



## Bioaccumulation of lead (Pb) and its effects on human: A review

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### ABSTRACT

Lead is a prevalent heavy metal that pollutes the environment and accumulates in the human body via absorption, bioavailability, bioconcentration, and biomagnification disrupts the neurological, skeletal, reproductive, hematopoietic, renal, and cardiovascular systems. Lead's distinctive physical and chemical characteristics make it ideal for a variety of uses. It has been linked to human activities for ages and is harmful to health. This review article examines the long-term health consequences of lead exposure in humans. Acute and chronic symptoms of lead poisoning include kidney, brain, reproductive organ, and CNS/PNS damage. Toxic metals have a long half-life in the bone matrix and brain (2–3 years), causing neurological problems and bone loss. The article also shows the problems of high BPb in both men and women during pregnancy. Renal system blood lead levels of 30–60 g/dL may cause kidney failure in severe circumstances. The oxidative stress that occurs in human cells has also been explored. Finally, lead poisoning and lead buildup prevention and therapy have been reviewed. The use of micronutrients and antioxidants has demonstrated a reduction in harmful effects. Adults with BPb >45 g/dL should have chelation, whereas children should receive succimer.

### 1. Introduction

The term heavy metal (HM) refers to a group of metals or metal-loids having toxic effects even at lower concentrations (part per billion level) and possess higher density (Sharma and Agrawal, 2005) and have poisonous nature at lower concentrations. HMs include essential metals (Cu, Zn, Co, Cr, Mn, and Fe), non-essential metals (Ba, Al, Li and Zr), less toxic metals (Sn and As), and highly toxic metals (Hg, Cd, and Pb) (Duffus, 2002). HMs enter into the food chain and relates to the accumulation in biological tissues. When the rate of intake of these HMs by biological systems exceeds the rate of excretion, then we call that bioaccumulation of HMs and this occurs in biological systems (Singh and Kalamdhad, 2011; Khan et al., 2015).

The incidence of heavy metals (HM) in the human body causes toxicity resulting in Alzheimer's, multiple sclerosis, Parkinson's disease, muscular dystrophy (Neeti & Prakash; K. 2013). HM poisoning can ei-

ther cause chronic effects like neurological disorders, physical abnormalities, muscular effects, genetic and hereditary problems, or acute effects like vomiting, dehydration, drowsiness, nausea, renal failure, and abdominal pain (Markich et al., 2001; Sun et al., 2018). The excess usage of HMs to satisfy human needs has heavily polluted the environment. Accumulation in living beings occurs when these metals are taken up and stored at a higher rate which thereafter is metabolized and excreted (Nędzarek et al., 2013). Lead toxicity in human's dates back to at least 5000 years ago when humans started to process lead (Gidlow, 2015).

Lead (Pb) is a naturally occurring metal and generally form lead compounds by combining with two or more elements. Lead reacts with air and water to form lead sulfate, lead carbonates or lead oxide. These compounds act as a protective barrier to prevent corrosion. Lead can also interact with both acid as well as base. It has a low melting point and located above hydrogen in the electromotive series. Although the

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existence of lead is indicated in nature but human activities has been found as the main reason for increasing lead content in the environment (Shahid et al., 2015). Lead is released in air from mining of lead, factories utilizing lead compounds, alloys, vehicle exhaust and burning of fossil fuels (Violante et al., 2010). The lead is removed from atmosphere by rain and transferred to soil or comes in contact with surface water. Moreover, lead is used as pesticide during vegetable and fruit cultivation (Gall et al., 2015). Disposal of lead containing waste products, removal of lead based paints from bridges, buildings and damaged battery from industries further results into the accumulation of lead in municipal landfills. Lead combines very strongly with the soil particles and present in the top layer of soil (Gupta et al., 2008). Lead enters water bodies or lakes when these soil particles are washed away by rain water. Thus, lead is transferred to animals and plants from air, water, soil and this cycle continues (Abadin et al., 2007).

