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Human exposure to heavy metals: toxicity mechanisms and health implications

Abstract

Human exposure to heavy metals is inevitable as heavy metals are continually present in air, water and food. Anthropogenic and industrial activities have rapidly increased the level of human exposure to heavy metals. Some heavy metals elicit deleterious health effects even at low levels in the body system. Every heavy metal has its own specific unique mechanistic process through which it exhibits toxicity. The major mechanisms through which most heavy metals such as Cr, As, Pb, Cu, Fe, Cd, Zn, Ni cause toxicity include the generation of reactive oxygen species (ROS), inhibition of enzyme activities and attenuation of antioxidant defense systems. Heavy metal ions are known to interfere with DNA and nuclear proteins leading to DNA structural and functional impairments as well as changes that initiate carcinogenesis, apoptosis as well as modulation of cell cycle. Heavy metal toxicity alters the activity of the central nervous system, and thereby causes mental disorder, alters blood composition, and liver, kidneys, lungs functions as well as other important body organs, resulting in the escalation of assorted human diseases. Prolonged human exposure and accumulation of heavy metals in the body aggravate the progression of physical, muscular and neurological degenerative processes that mimic certain diseases such as Alzheimer's disease and Parkinson's disease. Heavy metals mimic hormonal activities that alter the functions of the endocrine system. Thus, efforts must be made to mitigate the extent of human exposure and accumulation of heavy metals in the body as a result of anthropogenic and industrial activities in order to prevent incidences of deleterious health challenges.

Keywords: diseases, health, heavy metals, toxicity

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Introduction

Heavy metals are naturally occurring metallic elements whose densities are about 5 times greater than that of water (density > 5 g/cm^3).[1-3] Heavy metals pose serious health threats to humans. Specifically, Cr, As, Pb, Cu, Fe, Cd, Zn, Ni are among the metals that are of high public health concerns. These heavy metals are systemic toxicants that initiate arrays of organ dysfunction in humans, even at low levels in the body system.[4-7] Gender differences have been reported to correlate with heavy metal toxicity.[1,8] The toxicological potency of a heavy metal is also dependent on its concentration and exposure route. Other factors that affect metal toxicity include the age, genetic composition as well as the nutritional status of the individual exposed to heavy metals.[1]

Heavy metal toxicity is dose dependent.[9] At relatively low concentrations, heavy metals contribute positively to certain biochemical and physiological functions of the body system, whereas at higher concentrations above certain threshold, they become deleterious to human health.[10,11] Although heavy metals cause toxicity through assorted mechanisms, some of these processes are not very much elucidated. Every heavy metal has its own specific unique mechanistic process through which it exhibits toxicity. The major mechanisms through which most heavy metals cause toxicity include ROS generation, inhibition of enzyme activities and attenuation of antioxidant defense systems.[1,12] Heavy metal ions are known to interfere with DNA and nuclear proteins leading to DNA structural and functional impairments as well as changes that initiate carcinogenesis, apoptosis and modulation of the cell cycle.[13,14] Heavy metal toxicity alters the activity of the central nervous system, and thereby causes mental disorder, alters blood composition, and liver, kidneys, lungs functions as well as other important body organs, resulting in the escalation of assorted human diseases.[15] Prolonged human exposure and accumulation of heavy metals in the body system aggravates the progression of physical, muscular and neurological degenerative processes that mimic certain diseases such as Alzheimer's disease and Parkinson's disease.[16] Heavy metals mimic hormonal activities that alter the functions of the endocrine system.[17] Human exposure to heavy metals is inevitable as heavy metals are continually present in air, water and food. More so, anthropogenic and industrial activities have rapidly increased the level of human exposure to heavy metals.[8,12,18-20] The present review summarized the toxicity mechanisms of heavy metals and the associated health implications.

Evidence acquisition

This review were sourced online from scientific search engines, including ResearchGate, Google Scholar, Scopus, PubMed, Medline and Springer Link, using keywords such as 'heavy metals', 'heavy metals toxicity' heavy metals/health implications. A total number of 146 references published online between 1983 and 2021 were used as information sources and cited in this review.

Sources of human exposure to heavy metals

Heavy metals occur naturally in the environment.[21] However, the main routes of human exposure to heavy metals are anthropogenic activities such as mining, industrial and agricultural activities, indiscriminate solid waste disposal, municipal wastewater discharges, incineration, etc.[22] In the earth's crust, heavy metals occur as ores, and are obtained as minerals through the process of mining. Certain heavy metals such as Fe, Zn, Ar, Co, Ni and Pb occur as sulfides in most ores, while other heavy metals, namely; Mne, Al, etc. occur as oxides. Furthermore, heavy metals such as Co, Fe and Cu exist as both oxide and sulfide ores. Heavy metals are released into the

environment from ores during mining activities and subsequently deposited in the soil, distributed through air and water to various regions of human habitation.[2,15] Heavy metals are also released into the atmosphere during industrial combustion or deposited as effluents into the soil and water bodies. Furthermore, industrial products such as batteries, coatings, cosmetics, paints, etc. consist of heavy metals and are sources of human exposure to heavy metals. Heavy metals are distributed to various areas of human habitation through erosion, run-off or acid rain.[15,23,24] The use of agro-chemicals such as fertilizer, herbicides, pesticides, and manure as well as waste water irrigation and soil improvement in agricultural practices contribute to human exposure to heavy metals. These activities cause the deposits of large amounts of toxic heavy metals in the soil and air, which are inevitably absorbed by plants. These toxic heavy metals are assimilated by humans when such plants are consumed.[3]

Lead toxicity

Lead (Pb) is a noxious environmental contaminant that provokes toxic effects on various organs of the body. Although Pb is assimilated into systemic circulation through the skin, it is mostly absorbed from the respiratory and digestive systems.[12] Pb poisoning initiates anaemia through the suppression of two major enzymes of the heme biosynthesis pathway, namely: ferrochelatase and δ-aminolevulinic acid dehydratase (ALAD). The inhibition of these two major enzymes by Pb compromises the biosynthesis of heme, and thereby, induces anaemia[12,25] (Figure 1).

Furthermore, Dongre et al.,[26] reported that Pb significantly decreased red blood cell count, hemoglobin concentration, mean corpuscle hemoglobin concentration (MCHC), hematocrit and mean corpuscle volume (MCV), while diastolic blood pressure and systolic blood pressure are elevated. Series of respiratory disorders, atherosclerosis and chronic cardiovascular impairments are also associated with Pb toxicity. [27,28]

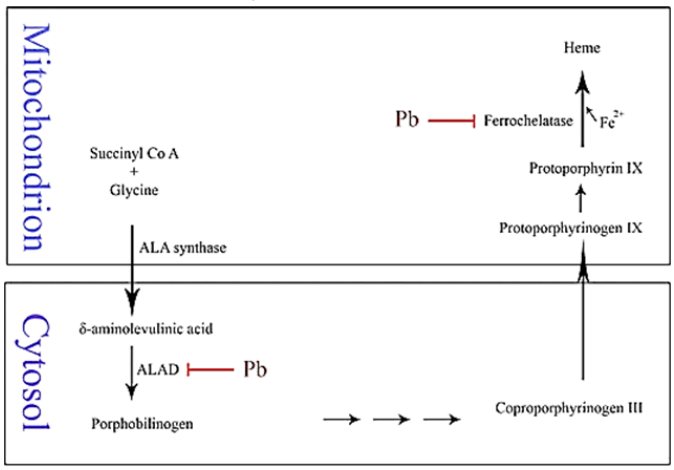

Figure 1 Inhibition of ferrochelatase and δ-aminolevulinic acid dehydratase (ALAD) in heme biosynthesis by Pb.[12]

ALA, δ-aminolevulinic acid

Human exposure to Pb causes deleterious alterations in the level of thiol antioxidant molecules {glutathione$_{reduced}$ (GSH), glutathione$_{oxidized}$ (GSSG)} and antioxidant enzymes {superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR)}, which leads to oxidative stress. Pb has the capability to lower tissue GSH levels as a result of its high binding affinity with the reactive sulfhydryl (–SH) group of GSH. The antioxidant functions of metallo proteins such as GPx, CAT, and SOD in the detoxification of free radicals are altered following human exposure to Pb. Organ oxidative damage, initiated by Pb, occurs through membrane lipid peroxidation elicited by decreased tissue levels of antioxidant factors.[29,30] Additionally, Mishra et al.,[31] had reported the inhibition of lymphocyte proliferation by phytohemagglutinin (PHA) and elevation in the level of interferon-γ (IFN-γ) in stimulated peripheral blood mononuclear cells (PBMCs) following human exposure to high Pb concentration.

