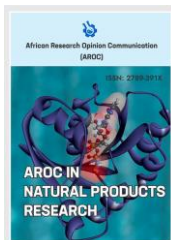




RESEARCH ARTICLE

Toxicological Implications and Therapeutic Approaches in Heavy Metal Exposure: Focus on Lead and Mercury

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ABSTRACT

Background: Heavy metals, including lead (Pb) and mercury (Hg), represent some of the most toxic environmental pollutants, posing significant risks to human health due to their persistence, bioaccumulation, and capacity to induce damage at very low concentrations. These metals are extensively used in numerous industrial, agricultural, and domestic applications, resulting in widespread environmental contamination and human exposure. Lead exposure is linked to neurodevelopmental impairment, renal dysfunction, cardiovascular complications, and hematological abnormalities, particularly affecting children due to their higher absorption and vulnerability. Mercury toxicity, especially in its organic and inorganic forms, manifests in severe neurological, renal, cardiovascular, and immunological dysfunctions. The underlying pathophysiology often involves oxidative stress, disruption of enzymatic systems, interference with calcium signaling, and damage to mitochondrial function. Diagnostic assessments include blood, urine, and hair analysis, while chelation therapy using agents such as EDTA and DMSA remains the cornerstone of treatment. This review explores the occurrence, sources, mechanisms of toxicity, clinical features, diagnosis, and current treatment strategies for lead and mercury intoxication, while highlighting the potential role of natural antioxidants in mitigating oxidative damage. It underscores the urgent need for environmental regulation, occupational safety, and therapeutic innovation to address the global burden of heavy metal toxicity.

Keywords: Heavy metals, Toxicity, Lead, Mercury, Oxidative Stress, Diagnosis, Chelation Therapy, Antioxidants, Environmental Health

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1.0 Introduction

Heavy metals such as lead, mercury, cadmium, and arsenic have garnered substantial attention due to their high toxicity and persistent nature in the environment. These elements are characterized by a high atomic weight and a specific gravity greater than 5 g/cm³, making them capable of inducing deleterious biological effects even at low concentrations. Unlike organic toxins, heavy metals are non-biodegradable and tend to bioaccumulate in the food chain, amplifying their risk to human health. The increasing pace of industrialization, mining, improper waste disposal, and the unregulated use of heavy metals in agriculture and manufacturing have led to the pervasive contamination of air, water, and soil. Among the numerous heavy metals, lead (Pb) and mercury (Hg) stand out due to their extensive

industrial applications and well-documented health impacts. Lead has been widely used in battery manufacturing, paint, gasoline additives, and plumbing, while mercury finds use in thermometers, dental amalgams, fluorescent lamps, and industrial catalysts. Both metals are capable of crossing biological membranes, including the blood-brain barrier and placental barrier, leading to systemic toxicity that can manifest as neurological, renal, cardiovascular, hematological, and immunological disorders. This review provides a detailed exploration of the toxicodynamic and clinical manifestations associated with lead and mercury exposure. It also delves into mechanisms of cellular injury, the role of oxidative stress, diagnostic methodologies, and current therapeutic strategies including chelation therapy.

Additionally, emerging evidence supporting the role of natural antioxidants as adjuncts in mitigating heavy metal toxicity is discussed. The overarching aim is to synthesize current knowledge to inform public health strategies, clinical interventions, and policy formulations for managing heavy metal exposure and its health consequences.

2.0 Heavy metals

Heavy metals such as mercury, and lead are classified among the most dangerous environmental pollutants due to their high toxicity and persistence. Characterized by a specific gravity exceeding 5 g/cm³, these metals can exert harmful biological effects even at trace concentrations (Tchounwou et al., 2004)

2.1 Lead (Pb)

Occurrence, Sources, and Human Exposure

Lead (Pb) is a naturally occurring metal that ranks among the most prevalent and historically utilized elements in the Earth's crust. It is a bright, silvery metal known for its low melting point, high malleability, and corrosion resistance. Despite its well-documented toxicity, lead continues to be used in over 900 industrial applications, including mining, smelting, battery production, paint manufacturing, cosmetics, and refining processes (Malekirad et al., 2010; Karrari et al., 2012).