Lead is not a foreign material to the human body as it is distributed to the brain, liver, kidney, and bones and is stored in bones and teeth. However, this is only 10  $\mu\text{g}/\text{dL}$  in adults and 1.4  $\mu\text{g}/\text{dL}$  in children (Jusko et al., 2008; Singh and Kalamdhad, 2011). The guideline value of lead indicated by world health organization is 0.01  $\text{mg}/\text{L}$  (Edition, 2011). The Nervous system is mainly affected by lead. The normal functioning of nervous system is influenced if an individual is exposed to lead for a long time. Moreover, longer exposure also causes severe effects on kidney as well as brain (Abadin et al., 2007). Lead is easily absorbed by the body. Children absorb higher amounts of lead than adults which is highly dangerous as they are developing (Lidsky and Schneider, 2003). In children lead is not absorbed by the bones like in the case of adults therefore they are at a higher risk of poisoning as the other soft tissues absorb the excess lead. Lead acts as a calcium analog, thus it is easily absorbed in people with calcium, zinc, and iron deficiencies. Lead affects the reproductive systems of both males and females (Flora et al., 2006). In the case of males, there is a reduction in sperm count and volume, the motility and the morphology of the sperm are also affected (Wu et al., 2012). In females who have high exposure to this metal, miscarriage, premature birth, low birth weight, and developmental problems are seen. When toxicity of lead has reached higher amounts, spontaneous abortion of the fetus occurs (D. C., 2005). Lead can damage cell structure, cell membrane and most importantly it interferes with DNA transcription (Yedjou et al., 2010). At developmental stages, lead passes through the placenta into the body of the fetus. At developmental stages, lead passes through the placenta into the body of the fetus (Mason et al., 2014).

When Pb exposed to atmosphere they form sulphates, oxides and carbonates (Sharma and Agrawal, 2005). Lead concentrations on the earth surface are product of a variety of natural and anthropogenic sources. Natural pathways include Geological process controlling Pb composition of silicates contributes to the natural Pb concentration and it is reported that Pb occurs < 50  $\text{mg}/\text{kg}$  in earth's crust and (Duffus, 2002). Pb mimics  $\text{Ca}^{2+}$  by binding to the same receptors in cell activities and its uptake by plants exhibits serious effects on humans when consumed, Ronnie Levin et al. reported that the natural pathway for lead accumulation in humans and plants also depends on the seasonality (Edition, 2011). The Pb concentration where found to be lower in spring and higher concentrations were observed when soil pH and salinity decreases. Temperature, humidity, bioavailability, Mobility, Environmental acidification, solar radiation also contributes to the increased Pb concentration. (Khan et al., 2015).

The anthropogenic influence on the environment has resulted in Pb impacting soils, waters, and the atmosphere. Since these medias are used for food, drinking water, and air, any contaminants can enter the biosphere and can potentially affect human health (Ismail et al., 2005). It is found that anthropogenic pathways contribute more in most cases of human Pb exposure, Common anthropogenic contributions are Gasoline, car batteries, sewage sludge, fertilizers and other anthropogenic exposure of Pb includes Mining, Pb bearing sulfide deposits, Pb additives in petrol, Pb water pipes, Pb added in paints (Singh and Kalamdhad, 2011).

Pb in drinking water is the major pathway of accumulation into human body which arises mainly due to the use of lead piping, still Pb piping are used in some places and records almost 29  $\text{mg}/\text{L}$  through such piping (K. Neeti and Prakash, 2013). Other sources of increased Pb concentration in water are Landfills, electroplating, Au-Ag-Pb-Zn mining etc. (Z. Sun et al., 2018, Zeng et al., 2007). Geochemical and anthropogenic Pb cycles showed changes in Pb's functions and forms for human needs, Jian-su MAO et al. traced these changes and it is found that Lead ore and scrap are two influencing anthropogenic sources of Pb. The major changes in forms of lead are the conversion of PbS Ore in to metal Pb,  $\text{PbO}_2$ , and  $\text{PbSO}_4$  (MAO et al., 2014). It should be noted that Small Pb particles potentially show trans boundary movement supported by evidences, whereas large particles tend to deposit and this anthropogenic pathway leads to the accumulation of Pb in human lungs resulting in serious health effects (Markich, 2001).

Both natural and Anthropogenic pathways of Pb can be traced effectively by Isotopic (Pb) fingerprinting technique, here isotopic ratios ( $^{208}\text{Pb}$ ,  $^{207}\text{Pb}$ , and  $^{206}\text{Pb}$ ) are analyzed by TIMS, ICP-QMS, and ICP-SFMS techniques. This proves to be a better alternative to traditional statistical analysis of large databases (Ali et al., 2019). Anthropogenic sources of Pb were analyzed by GIS-based data, and the metal distributions were analyzed by principal component analysis (PCA) and cluster analysis (CA). With supported data Harley T. Davis et al. experimentally determined that increased Pb Concentration in both urban and rural are due to anthropogenic sources (Balkhair and Ashraf, 2016). This review addresses various morphological, physiological, and biochemical effects of Lead toxicity in humans and also strategies adopted by humans for Pb detoxification and developing tolerance to Pb.

