IARJSET

ISSN (Online) 2393-8021
ISSN (Print) 2394-1588

International Advanced Research Journal in Science, Engineering and Technology

Vol. 6, Issue 10, October 2019

A Mini-review on Toxicology and Human Health effects of Heavy Metals: Lead (Pb) and Mercury (Hg)

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Abstract: Lead (Pb) and mercury (Hg) are non-essential and ubiquitous heavy metals that have been released in the environment as a result of natural processes as well as anthropogenic activities. They are marked by their high inherent toxicity, persistence in the environment and ability to be bioaccumulated along the food chain and pose significant and long-term risks to ecosystems and human health. Unlike metals that are considered essential, Pb and Hg have no known physiologic function and cause toxicity, even at very low concentrations. This mini-review gives a comparative view on the toxicological profile of these priority pollutants. It provides their different primary pathways of exposure, where the inhalation and ingestion pathways of lead sources from legacy sources are contrasted with the accumulation of organic methylmercury through the food chain. Furthermore, common and unique underlying mechanisms of molecular toxicity, which cluster on oxidative stress, enzyme inhibition by sulfhydryl binding, and ionic mimicry, are summarized in the review. Finally, it synthesizes their major adverse health impacts, as major focus on their neurotoxic (developmental and adult) critical role as well as significant nephrotoxic and cardiovascular implications.

Keywords: Non-essential Heavy Metals; Lead and Mercury Toxicity; Neurotoxicity; Renal and Cardiovascular Toxicity.

I. INTRODUCTION

Environmental toxicology is basically concerned with the harmful effects of chemical, biological and physical agents upon living organisms and ecosphere. Within this broad discipline, few classes of pollutants have been so heavily studied scientifically and subject to public health concern as "heavy metals." While there are many different definitions of what constitutes a heavy metal, they can all generally be defined as natural metallic elements with a high atomic weight and a density at least 5 times greater than that of water [1]. However, their significance to the environment is not as a result of their physical properties, but their inherent toxicity, persistence in the environment and complicated biogeochemical cycling. Unlike organic pollutants, which can frequently be broken down (e.g., by biology or chemistry) into less harmful material, metals are immortal and they are irrevocably indestructible, can only be transported or converted into other chemical species. Among the vast number of heavy metals, lead (Pb) and mercury (Hg) are of prime importance as examples of priority pollutants because of their worldwide distribution as well as their character as non-essential in human physiology and having profound consequences for human health at even minute levels of exposure [2]. The history of the relationship between humankind and these toxic metals is very ancient, and they are a long-standing paradox-one of the best examples of how useful properties of a substance can co-exist with very high biological dangers. The acknowledgment of their toxicity is not the word of prophecy but knowledge purchased through centuries of sick knowledge. One of the first metals that the human race smelted became pervasive in the Roman Empire: lead [3]. Its widespread use in aqueduct plumbing, pewter cookware and even as a sweetener for wine (which is made with lead acetate, or "sugar of lead"), caused widespread, chronic lead poisoning of the populace and the aristocracy. Historians and toxicologists have for many years hypothesized that the neurotoxic effects of lead contributed to the demise of the Western Roman civilization, representing an early, gross warning of the effects of widespread environmental contamination [4, 5]. Similarly, the adverse impacts of mercury have been known to history, probably most notoriously in the felt hat-making industry of the 18th and 19th centuries. The use of mercuric nitrate to cure the fur led to severe occupational neurotoxicity among workers and hence giving rise to the-phrase "mad as a hatter" due to the severe central nervous system impacts of mercury vapour inhalation [6]. What overruled this historical awareness is the industrial revolution and the technological explosion that occurred in the 20th century that exponentially grew the mobilization of these metals from the Earth's crust into the biosphere. The introduction of tetraethyl lead at mid-20th century, as a gasoline additive, for example, caused lead contamination of the earth's atmosphere of unprecedented proportions, depositing the neurotoxin in soil and dust even in the most remote parts of the planet [7]. It was not until the late 1956 that "Minamata disease" was officially recognized as the result of heavy metal consumption through seafood and a few more years before

