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Neurotoxic Heavy Metals in the Human Brain - III. The Lead - Alzheimer Connection

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Abstract

Lead (Pb) is a highly poisonous metal affecting almost every organ and system in the human body and can be dangerous to life and health. The primary cause of its toxicity is its predilection for interfering with the proper functioning of enzymes. It can cross the blood-brain barrier, degrade the myelin sheaths of neurons, reduce their numbers, interfere with neurotransmission routes, and decrease neuronal growth. It can cause severe damage to the brain and kidneys and, ultimately, death. In this article, the effects of Pb on the human brain and its connection to Alzheimer's disease (AD) will be investigated. After a brief review of the biomarkers of neurotoxic behavior and biological monitoring, the mechanisms of dysfunction and associations of neurotoxic exposure will be shown to involve mitochondrial dysfunction, oxidative stress, Calcium homeostasis disruption, structure damage, and metabolic inhibition. The Pb-induced neurotoxic effects on neurodevelopment will be discussed in the cases of children and adults. Lastly, the key effects on Alzheimer's pathology will be summarized.

Abbreviations

Aβ: Amyloid-beta; AD: Alzheimer's disease; ADD: Attention Deficit Disorder; ADHD: Attention-deficit hyperactivity disorder; ALS: Amyotrophic lateral sclerosis; ATP: Adenosine triphosphate; BBB: Blood-brain barrier; Bl-Pb: Blood Pb; BLS: (U.S.) Bureau of Labor Statistics; Bo-Pb: Bone-Pb; CAD: Coronary artery disease; Cd-B: Blood-CD; Cd-U: Urinary-Cd; CNS: Central nervous system; CVD: Cardiovascular disease; DNA: Deoxyribonucleic acid; GBDS: Global Burden of Disease Study; GI: Gastrointestinal; Ha-Pb: Hair-Pb; HD: Huntington's disease; MAM: Mitochondria-associated membranes; Mi-Pb: Micro-nuclei mt: mitochondria; MS: Multiple sclerosis; Na-Pb: Nails-Pb; NFT: Neurofibrillary tangles; OS:

Oxidative stress; PAD: Peripheral artery disease; Pl-Pb: Plasma-Pb; PD: Parkinson's disease; ROS: Reactive oxygen species; Sa-Pb: Saliva-Pb; Te-Pb: teeth-Pb; Ur-Pb: Urine-Pb.

Chemical elements: Al: Aluminum; As: Arsenic; Ca: Calcium; Cd: Cadmium; Gd: Fe; Iron; Gold; Hg: Mercury; Mn: Manganese; Pb: Lead; Pt: Platinum; Zn: Zinc.

Diseases mentioned: Alzheimer's disease; Amyotrophic lateral sclerosis; Anemia; Attention deficit disorder; Attention deficit hyperactivity disorder; Autism spectrum disorder; Birth defects; Cancer; Cardiovascular disease; Coronary artery disease; Gastrointestinal dysfunction; Huntington's disease; Hypertension; Immune system dysfunction; Multiple sclerosis; Nephropathy; Nervous system dysfunction; Parkinson's disease. Peripheral artery disease; Schizophrenia; Skin lesions; Stroke; Vascular damage.

Drugs listed: Dimercaprol; Disodium calcium edetate; Succimer.

Keywords: Alzheimer's disease; Calcium homeostasis disruption; Cognition; Lead poisoning; Memory impairment; Metabolic inhibition; Mitochondrial dysfunction; Neurotoxic heavy metals; Oxidative stress; Structural damage.

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Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by the accumulation of amyloid-beta (Aβ) plaques and hyperphosphorylated tau-protein neurofibrillary tangles (NFT) in the brain, leading to synaptic dysfunctions, cognitive decline, memory loss, and behavioral changes. The pathogenesis of AD is multifaceted, involving genetic, environmental, and epigenetic factors. It is associated with multiple environmental risk factors, including heavy metals. The exact mechanisms by which heavy metals cause AD are not fully understood, but they are believed to impair brain function by disrupting neurotransmitter balance and inducing oxidative stress (OS). Brain inflammation from heavy metal exposure may exacerbate the damage. Lead (Pb) is another heavy metal contaminant, which is also closely related to the incidence of AD. Exposure to Pb, particularly chronic accumulation in bones, is a significant risk factor for AD and cognitive decline, with high exposure linked to nearly three times the risk of AD. It promotes amyloid-beta plaques, tau tangles, neuroinflammation, and neuronal death, often accelerating dementia symptoms decades after early-life exposure. Diagnosing and treating heavy metal-induced dementia is challenging due to symptom overlap with other neurological conditions and the lack of definitive diagnostic tests. Treatment typically involves removing the exposure sources and providing supportive care to manage symptoms.

Articles 1 and 2 in this series dealt respectively with Aluminum (Al) and Cadmium (Cd) whereas this article is exclusively concerned with Pb. Sidebar 1 is an introduction to the physicochemical properties of Pb.

Introduction

Heavy metals are generally defined as metals with relatively high densities, atomic weights, or atomic numbers. They are commonly found in nature, including soil, mines, drinking water, and the Earth's crust. They are extensively used in various products such as pesticides, herbicides, paints and gasoline, with primary exposure routes being anthropogenic sources. Occupational exposure is significant in industries like mining, smelting, welding, and battery manufacturing, where workers face higher risks. Industrial pollutants also contaminate plant and marine life, indirectly impacting human health. In 2019, the (U.S.) Bureau of Labor Statistics (BLS) reported approximately 1200 nonfatal injuries and illnesses related to heavy metal

exposure in the U.S., resulting from inhalation, ingestion, or skin contact. Pb, Cd, Mercury (Hg), and Arsenic (As) are the most prevalent heavy metals.

