

Nickel Poisoning with Analytical Aspects and its Management

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Abstract

The increasing consumption of heavy metals in modern industries leads to an increase in the environmental burden. Nickel signifies a good example of a metal whose use is widening in modern technologies. As a result of the healthier consumption of nickel-containing products, nickel compounds are released to the environment at all stages of production and utilization. Nickel is a convenient metal, particularly in various alloys, in batteries and in nickel-plating. Nickel compounds are used specifically as catalysts and pigments. In nickel-producing or nickel-using industries, about 0.2% of the workforce may be exposed to considerable amounts of airborne nickel. In addition, nickel release e.g., into cutting oils, and skin contact with nickel-containing or nickel-plated tools and other items may add to an occupational nickel exposure. Nickel is extremely mobile in soil, particularly in acidic soils. There is minute proof that nickel compounds accumulate in the food chain. Management of nickel is done with the help of a detoxifying method, which is done by using vitamin C, dimercaptosuccinic acid (DMSA), 2,3-Dimercapto-1-propanesulfonic acid (DMPS), Garlic, etc. The detection and determination of nickel levels can be done by qualitative as well as quantitative methods etc., with the help of UV, AAS, Voltammetry method, NAA, etc.

Keywords: Nickel; Nickel toxicity; Heavy metals; Nickel poisoning; Pharmacokinetics; etc.

Introduction

Nickel is a naturally occurring element on earth and also it's the fifth most common element on earth. Pure nickel is lustrous, silvery-white metallic element with a slight golden touch. Nickel is also found in the meteorites and in the lumps of minerals on the floor of the ocean which is known as seafloor nodules. The earth's core is composed of 6 percent of nickel.

Chemically, Nickel is denoted as 'Ni', having atomic number 28 and atomic weight 58.69.

It's melting and boiling point is 1453°C and 2730°C respectively. Its density is 8.90 g/cm³ at a temperature of 25°C. It resists corrosion and oxidation and acts as a magnet at room temperature. It is very ductile. Nickel is widely used in a variety of products for consumer, industrial, military, transport, aerospace, marine, and architectural applications. Majorly, it is used in alloying, particularly with chromium and other metals to produce stainless and heat-resisting steels. Other uses are in making pots, pans, kitchen sinks, etc, as well in buildings, food processing equipment, medical equipment, and chemical plants.¹

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Approximate percent of uses of nickel:

- 65% of the nickel is used to manufacture stainless steel.
- 20% is used in other steel and non-ferrous alloys-often for highly specialized industrial, aerospace and military applications.
- 9% is used in plating and
- 6% in other uses, including coins, electronics, and in batteries for portable equipment and hybrid cars.²

Sources of Nickel

- It is found in two types of deposits: laterite deposits and magmatic sulfide deposits.
- It can be found in manganese nodules and crusts on the deep seafloor.
- Its main mineral sources are limonite, garnierite and pentlandite.
- It is found in a type of nickel ore known as pyrrhotite.
- It can also be found in large deposits of nickel in the Sudbury Basin in Canada.
- It can be found in jewelry.²

*Exposure To Nickel***Occupational**

In nickel-manufacturing industries, workers are exposed to airborne nickel. Occupational exposure may be caused due to release of nickel into cutting oils, and skin contact with nickel-containing or nickel-plated tools and other items, which may lead to the retention of 100 micrograms of nickel per day. Coins and stainless steel contain nickel. Some jewelry is plated with nickel or prepared from nickel alloys.^{3,4}

Domestic

The foods richest in nickel are nuts, peas, beans, chocolate, soy, lentils, oats, buckwheat, barley, corn. Banana and pears are the fruits that contain nickel. In the case of, Soft drinking-water and acid beverages, they may dissolve nickel metal from pipes and containers. An oral intake of nickel up to 1 mg/day may be contributed by Leaching or corrosion processes. Average of Scattered studies

show that dietary intake of nickel is about 200–300 micrograms/day. Artificial body parts which are made from nickel-containing alloys may contain nickel which is harmful to the patients.^{2,5}

