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NICKEL ESSENTIALITY, TOXICITY AND THE MECHANISM OF TOXICITY IN ANIMAL

RAJ NARAYAN ROY*

Department of Botany, Dr. B.N. Dutta Smriti Mahavidyalaya, Hatgobindapur, Purba-Bardman 713 407, West Bengal, India

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ABSTRACT

Nickel is one of the prevalent heavy metal pollutants. The sources of this pollutant are both natural as well as anthropogenic. The ongoing increase of the modern technology is gradually increasing the demand for nickel-containing product. The use of nickel in modern technology is gradually increasing that result in hastened consumption of nickel-containing product. Nickel compounds contaminate our environment during its manufacturing as well as its usage. Their rapid accumulation in different locations of the earth is hazardous. Human society is ultimate facing various adverse effects of nickel toxicity along with all other creatures on the earth. Though, as a micronutrient nickel is important for normal functioning of the animal system but at the elevated concentrations it causes various adverse effects. Through this review article efforts are being made for an analysis of the existing situation related to essentiality, effect and mechanism of nickel toxicity on animals. The investigation at the current scenario is extremely crucial for the realization of the extent of the crisis linked to nickel as an environmental toxicant to accelerate awareness and search for remedy.

KEY WORDS : Micronutrient, Environmental hazard, Heavy metal, Allergen, Animal

INTRODUCTION

Nickel, the silver-white heavy metal can exist in different oxidation states. However, the predominant oxidation state available at nature is Ni(II), the +2 valence state. The other valences (-1, +1, +3, and +4) are available in less frequently. Nickel is a silver-white metal available in different oxidation states (from -1 to +4), though the primarily available form in the biological system is [Ni(II)], +2 oxidation state (Coogan *et al.,* 1989). Natural sources of nickel include wind-blown grime from the process of weathering of rocks and soils, volcanic emanations, fires on forest and vegetation. However, nickel also release to environment due to the burning of coal and fuel oil, waste and sewage, and miscellaneous sources (Grandjean, 1984). The hassle less availability of a variety of nickel alloys rapidly accelerating it use in modern technologies. At present nickel is widely used in stainless steel, alloys of nickel and nickel cast iron together with objects including electrical equipment, artillery, machinery, tools, ornaments and domestic utensils. The nickel is also used for electroplating, electroforming, mordant of dye, batteries of nickel-cadmium alkaline, catalysts electronic equipment and other varied sources together with cement manufacture as well (Duda-Chodak and Blaszczyk, 2008). The advancement of the technology assures improved living standard but invites different defies on environmental security. Limitless industrialization along with urbanization without sufficient emission control as well as pollution diminution has thrust our lives to the threat. The inflowing of nickel in the human environment from natural and anthropogenic sources globally amounts around 150 000 and 180 000 metric tons respectively annually (Kasprzak *et al.,* 2003). Underdeveloped economic condition of the developing countries encourage them to bypass the guidelines related to environmental protection (Ikhuoria and Okieimen 2000; Sahu and Arora, 2008). To get the way of

remedy of nickel toxicity at this crucial moment it is necessary to have aneloquent idea on the nature and magnetite of toxicity on the living kingdom. Thisreview article will be helpful to create adequate awareness leading to find the way for its proper remedy that we have to come across.

Essentiality of Nickel in animal

Nickel is an essential trace element for the animal including human (Wintz *et al.,* 2002; Cempel and Nikel, 2006). The insufficiency of nickel is linked with the histological and biochemical changes as well as reduced iron reabsorption and interaction with haeme iron leads to anemia. It can perturb the absorption of calcium into skeleton resulting in parakeratosis-like damage (Anke *et al.,* 1984). King *et al.* (1985) are of opinion that nickel might provide as a cofactor for the activation of calcineurin, a calmodulin-dependent phosphoprotein phosphatase. The essential role of nickel ions consists of the action or the formation of cGMP, a signaling agent responsible for the regulation of various physiological processes. Among these, blood pressure control, sodium metabolism, cardiovascular health and sperm physiology are noteworthy.

