Published in final edited form as:
Rev Environ Health. 2011 ; 26(2): 81–92.

Exploring the Molecular Mechanisms of Nickel-Induced Genotoxicity and Carcinogenicity: A Literature Review

Keyuna S. Cameron[1], **Virginia Buchner**[2], and **Paul B. Tchounwou**[1,*]

[1]Environmental Toxicology Research Laboratory, NIH RCMI-Center for Environmental Health, Jackson State University, 1400 J.R. Lynch Street, Box 18750, Jackson, Mississippi 39217, USA

[2]The Weizmann Institute of Science, Rehovot, Israel

Abstract

Nickel, a naturally occurring element that exists in various mineral forms, is mainly found in soil and sediment, and its mobilization is influenced by the physicochemical properties of the soil. Industrial sources of nickel include metallurgical processes such as electroplating, alloy production, stainless steel, and nickel-cadmium batteries. Nickel industries, oil- and coal-burning power plants, and trash incinerators have been implicated in its release into the environment. In humans, nickel toxicity is influenced by the route of exposure, dose, and solubility of the nickel compound. Lung inhalation is the major route of exposure for nickel-induced toxicity. Nickel may also be ingested or absorbed through the skin. The primary target organs are the kidneys and lungs. Other organs such as the liver, spleen, heart and testes may also be affected to a lesser extent. Although the most common health effect is an allergic reaction, research has also demonstrated that nickel is carcinogenic to humans. The focus of the present review is on recent research concerning the molecular mechanisms of nickel-induced genotoxicity and carcinogenicity. We first present a background on the occurrence of nickel in the environment, human exposure, and human health effects.

Keywords

human exposure; target organs; toxicity; carcinogenesis; oncogenes; transcription factor

BACKGROUND

Nickel, a metallic compound, is the twenty-fourth most abundant element found in the earth's crust. The primary source of nickel is located deep in the earth's molten core, making it unobtainable for use. Other sources of nickel include volcanic eruptions, soils, ocean floors, and ocean water /1/. Nickel is used in industries to make stainless steel and other alloys. This constitutes the primary sources of nickel accounting for about 80%. Electroplating accounts for 10% usage. Approximately 5% of primary nickel is used in various foundry applications, and printing inks /2/. The distribution and the end uses of nickel are summarized in Figure 1 and Table 1 respectively. The different forms of nickel include elemental nickel (Ni), nickel oxide (NiO), nickel chloride ($NiCl_2$), nickel sulfate ($NiSO_4$), nickel carbonate ($NiCO_3$), nickel monosulfide (NiS), and nickel subsulfide (Ni_3S_2).

Correspondence: Dr. Paul B. Tchounwou, Associate Dean & Presidential Distinguished Professor, College of Science, Engineering & Technology, Jackson State University, 1400 Lynch Street, Jackson, Mississippi 39217, USA; paul.b.tchounwou@jsums.edu.

Nickel is released into the atmosphere during nickel mining and the industrial production of stainless steel and other nickel alloys, or by industries that use nickel and its compounds. Atmospheric deposition has also been associated with the industrial operations of oil-burning power plants, coal-burning power plants, and trash incinerators. In the atmosphere, nickel attaches to small particles of dusts that settle to the ground or are removed from the air by rain or snow. Nickel released from industrial wastewater into soil or sediment binds to iron or manganese particles. No evidence has been found to suggest that nickel can affect marine animals /3/. The focus of the present review is on recent research concerning the molecular mechanisms of nickel-induced genotoxicity and carcinogenicity. We first present a background on the occurrence of nickel in the environment, human exposure, and human health effects.

ENVIRONMENTAL EXPOSURE

Human exposure to nickel occurs by breathing air, drinking water, consuming food, or smoking tobacco containing nickel. The work of Coogan et al. /4/ supports the theory that dietary exposure and drinking water provide the highest intake of nickel and nickel compounds in the general population. Direct contact with nickel-containing products such as jewelry, stainless steel and coins are other sources of exposure. Nickel is also used to make artificial body parts, a process that exposes the recipients to nickel containing-alloys.

Deposition in soil and water near nickel-producing industries increases the chance of nickel contamination of drinking water. The average concentration of nickel in soil ranges from 4 to 80 ppm, but this number is significantly increased (up to 9,000 ppm) around nickel-producing industries /3/. Skin contact is the usual source of contamination from soil, except for children who are more likely to ingest soil particles. Foods such as tea, coffee, chocolate, soybeans, nuts, oatmeal, cabbage, spinach, and potatoes contain high levels of nickel, making such foods a major source of nickel exposure. The average amount of nickel unknowingly consumed in the diet is about 170 micrograms of nickel per day. Such amounts have no known effect on human or ecosystem health.

For the average person, inhalation accounts for about 0.1–1 μg nickel daily, excluding tobacco smoke. For workers in nickel industries, inhalation is the primary source of exposure. Total nickel is significantly higher in occupationally exposed individuals than in the general population /5/. Whereas the approximate amount of nickel likely to be inhaled by the general population would range from 0.1 to 0.25 mg nickel d^{-1}, in nickel refining operations such as matte handling or grinding, 0.3 to 0.8 mg nickel d^{-1} has been reported as the average amount of nickel likely to be inhaled. Inhalation amounts can range from < 0.02 to 1.0 mg nickel d^{-1}, depending upon the industry. For example, the average airborne nickel concentrations for powder metallurgy operations have been reported to exceed 1.0 mg m^3. Grandjean et al. /6/ reported that cigarette smoking increases exposure to nickel by 0.0004 mg d^{-1}.

Nickel Absorption and Deposition in the Body

Inhalation, dermal contact, and gastrointestinal ingestion are the primary routes of exposure to nickel. The deposition of nickel particles into the nasopharyngeal, pulmonary, or bronchial regions of the respiratory tract is dependent on the particle size. Particles are classified as respirable or irrespirable based on their size. Water insoluble nickel compounds enter cells by phagocytosis and are contained in cytoplasmic vacuoles, which are acidified thus accelerating the dissolution of soluble nickel from the particles /7/. Following exposure (48–72 h) of human lung (A549) cells to NiS particles, most of the nickel is contained in the nucleus, whereas cells exposed to soluble $NiCl_2$ exhibit most of the ions localized in the cytoplasm.

According to Vincent /8/, humans inhale particles with aerodynamic diameters less than 30 μm. Particles less than 10 μm are deposited in the lower regions of the lung. Removal of nickel from the respiratory tract occurs via mucociliary transport. Nickel metal is poorly absorbed by the skin, but compounds such as $NiCl_2$ and $NiSO_4$ can penetrate occluded skin, resulting in 77% absorption within one day /9/.

Nickel Toxicity

Acute toxicity in humans results from inhalation or absorption through the gastrointestinal tract[i]. The mechanisms of nickel toxicity have been recently reviewed by Das and Buchner /10/. Briefly, the primary route for the toxicity of nickel is though the depletion of glutathione levels and bonding to the sulfhydryl groups of proteins /11/. A study in humans by the US EPA /12/ revealed that nickel treatment causes irreversible lung damage, abnormal pulmonary functions, renal tubular necrosis, anemia, eosinophilia, and nasal septum ulceration. Alteration of physiological chemistry by reducing nitrogen retention, glucosurea, phospha-turea, and urinary excretion of calcium ion and zinc ion following nickel treatment has also been reported. The inhibition of ATPase activity can lead to neurological disorders, convulsions, and coma. Chronic exposure resulting in reduced nicotinamide can disrupt oxidative phosphorylation /13/.

Oxidative stress—Ni(II) induces oxidative stress in cultured human lymphocytes /14/. When compared with other metal species in one study, nickel was only mildly active in ROS induction; with the order of increasing toxicity being Ni(II) < Cr(VI) < Cd(II) /15/. By itself, Ni(II) does not cause efficient free-radical generation from oxygen, hydrogen peroxide, or lipid hydroperoxides; nevertheless, the reactivity of Ni(II) with oxygen derivatives can be modulated by chelation with certain histidine- and cysteine-containing ligands. Free radical generation from the reaction of Ni(II)-thiol complexes with molecular oxygen and/or lipid hydroperoxides could play an important role in the mechanism(s) of Ni(II) toxicity (reviewed in detail in Das & Buchner /10 /).

Hematotoxicity—A study in mice by Dieter et al /16/ demonstrated that the primary toxic effects of nickel sulfate occur in the myeloid system, expressed as a dose-related decrease in bone marrow cellularity, as well as in granulocyte-macrophage and pluri-potent stem-cell proliferative responses. In National Toxicology Program (NTP) inhalation studies in F344/N rats and B6C3F1 mice /17/, increases in hematocrit (PCV%), hemoglobin concentration, and erythrocyte counts were consistent with the production of erythropoietin in response to tissue hypoxia. Other studies have reported different results (reviewed in Das & Buchner, 2007).

