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Review Article

IDENTIFICATION OF SOURCES OF SOME PRIORITY HEAVY METALLIC POLLUTANTS CAUSING ENVIRONMENTAL DEGRADATION AND IT'S HEALTH IMPLICATIONS

EMMANUEL IGWE[1*] SOLOMON OLOCHE ONOJA[2], PRECIOUS TOCHUKWU NWODO[2], VALÉRIEN BAHARANE[3], SIMBO DIAKITE[4], FRANCESS SIA SAQUEE[4], BENEDICTHA CHINENYE UGWU[5], ODEKU JUNIOR AMECHI[2], OBED KOHOL NIAMBE[1], OCHOCHE SHAIBU[3], EVALISTUS ILOABUCHI NWANKWO[1], ABDULMAJEED ALLAN CKIKUKULA[1], MICHAEL ADEWOLE AJADI[2], CHUKWUKA OKPALACHUKWU ANIAGBOSO[2], FRANKA ANYAMA UNDIE[6],NNOLI EUCHARIA CHISOM[1], OSAZEMEN GODSWILL OSAYOGIE[1]

[1*]Department of Ecology and Nature Management, People's Friendship University of Russia Podolsk Highway, Moscow, Russia Federation
[2]Department of Epidemiology, First Moscow State Medical University, Sechenov Moscow Bol'shaya Pirogovskaya Ulitsa, Moscow, Russia Federation
[3]Department of Environmental Safety and Product Quality Management, People's Friendship University of Russia Podolsk Highway, Moscow, Russia Federation
[4]Department Agro biotechnology, Peoples Friendship University Russia, Ulitsa Miklukho-Maklaya, Moscow, Russia Federation
[5]Department of Agricultural Economics, Ebonyi State University, Hiltop Road Cas Campus, Abakaliki Ebonyi State, Nigeria
[6]Department of Mechanics and Control Processes, Academy of Engineering, Peoples' Friendship University of Russia, Moscow, Russian Federation

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ABSTRACT

Industrial activities in combination with the anthropogenesis of humans on the planet are the leading cause of heavy metal pollutants. The unabated continued loading of an ecosystem with these metallic contaminants has incidentally led to environmental degradation and human health complications. The study sort to review in clear terms how these heavy metals have caused damage to nature and reduce quality of life. We reported that the majority of these pollutants are emitted by mining activities and tag Lead (Pb), Arsenic (As), Mercury (Hg), Cadmium (Cd) and Chromium (Cr) as priority metallic pollutants which significantly impact negatively human health while causing ecological deterioration. Also, it was recorded that these metallic pollutants constituted components of agricultural inputs which at even in small concentrations, due to their tenacity, non-degradability, biological toxicity, and capacity to enter the food chain. Another critical environmental problem in recent years is soil pollution caused by excessive use of inorganic fertilizers. It was investigated that when these metallic ions upon entering into food chain *via* contaminated soils and water, reaching critical concentrations, causing harmful metabolites in the body, and having adverse effects on living organisms such as kidney damage, hypertension, mutagenicity, carcinogenesis, diabetes, liver disease, cardiovascular disease, and various types of cancer are some ramifications caused by exposure to high contents of Arsenic (As) element. Chromium (Cr) had been identified as carcinogenic to humans capable of causing liver necrosis, nephritis, and death. Lead in the human system pose a threat to the tree-sensitive organs of the hematopoietic.

***Corresponding author's email: emmaigwe05@gmail.com**

INTRODUCTION

The expansion of industrial infrastructure and unsustainable anthropogenic activities is the main driver of environmental deterioration and reduction of quality of life and expectation in the ecosystem. This normally occurs as noxious discharge, untreated wastewater or sludge containing a variety of heavy metals into the water body. These dangerous metals in turn are leading causes of health risks for living beings as causative factors for allergies, infection, defects and diseases globally. High contamination of heavy metals in the environment from continuous unabated emission from anthropogenesis is recognized with aroused ecological and global public health concerns worldwide (Smith, et al., 2000). Heavy metals are naturally present in trace amounts (ppb range to less than 10 ppm), and there are countless measures, man activities can trigger the release and emission of these major metallic pollutants like lead, arsenic, mercury, cadmium and chromium into the environment. These toxic metals are directly or indirectly deteriorating ecological systems and natural resources thus, accelerating health risks (Cardoso, et al.,2020). It is essential not to underscore the likely dangerous effect that comes with this potential threat to nature.

Heavy metallic contamination and human exposure occur when these metals exceed their respective background levels thereby loading the ecosystem beyond natural threshold limits for human tolerance. Therefore, at this point, these metal pollutants pose a serious threat to aquatic as well as terrestrial ecosystems. It has been investigated that metallic contaminants differ from organic that are biodegradable by the physical and biological process as a result it makes this pollutant to accumulates in the environment (Abernethy, et al., 2010). The natural environment's physio-chemical and biological range is altered when these heavy metals are in excess beyond restoration level in a particular vicinity, as a result, human toxicity happens when their concentrations in soils, and suspended particulates exceed the natural background concentrations (Aguilera, et al., 2021). A study by concluded that due to human activities, heavy metal exposure in humans has grown exponentially in recent decades with the highest contact means from agriculture, industry, household, and technology. In addition, emissions from industries, mining, smelters, and coal-based power plants are the predominant responsible for environmental pollution (Ahmad, et al., 2019).

