

## Review

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# Primary concept of nickel toxicity – an overview

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**Abstract:** Toxic metals, including excessive levels of essential metals tend to change biological structures and systems into either reversible or irreversible conformations, leading to the derangement of organ functions or ultimate death. Nickel, a known heavy metal is found at very low levels in the environment. Nickel is available in all soil types and meteorites and also erupts from volcanic emissions. In the environment, nickel is principally bound with oxygen or sulfur and forms oxides or sulfides in earth crust. The vast industrial use of nickel during its production, recycling and disposal has led to widespread environmental pollution. Nickel is discharged into the atmosphere either by nickel mining or by various industrial processes, such as power plants or incinerators, rubber and plastic industries, nickel-cadmium battery industries and electroplating industries. The extensive use of nickel in various industries or its occupational exposure is definitely a matter of serious impact on human health. Heavy metals like

nickel can produce free radicals from diatomic molecule through the double step process and generate superoxide anion. Further, these superoxide anions come together with protons and facilitate dismutation to form hydrogen peroxide, which is the most important reason behind the nickel-induced pathophysiological changes in living systems. In this review, we address the acute, subchronic and chronic nickel toxicities in both human and experimental animals. We have also discussed nickel-induced genotoxicity, carcinogenicity, immunotoxicity and toxicity in various other metabolically active tissues. This review specifically highlighted nickel-induced oxidative stress and possible cell signaling mechanisms as well.

**Keywords:** carcinogenicity; genotoxicity; heavy metals; immunotoxicity; nickel; oxidative stress.

## Introduction

Heavy metals are chemical elements that have a specific gravity that is at least five times that of water. They are innate ingredients of the earth's outer layer and are found in varying concentrations in all ecosystems. The heavy metals constitute key portions of the periodic table and include metals from groups IIA (most of the alkaline earth metals) to VIA (chalcogens like selenium, polonium, tellurium etc.) of the periodic table. Among the environmental heavy metal pollutants, nickel is considered as an industrial and occupational health risk, as many nickel compounds are accessible in the human environment [1]. Swedish chemist Axel Cronstedt in 1751 was the first person to obtain purified nickel, the 28th element in periodic table. Earlier, copper miners mistook nickel ore for copper ore and described it as *kupfernickel* or “the devil's copper”. It appears as a silvery white metal, which is found to be in multiple states of oxidation, commencing from  $-1$  to  $+4$  [2]. It has also been observed that the  $+2$  oxidation or divalent state nickel is the main widespread analogue of nickel in biological systems. Most nickel subsists as a firm form of hydroxides at  $\text{pH} > 6.7$  whereas all the nickel complexes are found to be relatively soluble at  $\text{pH} < 6.5$  [3].

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## Metal toxicity

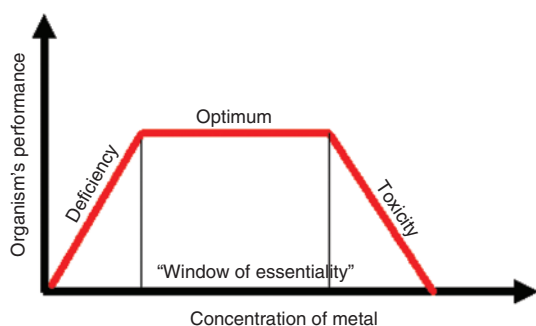
The beneficial and adverse effects of metals are well known to many branches of life sciences, but their influences in physiological chemistry have been studied in-depth only in recent decades. Metals play an integral role by conjugating at the dynamic sites of enzymes and contributing directly in the catalytic process, thus stabilizing the macromolecular structures of proteins and nucleic acids and affecting the structural and functional integration.

The possible recognition of the essential biological roles of metals in no way obviates the primary objective of ecological and toxicological investigation, that is, to eliminate the hazards created by metals. Thus, it is important to understand the actions of metals in the physiological and toxicological aspects [4]. Metals induce a two-fold, elevated, biphasic dose response curve, which allows a gross division into two general regions (Figure 1)

- (i) Potentially, each of the element has a biological meaning which can be evaluated properly only against a milieu of deficit state.
- (ii) Potentially, every element is toxic when presented to an organism in high enough concentration or threshold level.