Environmental

Level of Environmental nickel depends upon natural sources, pollution from nickel producing or nickel-using industries and airborne particles from combustion of fossil fuels. Nickel is very useful in various alloys, in batteries, and in nickel-plating. Its compounds are also used especially as catalysts and pigments. In nickel-manufacturing industries, about 0.2% of the workers may be exposed to considerable amounts of airborne nickel.⁶

*Pharmacokinetics of Nickel***Absorption**

The major route of concern for nickel-induced toxicity is pulmonary absorption. Nickel may well be absorbed as the soluble nickel ion (Ni²⁺). Following inhalation contact, in the lungs of humans about 20–35% of nickel deposited is absorbed into the bloodstream. Absorption from the respiratory tract, it is dependent on the solubility of the nickel compound, if higher urinary nickel level is observed in workers who are exposed to soluble nickel compounds (nickel chloride, nickel sulfate) than in those who are exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide).⁷ In the oral exposure, in drinking water about 27% of the nickel is absorbed in humans, however, when nickel is given with food it is about only 1% absorbed. If nickel is applied directly to the skin it can be absorbed into the skin where it may persist rather than entering the bloodstream.^{8,9}

Distribution

The foremost carrier protein of nickel is albumin which is present in serum, but nickel is also bound to β -2 macroglobulin and histidine. The workers who are occupationally exposed to nickel have higher lung problems of nickel than the general population. The body liability of nickel is about 0.5 mg per 70 kg in an adult human. In the lungs and in the thyroid and adrenal gland (about 20–25 μ g/kg weight) the highest concentration is found.

Reference values for nickel concentrations from healthy persons in urine and serum without occupational exposure to nickel compounds have been recently assembled. The range of values for

serum/plasma is 0.14–0.65 µg/L, most reliable values seem to be around 0.2 µg/L. Corresponding values for urine are 0.9–4.1 µg/L, with the most reliable values of 1–2 µg/L. For whole blood, the values are 1.4 to 3.4 µg/L. Several diseases like myocardial infarction, acute stroke, thermal burns, hepatic cirrhosis affect the kinetics of nickel metabolism.^{8,10}

Metabolism and Excretion

The extracellular metabolism of nickel comprises of ligand exchange reactions. Nickel binds to albumin, L-histidine, and α₂-macroglobulin in human serum. The major binding locus of nickel to serum albumins in the histidine residue at the 3rd position from the amino terminus in humans. Under the redox metabolism nickel may generate the trivalent form thus forming reactive oxygen species. An important metabolic pathway is the release of intracellular nickel ion following phagocytosis of particles of oxidic and/or sulfidic nickel.¹¹

Nickel contains the minute particles which have been demonstrated close to the nuclear membrane. Parenteral administration of nickel persuades variations in the tissue distribution of other metals, and several physiological divalent cations impact nickel metabolism.

Through urine absorbed nickel is eliminated. Excretion via sweat, secretion via saliva and deposition in hair has been conveyed. Conversely, urinary excretion is the main clearance route. The nickel's biological half-time is depended on the nickel species tested. In humans; the half-time of plasma nickel is 11–39 hours, for soluble compounds. Moreover, for the particulate compounds, the half-time is 30–54 hours.⁸

Mechanism of action/toxicity

The most important route of nickel exposure in the workplace is Inhalation. The particles of nickel gets Deposited, absorbed, and its retention in the respiratory tract will depend on many of the factors such as:

- aerodynamic size of the particles
- whether the particles are inhalable
- the concentration of the nickel that is inhaled
- the minute ventilation rate of a worker
- whether breathing is nasal or oronasal
- the use of respiratory protection equipment

- personal hygiene practices, and
- general work patterns.

In skin contact, divalent nickel penetrates the skin fastest at sweat ducts and hair follicles, which is determined by the diffusion rate through the layer of the epidermis. For an administered dose of nickel chloride in excised human skin, the percent permeation ranges from 0.23 percent (non-occluded skin) to 3.5 percent (occluded skin).^{12,13}

Onset and Duration of Action

The symptoms appear in a day to weeks after exposure however higher the dose, symptoms may occur the earlier. Symptoms occur with respect to different forms of toxicity either elemental and vaporized. Symptoms of nickel poisoning are difficult to analyze and may take weeks, months or years to develop in some individuals.⁷

