disposal.

Human exposure to nickel occurs primarily via inhalation and ingestion and is particularly high among nickel metallurgy workers. In addition, implantation of nickel-containing endoprostheses and iatrogenic administration of nickel-

contaminated medications leads to significant parenteral exposures. Exposure to nickel compounds can produce a variety of adverse effects on human health. Nickel allergy in the form of contact dermatitis is the most common reaction.

A frontal headache, vertigo, nausea, vomiting, insomnia, and irritability are the most common signs of acute poisoning with nickel compounds. The respiratory tract, kidneys and liver suffer the most significant changes like nickel pneumoconiosis, chronic rhinitis and sino-nasal tumors and transitory nephropathy. Although the accumulation of nickel in the body through chronic exposure can lead to lung fibrosis, cardiovascular and kidney diseases, the most serious concerns relate to nickel's carcinogenic

activity. Nickel compounds are carcinogenic to humans and metallic nickel is possibly carcinogenic to humans.

Annual unadjusted and age-adjusted attack rates and mortality rates indicate a slight but steady increase in both men and women. The disease has been registered in both sexes after 30 years of age, its incidence is highly increased after the age of 44 and it reaches its maximum in patients older than 70. The acute myocardial infarction affected women were older than the disease-struck men. The mean twenty-eight-day case-fatality after acute myocardial infarction was higher in women than in men. A decrease of case-fatality was registered in women from 2003.

References

- International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Chromium, Nickel and Welding vol 49; Lyon: IARC Scientific Publications, Lyon, France 1990. pp. 257-445.
- Barceloux DG. Nickel. *Clin Tox* 1999; 37:239-58.
- Denkhaus E, Salnikow K. Nickel essentiality, toxicity, and carcinogenicity. *Crit Rev Oncol Hematol* 2002; 42:35-56.
- Hausinger RP. *Biochemistry of Nickel*. New York: Plenum Press; 1993.
- Nieboer E, Nriagu JO. (Eds.), *Nickel and Human Health*. New York: Wiley; 1992.
- Ragsdale SW. Nickel biochemistry. *Curr Opin Chem Biol* 1998; 2:208-15.
- Savolainen H. Biochemical and clinical aspects of nickel toxicity. *Rev Environ Health* 1996;11:167-73.
- Sunderman FW. Nickel. In: *Clinical Environmental Health and Toxic Exposures*, Sullivan J.B. Jr., Krieger GR. (Eds.). Baltimore:Williams and Wilkins 2001, pp. 905-10.
- Sunderman FW, Aitio A, Morgan LM, Norseth T. Biological monitoring of nickel. *Toxicol Ind Health* 1986;2:17-8.
- Hopfer SM, Linden JV, Crisostomo MC, Catalanatto FA, Galen M, Sunderman FW. Hypernickelemia in hemodialysis patients. *Trace Elem Med* 1985; 25:68-72.
- Fell GS, Maharaj D. Trace metal contamination of albumin solutions used for plasma exchange. *Lancet* 1986;2:467-8.
- Leach CN, Sunderman FW. Nickel contamination of human serum albumin solutions. *N Engl J Med* 1985;313:1232-3.
- Leach CN, Sunderman FW. Hypernickelemia following coronary arteriography, caused by nickel in the radiographic contrast medium. *Ann Clin Lab Sci* 1987;17:137-44.
- Gordon PM, White MI, Scotland TR. Generalized sensitivity from an implanted orthopaedic antibiotic minichain containing nickel. *Contact Dermat* 1994;30:181-2.
- Hostynek JJ, Maibach HI. *Nickel and the Skin*. CRC Press: Boca Raton; 2002, pp. 1-249.
- Norseth T, Piscator M, Nickel. In: L. Friberg, GF. Nordberg, VB. Vouk (Eds.), *Handbook on the Toxicology of Metals*, Amsterdam, Elsevier/North-Holland Biomedical Press, 1979. pp. 541-553.
- Stojanovic D, Nikic D, Lazarevic K. The level of nickel in smoker's blood and urine. *Cent Eur J Public Health* 2004;12(4):187-9.
- Grandjean P. Human exposure to nickel. In: Sunderman FW. (Ed.), *Nickel in the Human Environment* vol. 53. Lyon: IARC Scientific Publications; Lyon France 1984. pp. 469-85.
- Weast RD, editor. *Handbook of chemistry and physics*, 52nd ed. Cleveland: The Chemical Rubber Co; 1971.
- Falbe J, Regitz M, editors. *RO-MPP Kompakt: Basislexikon Chemie*. Stuttgart, NY: Georg Thieme; 1999.
- Cotton FA, Wilkinson G. *Advanced inorganic chemistry*, 4th ed. New York: Wiley, 1980.
- Boldt JR. *Comprehensive inorganic chemistry*. New York: Methuen; 1967. pp. 1109-61.
- Merian E. Introduction on environmental chemistry and global cycles of chromium, nickel, cobalt, beryllium, arsenic, cadmium, and selenium, and their derivatives. *Toxicol Environ Chem* 1984;8:9-38.
- Norseth T, Piscator M. Nickel. In: *Handbook on the toxicology of metals*. Friberg L, Nordberg GF, Vouk VB, editors. Amsterdam: Elsevier/North-Holland Biomedical Press, 1979.
- Forstner V, Wittmann GTW. *Metal pollution in the aquatic environment*. New York: Springer Verlag; 1983.
- Nielson FH. Nickel. In: *Trace elements in human and animal nutrition*, vol. 1, 5th ed. Mertz W, editor. San Diego: Academic Press, 1987, pp. 245-73.
- Anke M, Angelow L, Gleis M, Muller M, Illing H. The biological importance of nickel in the food chain. *Fresenius J Anal Chem* 1995;352:92-6.
- Nielson FH, Shuler TR, McLeod TG, Zimmermann TJ. Nickel influences iron metabolism through physiologic, pharmacologic, and toxicologic mechanisms in the rat. *J Nutr* 1984;114:1280-8.
- Nielsen FH. Nutritional requirements for boron, silicon, vanadium, nickel, and arsenic: current knowledge and speculation. *FASEB J* 1991;5:2661-7.
- Kasprzak K, Stangl F, Kirchgessner M. Nickel deficiency alters liver lipid metabolism in rats. *J Nutr* 1996;126:2466-73.
- Maroney MJ. Structure function relationships in nickel metallochemistry. *Curr Opin Chem Biol* 1999;3:188-99.
- International Agency for Research on Cancer (IARC). *IARC monographs on the evaluation of carcinogenic risks to humans*. Schistosomes, Liver Flukes and *Helicobacter pylori*, vol. 61. Lyon: IARC; 1994.
- Trupschuh A, Anke M, Müller M, Illing-Gunther M, Hartmann E. Reproduction toxicology of nickel, 2nd communication: effect of excessive nickel amounts on manganese content of organs and tissues. In: *Mengen und Spurenelemente*. Anke M, Arnhold W,