The activities of the central nervous system (CNS) are obstructed through the alteration of intracellular second messenger systems following human exposure to Pb.[32] The mechanism through which Pb induces carcinogenesis encompasses the destruction of DNA, alterations in the DNA repair system and cellular tumor regulatory genes by ROS production. The ROS generated play a major role in the alteration of the structure and sequence of human chromosomes. Pb obstructs the process of transcription by displacing Zn in some regulatory proteins.[15] According to Martin and Griswold,[33] acute Pb toxicity initiates hallucinations, pain in the abdomen, headache, lethargy, loss of appetite, kidney function impairment, dizziness and arthritis. Conversely, chronic Pb toxicity leads to birth disorders, renal failure, neurological impairments, allergies, mental disorders, learning disability, and autism, muscles weakness, coma and possibly death. The process that leads to assorted diseases in humans due to high level of Pb in the blood is presented in Figure 2.

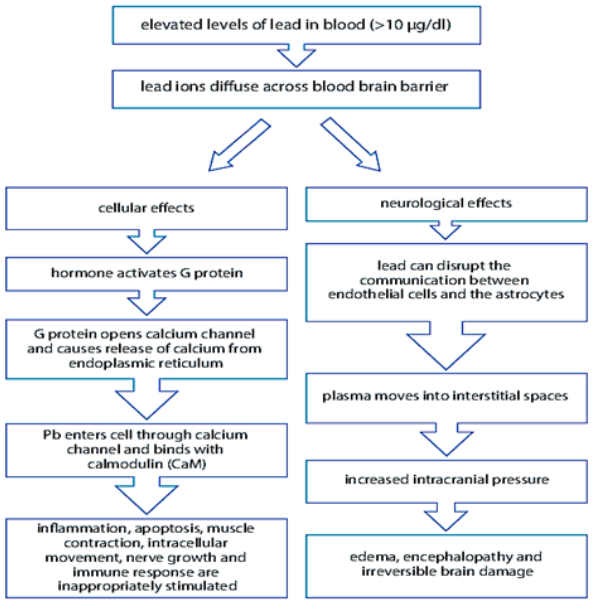

Figure 2 Processes leading to assorted diseases in humans due to high level of Pb in the blood.[34]

Copper toxicity

Copper (Cu) occurs in nature in the form of an element and compounds. Cu ions exist in the oxidized state or reduced state as cupric ion (Cu^{2+}) or cuprous ion (Cu^{+}) respectively.[35] Cu is released into the air from natural sources such as volcanoes, forest fires, and windblown dust as well as industrial processes and anthropometric activities such as iron and steel production, municipal incinerators, Cu smelters, etc. Environmental sources of Cu include contaminated drinking water, vitamin and minerals supplements, birth control pills, Cu cookware, Cu intrauterine devices, Cu water pipes, etc.[36] In biologic systems, Cu ions initiate ROS generation and undergo reduction to Cu^{+} in the presence of biological reductants such as ascorbic acid or GSH. The Cu^{+} promotes hydrogen peroxide (H_2O_2) decomposition

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leading to the formation of hydroxyl radical ($OH^{\bullet}$) through the Fenton reaction (Equation 1).[37]

$$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^{\bullet} + OH^{-} \quad \text{Equation 1}$$

The $OH^{\bullet}$ generated undergo reaction with various biomolecules, which engenders deleterious outcomes. Cu has also been implicated to initiate breaks in DNA strands as well as DNA base oxidation from ROS generation.[38]

Cu accumulation in the liver and other organs of the body is accompanied by hepatic and neurological disorders such as hepatitis, cognitive or psychiatric impairments and motor deficits. The presence of Cu in the hepatocytes initiates Wilson's disease.[35] Cu induces apoptosis in humans via the p53 dependent and independent pathways. Apoptotic disorder, initiated by Cu toxicity, has been reported to be involved in hepatotoxic and neurotoxic abnormalities.[39] Cu^{2+} has been reported to induce apoptosis of the liver cells via the activation of acidic sphingomyelinase and the release of ceramide (an apoptotic signal). The release of ceramide is made possible through the activation of acidic sphingomyelinase from white blood cells.[40] Furthermore; acidic sphingomyelinase is known to trigger tumor necrosis factor (TNF)-induced lethal hepatitis through the inhibition of liver-specific methionine adenosyltransferase 1A. The plasma levels of acidic sphingomyelinase and ceramide have also been reported to be high in persons suffering from Wilson disease.[41,42] These findings therefore confirm the major role that Cu^{2+} plays in the induction of the apoptosis of liver cells through the activation of acidic sphingomyelinase and ceramide release.

Arsenic toxicity

Arsenic (As) toxicity is one of the major concerns of the public health sector. Human exposure to as occurs through the consumption of contaminated water and food or through occupational activities. As is known as a metalloid or medicinal product; it is notoriously referred to as the king of poisons and poison of kings.[43] As occurs in the forms of inorganic (As^{3+} and As^{5+}), organic, metalloid (As^{0}) as well as arsine (AsH_3), and their decreasing order of toxicity are as follows: AsH_3 > As^{3+} > As^{5+} > As^{0} > organic arsenicals.[44-46] The major route of As absorption is through the small intestine. Skin contact and inhalation are also exposure routes.[12]

Continuous human exposure to inorganic As is accompanied by cardiovascular impairments such as atherosclerosis, ischemic heart diseases, ventricular arrhythmias and hypertension.[47] As activates NADPH oxidase in the plasma membrane of vascular endothelial cells and vascular smooth muscle cells (VSMC) to trigger the formation of ROS e.g. H_2O_2 and superoxide ion ($O^{\bullet}_2$).[48] The ROS formed in conjunction with nitric oxide (NO) generates strong oxidant known as peroxynitrite which is involved in the upregulation of inflammatory mediators e.g. cyclooxygenase-2 (COX-2).[49] This ROS also elevates atherosclerosis related genes expression such as monocyte chemo-attractant protein (MCP-1), interleukin-6 (IL-6), and heme oxygenase-1 (HO-1), and thereby triggers the adhesion, penetration and movement of monocytes in the VSMC.[50] As causes the transformation of the focal adhesion proteins in VSMCs resulting in their proliferation and migration.[51] Also, As is known to trigger atherosclerosis pathogenic events by stimulating the generation of inflammatory mediators, nuclear factor kappa B (NF-KB) and tumor necrosis factor-alpha (TNF-α).[52,53] Chen et al.,[54] reported that As initiates neurogenic inflammation of the blood vessel by elevating the generation rate of endothelial neurokinin-1 and substance P. Additionally, reports showed that As aggravates the function of endothelial nitric oxide synthase (eNOS) as well as Akt/protein kinase B, which in turn reduces NO concentration, which results in vascular endothelial dysfunction and related cardiovascular impairments.[55,56] As induces vasoconstriction of the blood vessels through phosphorylation of myosin light chain kinase (MLCK), and enhance calcium sensitization, and thereby cause hypertension.[57] Chronic As toxicity stimulates oxidative stress as well as initiates changes in the production of vasoactive mediators in the blood vessel that provokes hypertension.[58] Ventricular arrhythmia has been attributed to arsenic trioxide toxicity through the induction of elongated Q-T interval and action potential duration.[47,59] Generally, As initiates cardiovascular dysfunction through the stimulation of high oxidative stress, hindered eNOS stimulation, and activation of MLCK phosphorylation[60] (Figure 3).