Furthermore, a revealed danger related to natural resources, microorganisms and their survival rate as the result of accumulation of these pollutants in sediments impacting the microbial community diversity, structure, and functional dynamics. Globally, continued anthropogenic activities drive socio-economic gain, and urban development especially around coastal areas gets rise to the release of metallic contaminants such as metals. Although research has shown, the ecosystem has the ability to self-cleaning through its homeostasis with a fast response to environmental disturbances and metabolic diversity (Al-Khashman, et al., 2004). Biochemical process plays a relevant role in the nutrient re-mineralization. The self-regulatory function of the ecosystem makes them available to the entire trophic web (Al-Khashman, et al., 2007). But it's understandable that the rate of degradation caused by this heavy metal is beyond the regulatory capability of the natural restoration process (Altaf, et al.,2008).

This review paper aims at identifying various sources of priority metal pollutants and their effects on the environment and human health (Aramjoo, et al.,2022). Hence could be a handful for both environmental policymakers' and physicians' assessment of causes of the ecological crisis as well as provide the medical officer with preliminary guidance when diagnosing patients living in polluted vicinity (Suljević, et al., 2020).

This study will focus on arsenic, chromium, lead, mercury, and cadmium because they constituted the top priority metals pollutant to the environment which also has risen some important questions concerning public health safety due to their high toxicity (Ashraf, et al., 2012).

LITERATURE REVIEW

Sources of Heavy Metals and its Effects in the Enviroment

It's important to know that the majority of these pollutants are component of pesticides, insecticides and fertilizers that are naturally subjected to biological metabolism, unfortunately, due to their high dosage, it enters into the food chain (Tripathy, et al., 2022). It shows the negative effects of ionic pollutants are manifested in the flora and fauna component of the ecosystem. Meanwhile, some priority heavy metals and metalloids originate from waste, as well as by-products from mining, and manufacturing activities which have a high propensity to cause leading negative effects on environmental and human health diseases (Wionczyk, et al., 2006). The top priority heavy metals like (Pb, As, Hg, Cd and Cr) natural occurs in the earth's crust, its also released human activities such as the burning of fossil fuels in households and factories, mining, and the manufacture of a variety of items (Basha, et al., 2010).

Sources of lead exposure to the environment: Lead is the second most toxic metal with significantly high mortality after arsenic. It comprises 0.002% of Earth's crust it is naturally found in a very limited amount but it is mostly produced due to deliberate man action resulting from Anthropocene (Belay, et al., 2010).

The majority of the lead salts/oxides originated from dust, batteries vent, lead paint, and contaminated diet with lead (Bermejo, et al., 2022). Surprisingly, canned food industries are a main cause of lead consumption due to the leaching out of lead ions into public food. This makes Pb common in the environment and nature presents it to lives that feed on any Pb-contaminated product during ingestion (Bootman, et al., 2012). A study results show food chain process from production, harvesting,

processing, and storage phases introduce this pollutant substance into the food. It was reported as the result of the persistent nature of these pollutants accumulating in the human body after it gets into the human system through direct ingestion, inhalation, and dermal contact (Bouton, et al., 2001).

The continuous unabated release of lead significantly affect the quality of aquatic life, and change water composition thereby causing serious ecological crisis and health complication to both human and animals.

A study by Caruso revealed lead availability in soil is mostly absorbed by plants from the soil with ambient pH, although moisture is a prerequisite to sustaining its availability for plant absorption (Caruso, et al., 2016). In addition, a study by Cheng shares a similar view which reported that the pH of the soil is the major factor that controls lead accessibility to plants (Cheng, et al., 2000). Furthermore, the accumulation of lead ions Pb $(OH)^{+}$ and finally $[Pb_4 (OH)_4] 4^{+}$) in the soil is harmful to the natural environment, in its aqueous state it forms acidic soil pH<6, whereas lead forms a complex with OH ions in alkaline soil pH>7. When plants absorbed it can indirectly be transmitted to humans and any other living that feeds on this contaminated food chain. This transmission process continues and it can erupt a massive population of habitat (Choudhari, et al., 2010).

Another study revealed that Lead (Pb) is an element with larger bulk and atomic mass that disturb human health and the environment (Cuypers, et al., 2010). Nevertheless, metal pollution in the ecosystem is one of the deadliest environmental distress upsetting plants, animals, and humans as the leading factor for the global ecological crisis. This pollutant remains in the environment for generations due to its not recyclable property and high concentration (de Flora, et al., 2008).

Sources of arsenic exposure to the environment: Arsenic is a ubiquitous element that may be encountered at very trace levels. It's a well-known human toxic and carcinogen that can be found in groundwater, food, soil, and air. Arsenic exposure through the oral route, i.e., ingestion, inhalation, and interaction and its concentrations in the air fluctuate from 1 to 3 ng/m_3, however in cities, concentrations range from 20 to 100 ng/m_3 (Dell'Anno, et al., 2003). Specifically, the global arsenic metallic substance is transferred into the environment in multiple directions consisting of natural and anthropogenesis. Research has shown that arsenic is a priority toxic metalloid ubiquitously distributed in the environment e.g., water, soil, and air (Pan, et al., 2016). Humans are exposed to arsenic from both natural and anthropogenic sources mainly through drinking water (groundwater) and food. Tentatively arsenic-contaminated foods include rice, vegetables, meat, fish, eggs, and milk. To better understand the level of pollution caused by arsenic globally, a study Pan reported more than 200 million people around the world are potentially exposed to the higher level of arsenic in groundwater and mostly from Asia(Dou, et al., 2011). It was further reported by arsenic contamination of groundwater has been reported in many countries around the world, including Pakistan, Indonesia, Afghanistan, Vietnam, Nepal, Philippines, Chile, Argentina, India, Myanmar, Mongolia, China, United States, Mexico and Taiwan (Dribben, et al., 2011).

