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Full Length Research Paper

Combined effect of vanadium and nickel on lipid peroxidation and selected parameters of antioxidant system in liver and kidney of male rat

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In this investigation, hepatorenal antioxidant effects of combined oral administration of ammonium metavanadate (AMV; 0.15 mg V/ml) and nickel sulfate (NS; 0.18 mg Ni/ml) in male albino rats over a 21-day period have been evaluated. After administration of vanadium, lipid peroxidation (LPO) increased significantly ($p < 0.001$) in kidney and insignificantly ($p > 0.05$) in liver, superoxide dismutase (SOD) and glutathione –S-transferase (GST) activities increased significantly in kidney ($p < 0.01$) and decreased in liver ($p < 0.001$) whereas glutathione (GSH) content decreased ($p < 0.001$) in both organs. The exposure to nickel led to a significant decrease ($p < 0.001$) in SOD, GST activities in liver and GSH content in kidney and a significant ($p < 0.001$) increase in the hepatic MDA content and renal SOD activity. When the metals were administered in combination, the elevation of lipid peroxidation did not potentiate. However, the inhibition in hepatic SOD was augmented. In the other hand, the combined metals treatment slightly improved the decreased hepatic GST activity and induced the hepatorenal content of GSH. Signs of toxicity were observed following treatment with vanadium, not nickel nor combined vanadium and nickel. A reduction in cellular enzymatic (SOD) and non-enzymatic (GSH) antioxidants is clearly indicative of oxidative stress. The results of this study indicate that kidney is more vulnerable to the caused by vanadium and/or nickel-induced oxidative stress than liver, the oxidative capacity of nickel is much lower than vanadium as well as that the oxidative capacity of combined vanadium and nickel may be more markedly decreased than at separate exposure.

Key words: Oral, vanadium, nickel, antioxidant, hepatorenal, rats.

INTRODUCTION

Today, heavy metals are abundant in our drinking water, air and soil. They are present in virtually every area of modern consumerism-from construction materials to cosmetics, medicines to processed foods, fuel sources to agents of destruction, appliances to personal care products. It is very difficult for anyone to avoid exposure to any of the many harmful heavy metals that are so prevalent in our environment.

Vanadium is an element found in the earth's crust, minerals, fossil fuels, and most living organisms. It has a very complex chemistry and different states of protonation and conformations can occur simultaneously in equilibrium in vanadate solutions (Chasteen, 1983; Amado et al., 1993; Crans, 1994). Occupational poisoning occurs mainly during the industrial production and use of vanadate in oil fields (WHO, 1990). Vanadium role in humans has been discussed at length with no definitive information to name it as an essential element (WHO, 1988). It is widely recognized in its different forms as a potentially toxic environmental pollutant, it causes the inhibition of certain enzymes with animals, which has several neurological effects. Next to the neurological effects, vanadium can cause breathing disorders,

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paralyses and negative effects on the liver and kidneys. In biological systems, animal studies have shown that vanadium compounds induce oxidative stress and lipid peroxidation *in vivo* (Stohs and Bagchi, 1995). Different vanadate-induced effects in biological systems were described to be dependent on the oligomeric species present (Aureliano and Madeira, 1994; Aureliano et al., 2002; Borges et al., 2003; Tiago et al., 2004).

There has also been a growing interest in nickel (Ni); nickel is a metallic element that is naturally present in the earth's crust. Due to unique physical and chemical properties, metallic nickel and its compounds are widely used in modern industry. The high consumption of nickel-containing products inevitably leads to environmental pollution by nickel and its by-products at all stages of production, recycling and disposal. Human exposure to nickel occurs primarily via inhalation and ingestion. Significant amounts of nickel in different forms may be deposited in the human body through occupational exposure and diet over a lifetime. Since nickel has not been recognized as an essential element in humans it is not clear how nickel compounds are metabolized. It is known, however, that nickel salts are considered to be an occupational hazard and were reported to produce undesirable effects and/or carcinogenicity in humans and animals (Obone et al., 1999).