Fatal Dose and Fatal Period

The fatal dose of nickel is considered to be approximately 1–4 grams in general. For an adult, it ranges approximately 7–36 mg/kg. Death may occur within a few hours but is usually delayed for 3–5 days.⁹

Normal and Reference Values

In unexposed individuals, the level of nickel in the blood usually remains less than 0.4 µg/L. In acute toxicity blood nickel level remains high 1.4 to 3.4 mg/L. Nickel levels in hair and nails tend to increase, therefore the value is 2.79 µg/g and 18.22 µg/g.^{14–16} (Table 1)

Table 1: Normal and Reference values of Nickel in biological materials.

Matrix	Normal Level	Toxic Level
Blood-plasma/serum	0.14–0.65 µg/L	More than 0.65 µg/L
Urine	1–3 µg/L	More than 4 µg/L
Hair	0.12 µg/g	2.79 µg/g
Nails	0.042–7.50 mg/kg	18.22 µg/g

Systemic Effects on Body

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

Respiratory Effects

Many changes in the lungs due to nickel exposure including alveolar wall damage, with fibrotic changes and edema in the alveolar space. A dose-response trend was also found for soluble nickel among cases in the three highest cumulative exposure groups (0.04–≤0.15, 0.15–≤0.6, and >0.6 mg/m³ × years), after adjusting for age, smoking, and exposure to asbestos. Asthma induced by occupational exposure to nickel has been recognized in a small number of individuals.^{16,17}

Renal Effects

Marked tubular necrosis was observed in the kidneys exposed to a very high concentration of metallic nickel of small particle size. Urinary β₂-microglobulin concentration level is also increased in the individual who is exposed to nickel.¹⁶

Cardiovascular Effects

Nickel sulfate crystals (rough estimate of 570 mg Ni/kg) were accidentally ingested by a 2-year-old child. Four hours after ingestion, the cardiac arrest happened, and the child died 8 hours after exposure.¹⁶

Dermal Effects

Contact dermatitis, which effects from dermal exposure to nickel, is the most prevalent effect of nickel in the general population. Several studies indicate that a single oral dose of nickel assumed as nickel sulfate can result in a flare-up in dermatitis in nickel-sensitive individuals. Observed effects included erythema on the body, worsening of hand eczema, and a flare-up at the patch test site.¹⁶

Toxicological effects

The acute inhalation exposure to nickel carbonyl causes severe lung disease. Exposure to inorganic nickel, the reversible renal effects (in workers), allergic dermatitis (most prevalent in women), and mucosal irritation and asthma (in workers) have been reported. In the general population and in nickel workers the allergic skin reactions to nickel (dermatitis) have been documented. Though, the impact of nickel as a cause of occupationally-induced skin reaction is decreasing. In the general population, especially in women, there is evidence that nickel is increasingly a major allergen. The risk of nickel sensitization increases by ear-piercing. There was no effect found in the workers exposed to nickel carbonyl.^{2,16}

Carcinogenic effects

In nickel workers, laryngeal cancer, kidney cancer, and cancer of the prostate or bone have also been found. Much of the risk was associated to work at the linear calcanei where nickel exposure levels were 10–100 mg/m³ 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 as compared to that to the particulate form, analysis shows that exposure to soluble forms organized with the oxidic or sulfidic forms increases the risk.¹²

Critical organs, tissues, and effects

The critical organ resulting in inhalation exposure is the respiratory tract. After short-term high-dose inhalation exposure, lung irritation and pneumonia are acute effects.

Clinical Appearances/Symptoms in Case of Nickel Poisoning

Clinical appearance in case of Nickel poisoning will depend on different forms of Nickel and doses taken, which has been discussed below:¹⁴

In the case of Acute poisoning

In case of Acute poisoning the symptoms are :

- Headache, Nausea, Vomiting, Dizziness, Irritability, Difficulty Sleeping, Chest Pains, Sweating, Rapid Heart Beat and Dry Cough, respiratory tract irritation and neurological effects.
- For example -Nickel sulfate or nickel carbonyl poisoning, death occurs due to cardiac arrest, pneumonia or brain hemorrhage.
- Nickel metal can cause allergic contact dermatitis (ACD) from contact with jewelry, white gold, wristwatches, metal clothing fasteners, piercing, etc.
- It can also cause Asthma.