Heavy metals are non-biodegradable and persist in the environment, with the potential to enter the food chain through crop plants and eventually accumulate in the human body through biomagnification. Heavy metal contamination poses a serious threat to human health and the ecosystem. Millions of people worldwide are affected by heavy metal exposure, which is a global health concern. Exposure to these substances can lead to a range of neurological disorders and cognitive impairments. Neurotoxic metals and metalloids, such as arsenic, cadmium, lead, mercury, and manganese, can interfere with synaptic structure and function, resulting in a loss of synaptic connectivity and more severe changes such as neurodegeneration.

Heavy metal toxicity can lead to numerous diseases and disorders by binding to cellular components, disrupting organ function, and causing heavy metal poisoning. This can result in gastrointestinal and kidney dysfunction, nervous system disorders, skin lesions, vascular damage, immune system dysfunction, birth defects, and cancer. Heavy metals can also damage blood constituents and vital organs like the lungs and liver, promoting various disease conditions. The human brain is particularly susceptible to heavy metals, which can damage the central nervous system (CNS) and lead to cognitive and behavioral impairments. Recent studies have raised concerns about the impact of heavy metals on neurological health, linking exposure to neurodegenerative diseases like AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and attention-deficit hyperactivity disorder (ADHD). These conditions manifest symptoms such as memory loss, motor dysfunction, muscle weakness, and speech difficulties.

However, significant gaps remain in our understanding of AD and dementia, especially regarding the influence of environmental factors on disease incidence. Among such potential factors, Pb has gained attention due to its widespread exposures and neurotoxic potential, and growing evidence suggests Pb exposure may increase dementia risk, but evidence from human studies is limited. With common exposure pathways including air, dust, water, and food, Pb toxicity has been linked to AD hallmark pathologies. Pb neurotoxicity, including the promotion of formation and spread of Aβ-plaques and tau-NFTs extends to oxidative stress (OS), neuronal apoptosis, and neuroinflammation. Regretfully, however, epidemiological evidence supporting Pb exposure impacts on incident AD and all-cause dementia is limited because of the lack of temporally relevant biomarkers of Pb exposure that reflect cumulative exposures. Thus, in their recent study, Wang et al. (2026) concluded that "… higher cumulative Pb exposure is associated with increased risk of incident AD and all-cause dementia. These findings underscore the role of Pb as an environmental risk factor for these neurodegenerative conditions and advocate for urgent public health interventions to mitigate Pb exposure, potentially reducing the burden of AD and dementia" and also "… emphasized the necessity of incorporating environmental risk factors into dementia research and clinical practice to better understand and mitigate their contribution to the development of neurodegenerative diseases".

Biological monitoring and biomarkers of neurotoxic exposure

Biological monitoring

Biological monitoring has been defined as "… the measurement and assessment of agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risks compared with an appropriate reference". Biological monitoring techniques are useful for risk assessment of toxic agents in the field of environmental health. The term biological marker (biomarker) is a

general term used for "… a system that specifically measures an interaction between a biological system and a chemical, physical, or biological environmental agent". Biomarkers are generally classified into three groups: biomarkers of exposure, effect, and susceptibility, as further discussed below.

Biomarkers of exposure

A variety of biomarkers are available to monitor human exposure to Pb. Their appropriate selection is critically important for health care management purposes, public health decision making, and primary prevention synthesis. Different biologic tissues and fluids (blood, urine, bone, tooth, hair, and nail) have been used. The difficulty in assessing the exact nature of Pb exposure depends on the complex Pb toxico-kinetics within various body compartments (namely, Pb cycling between bone, blood, and soft tissues).

• **Blood-Pb (Bl-Pb):** This is the primary biomarker used for the assessment of Pb exposure, both for screening and diagnostic purposes and for biomonitoring the body burden and absorbed (internal) doses of the metal. In adult humans, up to 50% of inhaled Pb is transferred to the bloodstream and of the ~10% absorbed dietary Pb, more than 98% is found in blood cells. Bl-Pb measurements reflect both recent and past exposures, the latter resulting from mobilization from bones back into the blood. Even in persons without excessive Pb exposure, bone can contribute from 45% to 55% of Bl-Pb. In a study of the environmental, dietary, demographic, and activity variables associated with biomarkers of Pb exposure, Bl-Pb was found to be associated with: (a) house dust concentrations of Pb; (b) duration of time spent working in a closed workshop; and (c) the year in which the subject moved into the residence. An important weakness of Bl-Pb is its poor response to changes in exposure at high levels.

• **Plasma-Pb (Pl-Pb):** As the plasma fraction is rapidly exchangeable in the blood, the toxic effects of Pb are assumed to be primarily associated with Pl-Pb). Although Pl-Pb should be more germane than Bl-Pb to Pb exposure and distribution, little is known about the association between Pl-Pb and clinical outcome. The determination of Pl-Pb is problematic because the metal can be shifted into the plasma and thus artificially increase Pl-Pb levels.

• **Micronuclei-Pb (Mi-Pb):** Micronuclei are chromosome fragments that are not incorporated into the nucleus at cell division. Their assay in peripheral blood is considered a reliable biomarker of genotoxic exposure to both physical and chemical agents. Sister chromatid exchanges and DNA-protein cross-links have also been shown to be reliable biomarkers for monitoring workers exposed to Pb and clearly indicate health effects from their occupational exposure to it.

• **Bone-Pb (Bo-Pb), feces-pb (Fe-Pb), urine-Pb (Ur-Pb):** Other currently available biomarkers of internal Pb dose have not yet been accepted by the scientific community as a reliable substitute for Bo-Pb measurement. Nevertheless, in certain cases Bo-Pb for bone or teeth (for past exposures), Fe-Pb (for current gastrointestinal exposure), and Ur-Pb (for organic Pb) are sometimes more useful than Bo-Pb. Many researchers accept that a cumulative Pb exposure integrated over many years rather than a single Bo-Pb measurement may be the most important determinant of some forms of toxicity. Bo-Pb accounts for > 94% of the adult body burden of Pb (70% in children). The most informative recent epidemiologic studies of the impact of Pb on health are those that could derive estimates of both recent (Bl-Pb) and cumulative (Bo-Pb) exposure for each participant.