Several studies have been conducted that demonstrate the *in vivo* and *in vitro* toxicity of V and Ni (Dreher et al., 1997; Dye et al., 1999; Kadiiska et al., 1997; Kodavanti et al., 1997). Such studies primarily highlight the general oxidative stress effects of the metals as their mechanism of toxicity. Oxidative stress is a pathophysiological process in which intracellular balance between endogenous as well as exogenous pro-oxidants and antioxidants is shifted towards pro-oxidants, leaving cells unprotected from free radical attack, which in turn may cause neurotoxicity, hepatotoxicity and nephrotoxicity in humans and animals (Chen et al., 2001). As the liver and kidneys are major "filters" of the blood system; they remove toxic wastes and debris. The kidneys especially aid in ridding the body of excess "acids" while rebalancing critical pH. Their damage, make our blood laden with debris and heavy metals that could travel to our brain and cause a stroke. This study is thus aimed at establishing the toxic effects of vanadium and/or nickel on the activity of some antioxidant enzymes and lipid peroxidation in liver and kidney of male albino rats.

MATERIALS AND METHODS

Reagents

The kits for glutathione (GSH), superoxide dismutase (SOD), glutathione-S-transferase (GST), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were obtained from Cayman chemical, E. Ellsworth Road, Ann Arbor, USA. Ammonium metavanadate (NH_4VO_3), nickel sulfate ($NiSO_4.7H_2O$), 2-thiobarbituric acid (TBA), Trichloroacetic acid (TCA) and Ethylene diamine tetraacetic acid (EDTA) and other chemicals used were purchased from high commercial company from Almaty, Kazakhstan.

Animal treatment

Outbred 3-month-old male albino rats, weighing between 230 to 235 g (mean) at the beginning of experiment, were obtained from the Animal House, Faculty of Biology and Biotechnology - Almaty – Kazakhstan, and acclimatized for 3 weeks before putting them on different treatments. Animals were randomly assigned into four groups of 4 animals per group. They were housed in plastic cages placed in a well-ventilated rat house, provided rat pellets (protein 21%, fat 6.78%, fiber 3.26%, salts and vitamins) and water *ad libitum*, and subjected to natural photoperiod of 12/12 h light–dark, constant temperature: 19 to 20ºC. All animals were housed according to the ethical rules in compliance with institutional guidelines.

The animals were received daily: Group I (Control)—were given deionized water to drink; Group II—were given vanadium in the form of NH_4VO_3 at a concentration of 0.15 mg V/ml; Group III—were given nickel in the form of $NiSO_4.7H_2O$ at a concentration of 0.18 mg Ni/ml and Group IV—were given water solution of AMV–NS at the same concentrations as in Group II and III for V and Ni, over a 21-day period. pH of AMV solution administered to rats in drinking water was about 6.97 ± 0.02. During the whole experiment food, fluids and water intake were monitored daily and body weight gain was checked weekly. Vanadium and nickel concentration in drinking water was chosen on the basis of previous studies of other authors (Russanov et al., 1994; Zaporowska, 1994) and (Sidhu et al., 2004; 2005), respectively.

Biochemical analysis

Blood samples were taken by puncturing the abdominal aorta of the animals after giving light ether anesthesia. The collected blood samples were kept at room temperature for 30 min and then were centrifuged at 2000 rpm for 10 to 15 min to separate the serum. Serum was used for the estimation of the liver marker enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Then the animals were sacrificed by exsanguination under light anesthesia. Liver and kidneys were removed immediately and one part of the lobe was processed immediately for the estimations enzymes activities and perfused with normal saline (0.9%, w/v) in order to take care of red blood cell contamination.

The activity of superoxide dismutase (SOD) was determined spectrophotometrically in the liver and kidney tissues at wave length 450 nm according to the method of Marklund (1980) and its activity was measured as (unit/ml).

The activity of glutathione-S-transferase (GST) was determined spectrophotometrically in the liver and kidney tissues at wave length 340 nm according to the method of Habig et al. (1974) and its activity was measured as (nmol/min/ml).

The content of glutathione (GSH) was determined spectrophotometrically in the liver and kidney tissues at wave length 405 nm according to the method of Baker et al. (1990) and its content was expressed as (µM).

The content of malondialdehyde (MDA) was determined spectrophotometrically in the liver and kidney tissues at wave length 532 nm according to the method of Burlakova et al. (1975) and its content was expressed as (nmol/g).

Statistical analysis

All data expressed as mean ± SE and statistical analysis was made

Table 1. Changes in fluid and food intake and body weight gain in of vanadium-, nickel-, and vanadium + nickel-exposed rats.

