Review Article

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

Franklyn Okechukwu Ohiagu,[1] Paul Chidoka Chikezie,[2] Clinton Chinazaekpere Ahaneku,[2] Chinwendu Maureen Chikezie[1]

[1]Department of Biochemistry, Federal University of Technology, Nigeria
[2]Department of Biochemistry, Imo State University, Nigeria

Correspondence: Franklyn Okechukwu Ohiagu, Department of Biochemistry, Federal University of Technology, Owerri, Nigeria, Tel +2347066725130, Email ohiagufranklyn@gmail.com

Received: July 06, 2022 | **Published:** July 15, 2022

Introduction

Heavy metals are naturally occurring metallic elements whose densities are about 5 times greater than that of water (density > 5 g/cm³).[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]
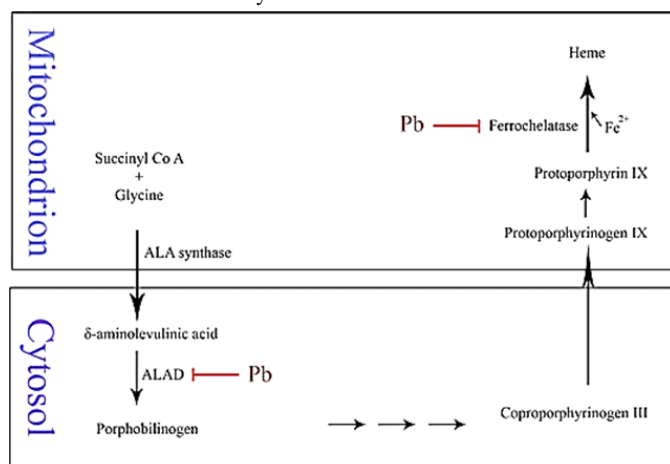

Figure 1 Inhibition of ferrochelatase and δ-aminolevulinic acid dehydratase (ALAD) in heme biosynthesis by Pb.[12]

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.
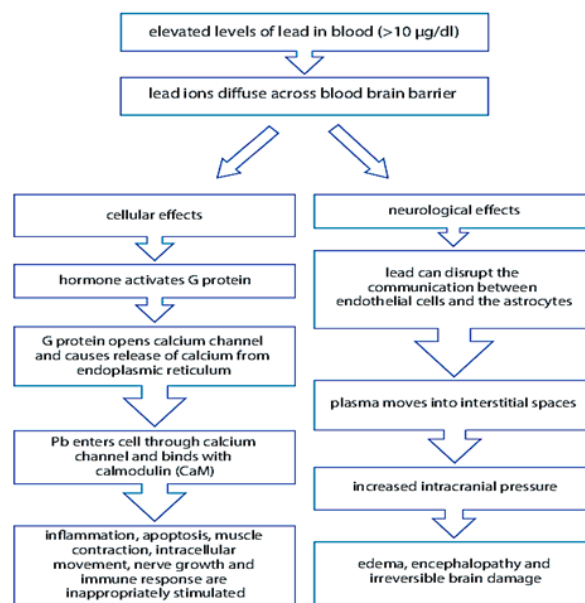

Figure 2 Processes leading to assorted diseases in humans due to high level of Pb in the blood.[34]

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

leading to the formation of hydroxyl radical (OH·) through the Fenton reaction (Equation 1).[37]

$$Cu^+ + H_2O_2 \rightarrow Cu^{2+} + OH^• + OH^- \quad \text{Equation 1}$$
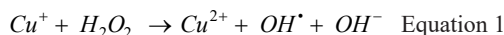
The OH· generated undergo reaction with various biomolecules, which engenders deleterious outcomes. Cu has also been implicated to initiate breaks in DNA strands as well as DNA base oxidation from ROS generation.[38]

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 ($O^{·-}_2$).[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).
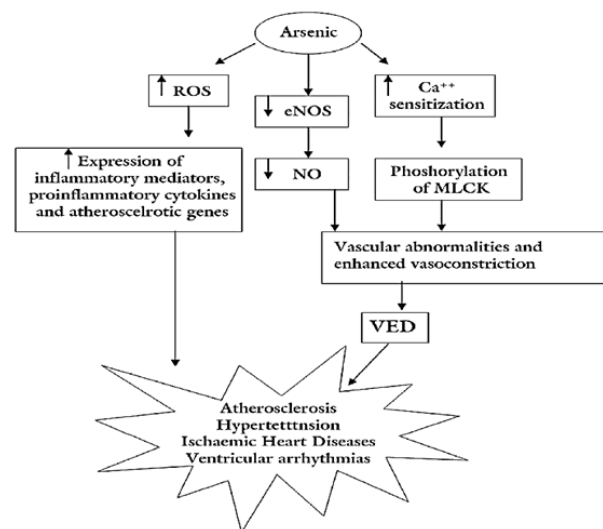
Figure 3 Pathways for As-induced cardiovascular dysfunction.[60]

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]
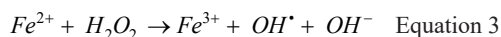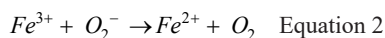
Furthermore, as has also been reported to initiate carcinogenicity and diabetes mellitus in humans. As triggers carcinogenicity by enhancing oxidative stress, genotoxicity, disruption in the expression of growth factors as well as alteration in the DNA repair process.[68-70] As induces diabetes mellitus 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]

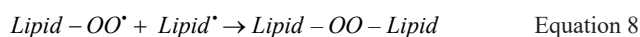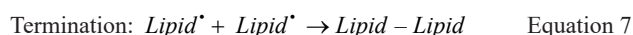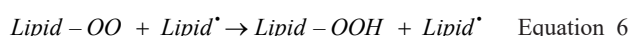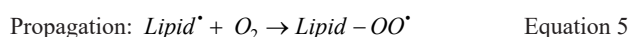Fe, in its free state, produces OH· as represented in the Fenton reaction (Equations 2 and 3).