• **Saliva-Pb (Sa-Pb):** This is a convenient source and a potential substitute for Bl-Pb as a biomarker for Pb exposure. Nevertheless, saliva has not been generally accepted as a reliable biomarker of Pb exposure because of conflicting and unreliable Sa-Pb measurements. Some studies have even suggested that saliva is not a suitable material for biological monitoring with respect to Pb exposure.

• **Urine-Pb (Ur-Pb):** The collection of Urine Pb) is favored for long-term biomonitoring, especially for

occupational exposures.

• **Hair-Pb (Ha-Pb):** Although Pb excreted in hair has been suggested for the assessment of Pb exposure, an extensive debate ensues about Ha-Pb as a biomarker. Hair is a biological specimen that is easily and non-invasively collected with minimal cost and is easily stored and transported to the laboratory for analysis. Such advantages should make hair an attractive biomonitoring substrate, at least superficially.

• **Nails-Pb (Na-Pb):** Like hair, nails have many superficial advantages as a Pb exposure biomarker, especially as specimen collection is noninvasive, simple, very stable after collection, and not requiring special storage conditions. Na-Pb is considered to reflect long-term exposure because this compartment remains isolated from other metabolic activities in the body. Because toenails are less affected than fingernails by exogenous environmental contamination, toenails have been preferred for Pb exposure studies. The Pb concentration in nails depends on the age of the subject, but apparently not on the subject's gender.

• **Teeth-Pb (Te-Pb):** In comparison to bone, teeth accumulate Pb over the long term. Some evidence has shown that teeth are superior to bone as an indicator of cumulative Pb exposure because the losses from teeth are much slower. Moreover, deciduous teeth are relatively easy to collect and analyze and are very stable for preservation purposes.

Mechanisms of dysfunction and associations of neurotoxic exposure

The mechanisms of dysfunction and associations of neurotoxic exposure involve mitochondrial dysfunction, OS, oxidative stress, Calcium (Ca) homeostasis disruption, structure damage, and metabolic inhibition.

Mitochondrial dysfunction

Metals are actively involved in multiple catalytic physiological activities. Metal overload may result in neurotoxicity as it increases the formation of reactive oxygen species (ROS) - an umbrella term for a variety of highly reactive molecules or oxidants. The most prominent members include superoxide, hydroxyl, and peroxy radicals. The mitochondria are their main production site (see Figure 1).

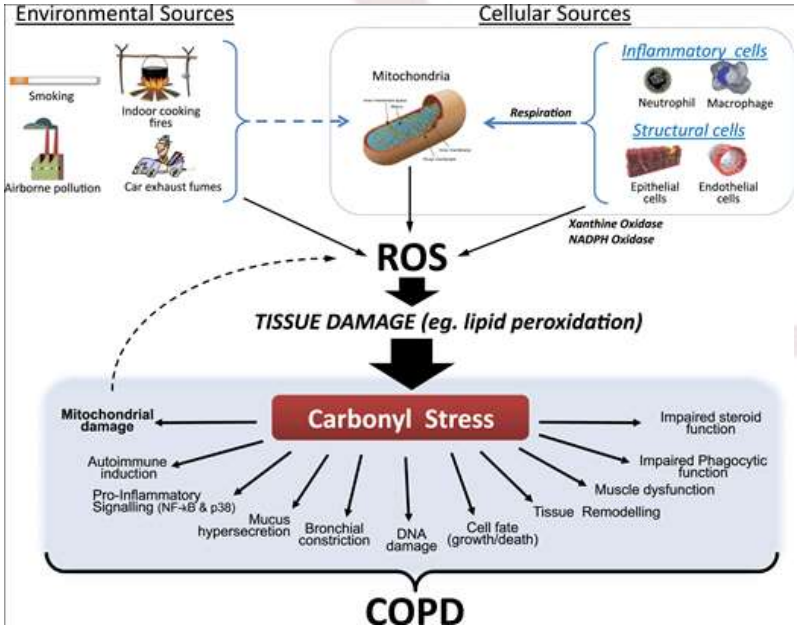

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Figure 1: Illustrating reactive oxygen species production and effects

ROS are produced by all cell types that line blood vessels, muscles, and connective tissue with the help of numerous enzymes. They are also produced by neutrophils and macrophages during inflammation, which is needed short-term to help the body fight off infections. However, excessive production of ROS may elevate OS in the nervous system, cause mitochondrial structural damage and oxidative damage to proteins, DNA, and lipids.

Given their role in energy production. mitochondria are a key target of metal-induced toxicity. They play a key role in many cellular physiological and pathological processes, including energy metabolism, Ca homeostasis, lipid biosynthesis, and apoptosis. One of their main functions is to produce adenosine triphosphate (ATP). Mitochondrial dysfunction has been implicated in a variety of diseases, and is a causative factor in several neurodegenerative diseases, including AD, Parkinson's disease (PD), Huntington's disease (HD), autism, and amyotrophic lateral sclerosis (ALS).

Pb exposure causes significant mitochondrial dysfunction by inducing OS, disrupting Ca homeostasis, and damaging mitochondrial structure, particularly affecting the brain, kidneys, and nervous system. In the latter instance, Pb disrupts mitochondrial dynamics (fission/fusion), lowers ATP production, and acts as a neurotoxicant, leading to cognitive decline, learning disabilities, and neurodegenerative diseases. Indeed, as the brain consumes a large amount of energy, mitochondrial dysfunction and the subsequent decrease in ATP levels may significantly disrupt brain function, resulting in neuronal cell death and ensuing neurological disorders.