Immunotoxicity—An allergic skin reaction is the most common effect in people with sensitivity to nickel (reviewed in /18/). Nickel is capable of evoking a dual response in the human immune system, both immunomodulatory and immunotoxic effects, sometimes in the same individual. Human studies on the potential immunotoxicity of nickel are limited. Inhalation exposure is a primary route for nickel-induced toxicity in the workplace. Skin allergies, lung fibrosis, and respiratory tract cancer are some of the conditions/diseases related to exposure to highly nickel-polluted environments. Research has shown a correlation between nickel-induced facial dermatitis and cell phone use /19–22/. Thyssen and Maibach /23/ tested inexpensive jewelry for various nickel concentrations. Hair clamps, earrings, and necklaces for women showed nickel concentrations of 19.3 %, 14.8%, and 12.9% respectively which leads to cutaneous skin allergies. Hair clamps and finger rings for children were tested indicating nickel levels of 79.4% and 20 % respectively /24/. Children's clothing fasteners were also identified as a source of excessive nickel concentrations leading to cutaneous skin allergies/25/.

NICKEL-INDUCED CARCINOGENICITY

The ability of nickel compounds to raise the intracellular concentration of nickel ions established the basis for its carcinogenic potential. Human and animal studies have demonstrated that exposure to nickel refinery dusts and Ni_3S_2 increases the probability of lung and nasal cancer in workers. Nickel refinery dust and Ni_3S_2 are classified as human carcinogens (Group A) by the United States Environmental Protection Agency (US EPA) and Group 1 by the International Agency for Research on Cancer /26/, as well as the US Department of Health and Human Services (DHHS) /27/. An increased incidence of cancers occurred in mice following nickel administration via inhalation or injection. The US EPA classifies nickel carbonyl as a probable human carcinogen (Group B2) based on the incidences of pulmonary carcinomas and malignant tumors in rats after exposure by inhalation and intravenous injection /28/.

Chronic inhalation to nickel has been linked to chronic bronchitis and several cancers /3/. Current evidence shows a close relation between nickel exposure and increased lung cancer risk in nickel refineries /29,30,31/. The primary areas commonly researched include investigations of nickel species-specific effects, as well as possible dose-response relations between nickel exposure and lung cancer. Assessments have been usually based on the measurement of nickel concentration in lung tissue to estimate the exposure level.

A general feature of metallic compounds is their property to enhance the mutagenicity and carcinogenicity of directly acting genotoxic agents /32/. The characterization of this property is based on their ability to inhibit the repair of damaged DNA. The induction of DNA damage has been linked to the ability of nickel to bind to DNA and nuclear proteins /32/. Nickel also interferes with nucleotide and base-excision repair at low, non cytotoxic concentrations. Both soluble and insoluble forms of nickel impair the repair of DNA adducts caused by benzo[a]pyrene /33/. Other evidence supports the theory that carcinogenic metal compounds change gene expression motifs, contributing to stimulated cell proliferation, either by activation of proto-oncogenes or interfering with tumor-suppressor genes responsible for down-regulating cell growth /34/.

The suppressive effect of nickel on natural killer (NK) cell activity and interferon production on the involvement of nickel carcinogenesis has been at the forefront of several immunologic studies /35, 36/. The ability of nickel to cause chromosomal damage both in vitro and in vivo is in agreement with its mutagenic characteristics.

The carcinogenic potential of nickel is directly proportional to the metal’s ability to enter cells and increase intracellular levels of nickel ions. A relation between respiratory carcinogenic potential and the bioavailability of nickel ion at nuclear sites within respiratory target cells has been shown /37/, helping to reconcile the human, animal, and mechanistic data for soluble nickel compounds. Water-soluble nickel compounds by themselves are not considered complete human carcinogens due to the predicted lack of bioavailability of nickel ion at target sites. By contrast, the inhalation of concentrations high enough to induce chronic lung inflammation will augment the carcinogenic risks associated with inhalation exposure to other substances /37/.

Both NiS and Ni_3S_2 are water-insoluble forms of nickel that enter cells by phagocytosis and potently increase the likelihood of tumor formation in vitro. Water-insoluble nickel compounds are understood to be more potent forms of carcinogens compared with the soluble forms /37/. A dye that fluoresces when bound to intracellular nickel ions was used to track the fate of both forms of nickel in a time-dependent study /37/. The results showed that within 10 h after $NiCl_2$ removal from the culture medium, the nickel ions disappeared from the nucleus and by 16 h were not detected in the cells, whereas following nickel removal,

insoluble Ni_3S_2 yielded nickel ions that persisted in the nucleus after 16 h and were still detected in the cytoplasm even after 24 h.

Between 1901 and 1923, the International Nickel Company (INCO) operating the nickel refinery in Clydach, Wales, UK, reported a total of 365 respiratory cancers, including 85 nasal cancers and 280 lung cancers among their workers /29/. Due to the alarming cancer incidences, orcelite, a nickel arsenide, was eliminated from the refinery process. In 2003, Clemens et al. /29/ tested 1920 and 1929 refinery dust samples obtained from INCO and found that the 1920 orcelite samples induced a dose-dependent, morphologic transformation of C3H/10T1/2 Cl 8 (10T1/2) cells, a mouse fibroblastic cell line derived from C3H mouse embryos /39/. Their findings correlated with the increased incidence of respiratory tract carcinogenicity found in the workers before the removal of orcelite from the refinery process, suggesting that orcelite played a critical role in the induction of nasal and lung cancers. The 1929 dust sample did not produce any morphologic change in the cultured cells. Subsequent to the reduction of nickel arsenide in the recycling process, the incidencesof nasal and respiratory cancers greatly decreased from 1925to 1930 /40/.

In addition to the primary routes of exposure, another source emerged in Nigeria. Nduka et al. /41/ sampled various pediatric cough suppressants for the presence of heavy metals. Of the metals tested, nickel was present in two brands (Magcid and Gaviron) of oral suspensions at concentrations of 4.13 mg/L^{-1} and 0.79 mg/L^{-1}, respectively. Based on these findings, the authors recommended that precautions should be a taken when using the suspensions due to a significant source of heavy metal exposure in children. In addition to caution, the pediatric syrups should be considered a public health problem /41/.

Clinical Studies

Epidemiologic studies confirmed a significant increase in nasal and lung carcinogenesis during exposure to nickel compounds, especially in workers in the nickel industry /30, 31, 42,43,44/. Respiratory carcinogenicity assessment of soluble nickel compounds has provided evidence of lung and nasal cancers among exposed subjects. For a Norwegian nickel refinery, Grimsrud et al. /42/ studied time- and department-specific exposure to nickel, arsenic, sulfuric acid mists, and cobalt, as well as asbestos, to determine whether lung cancer risk was related only to nickel. Length of time and duration of work were the experimental variables. The results suggested a correlation between total exposure to water-soluble nickel and lung cancer risk. To support Grimsrud's findings, other researchers reported similar results related to exposure to nickel compounds. In Harjavalta, Finland, 1155 workers were exposed to nickel for 25 years in the smelter, repair shop, and refinery /30/. Workers in the refinery, who were exposed primarily to $NiSO_4$ at levels below 0.5 mg m^3, as well as to low concentrations of other nickel compounds, showed increased risk for nasal cancer (SIR 41.1, 95% CI 4.97–148), positively associated with latency and duration of employment, and an excess risk for lung cancer (SIR 2.61, 95% CI 0.96–5.67). This study provided evidence that elevated nasal and lung cancer can result from primary exposure to $NiSO_4$ /26/. According to the National Toxicology Program, Ni_3S_2, NiO, and $NiSO_4$ hexahydrate are linked to cancer /43/.

Kiilunen et. al. /31/ performed nickel analysis in air, blood, and urine on workers in a nickel refinery industry where an increased number of nasal cancers had been reported. Acridine orange-stained smears of micronuclei from the buccal mucosa of workers were used to study genotoxic effects. Respirators used in high-exposure areas in 1966–1988 yielded a nickel concentration of 0.9–2.4 $\mu g\ m^{-3}$. Nickel concentrations in the breathing zone were 1.3 $\mu g\ m^{-3}$, and airborne nickel concentrations (stationary sampling) varied between 230 and 800 $\mu g\ m^{-3}$ with no systematic change. Follow-up tests revealed lower concentrations (170–460 $\mu g\ m^{-3}$). After shift, the urinary concentrations of nickel were 0.1–2 $\mu mol\ L^{-1}$, showing no

correlation with nickel concentrations in air. Following a 2–4 week vacation, concentrations of nickel in the urine were still elevated /31/.