Drawing reference from the World Health Organization (WHO) the deadliest metallic pollutant is considered to be arsenic, with a high propensity of poisoning public health largest mass poisoning of a population in history further revealed arsenic metallic ions to be sources of chronic diseases like cancers and skin lesions) while also causing acute illnesses like nausea, vomiting, burning in the stomach and esophagus, abdominal pain, and diarrhea which are leading sicknesses the public face daily in the environment (Drobna, et al., 2009). Another study supports the claim above that arsenic exposure-linked common adverse health consequences include cancers in the lung, bladder, kidney, skin, and liver, neurological disorders, cardiovascular diseases, hypertension, gangrene, diabetes, respiratory diseases, renal and reproductive diseases. However, it established that the level of arsenic poisoning mainly depends on the amount of arsenic intake, nutritional status, exposure duration and immune response of the individual (Duan, et al., 2022).

Mercury Spreading Mechanism

Recently there is increasing alarming concerns over high mercury (Hg) pollution unlike past decades in fact it becoming uncontrollable with global concerns that have been debated in several like the UN Stockholm convention. This metallic substance being persistent, high toxicity and bioavailability make it one of the priority pollutants in the food web system Duran reported that, except for Asia and Oceania, the other continents have been reducing the anthropogenic emission of mercury(Duran, et al., 2015). Due to the high accumulative nature of this pollutant, there are no significant reductions in its volume even as anthropogenic Hg emission is meter down. This could be the result of its persistent nature.

Naturally, mercury is existing in metal (Hg0), inorganic (Hg^{+} and Hg^{2+}), and organic ($MeHg^{+}$ and Me2Hg) states. Mineral cinnabar (α-HgS) is a familiar form it exists in nature, while the highest levels of α-HgS are found in volcanically active zones. It has been established by Shaji that Almadén in Spain was the largest known mine of cinnabar in the world and produced about one-third of Hg on the planet(Shaji, et al., 2021). Tentatively, mercury (Hg) can be released into the air, water and soil by anthropogenic activities like, burning of carbon fuel fossil, agrochemical application, and as a result, it's possible to come in contact with it on a daily basis(Lamsal, et al., 2015). Other mediums such as metal and cement production, use of organo-mercurial fungicides in agriculture, extraction of fuel, and biomass burning, Esmaeilzadeh support this finding (Esmaeilzadeh, et al., 2019). Artisanal and Small-Scale Gold Mining (ASGM) is the largest source of environmental mercury pollution. A study con-

ducted by Ferraro PM revealed that elemental Hg is used to extract gold from ore, forming an amalgam. However, Hg is useful through amalgam is isolated and then heated to evaporate the Hg and isolate the gold with record Hg released from ASGM accounting for ~37% (410 to 1400 t) of the global Hg emissions(Ferraro, et al., 2010).

Cadmium mode of transmission into the environment: Cadmium (Cd) naturally exists in zinc, lead, and copper ores as a divalent cation in the Earth's crust and marine environments at low concentrations and accumulates in air water and soil through volcanic activity and erosion (Flemming, et al., 2010). Cadmium (Cd) is one of the important toxic metals that is a naturally occurring element present as a dietary component in meat products, cereals, nuts and starch items , cadmium is incorporated into a daily diet (Florea, et al., 2013). It becomes significantly dangerous when its concentration in food is high thereby causing toxicity to the food hence contaminating feed products and water which makes it unsafe for living organisms. Research by Environmental Protection Agency (EPA) shows that the main sources of cadmium toxicity are the paint industry, electroplating industry, batteries, nuclear power plants and electronic wastes, (Flores-Montoya, et al., 2015). Again the continuous exposure to such wastes and byproducts into land, water, and air leads to the loading of the ecosystem which of course is a serious threat to nature. Haven said this, the utmost limit of cadmium existence in water set by the United States Environmental Protection Agency (EPA) is 0.003 mg/dm3, unfortunately, anthropogenic activities led to an upsurge of this toxic metal (Froehlich, et al., 2009).

According to Froehlich national laboratories-US (2010) cadmium is absorbed and then transported into the body, its traces can be found in the kidney and respiratory. More so, the quantity of oxidative stress and oxidative damage it causes also affects lingers tissue injury and apoptosis of tubular cells, respectively (Fujiwara, et al., 2012). Again cadmium constitutes one of the components present in cigarettes, with warning lung protracted illness. While trace amounts of Cd in the environment are byproducts of these processes, the majority of environmental Cd is the result of industrial and agricultural usage (Bjørklund, et al., 2020). Soluble Cd ions from phosphate fertilizers can contaminate water and soil and subsequently accumulate in aquatic organisms or plants such as tobacco, grains, and root vegetables (Ghosh, et al., 2016). Because of accumulation in tobacco plants, individuals who smoke are exposed to significant levels of Cd through the inhalation of cigarette smoke. Once ingested, ionized Cd^{2+} binds to albumin and the resulting complexes are then transported to target organs, including the kidney, bone, liver, and lung. Cd is taken up into hepatocytes *via* Ca^{2+} channels and membrane transporters (Giridhar, et al., 1991).