Oxidative stress

Oxidative stress (OS) stems from an imbalance of free radicals (unstable molecules) relative to antioxidants in the body, leading to cell and tissue damage. It means that more free radicals are being produced than can be neutralized or removed from the cells, tissues, or the body. OS is when prooxidants override antioxidant defense.

Calcium homeostasis disruption

Pb mimics Ca^{2+}, disrupting its homeostasis and leading to abnormal Ca release, particularly in neurons. Neurons are highly polarized cells that are heavily dependent on the energy generated by mitochondria. The brain consumes about 20% of the body's resting ATP, while it accounts for only about 2% of the body's mass. In addition, mitochondria are necessary Ca-buffering organelles in neurons as they regulate local Ca dynamics to control neurotransmitter release.

Structural damage

Pb disrupts the fusion and fission processes (mitochondrial dynamics), affecting the shape, movement, and self-healing abilities of mitochondria.

Metabolic inhibition

Pb exposure can inhibit mitochondrial metabolism, including enzymes responsible for heme synthesis, leading to energy failure.

Lead-induced neurotoxic effects

Knowledge of Pb neurotoxicology has advanced in recent decades due to revelations regarding its mechanisms and cellular specificity. Potential mechanisms of Pb-induced cognitive deficits have been investigated using cellular models of learning and memory. New research provides convincing evidence that: (a) Pb exposures have adverse effects on the CNS; (b) environmental factors augment Pb susceptibility; and (c) exposures in early life can cause neurodegeneration in later life.

As the main target for Pb toxicity is the CNS, the brain

is the organ most studied. Pb neurotoxicity occurs when exposure to Pb alters the normal activity of the CNS and causes damage to it. The direct Pb neurotoxic actions include: (a) apoptosis (programmed cell death); (b) excitotoxicity affecting neurotransmitter storage; and (c) release and alteration of neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, astroglia and oligodendroglia. Symptoms can appear immediately after exposure or may be delayed and include loss of memory, vision, cognitive and behavioral problems, and brain damage/mental retardation. Most early studies concentrated on the Pb neurocognitive effects, but recently higher exposures have been associated with such morbidities as antisocial behavior, delinquency, and violence.

Effect of Pb on neurodevelopment

Many studies have examined the effects of lead on children's development outcomes covering varying ages at which Bo-Pb was measured and varying ages over which Bo-Pb levels were averaged. Statistically significant associations have been identified between average Bo-Pb levels over a specific period (for example, 0–5 years) and various adverse health outcomes. Other studies have reported statistically significant associations with a single Pb measurement at a specific age (for example, prenatal, 24 months, 6.5 years) or with a peak measurement. In contrast to adults, CNS effects are more prominent than peripheral effects in the developing nervous system. The developmental effects of Pb occur during a critical time window (age < 2 years of age). A child's Bo-Pb measurement is estimated to account for 2%- 4% of variance in neurodevelopment measures. Nonetheless, a child's family and personal psychosocial experiences are strongly associated with performance on neurodevelopment measures and account for a greater proportion of the explained variance in these measures than Bo-Pb levels. While no threshold has yet been identified, low-level Pb exposure to Pb during early childhood was shown to be inversely associated with neuropsychological development through the first 7 years of life.

Neurotoxicity in children

The effects of Pb exposure are a health concern for all humans, but especially during early childhood because children are most at risk. The extent and rate of Pb absorption through the gastrointestinal tract depend on the characteristics of the individual and on the physicochemical characteristics of the medium ingested. Children are at higher risk because they are more likely to play in the dirt, put their hands and other objects into their mouths, and absorb about half of an oral dose of water-soluble Pb. The preponderance of experimental and human evidence indicates that Pb has persistent and deleterious effects on brain function and forms the basis for subsequent cognitive impairments in Pb-exposed children. The specific effects on glutamatergic transmission, which is critically involved in development, neuronal plasticity, learning and memory, and mood consolidation, are of particular concern. Impairment of dopaminergic functioning (involved in motor control, attention, memory, and executive functioning) could induce a myriad of behavioral problems and cognitive impairments.

Exposure *in utero* in infancy or exposure in early childhood can slow mental development and cause lower intelligence that can persist beyond childhood. As the nervous system of a child is still developing, the Pb effects are more toxic than on a mature brain. In children, Pb poisoning can cause brain damage/mental retardation, behavioral problems, low IQ, hearing loss, hyperactivity, developmental delays, behavioral problems, diminished school performance, as well as deficits suggestive of (ADD).

Neurotoxicity in adults

The documentation of Pb as a toxin for adults preceded

the first description of childhood Pb poisoning by several millennia, having been recorded as early as 2000 BC. In adults, Pb poisoning can cause nerve damage to the sense organs and nerves controlling the body, leading to neurodegenerative diseases like AD and PD, hearing and vision impairment, schizophrenia, and impaired cognitive function. Which cognitive domains are affected has only begun to be explored in detail. While most research on Pb exposure has focused on deficits in memory and learning, a large body of evidence shows that Pb also influences other behaviors such as mood (depression), anxiety, and violence/aggression. Observations of the relations between early Pb exposure and neuropsychological abnormalities have been carried out throughout the course of life.

Key effects on Alzheimer's pathology

The key effects on Alzheimer's pathology demonstrating the Pb-Alzheimer connection are:

• **Acceleration of AD pathologies:** Pb exposure induces the formation of amyloid-beta ($A\beta$) plaques and neurofibrillary tau tangles (NFT), which are AD's hallmark pathologies.

• **Neuroinflammation and cellular damage:** Pb induces oxidative stress, microglia activation, and neuronal apoptosis (cell death) in the hippocampus, a brain region critical for memory.

• **Long-term impact of early exposure:** Early-life exposure to Pb can cause cognitive decline and increase the presence of Alzheimer's-related proteins later in life.