Animal Studies

The National Toxicology Program /43/ conducted a two year study on male and female mice following exposure to NiO via inhalation for 16 days, 13 weeks, or 2 years. In addition, genetic toxicology tests were conducted in peripheral blood of mice exposed to NiO for 13 weeks. In the 16 days study, groups of five male and five female mice were exposed for a total of 12 exposure days to NiO, ranging from 0 to 30 mg NiO m^3, by inhalation for 6 hr per day, 5 days per week. Mice exposed to nickel >10 mg m^{-3} had a significant increase in absolute and relative lung weight compared with the control group. Pigment particles were present in the lungs of mice exposed to ≥ 2.5 mg m^{-3}. In both genders exposed to 10 and 30 mg m^{-3}, an accumulation of macrophages in alveolar spaces was observed. The concentrations of NiO in the lungs of all exposed groups of mice were significantly greater than those in the lungs of control animals (males, 32 to 84 mg Ni g^{-1} lung; females, 31 to 71 mg Ni g^{-1} lung).

The 13 week study involved 10 male and 10 female rats exposed to 0, 0.6. 1.2, 2.5, 5, and 10 mg NiO m^{-3} via inhalation for 5 days per week, 6 h per day. In this study, the researchers observed chemical-related non-neoplastic lesions in the lungs of both genders following exposure to concentrations of 2.5 mg m^{-3} or higher and were generally more severe with increased exposure concentration. In addition, an accumulation of alveolar macrophages, lymphoid hyperplasia pigmentation of the bronchial and mediastinal lymph nodes was observed in mice exposed to 2.5, 5, or 10 mg m^{-3}. In males exposed to 0.6, 2.5, or 10 mg m^{-3}, the concentration of NiO in the lungs was greater than that in the lungs of controls at 4, 9, and 13 weeks and continued to accumulate in the lung at the end of the 13-week exposures.

During the 2-year study, 65 male and 65 female mice were exposed to different concentrations of nickel oxide (0, 0.62, 1.25, and 2.5 mg NiO m^{-3}) over a 104-week study period, exposed for 5 days per week and 6 hours per day. At 2 years, pathology findings showed that the incidence of alveolar/bronchiolar adenoma in the 2.5 mg m^{-3} females was significantly greater than that of the controls, as was the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 1.25 mg m^{-3} females. The chronic lung inflammation increased with exposure concentration at 7 and 15 months. In groups exposed to ≥ 0.62 mg m^{-3}, alveolar and bronchial pigmentation was observed 7 months following exposure. At the conclusion of the 2-year study, bronchialization, proteinosis, inflammation, and pigmentation in the lung and lymphoid hyperplasia and pigmentation in the bronchial lymph nodes were observed in mice following exposure to nickel oxide by inhalation /43/.

Overall, the NTP study found some evidence of carcinogenic activity of NiO in male F344/N rats based on increased incidences of alveolar/ bronchiolar adenoma or carcinoma (combined) and increased incidences of benign or malignant pheochromocytoma (combined) of the adrenal medulla. Some evidence of carcinogenic activity of NiO was found in female F344/N rats based on increased incidences of alveolar/bronchiolar adenoma or carcinoma (combined) and increased incidences of benign pheochromocytoma of the adrenal medulla. No evidence of carcinogenic activity of NiO was found in male B6C3F1 mice exposed to 1.25, 2.5, or 5 mg m^{-3}. In female B6C3F1 mice, equivocal evidence of carcinogenic activity of NiO was observed based on marginally increased incidences of alveolar/bronchiolar adenoma in 2.5 mg m^{-3} females and of alveolar/ bronchiolar adenoma or carcinoma (combined) in 1.25 mg m^{-3} females. Exposure of rats to NiO by inhalation for 2 years resulted in inflammation and pigmentation in the lung, lymphoid hyperplasia and pigmentation in the bronchial lymph nodes, and hyperplasia of the adrenal medulla

(females). Exposure of mice to NiO by inhalation for 2 years resulted in bronchialization, proteinosis, inflammation, and pigmentation in the lung and lymphoid hyperplasia and pigmentation in the bronchial lymph nodes.

Nickel subsulfide (Ni_3S_2) is used in the production of lithium batteries and is found in the nickel ore refinery industry. Exposure to Ni_3S_2 through inhalation also contributes to lung cancer. The National Toxicology Program studied mice and rats exposed to 97% pure Ni_3S_2 by inhalation for 6 hours per day, 5 days per week for different periods of time (16 days, 13 weeks, or 2 years). The concentrations of Ni_3S_2 administered were 0, 0.6, 1.2, 2.5, 5, and 10 mg m^{-3}. The exposed animals showed increased inflammation of lung and atrophy of the nasal olfactory epithelium /44/.

The authors concluded that under the conditions of these 2-year inhalation studies, clear evidence emerged of carcinogenic activity of Ni_3S_2 in male and female F344/N rats. No evidence of carcinogenic activity of Ni_3S_2 was found in male or female B6C3F1 mice exposed to 0.6 or 1.2 mg m^{-3}. The findings suggest that both Ni_3S_2 and NiO and compounds reach the nucleus in larger quantities than do water-soluble nickel compounds like $NiSO_4$ /45/. Studies by Heim et al. /46/ support the theory that nickel inhalation is the primary route of exposure relevant to carcinogenic hazards and risks.

NICKEL GENOTOXICITY

In this section we discuss genetic and epigenetic studies that have been conducted to unravel the exact mechanisms of nickel-induced carcinogenesis. Experimental studies have shown that nickel disrupts DNA strands, DNA crosslinks, and DNA repair. Oxidative stress has been found to play a key role in nickel-induced carcinogenicity /47,48/. The production of reactive oxygen species (ROS) is facilitated by nickel's ability to bind with amino acids, peptides, and proteins.

A common fiber in all known cancers is the acquisition of abnormalities in the genetic material of the cancer cell. Cell hypoxia is believed to significantly affect the development of cancer and other cellular regulatory switches. Several studies have shown that both soluble and insoluble nickel compounds cause human lung and nasal cancers. Insoluble nickel compounds are phagocytized in acidic cytoplasmic vacuoles which expedite the dissolution of soluble nickel from the particles.

Oxidative Stress

Mutation and cell proliferation are the end products of the multistep process of chemical carcinogenesis. Oxidative stress can occur as the result of the overproduction of reactive oxygen and nitrogen species via endogenous and exogenous insults. A modification of gene expression and mutation caused by the upregulation and extended production of cellular oxidants are critical in the study of carcinogenesis /47/. The formation of ROS can be attributed to various events and pathways. The hydroxyl radical reacts with all components of the DNA molecule. Oxidative damage occurring as a result of permanent modification of genetic material represents the conception stage of mutagenesis, carcinogenesis, and aging. As a result of DNA damage, the arrest or induction of transcription, induction of signal transduction pathways, replication errors, and genomic instability all contribute to carcinogenesis. Metal-induced generation of oxygen radicals result in the attack on DNA in the cell nucleus in addition to other cellular components involving polyunsaturated fatty acid residues of phospholipids which are extremely sensitive to oxidation /48/.

DNA Damage

Several studies suggest that oxidative stress may be important in nickel-induced carcinogenesis (reviewed in /48/). In HL-60 human leukemia cells, long-term exposure to Ni^{2+} ions led to DNA fragmentation, cell death, and ROS. In contrast, a prevention of Ni^{2+}-induced DNA fragmentation and cell death was achieved with the addition of ascorbic acid (ASA) or N-acetyl-cysteine (NAC). Both H_2O_2-enhanced induction of DNA fragmentation and cell death are indicators of the ROS generation and cytotoxicity resulting from chronic exposure to nickel. In vivo studies have provided substantial evidence to support the in vitro results that ROS generation is one mechanism of cytotoxicity following chronic nickel exposure /49/.

Kasprzak et al. /50/ reported genotoxic and mutagenic activities in cells that had received high doses of nickel(II) via phagocytosis. Exacerbation of nickel(II) genotoxicity was linked to the generation of DNA-damaging ROS and inhibition of DNA repair /50/. Oxidative stress, genomic DNA damage, epigenetic effects, and the regulation of gene expression by the activation of specific transcription factors related to signal transduction pathways are the primary mechanisms of the carcinogenic actions of nickel compounds.

Oxidative DNA damage is one of the most important mechanisms associated with an array of terminal diseases including cancer. DNA damage can be initiated through radiation and chemical oxidation in addition to other methods not fully understood. Kelly et al. /51/ used HPLC-UV-EC to provide evidence of the oxidation of DNA mediated by nickel(II) through an oscillatory formation of 8-oxoguanine (8-oxoG) from free guanine and from guanine in DNA. The formation of oxidized-guanidinohydantoin (oxGH) from free guanine at pH 11, and the formation of guanidinohydantoin (GH) from DNA at pH 5.5 were observed using an HPLC-MS/MS method.