- Bergmann H, et al., editors. Leipzig: Harald Schubert; 1997. pp.706-12.
34. Chashschin VP, Artunina GP, Norseth T. Congenital defects, abortion and other health effects in nickel refinery workers. *Sci Total Environ* 1994;148(2-3):287-91.
 35. Boscolo P, Sabbioni E, Andreassi P, di Giacomo F, Giaccio M, di Gioacchino M. Immune parameters and blood and urine trace elements in nonallergic and nickel-sensitized humans. In: *Metal ions in biology and medicine*, vol. 5. Collery P, Bratter P, Negretti de Bratter V, Khassanova L, Etienne J-C, (editors). Paris: John Libbey Eurotext, 1998:545-55.
 36. Shi Z. Acute nickel carbonyl poisoning: a report of 179 cases. *Br J Ind Med* 1976; 43: 422-4.
 37. Daldrup T, Haarhoff K, Szathmary SC. Fatal nickel sulfate poisoning. *Beitr gerichtl Med* 1983;41:141-4.
 38. Webster JD, Parker TF, Alfrey AC, Smythe WR, Kubo H, Neal G. Acute nickel intoxication by dialysis. *Ann Intern Med* 1980;92:631-3.
 39. Sunderman FW, Dingle B, Hopfer SM, Swift T. Acute nickel toxicity in electroplating workers who accidentally ingested a solution of nickel sulfate and nickel chloride. *Ann J ind Med* 1988;14:257-66.
 40. Sunderman FW, Sunderman FW. Löffler's syndrome associated with nickel sensitivity. *Arch int Med* 1961;107:405-8.
 41. Tatarskaya AA. Occupational disease of upper respiratory tract in persons employed in electrolytic nickel refining departments. *Gig Tr prof Zabol* 1960; 6:35-8.
 42. Zislin DM, Ganyskina SM, Dubinia ES, Tushnyakova NV. Residual air in a complex evaluation of the respiratory system function in initial and suspected pneumoconiosis. *Gig Tr prof Zabol* 1969;13:26-9.
 43. Jones JG, Warner CG. Chronic exposure to iron oxide, chromium oxide, and nickel oxide fumes in metal dressers in a steelworks. *Br J ind Med* 1972;29:168-77.
 44. Keskinen H, Kalliomaki PL, Alanko K. Occupational asthma due to stainless steel welding fume. *Clin Allergy* 1980;10:151-9.
 45. Sanford WE, Nieboer E, Bach P, Stace B, Gregg N, Dobrota M. The renal clearance and toxicity of nickel. In: *Fourth International Conference on Nickel Metabolism and Toxicology, Abstracts*, Espoo, Finland, 5-9 September 1988, Helsinki, Institute of Occupational Health, p.17.
 46. Sunderman Jr, Salnikow K. Nickel carcinogenesis. *Mutation Research* 2003;533:67-97.
 47. Peto J, Cuckle H, Doll R, Hermon C, Morgan LG. Respiratory cancer mortality of Welsh nickel refinery workers. In: *Nickel in the human environment. Proceedings of a Joint Symposium*, Lyon, 8-11 March, 1983, Lyon, International Agency for Research on Cancer, pp. 37-46.
 48. Bencko V, Geist T, Arbetova D, Dharmadikari DM, Svandova E. Biological monitoring of environmental pollution and human exposure to some trace elements. *J Hyg Epidemiol Microbiol Immunol* 1986; 30:1-10.
 49. Grimsrud TK, Berge SR, Martinsen JI, Andersen A. Lung cancer incidence among Norwegian nickel-refinery workers, 1953-2000. *J Environ Monit* 2003;5:190-7.
 50. Doll R, Report of the International Committee on Nickel Carcinogenesis in Man. *Scand J Work Environ Health* 1990;16:9-82.
 51. Sunderman FW, Morgan LG, Andersen A, Ashley D, Forouhar FA. Histopathology of sinonasal and lung cancers in nickel refinery workers. *Ann Clin Lab Sci* 1989;19:44-50.
 52. Hughes K, Meek ME, Newhook R, Chan PKL. Speciation and health risk assessment of metals: evaluation of effects associated with forms present in the environment. *Regul Toxicol Pharmacol* 1995;22:213-20.
 53. Avery JK, Goldberg A, Kasprzak KS, Lucas LC, Millard HD, Natiella JR, et al. Local tissue reaction and carcinogenesis (Section Report). In: *Biocompatibility, Toxicity, and Hypersensitivity to Alloy Systems Used in Dentistry*, Lang BR, Morris HF, Razzoog ME, (Eds.). University of Michigan: Ann Arbor 1986. pp. 262-70.