Chromium transmission mode into the environment: Just like lead, arsenic, mercury and cadmium, chromium–Cr (IV) is one of the most ranked toxic elements polluting the earth's crust, it poses hexavalent valence according to a study by Glass, et al., 2009. Chromium metals are generated through industrial operations, agricultural activities, transportation and mining processes. Components of chromium known as chromium salts are considered to be the most extensively used compound for tanning purposes although a greater percentage of it is used as chromium sludge. Research carried out by Harrison shows that the tanning industry induces several environmental problems and death traps (Harrison, et al., 2017). Meanwhile Hassanin reported some industries that perform metal cleaning, galvanization, cement, leather, paint and pharmaceuticals involve chromium usage, and make use of this chemical, hence, its release into the environment in different physical and chemical states which ends in metal accumulation (Hassanin, et al., 2016). This active toxic metal serves as a death trap for plants, clams, crabs and fishes.

Clinical Effects of Heavy Metals Pollutants in Humans and Animals

This section of the paper closely looks in detail at how these heavy metals contributed to the abnormality of public health. Taking into account the specific illness each metallic contaminated product causes highlights the transmission process (Hong, et al., 2014).

Lead: The mechanisms by which lead disrupts the brain and behavior are complex and poorly understood. Nonetheless, cellular and molecular work has resulted in a growing understanding of the effects of lead on brain function. Of particular importance are the effects of lead on calcium-dependent cellular processes. Calcium is a critical ion in neuronal function, including cell growth and differentiation, neurotransmitter release, and intracellular biochemical cascades (Mohanty, et al., 2017).

Lead and calcium are divalent cations of similar size and ionic charge. The ability of lead to mimic or inhibit calcium-mediated effects is central to its biological and behavioral effects. Unlike calcium, which is a highly regulated ligand in the body, lead is an unregulated heavy metal. Lead binds to sites at which calcium acts and enters the cell through calcium channels, thus displacing, inhibiting, substituting, and/or activating calcium-dependent processes (Podgorski , et al., 2020). Given the ubiquity of calcium in cellular signaling, and the critical role of the spatial and temporal patterning of calcium signals in cell function, disruption of calcium-dependent processes can have profound cellular consequences (Kim, et al., 2016). The effects of lead on neuronal calcium dynamics help to explain many far-reaching changes in brain function and behavior (Jalali, et al., 2020).

NMDA receptors: Lead is a non-competitive, N-Methyl-D-Aspartate Receptor (NMDA-R) antagonist. NMDA are inotropic receptors that are activated by the neurotransmitter glutamate, and are involved in many processes, including neural development, neuronal plasticity, learning and memory, and long-term potentiation (Jalili, et al., 2021). Activation of NMDA-Rs by glutamate produces an influx of calcium through a ligand-gated ion

channel, which can produce an excitatory post-synaptic potential, as well as strongly influence neuronal function by activating calcium-dependent second messenger cascades (Jin, et al., 2020). By blocking postsynaptic NMDARs, lead inhibits activity-dependent calcium influx, which in turn can disrupt NMDA receptor-dependent developmental processes, neural plasticity, learning and memory, and Long-Term Potentiation (LTP). Chronic, developmental lead exposure increases the threshold for induction of LTP at a wide range of lead concentrations and this is associated with impaired learning and memory (Jomova, et al., 2011). Disruption of LTP and learning may be related to NMDA receptor blockade or other downstream effects of lead on calcium-dependent processes (Ebinghaus, et al., 2009).

Another consequence of NMDA receptor blockade is apoptosis, programmed cell death produced by a well-characterized biochemical cascade that leads to disruptions in normal brain development. Apoptosis is normally involved in pruning unneeded connections and 'sculpting' the brain during development. However, under certain conditions, pathological apoptosis can occur. Developmental exposure to lead has also been found to produce apoptosis and disrupt brain development at low concentrations in both mammalian and zebra fish models *via* the blockade of NMDA receptors (Khan, et al., 2019). Given the critical role of NMDA receptors in a variety of neural and behavioral processes, and the ability of lead to block NMDA receptors, these receptors are essential to a complete understanding of the effects of lead on the brain and behavior (Esdaile, et al., 2018).

Another target of lead is Calmodulin (CaM), or "Calcium-Modulated Protein," a major calcium-activated intracellular protein (Muharrem, et al., 2017). Calmodulin is important in many neuronal processes, including transduction of calcium signaling, regulation of neurotransmitter receptors and ion channels, and neuronal plasticity (Lee, et al., 2021). Calmodulin has four binding sites at which calcium is the natural ligand. When calcium is bound at all four sites, calmodulin is functionally active. At physiologically-relevant levels, lead binds with greater affinity than calcium to calmodulin and activates the protein (Li, et al., 2020). When this occurs, calmodulin is activated in a non-physiological manner. Calmodulin signaling becomes tonically activated and stimulus-independent. Given the broad role of calmodulin in calcium signaling, unregulated calmodulin activation can have many consequences, ranging from disruption of calmodulin-dependent signal transduction to interference with calmodulin-dependent learning and memory (Lidsky, et al., 2003).