Researchers tested different metals at concentrations ranging from 0.5 to 5.0 mM to assess DNA damage, apoptosis, necrosis, and proliferation responses of a human T-helper lymphocyte (Jurkat) cell line after exposure /52/. In addition to vanadium, nickel was the only metal to induce DNA damage at nearly the same concentrations that induced >50% apoptosis (i.e., < 0.05 mM). Another study by Wu et al. /53/ investigated the effects of nickel-refining dusts in mouse NIH/3T3 cells. DNA damage was determined using the single cell gel electrophoresis (SCGE) technique. The percentage of tail DNA increased with increasing doses of nickel-refining dusts under the same condition of the same treatment time. After 4 h of exposure, DNA strand breaks reached the peak value in comparison with 2-h and 24-h exposure times.

Genotoxic stress assists in the mobilization of transposons, which are the source of genome instability. One example of a genotoxic effect is a double-stranded DNA break that threatens the integrity of the genome, activates cell-cycle checkpoints, and, in some cases, causes cell death. In the modern day human genome, L1 retro-transposons are the most active autonomous mobile elements /54/. Nickel chloride has been shown to stimulate L1 retrotransposition about 2.5 foldm. Stimulation of the L1 transposons occurs at the post-transcriptional level, probably during the integration process. Determination of the exact mechanism of the L1 stimulation is limited due to the highly complex nature of the effect of nickel on the cell. The stimulation results from a decrease in DNA-repair activities that influence the downstream events of retrotransposition. These findings provide a novel mechanism that must be considered when dealing with genomic damage/ instability in response to environmental agents /55/.

Testicular DNA damage

Epidemiologic studies suggest that certain paternal exposures to metals may increase the likelihood of cancer in progeny. Such routes include exposure to metal dusts and fumes, including welding fumes. Nickel is one of the primary suspects capable of producing pro-mutagenic damage to sperm DNA. Protamines are found tightly packed in sperm DNA, which can isolate and sequester carcinogenic transition metals and modulate oxidative damage. Studies have shown that human protamine P2 has a nickel $(II)^{-}$ and $Cu(II)^{-}$ binding amino acid pattern at its N-terminus, Arg-Thr-His-, which attracts metals. Liang et al /56/ found that nickel(II) and Cu(II) bound to a pentadecapeptide modeling [Arg-Thr-His-Gly-Glnn-Ser-His-Tyr-arg-Arg-Arg-His-Cys-Ser-Arg-amide] were able to mediate oxidative DNA double-strand scission and generation of 8-oxo-2′-deoxyguanosine (8-oxo-dG) from free 2′ deoxyguanosine (dG) and from DNA by hydrogen peroxide. The data suggest that nickel(II) may be mechanistically involved in the reproductive toxicity and carcinogenicity of metals.

Li and Wang /57 / reported that exposure of male mice to Ni^{2+} chloride resulted in a transient amount of Ni^{2+} in testes accompanied by a reduced sperm count and chromosomal aberrations. In addition to the aforementioned change, Ni^{2+} treatment slightly increased Cu^{+2} levels in the testes. DNA damage by ROS, including base alteration, crosslinking, strand cleaving /58/, and/or depurination, generated in $Ni^{2+\,-}$ and $Cu^{2+\,-}$ mediated redox reactions with the participation of endogenous oxidants /59/ are possible causes of these aberrations (discussed in /56/).

Molecular and Cellular Interactions

Cell Surface Receptors—Recent studies have found that nickel compounds are capable of interacting with cell surface receptors, such as the widely distributed extracellular Ca^{2+}-sensing receptor (CaSR) that may be activated by divalent cations. Cortijo et al. /60/ reported that nickel triggers intracellular Ca^{2+} mobilization in human airway epithelial cells through the activation of CaSR, which translates into pathophysiological outputs potentially related to pulmonary disease. The interaction between nickel and cell surface receptors activates cell signaling, which induces the calcium and hypoxia-inducible factor pathway, as described in /17/. After the induction of hypoxia-inducible factors, cells have the potential to survive in an anaerobic environment, enabling previously initiated cancer cells to advance into a full malignant state and metastasize /61/.

The nucleotide excision repair (NER) pathway has been shown to be affected by water-soluble and particulate nickel compounds /62/.

Nickel compounds have been found to raise the intracellular concentration of nickel ions, thereby establishing a basis for carcinogenic potential. According to Costa et al. /61/, nickel-induced carcinogenesis is related to the molecular and cellular events related to the compound. Nickel compounds enter the nucleus and interact with chromatin to induce carcinogenic activity. Heterochromatinization has recently been proposed as a potential mechanism of nickel-induced carcinogenesis /63 /.

Hypoxia-Inducible Signaling Pathway—The results of some studies have indicated that nickel exposure is responsible for a hypoxic cellular environment by depletion of iron from the cell /64, 65/. Hypoxia signaling is one pathway that contributes to metal ion-induced carcinogenesis by disrupting cellular iron homeostasis though competition with iron transporters or iron-regulated enzymes In-vitro studies of human and rodent cells by Salnikow et al. /17/ showed that the HIF-1 signaling pathway is activated by exposure to carcinogenic nickel compounds. Following acute exposure to nickel, an accumulation of

HIF-1 strongly activated hypoxia-inducible genes, including the recently discovered tumor marker NDRG1 (Cap43) /17/. Mice embryos were exposed to $NiCl_2$ to identify HIF-1-dependent nickel inducible genes and to understand the function of the HIF-1 dependent signaling pathway related to nickel-induced transformation. Nickel induced genes coding for glycolytic enzymes and glucose transporters, which are regulated by HIF-1 transcription factor, only in HIF-1 alpha-proficient cells. In addition, several other hypoxia-inducible genes were up-regulated by nickel in a HIF-dependent manner. Additionally, other genes were induced by nickel in an HIF-1-independent manner, suggesting that nickel exposure activates several signaling pathways. Assessing the induction of these pathways after exposure is essential to the understanding of cancer development related to nickel exposure / 17/. The results of a further study by Salnikow et al. /66/ indicated that nickel sulfate can induce hypoxia-inducible genes and IL-8 production in human lung cells with or without interference with iron metabolism.

Subsequent studies by Li et al. /67 / revealed the mechanism for the significant stabilization and elevation of HIF-1α protein, which involves a loss of cellular iron, as well as an inhibition of HIF-1α-dependent prolyl hydroxylases that target the binding of VHL ubiquitin ligase and degrade HIF-1α.

8-hydroxydeoxyguanosine formation—Further research by Kawanishi et al. /68/ helped clarify the mechanism of nickel carcinogenesis. In cultured HeLa cells, Ni_3S_2 induced a significant increase in 8-hydroxydeoxyguanosine (8-OH-dG) formation, whereas NiO, NiO, and $NiSO_4$ did not. On the other hand, intra-tracheal instillation of all these nickel compounds in rats significantly increased 8-OH-dG content in the lungs. The authors concluded that two different mechanisms, direct and indirect, for nickel-induced oxidative DNA damage could account for the disparities in DNA damage between cultured cells and animals. In direct oxidative DNA damage, supported by oxidative damage to isolated DNA treated with Ni(II) and hydrogen peroxide (H_2O_2), Ni(II) enters the cells and then reacts with endogenous and/or NiS-produced H_2O_2 to give reactive oxygen species that cause DNA damage, whereas indirect oxidative DNA damage results from inflammation. Such as double mechanism for DNA damage could explain the relatively high carcinogenic risk associated with Ni_3S_2. In another study, $NiSO_4$ was shown to significantly increase the level of testicular lipid peroxide and decrease all antioxidant enzymes activities and glutathione levels in Wister strain male albino rats /69/.

Epigenetic Mechanisms—Recent evidence has shown that the onset of cancer is preceded by both genetic and epigenetic abnormalities. Epigenetics refers to heritable patterns of gene expression that do not depend on alterations of the genomic DNA sequence. Because nickel compounds have shown carcinogenicity in the absence of mutagenesis, the mechanism of carcinogenesis is partly epigenetic in nature. Epigenetics involves genomic reprogramming in cancer cells, such as DNA methylation, chemical modification of the histone proteins, and RNA-dependent regulation /70/. Many studies have shown that nickel induces epigenetic silencing or reactivation of gene expression by the induction of DNA methylation. /17,61,69,71, Broday et al /72/, Kluz et al, /73/, which in turn induces a loss of histone H4 and H3 acetylation and DNA hypermethylation /74/. As a result of gene silencing, the cell is altered to a higher state of neoplastic transformation.