Nickel is consistently exists in RNA and is linked to several biological components such as proteins (insulin, keratin), amino acids and serum albumin (Yokoi *et al.,* 2002). Insufficiency of nickel may lead to disturbing in the transmission of the genetic code. Insufficiency of nickel also hinders the growth, decrease reproductive rates and change the metabolism of glucose and lipid that are linked to anemia, hemoglobin reduction, alternations of metal ion contents, and reduced efficiency of several enzymes (Samal and Mishra, 2011). In the course of nerve transmission, muscle excitation and contraction, nickel can alternate for calcium (Howard, 2003).

It exists in the human being as well as rabbit serum in three forms i.e., nickel bound to ultrafilterable ligands, albumin-bound nickel and macroglobulin bound nickel. The chief transport protein for this metal is albumin in the human being; rat as well as in bovine sera. Nickeloplasmin, a metalloprotein has been separated from the rabbit sera (α -2 macroglobulin) and the human being (α-glycoprotein) (USPHS 1993). Ultrafilterable nickel binding ligands take an important part in extracellular transportation and exclusion of nickel in urine. L- histidine of human serum found as nickel-binding ingredient with greater affinity than that of albumin. Albumin nickel L- histidine, a ternary complex intervene the replace and relocate nickel between L - histidine and albumin (Sigel and Sigel, 1988).

Toxic effect of nickel on animal

Genotoxicity: Nickel can induce a number of genetic abnormalities such as DNA strand break (Liu *et al.,* 2013), DNA methylation (Sun *et al.,* 2013), DNA-protein cross-links (Tretyakova *et al.,* 2015), nucleotide excision repair system (Hartwig *et al.,* 2002), gene mutations (Morales *et al.,* 2016), epigenetic gene silencing (Sun *et al.,* 2013), exchanges of sister chromatid, micronuclei, nucleic acid concentration alteration as well as cell transformation (Coogan *et al.,* 1989; Costa, 1991; Das and Dasgupta, 2000) in higher organisms. Inhibition of the ligation step of excision repair within the ovary cells of Chinese hamster by nickel has also reported (Lee-Chen *et al.,* 1993).

It appears that protein is the primary objective for nickel insult (Lynn *et al.,* 1997). Nickel may accountable for the increased concentration of endogenous cellular hydrogen peroxide and its short-lived ROS (Lynn *et al.,* 1997; Das *et al.,* 2001). Through the damage of nuclear protein, nickel may cause an epigenetic alteration by reducing the activity of enzymes essential for DNA replication, transcription and recombination repair (Sun *et al.* 2013).

Developmental toxicity: Chashschin *et al.* (1994) have reported structural malformations within the newborns of women worker of a hydrometallurgy refining plant of nickel. In experimental rats inhalation of high levels of nickel during gestation may result in decreased fetal body weight (Weischer *et al.,* 1980). Parental administration of this heavy metal may also affect the developmental process in animals (Chernoff and Kavlock, 1982). Nickel is not able to cross the placental barrier (Clarkson *et al.,* 1985; Odland *et al.,* 1999). *In vitro* study advocates that nickel salts have the potential to damage the placental tissue (Chen and Lin, 1998).

Neurotoxicity: Neurological effects such as giddiness, weariness etc has observed in persons unintentionally open to the nickel and boric acid in drinking water (Sunderman *et al.,* 1988). Prolong nickel toxicity may lead to neurological signs such as lethargy, ataxia, prostration, within experimental rats (American Biogenics Corporation, 1988). Recently, it has established that nickel-induced

toxicity produces oxidative stress in mitochondria that make it dysfunctional that ultimately damages nerve (Xu *et al.,* 2010; Song *et al.,* 2017).