Protein Kinase C Protein Kinase C (PKC) is a calcium- and phospholipid-dependent, intracellular signaling enzyme that is involved in a variety of cellular functions. PKC phosphorylates proteins *via* the transfer of phosphate from ATP. PKC-mediated phosphorylation of transport proteins is important for the regulation of cellular growth and differentiation. PKC is also implicated in cytoskeletal function and signal transduction and plays a role in learning and memory (Kumar, et al., 2021). At a clinically-relevant, Pico molar concentration, lead substitutes for calcium in the activation of PKC, increasing intracellular calcium and interfering with neurotransmitter release (Masindi, et al., 2018). Specifically, at the synaptotagmin site, lead mimics and competes for calcium and does so with greater affinity than calcium (McCue, et al., 2010). Prolonged lead-induced increases in PKC activity produce a compensatory decrease in activity perhaps by down regulation or decreased efficacy of calcium activity (EPA, 2006). PKC is important for calcium-mediated LTP; in fact, PKC inhibitors, such as polymyxin B block the induction and maintenance of calcium-induced LTP (Moncur, et al., 2005). Lead-induced impairment of learning and memory processes is thought to be due, at least in part, to the disruption of normal PKC functioning. In addition, lead effects on PKC activity impact cell division, neuronal communication, neural plasticity, and structural organization of the cytoskeleton (EPA, 2006), as well as cellular proliferation and differentiation (Morabito, et al., 2017).

Mitochondria are organelles responsible for cellular respiration and energy production and, thus, are known as the powerhouses of eukaryotic cells. In addition to other functions, mitochondria store unbound calcium that regulates essential cellular activities such as cellular differentiation, neurogenesis, apoptosis, and signaling. Mitochondria can be found in dendrites and axon terminals where they are associated with the synthesis, storage, release, and reuptake of neurotransmitters. Lead accumulates in mitochondria leading to oxidative stress and degradation of energy metabolism (Nagajyoti, et al., 2010). Mitochondrial efflux of both calcium and lead occurs through a calcium uniporter. Lead competitively inhibits the energy-dependent intake of calcium into the mitochondrial matrix at the calcium uniporter, depleting necessary mitochondrial calcium stores (Nickens, et al., 2010). Depletion of mitochondrial calcium stores is implicated in lead-induced apoptosis and excitotoxicity, as well as oxidation of pyridine nucleotides, and decay in membrane potential. Lead depletion of mitochondria-generated ATP energy metabolism also contributes to the disruption of neuronal function (Nishida, et al., 2020).

Arsenic: Chronic exposure to inorganic arsenic has been associated with an increased risk for cardiovascular disease and its risk factors, including hypertension, diabetes mellitus, carotid atherosclerosis, and peripheral artery disease (Notariale, et al., 2021). Importantly, arsenic exposure has been related to cardiovascular mortality and adverse cardiac events, particularly, ischemic heart disease and other forms of heart disease (Notariale, et al., 2022). However, the relationship of arsenic exposure with adverse cardiac outcomes is not fully understood. Inorganic arsenic is related to hypertension and diabetes mellitus, the main risk factors for the development of cardiac dysfunction (Nriagu, et al., 2007). It is unknown

whether inorganic arsenic is related to cardiac structure and functioning or if the observed adverse outcomes are secondary to a worse cardio metabolic profile of arsenic-exposed individuals.

Cardiac geometry and functioning, notably the dimension and function of the Left Ventricle (LV), can be reliably and reproducibly assessed with Transthoracic Echocardiography (TTE) [70]. LV Hypertrophy (LVH), LV systolic dysfunction, and LV diastolic dysfunction are strong independent predictors of survival in both individuals with a history of cardiac disease and individuals free of overt cardiovascular disease (OBrien, et al., 2013). A change in the magnitude or direction of baseline values of TTE-based measures of LV mass and functioning is followed by a corresponding change in risk for fatal and nonfatal cardiovascular events. In addition, treatment targeting asymptomatic patients with LVH, LV systolic dysfunction, or LV diastolic dysfunction may slow the natural progression to heart failure and reduce subsequent morbidity and mortality. Accordingly, abnormal TTE-based measurements of cardiac geometry and function are established surrogates for heart failure and adverse cardiac outcomes. Nevertheless, the risk factors and pathophysiological mechanisms involved in the disproportionate growth of the heart and consecutive alteration in cardiac function is not fully understood (Nogara, et al., 2019).

Inorganic arsenic has been positively related to cardiovascular surrogate endpoints, including subclinical atherosclerosis, QT interval prolongation, and circulating markers of endothelial dysfunction (Tchounwou, et al., 2012). In a small cross-sectional study of children in Central Mexico, arsenic exposure was associated with a higher LV mass and a lower systolic function (Perrone, et al., 2023). Animal studies have shown that exposure to arsenic is followed by cardiac dysfunction, including myocyte apoptosis, fibrosis, and subsequent LVH. In contrast, the potential impact of arsenic exposure on LVH, LV systolic dysfunction, and LV diastolic dysfunction in adult populations free of cardiovascular disease has not been studied before (Peterson-Roth, et al., 2005).

