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Review

Nickel: A Review of Its Sources and Environmental Toxicology

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Abstract

Nickel is a metal of widespread distribution in the environment: there are almost 100 minerals of which it is an essential constituent and which have many industrial and commercial uses. Nickel and nickel compounds belong to the classic noxious agents encountered in industry but are also known to affect non-occupationally exposed individuals. The general population may be exposed to nickel in the air, water and food. Inhalation is an important route of occupational exposure to nickel in relation to health risks. Most nickel in the human body originates from drinking water and food; however, the gastrointestinal route is of lesser importance, due to its limited intestinal absorption. The toxicity and carcinogenicity of some nickel compounds (in the nasal cavity, larynx and lungs) in experimental animals, as well as in the occupationally exposed population, are well documented.

The objective of this paper is to summarize the current overview of the occurrence and sources of nickel in the environment, and the effect of this metal and its compounds on living organisms. As this topic is very broad, this review is briefly concerned with the toxicokinetics of nickel, its health effects and biological monitoring.

Keywords: nickel, environment, sources, toxicokinetics, pollution

Introduction

Nickel is a nutritionally essential trace metal for at least several animal species, micro-organisms and plants, and therefore either deficiency or toxicity symptoms can occur when, respectively, too little or too much Ni is taken up. Although a number of cellular effects of nickel have been documented, a deficiency state in humans has not been described [1-6]. Nickel and nickel compounds have many industrial and commercial uses, and the progress of industrialization has led to increased emission of pollutants into ecosystems. Although Ni is omnipresent and is vital for the function of many organisms, concentrations in some areas from both anthropogenic release and naturally varying levels may be toxic to living organisms [6-8].

Inhalation exposure in occupational settings is a primary route for nickel-induced toxicity, and may cause toxic effects in the respiratory tract and immune system [9]. The exposure of the general population to nickel mainly concerned oral intake, primarily through water and food, as a contaminant in drinking water or as both a constituent and contaminant of food [7, 10]. It is also known to affect non-occupationally exposed individuals, especially those handling stainless steel and nickel-plated articles of everyday use, because nickel is a common sensitizing agent with a high prevalence of allergic contact dermatitis [1, 11, 12].

This paper presents a current overview of the occurrence and sources of nickel in different parts of the environment (air, water, soil, food) with particular emphasis on Polish measurements, as well as the effect of nickel on living organisms.

Occurrence and Sources

Nickel (Ni) is the 24th most abundant element in the Earth's crust, comprising about 3% of the composition of the earth. It is the 5th most abundant element by weight after iron, oxygen, magnesium and silicon. It is a member of the transition series and belongs to group VIII B of the periodic table along with iron, cobalt, palladium, platinum and five other elements. Nickel is a naturally occurring element that can exist in various mineral forms. As a member of the transition metal series, it is resistant to corrosion by air, water and alkali, but dissolves readily in dilute oxidizing acids. Natural nickel is a mixture of five stable isotopes; nineteen other unstable isotopes are known. Although it can exist in several different oxidation states, the prevalent oxidation state under environmental conditions is Ni(II), nickel in the +2 valence state. Other valences (-1, +1, +3, and +4) are also encountered, though less frequently [9, 10, 13].

Nickel and nickel compounds have many industrial and commercial uses. Most nickel is used for the production of stainless steel and other nickel alloys with high corrosion and temperature resistance. Nickel metal and its alloys are used widely in the metallurgical, chemical and food processing industries, especially as catalysts and pigments. The nickel salts of greatest commercial importance are nickel chloride, sulphate, nitrate, carbonate, hydroxide, acetate and oxide [14, 15].