Histones are the major proteins found in chromatin that are responsible for shortening the length of DNA. Histone alterations have been linked to the deregulated expression of many genes that play critical roles in cancer development and progression. Quingdong et al. /75/ provided evidence that nickel causes the phosphorylation of histones at serine 10. Their study pointed out that this induction occurs via the c-jun N-terminal kinase (JNK)/stress-activated protein kinase in an (SAPK)-dependent manner, yet, no observable effect was seen

on the phosphorylation states of the extracellular signal-regulated kinase or p38 mitogen-activated protein kinases. The evidence was based on a total loss of nickel ion-induced phosphorylation using RNAi /75/.

Studies have also demonstrated that Ni^{2+} restricts the acetylation of histone H4 by binding with its N-terminal histidine-18. Notably, Ni^{2+} readily produces ROS in vivo, which is an inversely related critical factor with the occurrence of resistance of mammalian cells to Ni^{2+}. A recent study suggests that a high concentration of Ni^{2+} (no less than 600 μM) causes a cogent decrease of histone acetylation in human hepatoma cells. The result of the inhibition was shown primarily from the influence of Ni^{2+} on the overall histone acetyltransferase (HAT) activity. Simultaneously, the exposure of hepatoma cells to Ni^{2+} generated ROS. Two antioxidants, 2-mercaptoethanol (2-ME) at 2mM or N-acetyl-cysteine (NAC) at 1mM, with Ni^{2+} together completely suppressed ROS generation and significantly reduced the induced histone hyperacetylation, providing evidence that the ROS generation plays a role in the inhibition of histone acetylation. It also serves as a template suggesting that gene expression and carcinogenesis is caused by Ni^{2+} /76/. Nickel has also been shown to inhibit dioxygenases by impairing epigenetic processes leading to cancer development /77/.

Chromosomal Aberrations—Chemical and genetic synergism yields two types of DNA alterations: first, molecular changes in genes, and second, chromosomal aberrations secondary to breaks in linear coherence of chromosomes. The segregation of chromosomes through the interaction with the spindle fiber mechanism is another type of genetic mutation caused by chemicals. This alteration creates non-disjunction and a deviant number of chromosomes. Induced chromosome aberrations produces changes which functionally altered the cell function leaving it capable of proliferation. The results of chromosome aberrations include cell death or at least an inability to complete mitosis /78/. Mammalian cell studies by nickelshimura et al. provide evidence that certain nickel compounds [$NiCl_2$ and $Ni(CH_3COO)_2$] produce chromosomal aberrations /79/. Nickel sulfate has been found to produce genetic and chromosomal alterations in V79 Chinese hamster cells /80/.

Tumor suppressor gene (p53) alteration—One of the first phenotypic changes in the multistage and multifactorial process of carcinogenesis is cellular immortality. Some of these changes activate proto-oncogenes while others functionally inactivate tumor suppressor genes. P53 has been tagged a tumor suppressor gene by various studies. Normal cell proliferation and neoplastic transformation is attributed to the nuclear p53. Mutated p53 is commonly found in human cancers. This mutated p53 is usually joined to a 17p deletion in tumors. Studies of normal rodent cells with p53 mutation have revealed cell immortalization, cooperation with transfected ras oncogene, and predisposition to neoplastic transformation. Researchers have found that nickel induces immortalization and point mutation in the conserved region of the p53 gene in human kidney epithelial cells. Prokaryotic systems and mammalian cell mutagenicity assays provide evidence of mutagenic nickel compounds. Cohort studies by Maehle et al. /81/ and Chiocca et al. /82/ provided evidence that nickel induces a duplication of the region containing MuSVts 110 3′ splice site, suggesting nickel's ability to act as a mutagen in mammalian cells. A more detailed determination of genetic changes during the stepwise progression of neoplastic transformation after nickel treatment is presently being investigated. Future studies will determine the p53 mutation spectra in nickel (II)- associated renal and lung human cancer in comparisons with a spectra with those found in renal and lung cancers occurring in the general population /81/.

Lu et al. /44/ suggested that exposure to nickel compounds activates various transcription factors related to corresponding signal transduction pathways that are associated with nickel carcinogenesis. Using GeneChip analysis to compare genetic alterations caused by both

soluble and insoluble nickel compounds, Sanilkow et al /83/ confirmed that both forms of nickel induce similar signaling pathways by activating a number of transcription factors, including p53 and HIF-1 leading to cell transformation. Normal human epithelial cells (NHKE) treated with Ni^{2+} in vitro resulted in the immortalization of the cells. In vivo, the combination of Ni^{2+} and v-Ha-ras oncogene fully transformed the cells to tumoriogenicity. Sequence analysis of DNA from the immortalized human kidney epithelial cells indicated a point mutation in the p53 gene at codon 238 with T→C transition, suggesting the nickel-induced mutation in the p53 gene can be involved in the immortalization of the NHKE cells /84/.

Ect2 Proto-Oncogene Amplification—In an effort to understand the mechanisms of nickel ion-induced cell transformation and the development of biomarkers of nickel ion exposure and nickel-ion-induced cell transformation, Clemens et al /85/ isolated mRNA from green NiO-, crystalline NiS-, and 3-methylcholanthrene (MCA)-transformed C3H/10T1/2 Cl 8 mouse fibroblast cell lines. An mRNA differential display revealed that nine mRNA fragments were differentially expressed between nickel-transformed and non-transformed 10T1/2 cell lines. Expression of fragment R2-5 was observed at higher steady-state levels in transformed cell lines. The R2-5 fragment showed 100% sequence identity to part of the coding region of Ect2, a mouse proto-oncogene encoding a GDP-GTP exchange factor. The 3.9-kb Ect2 transcript was expressed at 1.6- to 3.6-fold higher steady-state levels in four Ni-transformed and in two MCA-transformed, cell lines. In both cell lines, the metal also increased the expression of the Ect2 protein to a 3.0 to 4.5 fold higher steady state level. The Ect2 gene was amplified by 3.5- to 10-fold in Ni-transformed, and by 2.5- to 3-fold in MCA transformed cell lines. The gene amplification was likely caused by the binding of nickel ions to enzymes of DNA synthesis. The authors concluded that the microtubule disassembly and cytokinesis resulting from Ect2 gene amplification and over-expression of Ect2 mRNA and protein contributed to the induction and maintenance of morphological, anchorage-independent, and neoplastic transformation of both cell lines /85/.

C-Myc Transcription Factor—The complex nature of cancer formation can also be attributed to the deregulation in various steps of translational control. The c-Myc protein is a transcription factor that is associated with the control of cellular proliferation and differentiation. The protein binds DNA at specific sites and determines which genes should be transcribed into mRNA to make additional or other new proteins. Among the numerous biological activities of the c-myc gene are transformation, immortalization, blockage of cell differentiation, and induction of apoptosis. Furthermore, c-Myc is required but not absolutely essential for efficient progression through the cell cycle (reviewed in /86,87,88/.

The involvement of the oncogene c-myc in the genesis of neoplasia is well documented for several systems. The c-Myc protein controls 15% of human genes. Both c-Myc mRNA and protein are generally expressed at low levels in normal proliferating cells but are frequently overexpressed in cancer cells. The c-Myc transcription factor also plays a critical role in the control of translation /89/. Myc has a direct impact on increasing protein synthesis rates by controlling the expression of multiple components of the protein synthetic machinery, including ribosomal proteins and initiation factors of translation, Pol III, and rDNA. Studies have indicated that c-Myc oncogenic signaling has the ability to dominate the translational machinery by eliciting cooperative effects on cell growth, cell cycle progression, and genomic instability leading to the initiation of cancer /89/.

Gordan et al /90/ demonstrated that HIF-2α enhances c-Myc transcriptional activity, thereby promoting hypoxic cell proliferation. Li et al /91/ investigated the effect of nickel on c-myc levels. The results demonstrated that nickel, hypoxia, and other hypoxia mimetics degraded c-Myc protein in a number of cancer cells and this degradation was dependent upon both

HIF-1α and HIF-2α. The study also disclosed evidence of two potential pathways mediated nickel induced c-Myc protein degradation: (1) through the phosphorylation of c-myc at T58 by significantly increasing cells exposed to nickel, or (2) hypoxia, leading to increased ubiquitination through Fbw7 ubiquitin ligase, and the other through a decrease in the c-myc de-ubiquitinating enzyme, USP28, following nickel and hypoxia exposure. Phosphorylation of c-myc at T58 was significantly increased in cells exposed to nickel or hypoxia, leading to increased ubiquitination through Fbw7 ubiquitin ligase. In addition, nickel and hypoxia exposure decreased USP28, a c-Myc de-ubiquitinating enzyme, contributing to a higher steady state level of c-Myc ubiquitination and promoting c-Myc degradation. These mechanisms are important factors in enhanced c-myc ubiquitination and proteasomal degradation /90/.