Treatment	Initial weight (g)	Final weight (g/ 3 weeks)	Fluid intake (mL/kg b.w./24 h)	Food intake (g/kg b.w./24 h)
Control	230.75 ± 2.21 (100)	249.00 ± 2.97 (100)	109.50 ± 3.30 (100)	93.50 ± 3.77 (100)
AMV	229.50 ± 2.33 (99.46)	169.25 ± 3.28** (67.97)	69.25 ± 3.71** (63.2)	40.00 ± 3.56** (42.8)
NS	233.00 ± 2.65 (100.98)	223.75 ± 2.69** (89.86)	94.75 ± 4.03* (86.5)	86.00 ± 3.46 (91.98)
AMV—NS	232.00 ± 2.42 (100.54)	254.25 ± 3.22 (102.11)	97.25 ± 3.68† (88.8)	93.00 ± 3.11 (99.46)
ANOVA				
F- ratio	0.399	162.695	20.992	54.153
p- value	0.756	0.000**	0.000**	0.000**

Values are significant in comparison with control mean ± SE; NS = nickel sulfate; AMV = ammonium metavanadate. Significant, $^{\dagger}p < 0.05$; *$p < 0.01$ and **$p < 0.001$. Figures in parentheses indicate percent (%) values.

using the Statistical Package for Social Sciences (SPSS 18.0 software and Microsoft Excel 2010). For tests, analysis of differences between groups consisted on a one-way analysis of variance (ANOVA) with repeated measures, followed by post-hoc comparisons (LSD test). Differences were considered statistically significant at $p < 0.05$ and marked as (†), highly significant at $p < 0.01$ and marked as (*), and very highly significant at $p < 0.001$ and marked as (**) (Landu and Everitt, 2004).

RESULTS

Health and clinical observations

Animals on multiple dosing with ammonium meta-vanadate (AMV) suffered from conjunctivitis, congested facial vessels, dehydration, loss of appetite, weight loss, distress, emaciation, spinal degeneration and kyphosis, owing to this, the chances for the survival of these animals were reduced while in animals on multiple dosing with NS alone or in combination with AMV, There were no treatment-related clinical observations because the rats remained in relatively good health throughout the period of experiment.

Body weight gain and fluid consumption

The administration of AMV at a concentration of 0.15 mg V/ml or nickel sulfate (NS) at a concentration of 0.18 mg Ni/ml for 3 weeks had significantly ($p < 0.001$) reduced body weight gain by (32.03 and 10.14%) respectively, compared with control. The body weight gain of animals co-exposed to AMV and NS was insignificantly ($p < 0.05$) changed (Table1).

Drinking fluids consumption was significantly ($p < 0.001$, 0.01 and 0.05) depressed at all exposed group (vanadium, nickel and vanadium plus nickel) by 36.8, 13.5 and 11.2%), respectively, compared with control (Table 1).

Changes in GSH, MDA contents, SOD and GST activities in the liver

The liver content of GSH, significantly ($p < 0.001$) decreased as a result of vanadium exposure by 53.5% and insignificantly ($p > 0.05$) increased as a result of nickel exposure by 6.1% while in vanadium and nickel co-exposure, it significantly ($p < 0.001$) increased by 16.6%. The activities of SOD and GST significantly ($p < 0.001$) decreased at AMV, NS and AMV-NS treatment by (28.9, 30.3 and 40%) and (33.1, 19.7 and 18.7%), respectively whereas the content of MDA increased insignificantly ($p > 0.05$) in vanadium exposed group by 5.7% and significantly ($p < 0.001$) in nickel and nickel plus vanadium exposed groups by 30% (Table 2).

Changes in GSH, MDA contents, SOD and GST activities in the kidney

Exposure to vanadium alone resulted in significant ($p < 0.001$, 0.01 and 0.001) increase in the activities of SOD, GST and the content of MDA by (150, 117 and 56.8%), respectively, whereas the content of GSH significantly ($p < 0.001$) decreased by (36.5%).

Significant ($p < 0.001$) increase in the activity of SOD by (25%), a significant ($p < 0.001$) decrease in the content of GSH by (60.3%) and insignificant ($p > 0.05$) increase in GST activity and MDA content by (0.6 and 10.8%) respectively were noted in rats treated with nickel alone. Different patterns of changes of the studied parameters of oxidative status were observed as a result of combined exposure to vanadium and nickel, the content of GSH and MDA increased significantly ($p < 0.01$ and 0.001) by (23.7 and 35.1%) respectively, whereas SOD activity insignificantly ($p > 0.05$) increased by 12.5% and GST activity insignificantly ($p > 0.05$) decreased by 7.8% (Table 3).

