J. Elementol. 2008, 13(4): 685-696

Review paper

THE IMPACT OF NICKEL ON HUMAN HEALTH

Aleksandra Duda-Chodak, Urszula Błaszczyk

Department of Fermentation Technology and Technical Microbiology
Agricultural University in Krakow

Abstract

In 2008, nickel received the shameful name of the "Allergen of the Year." According to dermatologists the frequency of nickel allergies is still growing, and it cannot be explained only by fashionable piercing and nickel devices used in medicine (like coronary stents).

Occupational exposure of several million workers worldwide has been shown to give rise to elevated levels of nickel in blood, urine and body tissues. In these cases, workers are exposed to airborne fumes and dusts containing nickel and its compounds and therefore inhalation is the main route of uptake. Nonoccupational sources of nickel exposure for the general population include mainly drinking water and food. Recently, tests of kitchen kettles showed substantial leaching of nickel into drinking water when boiled in kettles with exposed nickel-plated elements.

Three types of adverse health impacts as a result of exposure to nickel are discussed in the text. Acute health effects generally result from short-term exposure to high concentrations of pollutants. Chronic noncancer health effects may result from long-term exposure to relatively low concentrations of pollutants. Inhalation of nickel also can cause cancer of the lungs, nose and sinuses. Cancers of the throat and stomach have also been attributed to inhalation of nickel. However, the exact mechanism by which nickel causes cancer is still questionable and needs further investigation. The most popular hypotheses to explain this phenomenon are presented in the text.

Key words: nickel, sources of nickel, exposure, toxicity, carcinogenesis, human.

Aleksandra Duda-Chodak, PhD, Department of Fermentation Technology and Technical Microbiology, Agricultural University in Krakow, ul. Balicka 122, 30-149 Krakow, Poland, phone: 48 12 662 47 92, e-mail: aduda-chodak@ar.krakow.pl

WPŁYW NIKLU NA ZDROWIE CZŁOWIEKA

Abstrakt

W 2008 nikiel zyskał niechlubne miano „alergenu roku". Według dermatologów, wciąż rosnąca częstość alergii na nikiel nie może być tłumaczona jedynie modą na przekłuwanie ciała lub zwiększone zastosowanie w medycynie urządzeń zawierających nikiel (np. stenty naczyń wieńcowych). Wykazano, że kilka milionów robotników na całym świecie narażonych zawodowo na nikiel i jego związki, ma podwyższony poziom tego pierwiastka we krwi, moczu i tkankach organizmu. W tych przypadkach pracownicy są wystawieni na opary i pyły zawierające nikiel, a zatem głównym sposobem pobierania tego pierwiastka jest inhalacja. Dla większości populacji źródła niklu stanowią jednak woda pitna i żywność. Niedawno w testach czajników kuchennych z odsłoniętymi elementami grzewczymi, wykonanymi ze stopów niklu wykazano uwalnianie znacznych ilości niklu do wody pitnej.

W pracy omówiono trzy główne typy szkodliwego dla zdrowia wpływu ekspozycji na nikiel. Ostre zatrucia, jako wynik krótkoterminowej ekspozycji na wysokie stężenia polutantów, chroniczne nienowotworowe efekty powstające na skutek długotrwałej ekspozycji na stosunkowo niskie dawki oraz nowotwory płuc, nosa i zatok spowodowane inhalacją powietrza zanieczyszczonego niklem. Również rak gardła i żołądka przypisuje się wdychaniu związków niklu. Dokładny mechanizm kancerogenezy wywołanej przez nikiel pozostaje niejasny i wymaga dalszych badań. W pracy omówiono najbardziej popularne hipotezy wyjaśniające to zjawisko.

Słowa kluczowe: nikiel, źródła niklu, ekspozycja, toksyczność, kancerogenność, człowiek.

INTRODUCTION

Nickel is the 28th element in the periodic table. It is a silver-white metal found in several oxidation states (ranging from -1 to +4), however, the +2 oxidation state [Ni(II)] is the most common in biological systems (DENKHAUS, SALNIKOW 2002). Nickel easily forms nickel-containing alloys, which have found an ever increasing use in modern technologies for over a hundred years now. Global input of nickel to the human environment is approximately 150 000 and 180 000 metric tonnes per year from natural and anthropogenic sources, respectively, including emissions from fossil fuel consumption, and the industrial production, use, and disposal of nickel compounds and alloys (KASPRZAK et al. 2003).

SOURCES OF NICKEL

Nickel is widely distributed in the environment, and can be found in air, water, and soil. Natural sources of atmospheric nickel include dusts from volcanic emissions and the weathering of rocks and soils. The level of nickel in ambient air is small (about 6-20 $ng \cdot m^{-3}$), but levels up to

150 ng Ni·m^{-3} could be present in air contaminated by anthropogenic sources. In water, nickel derives from biological cycles and solubilization of nickel compounds from soils, as well as from the sedimentation of nickel from the atmosphere. Uncontaminated water usually contain about 300 ng Ni·dm^{-3}. Farm soils contain approximately 3-1000 mg Ni·kg^{-1} soil, but the Ni concentration can reach up to 24 000-53 000 mg·kg^{-1} Ni in soil near metal refineries and in dried sludge, respectively. At pH<6.5, nickel compounds in soil are relatively soluble, whereas at pH>6.7, most nickel exists as insoluble hydroxides. Nickel salts of strong acids (chloride, nitrate, and sulfate) and organic acids are soluble in water whereas nickel salts of weak inorganic acids, as well as metallic nickel, nickel sulfides, and nickel oxides are poorly water-soluble (Barceloux 1999, Denkhaus, Salnikow 2002, Sutherland, Costa 2002).

The majority of nickel production is used for the creation of stainless steel, nickel alloys, and nickel cast iron that comprise objects, such as coins, electrical equipment, tools, machinery, armaments, jewelry, and household utensils. Nickel compounds are used also for electroplating, electroforming, nickel-cadmium alkaline batteries, dye mordant, catalysts, and electronic equipment. Nickel containing alloys include nickel plating of nonprecious metals, surgical steel (0.5-30% Ni), white gold (10-15% Ni), German silver (10-15% Ni), solders, hard-gold plating, and sterling silver. As the result of increasing consumption of nickel-containing products nickel compounds are released to the environment at all stages of production and utilization and may constitute a hazardous factor to human health (Barceloux 1999, Denkhaus, Salnikow 2002).