Another study found that c-Myc protein expression was increased by nickel ions in non-tumorigenic human bronchial epithelial cells (Beas-2B) and keratinocyte HaCaT cells. Further studies in the Beas-2B cells revealed that nickel ion increased the c-Myc mRNA level and c-Myc promoter activity, but did not increase c-Myc mRNA and protein stability. The results demonstrated that c-Myc induction by nickel ions occurs via the Ras/Raf extracellular signal-regulated kinase (ERK)-dependent signaling pathway /92/, which plays a crucial role in nickel-induced apoptosis in human bronchial epithelial cells /93/.

Embryotoxicity

Nickel can cross the human placenta, producing teratogenesis and embryotoxic effects. Chen et al /60/ conducted a time-course experiment on human-term placentas incubated with 2.5 mM nickel. Permeability, lipid peroxidation, and nickel concentration were significantly increased compared with the control, indicating nickel toxicity due to lipid peroxidative damage to the placental membrane. The result of this metabolic change may be responsible for decreased placental viability, altered permeability, and potential subsequent embryotoxicity. Research also suggests that the prenatal effects of nickel may be due to production of certain mutations in the mitotic apparatus provoking cellular death at critical times of fetal development /94/.

CONCLUSIONS

Nickel, an element that occurs naturally in the earth’s crust, is found in soils, sediments, water resources, air, plants and animals. Large amounts of nickel are released into the environment as a result of such natural phenomena as volcanic eruptions or from industrial activities like nickel mining, nickel alloy production and use, power plants, and incinerators operations. Human exposure to nickel occurs via inhalation of dust particles, ingestion of contaminated food and water, and dermal contact with nickel-containing materials or soil. Although the allergic reaction to nickel is the most common adverse health effect in humans, nickel exposure has also been associated with lung cancer, especially in workers of nickel refineries and processing plants.

Experimental studies have shown that nickel-induced carcinogenicity involves multiple molecular mechanisms. The proposed mechanisms discussed here suggest the following chain of events—nickel compounds enter the cell, activate the receptor CaSR, triggering intracellular Ca^{2+} mobilization and induction of the calcium and hypoxia-inducible factor pathways. Nickel enters the nucleus, directly binds to DNA and reacts with H_2O_2 to form reactive nickel-oxygen complexes, resulting in the oxidation of thymine and cytosine residues accompanied by 8-OH-dG formation. The oxidative stress generated severely damages DNA and inhibits DNA repair pathways. Nickel compounds also induce indirect damage through inflammation by stimulating polymorphonuclear leukocytes to produce ROS. Nickel also damages heterochromatin, thereby silencing the expression of genes

located near heterochromatin, which in turn induces an epigenetic loss of histone H4 and H3 acetylation and DNA hypermethylation /94/ As a result of gene silencing, the cell is more susceptible to neoplastic transformation. In addition, nickel down-regulates the tumor suppressor gene p53, activates the proto-oncogene c-Myc and induces the AP-1 transcription factor, resulting in cellular proliferation and cancer development.

Acknowledgments

This research was supported in part by a grant from the National Institutes of Health RCMI-Center for Environmental Health (2G12RR013459), and in part by a grant from the U.S. Department of Education Title III Graduate Education Program (PO31B040101) at Jackson State University.

References

1. Stimola, A. Understanding the elements of the periodic table. 1. New York: The Rosen Publishing Group; 2007.
2. Nickel Institute. Nickel and its uses. 2006. Available at www.nickelinstitute.org
3. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Nickel (Update). Atlanta, GA: U.S. Department of Public Health and Human Services, Public Health Service; 2005. Available at: http:/www.atsdr.cdc.gov
4. Coogan TP, Latta DM, Snow ET, Costa M. Toxicity and carcinogencity of nickel compounds. Crit Rev Toxicol. 1989; 19(4):341–84. [PubMed: 2663022]
5. Ohio Environmental Protection Agency. Nickel and nickel compounds. 2002. Available at http://www.epa.state.oh.us/ocapp/p2/mercury_pbt
6. Grandjean, P.; Nielson, GD.; Anderson, O. Human nickel exposure and chemobiokinetics. In: Maibach, HE.; Menné, T., editors. Nickel and the skin: immunology and toxicology. Boca Raton, FL: CRC Press; 1989. p. 9-34.
7. Costa M, Davidson TL, Chen H, Ke Q, Zhang P, Yan Y, Huang C, Kluz T. Nickel carcinogenesis: epigenetics and hypoxia signaling. Mutat Res. 2005; 592(1–2):79–88. [PubMed: 16009382]
8. Vincent, JH. Aerosol sampling: science and practice. Chichester, UK: John Wiley & Sons, Inc; 1989. p. 390
9. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Nickel (Update). Atlanta, GA: U.S. Department of Public Health and Human Services, Public Health Service; 1988. Available at: http:/www.atsdr.cdc.gov
10. 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(2):157–173. [PubMed: 17894205]
11. Valko M, Morriss H, Cronin MT. Metals, toxicity, and oxidative stress. Curr Med Chem. 2005; 12(10):1161–1208. [PubMed: 15892631]
12. U.S. Environmental Protection Agency (EPA). EPA 600R94111. Methods for the determination of metals in environmental samples, supplement 1. U.S. EPA National Exposure Research Laboratory; 1994.
13. Nielsen, FH. Clinical and biochemical nutritional aspects of trace elements. New York: Alan R. Liss Inc; 1982. Possible future implications of nickel, arsenic, silicon, vanadium, and other ultra trace elements in human nutrition; p. 379-404.
14. M'Bemba-Meka P, Lemieux N, Chakrabarti SK. Role of oxicative stress, mitochondrial membrane potential, and calcium homeostasis in human lymphocyte death induced by nickel carbonate hydroxide in vivo. Arch Toxicol. 2006; 80(7):405–20. [PubMed: 16758152]
15. Schmid M, Zimmermann S, Krug HF, Sures B. Influence of platinum, palladium, and rhodium as compared with cadmium, nickel and chromium on cell viability and oxidative stress in human bronchial epithelial cells. Environ Int. 2007; 33(3):385–90. [PubMed: 17250893]
16. Dieter MP, Jameson CW, Tucker AN, Luster MI, French JE, Hong HL, et al. Evaluation of tissue deposition myelopoietic and immunologic responses in mice after long term exposure to nickel sulfate in drinking water. J Toxicol Environ Health. 1988; 24:357–72. [PubMed: 3398077]