• **Cumulative exposure risk:** Bone lead is a superior biomarker for assessing chronic, long-term exposure compared to blood lead, which generally reflects recent exposure. High cumulative Pb exposure significantly increases the risk of Alzheimer's and all-cause dementia.

Conclusions and take-aways

- Lead Pb) is a highly poisonous metal affecting almost every organ and system in the human body and can be dangerous to life and health. The primary cause of its toxicity is its predilection for interfering with the proper functioning of enzymes. It can cross the blood-brain barrier, degrade the myelin sheaths of neurons, reduce their numbers, interfere with neurotransmission routes, and decrease neuronal growth. It can cause severe damage to the brain and kidneys and, ultimately, death.

- Heavy metals are non-biodegradable and persist in the environment, with the potential to enter the food chain through crop plants and eventually accumulate in the human body through biomagnification.

- Exposure to neurotoxic heavy metals can lead to a range of neurological disorders and cognitive impairments and can interfere with synaptic structure and function, resulting in a loss of synaptic connectivity and more severe changes such as neurodegeneration.

- Heavy metal toxicity can lead to numerous diseases and disorders by binding to cellular components, disrupting organ function, and causing heavy metal poisoning. They can also damage blood constituents and vital organs like the lungs and liver, promoting various disease conditions. The human brain is particularly susceptible to heavy metals and lead to cognitive and behavioral impairments.

- Recent studies have raised concerns about the impact of heavy metals on neurological health, linking exposure to neurodegenerative diseases

like Alzheimer′s disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and attention-deficit hyperactivity disorder.

- Biomarkers are available to monitor human exposure to Pb. Their appropriate selection is critically important for health care management purposes, public health decision making, and primary prevention synthesis. Different biologic tissues and fluids (blood, urine, bone, tooth, hair, and nail) have been used. The difficulty in assessing the exact nature of Pb exposure depends on the complex Pb toxico-kinetics within various body compartments (namely, Pb cycling between bone, blood, and soft tissues).

- The mechanisms of dysfunction and associations of neurotoxic exposure involve mitochondrial dysfunction, OS, oxidative stress, Calcium (Ca) homeostasis disruption, structure damage, and metabolic inhibition.

- Knowledge of Pb neurotoxicology has advanced in recent decades. New research provides convincing evidence that Pb exposures have adverse effects on the central nervous system, environmental factors augment Pb susceptibility, and exposures in early life can cause neurodegeneration in later life.

- Neurotoxicity occurs when exposure to Pb alters the normal activity of the central nervous system and causes damage to it. The direct Pb neurotoxic actions include apoptosis (programmed cell death), excitotoxicity affecting neurotransmitter storage, and release and alteration of neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, astroglia and oligodendroglia.

- Symptoms can appear immediately after exposure or may be delayed and include loss of memory, vision, cognitive and behavioral problems, and brain damage/mental retardation.

- In children, significant associations have been identified between average bone-Pb levels over a specific period (for example, 0−5 years) and various adverse health outcomes. In contrast to adults, central nervous system effects are more prominent than peripheral effects in the developing nervous system.

- A child′s family and personal psychosocial experiences are strongly associated with performance on neurodevelopment measures. Low level Pb exposures to Pb during early childhood are inversely associated with neuropsychological development through the first 7 years of life.

- In adults, Pb poisoning can cause nerve damage to the sense organs and nerves controlling the body, leading to neurodegenerative diseases like Alzheimer′s disease, Parkinson′s disease, hearing and vision impairment, schizophrenia, and impaired cognitive function.

- While most research on Pb exposure has focused on deficits in memory and learning, a large body of evidence shows that Pb also influences other behaviors such as mood (depression), anxiety, and violence/aggression. Observations of the relations between early Pb

exposure and neuropsychological abnormalities have been carried out throughout the course of life.

- Key effects on Alzheimer′s pathology demonstrating the Pb-Alzheimer connection are acceleration of AD pathologies, neuroinflammation and cellular damage, long-term impact of early exposure, and cumulative exposure risk.

Sidebar 1 – Physicochemical properties of Lead

Pb's per-particle abundance in the Solar System is 0.121 ppb (parts per billion), which is 2.5 times higher than that of Platinum (Pt), 8 times more than Mercury (Hg), and 17 times more than Gold (Gd). The Pb amount in the Universe is slowly increasing as most heavier atoms (all of which are unstable) gradually decay to Pb. The Pb abundance in the Solar System since its formation 4.5 billion years ago has increased by about 0.75%. It is a heavy and denser metal than most common materials. It is soft, malleable, and has a relatively low melting point. It has the highest atomic number (82) of any stable element, and three of its isotopes (Pb-204, Pb-206, and Pb-208) are endpoints of major nuclear decay chains of heavier elements. It was mostly created because of repetitive neutron capture processes occurring in stars.

Pb is a neurotoxin that accumulates in soft tissues and bones. It damages the nervous system, interferes with biological enzymes, and can cause neurological disorders ranging from behavioral problems to brain damage. It also affects cardiovascular and renal systems.

Physical properties

Pure Pb has a bright, shiny gray appearance with a faint blue tint. It tarnishes when exposed to moist air, developing a dull surface the color of which depends on environmental conditions. Pb is characterized by high density, malleability, ductility, and resistance to corrosion. It is soft and can be scratched with a fingernail. Its melting point 327.5 °C (621.5 °F) is relatively low compared to most metals. Its boiling point 1,749 °C (3,180 °F) is the lowest among the carbon-group elements. Its electrical resistivity at 20 °C is 192 nano-ohmmeters, almost an order of magnitude higher than that of good conductors. It a superconductor below 7.19 K, which is the highest critical temperature among type-1 superconductors and the third highest among the elemental superconductors.