Changes in aminotransferases (ALT and AST) activities in the serum

Changes in serum ALT and AST activities were significantly ($p < 0.001$) increased by (101.79, 248.2 and126.8%) and (101.75, 56.1 and 71.9%) at AMV, NS and AMV-NS treatments, respectively (Table 4). The

Table 2. Changes in MDA, GSH content, and the activity of SOD and GST in liver of vanadium-, nickel-, and vanadium + nickel-exposed rats.

Liver				
Treatment	**MDA content (nmol/g)**	**SOD activity (U/ml)**	**GST activity (nmol/min/ml)**	**GSH content (µM)**
Control	0.070 ± 0.001 (100)	0.076 ± 0.004 (100)	246.70 ± 4.74 (100)	20.43 ± 0.59 (100)
AMV	0.074 ± 0.002 (105.7)	0.054 ± 0.003** (71.1)	165.11 ± 1.42** (66.9)	9.50 ± 0.31** (46.5)
NS	0.091 ± 0.003** (130)	0.053 ± 0.004** (69.7)	197.99 ± 2.21** (80.3)	21.68 ± 0.14 (106.1)
AMV—NS	0.091 ± 0.001** (130)	0.045 ± 0.003** (59.2)	200.50 ± 2.94** (81.3)	23.83 ± 0.47** (116.6)
ANOVA				
F- ratio	29.916	17.127	118.351	239.373
p- value	0.000**	0.000**	0.000**	0.000**

Values are significant in comparison with control mean ± SE; NS = nickel sulfate; AMV = ammonium metavanadate. Significant, **p < 0.001; Figures in parentheses indicate percent (%) values.

Table 3. Changes in MDA, GSH content, and the activity of SOD and GST in kidney of vanadium-, nickel-, and vanadium + nickel-exposed rats.

Kidney				
Treatment	**MDA content (nmol/g)**	**SOD activity (U/ml)**	**GST activity (nmol/min/ml)**	**GSH content (µM)**
Control	0.37 ± 0.03 (100)	0.08 ± 0.001 (100)	103.78 ± 3 (100)	1.56 ± 0.05 (100)
AMV	0.58 ± 0.01** (156.8)	0.20 ± 0.003** (250)	121.39 ± 2* (117)	0.99 ± 0.04** (63.5)
NS	0.41 ± 0.013 (110.8)	0.10 ± 0.002** (125)	104.37 ± 0.27 (100.6)	0.62 ± 0.03** (39.7)
AMV—NS	0.50 ± 0.016** (135.1)	0.09 ± 0.002 (112.5)	95.67 ± 4.93 (92.2)	1.93 ± 0.13* (123.7)
ANOVA				
F- ratio	21.005	548.194	12.481	61.393
p- value	0.000**	0.000**	0.001**	0.000**

Values are significant in comparison with control mean ± SE; NS = nickel sulfate; AMV = ammonium metavanadate. Significant, *p < 0.01; **p < 0.001; Figures in parentheses indicate percent (%) values.

levels of serum transaminases are taken as a measure of liver function tests.

DISCUSSION

The purpose of this study was to assess the changes in the level of lipid peroxidation, GSH content and the activity of some antioxidant enzymes in liver and kidney of rats during exposure to vanadium and/or nickel. In this study, a significant reduction was observed in the body weight of the vanadium or nickel alone exposed groups. A consistent reduction in body weight by vanadium has also been reported by Thompson and McNeill (1993). The decreased body weight in our study is concomitant with that of Seidenberg et al. (1986); Smialowicz et al. (1987) and Junaid et al. (1996) who have also reported decreased body weight in nickel exposed rats. This reduction in weights might be due to low food consumption and reduction in protein levels. As the nickel ions have a higher affinity for proteins and amino acids and have shown to produce oxidation of proteins in cells (Costa et al., 1994).

Administration of vanadium and/or nickel caused significant decrease in fluid intake. Decreased consumption of drinking water containing vanadium has been reported and discussed by Scibior and Zaporowska (2010). Due to the reduced fluids intake, it is possible that the rats exposed to vanadium and/or nickel were affected by some degree of dehydration, which might to some extent contribute in the cause of animals death in this study and thus has to be taken into account under interpretation of the results.