## Nickel toxicities (human and experimental)

The hazards from heavy metals, such as nickel, are absolutely man made and the selected groups who are occupationally exposed to it are the main victims of toxicities. The toxic effects are restricted to a relatively slender group of individuals who are exposed to toxic metals in their workplace [5]. During last few decades, trace metal toxicity-related health problems outshined the mere understanding of occupational health issues of professionally exposed individuals. The broad scope of environmental changes in the air, water and soil, through industrialization, urbanization, transportation and the overuse of



**Figure 1:** The characteristic of metals as environmental pollutants.

chemicals in agriculture-related industries has threatened the physical well-being of individuals through nutrition and has caused grave concern in terms of exposure to certain trace metals [6–8].

Environmental nickel levels depend especially on natural sources, pollution from nickel-manufacturing industries and airborne particles from combustion of fossil fuels. Absorption from atmospheric nickel pollution is of least concern. Interestingly, vegetables usually contain more nickel than do other food items; high levels of nickel have been found in legumes, spinach, lettuce and nuts. Certain products, such as baking powder and cocoa powder, have also been found to contain excessive amounts of nickel, perhaps related to nickel leaching during the manufacturing process. Soft drinking-water and acid beverages may dissolve nickel from pipes and containers. Leaching or corrosion processes may contribute significantly to the oral nickel intake, occasionally up to 1 mg/day [9].

The environmental sources of lower levels of nickel include tobacco, dental or orthopedic implants, stainless steel kitchen utensils and inexpensive jewelry [10]. Tobacco smoking is another source of non-occupational exposures to nickel. It has been observed that each cigarette contains 1.1–3.1  $\mu\text{g}$  of nickel and that about 10%–20% of the nickel inhaled is present in the gaseous phase. According to some studies, 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 from one another in terms of nickel content [11, 12].

The route of nickel exposure is mainly responsible for the severity of the impact on system biology, immunology, neurology, reproduction, development and carcinogenicities, either through acute (01 day), subchronic (10–100 days) and chronic (>100 days) exposure periods. One of the most common pathways to nickel toxicity is an allergic skin reaction sensitive population. A report indicated that nickel is a potential immunomodulatory and immunotoxic agent aside from its action as an allergen in humans [13, 14]. The International Agency for Research on Cancer (IARC) [15] and the U.S. Department of Health and Human Services classified nickel compounds as human carcinogens on the basis of various studies in human and experimental animals [16].

### Acute toxicity (01 day)

#### Humans

Acute toxicity in humans resulting from absorption through the gastrointestinal tract or by inhalation through

lungs was primarily reported by Sunderman [17]. Nickel carbonyl inhalation causes two kinds of acute toxic effects: instant and delayed. The symptoms of acute toxicities include nausea, vomiting, vertigo, irritation, etc. These symptoms last for a few hours to a couple of days. Instant symptoms are followed by delayed symptoms like stiffness of the chest, constant cough, dyspnea, cyanosis, tachycardia, palpitations, sweating, visual disturbances and weakness etc. [18]. Death due to cardiac arrest has been reported in a 2 1/2 year old girl, who consumed nickel sulfate accidentally [19]. Deaths due to respiratory distress syndrome (ARDS) among spray painting workers exposed to nickel have already been documented [20]. Sunderman et al. reported shortness of breath and giddiness among electroplating workers who accidentally drank nickel chloride-polluted water (1.63 g/L) [21].

### Experimental animals

One observation in a single- dose nickel chloride injection in male rats showed elevated circulating prolactin levels after 1 day and elevated levels for 4 consecutive days [22]. Acute nickel toxicity also caused renal damages and frank hematuria [23]. Water-soluble nickel compounds are more toxic than the less soluble compounds. The less soluble nickel compounds like nickel oxide and subsulfide have been found to have LD50 greater than 3600 mg Ni/kg.b.wt. in rats, whereas soluble nickel compounds, i.e. nickel sulfate and acetate, exhibited an LD50 range of 39–141 mg Ni/kg.b.wt. in rats and mice [24].

