Review

Kusal K. Das*, R. Chandramouli Reddy, Ishwar B. Bagoji, Swastika Das, Shrilaxmi Bagali, Lata Mullur, Jyoti P. Khodnapur and M.S. Biradar

Primary concept of nickel toxicity – an overview

https://doi.org/10.1515/jbcpp-2017-0171
Received October 17, 2017; accepted June 29, 2018; previously published online September 4, 2018

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.

***Corresponding author: Kusal K. Das,** PhD, Department of Physiology, Laboratory of Vascular Physiology and Medicine, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur-586103, Karnataka, India, Phone: +91 8352 262770 (Ext. 2262), E-mail: kusaldas@yahoo.com, research@bldeuniversity.ac.in
R. Chandramouli Reddy: Department of Biochemistry, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, Karnataka, India
Ishwar B. Bagoji: Department of Anatomy, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, Karnataka, India
Swastika Das: Department of Chemistry, BLDEA's Dr. P.G. Halakatti College of Engineering and Technology, Vijayapur, Karnataka, India
Shrilaxmi Bagali, Lata Mullur and Jyoti P. Khodnapur: Department of Physiology, Laboratory of Vascular Physiology and Medicine, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, Karnataka, India
M.S. Biradar: Department of Medicine, Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapur, Karnataka, India

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 1951 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 pH >6.7 whereas all the nickel complexes are found to be relatively soluble at pH <6.5 [3].

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 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].

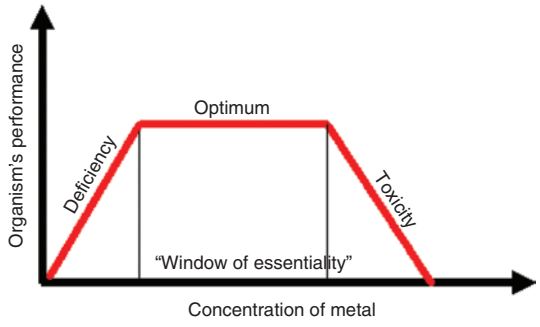

Figure 1: The characteristic of metals as environmental pollutants.

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 µg 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 ½ 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^3) 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/m3 average concentration), they showed elevated urinary protein, β2-microglobulin, retinal binding protein and N-acetyl-β-D-glucosaminidase [26]. Such changes of biomarkers reflect tubular dysfunction. Interestingly, another study on workers exposed to nickel sulfate did not observe any proteinurea [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 $NiCl_2$ 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^3) 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 mg nickel/m^3) developed emphysema and other proliferative and inflammatory changes in rats [43]. Rats that consumed nickel sulfate (100 mg/L)-contaminated water has resulted in serious loss of kidney weights with significant albuminurea [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 ≥1.3 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 phosphorybosyl 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 mg Ni/m^3; 6 h/day; 5 days/week) [58]. However, the inhalation of 6.3 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 1–2 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 α1-antitrypsin, α2-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^3 as nickel oxide demonstrated adrenal medullary hyperplasia with benign pheochromocytoma [24, 69, 70]. Nickel chloride given orally at doses of ≥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 ($NiSO_4$; 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 Hs 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^3) caused delayed bradycardia, hypothermia and arrhythmogenesis [81]. In another study, a long-term average ambient air level of Ni (1.9 ng/m^3) in the United States resulted in a significant progression of cardiovascular mortality in humans [82]. A study on nickel exposure (100 mg/L $NiSO_4$) 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^3 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/m3; 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^3; 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 histopathogical 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 remained 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-1α (HIF-1α) 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-1α transcription factor is that Ni(II) replaces Fe(II) in the oxygen carrier and produces a hybrid form of nonfunctional hemoglobin. This phenomenon develops into permanent intracellular hypoxia, which then activates HIF-1α [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_2O_2, 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].