In case of Chronic poisoning

In case of Chronic poisoning the symptoms are :

- Rhinitis, sinusitis, anemia and in extreme cases perforation of the nasal septum.
- Outbreaks of dermatitis.
- Carcinogenic to humans.²

In case of Adverse pregnancy outcomes

It can happen due to occupational exposure which can lead to adverse outcomes such as Spontaneous abortion, Congenital structural malformations, Chromosomal aberrations, Cancer (occupational inhalation exposure), harm lung, larynx, nose, and pharynx.

Some additional symptoms of nickel toxicity

1. *Vitamin A deficiency:* Mouth ulcers, poor night vision, acne, frequent colds or infections, dry flaky skin, dandruff, diarrhea can all be indications of nickel toxicity.
2. *Vitamin D deficiency:* Joint pain or stiffness, backache, tooth decay, muscle cramps, hair loss can all be signs of nickel toxicity.
3. *Vitamin E deficiency:* Lack of sex drive, exhaustion after light exercise, easy bruising, slow wound healing, varicose veins, loss of muscle tone, infertility can all be indications of nickel toxicity.
4. *Vitamin K deficiency:* Easy bleeding, deficiency of good bacteria in the gastrointestinal tract. Overgrowth of bad bacteria.
5. *Histidine deficiency:* Pitiabile recovery from illness and injury, allergy reactions, inflamed muscles, painful muscles, fibromyalgia, high blood pressure, anemia, and kidney failure.
6. *Essential Fatty Acids deficiency:* Omega 3, Omega 6, Omega 9 EPA and DHA can be hampered with by nickel toxicity, symptoms combined are broad however here are the main problems to look for dry skin, eczema, dry hair otherwise dandruff, extreme thirst, excessive sweating, poor memory or learning difficulties, inflammatory health complications e.g. arthritis, high blood lipids, depression, breast pain, water retention, hair loss, itchy skin, dry eyes, stiff painful joints, craving for fatty foods.¹⁸

Diagnostic Investigation in Case of Nickel Poisoning

Diagnosis of nickel allergy is based on skin's appearance and recent exposure to items that may contain nickel.¹⁴

Patch test

During a patch test, very small quantities of potential allergens (including nickel) are applied to your skin and enclosed with small patches. The

patches remain on the skin for two days before the doctor removes them. If you have a nickel allergy, then, the skin under the nickel patch will be inflamed when the patch is removed or in the days after removal of the patch. Because of the low concentrations of allergens used, patch tests are harmless even for people with severe allergies.¹⁸

Chemical Tests of Nickel Poisoning

Qualitative Analysis¹⁸

1. *α -Nitroso β -Naphthol (1% solution in ethanol) Test :* One drop of mildly acidic solution of the extract is placed on a drop reaction paper. One drop of α -Nitroso β -Naphthol reagent is added to it. A brown precipitate is formed which is soluble in hydrochloric acid, which confirms the presence of nickel.
2. *Dimethyl Glyoxime Reagent (1% solution in ethanol) Test:* One drop of the extract is placed on a reaction paper. One drop of Dimethyl Glyoxime reagent is added to it, and the paper is exposed to ammonia vapors. A red spot is observed which confirms the presence of nickel.
3. *Salicylaldehyde Test:* 2.22 gm of pure salicylaldehyde dissolved in 8 ml of rectified spirit is added to 1.27 g. of A.R. hydroxylamine hydrochloride dissolved in 2 ml of water. The resulting solution is diluted with 15 ml of rectified spirit and is poured slowly and with stirring into 225 ml of water at 80°C. After cooling down the solution, it is filtered if necessary and stored in an amber bottle. Resulting reagent is then added to the test solution. Green color is observed, which confirms the presence of nickel.
4. *Furildioxime Test:* Furildioxime reagent is added to the test solution. A red color precipitate is obtained, which confirms the presence of nickel.