Hematotoxicity: Through the studies of Weischer *et al.* (1980) and the National Toxicology Programme, (NTP 1996)[a, b, c] a number of hematological alterations have observed as an effect of nickel toxicity. Nickel above the permissible level may cause a transient rise in blood reticulocytes (Sunderman *et al.,* 1988). Works of literature are available about an increase in leukocyte as well as platelet counts and levels (American Biogenics Corporation, 1988), decreased the erythrocyte count, hematocrit value, and hemoglobin concentration (Das *et al.,* 2007). Such a decrease could create nickel-induced anemia (nonregenerative anemia) initiating from injury of haematopoietic stem cells. In rats, nickel toxicity may consequences in decreases of all kinds of blood cells by hampering the activity of the bone marrow (Das *et al.,* 2007). Nickel deficiency has not been made known to be a concern in humans, despite this; it may cause biochemical changes, such as reduced Fe resorption that directs to anemia (Divya and Karthikeyan, 2017).

Immunotoxicity: Nickel can be responsible for noticeable immune and allergic reactions (Dearman and Kimber, 1992; Kimber and Dearma, 1994; Guimaraens *et al.,* 1994; Das *et al.,* 2008). Exposure of animals, including human to nickel extensively boost in the level of immunoglobulin G (IgG), IgA and IgM. However, there a noteworthy drop off in IgE levels has been noticed (Das *et al.,* 2008). A sizeable rise in other serum proteins, including á1-antitrypsin, α2-macroglobulin, ceruloplasmin, may be connected with the cell-mediated immunity that has also been recognized (Bencko *et al.,* 1983; Bencko *et al.,* 1986). Exposure to nickel significantly increases vulnerability to infection of *Streptococcus* (Adkins *et al.,* 1979), reduce in antibody titers against viral antigen (Figoni and Treagon, 1975; Graham *et al.,* 1978). Li and Zhong (2014) reported that $NiCl_2$ increases the secretion of a pro-inflammatory cytokine, interleukin-1_ (IL-1_), in bone marrow-derived macrophages and bone marrow dendritic cells.

Reproductive toxicity: Nickel beyond its permissible level may amplify the rate of spontaneous abortions in human (Chashschin *et al.* 1994). The toxic effect of this heavy metal has linked with the testicular degeneration (NTP 1996 a,b,c). Several testicular malformations, such as proliferation of interstitial cell, decline in the count of spermatozoa and effect on a number of testicular enzymes viz., steroid 3ß hydroxysteroid dehydrogenase were also seen in male due to nickel toxicity (EPA 1985). Das *et al.* (2001) have pointed decreased count and motility of sperm and modification of steroidogenesis in nickel-treated rats. Nickel exposure at toxic concentration elevates the level of testicular lipid peroxidation and reduces the functionality of the antioxidant enzyme in rats (Gupta *et al.* 2007). Kakela *et al.* (1999) observed that $NiCl_2$ encourage shrinkage of the seminiferous tubules and reduced the count of spermatogonia within the tubules.

Carcinogenicity: Ni^{+2} compounds are powerful carcinogens and capable to persuade malignant transformation of the cells of rodent as well as human beings (Oller *et al.,* 1997; Kasprzak *et al.,* 2003; Goodman *et al.,* 2009; Xu *et al.,* 2010). It was found experimentally that exposure to elevated concentrations of nickel may result in adenomas, adenocarcinomas, carcinomas of squamous cell and fibrosarcoma (Ottolenghi *et al.,* 1974; Horie *et al.,* 1985).

However, a considerable rise in the occurrence of alveolar/ bronchiolar adenoma or carcinoma has been reported in male and female rats exposed due to nickel toxicity (National Toxicology Programme 1996c). The available works of literatures advocate that mechanistically, nickel carcinogenicity is utmost likely to be the consequence of genetic factors and/ or direct or indirect epigenetic factors. Conformational change is the important direct epigenetic factor, whereas in case of an indirect epigenetic factor, the generation of oxygen radicals is important. In addition, certain nickel compounds uphold cell proliferation, through the conversion of repairable DNA lesions into non-repairable ones (Das *et al.,* 2008).