### Subchronic toxicity (10–100 days)

#### Humans

A study on 6-week exposure to nickel fumes (0.07–1.1 mg nickel/m<sup>3</sup>) to welders caused a breathing rate increase and visual dysfunctions with tiredness [25]. In the case of women who were occupationally exposed to soluble nickel compounds (0.75 mg Ni/m<sup>3</sup> average concentration), they showed elevated urinary protein,  $\beta$ 2-microglobulin, retinal binding protein and N-acetyl- $\beta$ -D-glucosaminidase [26]. Such changes of biomarkers reflect tubular dysfunction. Interestingly, another study on workers exposed to nickel sulfate did not observe any proteinuria [27].

### Experimental animals

A study on rats showed remarkable reductions in body weight and signs of liver and kidney failures due to

exposure to oral nickel intake in a 3-week study [28]. This has also been observed that significant dose-dependent hyperglycemia, decrease in serum urea and significant increase in urine urea in male rats treated with NiCl<sub>2</sub> in different doses (0.38, 0.75 or 1.5 mg/kg/day, 28 days) [29]. A decrease in blood hemoglobin and Packed Cell Volume after nickel exposure has also been reported [30]. Nickel-treated rats also showed toxic symptoms like ataxia, hypothermia, salivation and diarrhea [13]. A study on rats treated with 5, 35 or 100 mg nickel/kg/day for 2 months showed complete mortality among high-dose group B [31]. A dose of 35 mg/kg of nickel sulfate showed high WBC and platelets counts with lower blood glucose levels in rats [32]. Several weeks' exposure to dietary nickel acetate, a degenerative change in kidney tubular systems has also been reported [33]. The Inhalation Toxicology Research Institute's 13-week inhalation study on rodents exposed to various nickel compounds revealed inflammation and fibrosis of the lungs as well as alveolar macrophage hyperplasia corresponding to the water solubility of the nickel compounds, with nickel sulfate as the most toxic effect [34].

### Chronic toxicity (>100 day)

#### Humans

Occupational exposure to nickel dust or nickel vapors resulting from welding nickel alloys is the most common chronic exposure routes in humans. Chronic inhalation and exposure to nickel dusts and aerosols contribute to all the types of respiratory disorders, including asthma, bronchitis, etc. [35]. Another study reported that nickel refinery workers were displaying higher incidences of pulmonary and nasal cancer [36, 37]. A study on women working in a nickel refinery did not suggest any type of growth or reproductive hazards [38]. However, incidental occupational nickel exposure (0.13–0.2 mg nickel/m<sup>3</sup>) in men has been found to be hazardous to growth and reproductive health [39].

The main cause of concern when handling nickel, its alloys or its salts, is its ability to produce allergic dermatitis. Such reactions can occur through soil, water or direct contact with metal that contains nickel and even metallic jewelry or coins. Due to its omnipresence and occurrence in daily-use items, nickel is the most common reason of immediate and delayed hypersensitivity in occupationally exposed and non-exposed population [40]. Chronic nickel also induced increase loss of nitrogen, urinary glucose output as well as loss of urinary phosphates, calcium and zinc ions. Chronic exposure resulting in reduced nicotinamide induces a

disruption in oxidative phosphorylation [41]. Thus far, no intermediate-duration human inhalation exposure studies have been identified; rather, some chronic exposure studies have examined the potential of nickel and nickel compounds to induce respiratory effects in workers. Most of these studies are cohort mortality studies that have been unable to find significant increases in the number of deaths from nonmalignant respiratory system diseases [42].

