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INFLUENCE OF TRANSITION METALS ON ANIMAL AND HUMAN HEALTH: A REVIEW

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Summary: *Niobium, osmium, scandium, tungsten and vanadium are transition metals naturally occuring in the environment, particularly in the Earth's crust. Anthropogenic activities, primarily industrial technologies, have precipitated significant alternations in the concentration and distribution of these metals. Such a dramatic change resulted, by all means, in the bigger potential of the environmental exposure, which poses a threat not only to humans but to all biological systems. Certain elements naturally occur in the animal and human plasma and tissues, but their concentrations are sometimes too low to be detected using the existing modern technologies. In small amounts, such elements are not harmful and some of them have even been suggested to have a beneficial role in the human or animal physiology. However, exposure to excessive antropogenically elevated levels can exert serious negative effects on the environment, agriculture and health. The findings summarized in this paper provide a review of the current knowledge about the implications of the transition metals considered on the health, accentuating the insufficiency and need for more relevant data.*

Key words: *niobium, osmium, scandium, tungsten, vanadium*

INTRODUCTION

Over the past decades, a widespread and intensively increasing relevance of transition metals has been observed in a number of industrial, agricultural and medical technologies (Bernot et al., 2006; Hayes, 2008; Ayanda and Adekola, 2011; Rehder, 2016). New technological processes and applications focus on chemical elements that were overlooked in the past only to be recently rediscovered as desirable for the industrial use. The class of industrially attractive chemicals involves a number of transition metals including nionium, osmium, scandium, tungsten and vanadium (Bernot et al., 2006; Hayes, 2008; Ayanda and Adekola, 2011; Rehder, 2016). Most of the elements on the rise are believed to dispose of lower environmental burden and toxicity more readily than extensively used heavy metals such as lead, cobalt, cadmium, etc. For these reasons, the global demand for transition metals, linked to rapidly developing modern technologies, will continue to rise in the future. A sharp increase in the extraction, manufacturing and processing of these metals results in the growing environmental distribution and

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availability. Therefore, animal and human exposures to anthropogenically elevated concentrations are yet more feasible. Despite the potential environmental and health risks, the toxicological investigations were relatively scarce in the past. Heavy metals represent an intensively studied class of environmental pollutants. Many of them play an essential role in the animal and human physiology (Anderson and Wang, 2012; Zambelli and Ciurli, 2013; Zhang, 2014; Czarnek et al., 2015). Nevertheless, exposure to excessive concentrations causes serious damage to diverse organ systems and tissues (Knazicka et al., 2013; Jaishankar et al., 2014; Knazicka et al., 2015). The literature on heavy metals regarding health implications is indeed very ample (Kročková et al., 2011; Forgacs et al., 2012; Tchounwou et al., 2012; Jaishankar et al., 2014; Knazicka et al., 2013; Knazicka et al., 2015;)

However, there is a limited body of information on transition metals such as nionium, osmium, scandium, tungsten and vanadium. The insufficiency of the information may emanate from the fact that such metals have recently started to be applied in industry, especially the electronic, agriculture and biomedical industries. The current state of our knowledge leaves many questions unanswered regarding possible adverse effects of increasing pollution, toxicity mechanisms and environmental (and also occupational) exposures of living organisms (including humans). Therefore, the purpose of this review is to summarize the current information on the trace transition metals widely used in industry, relative primarily to human and animal health implications arising from the elevated risk of exposure.

NIOBIUM

Niobium (Nb) is a ductile transition metal which is strongly associated with tantalum and is often found in many minerals and rocks (Parker and Fleischer, 1968; Ayanda and Adekola, 2011). The crustal Nb concentration is estimated to range from 10 to 14 ppm (Rudnick and Gao, 2003). The industrial use of Nb is concentrated mostly on superconducting magnets, commemorative coins and optical lens (Ayanda and Adekola, 2011). Titanium-aluminium-niobium alloys are, due to their excellent mechanical properties and the corrosion resistance, largely used for orthopedic surgery (Semlitsch et al., 1992). Moreover, radioactive niobium microspheres are applied in biomedicine and experimental studies of the blood flow (Rydzinski and Pakulska, 2012).