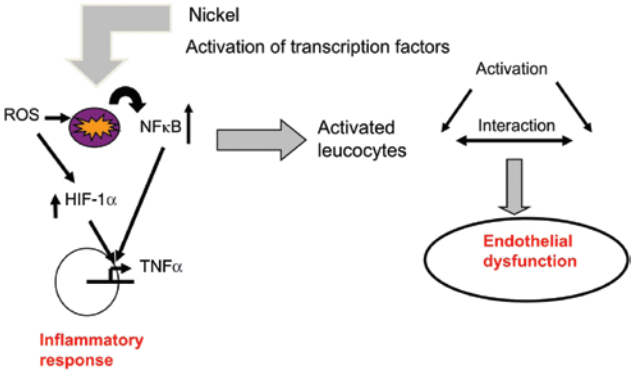

Figure 2: The nickel-induced inflammatory pathways.
ROS, reactive oxygen species; NF-κB, nuclear factor κB; HIF-1α, hypoxia inducible factor 1α; TNFα, tumor necrosis factor-α.

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

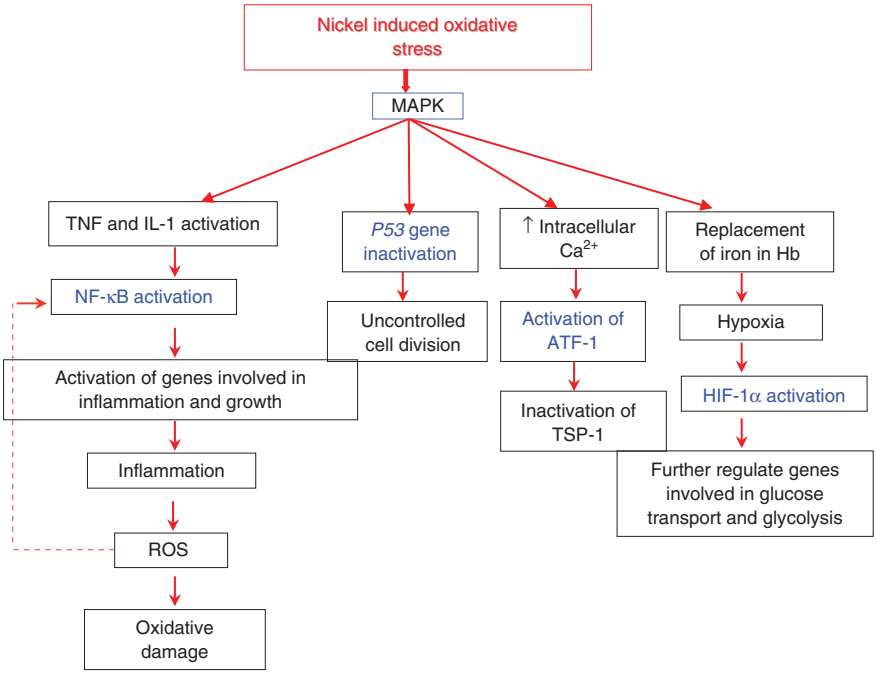

Figure 3: The nickel-induced oxidative stress.
MAPK, mitogen-activated protein kinase; TNFα, tumor necrosis factor α; IL-1, interleukin 1; NF-κB, nuclear factor κB; HIF-1α, hypoxia inducible factor 1α; ARF-1, Cyclic AMP-dependent transcription factor; TSP-1, Thrombospondin 1; ROS, reactive oxygen species.

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 κB (NF-κB) 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-κB. ROS and metal ions primarily inhibit phosphor-serine/threonine-, phosphotyrosine- and phospholipid-phosphatases by interacting with sulphydryl 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-κB, 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.

Acknowledgments: The first author greatly acknowledges the Life Sciences Research Board, DRDO, Ministry of Defence, Government of India, New Delhi, for providing a research grant to him [No.CC R&D(TM)/81/48222/LSRB-285/EPB/2014 Dated 18/11/2014]. The authors also thank the Vision Group of Science and Technology and the Government of Karnataka (VGST-KFIST/1230/2015-16 Dated 22/6/2016) for the financial assistance provided under the K-FIST, Level 2 program.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved its submission.