In agriculture, it has also been employed in the formulation of certain pesticides and fertilizers. The extensive and often unregulated use of lead has contributed to widespread environmental contamination and poses significant public health risks globally (Ibrahim et al., 2006; Desta, 2008). Lead exposure is particularly concerning in urban and industrialized regions, where emissions from factories and traffic contribute to high ambient concentrations. Its persistence in the environment means that lead can accumulate in soil and groundwater, leading to long-term ecological damage and increased human exposure (Jalali et al., 2008; Parizanganeh et al., 2010).

Occupational exposure is common among workers in industries involving lead processing, while the general population may be exposed through contaminated air, water, food, and consumer products. To mitigate these risks, the World Health Organization and other regulatory agencies have established safety thresholds, with the maximum allowable concentration of lead in drinking water set at 10 µg/L (Karrari et al., 2012).

Mechanisms of lead toxicity

Lead exerts its cellular toxicity by generation of free radicals such as peroxynitrite, hydroxyl, nitric oxide and superoxide, radicals (Singh et al., 2017), and induction of oxidative stress. The oxidative stress is caused by the imbalance between the production of free radicals and the ability of antioxidants to detoxify the reactive intermediates or to repair the resulting damage. However, studies have established the fact that natural product particularly from plant extract

exhibit significant preventive and therapeutic effect against oxidative stress (Yusuf et al., 2018; Adegbesan et al., 2021).

Lead is also known to interfere with cellular nerve transmission by blocking the neuronal calcium and K⁺ channels as well as responses to activation of angiotensin, acetylcholine, adrenergic, and glutamate receptors (Anetor et al., 2008). The ability of lead to substitute other bivalent cations in various biological processes also account for the ionic mechanism of lead toxicity (Jaishankar et al., 2014). However, antioxidants derived from synthetic and natural compounds have shown promise in neutralizing lead-induced oxidative injury (Ogunlakin et al., 2024).

Clinical Features

Children are at higher risk of lead-induced toxicity due to the vulnerability of their under developed nervous systems and high intestinal Pb absorption (Karrari et al., 2012). Acute lead exposure can cause fatigue, hypertension, arthritis, sleeplessness, renal dysfunction and hallucinations, while chronic exposure may cause psychosis, birth defect, autism, liver and kidney impairment, haematological alterations, reproductive deficiency, intellectual disability, brain damage, dyslexia, allergies, paralysis and even death (Papanikolaou et al., 2005; Edema et al., 2023).

Lead is a well-known neurotoxicant than any other environmental chemical. The neurotoxicity activity of lead is associated with presynaptic dysfunction which has been identified in many neurological abnormalities such as schizophrenia, autism, dementia, Down syndrome and bipolar disorder (Neal et al., 2012). Palour and palsy were the classic signs of lead poisoning (Anetor et al., 2008). Lead has also been reported to be nephrotoxic, it impaired energy production by compromising the integrity of renal mitochondrial (Kim et al., 2015), and consequently results to renal failure (Sarah et al., 2017). A case study in Romania reported that about 17% of lead exposed workers developed renal impairment (Gonick, 2018).

Effects of Lead on the Neurological System

The preliminary effects of lead on neuronal activities in children and adults manifest in symptoms of headache, irritability, memory loss, lack of concentration and cognitive deficiency (Phillip et al., 1994). However, the most frequently encountered neurological effects of lead intoxication are peripheral neuropathy in adults, typically involving extensor muscle groups. There is little sensory involvement and if radial or peroneal nerves are involved, the neuropathy will be exhibited as wrist or foot drop (Phillip et al., 1994). Lead competes with calcium for binding sites in the cerebellum for phosphokinase C. This prevents the entry of calcium into cells, impaired calcium-dependent pathways and neuronal signalling (Barry, 1975; Bressler et al., 1991). This elevates the release of neurotransmitter and altered the control release of other metabolite (Needleman et al., 2004). This deleterious effect is more pronounced in the