On liver: Liver is badly affected due to nickel toxicity. It may be associated with increased serum bilirubin, induced a degenerative effect on hepatic tissue (Das *et al.,* 2006), massive alteration at normal hepatic architecture along with the manifestation of vacuolated cytoplasm (fatty liver), eccentric nuclei and Kupffer cell hypertrophy. The decreased in functionality of hepatic and renal transaminase due to nickel toxicity have also reported in rats. The activity has found more adverse in a protein-restricted diet schedule (Das and Buchner, 2007). A decrease in liver ascorbic acid, as well as cholesterol levels, may also result due to nickel toxicity (Das and Dasgupta, 1998). A significant rise in hepatic lipid

peroxides, a decline in antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) as well as glutathione peroxidase (GSH-Px) activities and in the concentration of hepatic glutathione has been reported due to the toxicity of nickel in rats (Das *et al.*, 2001)

Toxicity on lungs: Nickel toxicity may responsibility for histological alteration of the lungs. Induced alveolar wall damage, fibrotic changes along with oedema in the alveolar space leading to lung cancer have reported due to nickel toxicity (Lu *et al.*, 2005). Substantial raise in the rate of recurrence deaths owing to respiratory disease has also documented in welders (Cornell and Landis, 1984). Inhalation exposure to various compounds of nickel such as nickel sulphate, nickel subsulphide, or nickel oxide may lead to the most well-known effect in the lungs as chronic active inflammation (ATSDR, 2003). Water-soluble nickel sulphate may have an intense consequence on the tissue of the lung as well as its enzyme system responsible for antioxidant activities (Gupta *et al.*, 2006). A noteworthy rise in the level of lipid peroxide in lung tissue and, lung SOD, CAT and the significant decrease in GSH-Px activities has also been reported (Gupta *et al.*, 2006).

Toxicity on kidneys: Nickel, after its entry within the body, it is carried by blood and retains by different tissues or excretes mainly through urine. As a result, the kidney becomes vital vulnerable target organ of nickel toxicity as well as carcinogenicity (Kadi and Dahdouh, 2016). Cytotoxicity of the nickel is well recognized that may consist of diverse cell lines together with kidney cells (Kadi and Dahdouh, 2016). Nickel toxicity may generate reactive oxygen species which may lead to lipid peroxidation and oxidation of DNA as well as proteins resulting in cell apoptosis and nephrotoxicity (Chakraborty and Bai, 1999; Wang *et al.*, 2012). Transient increase of albumin in urine has also been documented (Sunderman *et al.* 1988).

Increased concentrations of nickel in urine among the workers of nickel refinery are considerably associated with urinary α2-microglobulin levels (Sunderman, 1981). The incidence of damage of renal tubular at the junction of corticomedullary has also observed (Sunderman *et al.*, 1988). A significant drop off in the volume of urine as well as levels of glucose in urine and an increase in relative kidney weight has also documented (Obone *et al.*, 1999).

Toxicity on skin: In 1925, dermatitis among the workers of the nickel-plating industry has been reported (Counts *et al.*, 2002). This is an allergic reaction commence due to make get in touch with nickel (Namikoshi *et al.*, 1990; Counts *et al.*, 2002). Presently most of the reported common allergens reactions are owing to the contact of nickel. As incidences are gradually increasing, it is turning as foremost health and socio-economic a problem of several countries (Wojciechowska *et al.*, 2015). It is reported that adults and children are hypersensitive to nickel 13% and 8% respectively (Czarnobilska *et al.*, 2007).