NICKEL EXPOSURE

Exposures by inhalation, ingestion or skin contact occur in nickel and nickel alloy production plants as well as in welding, electroplating, grinding and cutting operations. Airborne nickel levels in excess of 1 mg·m^{-3} have been found in nickel refining, in the production of nickel alloys and nickel salts, and in grinding and cutting of stainless-steel. Although in these industries, modern control technologies have markedly reduced exposures in recent years, several million workers worldwide are exposed to airborne nickel and its compounds (Kasprzak et al. 2003, Seilkop, Oller 2003).

Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake. Nonoccupational sources of nickel exposure include food, air and water, but the levels found are usually several orders of magnitude lower than those typically found in occupational situations.

Drinking water and food are the main sources of exposure for the general population. The maximum concentration of total nickel allowed by law in Poland in drinking water is 20 $\mu g \cdot dm^{-3}$ (Dz.U.07.61.417). Average concentrations of total nickel in drinking water ranges from 3-7 $\mu g \cdot dm^{-3}$, but it increases in vessels that contain corroded nickel plating. The first drawn water from hot water taps plated with nickel may contain concentrations of 1-1.3 mg $Ni \cdot dm^{-3}$ (Barceloux 1999). Moreover, some domestic appliances contain nickel alloys. Tests of kitchen kettles showed substantial leaching of nickel into water when boiled in kettles with exposed nickel-plated elements. The concentration of nickel in boiled water increased from 4.55 and 0.8 $\mu g \cdot dm^{-3}$ (unboiled hard and soft water) up to 244 and 51 $\mu g \cdot dm^{-3}$, respectively. When water was boiled in concealed element kettle, the concentrations of nickel were 5.23 and 1.9 $\mu g \cdot dm^{-3}$, respectively (Cot 2003). Most food contains below 0.5 mg $Ni \cdot kg^{-1}$ wet weight. Foodstuffs with high nickel contents are cocoa (up to 8.2-12 $mg \cdot kg^{-1}$ fresh wet weight), oatmeal, spinach, dry legumes, hazelnuts, dark chocolate, soya beans, and soya products (Sutherland, Costa 2002).

In vitro studies suggest that stainless steel endoprosthesis (14-36% nickel) may release nickel; however, the clinical significance of this amount of nickel remains to be determined. Also administration of nickel-contaminated medications (e.g., albumin, radiocontrast media, hemodialysis fluids) leads to significant exposures (McGregor et al. 2000, Kasprzak et al. 2003). The amount of nickel absorbed during medical procedures depends on the composition of the equipment in contact with the blood and body fluids. For example, the estimated uptake of nickel during a typical dialysis procedure in the 1980s was 100 mg Ni per treatment (Sunderman 1983).

NICKEL EFFECT ON HEALTH

Human exposure to highly nickel-polluted environments causes a variety of pathologic effects. The toxic effects of nickel on the lung were recognized first by Agricola in the 16th century. Some fatal cases were noted following exposure to nickel carbonyl, and by the early 1930s, nickel was a recognized cause of contact dermatitis. Elevated incidences of lung and nasal cancer in workers exposed to nickel were also observed (Sunderman et al. 1988, Seilkop, Oller 2003). In 2008, nickel received the shameful name of "Allergen of the Year" (Gillette 2008). According to the dermatologist the frequency of nickel allergy is still growing, and it can't be explained only by fashionable piercing and nickel devices used in medicine (like coronary stents and endoprostheses). All those observations caused that the interest in the nickel impact on human health increased (Sivulka 2005).

Like many environmental agents, the toxic effect of nickel is related to the way it gets into an organism. Nickel can enter body *via* inhalation, ingestion and dermal absorption, but the route by which nickel enters cells is determined by its chemical form. For example, fat soluble nickel carbonyl can cross cell membranes by diffusion or through calcium channels (CANGUL et al. 2002), while insoluble nickel particles enter the vertebrate cells by phagocytosis (HECK, COSTA 1982).

The main transport protein of nickel in blood is albumin, but nickel can bind also to histidine and α2-macroglobulin (GLENNON, SARKAR 1982, KASPRZAK et al. 2003), and in this form is distributed throughout the tissues. A number of nickel-binding proteins including α1-antitrypsin, α1-lipoprotein and prealbumin were also described (NIELSEN et al. 1994). The highest nickel concentrations are found in the bone, lung, kidney, liver, brain and endocrine glands. Nickel is also found in breast milk, saliva, nails and hair. Transplacental transfer of nickel has been demonstrated in rodents. Nickel does not accumulate in the body; it is excreted in the urine, feces, bile and sweat (VALKO et al. 2005).

Contact with nickel compounds can cause a variety of adverse effects on human health, such as nickel allergy in the form of contact dermatitis, lung fibrosis, cardiovascular and kidney diseases and cancer of the respiratory tract (OLLER et al. 1997, MCGREGOR et al. 2000, SEILKOP, OLLER 2003). Chronic noncancer health effects may result from long-term exposure to relatively low concentrations of pollutants. Acute health effects generally result from short-term exposure to high concentrations of pollutants and they manifest as a variety of clinical symptoms (nausea, vomiting, abdominal discomfort, diarrhea, visual disturbance, headache, giddiness, and cough).

The most common type of reaction to nickel exposure is a skin rash at the site of contact. Skin contact with metallic or soluble nickel compounds can produce allergic dermatitis. This health problem caused by exposure to nickel affects people both at and away from work. Data indicate that women have greater risk for dermatitis, possibly due to a more frequent contact with nickel-containing items: jewelry, buttons, watches, zippers, coins, certain shampoos and detergents, pigments etc. (VAHTER et al. 2002, SZCZEPANIAK, PROKOP 2004). About 10% of women and 2% of men in the population are highly sensitive to nickel. Sensitization to the metal is generally caused by direct and prolonged skin contact with items that release nickel ions.