Despite the great industrial value and the resulting increase in the Nb distribution, the knowledge about the element in relation to health is indeed very scarce. To present, no biological role has been attributed to Nb, and there are scarce data on its toxicity. The limited number of recent studies on Nb is devoted mainly to the eligibility of metallic implants produced of Nb containing alloys (Rogers et al., 1997; Hallab et al., 2006; Pennekamp et al., 2006).

Since Nb is a rare element, the occupational exposure is of paramount importance (Juliao et al., 2007). Only a few studies have monitored the blood serum levels of Nb. Schroeder et al. (1967) reported the blood serum values of 0.3–0.74 ppm and 4.19–6.4 ppm in red blood cells. Other authors have determined the mean blood concentrations of 4–4.7 pg/L in healthy humans (Rydzinski and Pakulska, 2012). Nonetheless, people employed in the mineral processing industry are exposed to significantly higher levels, which reflected in the elevated urine Nb concentrations (Juliao et al., 2007). Occupational exposure does not represent the only danger. A study by Wappelhorst et al. (2002) revealed that children might be endangered by the Nb exposure through breast milk. The authors monitored the transfer of several elements from food to human milk. Among the studied elements, Nb showed the third highest transfer factor of 20.7 after molybdenum (77.4) and uranium (21.3).

Niobium toxicity is still to be elucidated since it has been studied mostly in relation to orthopedic implants. Zhou et al. (2013) argued that extracts from zirconium-niobium alloys did not induce a significant toxic effect on osteoblast-like cells. Conversely, other experimental results demonstrate that Nb is not utterly innocuous. Hallab et al. (2006) suggest that Nb is less toxic to cells than vanadium and has a less inhibitory effect on human osteoblasts, fibroblasts and lymphocytes proliferation (but is more toxic than Zr). An early research by Wong and Down (1966) observed the toxic effects of Nb in the form of potassium niobate on the function and histology of renal system in dogs and rats. Soluble Nb may act in a metal- and concentration- specific manner to induce adverse local or remote tissue responses (Hallab et al., 2006). However, more attention needs to be devoted to such Nb effects and its behaviour in living systems.

OSMIUM

Osmium (Os) belongs to the group of platinum metals and is considered the least abundant stable element in the Earth’s crust (Wedepohl, 1995). Its average continental crustal abundance is 0.031 ppb. Its environmental concentration is increasing due to intense human activities. The element forms various complexes, among which osmiridium is the most important source of Os (Smith et al., 1974). The major use of the metal is in the osmium tetraoxide form, for example in catalytic converters in the automobile industry. In biology, the compound is used for staining of adipose tissue (Hayes, 2008).

Several classes of Os complexes display suitable properties such as the inertness toward ligand substitution and sufficient stability under physiological conditions (Hanif et al., 2014). Several compounds were therefore suggested to represent alternatives to so far applied anticancer agents (Fu et al., 2010; Maillet et al., 2013; Hanif et al., 2014). These complexes display diverse modes of action: some are able to induce cell cycle arrest as a result of DNA damage (Hanif et al., 2014), whereas others reduce tumor growth without severe adverse effects (Ni et al., 2011). In cancer cells, osmium clusters were shown to induce chromatin condensation, DNA fragmentation, elevated levels of p53 and disrupt microtubules, finally leading to apoptosis (Kong et al., 2009).