### Experimental animals

Prolonged exposure to nickel oxide ( $42 \text{ mg nickel/m}^3$ ) developed emphysema and other proliferative and inflammatory changes in rats [43]. Rats that consumed nickel sulfate ( $100 \text{ mg/L}$ )-contaminated water has resulted in serious loss of kidney weights with significant albuminuria [26]. Further, it has been observed that rats fed with nickel for 2 long years showed severe reduction of body weight [26]. The available chronic-duration database was considered inadequate for minimum risk level (MRL) derivation given that intermediate-duration studies found an overall significant decrease in survival of the offspring of rats exposed to  $\geq 1.3 \text{ mg Ni/kg/day}$  [44].

## Some specific aspects of nickel toxicities

### Genotoxicity

An increase in the incidence of chromosomal abnormalities but with no chromosome distortion was reported among nickel refinery workers, which were found to be similar with another report on workers exposed to manganese, nickel and iron [45, 46]. Most of the *in vivo* studies revealed that nickel and its compounds are not mutagenic, although some oral and intra peritoneal studies have reported the presence of micronuclei in the bone marrow in nickel exposed rodents [47, 48]. Nickel subsulfide exposure to both nickel-sensitized and non-sensitized individuals showed genotoxicity like the alteration of DNA configuration, resulting in cross linking and strand break in the human lymphocyte [49–52]. A very high degree of mutagenicity at the guanine phosphoribosyl transferase gene with low soluble nickel compound exposure in the Chinese hamster G12 cell line has been reported [53]. Nickel causes the mutation of the p53 gene, which is an important tumor suppressor gene and transcription factor, in kidney epithelial cells [54]. Nickel also inhibits DNA repairing by possibly binding to DNA-repair enzymes and generates free radical result in irreversible protein degradation [48, 55].

### Carcinogenicity

Nickel exposure to various workers in nickel industries demonstrated carcinogenic effects. Possibility, multiple carcinogenic factors that are also found along with nickel may be the reasons for such a phenomenon. Various studies have reported that divalent nickel is a potent carcinogen that can induce malignancy in both humans and rodents. Human exposure of nickel through industries like refinery, mining and smelting, stainless steel industries, and battery manufacturing facilities causes cancer, although it is difficult to identify the speciation of nickel compounds. The International Committee on Nickel Carcinogenesis is currently working on identifying the specific nickel carcinogen [56].

Animal studies have shown the carcinogenic potential of various nickel compounds like nickel subsulphide, nickel chloride, nickel oxide, and nickel sulfate, etc. [57]. A study on rodents showed lung tumors, including adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma with an exposure to nickel oxide ( $7 \text{ mg Ni/m}^3$ ;  $6 \text{ h/day}$ ;  $5 \text{ days/week}$ ) [58]. However, the inhalation of  $6.3 \text{ mg Ni/m}^3$  as nickel oxide for 1 month did not show any significant increase in lung cancer in rats [59], although rats exposed to nickel oxide of about  $1\text{--}2 \text{ mg Ni/m}^3$  showed alveolar/bronchiolar carcinoma or adenoma [60]. Results suggest that the genetic factors, including epigenetic factors and oxidative stress, are the probable causes of nickel-induced carcinoma. It has also been reported that some of the nickel compounds induce cell proliferation, which may induce mild DNA abrasions into extreme mutations [3].

### Immunological effects

Nickel generates multiple reactions in the human immune system in a diverse fashion [40]. Experimental works have proven that nickel is an immunomodulatory and immunotoxic agent. It has been reported that nickel contact caused allergic dermatitis and immunologic urticarial; hence, nickel can be marked as both immune sensitive as well as an allergen [14, 61–63]. However, it remains unclear how a small nickel particle generates allergic manifestation. When metal oxidizes, it develops a substance named hapten, which can elicit an immune response by binding with tissue protein like large molecules [13]. Nickel exposure to workers has been found to have a significant impact on the increase of IgG, IgA and IgM with the concomitant decrease in IgE levels [64, 65]. Further significant elevations of other serum proteins of cell-mediated immunity,

including  $\alpha$ 1-antitrypsin,  $\alpha$ 2-macroglobulin and ceruloplasmin, have also been observed [61]. Nickel can also significantly reduce the circulating antibody response of immunized rats treated with a viral antigen [61, 66, 67].