fetus nervous system, because they do lack lead-adhering proteins found in mature astroglia, which protect against lead toxicity by sequestration and elimination of the lead. Lead is more neurotoxic during fetal development and early infancy, because, lead also hampered the formation of the blood-brain barrier (BBB) in fetal and infant by poisoning the immature astrocytes and interfering with myelin formation, a process necessary for the formation of BBB (Phillip *et al.*, 1994). When the formation of BBB is hampered, proteins like albumin penetrate the tissues of the central nervous system, which results in edema, increased intracranial pressure, and encephalopathy (Holtzman *et al.*, 1984).

Children are more vulnerable to lead induced neurotoxicity than adults because they absorb a large amount of bioavailable lead and their developing system of cell growth and differentiation are more vulnerable to attack (Needleman *et al.*, 2004). Lead induced neurotoxicity is one of the most well studied sensitivity of a developing human to a toxicant. Lead can permanently have altered brain function because it hampers glial cell growth, synaptogenesis, cell migration and other neural development process (Holtzman *et al.*, 1984; Krigman, 1978).

Exposure to lead toxicant during infancy and early childhood have been associated with decreased play activity, reading disabilities, inability to concentrate and disturbances in fine motor function. Lead concentrations of 10-35 µg/dL have been associated with lowered IQ, poor attentiveness and exam failure (Papanikolaou *et al.*, 2005; Needleman *et al.*, 2004). Lead can cause impaired neurobehavioral activity at 10-15 µg/dL (Davis, 1990). A study has shown positive correlation between blood lead concentration of below 10 µg/dL and neurobehavioral effect (Shanphear *et al.*, 2000).

However, an inverse relationship between the blood lead level and reading, comprehension testing and math test scores. Higher effects of PbBs and tests of cognitive ability, number skills, and word reading in 501 children ages 6-9 years, was observed in children with PbBs level range of 5-10 µg/dL than those with lead levels of 10-20 µg/dL (Fulton *et al.*, 1987). Similarly, a study of relationship between IQ and lead exposure in 172 children recorded a significant inverse relationship with a total decrease in IQ of 7.4 points in children with lead exposure levels of 1-10 µg/dL significantly higher than the loss of IQ points in children with average PbBs of 10-20 µg/dL (Canfield *et al.*, 2003). Numerous metabolic processes have been implicated in neurological effect of lead intoxication which contributes to fatigue, depression and irritability observed during lead intoxication (Patrick, 2016). However, alcohol has been reported to ameliorate lead toxicity by acting as a sedative for lead-induced irritability in animal experiment (Nation *et al.*, 1986).

Effects of Lead on the Cardiovascular System

Reports on lead associated hypertension are well established and documented in literature (ATSDR, 2005). A numbers of clinical trials on different

population groups of occupational lead exposure correlate lead exposure with increased incidence rates of high blood pressure, cardiovascular and cerebrovascular abnormalities (Fanning, 1988; Sokas *et al.*, 1997). Human and animals study involving chronic exposure of lead has proven that lead exposure even at low dose contributed to the development of hypertension (ATSDR, 2005), while high level (20-29 µg/dL of PbBs) has been associated with cardiovascular and circulatory induced mortality (Lustberg *et al.*, 2002).

African-Americans are considered more vulnerable to the lead induced hypertension and mortality even at lower levels of exposure than Caucasians, this is due to the high levels of arterial blood pressure in African-American populations when compared to Caucasian populations (Vupputuri *et al.*, 2003). Meta-analyses of collective investigations revealed a positive association between increasing levels of lead in blood and elevated diastolic and systolic blood pressure with rises in arterial pressures by 0.6 mmHg and 1.0-1.25 mmHg per doubling of PbBs concentrations (Staessen *et al.*, 1994; Schwartz, 1995; Nawrot *et al.*, 2002).