In large doses (>0.5 g), some forms of nickel may be acutely toxic to humans when taken orally (DALDRUP et al. 1983, SUNDERMAN et al. 1988). The acute lethality of nickel following oral exposure is dependent on the chemical form of nickel. A fatal case of nickel poisoning was reported for a $2^1/_2$--year-old girl who had ingested 15 g of $NiSO_4$ (3.3 g elemental Ni) and died of a cardiac arrest (DALDRUP et al. 1983). Death due to nickel-induced Adult Respiratory Distress Syndrome was reported for a worker spraying nickel using a thermal arc process (RENDALL et al. 1994). Death occurred after

13 days, and a total nickel intake was estimated at nearly 1 g. Nausea, vomiting, abdominal, headache, cough, shortness of breath, and giddiness were reported for 32 workers of an electroplating plant who drank water contaminated with nickel chloride and nickel sulfate (1.63 $g \cdot dm^{-3}$) (SUNDERMAN et al. 1988). Some studies have also provided information indicating the deterioration of nickel-induced dermatitis for women following exposure to dietary nickel (ATSDR 1988, SUTHERLAND, COSTA 2002).

Only a small portion of nickel ingested is absorbed by the body. From nickel balance experiments, HORAK and SUNDERMAN (1972) have estimated that about 10% of the nickel in a normal diet is absorbed. Alternatively, other studies have shown that an average nickel resorption from a normal diet is between 20 and 25% (MYRON et al. 1978, FLYVHOLM et al. 1984). Adverse health effects after oral exposure occurred only when nickel levels exceed many times levels of the metal normally occurred in food or drinking water and are decidedly rare cases.

The most hazardous route of exposure to nickel is by inhalation (SUTHERLAND, COSTA 2002). The chemical form of the metal and its solubility is a key determining factor in the toxicity mechanisms. Water-soluble nickel compounds can be absorbed by the lungs into the bloodstream and removed by the kidneys. Insoluble nickel compounds, however, can build up and remain in the lungs for a longer time. Inhalation of soluble nickel causes irritation of the nose and sinuses and can also lead to loss of the sense of smell or perforation of the nasal septum. Long-term exposure may lead to asthma, bronchitis or other respiratory diseases. The most acute nickel poisoning is caused by $Ni(CO)_4$. Exposure to nickel carbonyl can cause headaches, nausea, vomiting, chest pain and breathing problems, in the case of high exposure it may even lead to pneumonia and death. Inhalation of nickel can also cause cancer of the lungs, nose and sinuses (ZHICHENG 1994). Cancers of the throat and stomach have also been attributed to inhalation of nickel. Nickel carbonyl and insoluble nickel compounds (Ni_3S_2, NiO) are the forms of nickel responsible for cancer. Epidemiological studies have demonstrated increased mortality from cancers of the lung and nasal cavities in nickel refinery workers who were chronically exposed by inhalation of nickel-containing dusts and fumes (SEILKOP, OLLER 2003).

Nickel subsulphide (Ni_3S_2) is a well-known respiratory carcinogen. When it is inhaled, particles of Ni_3S_2 lodge themselves deep in the lungs, where they reside in contact as a solid with epithelial cells. These particles are cleared by macrophage cells, which remove them through the digestive tract. Under a condition of high exposure, the macrophage capacity for removal could be perturbed and Ni_3S_2 particles may be taken into epithelial cells by endocytosis. In this way nickel is delivered to the nucleus of lung epithelial cells and can cause a heritable change in chromosomes. It was also demonstrated that Ni_3S_2 induced lesions of both double- and single-stranded DNA in human cells; Ni_3S_2 treatment of cultured HeLa cells induced a 1.5-fold

increase in 8-hydroxy-2'-deoxyguanosine compared with a control (KAWANISHI et al. 2001).

When mice were orally administered acute doses of $NiCl_2$ (from 3.4 to 108.8 $mg \cdot kg^{-1}$ body weight), a significant dose-dependent increase in DNA damage was observed in comparison with controls (DANADEVI et al. 2004). The results of research by CAVALLO et al. (2003) confirm involvement of nickel ($NiSO_4$) in production of reactive oxygen metabolites and in inhibition of DNA repair at doses comparable to environmental exposures such as concentrations found in biological fluids. It was demonstrated that some nickel complexes such as $[NiCR]^{2+}$ and $[Ni(CR\text{-}2H)]^{2+}$ bind to the minor groove of double-stranded DNA (MATKAR et al. 2006). Moreover, macrocyclic nickel complex $[Ni(CR\text{-}2H)]^{2+}$ can damage DNA *in vivo* and *in vitro* even in the absence of oxidizing agents. This activity leads to DNA strand breaks and *in vivo* cytotoxicity. Nuclear nickel may be also involved in production of oxygen radicals ($^{\bullet}OH$, H_2O_2) which could damage DNA. CHEN et al. (2003) showed that the level of hydroxyl radical in the Ni-treated group was much higher than in control. Moreover, nickel has been also shown to inhibit DNA repair in a way that may play a role in its toxicity. It has been proposed that nickel may bind to DNA-repair enzymes and generate oxygen-free radicals which cause *in situ* protein degradation. This irreversible damage to the proteins involved in DNA repair, replication, recombination, and transcription could be important for the toxic effects of nickel (LYNN et al. 1997). It happens especially when such DNA is associated with tumor suppression genes; under this condition, cancer cells could replicate at a high rate, thus reducing the time available for repair of the DNA damages (SUTHERLAND, COSTA 2002).

Often co-exposure to a second carcinogen caused a synergistic cancer increase. For example, intramuscular injection of nickel sulfide with 3,4-benzopyrene in rats produced more sarcomas in shorter time than with nickel sulfide alone (MAENZA et al. 1971). When the transforming potential of soluble nickel(II) was compared with such potential of other carcinogens, the efficiency of immortalization by nickel(II) was found to be higher than that by other carcinogens, including benzo[a]pyrene, diol epoxide, N-methyl-N-nitrosourea or, g or X-rays (TROTT et al. 1995).