EPIDEMIOLOŠKI I PATOGENETSKI ASPEKTI TROVANJA NIKLOM

Vladimir Ilić, Vladmila Bojanić i Biljana Jović

Nikl ima veliku zastupljenost u čovjekovom okruženju, a po rasprostranjenosti u zemljinjnoj kori, zauzima dvadeset četvrto mesto. Podaci ukazuju da se godišnje u čovjekovu okolinu ubaci oko 150000 tona nikla iz prirodnih izvora i 180000 poreklom od ljudske aktivnosti, pre svega, tokom emisije sagorevanja fosilnih goriva, industrijske proizvodnje i industrijskog otpada bogatog niklom. Čovek je konstantno izložen ovom ubikvitarnom elementu u manjoj ili većoj meri. Ljudska izloženost niklu je najčešća preko inhalacije i ingestije i naročito je visoka kod radnika u metalurgiji koji se bave preradom nikla. Zahvaljujući njegovoj velikoj prisutnosti, deficijentnost nikla se ne javlja, čak je i teško držati dijetu da se ne unosi nikl, zbog velikog prisustva u najrazličitijoj hrani.

Respiratorni trakt, bubrezi i jetra, najizloženiji su promenama pri ekspoziciji sa niklom. Najbolje opisane promene na ovim organima su pneumokonize sa niklom, hronični rinitisi i tumori nosnih šupljina i tranzitorna bubrežna nefropatija. Nespecifična simptomatologija se sreće kod oštećenja CNS niklom u vidu glavobolja, mučnine i povraćanja. Pojedina niklova jedinjenja i sam nikl, pored izrazite toksičnosti, ispoljavaju i kancerogene efekte na čoveka. *Acta Medica Mediana* 2007;46(2):37-44.

Ključne reči: trovanje, nikl, epidemiologija, karcinogeneza