The altered geochemical cycles of Os caused by human activities may be a potential source of dangerous interactions with living organisms. Despite a dramatically elevated use, the health hazards arising thereof are barely studied. Metallic osmium is not considered to be toxic, however, osmium tetraoxide has been found to have irritant and toxic effects on animal and human organisms even at low levels (Brunot, 1933; Luttrell and Giles 2007). The extreme extent of its poisonous effects gives it the potential of a chemical weapon (Bhattacharya, 2004). The lethal concentration time for osmium tetroxide is considered to be 1316 mg/min/m3, and the maximal tolerated concentration for humans is 0,1 ppm in air for 1,5 hours or 0,0001 ppm for 6 hours without harmful effects (Makarovsky et al., 2007). Osmium tetroxide is a rapid, indiscriminative oxidizer of both organic tissue and inorganic materials. Most exposures are to osmium tetroxide vapor, which can cause severe chemical burns to the eyes, skin and respiratory tract (Grant, 1974). Despite grave threats resulting from the high toxicity of the compound, relevant recent research publications are still scarce. Only a small number of early toxicology studies reported on the Os induced toxicity and damage (Brunot, 1933; Hamilton and Hardy, 1974). In the study by Brunot (1933), rabbits exposed to osmium tetraoxide at a concentration of 130 mg/m3 died from pulmonary edema after 4 days. The administration of the compound also caused serious corneal damage and opacity in rabbits (Brunot, 1933), and expressed detrimental effects to the guinea pig bone marrow (Hamilton and Hardy, 1974). In other cases, osmium tetroxide caused nose and throat irritations (Hamilton and Hardy, 1974), lacrimation and vision , or even had fatal consequences (McLaughin et al., 1964).

The chemical properties of osmium tetroxide (volatility and solubility in water) create conditions for broad anthropogenic contamination of the atmosphere and water ecosystems (Smith et al., 1974, Chen et al. 2009). Therefore, the need for detailed studies on the Os effects on biological systems should not be disregarded.

SCANDIUM

Scandium (Sc) belongs to the class of rare earth elements among which it is the lightest and the most durable (Gillespie, 1993). The average continental crust value of Sc is 22 ppm (Rudnick and Gao, 2003), whereas China has the largest Sc deposits. Generally, REEs are thought to be non-toxic, non-polluting and environmentally friendly. For these reasons, they are increasingly replacing heavy metals in industry. Scandium has an abundant range of technological applications including the production of scandium-aluminium alloys, magnets, glass, ceramics (Bernot et al., 2006) and utilization in ever-increasing electronics and appliances markets. Recently, REEs have been recognized as environmental pollutants, representing a major issue especially in China. Very little data are available concerning the physiological and/or toxicological effects of Sc. Rapidly developing REE technologies emphasise a need for additional information on the health effects of potential exposure to the elements.

The average plasma concentration of Sc in healthy population is around 28.6 ng/L (Sánchez-González et al., 2013). It was revealed that elemental concentrations in the serum were responsive to physical activity whereby Sc and W levels decreased after physical exercise (Otag et al., 2014). Sc is transported primarily by transferrin in the organism (Ford-Hutchinson and Perkins, 1971), where binding with other proteins such as albumin and globulins occurs as well (Rosoff and Spencer, 1979). Like other REEs, Sc is partially eliminated via urine, although in very small amounts (Tanida et al., 2009; Kitamura et al., 2012; Sánchez-Gonzales et al., 2013). According to Øksendal (1993), ionic REEs in the blood are rapidly changed into colloidal REEs (such as hydroxides and phosphates) and are taken up by the reticuloendothelial system in the liver. It is presumed that the reticuloendothelial system acts as a deposit, which leaves only a small portion for urine excretion (Øksendal, 1993). Despite the considerations mentioned above, the Sc excretion is still proposed to be a useful tool for exposure monitoring, when using a suitable and sensitive technique (Tanida et al., 2009; Kitamura et al., 2012).

Scandium has no known biological function. It is considered of low toxicity under the US Toxic Substances Control Act. However, scandium chloride is poisonous by the intraperitoneal route and moderately toxic by ingestion (Sax and Lewis, 1992). The knowledge about changes in molecular mechanisms caused by the Sc exposure is indeed insufficient. Only a few studies have focused on the effects of RREs on different tissues and organs (Gebhart and Rossman, 1991; Horovitz, 2000; Tanida et al., 2009; Sánchez-Gonzales et al., 2013) and documented the Sc driven mutagenic, teratogenic (Gebhart and Rossman, 1991) and carcinogenic effects (Horovitz, 2000). The element was found to act as a harmful substance to the liver, lungs, skin (Horovitz, 2000) or renal system (Tanida et al., 2009; Sánchez-Gonzales et al., 2013). An increase in the Sc circulating levels in the human plasma was associated with chronic kidney disease (Sánchez-Gonzales et al., 2013). Scandium has a high affinity toward proteins due to which it acquires the potential to displace essential metals in many biochemical events (Brown et al., 1990). It was indicated that RREs combined with globulin or albumin affect the immune function (Sotogaku et al., 1999; Liu et al., 2002; Zhu et al., 2005). Negative effects of the Sc exposure were observed also on bacteria, in contrast, eventually having beneficial outcome for a host. Scandium complexes were shown to dispose of the bacteriostatic effect in the serum, probably by interfering with enterocholin system and thus interrupting bacterial iron supply (Rogers et al., 1980). Moreover, the RREs-realted health impacts are not elucidated, and systemic and basic knowledge on Sc needs to be broadened.