It was also found that nickel(II) chloride with a classical carcinogen, such as UV radiation (UVR) had synergistic effect on skin cancer induction in Skh1 hairless mice (UDDIN et al. 2007). Mice drinking water containing Ni had significantly higher skin concentration of nickel compared with mice having no nickel in water. It was shown that co-carcinogenic effect of oral nickel with UVR as a matter of cancer yield and incidence was directly correlated with nickel concentration in the skin. Since humans are exposed to both UVR from sunlight and to nickel *via* environmental exposure, there is a potential co-carcinogenic hazard posed by environmental metals (arsenic, chromium, nickel) with UVR, which may be more serious than the hazard of the metals alone (UDDIN et al. 2007).

Some studies have also revealed that compounds of the essential metals: Mn(II), Mg(II) and Zn(II) given to rats with Ni_3S_2, significantly reduced local tumor incidence in a dose dependent manner. Mg(II) was the strongest and Zn(II) was the weakest inhibitor (KASPRZAK et al. 2003).

MOLECULAR MECHANISMS OF NICKEL CARCINOGENESIS

According to the IARC evaluation (IARC 1997) there are sufficient evidences in humans for the carcinogenicity of nickel sulfate and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry. Hence, they can be classified in Group 1, i.e. cancerogenic to humans. As there is inadequate evidence in humans for the carcinogenicity of metallic nickel, it may be carcinogenic to humans (Group 2B).

The mechanism by which nickel causes cancer is still questionable and needs further investigation. Exposure of cells to the metal induces a variety of gene expression changes.

Nickel is known to be a calcium channel blocker (ZAMPONI et al. 1996), and several studies related toxic and carcinogenic effect of nickel with changes in calcium metabolism. It has been suggested also that high levels of nickel may impair absorption or utilization of iron when iron status is low.

It was revealed that acute treatment of rodent cells with nickel is very efficient at turning off the expression of thrombospondin I (TSP I) (SALNIKOW et al. 1994, SALNIKOW et al. 1997). The TSP protein is a regulator of tumor development; high level of TSP suppresses growth of blood vessels into the tumor body. It was shown, that ATF-1 transcription factor is hyperactivated in nickel-transformed cells and plays the role of a negative regulator of thrombospondin I. Therefore, the loss of TSP I expression in tumors promotes angiogenesis and stimulates tumor growth. Another transcription factor, which level was found to be increased after acute exposure to nickel, is hypoxia-inducible factor 1 (HIF-1) (SALNIKOW et al. 2002). During tumor development, HIF-1 facilitates angiogenesis that is essential for tumor growth. Like hypoxia, Ni(II) induces HIF-1 and therefore activates genes responsible for the up-regulation of glucose metabolism and glycolysis even in the presence of oxygen, the vascular endothelial growth factor, and the tumor marker *Cap43* (ZHOU et al. 1998, SALNIKOW et al. 2000).

Nickel is also known to cause inflammatory response for example through regulation of expression of transcription factors involved in inflammatory processes. It was shown that activation of NF-κB by nickel causes modulation of cellular and tissue responses, and can explain nickel-induced allergic effects and contact skin hypersensitivity (VIEMANN et al. 2007). NF-κB is a transcription factor important for apoptosis, inflammatory

response, and expression of adhesion molecules. Intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1 were found to be up-regulated by Ni(II) in cultured human endothelial cells (GOEBELER et al. 1993). A strong increase of NF-κB binding with DNA was found after stimulation of HUVEC with Ni(II) (GOEBELER et al. 1995, DENKHAUS, SALNIKOW 2002, KASPRZAK et al. 2003).

There is also a possibility of involvement of *p*53 gene mutations in nickel-induced transformation (DENKHAUS, SALNIKOW 2002). *P*53 is a tumor suppressor gene and transcription factor involved in the regulation of cell proliferation and apoptosis. Mutations in *p*53 are the most common genetic alterations found in human cancer. The *p*53 gene was reported to be mutated in human kidney epithelial cells chronically exposed to and eventually transformed by nickel (MAEHLE et al. 1992).

The *FHIT* (Fragile Histidine Triad) is a tumor suppressor gene located in a fragile chromosomal site sensitive to deletions. Its expression is frequently reduced or lost in tumors and pre-malignant lesions. The product of the gene, Fhit protein (phosphohydrolase), induces apoptosis through a complex interaction with its substrate, diadenosine triphosphate. Ni(II) was found to strongly inhibit the enzymatic activity of Fhit protein *in vitro* and also suppress Fhit expression in nickel-transformed BALB/c-3T3 cells (KOWARA et al. 2004).

In another study, nickel chloride was found to induce lipid peroxidation in the plasma of human blood *in vitro* in a concentration-dependent and time-dependent manner. The hydroxyl radical production increased in a concentration-dependent manner after Ni treatment for 1 h. Furthermore, a decreasing trend in a-tocopherol levels in plasma was observed after nickel exposure. Incubation with gluthathione, catechin, and mannitol decreased lipid peroxidation and reduced hydroxyl radical formation induced by Ni, but a greater decrease of a-tocopherol levels in plasma occurred with catechin (CHEN et al. 2002).

Further progress in understanding molecular mechanisms of nickel carcinogenicity has been achieved by the finding that nickel compounds increase the extent of DNA methylation and histone deacetylation, which leads to the inactivation of gene expression. Although the mechanisms by which nickel induces DNA hypermethylation are unknown, a possible model including the ability of nickel to substitute for magnesium, increase chromatin condensation and trigger *de novo* DNA methylation has been proposed (LEE et al. 1995). It is possible that inactivation of tumor suppressor gene by hypermethylation could assist in nickel-induced cell transformation. In addition to gene silencing by hypermethylation, a suppressive effect of nickel on histone H4 acetylation *in vitro* has been reported for both yeast and mammalian cells (BRODAY et al. 2000). Despite numerous reports of the DNA and chromatin damage observed in nickel-exposed cells and tissues, the mutagenic potential of this metal is generally considered to be low (FLETCHER et al. 1994).