17. Salnikow K, Davidson T, Zhang Q, Chen LC, Su W, Costa M. The involvement of hypoxia-inducible transcription factor-1-dependent pathway in nickel carcinogenesis. Cancer Res. 2003; 63(13):3524–30. [PubMed: 12839937]
18. Hostynek JJ. Sensitization to nickel: etiology, epidemiology, immune reactions, prevention, and therapy. Rev Environ Health. 2006; 21(4):252–80.
19. Moennich JN, Zirwas M, Jacob SE. Nickel-induced facial dermatitis: adolescents beware of the cell phone. Cutis. 2009; 84(4):199–200. [PubMed: 19911674]
20. Luo J, Bercovitch L. Cellphone contact dermatitis with nickel allergy. CMAJ. 2008; 178(1):23–24. [PubMed: 18166725]
21. Livideanu C, Giordano-Labadie F, Paul C. Cellular phone addiction and allergic contact dermatitis to nickel. Contact Dermatitis. 2007; 57 (2):130–31. [PubMed: 17627662]
22. Wöhrl S, Jandl T, Stingl G, Kinaciyan T. Mobile telephone as new source for nickel dermatitis. Contact Dermatitis. 2007; 56(2):113.
23. Thyssen JP, Maibach HI. Nickel release from earrings purchased in the United States: the San Francisco earring study. J Am Acad Dermatol. 2008; 58(6):1000–05. [PubMed: 18406493]
24. Thyssen JP, Menné T, Johansen JD. Nickel release from inexpensive jewelry and hair clasps purchased in an EU country Are consumers sufficiently protected from nickel exposure? Sci Total Environ. 2009; 407(20):5315–18. [PubMed: 19631967]
25. Heim KE, McKean BA. Children's clothing fasteners as a potential source of exposure to releasable nickel ions. Contact Dermatitis. 2009; 60 (2):100–05. [PubMed: 19207381]
26. World Health Organization, International Agency for Research on Cancer. Nickel compounds (Group 1), Metallic nickel (2B). IARC monographs on the evaluation of carcinogenic risks to humans, vol 49. Chromium, nickel, and welding. Nickel and Nickel Compounds.
27. 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. p. 262-269.
28. United States Environmental Protection Agency (EPA). Nickel Compounds. Washington, D.C: 2000. Available at http://www.epa.gov/ttn/atw/hlthef/nickel.html
29. Clemens F, Landolph JR. Genotoxicity of samples of nickel refinery dust. Toxicol Sci. 2003; 73(1):114–123. [PubMed: 12657748]
30. Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int Arch Occup Environ Health. 1998; 71 (4):245–50. [PubMed: 9638480]
31. Kiilunen M, Utela J, Rantanen T, Norppa H, Tossavainen A, Koponen M, et al. Exposure to soluble nickel in electrolytic nickel refining. Ann Occup Hyg. 1997; 41(2):167–88. [PubMed: 9155238]
32. Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect. 1994; 102 (1):275–82. [PubMed: 8187719]
33. Hartwig A, Schwerdtle T. Interactions by carcinogenic metal compounds with DNA repair processes: toxicological implications. Toxicol Lett. 2002; 127(1–3):47–54. [PubMed: 12052640]
34. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol. 2008; 82(8):493–512. [PubMed: 18496671]
35. Kasprzak KS, Ward JM, Poirier LA, Reichardt DA, Denn AC 3rd, Reynolds CW. Nickel--magnesium interactions in carcinogenesis: dose effects and involvement of natural killer cells. Carcinogenesis. 1987; 8(7):1005–11. [PubMed: 3594718]
36. Zeromski J, Jezewska E, Sikora J, Kasprzak KS. The effect of nickel compounds on immunophenotype and natural killer cell function of normal human lymphocytes. Toxicology. 1995; 97(1–3):39–48. [PubMed: 7716791]
37. Oller AR. Respiratory carcinogenicity assessment of soluble nickel compounds. Environ Health Perspect. 2002; 110(5):841–44. [PubMed: 12426143]
38. Qingdong K, Davidson T, Kluz T, Oller A, Costa M. Fluorescent tracking of nickel ions in human cultured cells. Toxicol Appl Pharmacol. 2007; 219 (1):18–23. [PubMed: 17239912]

39. Reznikoff CA, Brankow DW, Heidelberger C. Establishment and characterization of a cloned line of C3H mouse embryo cells sensitive to post-confluence inhibition of division. Cancer Res. 1973; 33:3231–3238. [PubMed: 4357355]
40. Draper MH, Duffus JH, Metcalf JP, Morgan L, Park M, Weitzner MI. Analysis of nickel refinery dusts. Sci Total Environ. 1994; 48(2–3):263–273. [PubMed: 8029701]
41. Nduka JK, Orisakwe OE. Heavy metal hazards of pediatric syrup administration in Nigeria: a look at chromium, nickel and manganese. Int J Environ Res Public Health. 2009; 6(7):1972–79. [PubMed: 19742165]
42. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? Epidemiol. 2005; 16(2):146–54.
43. National Toxicology Program (NTP). Toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344 rats and B6C3F1M6 (inhalation studies). NTP Tech Rep Ser. 1996; 451:1–381.
44. Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035-72-2) in F344 Rats and B6C3F$_1$ Mice (Inhalation Studies) [Abstract]. Availableat:http://ntp.niehs.nih.gov/index.cfm?objectid=070A4899-D23F-D3D3-AB792B1CF9432DEA
45. Dunnick JK, Elwell MR, Radovsky AE, Benson JM, Hahn FF, Nikula KJ, et al. Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. Cancer Res. 1995; 55(22):5251–56. [PubMed: 7585584]
46. Heim KE, Bates HK, Rush RE, Oller AR. Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats. Toxicol Appl Pharmacol. 2007; 224(2):126–37. [PubMed: 17692353]
47. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. Annual Rev Pharmacol Toxicol. 2004; 44:239–67. [PubMed: 14744246]
48. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006; 160(1):1–40. [PubMed: 16430879]
49. Jia J, Chen J. Chronic nickel-induced DNA damage and cell death: the protection role of ascorbic acid. Environ Toxicol. 2008; 23(3):401–6. [PubMed: 18214889]
50. Kasprzak KS, Sunderman FW Jr, Salnikow K. Nickel carcinogenesis. Mutat Res. 2003; 533(1–2): 67–97. [PubMed: 14643413]
51. Kelly MC, Whitaker G, White B, Smyth MR. Nickel (II) catalysed oxidative guanine and DNA damage beyond 8-oxyguanine. Free Radic Biol Med. 2007; 42(11):1680–89. [PubMed: 17462536]
52. Caicedo M, Jacobs JJ, Reddy A, Hallab NJ. Analysis of metal ion-induced DNA damage, apoptosis, and necrosis in human (Jurkat) T-cells demonstrates Ni2+ and V3+ are more toxic than other metals: Al3+, Be2+, Co2+, Cr3+,Cu2+, Fe3+, Mo5+, Nb5+, Zr2+ J Biomed Mater Res A. 2008; 86(4):905–13. [PubMed: 18050301]
53. Wu YH, Wang J, Zhao G, Yu CP. Experimental study on the DNA damage of NIH/3T3 cells induced by nickel-refining dusts. 2005; 23(5):326–8.
54. Farkash EA, Prak ET. DNA damage and L1 retrotransposition. J Biomed Biotechnol. 2006; (1): 37285. [PubMed: 16877815]
55. El-Sawy M, Kale SP, Dugan C, Nguyen TQ, Belancio V, Bruch H, et al. Nickel stimulates L1 retrotransposition by a post-transcriptional mechanism. J Mol Biol. 2005; 354(2):246–57. [PubMed: 16249005]
56. Liang R, Senturker S, Shi X, Bal W, Dizdaro-gluand M, Kasprzak KS. Effects of Ni(II) and Cu(II) on DNA interaction with the N-terminal sequence of human protamine P2: enhancement of binding and mediation of oxidative DNA strand scission and base damage. Carcinogenesis. 1999; 20(5):893–98. [PubMed: 10334208]
57. Li J, Wang X. Toxic effects of nickel chloride on testis of mice. Weisheng Dulixue Zazhi. 1989; 3:222–224.
58. Doreswamy K, Shrilatha B, Rajeshkumar T, Mouralidhara. Nickel-induced oxidative stress in testis of mice: evidence of DNA damage and genotoxic effects. J Androl. 2004; 25(6):996–1003. [PubMed: 15477375]