The results obtained regarding the SOD, GST activities and the contents of GSH and MDA (an indicator of lipid peroxidation) in the liver and kidney clearly indicate that vanadium and nickel are able to induce oxidative stress during repeated separate administration as well as duringco-exposure. Chemically induced oxidative stress causes derangement of antioxidant mechanisms in tissues (Videla et al., 1990), may lead to LPO (Comporti, 1985), and may cause stimulation of cellular proliferation and/or apoptosis (Corcoran et al., 1994) that may finally result in cell injury (de Groot and Littauer, 1989). LPO is a

Table 4. Changes in aminotransferases (ALT and AST) activities in serum of vanadium-nickel-, and vanadium + nickel-exposed rats.

Treatment	ALT (mMol/h.L)	AST (mMol/h.L)
Control	0.56 ± 0.047 (100)	0.57 ± 0.017 (100)
AMV	1.13 ± 0.033** (201.79)	1.15 ± 0.002** (201.75)
NS	1.95 ± 0.043** (348.2)	0.89 ± 0.01** (156.1)
AMV—NS	1.27 ± 0.037** (226.8)	0.98 ± 0.01** (171.9)
ANOVA		
F- ratio	202.752	437.918
p- value	0.000**	0.000**

Values are significant in comparison with control mean ± SE; NS = nickel sulfate; AMV = ammonium metavanadate. Significant, **p < 0.001; Figures in parentheses indicate percent (%) values.

cause rather than an effect of necrotic tissue damage (Biasi et al., 1995). Corroborating with present data, (Russanov et al., 1994) have also reported high level of LPO in liver and kidney of vanadium treated rats. Nickel was also found to affect LPO thus leading to cell injury. Studies by (Misra et al., 1990; Das et al., 2001; Rao et al., 2006) corroborate with our findings. Evidence gathered from the available literature suggest that nickel induced enhancement of LPO could be due to accumulation of iron, which seems to trigger peroxidative damage by hydroxyl radicals involving Fenton reaction (Stohs and Bagchi, 1995; Chen et al., 1998; Chakrabarti and Bai, 1999; Cempel and Nikel, 2006).

GSH is capable of chelating and detoxifying metals soon after they enter the cell due to its ability to directly react with hydrogen peroxide, superoxide anion, hydroxyl and alkoxyl radical (Meister and Anderson, 1983). This proposal is based on observations that the depletion of GSH potentiates metal toxicity in rats and mice (Fukino et al., 1986; Singhal et al., 1987). In this study, decreased GSH content in the liver and kidney following AMV administration indicates that high levels of reactive oxygen species (ROS) are generated following their administration and GSH is oxidized to disulfide form (GSSG) by the activity of GPx during its involvement in the detoxification process. Depletion of GSH not only decreases the antioxidant defense, but also prevents regeneration of a vital lipid-soluble antioxidant, increasing the vulnerability of phospholipid-rich bio-membranes to oxidative stress and LPO. As the depletion of GSH may play a primary role in the nickel toxicity (Stohs and Bagachi, 1995), its decrease in the kidney following nickel administration indicates organ toxicity while its slight increase in the liver indicates that the liver scavenge the toxic effect of this metal. Nickel at the concentration ingested (0.18 mg Ni /ml) at co-exposure to AMV decreased the deleterious effect of vanadium, that may be explained by the increased GSH content following combined metals administration. Tissue GSH was shown to participate directly in vanadate inactivation (Kretzschmar and Braunlich, 1990). The increased GSH content reduces damage and promotes better survival under the conditions of oxidative stress. Studies by Misra et al. (1990); Das et al. (2001) and Bagchi et al. (2002) have also reported decreased GSH levels after nickel intoxication. The decreased content of GSH by vanadium administration as reported by Scibior and Zaporowska (2010) is in support of our data. Nickel has also been shown to reduce the action of GSH (Misra et al., 1990; Shainkin-Kestenbaum et al., 1991).

SOD is considered as the first line of defense against deleterious effects of oxy radicals in the cell by catalyzing the dismutation of superoxide radicals to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) (Mates et al., 1999). Its absence or decrease in its activity may induce noxious metabolic outcomes as it plays an important role in free radical activity detoxification. So the decrease in the activity of this enzyme in the liver after vanadium and/or nickel exposure in this study could result in the accumulation of $O_2.^-$ within the cell. One important reaction of $O_2.^-$ is with H_2O_2 to form the hydroxyl radical (OH.), which is the most potent oxidant known (Bucker and Martin, 1981). While the observed increase in SOD activity of the rats' kidney may be an improved attempt by kidney to mop up MDA produced and may be an adaptive feature. The interesting observation of a higher SOD in the kidney compared with that in the liver indicate that the adaptive mechanism is elaborated in kidney than liver.