Natural Pb consists of four stable isotopes with mass numbers 204, 206, 207, and 208, along with traces of six short-lived radioisotopes with mass numbers 209–214. Pb-207 exhibits nuclear magnetic resonance, a property used to study its compounds in biological systems such as the human body.

Chemical properties

When exposed to moist air, bulk Pb develops a protective surface layer of variable composition, which renders bulk lead effectively inert under atmospheric conditions. The metal resists attack by sulfuric and phosphoric acids but not by hydrochloric or nitric acids.

Pb exhibits two principal oxidation states: +4 and +2 although some Pb compounds exist in other formal oxidation states. It can form multiple bonded chains (called organoleads I, II, III, and IV) although it predominantly forms organolead IV compounds.

As of 2014, Pb production has increased worldwide due to its use in lead–acid batteries. Other applications of Pb compounds are very specialized and often fading.

Biological effects and toxicity

Pb has no confirmed biological role, and there is no confirmed safe level of Pb exposure. A 2009 Canadian–American study concluded that even at levels that are considered to pose little to no risk, Pb may cause "adverse mental health outcomes". Its prevalence in the human body—at an adult average of 120 mg—is nevertheless exceeded only by Zinc (2500 mg) and Iron (4000 mg) among the heavy metals. Pb salts are very efficiently absorbed by the body. A small amount of Pb (1%) is stored in bones; the rest is excreted in urine and feces within a few weeks of exposure. Only about a third of Pb is excreted by a child. Continual exposure may result in bioaccumulation.

Pb is a highly poisonous metal (whether inhaled or swallowed), affecting almost every organ and system in the human body. At airborne levels of 100 mg/m3, it is immediately dangerous to life and health. Most ingested Pb is absorbed into the bloodstream. The primary cause of its toxicity is its predilection for interfering with the proper functioning of enzymes.

Pb can cause severe damage to the brain and kidneys and, ultimately, death. By mimicking Ca, Pb can cross the blood-brain Barrier (BBB). It degrades the myelin sheaths of neurons, reduces their numbers, interferes with neurotransmission routes, and decreases neuronal growth.

Symptoms of Pb poisoning include nephropathy, colic-like abdominal pains, and possibly weakness in the fingers, wrists, or ankles. Small blood pressure increases, particularly in middle-aged and older people, may be apparent and can cause anemia. Several studies, mostly cross-sectional, found an association between increased Pb exposure and decreased heart rate variability. In pregnant women, high levels of Pb exposure may cause miscarriage. Chronic, high-level exposure has been shown to reduce fertility in males.

In a child's developing brain, Pb interferes with synapse formation in the cerebral cortex, neurochemical development (including that of neurotransmitters), and the organization of ion channels. Early childhood exposure has been linked with an increased risk of sleep disturbances and excessive daytime drowsiness in later childhood. High blood levels are associated with delayed puberty in girls.

Exposure sources

Pb exposure is a global issue since Pb mining and smelting, and battery manufacturing, disposal, and recycling, are common in many countries. Pb enters the body via inhalation, ingestion, or skin absorption. Almost all inhaled Pb is absorbed into the body; for ingestion, the rate is 20–70%, with children absorbing a higher percentage than adults.

Poisoning typically results from ingestion of food or water contaminated with Pb, and less commonly after accidental ingestion of contaminated soil, dust, or lead-based paint. Seawater products can contain Pb if affected by nearby industrial waters. Fruit and vegetables can be contaminated by high levels of Pb in the soils they were grown in. Soil can be contaminated through particulate accumulation from Pb in pipes, lead paint, and residual emissions from leaded gasoline.

Treatment

Treatment for Pb poisoning normally involves the administration of Dimercaprol and Succimer. Acute cases may require the use of Disodium calcium edetate.

Disease burden

The global disease burden caused by Pb is enormous, with various estimates attributing millions of annual deaths to Pb exposure. The Global Burden of Disease Study (GBDS) attributed 850,000 deaths in 2019 to hypertension caused by Pb exposure, and a 2023 study in *Lancet Planetary Health* estimated that nearly 5.5 million annual deaths from cardiovascular disease

(CVD) were caused by Pb. A 2022 study in the *Journal of the American College of Cardiology* estimated that Pb exposure caused 1.57 million deaths worldwide in 2021, through "hypertension, stroke, coronary artery disease, peripheral artery disease, and other CVDs".

Pb exposure is the primary environmental cause for cognitive impairment. Even slightly elevated Pb levels around the age of 24 months are associated with intellectual and academic performance deficits at age 10 years. Half of the U.S. population is estimated to have had a blood Pb level over 5 µg/dL in early childhood.

Environmental effects

The extraction, production, use, and disposal of Pb and its products have caused significant contamination of the Earth's soils and waters. Atmospheric emissions of Pb were at their peak during the Industrial Revolution and the leaded gasoline period in the second half of the twentieth century.

Pb releases originate from natural sources, industrial production, incineration and recycling, and mobilization of previously buried lead. Elevated concentrations of Pb persist in soils and sediments in post-industrial and urban areas; industrial emissions, including those arising from coal burning, continue in many parts of the world, particularly in the developing countries.