TUNGSTEN

Tungsten (W) is a unique transition metal naturally occuring in the nature. It occurs as a component of rocks and minerals combined with other chemicals, but never as a pure metal (Lassner and Schubert, 1999; Stiefel, 2002). It is present in the Earth's crust at an average concentration of 60 ppm and, as in the case of Sc, China boasts the largest W reserves. Tungsten has the highest melting point and lowest vapor pressure of all metals (van der Voet et al., 2007). Many of W attributes are favourable for industrial uses, namely metallurgy, production of wire in lamp bulbs, electronic devices, but also implanted medical devices.

Being a naturally occurring element, W has an important function in the soil microbiology (Kletzin and Adams, 1996). It plays an essential role for microbial organisms (Kletzin and Adams, 1996), where it exists as a component of specific microbial enzymes (Hille, 2002; L'vov et al., 2002). However, unnatural, anthropogenically altered levels of W trigger changes in soil microbial communities and lead to the death of a substantial portion of the bacterial component. Moreover, it can also induce the death of different plants and red worms (van der Voet et al., 2007).

Exposure to very low, natural levels of W occurs by breathing air, eating food, or drinking water (van der Voet et al., 2007). Moreover, the iatogenic exposure in humans may represent another way of the W administration, particularly in patients with embolization coils (which were shown to corrode or even dissolve) (Butler et al., 2000; Bachthaler et al., 2004). For humans, W and its compounds are not regarded as very toxic and, as yet, no essential function is attributed to the metal in the biology of humans. In the human serum of control individuals, W levels of 0.44 μg/L were determined (Butler et al., 2000). When present in the human or animal organism, W is excreted from the body through kidneys (Lagarde and Leroy, 2002). Regardless of the very rapid excretion via the renal system, W accumulates in diverse organs and tissues. Bone was discovered to be the place of the preferential W accumulation, which occurs in a dose-dependent manner (Kelly et al., 2013). Tungsten was proposed to share some similarities in biological behaviour with essential elements such as molybdenum and phosphorus. It was shown that W in the form of tungstenate can substitute phosphate in the bone (Fleshman et al., 1966). The chemical similarity was used to produce experimental molybdenum deficiency in animals, since W as an analogue prevents the incorporation of Mo into certain enzymes (Cardin and Mason, 1976).

The preferential accumulation in the bone makes it a site for the manifestation of W harmful effects. Tungsten was shown to alter the differentiation of bone marrow-resident mesenchymal cells (Bolt et al., 2016). Even after cessation of the primary exposure, the endogenous exposure still persists. This effect is due to the continuous release from skeleton as the secondary storage reservoir (Kelly et al., 2013). The accumulation of W is a much faster process than the depletion from the bone (Kelly et al., 2013) and it is estimated that some amounts of W can remain in the skeleton even several years after the cessation of the administration (Leggett, 1997). Recent study demonstrated differences in the W accumulation in bones relative to age (Bolt et al., 2016). However, the regulation processes are essential for a better understanding of the accumulation mechanisms.