CONCLUSIONS

Nickel is a ubiquitous metal, which finds increasingly more applications in modern technologies. Contact with nickel compounds (both soluble and insoluble) can cause a variety of adverse effects on human health. The most important and frequent are nickel allergy in the form of contact dermatitis, lung fibrosis, cardiovascular and kidney diseases, and lung and nasal cancers. There is evidence that some nickel compounds are carcinogens to humans. However, the exact mechanism of nickel-induced carcinogenesis is still unclear.

In 2008, nickel received the name of the "Allergen of the Year". According to dermatologists the frequency of nickel allergies is still growing and all the sources of human exposure to nickel should be recognized and examined.

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1988. *Toxicological profile for nickel*. ATSDR/U.S. Public Health Service, ATSDR/TP-88/19.

Barceloux D.G. 1999. *Nickel*. Clin. Toxicol., 37(2): 239-258.

Broday L., Peng W., Kuo M.H., Salnikow K., Zoroddu M., Costa M. 2000. *Nickel compounds are novel inhibitors of histone H4 acetylation*. Cancer Res., 60: 238-241.

Cangul H., Broday L., Salnikow K., Sutherland J., Peng W., Zhang Q., Poltaratsky V., Yee H., Zoroddu M.A., Costa M. 2002. *Molecular mechanisms of nickel carcinogenesis*. Toxicol. Lett., 127: 69-75.

Cavallo D., Ursini C.L., Setini A., Chianese C., Piegari P., Perniconi B., Iavicoli S. 2003. *Evaluation of oxidative damage and inhibition of DNA repair in an in vitro study of nickel exposure*. Toxicol. in Vitro, 17: 603-607.

Chen C.Y., Su Y.J., Wu P.F., Shyu M.M. 2002. *Nickel-induced plasma lipid peroxidation and effect of antioxidants in human blood: involvement hydroxyl radical formation and depletion of alpha-tocopherol*. J. Toxicol. Environ. Health A, 65(12): 843-852.

Chen C.Y., Wang Y.F., Lin Y.H., Yen S.F. 2003. *Nickel-induced oxidative stress and effect of antioxidants in human lymphocytes*. Arch. Toxicol., 77: 123-130.

COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment). 2003. *Nickel leaching from kettle elements into boiled water*. Annex A TOX/2003/02, 3-11 (available on-line: http://www.food.gov.uk/multimedia/pdfs/2003-02.pdf)

Daldrup T., Haarhoff K., Szathmary S.C. 1983. *Toedliche nickel sulfate-intoxikation*. Berichte zur Gerichtlichen Medizin, 41:141-144.

Danadevi K., Rozatia R., Saleha Banu B., Grover P. 2004. *In vivo genotoxic effect of nickel chloride in mice leukocytes using comet assay*. Food Chem. Toxicol., 42: 751-757.

Denkhaus E., Salnikow K. 2002. *Nickel essentiality, toxicity, and carcinogenicity*. Crit. Rev. Oncol./Hematol., 42: 35-56.

Fletcher G.G., Rossetto F.E., Turnbull J.D., Nieboer E. 1994. *Toxicity, uptake, and mutagenicity of particulate and soluble nickel compounds*. Environ. Health Perspect., 102: 69-79.

FLYVHOLM M.A., NIELSON G.D., ANDERSON A. 1984. *Nickel content of food and estimation of dietary intake.* Z. Lebensm. Unters. Forsch., 179: 427-31.

GILLETTE B. 2008. *Nickel named «Allergen of the Year». ACDS adds to list of substances warranting more attention*. Dermat. Times, 4: 15-16.

GLENNON J.D., SARKAR B. 1982. *Nickel(II) transport in human blood serum: studies of nickel(II)-binding human albumin and to native-sequence peptide, and ternary complex formation with L-histidine*. Biochem. J., 203: 15-23.

GOEBELER M., MEINARDUS-HAGER G., ROTH J., GOERDT S., SORG C. 1993. *Nickel chloride and cobalt chloride, two common contact sensitizers, directly induce expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule (ELAM-1) by endothelial cells.* J. Invest. Dermatol., 100: 759-765.

GOEBELER M., ROTH J., BROCKER E.B., SORG C., SCHULZE-OSTHOFF K. 1995. *Activation of nuclear factor-kappa B and gene expression in human endothelial cells by the common haptens nickel and cobalt*. J. Immunol., 155: 2459-2467.

HECK J.D., COSTA M. 1982. *Surface reduction of amorphous NiS particles potentiates their phagocytosis and subsequent induction of morphological transformation in Syrian hamster embryo cells.* Cancer Lett., 15: 19-26.

HORAK S.E., SUNDERMAN F.W. JR. 1972. *Fecal nickel excretion by healthy adults*. Clin. Chem., 19: 429–30.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 1997. *Chromium, nickel and welding*, World Health Organization International Agency for Research on Cancer, vol 49.

KASPRZAK K.S., SUNDERMAN JR. F.W., SALNIKOW K. 2003. *Nickel carcinogenesis*. Mutat. Res., 533: 67-97.

KAWANISHI S., INOUE S., OIKAWA S., YAMASHITA N., TOYOKUNI S., KAWANISHI M., NISHINO K. 2001. *Oxidative DNA damage in cultured cells and rat lungs by carcinogenic nickel compounds*. Free Radic. Biol. Med., 31: 108-116.

KOWARA R., SALNIKOW K., DIWAN B.A., BARE R.M., WAALKES M.P., KASPRZAK K.S. 2004. *Reduced Fhit protein expression in nickel-transformed mouse cells and in nickel-induced murine sarcomas*. Mol. Cell. Biochem., 255: 195-202.

LEE Y-W., KLEIN C.B., KARGACIN B., SALNIKOW K., KITAHARA J., DOWJAT K., ZHITKOVICH A., CHRISTIE N.T., COSTA M. 1995. *Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: a new model for epigenetic carcinogens*. Mol. Cell. Biol., 15: 2547-2557.