Research funding: Life Sciences Research Board, DRDO, Ministry of Defence, Government of India, New Delhi [No.CC R&D(TM)/81/48222/LSRB-285/EPB/2014 Dated 18/11/2014], VGST-KFIST/1230/2015-16 Dated 22/6/2016.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Venugopal B, Luckey TD. Metal toxicity in mammals, vol. 2. New York, NY: Plenum Press, 1978:289–97.
2. Barceloux DG. Nickel. J Toxicol Clin Toxicol 1999;37:239–58.
3. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr Med Chem 2005;12:1161–208.
4. Bertrand G. On the role of trace substances in agriculture. Eighth Int Congr Appl Chem 1912;28:30–40.
5. Browning E. Chromium. In: Toxicity of industrial metals, 2nd ed. London: Butterworths and Co, 1969.
6. Sabbioni E, Goetz L, Springer A, Pietra R. Trace metals from coal-fired power plants: derivation of an average data base for assessment studies of the situation in the European communities. Aci Total Environ 1983;29:213.
7. Sabbioni E, Edel J, Goetz L. Trace metal speciation in environmental toxicology research. Nutr Res Suppl 1985;1:32–43.
8. Sabbioni E, Hamdard P. Trace metals and nutrition. Nutr Res Suppl 1985;28:33–48.
9. Grandjean P. Human exposure to nickel. IARC Sci Publ 1984;53:469–85.
10. Colloidal minerals. Nickel. 1992. Available at: http://www.eagle-min.com/faq/faq 101.htm. Accessed: 21 Aug 2017.
11. Cempel M, Nikel G. Nickel: a review of its sources and environmental toxicology. Polish J Environ Stud 2006;15:375–82.
12. Environmental health criteria 108. Nickel. Geneva: WHO, 1991.
13. Das KK, Buchner V. Effect of nickel exposure on peripheral tissues: role of oxidative stress in toxicity and possible protection by ascorbic acid. Rev Environ Health 2007;22: 133–49.