Available evidence on the relationship between arsenic exposure and echocardiographic measures of cardiac geometry and function in humans is scarce and limited to populations of children. It remains unclear whether the impact of arsenic exposure on LV measures was independent of BP. The heart is responsive to physiological and pathological stimulants. Pressure overload in cardiac chambers due to systemic arterial hypertension is considered the main determinant of LVH (Sohrabi, et al., 2016). However, changes in cardiac form and mass are mediated by complex mechanical, neurohumoral, inflammatory, and oxidative processes that involve all cardiac cell types and ultimately lead to disproportionate growth of cardiac chambers and altered cardiac functioning (Pringault, et al., 2008). Arsenic has been shown to induce calcium overload and inhibit potassium current in cardiac muscle cells, leading to adverse electrophysiological effects and ultimately to apoptosis. Along with functional changes affecting ion channels, arsenic-related cardio toxicity might be mediated by oxidative stress and reactive oxygen species formation. In addition, arsenic-induced apoptosis of cardiomyocytes *via* alteration of mitochondrial permeability and activation of MAP (Mitogen-Activated Protein) kinases has been reported by Singh (Singh, et al., 2015).

The potential mechanisms of arsenic-induced toxicity are not limited to cardiac muscle cells. In animal models, arsenic promoted collagen production and TGF (Transforming Growth Factor)-β1 expression, resulting in fibrosis of cardiac tissue and subsequently in an increase in cardiac mass. Moreover, arsenic has been related to endothelial dysfunction *via* reactive oxygen species formation and accumulation in vascular smooth muscle cells, lipid peroxidation, and loss of vasodilators in numerous studies (Ávila, et al., 2014). In view of all potential mechanisms of arsenic-induced cardio toxicity, it is biologically plausible that arsenic might exert adverse effects on cardiac structure and mass independent of traditional risk factors (Rahimzadeh, et al., 2014).

Mercury: Some reports demonstrate the relationship between mercury toxicity and ERS. It is well known that mercury can bind to native proteins and inhibit their biological activity by oxidizing and covalently bound with sulfhydryl groups from functional side chains, or also by displacing enzymes cofactors (Reynolds, et al., 2004). All of these events promote renal dysfunction; our results show that $HgCl_2$ causes AKI because it reduces in a temporary course the clearance of creatine with an increase of uric acid, BUN, glycosuria, and proteinuria (Robles-Osorio, et al., 2015).

One of the responses of the kidney cells against mercury chloride intoxication is the overexpression of Heat-Shock Proteins (HSP) and Glucose-Regulated Proteins (GRP), with the purpose of enhancing the degradation of misfolded and unfolded proteins. Additionally, it increases the expression of genes encoding many other ER proteins to prevent the excessive accumulation of unfolded or misfolded proteins (Bhowmick, et al., 2018). It is believed that mercury enhanced the expression of these proteins as GADD34, and it is in accordance with other research groups that found that in the rat, the administration of $HgCl_2$ enhances the expression of HSP72, HSP60, and GRP75, which are critical players in the assembling, transport, and refolding of proteins during oxidative damage (Mohanty, et al., 2017). However, there were no studies relating these events with the activation of the three pathways of ERS. Findings suggest that HgCl2KI partially activated the PERK pathway during the first 48 h through the activation of two pathways. One pathway involved PERK-immediate substrate nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is independent of eIF2a phosphorylation, and it is one of the primary regulators of cytoprotective responses to oxidative stress, as we can observe in the result above (Sedman RM, et al., 2006). Thus, Nrf2 could act as a potent

activator for the transcription of antioxidant enzymes like Glutathione S-Transferase (GST) and GR as we can observe in the temporary result of this study, particularly 48 h after mercury intoxication (Shankar, et al., 2014). These mechanisms have a relationship with the mercury bioaccumulation process in kidney cells more than antioxidants or detoxifying compensatory action. Moreover, it has an association between GADD153 and the oxidative stress process because it induces the overexpression and over-activity of Endoplasmic Reticulum Oxidoreductin 1 (ERO-1) which enhances H_2O_2 production and cytoplasm Ca2þ overload to promotes oxidative stress (Shirran, et al., 2009). Also, it has been reported that Sirt1/Nrf2/OH-1 pathway is insufficient to respond to the mercury chloride causes oxidative stress because $HgCl_2$ blocks the positive feedback loop Sirt1/Keap1/Nrf2/ARE that is an antioxidant pathway (Sobin, et al., 2017). The second mechanism involved the phosphorylating eIF2a which attenuates global protein translation and also it activates ATF-4-dependent transcription. We proposed that the second route is progressively activating from 48 h until 72 h because there is a rise in the expression of ATF-4, which can induce the expression of GADD-34, a protein that is associated with Protein Phosphatase 1 (PP1) and promotes DE phosphorylation of eIF2a (Tsamesidis, et al., 2020). Thus, it attenuates the PERK/eIF2a pathway to promote cell death. After 72 h of mercury intoxication, ATF-4 and GADD-153 have the same pattern of expression. Thus ATF-4 mediated GADD-153 translation through GADD 34 (Azhar, et al., 2022). Meanwhile, GADD34 is a target molecule of ATF6 and IRE1a pathways. In our result, IRE1a had the same pattern expression of GADD34, but ATF6 presented a stepwise expression increase, and so did XBP-1. These molecular mechanisms promote the synthesis of new ERS mediators and cell-death promoters like GADD-153 (Velea, et al., 2009). 72 h after mercury exposition, the apoptosis process is activated because the IRE1a kinase domain forms a complex with adaptor protein TNF Receptor-Associated Factor 2 (TRAF2), the Apoptosis Signal Regulator Kinase 1 (ASK1), and the c-Jun Kinases (JNK) (Anderson, et al., 2016). This hypothesis is supported because mercury reduces the expression of BCL2 y BCLXL with an increase of BAX, BAK, and caspase-12 (Verma A, et al., 2020). This molecular event participates in the formation of the Mitochondrial Transition Pore (MTP), which allows the release of cytochrome c from mitochondria to the cytoplasm to form the apoptosome (Voorhees, et al., 2017). This idea is supported because our results show the overexpression pattern of GAD153 agrees with the expression of caspase 12 and the over-activity of caspase 3. Finally, the increase of the oxidative and ERS promotes the over-expression of annex in-V with evident histological damage characterized by the hematoxylin–eosin stain edema, the cellular atrophy of distal and proximal tubules, distortion of cellular continuity, nucleus loss, and hyper chromatic nuclei. All of these biochemical, molecular, and morphological change promotes renal dysfunction.