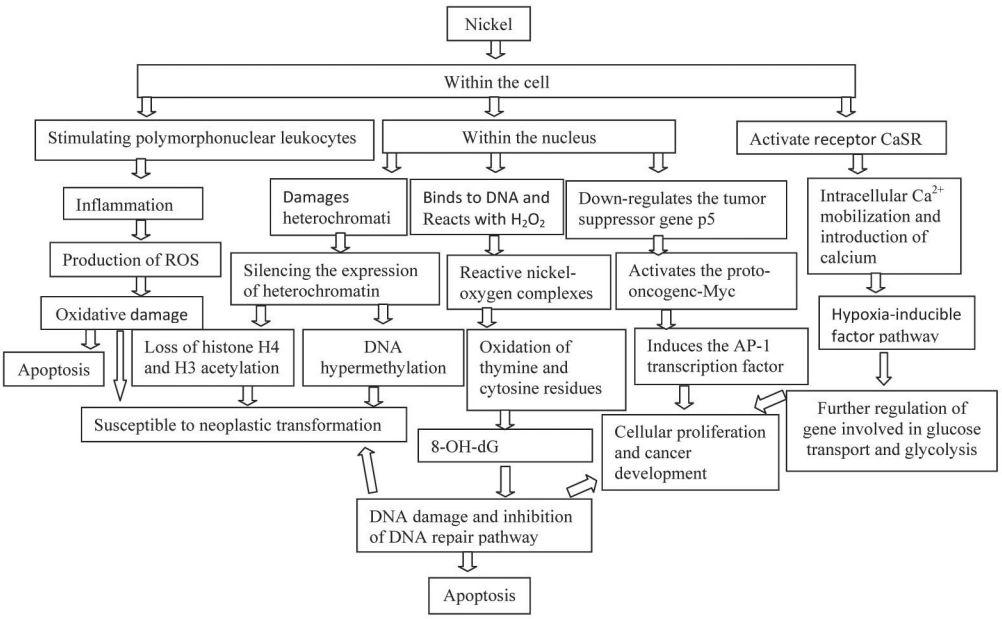

Fig. 1. Molecular mechanism of nickel toxicity in animal

Nickel is accountable for creation sensitivity reactions which may be of both short- and long-lasting. Females are more susceptible to nickel toxicity in comparison to that of the male due to wearing of nickel-containing ornaments (McDonagh *et al.,* 1992). Once developed, it continued for the rest of life (Sharma, 2007). Allergy to nickel may have cutaneous as well as systemic manifestations. A systemic nickel allergy syndrome is a harsh type of allergy. It can be clinically distinguished by cutaneous symptom with a chronic course and systemic symptoms. The cutaneous manifestations include contact dermatitis, pompholyx, hand dermatitis dyshidrosis as well as urticaria. Most of the important systemic symptoms are itching, asthenia, headache and gastrointestinal disorders associated with histopathological variations of gastrointestinal mucosa, borderline with celiac disease (Tammaro *et al.,* 2011).

Allergic nickel dermatitis is also a major occupational hazard as work tools and ingredients may discharge nickel in profuse quantity leading to professional exposure in industries (Thyssen *et al.,* 2011). In 2008, nickel has received the disgraceful indication of the "Allergen of the Year" (Gillette, 2008).

Mechanism of toxicity of nickel on animal

Though the molecular means of toxicity on the animal has must investigate but it is not much clear about their detail mechanism. We have tried to give a diagrammatic representation of conceivable idea about the molecular means of nickel toxicity from the literature available (Fig. 1). It has documented that nickel may as active as a blocker of calcium channel and liable for alteration in calcium metabolism (Zamponi *et al.,* 1996). At elevated concentrations, nickel may impair absorption or utilization of iron when its concentration is low. Nickel beyond permissible level is very efficient at turning off the expression of thrombospondin I (TSP I) a protein liable for the regulator of tumor expansion (Salnikow *et al.,* 1997). TSP at high concentration suppresses the progression of blood vessels into the tumor body.

In nickel-transformed cells ATF-1, the transcription factor is hyper-activated and acts on thrombospondin I like a negative regulator. Therefore, repression of TSP I expression in tumors accelerate angiogenesis and stimulates tumor growth. The concentration of another transcription factor, hypoxia-inducible factor 1 (HIF-1) is also increased due to nickel toxicity (Salnikow *et al.,* 2002a,b). HIF-1 facilitates angiogenesis which is crucial for tumor development. Like hypoxia, Ni(II) induces HIF-1 and therefore activates genes liable for the up-regulation of metabolism of glucose as well as glycolysis even in the occurrence of oxygen, the vascular endothelial growth factor, and the tumor marker Cap43 (Zhou *et al.,* 1998; Salnikow *et al.,* 2000a,b).