14. Das KK, Das SN, Dhundasi SA. Nickel: molecular diversity, application, essentiality and toxicity in human health. In: Blanc G, Moreau D, editors. Biometals: molecular structures, binding properties and applications. New York, NY: Nova Science Publishers, 2010:33–58.
15. IARC (International Agency for Research on Cancer). IARC Monograph on the evaluation of carcinogenic risks to humans, vol. 49. Lyans, France: IARC, 1990:318–411.
16. U.S. Department of Health and Human Services (DHHS). Seventh annual report on carcinogens: summary 1994. Research Triangle Park, NC, USA: DHHS, National Institute of Environmental Health Sciences, 1994:262–9.
17. Sunderman FW, Kincaid JF. Nickel poisoning. II. Studies on patients suffering from acute exposure to vapors of nickel carbonyl. J Am Med Assoc 1954;155:889–94.
18. Sunderman FW Jr, Coulston F, Eichhorn GL. Nickel. Washington DC: National Academy of Science, 1975:97–143.
19. Daldrup T, Haarhoff K, Szathmary SC. Toedliche nickel sulfayeintoxikation. Berichte zur Serichtlichen Medizin 1983;41:141–4.
20. Rendall RE, Phillips JI, Renton KA. Death following exposure to fine particulate nickel from a metal arc process. Ann Occup Hyg 1994;38:921–30.
21. Sunderman FW Jr, Dingle B, Hopfer SM, Swift T. Acute nickel toxicity in electroplating workers who accidentally ingested a solution of nickel sulfate and nickel chloride. Am J Ind Med 1988;14:257–66.
22. Clemons G, Garcia JF. Neuroendocrine effects of acute nickel chloride administration in rats. Toxicol Appl Pharmacol 1981;61:343–8.
23. Kasprzak K, Gabryel P, Jarezewska K. Nickel toxicology. Proc Int Conf 1980;2:59–62.
24. ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological profile for nickel. Atlanta, GA, USA: ATSDR/U.S. Public Health Service, ATSDR/TP-88/19, 2003.
25. Akesson B, Skervfing S. Exposure in welding of high nickel alloy. Int Arch Occup Environ Health 1985;56:111–7.
26. Vyskocil A, Senft V, Viau C, Cízková M, Kohout J. Biochemical renal changes in workers exposed to soluble nickel compounds. Hum Exp Toxicol 1994;13:257–61.
27. Wall LM, Calnan CD. Occupational nickel dermatitis in the electroforming industry. Contact Dermatitis 1980;6:414–20.
28. Weber CW, Reid BL. Nickel toxicity in young growing mice. J Anim Sci 1969;28:620–3.
29. Weischer CH, Kordel W, Hochrainer D. Effects of $NiCl_2$ and NiO in Wistar rats after oral uptake and inhalation exposure, respectively. Zentral Bakteriol Mikrobiol Hyg (B) 1980;171:336–51.
30. Whanger PD. Effects of dietary nickel on enzyme activities and mineral content in rats. Toxicol Appl Pharmacol 1973;25:323–31.
31. Hsie AW, Johnson NP, Couch DB. Quantitative mammalian cell mutagenesis and a preliminary study of the mutagenic potential of metallic compounds. In: Kharasch N, editor. Trace metals in health and disease. New York: Raven Press, 1979:55–69.
32. American Biogenics Corporation (ABC). Ninety day gavage study in albino rats using nickel. Final report submitted to U.S. Environmental Protection Agency, Office of Solid Waste. Study 410-2520. Submitted by Research Triangle Institute and American Biogenics Corporation, NY, 1988.
33. Das KK, Saha S. L-ascorbic acid and α tocopherol supplementation and antioxidant status in nickel- or lead-exposed rat brain tissue. J Basic Clin Physiol Pharmacol 2010;21:325–46.
34. Dunnick JK, Elwell MR, Benson JM, Hobbs CH, Hahn FF, Haly PJ, et al. Toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulphate, or nickel sulphate hexahydrate in F344/N rats and B6C3F1 mice. Fundam Appl Toxicol 1989;12:584–94.
35. United State Air Force (U.S. Air Force). Nickel. In: Harry G, editor. Installation restoration program toxicology guide, vol. 5. Wright Patterson AFB, OH: Armstrong Aerospace Medical Research Laboratory, 1990.
36. NAS. Nickel. National academy of sciences. Washington, DC: National Academy Press, 1975:4–17.
37. Enterline PE, Marsh GM. Mortality among workers in a nickel refinery and alloy plant in West Virginia. J Natl Cancer Inst 1982;68:925–33.
38. Warner JS. Nickel carbonyl. Prenatal exposure. Science 1979;203:1194–5.
39. Chashschin VP, Artunina GP, Norseth T. Congenital defects, abortion and other health effects in nickel refinery workers. Sci Total Environ 1994;148:287–91.
40. Hostynek JJ. Sensitization to nickel: etiology, epidemiology, immune reactions, prevention, and therapy. Rev Environ Health 2006;21:253–80.
41. Nielsen FH. Possible future implications of nickel, arsenic, silicon, vanadium and other ultra trace elements in human nutrition. In: Prasad AS, editor. Clinical and biochemical nutritional aspects of trace elements. New York, NY, USA: Alan R. Liss Inc, 1982:379–404.
42. Arena VC, Sussman NB, Redmond CK. Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort. J Occup Environ Med 1998;40:907–91.
43. Wehner AP. Health and environmental effects of aerosols: biological effects and fate of inhaled man-made and natural aerosols in animal models. J Aerosol Sci 1986;17:305–15.
44. Ambrose AM, Larson PS, Borzelleca JF, Hennigar Jr GR. Long term toxicologic assessment of nickel in rats and dogs. J Food Sci Technol 1976;13:181–7.
45. Waksvik M, Boysen M. Cytogenetic analysis of lymphocytes from workers in a nickel refinery. Mutat Res 1982;103:185–90.
46. Elias Z, Mur JM, Pierre F, Gilgenkrantz S, Schneider O, Baruthio F, et al. Chromosome aberrations in peripheral blood lymphocytes of welders and characterization of their exposure by biological samples analysis. J Occup Med 1989;31:477–83.
47. Dhir H, Agarwal K, Sharma A, Talukder G. Modifying role of Phyllanthus emblica and ascorbic acid against nickel clastogenicity in mice. Cancer Lett 1991;59:9–18.
48. Das KK, Dasgupta S. Alteration of testicular biochemistry during protein restriction in nickel treated rats. Biol Trace Elem Res 1997;60:243–9.
49. Arrouijal FZ, Marzin D, Hildebrand HF, Pestel J, Haguenoer JM. Differences in genotoxic activity of alpha-Ni3S2 on human-lymphocytes from nickel-hypersensitized and nickel-unsensitized donors. Mutagenesis 1992;7:183–7.
50. Robison SH, Costa M. The induction of DNA strand breakage by nickel compounds in cultured Chinese hamster ovary cells. Cancer Lett 1982;15:35–40.
51. Patierno SR, Costa M. Effects of nickel (II) on nuclear protein binding to DNA in intact mammalian cells. Cancer Biochem Biophys 1987;9:113–26.
52. Das KK, Dasgupta S. Effect of nickel on testicular nucleic acid concentrations of rats on protein restriction. Biol Trace Elem Res 2000;73:175.