Scibior and Zaporowska (2010) reported reduced activity of SOD by vanadium in the erythrocyte. Therefore a reduction in cellular enzymatic (SOD) and non-enzymatic (GSH) antioxidants is clearly indicative of oxidative stress.

As far as GST activity is concerned, the reason for its decrease after vanadium exposure found in our experimental model is not fully clear, has been reported to be very vulnerable to oxidative stress and may be inactivated by H_2O_2 (Shen et al., 1991). Therefore, the most likely explanation of the inhibition of hepatic GST activity observed in our conditions is ammonium

metavanadate-induced ROS generation which can oxidize -SH groups of the enzyme leading to disulfide bond formation and thereby causing its inactivation (Shen et al., 1991). While increased GST level in kidney of rat treated with vanadium suggesting a mechanism for protection against its toxic effect was developed. Depletion of the GSH level, demonstrated in our study, and direct inhibition of hepatic GST by vanadium should also be taken into consideration. It is well known that the *in vivo* effects of many metals may result from their interactions with protein-bound essential groups.

In this study, increases in AST and ALT activities indicate liver damage as supported by the pathological findings, consistent with the findings of Saygy et al. (1991) and Uyanik et al. (2001). Therefore the increase in the activities of these enzymes is mainly due to the leakage out of these enzymes from the liver cytosol into the blood stream which gives an indication on the hepatoxic effect of these metals (Novelli and Barbosa, 1998).

Conclusion

In conclusion of this study, the result indicated that, vanadium and nickel induce an oxidative stress as evidenced by increased LPO and disturbed antioxidant enzymes. The kidney is more vulnerable to the caused by the vanadium and/or nickel-induced oxidative stress than the liver. The oxidative capacity of nickel is much lower than vanadium as well as that the oxidative capacity of combined vanadium and nickel may be more markedly decreased than at separate exposure. The examined concentration of vanadium was found to be toxic. Nickel at the concentration ingested at co-exposure to vanadium decreased this toxicity.

REFERENCES

Amado A, Aureliano M, Ribeiro-Claro PJ, Teixeira-Dias J (1993). Combined Raman and ^{51}VNMRspectroscopic study of vanadium (V) oligomerization in aqueous alkaline solutions. J. Raman Spectrosc. 24: 669-703.

Aureliano M, Joaquim N, Sousa A, Martins H, Coucelo JM (2002). Oxidative stress in toadfish (*Halobatrachus didactylus*) cardiac muscle: acute exposure to vanadate oligomers. J. Inorg. Biochem. 90: 159-165.

Aureliano M, Madeira VMC (1994). Interactions of vanadate oligomers with sarcoplasmic reticulum Ca^{2+} -ATPase. Biochim. Biophys. Acta. 1221: 259-271.

Bagchi D, Stohs SJ, Downs BW, Bagchi M, Preuss HG (2002). Cytotoxicity and oxidative mechanisms of different forms of chromium. Toxicology, 180: 5-22.

Baker MA, Cerniglia GJ, Zaman A (1990). Microtiter plate assay for the measurement of glutathione and glutathione disulfide in large numbers of biological samples. Anal. Biochem. 190: 360-365.

Biasi F, Bosco M, Lafranco G, Poli G (1995). Cytolysis does not per se induce lipid peroxidation: evidence in man. Free Radic. Biol. Med. 18: 909-912.

Borges G, Mendonça P, Joaquim N, Aureliano M, Coucelo JM (2003). Acute effects of vanadate oligomers on heart, kidney, and liver histology in the Lusitanian toadfish (Halobatrachus didactylus). Arch. Environ. Contamin. Toxicol. 45: 415-422.

Bucker ER, Martin SE (1981). Superoxide dismutase activity in thermally stressed *Staphylococcus aureus*. Appl. Environ. Microbiol. 41: 449-454.

Burlakova EB, Alesenko AV, Molochkina EM, Palmina NP, Khrapova NG (1975). Bioantioxidants for radiation damage and malignant growth. Nauka, Moscow, p. 214.