Nickel is one of many trace metals widely distributed in the environment, being released from both natural sources and anthropogenic activity, with input from both stationary and mobile sources. It is present in the air, water, soil and biological material. Natural sources of atmospheric nickel levels include wind-blown dust, derived from the weathering of rocks and soils, volcanic emissions, forest fires and vegetation. Nickel finds its way into the ambient air as a result of the combustion of coal, diesel oil and fuel oil, the incineration of waste and sewage, and miscellaneous sources [10, 14-18]. Environmental sources of lower levels of nickel include tobacco, dental or orthopaedic implants, stainless steel kitchen utensils and inexpensive jewellery [4]. Tobacco smoking is another, not negligible, source of non-occupational exposures to nickel. It has been estimated that each cigarette contains nickel in a quantity of 1.1 to 3.1 μg and that about 10-20% of the nickel inhaled is present in the gaseous phase. According to some authors, nickel in tobacco smoke may be present in the form of nickel carbonyl, a form which is extremely hazardous to human health. Pipe tobacco, cigarettes and other types of tobacco products do not greatly differ one from another in the content of nickel [1, 16].

Air

Nickel concentrations in ambient air vary considerably and the highest values have been reported from highly industrialized areas. Typical average levels of airborne nickel are: 0.00001-0.003 μg/m^3 in remote areas; 0.003-0.03 μg/m^3 in urban areas having no metallurgical industry; 0.07-0.77 μg/m^3 in nickel processing areas. In Poland the recommended nickel concentration in the atmospheric air is set as 0.025 μg/m^3 [1, 18, 19].

Occupational exposure to nickel compounds is dependent upon industrial processing and is usually substantially higher than work-unrelated nickel exposure. The form of nickel to which workers are exposed differs in the various industries in which nickel is used and occurs through inhalation or dermal contact (inhalation is the primary route of exposure), with ingestion taking place where there are poor industrial hygiene practices [10, 20]. It usually involves the inhalation of one of the following substances: dust of relatively insoluble nickel compounds, aerosols derived from nickel solutions (soluble nickel) and gaseous forms containing nickel (usually nickel carbonyl) [16]. Many measurements conducted at various workplaces at risk (casting, welding, battery manufacture etc.) have revealed that the occupational concentrations may vary in a wide range from micrograms to milligrams of nickel per m^3 of air [1]. In nickel-producing or nickel-using industries, about 0.2% of the work force may be exposed to considerable amounts of airborne nickel, which may lead to the retention of 100 μg of nickel per day [1, 10, 14, 16, 20].

Water

Drinking water generally contains nickel at concentrations less than 10 μg/l. Assuming a daily intake of 1.5 l of water and a level of 5-10 μgNi/l, the mean daily intake of nickel from water for adults would be between 7.5 and 15.0 μg. Tests conducted in the USA have revealed that 97% of the 2053 drinking water samples tested had nickel concentrations below 20 μg/l and 80% of the samples had less than 10 μg/l. In exceptional cases, values up to 75 μg/l are found and those as high as 200 μg/l were recorded only in the nickel ore mining areas. The incidence of health impairments due to higher nickel intakes in drinking water is extremely infrequent [16, 21].

The mean Ni content in 80 samples of drinking water in Poland collected from an area affected by industrial emissions (Stalowa Wola area) was 17 μg/l and in most of the analyzed water samples did not exceed the allowable concentration of 20 μg/l [22, 23].

The concentration of Ni in cold and hot water depends on the quality of the pipes. In the case of metal pipes, the level of Ni in hot water is lower than in cold water. However, when PVC pipes are used the concentrations are opposite [24].

Soft drinking water and acidic beverages may dissolve nickel from pipes and containers. Leaching or corrosion processes may contribute significantly to oral nickel intake, occasionally up to 1 mg/day. Nickel concentration in screened households' drinking water decreased significantly after 10 min. of flushing in the morning from average 10.79 μg/l to 7.23 μg/l, respectively [14, 25].

The major sources of trace metal pollution in aquatic ecosystems, including the ocean, are domestic wastewater effluents (especially As, Cr, Cu, Mn and Ni) and non-ferrous metal smelters (Cd, Ni, Pb and Se). Nickel is easily accumulated in the biota, particularly in the phytoplankton or other aquatic plants, which are sensitive bioindicators of water pollution. It can be deposited in the sediment by such processes as precipitation, complexation and adsorption on clay particles and via uptake by biota [16, 26, 27].