53. Klein CB, Kargacin B, Su L, Cosentino S, Snow ET, Costa M. Metal mutagenesis in transgenic Chinese hamster cell lines. Environ Health Perspect 1994;102(Suppl 3):63–7.
54. Maehle L, Metcalf RA, Ryberg D, Bennett WP, Harris CC, Haugen A. Altered p53 gene structure and expression in human epithelial cells after exposure to nickel. Cancer Res 1992;52:218–21.
55. Lynn S, Yew FH, Chen KS, Jan KY. Reactive oxygen species are involved in nickel inhibition of DNA repair. Environm Mol Mutagen 1997;29:208–16.
56. International Committee on Nickel Carcinogenesis in Man (ICNC). Report of the International Committee on Nickel Carcinogenesis in Man. Scand J Work Environ Health 1990;16:1–82.
57. Diwan BA, Kasprzak KS, Rice JM. Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. Carcinogenesis 1992;13:1351–7.
58. Ottolenghi AD, Haseman JK, Payne WW. Inhalation studies of nickel sulfide in pulmonary carcinogenesis of rats. J Nation Cancer Inst 1974;54:1165–72.
59. Horie A, Tanaka I, Haratake J, Kodama Y, Tsuchiya K. Electron microscopy of pulmonary lesions including carcinoma, induced by inhalation exposure of rats to nickel oxide aerosol. In: Brown SS, Sunderman FW Jr, editors. Progress in nickel toxicology. Proceedings of the 3rd International Congress on Nickel Metabolism and Toxicology. Oxford, UK: Blackwell, 1985:41–4.
60. National Toxicology Programme. NTP technical report on the toxicology and carcinogenesis studies of nickel sulphate hexahydrate (CAS No. 10101-97-0) in F344/N Rats and B6C3F1 Mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP-TRS No. 454, 1996.
61. Das KK, Das SN, Dhundasi SA. Nickel, its adverse health effects & oxidative stress. Indian J Med Res 2008;128:412–25.
62. Kimber I, Dearman RJ, Scholes EW, Basketter DA. The local lymph node assay: developments and applications. Toxicology 1994;93:13–31.
63. Dearman RJ, Kimber I. Divergent immune responses to respiratory and contact chemical allergens: antibody elicited by phthalic anhydride and oxazolone. Clin Exp Allergy 1992;22:241–50.
64. Bencko V, Wagner V, Wagnerová M, Reichrtová E. Immunobiochemical findings in groups of individuals occupationally and nonoccupationally exposed to emissions containing nickel and cobalt. J Hyg Epidemiol Microbiol Immunol 1983;27:387–94.
65. Bencko V, Wagner V, Wagnerová M, Zavázal V. Human exposure to nickel and cobalt: biological monitoring and immunobiological response. Environ Res 1986;40:399–410.
66. Graham JA, Miller FJ, Daniels MJ, Payne EA, Gardner DE. Influence of cadmium, nickel and chromium on primary immunity in mice. Environ Res 1978;16:77–87.
67. Figoni R, Treagan L. Inhibition effect of nickel and chromium upon antibody response of rats to immunization with T-l phage. Res Commun Chem Pathol Pharmacol 1975;12:335–8.
68. Das KK, Dasgupta S. Effect of nickel sulfate on testicular steroidogenesis in rats during protein restriction. Environ Health Perspect 2002;110:923–6.
69. National Toxicology Programme. NTP technical report on the toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344/N Rats and B6C3F1 Mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TRS No. 451, 1996.
70. National Toxicology Programme. NTP technical report on the toxicology and carcinogenesis studies of nickel subsulphide (CAS No. 12035-72-2) in F344/N Rats and B6C3F1 Mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP-TRS No. 453, 1996.
71. RTI. Two-generation reproduction and fertility study of nickel chloride administered to CD rats in the drinking water: 90-Day exposure of CD rats to nickel chloride administered in the drinking water. Final study report (I of III). Report to Office of Solid Waste Management, U.S. Environmental Protection Agency by Research Triangle Institute. Research Triangle Park, NC, 1986.
72. RTI. Two-generation reproduction and fertility study of nickel chloride administered to CD rats in the drinking water: fertility and reproductive performance of the Po generation. Final study report (II of III). Report to Office of Solid Waste Management, U.S. Environmental Protection Agency by Research Triangle Institute. Research Triangle Park, NC, 1988.
73. RTI. Two-generation reproduction and fertility study of nickel chloride administered to CD rats in the drinking water: fertility and reproductive performance of the F1 generation. Final study report (III of III). Report to Office of Solid Waste Management, U.S. Environmental Protection Agency by Research Triangle Institute. Research Triangle Park, NC, 1988.
74. Smith MK, George EL, Stober JA. Perinatal toxicity associated with nickel chloride exposure. Environ Res 1993;61:200–11.
75. Tikare SN, Gupta AD, Dhundasi SA, Das KK. Effect of antioxidants L-ascorbic acid and alpha-tocopherol supplementation in nickel exposed hyperglycemic rats. J Basic Clin Physiol Pharmacol 2008;19:89–101.
76. Sunderman Jr FW. Mechanisms of nickel carcinogenesis. Stand J Work Environ Health 1989;15:1–12.
77. Evans JE, Miller ML, Andringa A, Hastings L. Behavioral, histological, and neurochemical effects of nickel (II) on the rat olfactory system. Toxicol Appl Pharmacol 1995;130: 209–20.
78. Gupta AD, Das SN, Dhundasi SA, Das KK. Effect of garlic (Allium sativum) on heavy metal (nickel II and chromium VI) induced alteration of serum lipid profile in male albino rats. Int J Environ Res Public Health 2008;5:147–51.
79. Cornell RG, Landis JR. Mortality patterns among nickel/chromium alloy foundry workers. In: Sunderman Jr FW, Aitio A, Berlin A, editors. Nickel in the human environment. IARC scientific publication no. 53. Lyon, France: International Agency for Research on Cancer, 1984:87–93.
80. Obone E, Chakrabarty SK, Bai C, Malick MA, Lamantagne L, Subramanian KS. Toxicity and biaoaccumulation of nickel sulphate in Sprague-Dawley rats following 13 weeks of subchronic exposure. J Toxicol Environ Health 1999;57:379–401.
81. Campen MJ, Nolan JP, Schladweiler MC, Kodavanti UP, Evansky PA, Costa DL, et al. Cardiovascular and thermoregulatory effects of inhaled PM-associated transition metals: a potential interaction between nickel and vanadium sulfate. Toxicol Sci 2001;64:243–52.
82. Lippmann M, Ito K, Hwang J-S, Maciejczyk P, Chen LC. Cardiovascular effects of nickel in ambient air. Environ Health Perspect 2007;115:A294.