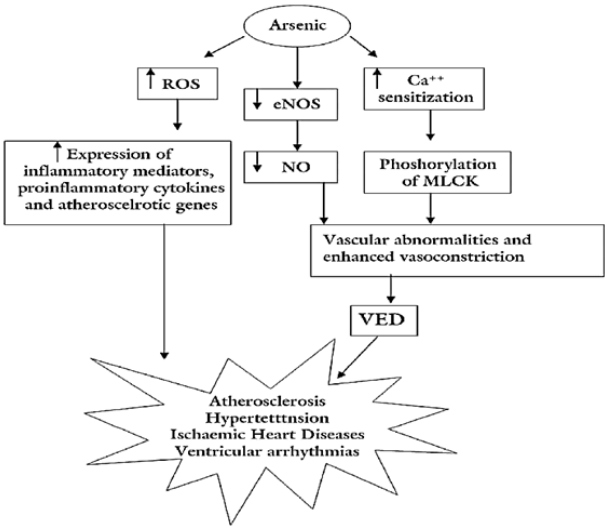

Figure 3 Pathways for As-induced cardiovascular dysfunction.[60]

Thus, hepatotoxicity and nephrotoxicity are initiated by as through oxidative stress, upregulation of transcription factors and apoptosis[61] (Figure 4). As accumulates in the kidney during urinary elimination and disrupts the activities of the proximal convoluted tubules.[61] Oxidative stress triggered by As stimulates the expression of HO-1 and mitogen-activated protein kinase (MAPK), which eventually initiates renal toxicity through the regulation of transcription factors, namely; activator protein-1 (AP-1), Elk-1 and activating transcription factor-2 (ATF-2).[62] As-induced acute renal impairment is associated with acute tubular necrosis, increase in blood creatinine and urea nitrogen levels.[63] As triggers the formation of ROS, which further stimulates lipid peroxidation as well as tissue damage of the kidney and liver.[64] Oxidative stress initiated by chronic human exposure to As stimulates c-Jun-N-terminal kinase (JNK) and p38MAPK, and upregulates pro-apoptotic proteins that triggers liver cells apoptosis.[65-67]

Furthermore, as has also been reported to initiate carcinogenicity and diabetes mellitus in humans. As triggers carcinogenicity by enhancing oxidative stress, genotoxicity, disruption in the expression of growth factors as well as alteration in the DNA repair process.[68-70] As induces diabetes mellitus through the reduction of peroxisome proliferator activated receptor-gamma (PPAR-γ) expression, alteration in the release of ATP-dependent insulin, disruption in glucocorticoid receptor mediated transcription and the suppression of 3-phosphoinositide-dependent kinase-I (PDK-1).[71-77]

Iron toxicity

Iron (Fe) is the second most abundant metal on the earth's crust. It is the 26th member of the periodic table. Fe occurs abundantly in

surface water through anthropogenic activities such as mining.[10] Fe is the cofactor for various proteins and enzymes.[78]

Fe, in its free state, produces OH• as represented in the Fenton reaction (Equations 2 and 3).

$$Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2 \quad \text{Equation 2}$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad \text{Equation 3}$$

The OH• is generated through the oxidation of Fe^{2+} to Fe^{3+}. The OH• has potentials of undergoing deleterious reactions with biological molecules such as lipids, proteins as well as DNA, and damaging them in the process. The 8-oxo-7, 8-dihydro-20-deoxyguanosine (8-oxo-dG) and 2, 6-diamino-5-formamido-4-hydroxypyrimidine (FAPy-G) are generated when OH• reacts with guanine. The 8-oxo-7, 8-dihydro-20-deoxyguanosine (8-oxo-dG) is a common biomarker for oxidative tissue damage.[79]

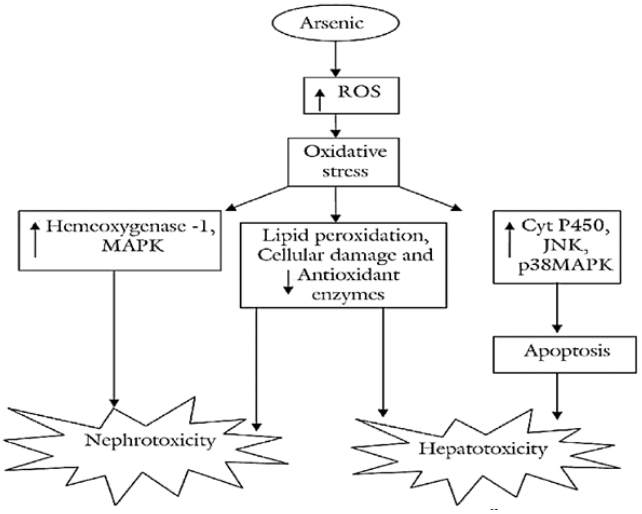

Figure 4 Pathways for As-induced nephrotoxicity and hepatotoxicity.[60]

Fe-generated OH• also initiates the oxidation of lipid membranes via lipid peroxidation as described by Bucher et al.,[80] The initiation stage of this process involves the attack on the lipid membrane by the radical R•/OH•, leading to the formation of a radical lipid (Lipid•). At the propagation stage, the radical lipid (Lipid•) reacts with dioxygen (O_2) molecule or a lipid to generate peroxyl lipid radical (Lipid−OO•), which eventually leads to damage of the lipid molecule. At the termination stage, two radical lipid molecules, or with a peroxyl lipid radical, react to generate a stable lipid molecule. Furthermore, malondialdehyde (MDA) is the main aldehyde product of lipid peroxidation, and functions as a biomarker for lipid peroxidation (Equations 4-8).

Initiation: $Lipid + R^{\bullet} / OH^{\bullet} \rightarrow Lipid^{\bullet}$ Equation 4

Propagation: $Lipid^{\bullet} + O_2 \rightarrow Lipid - OO^{\bullet}$ Equation 5

$Lipid - OO + Lipid^{\bullet} \rightarrow Lipid - OOH + Lipid^{\bullet}$ Equation 6

Termination: $Lipid^{\bullet} + Lipid^{\bullet} \rightarrow Lipid - Lipid$ Equation 7

$Lipid - OO^{\bullet} + Lipid^{\bullet} \rightarrow Lipid - OO - Lipid$ Equation 8

Cadmium toxicity

Cadmium (Cd) is occurs naturally in the soil, water as well as minerals such as sulfate, sulfide, chloride, carbonate and hydroxide salts. Industrial activities release significant amount of Cd into the air, soil and water, from where it is absorbed by humans. Consumption of Cd polluted food is one of the major human exposure to Cd. Smoking is also known to increase blood and urine Cd concentrations.[81-83] Cd alters the proliferation and differentiation of cells, which further influences the DNA repair mechanism, upregulates ROS generation and apoptosis.[84] Cd suppresses cellular respiration and oxidative phosphorylation in the mitochondria, and thereby lowers cellular energy generation.[85] Cd causes chromosomal aberrations, sister chromatid exchange, breaks in DNA strands, as well as DNA-protein crosslinks in cell lines. Cd initiates mutations and deletions in the chromosome.[86]

Cd exacerbates low tissue levels of GSH and suppresses the actions of antioxidant enzymes such as Cu/Zn-dismutase, manganese-SOD and CAT. Cd is induces the generation of reactive oxygen and nitrogen species (RONS) such as $O^{\bullet}_2$, NO• and OH• resulting in oxidative stress. These processes lead to organ toxicity, carcinogenicity and apoptotic cell death[22,87,88] (Figure 5). Cd causes skeletal demineralization through direct interaction with osteocytes. Cd also suppresses the production of collagen through the inhibition of procollagen C-proteinases. According to Rahimzadeh et al.,[22] Cd alters the metabolism of calcium, collagen and vitamin D_3, which leads to osteomalacia or osteoporosis especially in severe cadmium poisoning.

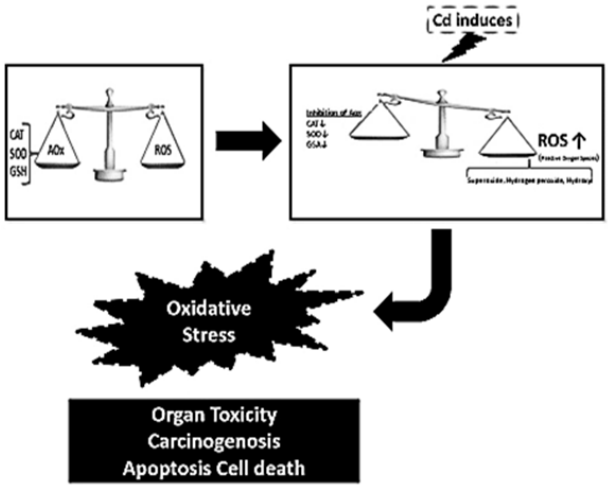

Figure 5 Effects of elevation in reactive oxygen species (ROS) and suppression of antioxidant levels induced by Cd.[22]

The most grievous form of chronic cadmium poisoning is the Itai-itai disease, which is characterized by osteopenic osteomalacia, renal anemia and tubular nephropathy. Two hypotheses have been proposed for the bone lesion pathogenesis, namely: the direct effect of Cd on bone and its indirect effect. The direct effect describes Cd impact on the osteoblasts and the inhibition of calcification at the ossification front. The indirect effect refers to nephrogenic osteopenia through the reduction in blood calcium and phosphate levels as well as hyperparathyroidism.[89] Cd has been reported by various studies to have effect on reproduction and development.[90] This is manifested in the male reproductive process through reduction in sperm levels and increase in the concentration of immature sperms.[91] Cases of negative alteration in spermatogenesis and sperm quality are accompanied with low libido, reduced serum testosterone level and finally infertility.[92]