### Endocrine effects

Nickel causes severe adverse effects on the hypothalamic-pituitary-gonadal axis, which is further aggravated in protein restricted dietary condition [68]. It has been reported that the inhalation of nickel causes no impact on endocrine profiles in humans but seriously impairs the functions of most of the vital endocrine glands of rats or mice [60, 69, 70]. Rats exposed to about 0.73–2 mg Ni/m<sup>3</sup> as nickel oxide demonstrated adrenal medullary hyperplasia with benign pheochromocytoma [24, 69, 70]. Nickel chloride given orally at doses of  $\geq 20$  mg Ni/kg/day for up to 30 weeks showed an increase of pituitary glands only in male rats [71–73]. Female rats treated with nickel chloride (31 mg Ni/kg/day, orally) showed a decrease of prolactin level [68, 74]. Histopathological observations in rats (187.5 mg Ni/kg/day) and dogs (62.5 mg Ni/kg/day) did not show any adverse effects on most of the endocrine glands [44]. An increase of blood glucose level in rats has been found after a 21-day treatment of nickel sulfate (2.0 mg/100 g b.wt.; i.p.) [75].

### Neurogenic effects

Neurologic effects, including giddiness, weariness and headache, have been observed in shift employees who consumed nickel-contaminated water [21]. One study on humans found that a person who ingested a single dose of nickel (NiSO<sub>4</sub>; 0.05 mg Ni/Kg, b.wt.) developed homonymous hemianopsia (intraocular effect) for 2 h. [76]. A microscopic examination on rats and mice showed no remarkable changes in whole brain pathophysiology after exposure to several nickel compounds though some atrophy of the olfactory epithelium [77]. Force feeding with nickel chloride for 3 months in rats resulted in severe neurological disorders, including sluggishness, abnormal breathing, impaired body temperature regulations and ataxia [32, 78].

### Cardiovascular effects

No increases in the number of deaths from cardiovascular diseases have been reported in workers exposed to

nickel [79]. Nickel chloride treatment (8.6 mg Ni/kg/day for 91 days) in rats showed a reduction in organ weights, including the heart [32]. Interestingly, increased heart weight in rats exposed to 75 mg Ni/kg/day as nickel sulfate for 2 years has been reported, although no histopathological changes on cardiac tissues have been observed [44, 80]. Inhalation of Ni in a low dosage (1.2 mg/m<sup>3</sup>) caused delayed bradycardia, hypothermia and arrhythmogenesis [81]. In another study, a long-term average ambient air level of Ni (1.9 ng/m<sup>3</sup>) in the United States resulted in a significant progression of cardiovascular mortality in humans [82]. A study on nickel exposure (100 mg/L NiSO<sub>4</sub>) showed significant increased lipoperoxide and total lipid concentrations in cardiac tissue. The mechanism through which nickel acts to increase cardiovascular risk factors remains unknown, although impaired antioxidants metabolism and oxidative stress may be considered as possibilities [83]. Another study showed no cardiovascular effects in rats or mice exposed to inhalation of 0.44, 1.83 or 7.9 mg Ni/m<sup>3</sup> as nickel sulfate, nickel subsulfide or nickel oxide, respectively, 6 h/day, 5 days/week for 13 weeks [69, 70]. Hence, it can be postulated that a low dose of nickel through inhalation does not show any significant cardiovascular abnormalities; however, a moderate to higher dose may induce pathophysiological changes relevant to atherogenic events, including increased oxidative stress, inflammatory response, and coagulation activity [84].

### Gastrointestinal effects

Workers who consumed water during one work shift from a water cascade contaminated with nickel showed symptoms related to gastrointestinal (GI) disorders [21]. The symptoms included nausea, abdominal cramps, diarrhea and vomiting. In the case of rats treated with nickel chloride (25 mg Ni/kg/day; 3 months), the animals showed severe gastritis, including diarrhea [30]. However, such GI disorders were not found in rats treated with dietary nickel sulfate (28.8 mg Ni/kg/day; 3 weeks) [80] or nickel sulfate (187.5 mg Ni/kg/day for 2 years) as well [44, 85, 86].