References

1. Althobaiti NA (2925). "Heavy metals exposure and Alzheimer's disease: Underlying mechanisms and advancing therapeutic approaches". Behavioral Brain Research 476:115212.
2. Arora M, Austin C, Sarrafpour B, Hernandez-Avila M, Hu H, Wright RO, and Tellez-Rojo MM (2014). "Determining prenatal, early childhood and cumulative long-term lead exposure using micro-spatial deciduous dentine levels". PLoS One 9:e97805.
3. Bakulski KM, Rozek LS, Dolinoy DC, Paulson HL, and Hu H (2012). "Alzheimer's disease and environmental exposure to lead: The epidemiologic evidence and potential role of epigenetics". Curr Alzheimer Res 9:563–73.
4. Bandeen-Roche K, Glass TA, Bolla KI, Todd AC, and Schwartz BS (2009). "Cumulative lead dose and cognitive function in older adults", Epidemiology 20:831-9.
5. Basha MR, Wei W, Bakheet SA, Benitez N, Siddiqi HK, Ge YW, et al. (2005). "The fetal basis of amyloidogenesis: exposure to lead and latent overexpression of amyloid precursor protein and beta-amyloid in the aging brain", J. Neurosci. 25:823-9.
6. Bihaqi SW, Huang H, Wu J, and Zawia NH (2011). "Infant exposure to lead (Pb) and epigenetic modifications in the aging primate brain: Implications for Alzheimer's disease." J Alzheimer's Dis 27:819–33.
7. Bihaqi SW, Bahmani A, Subaiea GM, Zawia NH (2014). "Infantile exposure to lead and late-age cognitive decline: relevance to AD", Alzheimer's & Dementia 10:187-95.
8. Borst K, Dumas AA, and Prinz M (2021). "Microglia: immune and non-immune functions". Immunity 54:2194-208.
9. Brown GC and Vilalta A (2015). "How microglia kill neurons", Brain Res. 1628:288-97.
10. Cai Y, Liu J, Wang B, Sun M, and Yang H (2022). "Microglia in the neuroinflammatory pathogenesis of Alzheimer's disease and related therapeutic targets", Front.Immunol.,13:856376.
11. Cheng H, Yang B, Ke T, Li S, Yang X, Aschner M, and Chen P (2021). "Mechanisms of metal -induced mitochondrial dysfunction in neurological disorders". Toxics 9(6):142. doi: 10.3390/toxics9060142.

12. Chettle D (2005). “Three decades of in vivo x-ray fluorescence of lead in bone”. X-ray Spectrom 34:446–50.
13. Choi YH, Hu H, Mukherjee B, Miller J, and Park SK (2012). “Environmental cadmium and lead exposures and hearing loss in U.S. adults: The National Health and Nutrition Examination Survey, 1999 to 2004”. Environ Health Perspect 120:1544–50.
14. Schaumberg DA, Mendes F, Balaram M, Dana MR, Sparrow D, and Hu H (2004).“Accumulated lead exposure and risk of age-related cataract in men’. JAMA 292:2750–4.
15. Cuomo D, Foster MJ, and Threadgill D (2023). “Systemic review of genetic and epigenetic factors underlying differential toxicity to environmental lead (Pb) exposure”. 29:35583-98.
16. Devóz PP, Gomes WR, De Araújo ML, Ribeiro DL, Pedron T, Greggi Antunes LM, et al. (2017). “Lead (Pb) exposure induces disturbances in epigenetic status in workers exposed to this metal”, J. Toxicol. Environ. Health, Part A, 80:1098-105.
17. Dissanayake V and Erickson TB (2012). “Ball and chain: The global burden of lead poisoning”. Clin Toxicol (Phila) 50:528–31.
18. Ericson B, Landrigan P, Taylor MP, Frostad J, Caravanos J, Keith J, and Fuller R (2016). “The global burden of lead toxicity attributable to informal used lead-acid battery sites”. Ann Glob Health 82:686–99.
19. Farooqui Z, Bakulski KM, Power MC, Weisskopf MG, Sparrow D, Spiro A 3rd, Vokonas PS, Nie LH, Hu H, and Park SK (2017). “Associations of cumulative Pb exposure and longitudinal changes in Mini-Mental Status Exam scores, global cognition and domains of cognition: The VA Normative Aging Study”. Environ Res 152:102–8.
20. Fathabadi B, Dehghanifiroozabadi M J, Aaseth G, Sharifzadeh S. Nakhaee, Rajabpour-Sanati, et al. (2018). “Comparison of blood lead levels in patients with Alzheimer's disease and healthy people”, 33:541-7.
21. Fymat AL (2026a). “Neurotoxic heavy metals in the human brain - 1. The Aluminum - Alzheimer connection”, Journal of Neurology & Psychology Research 6(4):1-25.
22. Fymat AL (2026b). “Neurotoxic heavy metals in the human brain - 2. The Cadmium - Alzheimer connection”, Journal of Neurology & Psychology Research 6(4):1-24.
23. Garza R, Vega E and Soto (2006). “Cellular mechanisms of lead neurotoxicity”, Med. Sci. Monit. 12:57-65.
24. Gu H, Territo PR, Persohn SA, Bedwell AA, Eldridge K, Speedy R, et al. (2020). “Evaluation of chronic lead effects in the blood-brain barrier system by DCE-CT”. J. Trace Elem. Med. Biol. 62:126648.
25. Hauptman M et al. (2017). “An update on childhood lead poisoning”, Clin. Pediatr. Emerg. Med.
26. Himani KR, Ansari JA, Mahdi AA, Sharma, Karunanand, DB et al. (2020). “Blood lead levels in occupationally exposed workers involved in battery factories of Delhi-NCR region: Effect on vitamin D and calcium metabolism”, Indian J. Clin. Biochem. 35:80-7.
27. Hu H, Rabinowitz M, and Smith D (1998). “Bone lead as a biological marker in epidemiologic studies of chronic toxicity: Conceptual paradigms”. Environ Health Perspect 106:1–8.
28. Huang D, Chen L, Ji Q, Xiang Y, Zhou Q, Chen X, Chen K, Zhang X, Zou F, Zhang X, Zhao Z, Wang T, Zheng G, and Meng X (2024). “Lead aggravates Alzheimer's disease pathology via mitochondrial copper accumulation regulated by COX17”. Redox Biology 69:102990.

https://doi.org/10.1016/j.redox.2023.102990.