In the female reproductive system, Cd inhibits the function of the ovary and oocytes development as well as presentation of ovarian hemorrhage.[90] Cd enhances the rate of spontaneous abortion and reduces the occurrence of live births.[91]

Reports according to Eum et al.,[93] showed that Cd hinders the actions of eNOS and inhibits acetylcholine induced vascular relaxation, which leads to hypertension. Additionally, Cd induces cytokines formation and destruction of the endothelial cells, leading to atherogenesis. Prolonged human exposure to Cd provokes peripheral arterial disease and cardiovascular mortality.[94,95] The compounds of Cd have been classified as human carcinogenic compounds by the International Agency for Research on Cancer (IARC).[96] Various studies have suggested that Cd leads to breast cancer and pancreas cancer as well as uncontrollable damages to the liver, stomach and bladder.[97] The molecular and cellular bases of Cd carcinogenicity include proto-oncogenes stimulation, tumor suppressor genes inhibition, obstruction in cell adhesion and suppression of DNA repair.[98] Other mechanisms through which carcinogenesis are directly or indirectly initiated by Cd includes alteration in the proliferation, differentiation and signaling of cells as well as apoptosis.[97]

Human exposure to Cd has been observed to be associated with renal dysfunction.[99] Cd drastically lowers the glomerular filtration rate (GFR) as well as the reserve filtration capacity. Furthermore, prolonged human exposure to Cd initiates nephrotoxicity in conjunction with disorders such as aminoaciduria, hypercalciuria, glucosuria, hyperphosphaturia, reduced buffering capacity and polyuria[100] Bernard,[101] reported that Cd causes the destruction of the proximal tubules, leading to the release of high levels of enzymes, proteins and calcium in urine.

Nickel toxicity

Nickel (Ni) is the 28th member of the periodic table. Ni occurs in various oxidation states, ranging from −1 to +4. However, the +2 oxidation state (Ni^{2+}) is the most abundant in the environment and biological systems.[102] Ni exists naturally in the earth's crust in combined form with sulfur and oxygen as sulfides and oxides respectively. Furthermore, Ni occurs together with other elements in the soil, meteorites and volcanic emissions. Large quantity of Ni is also present in the sea.[103] anthropogenic activities such as combustion of diesel oil, fuel oil, coal as well as burning of waste and sewage releases significant amount of Ni in the air. Other sources of Ni in the environment include tobacco smoking, kitchen utensils and stainless steel constructed as well as certain jewelries manufacturing process.[103,104] Additionally, certain vegetables, chocolate, cocoa and nuts contain reasonable amount of Ni.[105,106] Human exposure to areas that are highly contaminated with Ni causes an assortment of pathological effects.[107,108] High levels of Ni and its compounds in the body lead to various health impairments in humans such as lung fibrosis, kidney and cardiovascular infections and malignant growth of the respiratory tract.[109]

Ni nanoparticles initiate reproductive toxicity. At the molecular level, Ni nanoparticles have been reported to hinder the actions of SOD and CAT, and thereby increase tissue ROS, MDA-lipid peroxidation marker and NO. By implication, Ni nanoparticles cause mitochondrial expansion and vanishing of mitochondrial cristae. In addition, Ni increases RNA manifestations of the caspases (cysteine proteases) as well as the expression of Cyt C, Bax and Bid proteins in the ovaries, which is accompanied with the expression of B-cell lymphoma-2 (Bcl-2) protein.[103,110] The outcomes of numerous *in vivo* and *in vitro* studies suggested that nanoparticles of Ni and its oxide provoked lung toxicity, irritation, oxidative stress and apoptosis.[111-113] The International Agency for Research on Cancer (IARC) characterized dissolvable and non-dissolvable Ni compounds as Group 1 (cancer-causing agents to humans), and Ni and alloys as Group 2B (potentially cancer-causing to humans).[114] Water-soluble nickel compounds are taken in through the lungs and eliminated by the kidneys. Water-soluble Ni compounds cause irritation of the nose and sinuses, and likewise prompt lose in the sense of smell and perforation of the nasal septum.[109]

Ni ions stimulate hetero chromatinization by binding to DNA-histone complexes and starting chromatin buildup. Ni compounds create histone hyperphosphorylation (H3S10), hypermethylation (H3K4) and hyperubiquitination (H2A and H2B), instigating epigenetic impact that affects gene expression.[115,116] Both water-insoluble nickel sulfide (NiS) and water-dissolvable nickel sulfate ($NiSO_4$), and nickel chloride ($NiCl_2$) are human cancer-causing agents. However, insoluble Ni compounds are more potent cancer-causing agents than the dissolvable ones.[117] The cancer-causing potential of insoluble Ni compounds is due to their capacity to expedite epigenetic changes.[118] Insoluble nickel trisulfide (Ni_2S_3) is a cancer-causing agent of the respiratory tract. When Ni_2S_3 is breathed in, particles of NiS accommodate in the lungs, where they interact with epithelial cells. The Ni particles are taken out by macrophages in the digestive tract. Under high human exposure to Ni, the evacuation action of the macrophages could be disrupted, and Ni_2S_3 particles are taken into epithelial cells by endocytosis. The Ni particles are conveyed to the nucleus of lung epithelial cells, which cause a heritable change in chromosomes and DNA lesions in human cells.[103]

Ni represses numerous enzymes that do not require metal cations for catalysis. This inhibition occurs when the Ni binds to specific amino acids in the active site of the enzyme, like cysteine, histidine, glutamate and lysine, and thereby hinders enzymatic activity. Alternatively, Ni binds to secondary sites of the enzyme and allosterically alters enzyme activity. However, the inhibition mechanism is not well established in most cases. For instance, ATP: Cob (l) alamin adenosyltransferase from *Salmonella enterica* catalyzes the last step in the conversion of vitamin B_{12} to coenzyme B_{12}, which is referred to as adenylation of cobalamin/vitamin B_{12} to adenosylcobalamin/coenzyme B_{12}. The active site of ATP: Cob (l) alamin adenosyltransferase, which is composed of iron, is repressed in the presence of 100 μM Ni^{2+}, whereby up to 50% of its enzyme activity is lost. At Ni concentration > 100 μM, the activity of ATP: Cob (l) alamin adenosyltransferase did not exhibit reduced enzyme activity below 50%. This outcome, therefore, suggests that Ni did not displace iron from the catalytic site of the enzyme but binds to an allosteric site.[119-121]

Ni is known to induce cell apoptosis. There are two major pathways through which cells undergo apoptotic death; they include the intrinsic (mitochondrial pathway) and the extrinsic pathways. The intrinsic pathway is initiated by intracellular signals when cells are stressed and are associated with the release of Cyt C from the intermembrane space of mitochondria. The extrinsic pathway is triggered by extracellular ligands bound to cell-surface death receptors (TNF, TNF-receptor family), which prompts the production of the death-inducing signaling complex. In the intrinsic pathway, the cell kills itself due to cell stress, while in the extrinsic pathway; the cell kills itself due to signals received from different cells. The two pathways initiate cell death by stimulating caspases (cysteine proteases) or protein degrading enzymes. Ni ions permit the release of Cyt C from the mitochondria into the cytosol, where Cyt C splits procaspase-9 followed by the activation of caspase-9, which induces caspase-3, -6, and -7. These caspases act on PARP, which instigates apoptosis. On

the surface of the cell, the Ni ions supports the interaction between Fas (First apoptotic sign) and FasL (Fas Ligand) as well as the production of the death-inducing signaling complex, which is made up of FADD and procaspase-8 and -10 that are activated to caspase-8 and -10. In the cell, caspase-8 and -10 split and stimulate the effectors of proteases, namely, caspase-3, -6 and -7 which act on PARP, leading to apoptosis[103,122] (Figure 6). Defective apoptotic processes are linked with several pathologies. For instance, rapid cell death is associated with various neurodegenerative diseases. However, the failure of apoptosis results in immune system diseases and uncontrolled cell proliferation, like cancer.[103]