### Musculoskeletal effects

Similarly, workers accidentally consumed nickel in drinking water reported muscle pain [21]. However, any such skeletal muscle histological abnormality was not found in experimental nickel exposed rats (187.5 mg Ni/kg/day) [44].

### Dermal effects

Nickel exposure to skin causes contact dermatitis in the general population. Several investigations on single or multiple oral doses of nickel sulfate showed the increase of severity of dermatitis in nickel-sensitive individuals [14, 85–93]. The study further revealed body erythema, hand eczema and a flare-up at the patch test site after coming into contact with nickel sulfate. An oral challenge dose of nickel sulfate (0.014 mg/kg) showed signs and symptoms of dermatitis on subjects who had gone for patch testing 1 month before the test [94].

### Metabolic effects

An increase in serum glucose concentrations has been found in male rats exposed to nickel oxide (0.385 and 0.784 mg Ni/m<sup>3</sup>; 28 days) [29]. Interestingly, a decrease in serum glucose concentration has been observed in the case of female rats exposed to nickel oxide (0.8 and 1.6 mg Ni/m<sup>3</sup>; 28 days) [29]. Results clearly suggested a gender sensitive metabolism in nickel-exposed rats. It has been further revealed that a single-dose injection of nickel chloride (4.5 mg Ni/Kg b.wt.) significantly increased serum glucose concentration in rabbits along with histopathological changes in pancreatic cells [29]. Drinking nickel chloride for 28 days resulted in an increase of serum glucose concentrations in rats [94, 95]. Another study on rats showed a decrease of blood glucose levels after being treated with nickel (8.6 mg Ni/kg/day for 91 days) by force feeding [32]. However, it may be noted that in both studies, a significant reduction in body weight (20% and higher) has also been observed at the same dose effect levels. Hence, an ambiguity regarding altered metabolism due to the primary or secondary effects of nickel remains [24, 96].

### Ni(II) Induces oxidative stress

Divalent nickel enhances lipid peroxidation at all DNA bases by either *in vitro* or *in vivo* systems [52, 97, 98]. Nickel-induced oxidative stress is rather weak; however, depleting glutathione and oxidatively activating various transcription factors cannot be ignored as possible indications of oxidative stress [98–101]. Even though divalent nickel itself is not a good free radical generator from oxygen or hydrogen peroxide or lipid hydroperoxides,

the entire reactionary mechanisms with all those oxygen derivatives can be controlled by the process of chelation with some ligands like histidine or cysteine [102–104]. It has been observed that Ni(II) incubated with cysteine in the presence of an oxygen environment generates hydroxyl radicals, which then react with cysteine and produce a carbon-centered alkyl radical and, subsequently, free radicals from lipid hydroxyperoxides in presence of oligopeptides [105, 106].