59. Kasprzak KS. Possible role of oxidative damage in metal-induced carcinogenesis. Cancer Invest. 1995; 13:411–430. [PubMed: 7627727]
60. Cortijo J, Milara J, Mata M, Donet E, Gavara N, Peel SE, et al. Nickel induces intracellular calcium mobilization and pathophysiological responses in human cultured airway epithelial cells. Chem Biol Interact. 2010; 183(1):25–33. [PubMed: 19781536]
61. Costa M, Yan Y, Zhao D, Salnikow K. Molecular mechanisms of nickel carcinogenesis: gene silencing by nickel delivery to the nucleus and gene activation/inactivation by nickel-induced cell signaling. J Environ Monit. 2003; 5(2):222–23. [PubMed: 12729258]
62. Schwerdtle T, Albrecht S, Hartwig A. Effect of soluble and particulate nickel compounds on the formation and repair of stable benzo[a]pyrene DNA adducts in human lung cells. Carcinogenesis. 2002; 23(1):47–53. [PubMed: 11756222]
63. Ellen TP, Kluz T, Harder ME, Xiong J, Costa. Heterochromatinization as a potential mechanism of nickel-induced carcinogenesis. Biochemistry. 2009; 48 (21):4626–32. [PubMed: 19338343]
64. Kang GS, Li Q, Chen H, Costa M. Effect of metal ions on HIF-1alpha and Fe homeostasis in human A549 cells. Mutat Res. 2006; 610(1–2):48–55. [PubMed: 16877034]
65. Chen H, Costa M. Iron-and 2-oxoglutarate-dependent dioxygenases: an emerging group of molecular targets for nickel toxicity and carcinogenicity. Biometals. 2009; 22(1):191–6. [PubMed: 19096759]
66. Salnikow K, Li X, Lippmann M. Effect of nickel and iron co-exposure on human lung cells. Toxicol Appl Pharmacol. 2004; 196(2):258–65. [PubMed: 15081272]
67. Li Q, Chen H, Huang X, Costa M. Effects of 12 metal ions on iron regulatory protein 1 (IRP-1) and hypoxia-inducible factor-1 alpha (HIF-1alpha) and HIF-regulated genes. Toxicol Appl Pharmacol. 2006; 213:245–255. [PubMed: 16386771]
68. Kawanishi S, Oikawa S, Inoue S, Nishino K. Distinct mechanisms of oxidative DNA damage induced by carcinogenic nickel subsulfide and nickel oxides. Environ Health Perspect. 2002; 110(5):789–91. [PubMed: 12426132]
69. Gupta AD, Dhundasi SA, Ambekar JG, Das KK. Effect of l-ascorbic acid on antioxidant defense system in testes of albino rats exposed to nickel sulfate. J Basic Clin Physiol Pharmacol. 2007; 18(4):255–66. [PubMed: 18380167]
70. Kanwal R, Gupta S. Epigenetics and Cancer. J Appl Physiol. 2010
71. Broday L, Cai J, Costa M. Nickel enhances telomeric silencing in Saccharomyces cerevisiae. Mutat Res. 1999 Apr 6; 440(2):121–30. [PubMed: 10209334]
72. Yan Y, Kluz T, Zhang P, Chen HB, Costa M. Analysis of specific lysine histone H3 and H4 acetylation and methylation status in clones of cells with a gene silenced by nickel exposure. Toxicol Appl Pharmacol. 2003; 190(3):272–7. [PubMed: 12902198]
73. Yan Y, Kluz T, Zhang P, Chen HB, Costa M. Analysis of specific lysine histone H3 and H4 acetylation and methylation status in clones of cells with a gene silenced by nickel exposure. Toxicol Appl Pharmacol. 2003; 190(3):272–7. [PubMed: 12902198]
74. Qingdong K, Qin L, Thomas EP, Hong S, Costa M. Nickel compounds induce phosphorylation of histone H3 at serine 10 by activating JNK-MAPK pathway. Carcinogenesis. 2008; 29(6):1276–81. [PubMed: 18375956]
75. Kang J, Zhang Y, Chen J, Chen H, Lin C, Wang Q, et al. Nickel-induced histone hypoacetylation: The role of reactive oxygen species. Toxicol Sci. 2003; 74(2):279–86. [PubMed: 12773760]
76. Chen H, Giri NC, Zhang R, Yamane K, Zhang Y, Maroney M, et al. Nickel ions inhibit histone demethylase JMJD1A and DNA repair enzyme ABH2 by replacing the ferrous iron in the catalytic centers. J Biol Chem. 2009; 285(10):7374–83. [PubMed: 20042601]
77. Vainio H, Sorsa M. Chromosomal aberrations and their relevance to metal carcinogenesis. Environ Health Perspect. 1981; 40:173–80. [PubMed: 7023931]
78. Nishimura M, Umeda M. Induction of chromosomal aberrations in cultured mammalian cells by nickel compounds. Mutat Res. 1979; 68(4):337–49. [PubMed: 522882]
79. Susumu O. Induction of genetic instability and chromosomal instability by nickel sulfate in V79 Chinese hamster cells. Mutagenesis. 2003; 18(2):133–7. [PubMed: 12621068]

80. Mæhle 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(1):218–21. [PubMed: 1727381]

81. Chiocca SM, Sterner DA, Biggart NW. Murphy MuSVts110 thermosensitive splicing phenotype by a nickel-induced duplication of the 3′ splice site. Mol Carcinog. 1991; 4(1):61–71. [PubMed: 1848987]

82. Salnikow K, Davidson T, Kluz T, Chen H, Zhou D, Costa M. GeneChip analysis of signaling pathways effected by nickel. J Environ Monit. 2003; 5(2):206–9. [PubMed: 12729255]

83. Haugen A, Maehle L, Mollerup S, Rivedal E, Ryberg D. Nickel-induced alterations in human renal epithelial cells. Environ Health Perspect. 1994; 102(3):117–18. [PubMed: 7843084]

84. Clemens F, Verma R, Ramnath J, Landolph JR. Amplification of the Ect2 proto-oncogene and over-expression of Ect2 mRNA and protein in nickel compound and methylcholanthrene-transformed 10T1/2 mouse fibroblast cell lines. Toxicol Appl Pharmacol. 2005; 206(2):138–49. [PubMed: 15967202]

85. Cole MD, McMahon SB. The Myc oncoprotein: a critical evaluation of transactivation and target gene regulation. Oncogene. 1999; 18(19):2916–24. [PubMed: 10378688]

86. Facchini LM, Penn LZ. The molecular role of Myc in growth and transformation: recent discoveries lead to new insights. FASEB J. 1998; 12(9):633–51. [PubMed: 9619443]

87. Luscher B, Larsson LG. The world according to MYC. Conference on MYC and the transcriptional control of proliferation and oncogenesis. EMBO Rep. 2007; 8(12):1110–4. [PubMed: 18007654]

88. Ruggero D. The role of Myc-induced protein synthesis in cancer. Cancer Res. 2009; 69(23):8839–43. [PubMed: 19934336]

89. Gordan JD, Bertout JA, Hu CJ, Diehl JA, Simon MC. HIF-2alpha promotes hypoxic cell proliferation by enhancing c-myc transcriptional activity. Cancer Cell. 2007; 11(4):335–47. [PubMed: 17418410]

90. Li Q, Kluz T, Sun H, Costa M. Mechanisms of c-myc degradation by nickel compounds and hypoxia. PLoS One. 2009; 4(12):e8531. [PubMed: 20046830]

91. Bermudez Y, Yang H, Cheng JQ, Kruk PA. Pyk2/ERK 1/2 mediate Sp1- and c-Myc-dependent induction of telomerase activity by epidermal growth factor. Growth Factors. 2008 Feb; 26(1):1–11. [PubMed: 18365874]

92. Li Q, Suen TC, Sun H, Arita A, Costa M. Nickel compounds induce apoptosis in human bronchial epithelial Beas-2B cells by activation of c-Myc through ERK pathway. Toxicol Appl Pharmacol. 2009; 235(2):191–98. [PubMed: 19135467]

93. Chen CY, Lin TH. Nickel toxicity to human term placenta: in vitro study on lipid peroxidation. J Toxicol Environ Health A. 1998; 54(1):37–47. [PubMed: 9588347]

94. Leonard A, Jacquet P. Embryotoxicity and genotoxicity of nickel. IARC Sci Publ. 1984; (53):277–91. [PubMed: 6398285]

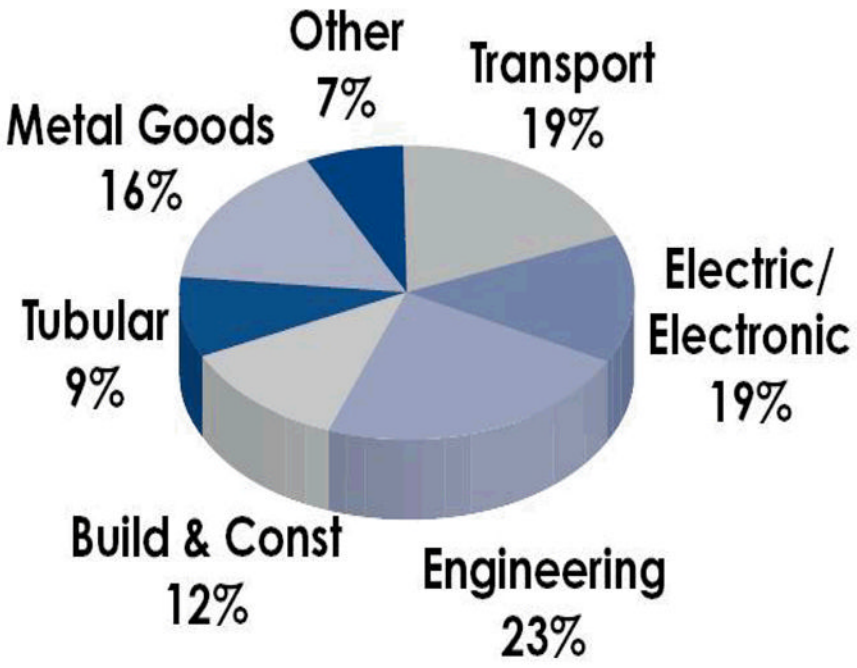

Fig. 1.
Primary distribution of nickel: Adapted from Nickel Institute, (2006)

Table 1

End uses of nickel: Adapted from Nickel Institute (2006)

SOURCE	DISTRIBUTION
Railway/Transportation Equipment	3%
Consumer Products	19%
Electric Power Generation	2%
Electronics	8%
Process Equipment	10%
Petroleum Industry	3%
Building and Construction Materials	17%
Nickel Chemicals	1%
Chemical Industry	8%
Aerospace Materials	3%
General Engineering	6%
Automotive Production	11%
Marine Equipment	2%
Other	4%