Most of the existing toxicology data on W are based on chronic occupational exposure. In cases of acute poisoning, a W concentration of 5 mg/L was determined in the blood (Marquet et al., 1996; Marquet et al., 1997). Occupational exposure focuses primarily on the inhalatory and the dermal route (van der Voet et al., 2007). The inhalation of tungsten-polluted dust and air often leads to pulmonary toxicity (Nemery et al., 2001; Roedel et al., 2012,). When inhaled, highest W concentrations are found in the lungs, followed by the bone (Rajendran et al., 2012). Tungsten was revealed to act as a cytotoxic and immunotoxic agent (Osterburg et al., 2010), to promote carcinogenesis (Laulicht et al., 2015) and enhance metastasis by targeting the tumor microenvironment (Bolt et al., 2015). Neuropsychological impairments, especially memory function impairments, were reported in individuals exposed to W found in the occupational environment (Jordan et al., 1993). According to the latest study, the co-exposure of W and other agents and stressors can result in higher toxicity and augment damages caused to the organism (Barceloux and Barceloux, 1999; Bolt and Mann et al., 2016). Tungsten carbide may modify the toxic action of cobalt, which alone does not have the same toxic effect (Barceloux and Barceloux, 1999).

Regarding the increasing awareness of hazards due to the W exposure, the information on the potential environmental effects of tungsten released in the environment are not sufficient to make an environmental risk assessment.

VANADIUM

Vanadium (V) is a transition metal widely distributed in the Earth's crust, mainly as a component of numerous rocks. The vanadium abundance in Earth's crust amounts to 135 mg.kg-1 (Rehder, 2016). Vanadium is mostly used in the production of alloys, ceramics and superconductive magnets. It naturally enters body via drinking water, consuming food and inhaling air. The intake of V through food occurs mostly in the form of vanadyl species (Rehder, 2016). Vanadyl compounds are subsequently converted to insoluble vanadyl hydroxide by saliva and are mostly excreted through the gastrointestinal tract, i.e. feces (Rehder, 2016). In the human plasma, V occurs at a concentration of 1.2 μg/L (Wang et al., 2014). It exists in the form of metavanadate and vanadyl in extracellular and intracellular body fluids, respectively (Barceloux and Barceloux, 1999; Rehder, 2015). The metal is usually complexed with proteins such as transferrin, albumin, hemoglobin or low molecular components of the plasma (citrate, lactate and phosphate) (Gruzewska et al., 2014; Rehder, 2015; Panchal et al., 2017). In such manner, it is transported to various tissues such as the liver, heart, kidney, brain, muscle and adipose tissue (Panchal et al., 2017). As with tungstenate, V occuring in the form of vanadater can act as a substitute for phosphate in the apatite of the bones and enzymes such as phosphatases and kinases (Rehder, 2015). Vanadium was also found to be transfered in very small amounts into milk (Heidaria et al., 2016). Hansard (1975) suggested that V displays only low dietary absorption rates (e.g. in sheep not higher than 1%), which might be the cause of low transfer.

Numerous publications deal with V as a trace metal having a beneficial function for maintaining animal and human health (Uthus and Nielsen, 1990; Haenlein and Anke, 2011; Heidaria et al., 2016; Jiang et al., 2016). At the beginning of the last century, the metal was even regarded as a panacea for treatment of numerous illnesses (Gruzewska et al., 2014). The possible nutritional essentiality of V is supported by a number of animal studies (Nielsen, 1990; Uthus and Nielsen, 1990; Cui et al., 2011; Haenlein and Anke, 2011). The long term V deficiency for over 15 generations suppressed feed intake and milk production, and even reduced survival rate and reproduction efficiency (Haenlein and Anke, 2011). Other studies reported that the V deficiency might lead to slow growth in rats (Nielsen, 1990) and poultry (Cui et al., 2011), or an increase in abortion rates in goats (Uthus and Nielsen, 1990). In cows, the V supplementation during the periparturient period increased milk production, which possibly resulted from the improvement of metabolic parameters such as higher glucose levels (Heidaria et al., 2016).

Vanadium is considered to have insulin-mimetic properties, rendering it a potential therapeutic agent for metabolic diseases (Zampella et al., 2006; Jiang et al., 2016). Vanadium is involved in the regulation of enzymes, the energy metabolism and the cardiovascular health, particularly with regard to glucose homeostasis (Panchal et al., 2017). Beneficial effects of V compounds on the blood pressure, ischemia and the metabolism of the thyroid were reported as well (Korbecki et al., 2012; Gruzewska et al., 2014). Taking into account the previous considerations, it is perfectly understandable why so much effort is currently being expended in the development of effective organic V compounds for the therapy of several diseases (Jiang et al., 2016). Vanadium was established as an essential element for several organisms including fungi, Streptomyces bacteria, lichens and algae (Rehder, 2016). However, the role of essential micronutrient for human health is still controversial and a subject of intense debates (Gruzewska et al., 2014).