83. Novelli EL, Diniz YS, Machado T, Proenca V, Tibirica T, Faine L, et al. Toxic mechanism of nickel exposure on cardiac tissue. Toxic Subs Mech 2015;19:177–87.
84. Alissa EM, Gordon FA. Heavy metal poisoning and cardiovascular disease. J Toxicol 2011;2011, Article ID 870125, https://doi.org/10.1155/2011/870125.
85. Burrows GE, Tyrl RJ, Edwards WC. Toxic plants of Oklahoma – thornapples and nightshades. J Okla Vet Med Assoc 1981;23:106–9.
86. Das KK, Dasgupta S. Studies on the role of nickel in the metabolism of ascorbic acid and cholesterol in experimental animal. Ind J Physiol Allied Sci 1998;52:58–62.
87. Christensen OB, Möller H. External and internal exposure to the antigen in the hand eczema of Nickel allergy. Contact Dermatitis 1975;1:136.
88. Cronin MJ, Faure N, Martial JA, Weiner RL. Absence of high affinity dopamine receptor in GH3 cells: a prolactin-secreting clone resistant to the inhibitory action of dopamine. Endocrinology 1980;106:718–23.
89. Gawkrodger DJ, Cook SW, Fell GS, Hunter JA. Nickel dermatitis: the reaction to oral nickel challenge. Br J Dermatol 1986;115: 33–8.
90. Hindsén M, Bruze M, Christensen OB. Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions. J Am Acad Dermatol 2001;44:616–23.
91. Jensen CS, Menne T, Lisby S, Kristiansen J, Veien NK. Experimental systemic contact dermatitis from nickel: a dose-response study. Contact Dermatitis 2003;49:124–32.
92. Kaaber K, Menne T, Tjell JC, Veien N, Antabuse R. Treatment of nickel dermatitis. Chelation – a new principle in the treatment of nickel dermatitis. Contact Dermatitis 1979;5: 221–8.
93. Veien NK, Hattel T, Justesen O, Nørholm A. Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt. Acta Derm Venereol 1987;67:321–5.
94. Kadota I, Kurita M. Hyperglycemia and islet cell damage caused by nickel chloride. Metabolism 1955;4:337–42.
95. Das KK, Das SN. Studies on the role of ascorbic acid on nickel induced hepatic nucleic acid concentrations in rats. J Basic Clin Physiol Pharmacol 2004;15:185–95.
96. Salnikow K, Gao M, Voitkun V, Huang X, Costa M. Altered oxidative stress responses in nickel-resistant mammalian cells. Cancer Res 1994;54:6407–12.
97. Coogan TP, Latta DM, Snow ET, Costa M. Toxicity and carcinogenicity of nickel compounds. In: McClellan RO, editor. Critical reviews in toxicology. Vol. 19. Boca Raton, FL: CRC Press, 1989:341–84.
98. Stinson TJ, Jaw S, Jeffery EH, Plewa MJ. The relationship between nickel chloride-induced peroxidation and DNA strand breakage in rat liver. Toxicol Appl Pharmacol 1992;117:98–103.
99. Li W, Zhao Y, Chou IN. Alterations in cytoskeletal protein sulfhydryls and cellular glutathione in cultured cells exposed to cadmium and nickel ions. Toxicology 1993;77:65–79.
100. Huang X, Zhuang Z, Frenkel K, Klein CB, Costa M. The role of nickel and nickel-mediated reactive oxygen species in the mechanism of nickel carcinogenesis. Environ Health Perspect 1994;102:281–4.
101. Huang C, Li J, Costa M, Zhang Z, Leonard SS, Castranova V, et al. Hydrogen peroxide mediates activation of nuclear factor of activated T cells (NFAT) by nickel subsulfide. Cancer Res 2001;61:8051–57.