Cadmium: Within the cell, Cd has been shown to impair electron transport chain complexes II and III, which impedes electron flow and generates ROS [87].

The generation of ROS promotes the binding of the Metal-regulated Transcription Factor 1 (MTF-1) to Metal Response Elements (MRE), which subsequently activates the transcription of Metallothionein (MT) (Wang, et al., 2009). Intracellularly, MT binds to Cd to create a MT–Cd complex, and a fraction of the complex is exported into the circulation. MT–Cd complexes are filtered freely by the glomerulus and are reabsorbed by proximal tubular epithelial cells *via* multiple mechanisms, including megalin and cubilin receptor-mediated endocytosis, ZIP8 and ZIP14, and the Divalent Metal Transporter 1 (DMT1) (Wang, et al., 2017). Environmental and occupational exposure to low levels of Cd has been shown to cause renal tubular injury. Owing to its toxic renal effects, chronic exposure to Cd increases the risk of developing CKD from 10% in the average population to 25% in exposed individuals (Xu, et al., 2014).

Studies suggest that exposure of diabetic individuals to Cd may exacerbate the renal injury and lead to CKD or enhance the progression of CKD by causing additional injury. Hypertension is another major risk factor for the development of CKD. A meta-analysis study of published literature found a positive association between hypertension and Cd levels in blood and hair (Xu, et al., 2021). Indeed, Cd has been shown to decrease plasma levels of Atrial Natriuretic Peptide (ANP), an important regulator of blood pressure. However there is a claim that Cd appears to reduce the affinity of the ANP receptor for ANP and also decreased the number of binding sites available (Zhang, et al., 2016). Reduced levels of ANP and reduced sensitivity of the receptor may decrease the ability to regulate blood pressure, which may lead to hypertension and subsequent renal injury. The development of hypertension is characterized by low ANP plasma concentrations and its suppressed ability to regulate blood pressure *via* inhibiting therenin–angiotensin–aldosterone system. In addition to causing vasodilation of the afferent arterioles, ANP binds to natriuretic peptide receptor-A, catalyzing the conversion of GTP to cGMP. cGMP phosphorylates and allosterically binds to basolateral sodium-potassium ATPase channels and apical cyclic nucleotide-gated, heteromeric channels of transient receptor potential V4 and P2 (Yao, et al, 2008).

While the mechanism remains entirely unclear, damage to the kidney's response to ANP may potentially be mediated by Cd-induced oxidative damage. In addition to the association with diabetes and hypertension, exposure to Cd has been shown to cause generalized cellular injury in renal epithelial cells. A major consequence of Cd exposure is intracellular oxidative stress. Studies reveal the association of Cd exposure to substantial activity reduction in antioxidant enzymes, including superoxide dismutase, catalase, and glutathione reductase that may amplify the progression of chronic kidney disease from oxidative species overwhelming antioxidants. In addi-

tion to oxidative stress, Cd has been shown to induce ER stress and autophagy (*via* BNIP3) in HK2 cells and SD rats. Studies in cultured rat Pheochromocytoma Cells (PC-12) showed that exposure to Cd enhanced autophagy (Yen, et al., 2012).

In contrast, studies in mice exposed to Cd showed that protein components of autophagosomes (e.g., p62, Sirt6, and LC3-II) accumulated in the cytoplasm of renal tubular cells rather than participate in the formation of autophagosomes. This resulted in the inhibition of autophagy and the initiation of apoptosis. Similarly, a study in cultured proximal tubular cells reported that treatment with Cd led to the accumulation of p62 in the cytoplasm and the inhibition of autophagy. Furthermore, it was reported that elevated levels of p62 led to increased nuclear translocation of Nrf2. Persistent activation of Nrf2 can lead to lysosomal dysfunction, which prevents the fusion of lysosomes and autophagosomes. Exposure to Cd has also been shown to disrupt cadherin-dependent cell adhesion in proximal tubular cells. Alterations in cellular adhesion have been shown to alter the membrane localization of the Na^+K^+ -ATPase, which can lead to alterations in transport (Zhitkovich, et al., 2011).