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

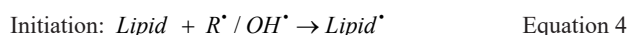$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^· + OH^- \quad \text{Equation 3}$$

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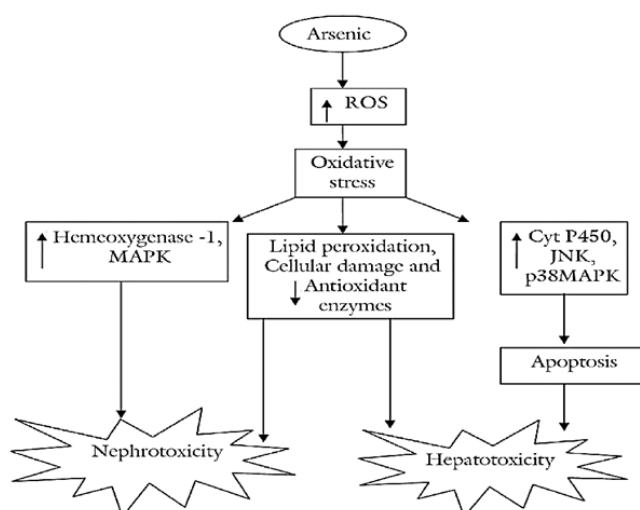
**Figure 4** Pathways for As-induced nephrotoxicity and hepatotoxicity.[60]

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).

$$\text{Initiation: } Lipid + R^· / OH^· \rightarrow Lipid^· \quad \text{Equation 4}$$

$$\text{Propagation: } Lipid^· + O_2 \rightarrow Lipid - OO^· \quad \text{Equation 5}$$

$$Lipid - OO + Lipid^· \rightarrow Lipid - OOH + Lipid^· \quad \text{Equation 6}$$

$$\text{Termination: } Lipid^· + Lipid^· \rightarrow Lipid - Lipid \quad \text{Equation 7}$$

$$Lipid - OO^· + Lipid^· \rightarrow Lipid - OO - Lipid \quad \text{Equation 8}$$

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 $O^·_2$, 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.
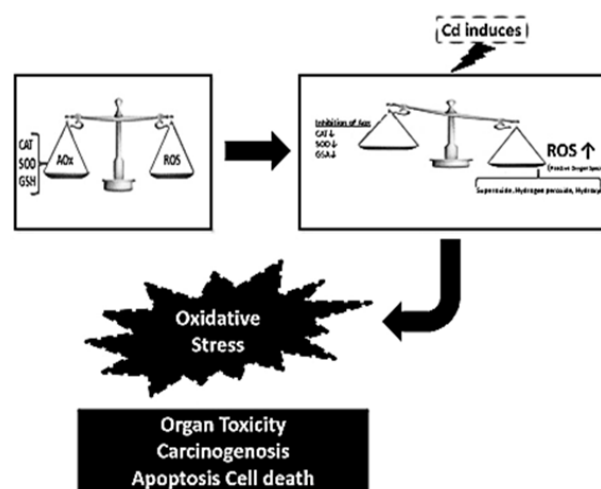
Figure 5 Effects of elevation in reactive oxygen species (ROS) and suppression of antioxidant levels induced by Cd.[22]

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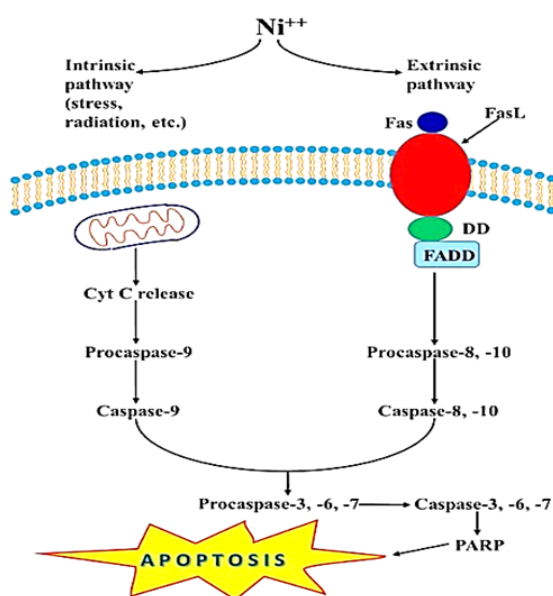
Figure 6 Ni^{2+}-induced mitochondria-apoptosis and caspase-dependent apoptosis.[103]

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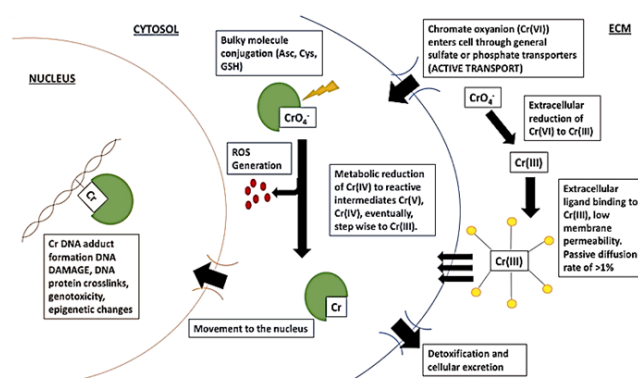
Figure 7 Mechanisms of Cr uptake and its effect in the cell.[133]

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.

Conflicts of interest

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

Acknowledgements

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