102. Shi XG, Sun XL, Gannet PM, Dalal NS. Deferoxamine inhibition of Cr (V)-mediated radical generation and deoxyguanine hydroxylation: ESR and HPLC evidence. Arch Biochem Biophys 1992;293:281–6.
103. Shi X, Dalal NS, Kasprzak KS. Generation of free radicals from hydrogen peroxide and lipid hydroperoxides in the presence of Cr (III). Biochimica et Biophysica Acta 1993;302:294–9.
104. Das KK, Gupta AD, Dhundasi SA, Patil AM, Das SN, Ambekar JG. Protective role of L-ascorbic acid on antioxidant defense system in erythrocytes of albino rats exposed to nickel sulfate. Biometals 2007;20:177–84.
105. Chen CY, Wang YF, Huang WR, Huang YT. Nickel induces oxidative stress and genotoxicity in human lymphocytes. Toxicol Appl Pharmacol 2003;189:153–9.
106. Chen CY, Wang YF, Lin YH, Yen SF. Nickel-induced oxidative stress and effect of antioxidants in human lymphocytes. Arch Toxicol 2003;77:123–30.
107. Stohs SJ, Bagchi D. Oxidative mechanisms in the toxicities of metal ions. Free Radic Biol Med 1995;18:321–36.
108. Lynn S, Shiung JN, Gurr JR, Jan KY. Arsenite stimulates poly (adp-ribosylation) by generation of nitric oxide. Free Radic Biol Med 1998;24:442–9.
109. Schmidt GA, Le Grande AN, Hoffmann G. Water isotope expressions of intrinsic and forced variability in a coupled ocean-atmosphere model. J Geophys Res 2007;112:D10103.
110. Manjuladevi M, Anitha Manonmani S. Kinetic study on adsorption of Cr(VI), Ni(II), Cd(II) and Pb(II) ions from aqueous solutions using activated carbon prepared from Cucumis melo peel. Appl Water Sci 2018;8:36.
111. M'Bemba-Meka P, Lemieux N, Chakrabarti SK. Role of oxidative stress and intracellular calcium in nickel carbonate hydroxide-induced sister-chromatid exchange, and alterations in replication index and mitotic index in cultured human peripheral blood lymphocytes. Arch Toxicol 2007;81:89–99.
112. M'Bemba-Meka P, Lemieux N, Chakrabarti SK. Role of oxidative stress, mitochondrial membrane potential, and calcium homeostasis in nickel subsulfide-induced human lymphocyte death in vitro. Sci Total Environ 2006;369:21–34.
113. Chakrabarti SK, Bai C. Role of oxidative stress in nickel chloride-induced cell injury in rat renal cortical slices. Biochem Pharmacol 1999;58:1501–10.
114. Gupta AD, Patil AM, Ambekar JG, Das SN, Dhundasi SA, Das KK. L-ascorbic acid protects the antioxidant defense system in nickel-exposed albino rat lung tissue. J Basic Clin Physiol Pharmacol 2006;17:87–100.
115. Sunderman FW Jr, Marzouk A, Hopfer SM, Zaharia O, Reid MC. Increased lipid peroxidation in tissues of nickel chloridetreated rats. Ann Clin Lab Sci 1985;15:229–36.
116. Gupta N, Shai V, Gupta R. Alkaline lipase from a novel strain Burkholderi multivorans: statistical medium optimization and production in a bioreactor. Process Biochem 2007;42:518–26.
117. Chen CY, Huang YL, Lin YH. Association between oxidative stress and cytokine production in nickel-treated rats. Arch Biochem Biophys 1998;356:127–32.
118. Andersen HR, Andersen O. Biol Effect of nickel chloride on hepatic lipid peroxidation and glutathione concentration in mice. Trace Elem Res 1989;21:255.