In lakes, the ionic form and the association with organic matter are predominant. On the basis of complex investigations on lakes (more than 100 km distant from the nearest source of pollution – enterprises of the copper-nickel industry), it was discovered that there is intensive precipitation of heavy metals and acid oxides within the catchment area of Lake Kochejavr. Levels of precipitation of Ni of 0.9 mg/m^2/year over long periods were found to be dangerous for biological systems of fresh water catchments [28].

In rivers, nickel is transported mainly as a precipitated coating on particles and in association with organic matter. The concentrations of nickel in the biggest and only navigable river in the South of Iran (River Karoon) were from 69.3 to 110.7 µg/l in winter, and from 41.0 to 60.7 µg/l in spring, respectively. The results show that the pollution has increased along the river, down to the estuary at Persian Gulf [8]. Part of the nickel is transported via rivers and streams into the ocean. In Poland, nickel is generally transported via rivers into the Baltic Sea and in this way the average value of anthropogenic Ni input is 57%. Generally, in sea water nickel is present at concentrations of 0.1- 0.5 µg/l [1, 16, 17, 29].

Soil

Nickel is generally distributed uniformly through the soil profile but typically accumulates at the surface from deposition by industrial and agricultural activities. Nickel may present a major problem in land near towns, in industrial areas, or even in agricultural land receiving wastes such as sewage sludge. Its content in soil varies in a wide range from 3 to 1000 mg/kg [1, 6, 17]. Nickel can exist in soils in several forms: inorganic crystalline minerals or precipitates, complexed or adsorbed on organic cation surfaces or on inorganic cation exchange surfaces, water-soluble, free-ion or chelated metal complexes in soil solution [6, 16, 21].

This metal apparently does not seem to be a major concern outside urban areas at this time but may eventually become a problem as a result of decreased soil pH caused by reduced use of soil liming in agriculture and mobilization as a consequence of increased acid rain [1, 6]. Mielke et al. [30] investigated the effect of anthropogenic metals on the geochemical quality of urban soils. The median nickel content was 3.9 µg/g for fresh alluvium samples and 9.8 µg/g for urban alluvial soils (New Orleans and stratified by census tracts). Overall, significantly higher metal values occur in the inner city and lower values occur in outlying areas.

In Poland, the level of nickel in 60 samples of the soil collected from the Stalowa Wola area, which is affected by industrial emissions, was higher (average 17.20 mg/kg) than that in the reference samples (average 9.72 mg/kg). All the values, however, were below the highest allowable concentration [31]. Similarly, nickel content in soils in allotment gardens in post-flooded industrialized areas of the Dolnośląski Region during 2000-01 also did not exceed the highest allowable concentration [32, 33]. According to the current Polish regulation the allowable limit for nickel in the soil depends on many factors, and for not industrialized areas is set as 50 mg/kg d.w. [27, 34].

Food

Nickel is considered to be a normal constituent of the diet and its compounds are generally recognized as safe when used as a direct ingredient in human food [35]. Little is known about the actual chemical forms of nickel in various foods or whether dietary nickel has distinct "organic" forms with enhanced bioavailability analogous to those of iron and chromium. Nickel levels in foodstuffs generally range from less than 0.1 mg/kg to 0.5 mg/kg. A few foods may have obtained nickel during the manufacturing process but in most it apparently occurred naturally [16, 36].

Food processing methods apparently add to the nickel levels already present in foodstuffs via: 1. leaching from nickel-containing alloys in food processing equipment made from stainless steel; 2. the milling of flour; 3. catalytic hydrogenation of fats and oils by use of nickel catalysts [15, 17]. Rich food sources of nickel include oatmeal, dried beans and peas, nuts, dark chocolate and soya products, and consumption of these products in larger amounts may increase the nickel intake to 900 µg/person/day or more [37].

A requirement for nickel has not been conclusively demonstrated in humans. Scattered studies indicate a highly variable dietary intake of nickel but typical daily intake of this metal from food ranges from 100-300 µg/day in most countries. In France, the estimated weekly intake for the general population of nickel from wine consumption was, on the basis of 66 l/year/resident, 30.6 µg/week (4.37 µg/day) [10, 14, 38].