LYNN S., YEW F.H., CHEN K.S., JAN K.Y. 1997. *Reactive oxygen species are involved in nickel inhibition of DNA repair*. Environ. Mol. Mutagen., 29: 208-216.

MAEHLE L., METCALF R.A., RYBERG D., BENNETT W.P., HARRIS C.C., HAUGEN A. 1992. *Altered p53 gene structure and expression in human epithelial cells after exposure to nickel*. Cancer Res., 52: 218-21.

MAENZA R.M., PRADHAN A.M., SUNDERMAN F.W. JR. 1971. *Rapid induction of sarcomas in rats by combination of nickel sulfide and 3,4-benzpyrene.* Cancer Res., 31: 2067-71.

MATKAR S.S., WRISCHNIK L.A., JONES P.R., HELLMANN-BLUMBERG U. 2006. *Two closely related nickel complexes have different effects on DNA damage and cell viability*. Bioch. Biophys. Res. Commun., 343: 754-761.

MCGREGOR D.B., BAAN R.A., PARTENSKY C., RICE J.M., WILBOURN J.D. 2000. *Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies – a report of an IARC Monographs Programme Meeting*. Eur. J. Cancer., 36: 307-313.

MYRON D.R., ZIMMERMANN T.J., SHULER T.R. 1978. *Intake of nickel and vanadium by humans*. Am. J. Clin. Nutr., 31: 527-31.

NIELSEN J.L., POULSEN O.M., ABILDTRUP A. 1994. *Studies of serum protein complexes with nickel using crossed immunoelectrophoresis*. Electrophoresis, 15: 666-71.

OLLER A.R., COSTA M., OBERDÖRSTER G. 1997. *Carcinogenicity assessment of selected nickel compounds*. Toxicol. Appl. Pharmacol., 143: 152-166.

RENDALL R.E.G., PHILLIPS J.I., RENTON K.A. 1994. *Death following exposure to fine particulate nickel from a metal arc process*. Ann. Occup. Hyg., 38: 921-930.

Rozporządzenie Ministra Zdrowia z dnia 29 marca 2007 r. w sprawie jakości wody przeznaczonej do spożycia przez ludzi. Dz.U.07.61.417

SALNIKOW K., COSENTINO S., KLEIN C., COSTA M. 1994. *Loss of thrombospondin transcriptional activity in nickel-transformed cells*. Mol. Cell. Biol., 14: 851-858.

SALNIKOW K., DAVIDSON T., COSTA M. 2002. *The role of hypoxia-inducible signaling pathway in nickel carcinogenesis*. Environ. Health Perspect., 110(suppl. 5): 831-834.

SALNIKOW K., SU W., BLAGOSKLONNY M.V., COSTA M. 2000. *Carcinogenic metals induce hypoxia-inducible factor-stimulated transcription by reactive oxygen species-independent mechanism*. Cancer Res., 60: 3375-3388.

SALNIKOW K., WANG S., COSTA M. 1997. *Induction of activating transcription factor 1 by nickel and its role as a negative regulator of thrombospondin I gene expression*. Cancer Res., 57: 5060-5066.

SEILKOP S.K., OLLER A.R. 2003. *Respiratory cancer risks associated with low-level nickel exposure: an integrated assessment based on animal, epidemiological, and mechanistic data*. Regul. Toxicol. Pharmacol., 37: 173-190

SIVULKA D.J. 2005. *Assessment of respiratory carcinogenicity associated with exposure to metallic nickel: A review*. Regul. Toxicol. Pharmacol., 43: 117-133.

SUNDERMAN F.W. JR. 1983. *Potential toxicity from nickel contamination of intravenous fluids.* Ann Clin. Lab. Sci., 13: 1–4.

SUNDERMAN F.W. JR., DINGLE B., HOPFER S.M., SWIFT T. 1988. *Acute nickel toxicity in electroplating workers who accidentally ingested a solution of nickel sulfate and nickel chloride*. Am. J. Indust. Med., 14: 257-266.

SUTHERLAND J.E., COSTA M. 2002 *Nickel.* In: *Heavy metals in the environment* Ed. B. SARKAR, Marcel Decker Inc., New York.

SZCZEPANIAK E., PROKOP J. 2004. *Wyprysk kontaktowy*. Post. Dermatol. Alergol., 21(4): 205-210.

TROTT D.A., CUTHBERT A.P., OVERELL R.W., RUSSO I., NEWBOLD R.F. 1995. *Mechanisms involved in the immortalization of mammalian cells by ionizing radiation and chemical carcinogens.* Carcinogenesis, 16(2): 193-204.

UDDIN A.N., BURNS F.J., ROSSMAN T.G., CHEN H., KLUZ T., COSTA M. 2007. *Dietary chromium and nickel enhance UV-carcinogenesis in skin of hairless mice.* Toxicol. Appl. Pharmacol., 221: 329-338.

VAHTER M., BERGLUND M., ÍKESSON A., LIDÉN C. 2002. *Metals and women's health.* Environ. Res., 88: 145-155.

VALKO M., MORRIS H., CRONIN M.T.D. 2005. *Metals, toxicity and oxidative stress*. Curr. Med. Chem., 12: 1161-1208.

VIEMANN D., SCHMIDT M., TENBROCK K., SCHMID S., MÜLLER V., KLIMMEK K., LUDWIG S., ROTH J., GOEBELER M. 2007. *The contact allergen nickel triggers a unique inflammatory and proangiogenic gene expression pattern via activation of NF-kappaB and hypoxia-inducible factor-1alpha*. J. Immunol., 178: 3198-3207.

ZAMPONI G.W., BOURINET E., SNUTCH T.P. 1996. *Nickel block of a family of neuronal calcium channels: Subtype- and subunit-dependent action at multiple sites*. J. Membr. Biol., 151(1): 77-90.

ZHICHENG S. 1994. *Nickel carbonyl: Toxicity and human health*. Sci. Total Environ., 148: 293-298

ZHOU D., SALNIKOW K., COSTA M. 1998. *Cap43, a novel gene specifically induced by Ni^{2+} compounds*. Cancer Res., 58: 2182-2189.