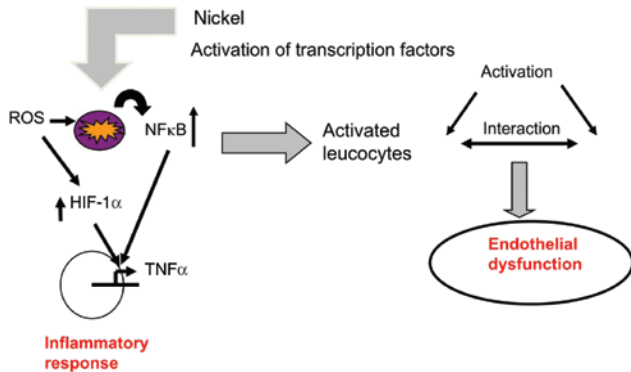
Hence it may be noted that Ni(II) toxicity lies on free radical generation from Ni(II) – thiol complexes or singlet oxygen or lipid hydroxyperoxides in a complex manner. It is possible that the nickel-induced accumulation of iron may be directly responsible for the formation of and the reactive oxygen species (ROS) subsequent enhancement of lipid peroxidation via redox pathways [107]. Nickel induces oxidative stress with generation of ROS may stimulate cell signaling pathways by developing an intracellular low-oxygen microenvironment. This, in turn, activates the hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) transcription factor and regulates all the hypoxia gene expressions. The pathway may turn into either adaptive response against nickel induced cellular hypoxia or apoptosis. Further, it was also observed that heavy metals like nickel(II) through ROS may mimic cellular hypoxia but may not always activate HIF-1 dependent genes [96]. The possible reason behind the nickel-induced activation of HIF-1 $\alpha$  transcription factor is that Ni(II) replaces Fe(II) in the oxygen carrier and produces a hybrid form of non-functional hemoglobin. This phenomenon develops into permanent intracellular hypoxia, which then activates HIF-1 $\alpha$  [108].

### Human studies

The oxidative effects of nickel on human lymphocytes *in vitro* manifested increased levels of intracellular ROS, lipid peroxidation and hydroxyl radicals after acute exposure to inorganic nickel, which supported the concept of nickel chloride induced oxidative stress [106]. In the human bronchial epithelial cell line BEAS-2B, however, nickel was only mildly active in inducing an oxidative stress response compared with other metal species measured as ROS [109]. Arranging various metal species in order of increasing toxicity yields the following: Ni(II) < Cr (VI) < Cd (II) [106, 110]. Several extensive studies on cell lines and blood lymphocytes clearly indicate nickel-induced oxidative stress in humans [111, 112]. Nickel carbonate hydroxide-induced genotoxicities and lymphocytic destructions are mediated through oxidative stress involving H<sub>2</sub>O<sub>2</sub>, singlet oxygen or

the hydroxyl radical [112]. The pretreatment with endogenous antioxidant enzymes like catalase (CAT) and superoxide dismutase (SOD) on human lymphocytes have been proven effective to reduce such nickel-induced oxidative stress [109, 113].

After controlling for confounders, plasma lipid peroxidation levels significantly increased and erythrocyte antioxidants significantly decreased in a group of nickel-plating workers [114].



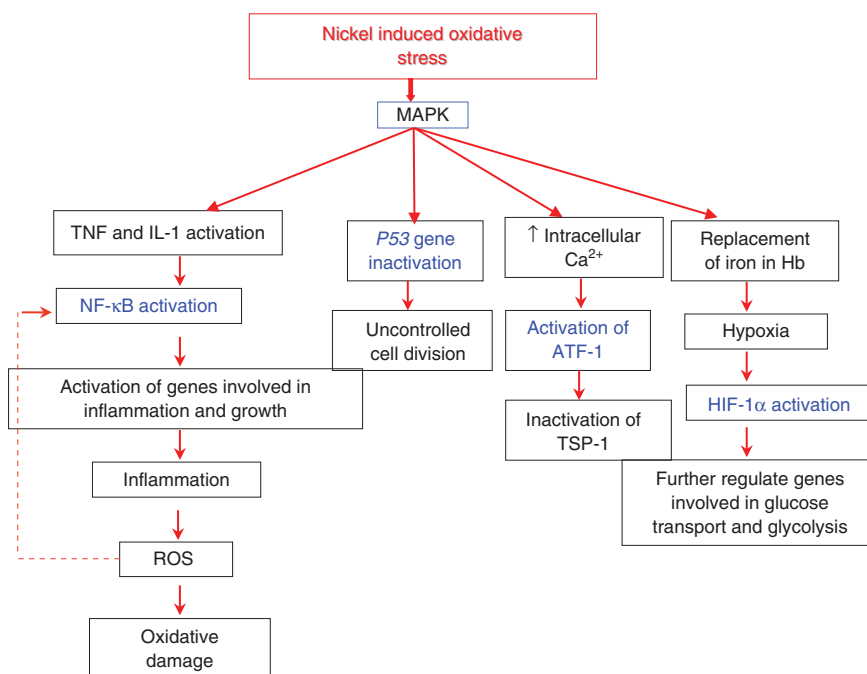
**Figure 2:** The nickel-induced inflammatory pathways. ROS, reactive oxygen species; NF-κB, nuclear factor κB; HIF-1α, hypoxia inducible factor 1α; TNFα, tumor necrosis factor-α.