Many measurements of nickel levels in several food products were performed in Poland. In 1990, a survey was conducted on twenty-seven whole-day alimentary rations at canteens in Lublin and Warsaw, as well as the food rations of manual workers' families in several Polish towns. It was observed that daily nickel intake values, according to the current dietary recommendations, may be considered as safe (187-302 µg/day for the canteen rations and 183-341 µg/day for the family rations) [39]. According to Leszczyńska and Gambuś [40], in 1996-1998

the dietary intake of nickel by Polish adult inhabitants of selected farms situated within an industrialized area was 132 μg/day.

Nickel levels in some vegetables and fruits, in fruit and vegetable juices, in wine and cocktails were within the limits of standards [41-44]. Similarly, nickel contents in instant coffee brands, in some natural ground coffees, in coffee beans and coffee infusions did not exceed the allowable concentration values stated in relevant Polish regulations. However, a significant relationship was observed between the levels of the nickel in coffee infusions and coffee beans [45, 46]. The concentrations of nickel in bee honey, confectionery products, dry herbs, tea leaves and granulated tea were also below the corresponding allowable values [47-50].

Toxicokinetics

Human nickel exposure originates from a variety of sources and is highly variable. Nickel is normally present in human tissues and, under conditions of high exposure, these levels may increase significantly [14, 16, 20]. In the general population, contributions to the body burden from inhalation of nickel in the air and from drinking water are generally less important than dietary intake and ingestion is considered to be the most important route of exposure. The absorption of nickel is dependent on its physicochemical form, with water-soluble forms (chloride, nitrate, sulphate) being more readily absorbed. In animals, 1-10% of the dietary nickel is absorbed by the gastrointestinal tract. It is important to note that the way in which nickel is consumed may greatly affect its bioavailability [3, 7, 17, 35].

Food intake, gastric emptying and peristalsis of the intestine are of substantial significance for the bioavailability of nickel, because absorption of ingested nickel is lower when it is administrated in food or in water together with a meal. The presence of food in the stomach significantly alters the bioavailability of nickel salts [3, 7, 51]. Absorption is influenced by the amount of food, the acidity of the gut and the presence of dietary constituents, possibly phosphate, phytate, fibres and similar metal ion binding components, which may bind nickel and make it much less available for absorption than nickel dissolved in water and ingested on an empty stomach. In particular, the levels of other minerals, such as iron, magnesium, zinc and calcium, may alter nickel absorption from the gut. Nickel binding to food components may also be pH-dependent and thereby depend on the time interval between food ingestion and ingestion of nickel [4, 36, 52].

In humans, the absorbed nickel average is 27 ± 17% of the dose ingested in water and 0.7 ± 0.4% of the dose ingested in food (40-fold difference) [4, 53]. In general, due to its slow uptake from the gastrointestinal tract, ingested nickel compounds are considered to be relatively non-toxic, with the primary action being mainly irritation. However, when taken orally in large doses (>0.5 g), some forms of nickel may be acutely toxic to humans [9, 13, 17, 21].

The metabolism of nickel involves conversion to various chemical forms and binding to various ligands. The organ distribution of nickel has been documented by a number of investigators. Although differences in distribution occur as a function of route of exposure, the solubility of the nickel compounds and time after exposure, the primary target organs for nickel-induced systemic toxicity are the lungs and the upper respiratory tract for inhalation exposure and the kidney for oral exposure. Other target organs include the cardiovascular system, the immune system and blood [4, 9, 13, 51].

Human exposure to highly nickel-polluted environments has the potential to produce a variety of pathological effects. Among them are skin allergies, lung fibrosis, cancer of the respiratory tract and iatrogenic nickel poisoning [15, 54]. A number of studies demonstrated the hepatic toxicity associated with nickel exposure and dose-related changes in serum enzyme activity were observed following animal treatment with nickel. Nephrotoxicity has been noted and aminoaciduria and proteinuria were the indices of nickel toxicity. Nickel exposure has been reported to produce haematological effects in both animals and humans. While no reproductive effects have been associated with nickel exposure to humans, several studies on laboratory animals have demonstrated fetotoxicity [13, 35, 55].