it was definitively identified as the Chisso factory effluent. The tragedy was worsened by the fact that methylmercury crossed the placenta. Mothers who experienced few or no symptoms gave birth to infants with severe cerebral palsy-like conditions that arose during gestation and proved the extreme sensitivity of the fetal brain to the toxin [8]. Minamata was a watershed moment It showed in a very graphic way that it was possible to biomagnify industrial metallic wastes in the environment into far more dangerous organic forms and transfer them into the human food supply with devastating consequences, far from where the initial discharge via a plant had occurred. By the mid-1950s, strange things started happening in the area: Cats would display erratic behavior; they would have convulsions, and run into the sea to drown ("dancing cat fever"). Soon, similar neurological symptoms showed up in humans - sensory disturbances, loss of coordination in movements, tremors, tunnel vision and in severe cases, coma and death. Unlike inorganic mercury, this organic form readily bioaccumulated in marine life and also biomagnified up the food chain reaching extremely high concentrations in the fish and shellfish that made up the local population's staple diet [9]. Today, the legacy of ancient application is combined with massive industrial applications of the past century such that Pb and Hg are still ubiquitous in the environment. While great regulatory efforts all over the world in the last few decades, such as phasing out leaded gasoline and paints and the recent Minamata Convention on Mercury, have ultimately succeeded in reducing emissions in many sectors, the threat has not been neutralized [10]. Legacy pollution in the soil, in older housing stock are among the main sources of lead exposure in children and artisanal gold mining and burning coal continue to drive the mercury circle around the globe. For that reason, the World Health Organization (WHO) has repeatedly included the presence of both lead and mercury in its list of top ten chemicals of major public health concern [11]. This mini review article highlights the importance of further research and more rigorous strategies must be implemented to monitor and remediate both these elements particularly in aqueous medium.

II. SOURCES OF EXPOSURE & TOXICOKINETICS

2.1 Lead (Pb)

While industrial emissions have continued to be a source, the inherent problem for general population poisoning and especially children are the legacy pollution. This includes deteriorating lead-based paint in the older housing stock, contaminated urban soil and dust, and lead leaching from aging lead water pipes and water fixtures [12, 13]. Exposure is mostly by ingestion (e.g., hand to mouth activity in children) and inhalation of contaminated dust. Leading of the bloodstream, the toxicokinetics of lead are defined as: Lead has an ability to act similarly to essential divalent cations like calcium (Ca^{2+}). This mimicry by ionic species enables Pb to use the calcium transport mechanisms to cross the cell membranes [14]. Once absorbed, lead is distributed to the blood, soft tissues and bone. Approximately 90-95% of total body burden of lead in adults is sequestered in bone in which it replaces calcium in hydroxyapatite matrix. This provides an internal repository that is long-term and may be mobilized back into the bloodstream during periods of high bone turnover, in pregnancy, lactation or osteoporosis [15].

2.2 Mercury (Hg)

Mercury toxicity is very dependent on the chemical speciation thus calling for a very important distinction between elemental/inorganic forms of mercury and the organic forms. Elemental mercury vapour is the main source of emission from the combustion of coal and artisanal small-scale gold mining (ASGM) resulting in significant occupational inhalation risks [16]. However, the most important route of non-occupational human exposure at the global level is the dietary uptake of organic methylmercury (MeHg). Inorganic mercury released into aquatic environments is transformed into MeHg by microorganisms (e.g. sulfate reducing bacteria). This organic form then gets bioaccumulated through the foodweb to high levels in predatory fish and marine mammals that humans eat [17]. MeHg is extremely toxic because of its special toxicokinetics is easily absorbed (95% or more) in the gastrointestinal tract [18]. Unlike inorganic mercury, organic structure of MeHg have an easy to cross the barrier function of the blood-brain barrier (BBB) and placental barrier with the facilitation of amino acid transporters, has the ability to directly act on the central nervous system in both adults and developing fetuses [19, 20].

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ISSN (Online) 2393-8021
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Table 1: Comparative Toxicokinetics, highlighting the various pathways through which these metals enter and store themselves within the human body.

Feature	Lead (Pb)	Methylmercury (MeHg)
Primary Environmental Sources	Leaching from old water pipes, lead-based paint and polluted urban soil/dust [12].	Bioaccumulation in aquatic food webs, predatory fish and marine mammals respectively [17].
Primary Routes of Absorption	Ingestion (especially hand-to-mouth intake among children) and inhalation of toxic dust [13].	More than 95% gastrointestinal absorption resulting dietary intake [18].
Key Mechanism of Transport	Ionic mimicry of calcium (Ca^{2+}), using calcium transport mechanisms for mediating the transport across membranes [14].	Molecular mimicry, the use of amino acid transporters to cross cell barriers [19].
Primary Long-Term Storage/Target	Sequestered in bone tissue (substituting for calcium in hydroxyapatite), with between 90 - 95% of the adult body burden [15].	Readily crosses the blood-brain barrier (BBB) and placental barrier to developing and adult central nervous system [19, 20].

2.3. Mechanisms of Toxicity

While the various forms of the clinical manifestations are dependent on the metal and age of exposure, Pb and Hg share basic molecular mechanisms of toxicity on the cellular level.

One of the major modes of action of both metals is the induction of oxidative stress. Pb and Hg disturb the cellular redox state by enhancing the production of reactive oxygen species (ROS), like superoxide and hydrogen peroxide, and at the same time, having depleted the cellular anti-oxidant defence (e.g. glutenin). This imbalance causes the peroxidation of lipids of cell membranes, DNA damage, and protein oxidation [21, 22].