Cempel M, Nikel G (2006). Nickel: a review of its sources and environmental toxicology. Pol. J. Environ. Stud. 15: 375-382.

Chakrabarti SK, Bai JY (1999). Role of oxidative stress in nickel-chloride-induced cell injury in renal cortical slices. Biochem. Pharmacol. 28: 1501-1510.

Chasteen N (1983). The biochemistry of vanadium. Struct. Bond. (Berl.) 53: 105-138.

Chen CY, Sheu JY, Lin TH (1998). Lipid peroxidation in liver of mice administered with nickel chloride: with special reference to trace elements and antioxidants. Biol. Trace Elem. Res. 61: 193-205.

Chen F, Ding M, Castranova V, Shi X (2001). Carcinogenic metals and NF-kappa B activation. Mol. Cell Biochem. 222: 159-171.

Comporti M (1985). Biology of disease, lipid peroxidation and cellular damage in toxic liver injury. Lab. Invest. 53: 599-623.

Corcoran GB, Fix L, Jones DP, Moslen MT, Nicotera P, Oberhaimmer FZ, Buttyan R (1994). Apoptosis: molecular control point in toxicity. Toxicol. Appl. Pharmacol. 128: 169-181.

Costa M, Salnikow K, Cosentio Z, Klein CB, Huang Xi, Zhuang Z (1994). Molecular mechanism of nickel carcinogenesis. Environ. Health Perspect. 102: 127-130.

Crans DC (1994). Aqueous chemistry of labile oxovanadate: relevance to biological studies. Comments Inorg. Chem. 16: 1-33.

Das KK, Das SN, DasGupta S (2001). The influence of nickel induced hepatic lipid peroxidation on rats. J. Basic Clin. Phys. Pharm. 12: 187-195.

de Groot H, Littauer A (1989). Hypoxia, reactive oxygen and cell injury. Free Radic. Biol. Med. 6: 541-551.

Dreher KL, Jaskot RH, Lehmann JR, Richards JH, McGee JK, Ghio AJ, Costa DL (1997). Soluble transition metals mediate residual oil fly ash induced acute lung injury. J. Toxicol. Environ. Health, 50: 285-305.

Dye JA, Adler KB, Richards JH, Dreher KL (1999). Role of soluble metals in oil fly ash-induced airway epithelial injury and cytokine gene expression. Am. J. Physiol. 277: L498-L510.

Fukino H, Hirai M, Hsueh YM, Moriyasu S, Yamane Y (1986). Mechanism of protection by zinc against mercuric chloride toxicity in rats: effects of zinc and mercury on glutathionine metabolism. J. Toxicol. Environ. Health, 19: 75-89.

Habig WH, Pabst MJ, Jakoby WB (1974). Glutathione S-transferases: the first enzymatic step in mercapturic acid formation. J. Biol. Chem. 249: 7130-7139.

Junaid M, Murthy RC, Saxena DK (1996). Embryotoxicity of orally administered chromium in mice. Exposure during the period of organogenesis. Toxicol. Lett. 84: 143-148.

Kadiiska MB, Mason RP, Dreher KL, Costa DL, Ghio AJ (1997). In vivo evidence of free radical formation in the rat lung after exposure to an emission source air pollution particle. Chem. Res. Toxicol. 10: 1104-1108.

Kodavanti UP, Jaskot RH, Costa DL, Dreher K L (1997). Pulmonary proinflammatory gene induction following acute exposure to residual oil fly ash: Roles of particle-associated metals. Inhal. Toxicol. 9: 679-701.

Kretzschmar M, Braunlich H (1990). Role of glutathione in vanadate reduction in young and mature rats: evidence for direct participation of glutathione in vanadate inactivation. J. Appl. Toxicol. 10: 295-300.

Landu S, Everitt BS (2004). A handbook of statistical Analyses using SPSS. Chapman and Hall/CRC press LLC. London, p. 337.

Marklund S (1980). Distribution of CuZn superoxide dismutase and Mn superoxide dismutase in human tissues and extracellular fluids. Acta Physiol. Scand. Suppl. 492: 19-23.

Mates JM, Perez-Gomez C, Nunez de Castro I (1999). Antioxidant enzymes and human diseases. Clin. Biochem. 32: 595-603.

Meister A, Anderson ME (1983). Glutathione. Annu. Rev. Biochem. 52: 711-760.