119. Doreswamy K, Shrilatha B, Rajeshkumar T, Muralidhara. Nickel-induced oxidative stress in testis of mice: evidence of DNA damage and genotoxic effects. J Androl 2004;25:996–1003.
120. Palmer HJ, Paulson KE. Reactive oxygen species and antioxidants in signal transduction and gene expression. Nutr Rev 1997;55:353–61.
121. Thannickal VJ, Day RM, Klinz SG, Bastien MC, Larios JM, Fanburg BL. Ras-dependent and -independent regulation of reactive oxygen species by mitogenic growth factors and TGF-beta1. Faseb J 2000;14:1741–8.
122. Lowenstein CJ, Dinerman JL, Snyder SH. Nitric oxide: a physiologic messenger. Ann Intern Med 1994;120:227–37.
123. Das KK, Saha S. Hypoxia, lead toxicities and oxidative stress: molecular interactions and antioxidant (Vitamin C) defense Curr Signal Transduc Ther 2014;9:113–22.
124. Storz P, Doppler H, Toker A. Protein kinase D mediates mitochondrion-to-nucleus signaling and detoxification from mitochondrial reactive oxygen species. Mol Cell Biol 2005;25:8520–30.
125. Poli G, Leonarduzzi G, Biasi F, Chiarpotto E. Oxidative stress and cell signaling. Curr Med Chem 2004;11:1163–82.