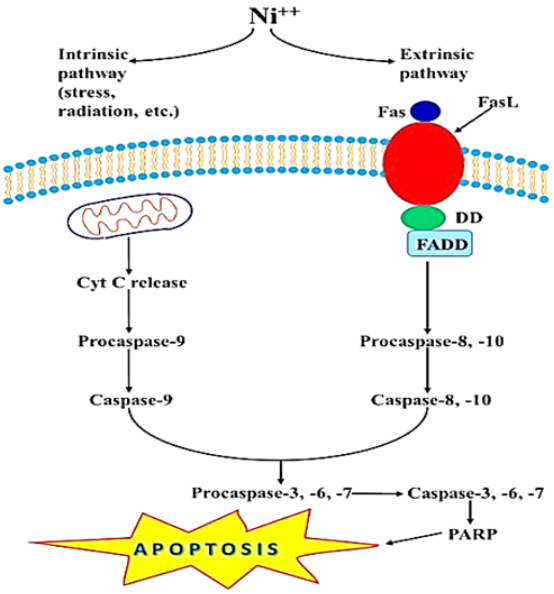

Figure 6 Ni^{2+}-induced mitochondria-apoptosis and caspase-dependent apoptosis.[103]

Chromium toxicity

Chromium (Cr) is abundant in the earth's crust and seawater. It is also released during industrial processes.[1] Cr exists in multiple oxidation states (−2 to +6), of which the most abundant stable forms are the trivalent and hexavalent states.[123] The chemistry of Cr contributes greatly to its ability to permeate biomembrane and exert toxic effects within the cell. In the environment, hexavalent Cr occurs widely in the form of chromate oxyanion (CrO_4). Because CrO_4 is structurally similar to sulfate oxyanion (SO_4), general sulfate transporters, located on the surface of the cell, facilitate its entry into the cell.[124] once inside the cell; the Cr (VI) elicits its toxic effects by undergoing reduction with ascorbate and biological thiols such as GSH or cysteine amino acid residues.[125,126] The reduction reaction processes especially with GSH usually leads to the formation of free radical species, namely; H_2O_2, which eventually generates elevated levels of oxidative stress, destroying cellular lipids, proteins, and DNA.[124,127] The mechanism of Cr uptake and its reductive actions in various biological compartments, as well as its effect on DNA targets are shown in Figure 7.[133]

Cr has the potency to change the epigenetic profile of cells both at the DNA methylation level and the histone modification level.[128-130]

Human exposure to Cr (VI) changes the epigenetic landscape through interacting directly with chromatin and the enzymes that are involved in the modification of the DNA. Cr (VI) alters the activities of epigenetic machinery e.g. the histone deacetylase (HDAC) enzymes, and renders them inactive.[131,132] Generally, human exposure to Cr (VI) initiates toxic and carcinogenic effects through a complex multi-front mechanism of action involving oxidative stress, epigenetic alterations, chromosome and DNA structural and functional impairments, as well as mutagenesis.[133]

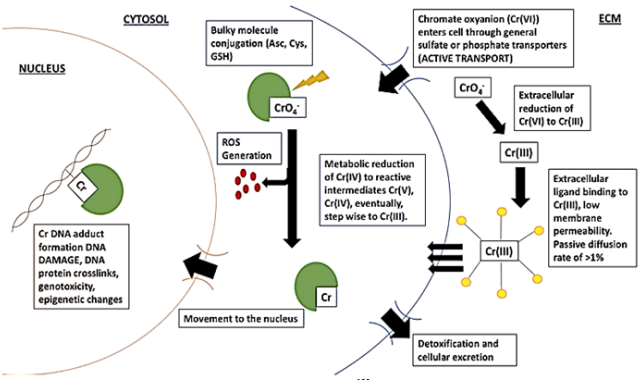

Figure 7 Mechanisms of Cr uptake and its effect in the cell.[133]

Zinc toxicity

Zinc (Zn) usually occurs naturally in its divalent state.[134] Zn toxicity has been reported to occur through inhalation from occupational sources, excessive intake of dietary supplements, application of denture cream, etc. The effect of some of these processes might lead to fatal conditions.[135,136] High human exposure to Zn disrupts Cu absorption that is facilitated by Zn-induced metallothionein. Cu has a very high affinity for metallothioneins, and therefore binds to zinc-induced metallothionein, which leads to the excretion of Cu in the faeces.[137] High circulating level of Zn disrupts the function of lymphocytes and neutrophils as well as lowers the concentrations of high-density lipoprotein-cholesterol (HDL-C) with concomitant elevation of low-density lipoprotein-cholesterol (LDL-C) in the serum.[138] Ingestion of the caustic agent, $ZnCl_2$, leads to irritation of the alimentary tract, while its inhalation initiates irritation of the pulmonary tract.[137]

The immune response to Zn (II) oxide in the respiratory tract has been linked with tissue inflammation and release of pyrogenic cytokines.[139] Zn (II) oxide has also been reported to impact negatively on the gastrointestinal system, and therefore causes nausea, vomiting, and abdominal pain.[140] High intracellular Zn concentration provokes apoptosis. The accumulation of intracellular Zn from exogenous sources or secretions from the intracellular stores by incidental consequences of ROS or nitrosation, induces pro-apoptotic molecules such as p38 and K^+ channels, which eventually leads to cell death.[141-144] Cell death could also be initiated by high levels of intracellular Zn through the suppression of energy metabolism.[145,146]

Conclusion

Humans are exposed to heavy metals through various means such as inhalation of contaminated air, intake of polluted water and food, occupational exposure as well as body to body contact through the skin. Some heavy metals elicit deleterious health effects even at low levels. Generally, heavy metals impair health through free radical generation, inhibition of enzyme activity, alteration of normal blood flow, damage of biological macromolecules such as lipids, proteins, and nucleic acids, initiation of carcinogenesis through the damage of the DNA with resultant organ and overall system dysfunction. Thus, efforts must be made to mitigate the extent of human exposure and accumulation of heavy metals in the body as a result of anthropogenic and industrial activities in order to prevent incidences of deleterious health challenges.

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Conflicts of interest

The authors declare no conflict of interest with respect to the publication of this manuscript.