Quantitative Analysis

- a. *Electrothermal Atomic Absorption Spectrophotometry method (ETAAS):* Atomic absorption spectrophotometry is a good technique for the determination of nickel in biological materials such as blood, serum and urine; acid digestion method is used for the sample preparation and the sample detection limit is 0.2 $\mu\text{g/L}$ fluid or 0.49 $\mu\text{g/kg}$ of tissue.¹⁹
- b. *Inductively Coupled Plasma- Atomic Emission Spectroscopy (ICP-AES):* Inductively Coupled

Plasma- Atomic Emission Spectroscopy is used to identify the different concentrations of nickel standard solutions. The preparation method for the sample blood is Polydithiocarbamate resin extraction; ash filter and resins in a low-temperature oxygen plasma asher or digest with HNO_3 ; HCl .²⁰

- c. *Stabilized Temperature Graphite Furnace Atomic Absorption (STPGFAA)*: Stabilized Temperature Graphite Furnace Atomic Absorption spectroscopy is an analytical technique that is used to determine the nickel concentration in urine.²¹
- d. *Proton Induced X-ray Emission spectroscopy (PIXE)*: Proton Induced X-ray Emission spectroscopy is an important tool for the quantitative estimation of nickel in the air or airborne particulates hot acid digestion method is used.¹⁵
- e. *Voltammetry method*: Trace metal analysis (TMA) is a good technique for the quantification of nickel. The procedures are based on nickel deposition to the metallic state and then its oxidation in the presence of dimethylglyoxime with the formation of the complex adsorbed on the electrode. The reduction of the complex is exploited in the detection step. Due to the application of a sufficiently negative deposition potential the interference from surfactants is minimized.^{1,22}
- f. *UV-Visible Spectrophotometry Method*: A simple and rapid method using two imine ligands, (E)-N1-(2-hydroxy-5-nitrobenzylidene) iso-nicotinoyl-hydrazone and 2-(4-fluoro benzylideneamino) benzenethiol for the analysis of nickel (II) is proposed. The ligands react with nickel (II) at pH 4.0 and 4.7 to form red and pale purple complexes respectively with a stoichiometric ratio of 1:1. The complexes obeyed Beer's law with an excellent linearity depicted by a correlation coefficient value of 0.9997.²³
- g. *Neutron Activation and Analysis (NAA)*: It is a sensitive method for the analysis of nickel metal. Samples were neutron-irradiated using nuclear reactors, and the radioactive assay was carried out using high-resolution gamma-ray spectrometry. Major trace mass fractions were determined using both relative and internal mono-standard, NAA methods as well as Optical Emission Spectroscopy (OES) methods.²⁴

Management/Treatment of Nickel Poisoning

Nickel toxicity can result from ingestion, skin contact, inhalation or parenteral routes of exposure; nickel may be absorbed from the gastrointestinal and respiratory tracts as well as percutaneously. Chronic poisoning with Nickel is diagnosed if

1. Blood nickel level is more than 7 mcg/L.
Normal plasma level – 1.4 to 3.4 mcg/L.
2. Urine nickel level is more than 4 mcg/L.

Exposure to all forms of Nickel should be treated as soon as possible. Ingestion of single and small amounts of Nickel is unlikely to cause systemic toxicity and the asymptomatic patient may be observed at home. However, the ingestion of a large amount of Nickel should be evaluated in the hospital. The patient with persistent vomiting or evidence of systemic toxicity should be admitted to a hospital for supportive measures.²⁵

Delay in confirmatory tests can cause irreversible damage, hence exposures of all forms of Nickel should be treated as soon as possible.

Household Remedies

Following household remedies should be followed:

1. Use of lotion such as calamine lotion may ease itching.
2. Moisturizing regularly using emollient creams or lotions, such as petroleum jelly or mineral oil, could reduce the need for topical corticosteroids.
3. Application of wet compresses help dry blisters and relieve itching.
4. Use of corticosteroid cream, nonsteroidal cream, oral corticosteroid, such as prednisone, an oral antihistamine, such as fexofenadine (Allegra) or cetirizine (Zyrtec), etc help reduce the skin irritation caused by a nickel allergy. However, over-the-counter ointments, such as antibiotic creams, which may contain ingredients must be avoided, as these can increase an allergic reaction.¹

Pre-Hospital Management¹²

- *Hot Zone*: Rescuers should be appropriately attired and trained before entering the Hot Zone. In cases of rescuer have not trained or unavailability of proper equipment, assistance from a well-equipped organization should be called.
- *Victim Removal*: If the victim is in a conscious

state, lead him out of the hot zone whereas who are unable to walk, they may be carefully carried or drag with safety using backboard or gurneys.