Reviewers of the Journal of Elementology Vol. 13(4), Y. 2008

Izabela Bojakowska, Wojciech Budzyński, Grażyna Ciepiela, Zbigniew Endler, Witold Grzebisz, Kazimierz Jankowski, Krzysztof Jankowski, Stanisław Kalembasa, Mikołaj Knaflewski, Jan Krzymański, Jan Kucharski, Edward Niedźwiecki, Roman Niżnikowski, Lech Smoczyński, Zofia Spiak, Wojciech Tyksiński, Lech Walasek, Jadwiga Wierzbowska, Barbara Wiśniowska-Kielian, Jadwiga Wyszkowska

Regulamin ogłaszania prac w „Journal of Elementology"

1. Journal of Elementology (kwartalnik) zamieszcza na swych łamach prace oryginalne, doświadczalne, kliniczne i przeglądowe z zakresu przemian biopierwiastków i dziedzin pokrewnych.
2. W JE mogą być zamieszczone artykuły sponsorowane, przygotowane zgodnie z wymaganiami stawianymi pracom naukowym.
3. W JE zamieszczamy materiały reklamowe.
4. Materiały do wydawnictwa należy przesłać w 2 egzemplarzach. Objętość pracy oryginalnej nie powinna przekraczać 10 stron znormalizowanego maszynopisu (18 000 znaków), a przeglądowej 15 stron (27 000 znaków).
5. Układ pracy: **TYTUŁ PRACY**, ***imię i nazwisko autora (-ów)*, nazwa jednostki, z której pochodzi praca, WSTĘP, MATERIAŁ I METODY, WYNIKI I ICH OMÓWIENIE, WNIOSKI, PIŚMIENNICTWO,** streszczenie w języku polskim i angielskim – minimum 250 słów. Streszczenie powinno zawierać: wstęp (krótko), cel badań, omówienie wyników, wnioski. Przed streszczeniem w języku polskim: ***imię i nazwisko Autora (-ów),* TYTUŁ PRACY,** Słowa kluczowe (maks. 10 słów), Abstrakt, **TYTUŁ ANGIELSKI,** Key words, Abstract. U dołu pierwszej strony należy podać tytuł naukowy lub zawodowy, imię i nazwisko autora oraz dokładny adres przeznaczony do korespondencji w języku polskim i angielskim.
6. Praca powinna być przygotowana wg zasad pisowni polskiej. Jednostki miar należy podawać wg układu SI np.: $mmol(+) \cdot kg^{-1}$; $kg \cdot ha^{-1}$; $mol \cdot dm^{-3}$; $g \cdot kg^{-1}$; $mg \cdot kg^{-1}$ (obowiązują formy pierwiastkowe).
7. W przypadku stosowania skrótu po raz pierwszy, należy podać go w nawiasie po pełnej nazwie.
8. Tabele i rysunki należy załączyć w oddzielnych plikach. U góry, po prawej stronie tabeli, należy napisać Tabela i numer cyfrą arabską, również w języku angielskim, następnie tytuł tabeli w języku polskim i angielskim wyrównany do środka akapitu. Ewentualne objaśnienia pod tabelą oraz opisy tabel powinny być podane w języku polskim i angielskim. Wartości liczbowe powinny być podane jako zapis złożony z 5 znaków pisarskich (np. 346,5; 46,53; 6,534; 0,653).
9. U dołu rysunku, po lewej stronie, należy napisać Rys. i numer cyfrą arabską oraz umieścić podpisy i ewentualne objaśnienia w języku polskim i angielskim.
10. Piśmiennictwo należy uszeregować alfabetycznie, bez numerowania, w układzie: Nazwisko Inicjał Imienia (kapitaliki) rok wydania. Tytuł pracy (kursywa). Obowiązujący skrót czasopisma, tom (zeszyt): strony od-do. np. Kowalska A., Kowalski J. 2002. *Zwartość magnezu w ziemniakach*. Przem. Spoż., 7(3): 23-27.
11. W JE można także cytować prace zamieszczone w czasopismach elektronicznych, wg schematu: Nazwisko Inicjał Imienia (kapitaliki) rok wydania. Tytuł pracy (kursywa). Obowiązujący skrót czasopisma internetowego oraz pełny adres strony internetowej. np. Antonkiewicz J., Jasiewicz C. 2002. *The use of plants accumulating heavy metals for detoxication of chemically polluted soils*. Electr. J. Pol. Agric. Univ., 5(1): 1-13. hyperlink „http://www" http://www.ejpau.media.pl/series/volume5/issue1/environment/art-01.html
12. Cytując piśmiennictwo w tekście, podajemy w nawiasie nazwisko autora i rok wydania pracy (Kowalski 1992). W przypadku cytowania dwóch autorów, piszemy ich nazwiska rozdzielone przecinkiem i rok (Kowalski, Kowalska 1993). Jeżeli występuje większa liczba nazwisk, podajemy pierwszego autora z dodatkiem i in., np.: (Kowalski i in. 1994). Cytując jednocześnie kilka pozycji, należy je uszeregować od najstarszej do najnowszej, np.: (Nowak 1978, Nowak i in. 1990, Nowak, Kowalska 2001).
13. Do artykułu należy dołączyć pismo przewodnie kierownika Zakładu z jego zgodą na druk oraz oświadczenie Autora (-ów), że praca nie została i nie zostanie opublikowana w innym czasopiśmie bez zgody Redakcji JE.
14. Dwie kopie wydruku komputerowego pracy (Times New Roman 12 pkt, z odstępem akapitu 1,5, bez dyskietki) należy przesłać na adres Sekretarzy Redakcji:

dr hab. Jadwiga Wierzbowska
Uniwersytet Warmińsko-Mazurski w Olsztynie
ul. Michała Oczapowskiego 8, 10-719 Olsztyn
jawierz@uwm.edu.pl
dr Katarzyna Glińska-Lewczuk
Uniwersytet Warmińsko-Mazurski w Olsztynie
pl. Łódzki 2, 10-759 Olsztyn
kaga@uwm.edu.pl

15. Redakcja zastrzega sobie prawo dokonywania poprawek i skrótów. Wszelkie zasadnicze zmiany tekstu będą uzgadniane z Autorami.
16. Po recenzji Autor zobowiązany jest przesłać w 2 egzemplarzach poprawiony artykuł wraz z dyskietką, przygotowany w dowolnym edytorze tekstu pracującym w środowisku Windows.