Misra M, Rodriguez RE, Kasprazak KS (1990). Nickel induced lipid peroxidation in the rat: correlation with nickel effect on antioxidant defense system. Toxicology, 64: 1-17.
Novelli ELP, Hernandes RT, Novelli JLV, Barbosa LL (1998). Differential/ Combined effect of water contamination with cadmium and nickel on tissues of rats. Environ. Pollut. 103: 295-300.
Obone E, Chakrabarti SK, Bai C, Malick MA, Lamontage L, Subramanian KS (1999). Toxicity and bioaccumulation of nickel sulfate in Sprague-Dawley rats following 13 weeks of subchronic exposure. J. Toxicol. Environ. Health, 57: 379-401.
Rao MV, Parekh SS, Chawla SL (2006). Vitamin E supplementation ameliorates chromium-and/or nickel induced oxidative stress *in vivo*. J. Health Sci. 52: 142-147.
Russanov E, Zaporowska H, Ivancheva E, Kirkova M, Konstantinova S (1994). Lipid peroxidation and antioxidant enzymes in vanadate-treated rats. Comp. Biochem. Physiol. Pharmacol. Toxicol. Endocrinol.107: 415-421.
Saygy S, Deniz G, Kutsal O, Vural N (1991). Chronic effects of cadmium on kidney, liver, testis and fertility of male rats. Biol. Trace Elem. Res. 31: 209-214.
Scibior A, Zaporowska H (2010). Effects of combined vanadate and magnesium treatment on erythrocyte antioxidant defence system in rats. Environ. Toxicol. Pharmacol. 30: 153-161.
Seidenberg JM, Anderson DJ, Decker RA (1986). Validation of in vivo developmental toxicity screen in the mouse. Teratog. Carcinog. Mutagen. 6: 361-374.
Shainkin-Kestenbaum R, Caruso C, Berlyne GM (1991). Effect of nickel on oxygen free radical metabolism. Inhibition of superoxide dismutase and enhancement of hydroxydopamine autoxidation. Biol. Trace Elem. Res. 28: 213-221.
Shen H, Tamai K, Satoh K, Hatayama I, Tsuchida S, Sato K (1991). Modulation of class Pi glutathione transferase activity by sulfhydryl group modification. Arch. Biochem. Biophys. 286: 178-182.
Sidhu P, Garg ML, Dhawan DK (2004). Protective role of zinc in nickel induced hepatotoxicity in rats. Chem. Biol. Interact. 150: 199-209.
Sidhu P, Garg ML, Morgenstern P, Vogt J, Butz T, Dhawan DK (2005). Ineffectiveness of nickel in augmenting the hepatotoxicity in protein deficient rats. Nutr. Hosp. 20: 378-385.
Singhal RK, Anderson ME, Meister A (1987). Glutathione, a first line of defense against cadmium toxicity. FASEB J. 1: 220-223.
Smialowicz R, Rogers R, Rowe D, Riddle M, Luebke AR (1987). The effects of nickel on immune functions in the rat. Toxicology, 44: 271-281.
Stohs SJ, Bagchi D (1995). Oxidative mechanisms in the toxicity of metal ions. Free Radic. Biol. Med. 18: 321-326.
Thompson KH, McNeill JH (1993). Effect of vanadyl sulfate feeding on susceptibility to peroxidative change in diabetic rats. Res. Commun. Chem. Pathol. Pharmacol. 80: 187-200.
Tiago T, Aureliano M, Gutiérrez-Merino C (2004). Decavanadate binding to a high affinity site near the myosin catalytic centre inhibits F-actin-stimulated myosin ATPase activity. Biochem. 43: 5551-5561.
Uyanik F, Eren M, Atasever A, Tuncoku G, Kolsuz AH (2001). Changes in some biochemical parameters and organs of broilers exposed to cadmium and effect of Zinc on cadmium induced alteration. Israel J. Vet. Med. 56: 128-134.
Videla LA, Barros SBM, Junquiera VBC (1990). Lindane-induced liver oxidative stress. Free Radic. Biol. Med. 9: 169-179.
World Health Organization (WHO) (1988). Environmental Health Criteria No. 81: Vanadium. Geneva.
World Health Organization (WHO) (1990). Vanadium and some vanadium salts: health and safety guide, No. 42, Geneva.
Zaporowska H (1994). Effect of vanadium on L-ascorbic acid concentration in rat tissues. Gen Pharmacol. 25: 467-470.