Chromium: Cr (VI) is able to induce oxidative stress *via* multiple pathways. First, the metabolic intermediates and ultimate products generated during Cr (VI) reduction can participate in Fenton-type reactions to generate hydroxyl radicals in the presence of hydrogen peroxide. Alternatively, in the presence of endogenous superoxide anion and hydrogen peroxide, Cr (V) and Cr (VI) can produce hydroxyl radicals *via* Haber-Weiss-like reactions. Moreover, by forming Cr-Asc, Cr-GSH and Cr-cys crosslinks, the reduction of Cr (VI) depletes cellular antioxidants and disrupts the redox balance in the cell. The lethal ingest of chromium-contaminated products leads to; carcinogenic, mutation-causing, and organ damage. Depending on the levels of ROS production, Cr (VI)-induced oxidative stress may lead to cell death (cytotoxicity) or tumor formation (carcinogenicity). High levels of ROS production directly target lipid and DNA to generate lipid peroxidation and DNA damage as well as many other cellular injuries, leading to cell death by both apoptosis and necrosis. Medium to low levels of ROS in cells may disrupt the cellular redox balance and accelerate cell proliferation, leading to tumor formation and progression. 8-oxo-dG, a marker for oxidative DNA damage, has been detected *in vitro* in Cr (VI) exposed cells in many studies. However, the levels of 8-oxo-dG were not induced in the intestine of mice following Cr (VI) exposure in drinking water for 9 months or 3 months. It is possible that a majority of ingested Cr (VI) was reduced to Cr (III) by the gastric juice, and the small amount of Cr (VI) absorbed by cells could not induce detectable 8-oxo-dG. It is worth noting that 8-oxo-dG has a relatively short lifetime in cells, and there is high background when measuring 8-oxodG suggesting some technical problems in assessing this DNA adduct (Zhitkovich, et al., 2005).

Cr (VI) itself does not bind to DNA or other macromolecules in cells. Instead, its metabolic intermediates Cr(V), Cr(IV) and the final product Cr(III), are highly reactive and readily form Cr-DNA adducts. Cr (III)-induced DNA adducts can be either binary (Cr-DNA) or ternary (ligand-Cr-DNA), where the ligand can be Asc, GSH, cysteine, histidine, or other cysteine-containing proteins. Binary Cr-DNA adducts can be repaired rather efficiently, within minutes after exposure by Nucleotide Excision Repair (NER) in cells. NER-deficient human cells are hypersensitive to Cr (VI) toxicity with a massive accumulation of Cr-DNA adducts, suggesting that DNA repair plays an important role in antagonizing Cr (VI)-induced DNA damage. Ternary Cr-DNA adducts are strong inhibitors of DNA replication and transcription. Interestingly, replication inhibition of ternary Cr-DNA adducts requires the presence of mismatch repair (MMR) proteins MMR-null mice and human cells were resistant to cytotoxicity induced by Cr (VI). In addition to binary and ternary Cr-DNA adducts, Cr (VI) reduction can generate several other DNA or chromosome lesions, including abasic sites, single- and double-strand breaks, protein-Cr-DNA crosslinks, DNA inter/intrastrand crosslinks DNA single or double-strand breaks have been detected in animals that were orally exposed to Cr (VI) by gavage. DNA-protein crosslinks were detected in liver cells but not lymphocytes from F344 rats that were exposed to potassium chromate *via* drinking water for 3-weeks. However, DNA-protein crosslink was not induced in mice exposed to Cr (VI) for 9 months *via* drinking water. The ability of these DNA lesions to induce DNA mutations has been extensively studied *in vitro* using the shuttle-vector system and *in vivo* using the Big Blue Mouse model. P53 point mutations have been reported at higher frequencies in lung tumors from chromate workers than in lung samples from non-chromate workers. Very few studies have examined DNA mutation in animals orally exposed to Cr (VI). In one study, K-Ras codon 12 GAT mutations were observed in both Cr (VI) treated and untreated mice, without a clear treatment-related trend (Priyanka, et al., 2017).

CONCLUSION

This study identified various sources of heavy metal pollutants in the environment and vividly pointed out how the industrial operation and anthropogenesis of man constituted leading emitting activity. This includes This mining activity, food production processes and natural phenomena. This pollutant starts to constitute ecological instability when its ranges go beyond capacity ecosystem can neutralize through self-cleaning (homeostasis) as a result these pollutants are absorbed by plants which then produce contaminated products that can indirectly be transferred to humans when after ingestion of this infected food. The second part of this study carefully highlighted the roles of various heavy metals as etiologic agents in the causation of various diseases around the globe. In summary, exposure to heavy metals had been clearly elucidated with their various medical and health implications ranging from cancers of various organs, al-

lergic reactions, and blood-related diseases to electrolyte crises leading to various organ damage and Chronic Kidney Disease (CKD). Reductions in exposure to various metals discussed in this article will reduce the burden of health challenges resulting from the intake of these various heavy metals. Importantly, government regulatory bodies should discourage and minimise the use of these heavy metals in food packaging and preservations, pesticides, herbicides and other agro-based practices. More so, the use of lead-based fuel and energy systems should be discouraged as this will help save the lives of many from diseases arising from these various metals.

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