29. Jacobs DE, Clickner RP, Zhou JY, Viet SM, Marker DA, Rogers JW, Zeldin DC, Broene P, and Friedman W (2002). “The prevalence of lead-based paint hazards in U.S. housing”. Environ Health Perspect 110:A599–606.
30. Jarvis P, Quy K, Macadam J, Edwards M, and Smith M (2019). “Intake of lead (Pb) from tap water of homes with leaded and low lead plumbing systems”. Sci. Total Environ. 644:1346-56.
31. Kabir MT, M.S. Uddin MS, Zaman S, Begum Y, Ashraf GM, Bin-Jumah MN, et al. (2021). “Molecular mechanisms of metal toxicity in the pathogenesis of Alzheimer's disease”. Mol. Neurobiol. 58:1-20.
32. Karri V et al. (2016). “Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction: A general review of metal mixture mechanism in brain”, Environ. Toxicol. Pharm.
33. Kumawat KL, Kaushik DK, Goswami, and Basu (2014). “Acute exposure to lead acetate activates microglia and induces subsequent bystander neuronal death via caspase-3 activation”. Neurotoxicology 41: 143-53
34. Leng F and Edison P (2021). “Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here?” 17:157-72.
35. Lin MT and Beal MF (2006). “Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases.” Nature 443:787–95.
36. Maloney B, and Lahiri DK (2016). “Epigenetics of dementia: Understanding the disease as a transformation rather than a state”, Lancet Neurol. 15:760-74.
37. Meyer PA, Brown MJ, and Falk H (2008). “Global approach to reducing lead exposure and poisoning”. Mutat Res 659:166–75.
38. Needleman HL, Schell A, Bellinger D, Leviton A, and Allred EN (1990). “The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report”. N Engl J Med 322: 83–8.
39. Onalaja AO and Claudio L (2000). “Genetic susceptibility to lead poisoning”. Environ Health Perspect 108 Suppl 1:23–8.
40. Papanikolaou NC, Hatzidaki EG, Belivanis S, Tzanakakis GN, and Tsatsakis AM (2005). “Lead toxicity update: A brief review”. Med Sci Monit 11:RA329–36.
41. Payton M, Riggs KM, Spiro III A, Weiss ST, and Hu H (1998). “Relations of bone and blood lead to cognitive function: The VA Normative Aging Study”. Neurotoxicol Teratol 20:19–27.
42. Raymond J and Brown MJ (2017). “Childhood blood lead levels in children aged <5 years — United States, 2009–2014”. MMWR Surveill Summ 66:1–10.
43. Sanders T, Liu Y, Buchner V, and Tchounwou PB (2009). “Neurotoxic effects and biomarkers of Lead exposure: A review”. Rev. Environ. Health 24:1.
44. Shetty SS et al. (2023). “Environmental pollutants and their effects on human health”, Heliyon.
45. Shih RA, Glass TA, Bandeen-Roche K, Carlson MC, Bolla KI, Todd AC, and Schwartz BS (2006). “Environmental lead exposure and cognitive function in community-dwelling older adults”. Neurology 67:1556–62.
46. Shih RA, Hu H, Weisskopf MG, and Schwartz BS (2007). “Cumulative lead dose and cognitive function in adults: A review of studies that measured both blood lead and bone lead”. Environ Health Perspect 115:483–92.
47. Srivastava AK, Gupta BN, Mathur N, Murty RC, Garg N, and Chandra SV (1991). “An investigation of metal concentrations in blood of industrial workers”. Vet Hum Toxicol 33:280–2.

48. Tiwari, Atluri SV, Kaushik A, Yndart A, and Nair M (2019). “Alzheimer's disease: pathogenesis, diagnostics, and therapeutics”, Int. J. Nanomed. 14:5541-54.
49. Tong S, von Schirnding YE, and Prapamontol T (2000). “Environmental lead exposure: A public health problem of global dimensions”. Bull. World Health Organ. 78:1068–77.
50. Wang L, Yin YL, Liu XZ, Shen P, Zheng YG, Lan XR, et al. (2020). “Current understanding of metal ions in the pathogenesis of Alzheimer's disease”, Transl. Neurodegener. 9:10.
51. Wang W, Moroi S, Bakulski K, Mukherjee B, Weisskopf MG, Schaumberg D, Sparrow D, Vokonas PS, Hu H, and Park SK (2018). ”Bone lead levels and risk of incident primary open-angle glaucoma: The VA Normative Aging Study”. Environ Health Perspect. 126:087002.
52. Wang X, Bakulski KM, Walker E, Mukherjee B, Dodge H, Albin RL, Paulson HL, and Park SK (2026). “Exposure to lead and incidence of Alzheimer's disease and all-cause dementia in the United States”, Alzheimer’s & Dementia 22:2. e71075. https://doi.org/10.1002/alz.71075.
53. Weisskopf MG, Wright RO, Schwartz J, Spiro III A, Sparrow D, Aro A, and Hu H (2004). “Cumulative lead exposure and prospective change in cognition among elderly men: The VA Normative Aging Study. Am J Epidemiol 160:1184–93.
54. World Health Organization (2010). “Exposure to lead: A major public health concern”. World Health Organization, Preventing Disease Through Healthy Environments.
55. Wright RO, Tsaih SW, Schwartz J, Spiro A 3rd, McDonald K, Weiss ST, and Hu H (2003). “Lead exposure biomarkers and Mini-Mental Status Exam scores in older men”. Epidemiology 14:713–8.
56. Xu L, Zhang W, Liu X, Zhang C, Wang P, and Zhao X (2018). “Circulatory levels of toxic metals (aluminum, cadmium, mercury, lead) in patients with Alzheimer’s disease: A quantitative meta-analysis and systematic review”. J Alzheimer’s Dis 62:361–72.
57. Zhao Y and Zhao B (2013). “Oxidative stress and the pathogenesis of Alzheimer’s disease”. Oxid Med Cell Longev 2013:316523.