This call for concern because, reduction in diastolic blood pressure by 2 mmHg can produce 6%, 15% and 17% reduction in the risk of coronary heart disease, stroke and ischemic attacks, and reduction in prevalence of hypertension respectively (Mulrow, 1998; Ogunlabi *et al.*, 2020), it is therefore expected that increase in diastolic blood pressure by 2 mmHg would produce a reverse effect. According to (Nash *et al.*, 2003) in a study involving 2,165 peri- and postmenopausal women, reported that postmenopausal women with mean PbBs value of 6.3 µg/dL had a 3.4-fold increased risk of diastolic hypertension when compared with mean PbBs value of 1.0 µg/dL and that loss of estrogen is implicated in this risk (Staessen *et al.*, 1998).

A total 2,125 participants were evaluated for the correlation between blood cadmium and lead levels with the incidence of peripheral arterial disease (PAD) (Navas-Acien *et al.*, 2004). The author reported that 98.3% of subjects had PbBs levels below 10 µg/dL. Subjects with PAD had 13.8 % higher PbBs and 16 % higher blood cadmium levels than those without PAD (Navas-Acien *et al.*, 2004) even though levels of these toxic metals in PAD subjects are still considered within normal limits (Navas-Acien *et al.*, 2004). A 10-µg/g increase in tibia lead levels has been associated with 2.23-fold increase risk of intraventricular block in men under 65 years and 1.2-fold increase risk for atrioventricular block in men above 65 years (Chang *et al.*, 1998).

Diagnosis and Treatment

Chelating agent such as dimercaptosuccinic acid (DMSA) and Calcium disodium EDTA are effectively used for treatment purposes and also as diagnostic agents to evaluate the level of lead burdens in the body (Pollock *et al.*, 1988; Wedeen, 1992). Analysis of 6 to 72 hours urine after intravenous administration of 1-2 g of EDTA has been shown to be a reliable

indicator of toxic fraction of lead body burden (Pollock *et al.*, 1988; Wedeen, 1992; Skerfving *et al.*, 1993).

The levels of lead chelate by EDTA have been correlated with renal impairment, peripheral nerve impairment, and neurobehavioral abnormalities (Batuman *et al.*, 1983; Araki *et al.*, 1986). Treatment of lead intoxication by continuous EDTA chelation has been successful for acute exposure in children, however, continuous EDTA chelation for children with lead exposure levels of up to 45 µg/dL is discouraged (CDC, 1991), because, evidence from animals study has indicated that acute EDTA therapy may redeploy lead into the CNS, however, the brain lead levels consistently declined upon continuous administration (Cory-slechta *et al.*, 1987).

On a contrary, animal study with radio-labelled lead do not support evidence that EDTA redistributes lead to the brain (Seaton *et al.*, 1999). Emerging protein-based therapeutics are also being explored for improved drug delivery and toxicity attenuation, especially in cancers impacted by heavy metal exposure (Ogunjobi *et al.*, 2025). Although EDTA chelation as a diagnostic tool for chronic lead exposure has been largely replaced by x-ray fluorescence (XRF), however, XRF is not readily available for standard diagnostic use and does not reflect bioavailable lead from the soft tissues (Lee *et al.*, 1995).

DMSA has also been evaluated for its potential as a biomarker for lead exposure, using DMSA urine testing 4 hrs after administration of 10 mg/kg DMSA to 95 male lead workers (Lee *et al.*, 2000). The levels of urinary lead derived from DMSA chelation provide a more accurate indicator of lead exposure than blood and urine lead, blood Zinc protoporphyrin and urinary concentration of aminolevulinic acid (Patrick, 2016). When DMSA provocation was compared to EDTA provocation it was discovered that, the levels of lead recovered in urine 8 hrs after EDTA provocation were 2.8 times higher than those resulting from DMSA (Lee *et al.*, 1995).