- **Decontamination Zone:** Exposure to Nickel needs to be decontaminated in the following way
 - a. ABC approach: to be followed ensuring a protected airway, adequate ventilation, and hemodynamic stability. Supplemental oxygen should be administered if required.
 - b. Basic Decontamination: Aabled victims must remove all their contaminated clothes and all personal belongings and pack them into a double bag. The exposed skin and hair should be washed under a shower. Irritated eyes should be washed with plain water or saline for at least 5 minutes.
 - c. Respiratory Protection: In case of unsafe exposure to Nickel, Self-contained breathing apparatus (SCBA) is recommended.
 - d. Skin Protection
 - i. The contaminated clothing is removed and the exposed area is washed thoroughly with soap and water.
 - ii. For dermatitis: Creams containing 3% clioquinol and 1% hydrocortisone have abolished the response to patch testing in several nickel-sensitized cases. However, toxicity in animal studies limits the utility of clioquinol.
 - iii. Topical cyclosporine (5% w/v) is effective in contact dermatitis.
 - iv. Oral tetra-ethylthiuramdisulfide (TETD) at doses ranging from 50 to 400 mg/day for up to 10 weeks improves nickel-dermatitis in some individuals.
 - v. Disulfiram in doses of 50 to 100 mg/day has been shown to be effective in clearing cases of nickel dermatitis.
 - vi. The topical administration of triclosan (0.3% in 96% alcohol) has significantly reduced the allergic responseto nickel patch testing.
 - vii. Trientine (triethylenetetramine) 300 mg daily may also be used.
 - viii. Several reports have shown the positive outcome of vitamin C as an antioxidant and scavenger of free radicals, which can reduce the toxicity of nickel in the body.¹⁸

Hospital Management

Following hospital management should be adopted:

1. Bronchodilators such as inhaled steroids and moist oxygen inhalation help to improve hypoxia and reduce pulmonary distress.
2. Pulmonary edema should be prevented by the early, adequate, short-range application of glucocorticoids, control of fluid input.
3. Sodium diethyldithiocarbamate (Dithiocarb or DDC), antibiotics, and corticosteroids may help reduce pneumonia and toxic myocarditis.
4. Symptomatic measures to relieve the specific symptoms should be initiated.
5. Severe poisoning can be oral sodium diethyldithiocarbamate (dithiocarb), 0.5 g each time, 4 times a day, while taking the same amount of sodium bicarbonate, according to the condition of the decision days, generally can be taken continuously 3 –7 days. Nebulization can also be used.
6. *Chelation:* Chelation therapy is the preferred medical treatment for reducing the toxic effects of metals. Chelating agents are capable of binding to toxic metal ions to form complex structures that are easily excreted from the body removing them from intracellular or extracellular spaces. Dithiocarb is an effective chelating agent for nickel and is administered intravenously in doses of 2 g daily orally in divided doses (every 4 hours) with sodium bicarbonate until urine nickel is normal. Also, the patient must be advised to avoid ethanol, since a disulfiram-like reaction may occur.²⁵
7. *Phototherapy:* Nickel dermatitis can be produced in contact with all nickel-containing objects including several types of jewelry, coins, and cooking utensils. Phototherapy is effective in the treatment of hypersensitivity reaction and this treatment involves exposing the skin to controlled amounts of artificial ultraviolet light. It is applied to patients not improving with topical or oral steroids. It can take months for phototherapy to have an influence on a nickel allergy reaction.²⁶

Conclusion

Testing for serum Nickel concentration is crucial for confirming systemic toxicity. Laboratory tests should include serum electrolytes, blood urea

nitrogen (BUN), liver function test and Patch test for the Nickel dermatitis. Nickel poisoning is usually either due to industrial exposure or due to environmental contamination. A few cases are related to excessive consumption of nickel-containing foods or beverages. Therefore, it is extremely important to avoid the exposure of nickel.

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