### Experimental animal studies

The intraperitoneal administration of nickel chloride results in increased hepatic, renal and pulmonary lipid peroxidation, as indicated by malondialdehyde (MDA) in fresh tissue homogenates [115–117]. Using a mouse model, a previous study reported that the intraperitoneal administration of nickel chloride enhances hepatic lipid peroxidation and depletes glutathione [118]. In a mouse study, multiple intraperitoneal doses of the compound elicited a moderate increase in lipid peroxidation in whole testis homogenates and higher dose-related increases in both mitochondrial and microsomal fractions [119]. The extent of the nickel-induced lipid peroxidation showed an inverse relationship with some of the endogenous cellular antioxidant defense systems, except SOD, CAT and glutathione-S-transferase. Moreover, the exposure of rat lymphocytes to nickel subsulfide increases the formation of ROS in a concentration-dependent manner [113].

### Oxidative stress and cell signaling by nickel

Inter and intra cellular communication with response to extracellular stimuli through biological mechanisms is



**Figure 3:** The nickel-induced oxidative stress. MAPK, mitogen-activated protein kinase; TNFα, tumor necrosis factor α; IL-1, interleukin 1; NF-κB, nuclear factor κB; HIF-1α, hypoxia inducible factor 1α; ARF-1, Cyclic AMP-dependent transcription factor; TSP-1, Thrombospondin 1; ROS, reactive oxygen species.

called “cell signaling” or “signal transduction”. These cell signaling pathways follow transcription mechanisms that are responsible for specific gene expressions via proteins named as transcription factors. These transcription factors bind with specific DNA sequences and further activate RNA polymerase II. The cell signal transduction pathways modulate various physiological functions, including gene expression, muscle contraction, nerve impulse propagation or inflammation. Interestingly ROS, which are found to damage cells and are harmful for physiological functions are found to be intracellular signaling regulators [120]. A study revealed that ROS influence several gene expressions through signal transduction pathways [121]. Given that ROS are oxidants and behave as secondary messengers, they control redox as per their concentration and are capable of inducing either cell proliferation or cell death [33, 122, 123]. Figure 2 shows the nickel-induced inflammatory pathways that are extended to even endothelial function regulations.

This cell signaling mechanism also includes cytosolic calcium concentration, which also regulates both inflammatory and endothelial functions, protein phosphorylation and the activation of nuclear factor  $\kappa$ B (NF- $\kappa$ B) and the AP-1 proteins [124]. Nickel induces mitogen-activated protein kinase (MAPK) upregulations, which in turn, activate TNF and the IL-1 pathways to further activate NF- $\kappa$ B. ROS and metal ions primarily inhibit phosphoserine/threonine-, phosphotyrosine- and phospholipid-phosphatases by interacting with sulphhydryl groups on their cystein residues, thus further generating disulphide bonds after oxidation [125].

These structural changes alter protein conformation, which leads to the upregulation of several signaling cascades, most important of which are the growth factor kinase-, src/Abl kinase-, MAPK- and PI3- kinase-dependent signaling pathways. Figure 3 presents the overall oxidative stress pathways, which make multiple cascades to activate redox-regulated transcription factors (AP-1, NF- $\kappa$ B, p53, HIF-1, NFAT).

## Conclusions

Based on the literature, including the research carried out in the authors’ laboratory, we can say that nickel is a potentially toxic heavy metal that affects multiple organs of living systems. Moreover, the toxicities of nickel manifested based on the manner of exposure, dose and duration. Further, nickel-mediated toxicity in organisms may occur through oxidative stress pathways.

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