Many harmful effects of nickel are due to the interference with the metabolism of essential metals, such as Fe(II), Mn(II), Ca(II), Zn(II), Cu(II) or Mg(II), which can suppress or modify the toxic and carcinogenic effects of nickel. The toxic functions of nickel probably result primarily from its ability to replace other metal ions in enzymes and proteins or to bind to cellular compounds containing O-, S-, and N-atoms, such as enzymes and nucleic acids, which are then inhibited [6, 13]. Nickel has been shown to be immunotoxic, altering the activity of all specific types involved in the immunological response, resulting in contact dermatitis or asthma [13].

Health Effects

Nickel is a ubiquitous metal frequently responsible for allergic skin reactions and has been reported to be one of the most common causes of allergic contact dermatitis, as reflected by positive dermal patch tests [11, 12, 15, 16, 35]. Gawkrodger et al. [56] suggested that the higher number of antigens, or perhaps the larger nickel load, in the extended metal series resulted in a larger proportion of patients reacting. In clinical cases, allergic contact hypersensitivity to nickel develops much more readily in inflamed skin than normal skin [11]. Sensitization might occur from any of the numerous metal products in common use, such as coins, jewellery (earrings, chains, wristwatches, bracelets) and even mobile phones [2, 14, 16, 24, 57]. Of the general population, approximately 8-10%

of women and 1-2% of men demonstrate a sensitivity to nickel. In Poland, using "flake" test with nickel sulphate, it was shown that 12.5% of the female population is allergic to nickel [58, 59].

Nickel dermatitis produces erythema, eczema and lichenification of the hands and other areas of the skin that contact nickel. Initial sensitisation to nickel is believed to result from dermal contact but recurring flares of eczema, particularly of the hands, may be triggered by ingestion. Numerous studies have been conducted to attempt to establish the relationship between nickel exposure and dermal irritation. However, no change in nickel toxicokinetics was found in relation to nickel allergy [51].

While nickel has long been recognized as a contact irritant, many studies have also demonstrated dermal effects in sensitive humans resulting from ingested nickel [35]. The existence of clinically relevant systemic reactions to oral nickel exposure, in particular systemic reactions to this metal in the daily diet, remains controversial. Several studies have shown that oral exposure to nickel may invoke an eruption or worsening of eczema in nickel-sensitive individuals; however, a dose-response relationship is difficult to establish. In most of these studies, the exposure dose of nickel used has been considerably higher than the nickel content in the normal daily diet [60].

Nickel hypersensitivity also causes asthma, conjunctivitis, inflammatory reactions to nickel-containing prostheses and implants, and systemic reactions after parenteral administration of nickel-contaminated fluids and medications. The sensitivity to nickel would emphasise the need to monitor nickel content in drinking water and nickel-allergic subjects should be aware of the increased absorption when drinking water on an empty stomach [51].

Epidemiological investigations and experimental studies have demonstrated that nickel metal dusts and some nickel compounds are extremely potent carcinogens after inhalation but also that the carcinogenic risk is limited to conditions of occupational exposure [7, 18, 20]. Nickel compounds have been well established as carcinogenic in many animal species and by many modes of human exposure but their underlying mechanisms are still not fully understood [10, 16, 18, 20, 61]. The bioavailability of nickel and the presence of constituents that promote oxygen-free radical reactions evidently influence the carcinogenicity of nickel oxides and related compounds. Not all nickel compounds are equally carcinogenic, because their carcinogenic potency is directly related to their ability to enter cells. Certain water-insoluble nickel compounds exhibit potent carcinogenic activity, whereas highly water-soluble nickel compounds exhibit less potency. The reason for the high carcinogenic activity of water-insoluble nickel compounds relates to their bioavailability and the ability of the nickel ions to enter cells quite efficiently via phagocytic processes. Subsequent intracellular dissolution yields very high cellular levels of Ni^{2+} [62, 63]. Water-soluble nickel salts do not readily enter cells. Therefore, these compounds are generally not carcinogenic in animals and, to a large extent, have not been considered potent human carcinogens, although recent studies have suggested an increase in cancer in nickel refinery areas where exposure to water-soluble nickel salts occurs [7].