2.2 Mercury (Hg)

Occurrence, Sources and Human Exposure

Mercury is a metallic odourless, silver-white liquid with many potential applications. It serves as an important components of measuring equipment (in thermometers, barometers, pyrometers, and hydrometers), mercury arc lamps, fluorescent lamps batteries and amalgams (dental preparations). It is the most toxic heavy metals. The toxicity and bioavailability varies with their natural occurring forms; metallic elements, organic compounds and inorganic salts (Jan *et al.*, 2015; Jaishankar *et al.*, 2014). The inorganic mercury occur in form of mercurous (Hg⁺) or mercuric (Hg²⁺) and are more water soluble and toxic than the metallic element (Hg) form (Clarkson, 1993). These forms of mercury are largely found in lakes, oceans and rivers due to anthropogenic activities like agriculture, , mining, incineration, industrial wastewater and municipal wastewater discharges (Chen *et al.*, 2012).

Consumption of mercury contaminated aquatic animal is the major route of human exposure to methyl mercury (Trasande *et al.*, 2005). Exposure to metallic mercury, however, occur by air inhalation through mining and burning processes; and by soil and water through erosion of natural depots, discharges from industries and runoff from landfill sites. About 2,200 metric tons of mercury was release to the environments on annual basis (Ferrara *et al.*, 2000).

Mechanism of toxicity

When release into the environment (water and soil), mercury are absorbed by aquatic microorganisms where they get transformed into methyl mercury and undergoes biomagnification causing significant implication to aquatic lives. Methylmercury is a neurotoxic agent that damage microtubules and mitochondrial, it induces lipid peroxidation accumulate glutamate, aspartate and serotonin which are all known neurotoxic agent (Patrick, 2002).

Clinical features

Exposure to high levels of metallic mercury can cause vomiting, nausea, diarrhoea, pulmonary impairment, impairment of mucous membrane, skin rashes, hypertension, hepatic and renal impairment, and neurologic abnormalities such as anxiety, tremors, depression and abnormal behaviour, carcinogenesis and organ-specific oxidative damage (Onah *et al.*, 2024; Bates, 2003; Asano *et al.*, 2000; Chang, 1977). Mercury vapours can cause bronchitis, asthma and respiratory disturbances. Mercury also plays an important role in damaging the integrity of cellular function and protein structures.

The cellular structure becomes hampered when methyl mercury got attached with sulfhydryl and selenohydryl groups. Chronic mercury poisoning could also lead to erethism and acrodynia. Erethism is a Parkinsonian-like syndrome effecting the cerebellum and basal ganglia while Acrodynia is an intricate symptoms of chronic mercury intoxication. It is also Known as Feer syndrome, pink disease, erythroderma, Feer-Swift disease and raw-beef hands and feet (Boyd *et al.*, 2000; Dally, 1997; Sedano, 1998). It is primarily found in children and infant, but has been documented in some adults populations (Dally, 1997).

In 1997, more than 3,500 cases of acute metal poisoning were documented by the American Association of Poison Control Centres. According to National Academy of Science, about 10% populations of American women have mercury levels that could cause neurological impairment in any child they gave birth to (Haley, 2005).

Cellular Effects of Mercury

At the cellular level, exposure to mercury has been implicated in compromised integrity and membrane permeability, altered conformational integrity of macromolecules because of its affinity for thiols and sulfhydryl groups and DNA damage (Naganuma *et al.*,

2002; Flora *et al.*, 2008). Mercury intoxication has also been shown to induce generation of free radicals, oxidative damage and mitochondrial impairment (Lund *et al.*, 1993) with consequent negative effect on lipid peroxidation and calcium homeostasis (Peraza *et al.*, 1998).

Cardiovascular Effects

Mercury intoxication could result to cardiomyopathy, due to its accumulation in the heart. It has been estimated that the levels of mercury in the cardiac tissue of individuals who died from idiopathic dilated cardiomyopathy were on average of 22 000 times higher than in individuals who died of other forms of heart disease (Haffner *et al.*, 1991; Frustaci *et al.*, 1999). Mercury intoxication may also lead to chest pain or angina, particularly in patient under age 45 (Frustaci *et al.*, 1999). The cardio protective activity of paraoxonase 1 has also been reported to be inhibited by MeHg (Drescher *et al.*, 2014).