Numerous conflicting findings regarding the V detrimental effects on humans or animals have been documented (Barth et al., 2002; Gruzewska et al., 2014; Jiang et al., 2016; Jung et al., 2017; Sun et al., 2017). For example, a diet supplemented with V in laying hens was shown to affect the egg quality. Concentrations of 5 and 10 mg/kg increased the egg V residual, reduced the egg albumen quality and bleached the shell color (Wang et al., 2017). The dietary V in excess of 30 mg/kg caused alternations in the amount and diversity of intestinal bacteria in broilers, implying the disruption of microbiota (Wang et al., 2012). Generally, the intoxication with V is unlikely to occur under ordinary environmental and nutritional conditions (Rehder et al., 2016). Cases of acute V poisoning are likewise rather infrequent. A study by Frank et al. (1996) provides a documented case of V poisoning of cattle from slag used as a fertilizer, which resulted in diminished milk production, impaired general state of health or even death. Another case reported on the human fatal intoxication caused by ammonium vanadate, wherein the plasma concentration of V was 6.22 mg/L (Boulassel et al., 2011).

The excessive accumulation of V can have a toxic influence on a variety of organs and tissues, among which the kidneys and liver are particularly vulnerable (Liu et al., 2012). Susceptibility to the V toxicity also varies considerably among diverse species (Suttle, 2010). Suttle (2010) proposed that poultry were the most and sheep were the least susceptible farm animal species. Excessive amounts of V were revealed to play a role in disorders of the blood, cardiovascular system, pulmonary system or intestinal inflammation (Jiang et al., 2016; Jung et al., 2017). In animals, V caused oxidative damage, renal and hepatic toxicity and lesions leading to the impairment of the renal and hepatic function (Liu et al., 2012). The over-exposure to V reflected in the damage of the reproductive system, developmental defects (Domingo, 1996), or even contributed to cancer formation (Clancy et al., 2012). Vanadium also appears to be implicated in neurobehavioral changes (Barth et al., 2002; Sun et al., 2017). The long-term

exposure from drinking water resulted in the V accumulation in striatum, its pathological changes, alternation in neurotransmitter contents, and was associated with diminished learning abilities and memory functions in animals (Sun et al., 2017). The association between V levels and reduced cognitive abilities including deficits in visuospatial abilities and attention was observed as well (Barth et al., 2002). Moreover, V was shown to alter the epigenetic regulation (Jung et al., 2017). The exposure to V via polluted air was associated with the altered DNA methylation of allergic and proinflammatory asthma genes (Jung et al., 2017).
On balance, despite the proposed essentiality and benefits of V and its compounds to health, there are numerous publications providing evidence of the adverse effect of the V administration or exposure. Therefore, further research on the issue should be conducted.

Table 1 Brief overview of natural concentration of selected transition metals and their biological role

Chemical element	Earth's crust concentration	Human plasma/serum concentration	Biological function in animals/humans
Niobium	10-14 ppm	0.53–0.74 ppm	no
Osmium	0.031 ppb	No data	no
Scandium	22 ppm	28.6 ng/L	no
Tungsten	60 ppm	0.44 μg/L	no
Vanadium	135 ppm	1.2 μg/L	Insulin-mimetic, energy metabolism, but controversial

CONCLUSIONS

For a long time, the trace elements mentioned above were not a topical issue as their bioavailability in nature is low. However, alternations in their distribution have recently urged researchers to gain a more comprehensive insight into their behavior. A plurality of publications imply beneficial outcomes in the animal physiology. However, a considerable number of studies also argue the negative effect of these elements. For a better understanding and elucidation of their function, mechanisms, and safety limits, more emphasis has to be placed on the need for in-depth scientific investigations.

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