Differences in the carcinogenic activities of nickel compounds may reflect variations in their capacities to provide nickel ions (e.g. Ni^{2+}) at critical sites within target cells. Ni^{2+} can initiate carcinogenesis, possibly by mutagenesis, chromosome damage, formation of Z-DNA, inhibition of DNA excision-repair or epigenetic mechanisms [52]. As suggested by the growing literature on nickel carcinogenesis, the initial events in environmentally induced cancers may be a combination of gene induction and gene silencing by epigenetic DNA methylation that leads to cancer cell selection [52, 62].

The U.S. EPA has not evaluated soluble salts of nickel as a class of compounds for potential human carcinogenicity because there are inadequate data to perform an assessment. However, nickel refinery dust and specific nickel compounds – nickel carbonyl and nickel subsulphide – have been evaluated [35]. Not only nickel compounds have been shown to be responsible for a number of human cancers in occupationally exposed workers but also carcinogenic nickel compounds have been shown to induce many different types of tumours in experimental animal systems. Ni^{2+} can function as a tumour by inhibiting NK cell activity [52, 62].

One possible mode by which nickel causes cell death and/or damage may involve oxidative reactions such as nickel-induced lipid peroxidation (LPO).

A number of recent studies have demonstrated enhanced lipid peroxidation in the liver, kidney, lung, bone marrow and serum, and dose-effect relationships for lipid peroxidation in some organs were observed [13, 55, 64-70]. Lipid peroxidation may be a contributing factor in Ni-induced tissue oxidative stress [64].

Probably the nickel-induced accumulation of iron may be directly responsible for the formation of reactive oxygen species and the subsequent enhancement of lipid peroxidation [71]. Research studies conducted up till now suggest that nickel-mediated enhancement of lipid peroxidation may be the result of depletion in the level of hepatic glutathione peroxidase with a concomitant increase in the level of iron, which seems to trigger peroxidative damage by hydroxyl radicals involving Haber-Weiss and Fenton chemistry (reactions) [64, 66, 68-70].

Biological Monitoring

Nickel is excreted in the urine and faeces, with relative amounts for each route being dependent on the route of exposure and chemical form [9, 10]. Numerous studies are available which suggest that occupationally exposed workers display higher serum and urine nickel levels than those exposed non-occupationally [1]. Urine and serum nickel concentrations may be used as biological indicators of occupational, environmental and iatrogenic exposures to nickel compounds. However, they do not give a

good picture of past exposure and they cannot be used for risk assessment as current knowledge is not sufficient to relate nickel concentrations in these indicator media to specific adverse health effects [1, 15, 20, 72]. Nickel concentrations in serum mainly reflect recent exposure because of the short biological half-time in this compartment. The nickel excretion in urine may reflect more extended exposure and is more practical than serum for the biological monitoring of nickel-exposed workers [20, 73]. Urine nickel measurement performed in Poland indicated that the majority of Wrocław's inhabitants are not more exposed to nickel in comparison with inhabitants of the countryside [74]. From other similar studies it is evident that there exists elevated environmental and occupational exposure in some regions of Poland [75].

Conclusion

Within the past few decades, interest in nickel among scientists has increased as a result of its progressive industrial and commercial significance as well as the improvement of analytical methods for nickel by electrothermal atomic absorption spectrometry. Up to the present, measurements in many countries, including Poland, indicate that the concentrations of nickel in the environment (air, water, soil, food) do not exceed legislative limits and should not be dangerous for the general population. However, everybody should keep in mind that, at present, nickel, although not released extensively into the environment, may represent a hazard to human health.

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