Haematological Effects

Mercury is a competitor of iron in binding with haemoglobin resulting in altered haemoglobin formation and thus predispose individual to hemolytic and aplastic anaemia. (Pyszel *et al.*, 2005). Experimental data has also implicated mercury in the aetiology of leukemia, and Hodgkin's disease (Kinjo *et al.*, 1996; Robinson, 1952).

Pulmonary Effects

Mercury intoxication has been linked with different pulmonary dilemma including Young's syndrome, pulmonary fibrosis, bronchitis and Young's syndrome (Hendry *et al.*, 1993; Tchounwou *et al.*, 2003). Vaporized mercury could easily penetrate respiratory tract into the circulation. Chronic inhalation of mercury even at low concentrations (0.7 to 42 µg/mL) could disturb sleep, induce tremor and impaired cognitive ability (Heyer *et al.*, 2004).

Effects On Digestive Systems

Mercury intoxication can also compromise the integrity of digestive system through inhibition of pathways that produce digestive and some non-digestive enzymes including chymotrypsin, trypsin and pepsin, dipeptyl peptidase IV and xanthine oxidase (Vojdani *et al.*, 2003). Symptoms include impaired digestion, abdominal pain, ulcer, inflammatory bowel disease, and bloody diarrhea. Mucosal inflammation has been observed in colitic models exposed to mercury or similar toxins (Omiyale *et al.*, 2024b).

Renal impairments

Chronic mercury intoxication could destroy intestinal flora which can increase the level of undigested food in the blood stream and cause immune response reactions and increase pathogenic infection (Summers *et al.*, 1993). Mercury intoxication has been implicated

in the aetiology of chronic renal disease, glomerulonephritis, membranous glomerulonephritis, subacute-onset nephrotic syndrome, tubular dysfunction, acute tubular necrosis, nephrotic syndrome and renal cancer (Li *et al.*, 2010; Park *et al.*, 2012; Oliveira *et al.*, 1987).

Effects on the Immune System

Polymorphonuclear leukocytes plays important role in immune system by destruction of foreign substances. Mercury compromises the integrity of immune system by inhibiting the production and impairing the normal function of polymorphonuclear leukocytes (PMNs). This effect of mercury on PMN is exerted through the suppression of adrenocorticosteroids production (Wada *et al.*, 2009). Mercury intoxication increases sensitive and vulnerability to allergies, asthma, and autoimmune diseases like rheumatoid (Rice *et al.*, 2014).

Mercury intoxication has been associated with increased bacteria, molds and yeasts level which are known to exhibit protective effect by absorbing excess mercury from the body. Therefore, uncontrolled uses of antibiotics could destroy the beneficial pathogens and thus cause the sudden high release of mercury and increase its burden of allergic disease, arthritis, amyotrophic lateral sclerosis, autoimmune thyroiditis, autism, eczema, psoriasis, epilepsy, rheumatoid arthritis, multiple sclerosis, schizophrenia, systemic lupus erythematosus and scleroderma (Gardner *et al.*, 2010; Omiyale *et al.*, 2024a; Warren, 1989; Singh, 2009; Johnson *et al.*, 2009).

Diagnosis of mercury intoxication

Diagnosis of mercury intoxication begins with the physical examination and evaluation of the patient history. Laboratory diagnosis includes 24-hour urine urinalysis, blood analysis, hair analysis, tissue biopsy and a urine challenge test (Magos *et al.*, 2006; Schoeman *et al.*, 2010). Direct correlation between the concentration of blood mercury and the severity of mercury intoxication may however, not be accurate because mercury can be easily removed from the blood and redistributed into other tissues (Rice *et al.*, 2014). However, shortly after mercury ingestion, it becomes tightly bound to the brain, ganglia, autonomic ganglia, spinal cord, and peripheral motor neurons (Rice *et al.*, 2014).

Conflict of interests

The authors declare that they have no Conflict of interests.

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