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References

1. Tchounwou PB, Yedjou CG, Patlolla AK, et al. Heavy metal toxicity and the environment. *Mol Clin Environ Toxicol*. 2012;101:133–164.
2. Ohiagu FO, Lele KC, Chikezie PC, et al. Pollution profile and ecological risk assessment of heavy metals from dumpsites in Onne, Rivers State, Nigeria. *Chem Afr*. 2020;4:207–216.
3. Enyoh CE, Ohiagu FO, Verla AW, et al. A chemometric review of heavy metals (Zn, Cd, Pb, Fe, Cu, Ni and Mn) in top soils of Imo state, Southeastern Nigeria. *Int J Environ Anal Chem*. 2020.
4. Yedjou CG, Tchounwou PB. Oxidative stress in human leukemia cells (HL-60), human liver carcinoma cells ($HepG_2$) and human Jerkat-T cells exposed to arsenic trioxide. *Metal Ions Biol Med.* 2006;9:298–303.
5. Sutton DJ, Tchounwou PB. Mercury induces the externalization of phosphatidylserine in human proximal tubule (HK-2) cells. *Int J Environ Res Public Health*. 2007;4(2):138–144.
6. Yedjou GC, Tchounwou PB. N-acetyl-cysteine affords protection against lead-induced cytotoxicity and oxidative stress in human liver carcinoma ($HepG_2$) cells. *Int J Environ Res Public Health.* 2008;4(2):132–137.
7. Patlolla A, Barnes C, Field J, et al. Potassium dichromate-induced cytotoxicity, genotoxicity and oxidative stress in human liver carcinoma ($HepG_2$) cells. *Int J Environ Res Public Health.* 2009;6:643–653.
8. Vahter M, Åkesson A, Lidén C, et al. Gender differences in the disposition and toxicity of metals. *Environ Res.* 2007;104(1):85–95.
9. Gorini F, Muratori F, Morales MA. The role of heavy metal pollution in neurobehavioral disorders: a focus on autism. *Rev J Autism Dev Disord.* 2014;1(4):354–372.
10. Jaishankar M, Tseten T, Anbalagan N, et al. Toxicity, mechanism and health effects of some heavy metals. *Interdiscip Toxicol.* 2014;7(2):60–72.
11. Ohiagu FO, Lele KC, Chikezie PC, et al. Bioaccumulation and health risk assessment of heavy metals in *Musa paradisiaca*, *Zea mays*, *Cucumeropsis manii* and *Manihot esculenta* cultivated in Onne, Rivers State, Nigeria. *Environ Anal Health Toxicol.* 2020;35(2).
12. Balali-Mood M, Naseri K, Tahergorabi Z, et al. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. *Front Pharmacol.* 2021;12:643–672.
13. Wang S, Shi X. Molecular mechanisms of metal toxicity and carcinogenesis. *Mol Cell Biochem.* 2001;222:3–9.
14. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol.* 2008;82(8):493–512.
15. Engwa GA, Ferdinand PU, Nwalo FN, et al. Mechanism and health effects of heavy metal toxicity in humans. *Poisoning in the Modern World – New Tricks for an Old Dog?* 2019;1–23.
16. Monisha J, Tenzin T, Naresh A, et al. Toxicity, mechanism and health effects of some heavy metals. *Interdiscipl Toxicol.* 2014;7(2):60–72.
17. Jarup L. Hazards of heavy metal contamination. *Br Med Bull.* 2003;68(1):167–182.
18. Mousavi SR, Balali-Mood M, Riahi-Zanjani B, et al. Concentrations of mercury, lead, chromium, cadmium, arsenic and aluminum in irrigation water wells and wastewaters used for agriculture in Mashhad, Northeastern Iran. *Int J Occup Environ Med.* 2013;4:80–86.
19. Ghorani-Azam A, Riahi-Zanjani B, Balali-Mood M. Effects of air pollution on human health and practical measures for prevention in Iran. *J Res Med Sci.* 2016;21:65.
20. Luo L, Wang B, Jiang J, et al. Heavy metal contaminations in herbal medicines: Determination of comprehensive risk assessments. *Front Pharmacol.* 2020;11.
21. Krishna AK, Mohan KR. Distribution, correlation, ecological and health risk assessment of heavy metal contamination in surface soils around an industrial area, Hyderabad, India. *Environ Earth Sci.* 2016;75:411.
22. Rahimzadeh MR, Rahimzadeh MR, Kazemi S, et al. Cadmium toxicity and treatment: An update. *Caspian J Intern Med.* 2017;8(3):135–145.
23. Engwa AG, Ihekwoaba CJ, Ilo US, et al. Determination of some soft drink constituents and contamination by some heavy metals in Nigeria. *Toxicol Rep.* 2015;2:384–390.
24. Unaegbu M, Engwa GA, Abaa QD, et al. Heavy metal, nutrient and antioxidant status of selected fruit samples sold in Enugu, Nigeria. *Int J Food Contam.* 2016;3(7):1–8.
25. Mense SM, Zhang L. Heme: a versatile signaling molecule controlling the activities of diverse regulators ranging from transcription factors to MAP kinases. *Cell Res.* 2006;16(8):681–692.
26. Dongre NN, Suryakar AN, Patil AJ, et al. Biochemical effects of lead exposure on systolic and diastolic blood pressure, heme biosynthesis and hematological parameters in automobile workers of North Karnataka (India). *Indian J Clin Biochem.* 2011;26(4):400–406.
27. Schober SE, Mirel LB, Graubard BI, et al. Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III mortality study. *Environ Health Perspect.* 2006;114(10):1538–1541.
28. Khazdair MR, Boskabady MH, Afshari R, et al. Respiratory symptoms and pulmonary function testes in lead exposed workers in Iran. *Red Crescent Med J.* 2012;14(11):737–742.
29. Gurer-Orhan H, Sabır HU, Özgüneş H. Correlation between clinical indicators of lead poisoning and oxidative stress parameters in controls and lead-exposed workers. *Toxicol.* 2004;195(2-3):147–154.
30. Kasperczyk S, Birkner E, Kasperczyk A, et al. Lipids, lipid peroxidation and 7-ketocholesterol in workers exposed to lead. *Hum Exp Toxicol.* 2005;24(6):287–295.
31. Mishra KP, Singh VK, Rani R, et al. Effect of lead exposure on the immune response of some occupationally exposed individuals. *Toxicol.* 2003;188(2–3):251–259.
32. Brown MJ, Margolis S. Lead in drinking water and human blood lead levels in the United States. *Morbidity and Mortality Weekly Report (MMWR)*. 2012;10;61(4):1–9.
33. Martin S, Griswold W. Human health effects of heavy metals. *Environ Sci Technol Brief Citizens*. 2009;15:1–6.
34. Brochin R, Leone S, Phillips D, et al. The cellular effect of lead poisoning and its clinical picture. *GUJHS.* 2008;5(2):1–8.
35. Gaetke LM, Chow-Johnson HS, Chow CK. Copper: toxicological relevance and mechanisms. *Arch Toxicol.* 2014;88(11):1929–1938.
36. Pohl HR, Roney N, Abadin HG. Metal ions affecting the neurological system. *Metal Ions Life Sci.* 2011;8:247–262.
37. Lloyd RV, Hanna PM, Mason RP. The origin of the hydroxyl radical oxygen in the Fenton reaction. *Free Radical Biol Med.* 1997;22:885–888.

38. Brezova V, Valko M, Breza M, et al. Role of radicals and singlet oxygen in photoactivated DNA cleavage by the anticancer drug camptothecin: an electron paramagnetic resonance study. *Phys Chem B*. 2003;107:2415–2425.

39. Rana SV. Metals and apoptosis: recent developments. *J Trace Elem Med Biol.* 2008;22:262–284.

40. Lang F, Ullrich S, Gulbins E. Ceramide formation as a target in beta-cell survival and function. *Expert Opin Ther Targets*. 2011;15:1061–1071.

41. Marí M, Colell A, Morales A, et al. Acidic sphingomyelinase downregulates the liver-specific methionine adenosyltransferase 1A, contributing to tumor necrosis factor-induced lethal hepatitis. *J Clin Invest.* 2004;113:895–904.

42. Brewer GJ. A brand new mechanism for copper toxicity. *J Hepatol.* 2007;47:621–622.

43. Gupta DK, Tiwari S, Razafindrabe B, et al. Arsenic contamination from historical aspects to the present. *in arsenic contamination in the environment.* 2017;1–12.

44. Shah AQ, Kazi TG, Baig JA, et al. Determination of inorganic arsenic species (As^{3+} and As^{5+}) in muscle tissues of fish species by electrothermal atomic absorption spectrometry (ETAAS). *Food Chem.* 2010;119(2):840–844.

45. Sattar A, Xie S, Hafeez MA, et al. Metabolism and toxicity of arsenicals in mammals. *Environ Toxicol Pharmacol.* 2016;48:214–224.

46. Kuivenhoven M, Mason K. Arsenic (arsine) toxicity. *Treasure Island, FL: StatPearls Publishing*. 2019.

47. Ohnishi K, Yoshida H, Shigeno K, et al. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. *Ann Intern Med.* 2000;133:881–885.

48. Smith KR, Klei LR, Barchowsky A. Arsenite stimulates plasma membrane NADPH oxidase in vascular endothelial cells. *Am J Physiol Lung Cell Mol Physiol.* 2001;280:442–449.

49. Bunderson M, Coffin JD, Beall HD. Arsenic induces peroxynitrite generation and cyclooxygenase-2 protein expression in aortic endothelial cells: possible role in atherosclerosis. *Toxicol Appl Pharmacol*. 2002;184:11–18.

50. Lee MY, Lee YH, Lim KM, et al. Inorganic arsenite potentiates vasoconstriction through calcium sensitization in vascular smooth muscle. *Environ Health Perspect.* 2005;113:1330–1335.

51. Pysher MD, Chen QM, Vaillancourt RR. Arsenic alters vascular smooth muscle cell focal adhesion complexes leading to activation of FAK-src mediated pathways. *Toxicol Appl Pharmacol.* 2008;231:135–141.

52. Tsai SH, Hsieh MS, Chen L, et al. Suppression of Fas ligand expression on endothelial cells by arsenite through reactive oxygen species. *Toxicol Lett.* 2001;123:11–19.

53. Bunderson M, Brooks DM, Walker DL, et al. Arsenic exposure exacerbates atherosclerotic plaque formation and increases nitrotyrosine and leukotriene biosynthesis. *Toxicol Appl Pharmacol.* 2004;201:32–39.

54. Chen SC, Tsai MH, Wang HJ, et al. Involvement of substance P and neurogenic inflammation in arsenic-induced early vascular dysfunction. *Toxicol Sci.* 2007;95:82–88.

55. Tsou TC, Tsai FY, Hsieh YW, et al. Arsenite induces endothelial cytotoxicity by down-regulation of vascular endothelial nitric oxide synthase. *Toxicol Appl Pharmacol.* 2005;208:277–284.

56. Balakumar P, Kaur J. Arsenic exposure and cardiovascular disorders: an overview. *Cardiovasc Toxicol.* 2009;9:169–176.

57. Lee PC, Ho IC, Lee TC. Oxidative stress mediates sodium arsenite-induced expression of heme oxygenase-1, monocyte chemoattractant protein-1, and interleukin-6 in vascular smooth muscle cells. *Toxicol Sci.* 2005;85:541–550.