In addition, both metals have a high affinity for sulfhydryl (-SH) groups (thiols) contained in proteins and enzymes [23]. Enteroviruses can inhibit crucial enzyme actions, cause disruption of structure proteins and other vital metabolic pathways by binding to these functional groups [24].

The peculiar nature of lead toxicity is stigmatized by harmonic mimicry. By substituting for calcium, lead interferes with important intracellular calcium signaling phenomena, release of neurotransmitters across synapses, and regulation of calcium-dependent enzymes (e.g. protein kinase C). Lead also interferes with zinc-dependent enzymatic processes, of which the most frequent are in the heme synthesis pathway, resulting in anemia at high exposure levels [25].

III. UNDENIABLE MAJOR ADVERSE HEALTH IMPACTS

3.1 Neurotoxicity (The Nervous System - Target of Primary Toxicity)

The nervous system is the important target organ for both metals, although there are considerable differences in susceptibility related to the developmental stage.

The developmental neurotoxin by Lead (Pb): In young children, however, because of developing blood-brain barrier and elevated absorption rates, chronic low-level exposure is causally associated with irreversible cognitive deficits and decreased Intelligence Quotient (IQ), as well as behavioral problems related to attention (i.e. AD/HD) and impaired academic performance [26, 27]. In adults, at higher levels of occupational lead exposure, slowed nerve conduction and motor weakness (historically known as "wrist drop") have been shown to be associated [28].

Mercury (Methylmercury): MeHg is namely equally devastating to the central nervous system. The occurrence of a historical ecological disaster in Minamata, Japan, pointed out its ability to cause severe damage to the central nervous system of adults, including ataxia, tremors, sensory disturbance and constriction of visual fields [29]. The developing fetal brain is however the most sensitive of targets. Prenatal exposure through maternal consumption of contaminated seafood may cause disturbances in neuronal migration and division and result in cerebral palsy-like symptoms, profound developmental delays and intellectual impairment despite the mother being asymptomatic [30, 31].

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Table 2. Critical Neurotoxic Consequence of Chronic Exposure Habitual to Exposure Age Difference, contrasting the effects of such metals on nervous system using the age at which the metals are exposed

Developmental Stage of Exposure	Lead (Pb) Neurotoxicity Outcomes	Methylmercury (MeHg) Neurotoxicity Outcomes
Fetal / Prenatal	Not stated explicitly in results section of the text given but implied from BBB crossing.	Disruption of neuronal migration and division causing symptoms similar to cerebral palsy and extreme developmental delay [30].
Child/ Developmental	Irreversible cognitive deficits, lower Intelligence Quotient (IQ) and behavioral problems related to attention like attention deficit hyperactivity disorder (ADHD) [26, 27].	Profound intellectual impairment, development delay, even in asymptomatic mothers [31].
Adult/ Occupational	Peripheral neuropathy with slow nerve conduction, motor weakness and classically, 'wrist drop' [28].	Severe neurological damage including ataxia, tremors, sensory disturbances and visual field contraction (depending on the amount of methyl mercury methyl bromide present in the body) [Minamata disease symptoms] [29].

3.2 Renal and Cardiovascular Toxicity

Outside of neurotoxicity, however, both metals seriously affect other major organ systems.

Kidneys: The kidneys represent the main route of excretion and one of the major sites of accumulation especially of inorganic forms of both Pb and Hg. Chronic, high level of exposure can cause nephrotoxicity with proximal tubular dysfunction, interstitial fibrosis and eventually, chronic renal failure [32, 33].

Heart: Epidemiological data has been used to demonstrate a strong link between the cumulative exposure to lead and cardiovascular disease in general. Even at relatively low levels of blood lead, Pb exposure is significantly related to development of hypertension (high blood pressure) and increased risk of ischemic heart disease and stroke. These effects are probably mediated by mechanisms involving oxidative stress, endothelial dysfunction and changes in the renin-angiotensin system [34, 35].

IV. CONCLUSION AND FUTURE PERSPECTIVES

The extensive toxicological evidence proves that lead and mercury are still widespread environmental hazards to human health with divergent modes of action. It is important to point out, however, that recent research suggests that there is no truly identifiable "safe" level of exposure to these metals, especially in relation to developmental neurological toxicity for fetuses and young children. The effects of low-level exposure are often subtle on an individual level but have a large effect at a population level. While sources of lead from legacy are still insisting on abatement efforts, the complex transboundary circulation of mercury is still demanding on-going international cooperation. Instruments such as the Minamata Convention on Mercury are an important step to reducing global emissions. Future public health efforts will need to continue by focusing on protection of vulnerable populations via more stringent regulations, remediation of contaminated sites, and effective public health advisories on the intake of mercury in the diet.

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