Redakcja Journal of Elementology uprzejmie informuje, iż w 2006 r. wprowadziła opłatę za druk prac.

Koszt wydrukowania maszynopisu (wraz z rysunkami, fotografiami i tabelami) o objętości nieprzekraczającej 6 stron formatu A4, sporządzonego wg następujących zasad:

– czcionka: Times New Roman, 12 pkt, odstęp 1,5;
– 34 wiersze na 1 stronie;
– ok. 2400 znaków (bez spacji) na 1 stronie;
– rysunki i fotografie czarno-białe

wynosi 250 PLN + VAT.

Koszt druku każdej dodatkowej strony (wraz z rysunkami, fotografiami i tabelami) wynosi 35 PLN + VAT. Koszt druku 1 rysunku lub fotografii w kolorze wynosi 150 PLN + + VAT.

Uwaga:

Z opłaty za druk pracy są zwolnieni lekarze nie zatrudnieni w instytutach naukowych, wyższych uczelniach i innych placówkach badawczych.

Komitet Redakcyjny

Guidelines for Authors „Journal of Elementology"

1. Journal of Elementology (a quarterly) publishes original scientific or clinical research as well as reviews concerning bioelements and related issues.
2. Journal of Elementology can publish sponsored articles, compliant with the criteria binding scientific papers.
3. Journal of Elementology publishes advertisements.
4. Each article should be submitted in duplicate. An original paper should not exceed 10 standard pages (18 000 signs). A review paper should not exceed 15 pages (27 000 signs).
5. The paper should be laid out as follows: **TITLE OF THE ARTICLE**, ***name and surname of the author(s)***, **the name of the scientific entity, from which the paper originates**, **INTRODUCTION**, **MAETRIAL AND METHODS**, **RESULTS AND DISCUSSION**, **CONCLUSIONS**, **REFERENCES**, abstract in the English and Polish languages, min. 250 words. Summary should contain: introduction (shortly), aim, results and conclusions. Prior to the abstract in the English language the following should be given: ***name and surname of the author(s)***, **TITLE,** Key words (max 10 words), Abstract, **TITLE**, Key words and Abstract in Polish. At the bottom of page one the following should be given: scientific or professional title of the author, name and surname of the author, detailed address for correspondence in the English and Polish languages.
6. The paper should be prepared according to the linguistic norms of the Polish and English language. Units of measurements should be given in the SI units, for example $mmol(+)\cdot kg^{-1}$; $kg\cdot ha^{-1}$; $mol\cdot dm^{-3}$; $g\cdot kg^{-1}$; $mg\cdot kg^{-1}$ (elemental forms should be used).
7. In the event of using an abbreviation, it should first be given in brackets after the full name.
8. Tables and figures should be attached as separate files. At the top, to the right of a table the following should be written: Table and table number in Arabic figures (in English and Polish), in the next lines the title of the table in English and Polish adjusted to the centre of the paragraph. Any possible explanation of the designations placed under the table as well as a description of the table should be given in English and Polish. Numerical values should consist of five signs (e.g. 346.5, 46.53, 6.534, 0.653).
9. Under a figure, on the left-hand side, the following should be written: Fig. and number in Arabic figures, description and possible explanation in Polish and English.
10. References should be ordered alphabetically but not numbered. They should be formatted as follows: Surname First Name Initial (capital letter) year of publication, Title of the paper (italics). The official abbreviated title of the journal, volume (issue): pages from - to. e.g. Kowalska A., Kowalski J. 2002. *Zawartość magnezu w ziemniakach.* Przem. Spoż., 7(3): 23-27.
11. It is allowed to cite papers published in electronic journals formatted as follows: Surname First Name Initial (capital letters) year of publication. Title of the paper (italics). The official abbreviated title of the electronic journal and full address of the website. e.g. Antonkiewicz J., Jasiewicz C. 2002. *The use of plants accumulating heavy metals for detoxication of chemically polluted soils*. Electr. J. Pol. Agric. Univ., 5(1): 1-13. hyperlink „http://www.ejpau.pl/series/volume5/issue1/environment/art-01.html" http://www.ejpau.pl/series/volume5/issue1/environment/art-01.html
12. In the text of the paper a reference should be quoted as follows: the author's name and year of publication in brackets, e.g. (Kowalski 1992). When citing two authors, their surnames should be separated with a comma, e.g. (Kowalski, Kowalska 1993). If there are more than two authors, the first author's name should be given followed by et al., e.g. (Kowalski et al. 1994). When citing several papers, these should be ordered chronologically from the oldest to the most recent one, e.g. (Nowak 1978, Nowak et al. 1990, Nowak, Kowalska 2001).

13. A paper submitted for publication should be accompanied by a cover letter from the head of the respective institute who agrees for the publication of the paper and a statement by the author(s) confirming that the paper has not been and will not be published elsewhere without consent of the Editors of the Journal of Elementology.
14. Two computer printed copies of the manuscript (Times New Roman 12 fonts, 1.5-spaced, without a diskette) should be submitted to the Editor's Secretary:

dr hab. Jadwiga Wierzbowska
University of Warmia and Mazury in Olsztyn
ul. Michała Oczapowskiego 8, 10-719 Olsztyn
jawierz@uwm.edu.pl

dr Katarzyna Glińska-Lewczuk
University of Warmia and Mazury in Olsztyn
pl. Łódzki 2, 10-759 Olsztyn, Poland
kaga@uwm.edu.pl

15. The Editors reserve the right to correct and shorten the paper. Any major changes in the text will be discussed with the Author(s).
16. After the paper has been reviewed and accepted for publication, the Author is obliged to sent the corrected version of the article together with the diskette. The electronic version can be prepared in any word editor which is compatible with Windows software.