58. Cifuentes F, Bravo J, Norambuena M, et al. Chronic exposure to arsenic in tap water reduces acetylcholine-induced relaxation in the aorta and increases oxidative stress in female rats. *Int J Toxicol.* 2009;28:534–541.

59. Raghu KG, Yadav GK, Singh R, et al. Evaluation of adverse cardiac effects induced by arsenic trioxide, a potent anti-APL drug. *J Environ Pathol Toxicol Oncol.* 2009;28:241–252.

60. Singh AP, Goel RK, Kaur T. Mechanisms pertaining to arsenic toxicity. *Toxicol Int.* 2011;18(2):87–93.

61. Parrish AR, Zheng XH, Turney KD, et al. Enhanced transcription factor DNA binding and gene expression induced by arsenite or arsenate in renal slices. *Toxicol Sci.* 1999;50:98–105.

62. Sasaki A, Oshima Y, Fujimura A. An approach to elucidate potential mechanism of renal toxicity of arsenic trioxide. *Exp Hematol.* 2007;35:252–262.

63. Kimura A, Ishida Y, Hayashi T, et al. Interferon-gamma plays protective roles in sodium arsenite-induced renal injury by up-regulating intrarenal multidrug resistance-associated protein 1 expression. *Am J Pathol.* 2006;169:1118–1128.

64. Kokilavani V, Devi MA, Sivarajan K, et al. Combined efficacies of DL-alpha-lipoic acid and meso 2, 3 dimercaptosuccinic acid against arsenic induced toxicity in antioxidant systems of rats. *Toxicol Lett.* 2005;160:1–7.

65. Suzuki T, Tsukamoto I. Arsenite induces apoptosis in hepatocytes through an enhancement of the activation of Jun N-terminal kinase and p38 mitogen-activated protein kinase caused by partial hepatectomy. *Toxicol Lett.* 2006;165:257–264.

66. Flora SJ, Mehta A, Gupta R. Prevention of arsenic-induced hepatic apoptosis by concomitant administration of garlic extracts in mice. *Chem Biol Interact.* 2009;177:227–233.

67. Jain A, Yadav A, Bozhkov AI, et al. Therapeutic efficacy of silymarin and naringenin in reducing arsenic-induced hepatic damage in young rats. *Ecotoxicol Environ Saf.* 2011;74:607–614.

68. Hays AM, Srinivasan D, Witten ML, et al. Arsenic and cigarette smoke synergistically increase DNA oxidation in the lung. *Toxicol Pathol.* 2006;34:396–404.

69. Kinoshita A, Wanibuchi H, Wei M, et al. Elevation of 8-hydroxydeoxyguanosine and cell proliferation via generation of oxidative stress by organic arsenicals contributes to their carcinogenicity in the rat liver and bladder. *Toxicol Appl Pharmacol.* 2007;221:295–305.

70. Suzuki S, Arnold LL, Pennington KL, et al. Effects of co-administration of dietary sodium arsenite and an NADPH oxidase inhibitor on the rat bladder epithelium. *Toxicol.* 2009;261:41–46.

71. Wauson EM, Langan AS, Vorce RL. Sodium arsenite inhibits and reverses expression of adipogenic and fat cell-specific genes during *in vitro* adipogenesis. *Toxicol Sci.* 2002;65:211–219.

72. Tseng CH. The potential biological mechanisms of arsenic-induced diabetes mellitus. *Toxicol Appl Pharmacol.* 2004;197:67–83.

73. Bodwell JE, Kingsley LA, Hamilton JW. Arsenic at very low concentrations alters glucocorticoid receptor (GR)-mediated gene activation but not GR-mediated gene repression: complex dose-response effects are closely correlated with levels of activated GR and require a functional GR DNA binding domain. *Chem Res Toxicol.* 2004;17:1064–1076.

74. Pal S, Chatterjee AK. Prospective protective role of melatonin against arsenic-induced metabolic toxicity in Wistar rats. *Toxicol.* 2005;208:25–33.

75. Díaz-Villaseñor A, Sánchez-Soto MC, Cebrián ME, et al. Sodium arsenite impairs insulin secretion and transcription in pancreatic beta-cells. *Toxicol Appl Pharmacol.* 2006;214:30–34.

76. Izquierdo-Vega JA, Soto CA, Sanchez-Peña LC, et al. Diabetogenic effects and pancreatic oxidative damage in rats subchronically exposed to arsenite. *Toxicol Lett.* 2006;160:135–142.

77. Paul DS, Harmon AW, Devesa V, et al. Molecular mechanisms of the diabetogenic effects of arsenic: inhibition of insulin signaling by arsenite and methylarsonous acid. *Environ Health Perspect.* 2007;115:734–742.

78. Albretsen J. The toxicity of iron, an essential element. *Vet Med.* 2006;82–90.

79. Valko M, Izakovic M, Mazur M, et al. Role of oxygen radicals in DNA damage and cancer incidence. *Mol Cell Biochem.* 2004;266:37–56.

80. Bucher JR, Tien M, Aust SD. The requirement for ferric in the initiation of lipid peroxidation by chelated ferrous iron. *Biochem Biophys Res Commun.* 1983;111(3):777–784.

81. Jiang JH, Ge G, Gao K, et al. Calcium signaling involvement in cadmium-induced astrocyte cytotoxicity and cell death through activation of MAPK and PI3K/Akt signaling pathways. *Neurochem Res.* 2015;40(9):1929–1944.

82. Richter P, Faroon O, Pappas RS. Cadmium and cadmium/zinc ratios and tobacco-related morbidities. *Int J Environ Res Public Health.* 2017;14(10):1154.

83. Cao ZR, Cui SM, Lu XX, et al. Effects of occupational cadmium exposure on workers' cardiovascular system. 2018;36(6):474–477.

84. Rani A, Kumar A, Lal A, et al. Cellular mechanisms of cadmium-induced toxicity: a review. *Int J Environ Health Res.* 2014;24:378–399.

85. Patrick L. Toxic metals and antioxidants: Part II The role of antioxidants in arsenic and cadmium toxicity. *Altern Med Rev.* 2003;8:106–128.

86. Joseph P. Mechanisms of cadmium carcinogenesis. *Toxicol Appl Pharmacol.* 2009;238:272–279.

87. Filipic M. Mechanisms of cadmium induced genomic instability. *Mut Res.* 2012;733:69–77.

88. Rani A, Kumar A, Lal A, et al. Cellular mechanisms of cadmium-induced toxicity: a review. *Int J Environ Health Res.* 2013;24(4):378–399.

89. Umemura T, Wako Y. Pathogenesis of osteomalacia in Itai-itai disease. *J Toxicol Pathol.* 2006;19:69–74.

90. Thompson J, Bannigan J. Cadmium: toxic effects on the reproductive system and the embryo. *Reprod Toxicol.* 2008;25:304–315.

91. Pizent A, Tariba B, Zivkovic T. Reproductive toxicity of metals in men. *Arh Hig Rada Toksikol.* 2012;63:35–46.

92. Chandel M, Chand JG. Toxic effects of transition metals on male reproductive system: a review. *J Environ Occup Sci.* 2014;3:204–213.

93. Eum KD, Lee MS, Paek D. Cadmium in blood and hypertension. *Sci Total Environ.* 2008;407:147–153.

94. Navas-Acien A, Selvin E, Sharrett AR, et al. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. *Circ*. 2004;109:3196–201.

95. Menke A, Muntner P, Silbergeld EK, et al. Cadmium levels in urine and mortality among US adults. *Environ Health Perspect.* 2009;117:190–196.

96. Kellen E, Zeegers MP, Hond ED, et al. Blood cadmium may be associated with bladder carcinogenesis: The Belgian case-control study on bladder cancer. *Cancer Detect Prevent.* 2007;31:77–82.

97. Waalkes MP. Cadmium carcinogenesis. *Mutat Res.* 2003;533:107–120.

98. Il'yasovam D, Schwartz GG. Cadmium and renal cancer. *Toxicol Appl Pharmacol.* 2005;207:179–186.

99. Jarup L. Cadmium overload and toxicity. *Nephrol Dial Transplant.* 2002;17:35–39.

100. Gonick HC. Nephrotoxicity of cadmium and lead. *Indian J Med Res.* 2008;128:335–352.

101. Bernard A. Renal dysfunction induced by cadmium: biomarkers of critical effects. *Biometals.* 2004;17:519–523.

102. Muñoz A, Costa M. Elucidating the mechanisms of nickel compound uptake: A review of particulate and nano-nickel endocytosis and toxicity. *Toxicol Appl Pharm.* 2012;260:1–16.