Nickel toxicity is also accountable for inflammatory response through regulation of expression of transcription factors responsible for inflammatory progression. The transcription factor NF-êB is activated due to nickel toxicity and transforms cellular as well as tissue responses. The consequence of which is nickel-induced allergic effects along with contact hypersensitivity of skin (Viemann *et al.,* 2007). NF-êB plays a significant role in apoptosis, inflammatory 693 responses, and expression of adhesion molecules. Nickel toxicityup-regulate intercellular adhesion molecule-1of human endothelial cells, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1 (Goebeler *et al.,* 1993).

The means through which nickel harm the animals, particularly in human, had the long been highlighted on oxidative reactions relating to lipids, proteins, and DNA. It is also known that nickel can binds to a diversity of biomolecules and alter their properties (Das *et al.,* 2008; Kasprzak and Salnikow, 2007). At present, it is documented that nickel is able to have intense effects on DNA or histone methylation ensuing in epigenetic effects as well as on DNA repair (Chen and Costa, 2009; Chen *et al.,* 2010; Sekirnik *et al.* 2010).

Nickel-induced transformation may be linked with the mutation of the gene p53 (Denkhaus and Salnikow, 2002). It is a tumor suppressor gene and transcription factor concerned with the regulation of cell proliferation and apoptosis. Human cancer is generally associated with the mutations in the p53 gene. Maehle *et al.* (1992) have documented that nickel toxicity may cause mutation of the p53 gene in epithelial kidney cells of the human being. Another gene FHIT (Fragile Histidine Triad) responsible for suppressor of the tumor is located in a fragile chromosomal site sensitive to deletions. In tumors as well as in pre-malignant lesions its expression is generally reduced or lost. During complex communication with diadenosine triphosphate, the gene product Fhit protein (phosphohydrolase) may induce apoptosis. *In vitro*

study has revealed that nickel creates a well-built inhibition on the enzymatic activity of Fhit protein and also represses Fhit expression in nickel-transformed BALB/c-3T3 cells.

Nickel toxicity increases the degree of DNA methylation and histone deacetylation resulting in the inactivation of the expression of the gene (Martinez-Zamudio and Ha, 2011). This inactivation of the gene accountable for tumor suppressor by hypermethylation could assist in nickel-induced cell transformation. Beside it, *in vitro* silencing of the gene through the hypermethylation, a suppressive outcome of nickel on acetylation of histone H4 has also been documented both in the cell of yeast and human being (Broday *et al.,* 2000). Works of literature on the damage of DNA and chromatin in nickel-exposed cells and tissues are abundant. However, the mutagenic potentiality of this nickel, in general, is considered to be low (Fletcher *et al.,* 1994).

CONCLUSION

In spite of being a heavy metal, nickel is necessary for animals to lead a successful life. In the animal deficiency of nickel may be associatedwith the alternation of the histological and biochemical characters and reduction of iron resorption as well as interaction with heme iron leads to anemia. This heavy metal may also be responsible for the progression of parakeratosis-like damage through perturbing the calcium absorption into the skeleton. Nickel has drawn much consideration as an intoxicating pollutant for the emergent anthropogenic stress on the environment. On the other hand, lung fibrosis, contact dermatitis, cardiovascular and kidney diseases, as well as lung and nasal cancers, is the most important and prevalence in animals. In 2008, nickel has marked through the disgraceful identity of the "Allergen of the Year". Still, it to be explored at the molecular level. Surplus nickel brings on oxidative stress. Although, the mechanism linked to generation of nickel toxicity at the protein and molecular level may be explored in detail. The reclamation of soils polluted by heavy metals can be achieved with dierent techniques and technologies including cost effective biological technique-the phytoremediation. However, the solutions to this problem are important and need further research. This review will be helpful to conceive an in-depth idea in related to the nature and magnitude of nickel toxicity in animal which is very essential to fight against this environmental issue.

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