103. Genchi G, Carocci A, Lauria G, et al. Nickel: human health and environmental toxicology. *Int J Environ Res. Public Health.* 2020;17(3):679.

104. Cempel M, Nikel G. Nickel: a review of its sources and environmental toxicology. *Pol J Environ Stud.* 2006;15:375–382.

105. Carocci A, Catalano A, Lauria G, et al. A review on mercury toxicity in food. *Food Toxicology*. 2016.

106. Lavinia B, Florina R, Augustin C. Is it possible a nickel-free diet? *Acta Medica Marisiensis.* 2018;64:5.

107. Zhao J, Shi X, Castranova V, et al. Occupational toxicology of nickel and nickel compounds. *J Environ Pathol Toxicol Oncol.* 2009;28:177–208.

108. Zambelli B, Ciurli S. Nickel and human health. Met Ions Life Sci. 2013;13:321–357.

109. Seilkop SK, Oller AR. Respiratory cancer risks associated with low-level nickel exposure: An integrated assessment based on animal, epidemiological, and mechanistic data. *Regul Toxicol Pharm.* 2003;37:173–190.

110. Kong L, Gao X, Zhu J, et al. Mechanisms involved in reproductive toxicity caused by nickel nanoparticle in female rats. *Environ Toxicol.* 2016;31:1674–1683.

111. Horie M, Stowe M, Tabei M, et al. Metal ion release of manufactured metal oxide nanoparticles is involved in the allergic response to inhaled ovalbumin in mice. *Occup Dis Environ.* 2016;4:17–26.

112. Latvala S, Hedberg J, Di BS, et al. Nickel release, ROS generation and toxicity of Ni and NiO micro- and nanoparticles. *PLoS ONE.* 2016;11(7).

113. Sutunkova MP, Privalova LI, Minigalieva IA, et al. The most important inferences from the Ekaterinburg nanotoxicology team's animal experiments assessing adverse health effects of metallic and metal oxide nanoparticles. *Toxicol Rep.* 2018;5:363–376.

114. IARC (The International Agency for Research on Cancer) Nickel and nickel compounds. *IARC Monogr Eval Carcinog Risk Hum.* 2012;100:169–218.

115. Ke Q, Li Q, Ellen TP, et al. Nickel compounds induce phosphorylation of histone H3 at serine 10 by activating JNK–MAPK pathway. *Carcinog* 2008;29:1276–1281.

116. Cantone L, Nordio F, Hou L, et al. Inhalable metal-rich air particles and histone H3K4 dimethylation and H3K9 acetylation in a cross-sectional study of steel workers. *Environ Health Perspect.* 2011;119:964–969.

117. Costa M, Davidson TL, Chen H, et al. Nickel carcinogenesis: epigenetics and hypoxia signaling. *Mutat Res.* 2005;592:79–88.

118. Arita A, Costa M. Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. *Metallomics.* 2009;1:222–228.

119. Buan NR, Suh SJ, Escalante-Semerena JC. The eutT gene of *Salmonella enterica* encodes an oxygen-labile, metal-containing ATP:Cob(I)alamin adenosyltransferase enzyme. *J Bacteriol.* 2004;186:5708–5714.

120. Johnson CL, Buszko ML, Bobik TA. Purification and initial characterization of the *Salmonella enterica* ATP:Cob(I)alamin adenosyltransferase. *J Bacteriol.* 2004;186:7881–7887.

121. Buan NR, Escalante-Semerena JC. Purification and initial biochemical characterization of ATP:Cob(I)alamin adenosyltransferase (EutT) enzyme of *Salmonella Enterica*. *J Biol Chem.* 2006;281:16971–16977.

122. Guo H, Cui H, Fang J, et al. Nickel chloride-induced apoptosis via mitochondria- and Fas-mediated caspase-dependent pathways in broiler chickens. *Oncotarget.* 2016;7:79747–79760.

123. Shekhawat K, Chatterjee S, Joshi B. Chromium toxicity and its health hazards. *Int J Adv Res.* 2015;3(7):167–172.

124. Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. *Chem Res Toxicol.* 2008;21(1):28–44.

125. Zhitkovich A, Chromium in drinking water: sources, metabolism, and cancer risks. *Chem Res Toxicol.* 2011;24(10):1617–1629.

126. Domingo-Relloso A, Grau-Perez M, Galan-Chilet I, et al. Urinary metals and metal mixtures and oxidative stress biomarkers in an adult population from Spain: The Hortega study. *Environ Int.* 2019;123:171–180.

127. Bagchi D, Bagchi M, Stohs SJ. Chromium (VI)-induced oxidative stress, apoptotic cell death and modulation of p53 tumor suppressor gene. *Mol Cell Biochem.* 2001;222(1-2):149–158.

128. Arita A, Shamy MY, Chervona Y, et al. The effect of exposure to carcinogenic metals on histone tail modifications and gene expression in human subjects. *J Trace Elem Med Biol.* 2012;26(2-3):174–178.

129. Chervona Y, Costa M. The control of histone methylation and gene expression by oxidative stress, hypoxia, and metals. *Free Radic Biol Med.* 2012;53(5):1041–1047.

130. Rager JE, Suh M, Chappell GA, et al. Review of transcriptomic responses to hexavalent chromium exposure in lung cells supports a role of epigenetic mediators in carcinogenesis. *Toxicol Lett.* 2019;305:40–50.

131. Macfie A, Hagan E, Zhitkovich A. Mechanism of DNA-protein cross-linking by chromium. *Chem Res Toxicol.* 2010;23(2):341–347.

132. Chen D, Kluz T, Fang L, et al. Hexavalent chromium (Cr(VI)) down-regulates acetylation of histone H4 at lysine 16 through induction of stressor protein nupr1. *PLoS One.* 2016;11(6).

133. DesMarais TL, Costa M. Mechanisms of Chromium-Induced Toxicity. *Curr Opin Toxicol.* 2019;14:1–7.

134. Terrin G, Berni CR, Di CM, et al. Zinc in early life: A key element in the fetus and preterm neonate. *Nutr.* 2015;7(12):10427–1046.

135. Grissinger MA. Fatal zinc overdose in a neonate: confusion of micrograms with milligrams. *PT*. 2011;36(7):393–409.

136. Greenberg MI, Vearrier D. Metal fume fever and polymer fume fever. *Clin Toxicol (Phila).* 2015;53(4):195–203.

137. Barceloux DG. Zinc. *Clin Toxicol.* 1999;37(2):279–292.

138. Chandra RK. Excessive intake of zinc impairs immune responses. *JAMA.* 1984;252:1443–1446.

139. Fine JM, Gordon T, Chen LC, et al. Metal fume fever: characterization of clinical and plasma IL-6 responses in controlled human exposures to zinc oxide fume at and below the threshold limit value. *J Occup Envion Med.* 1997;39:722–726.

140. Liu CH, Lee CT, Tsai FC, et al. Gastroduodenal corrosive injury after oral zinc oxide. Ann. *Emerg Med.* 2006;47:296.

141. Truong-Tran AQ, Carter J, Ruffin RE, et al. The role of zinc in caspase activation and apoptotic cell death. *Biometals.* 2001;14:315–330.

142. McLaughlin B, Pal S, Tran MP, et al. p38 activation is required upstream of potassium current enhancement and caspase cleavage in thiol oxidant-induced neuronal apoptosis. *J Neurosci.* 2001;21:3303–3311.

143. Watjen W, Haase H, Biagioli M, et al. Induction of apoptosis in mammalian cells by cadmium and zinc. *Environ Health Perspect.* 2002;110:865–867.

144. Wiseman DA, Wells SM, Wilham J, et al. Endothelial response to stress from exogenous Zn^{2+} resembles that of NO-mediated nitrosative stress, and is protected by MT-1 overexpression. *Am J Physiol Cell Physiol.* 2006;291:555–568.

145. Brown AM, Kristal BS, Effron MS, et al. Zn^{2+} inhibits alpha-ketoglutarate-stimulated mitochondrial respiration and the isolated alpha-ketoglutarate dehydrogenase complex. *J Biol Chem.* 2000;275:13441–13447.

146. Sheline CT, Behrens MM, Choi DW. Zinc-induced cortical neuronal death: contribution of energy failure attributable to loss of NAD(+) and inhibition of glycolysis. *J Neurosci.* 2000;20:3139–3146.

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