## 2. Lead intake by humans

Pb is an environmental pollutant. Despite the low amounts absorbed, prolonged exposure to Pb can accumulate in the human body system, resulting in lead poisoning or toxicity. Lead has a half-life of around 30 days in the blood, after which it diffuses into soft tissues such as the kidneys, brain, and liver and then distributed to bones, teeth and hair as lead phosphate (Engwa et al., 2019). ROS (Reactive oxygen species) such as hydroperoxide, hydrogen peroxide, and singlet oxygen are produced as a result of lead poisoning. Pb generates these free radicals which leads to oxidative stress causing cellular damage to the body cells. The body suffers oxidative stress when there is an imbalance of ROS and antioxidant defences. Oxidative stress causes cell and tissue destruction, which increases the likelihood of adverse health outcomes like cardiovascular disease and cancer (Flora, 2011). The Fig. 1 shows the effect of Pb accumulation in the human body. Increased oxidative stress causes lipid peroxidation, which damages cell membranes resulting in cell damage. Lead inhibits the activity of 5-aminolevulinic acid dehydratase, resulting in hemoglobin oxidation and lipid peroxidation, which can cause red cell hemolysis (Pourrut et al., 2011). Fig. 2 displays that when there is increase in concentration of Pb, the equilibrium between the ROS and antioxidants is altered. The rise in ROS production causes depletion of antioxidant defense causing oxidative stress which eventually leads to cell damage. Lead also interferes with the activity of other antioxidant enzymes including superoxide dismutase and catalase (Violante et al., 2010). Glutathione in the body helps to maintain ROS in balance. Ninety percent of glutathione in the cell is reduced, while ten percent is oxidized, and it serves as an antioxidant defense mechanism. Glutathione stabilizes ROS and is reduced back to GSH by glutathione reductase after being oxidized to glutathione disulfide (Sardar et al., 2013). By attaching to the sulfhydryl group of glutathione, Pb inactivates it, making GSH replenishment ineffective and increasing oxidative stress (Batool et al., 2017). The deposition of a small amount of Pb in the human body causes cellular malfunction and has a negative impact on an individual's health

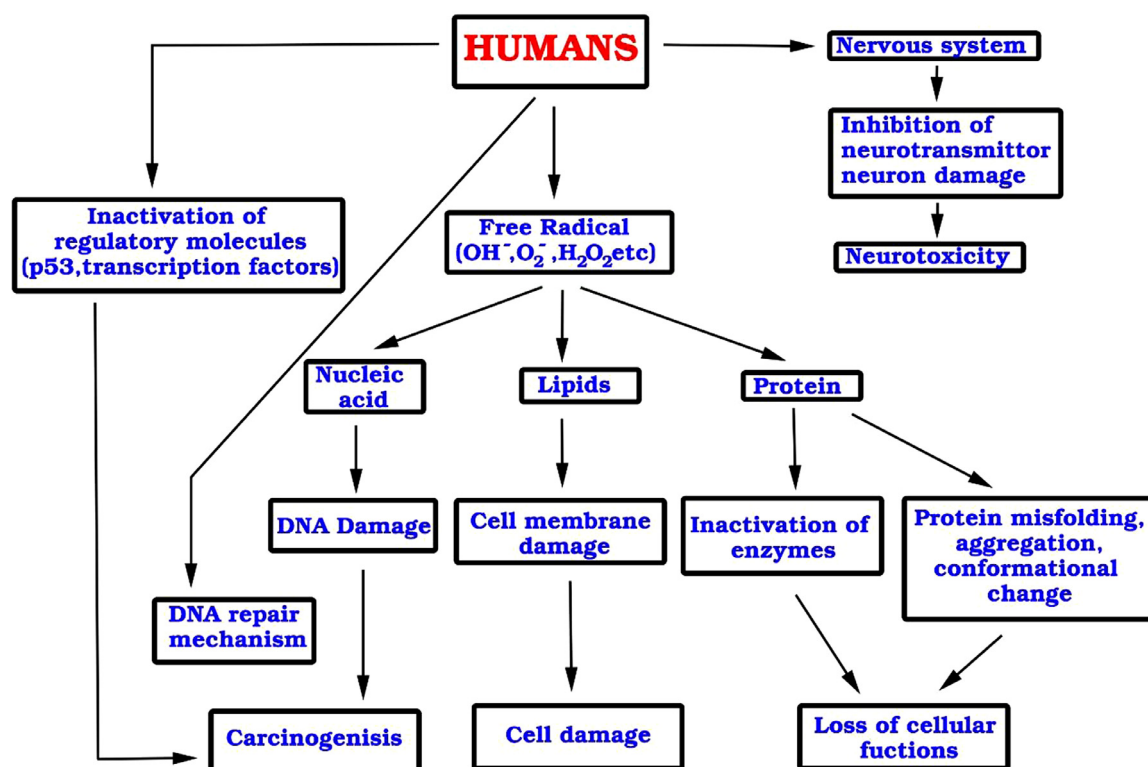


Fig. 1. Effects of heavy metal accumulation in human body.

### 3. Physiological and biochemical effects of lead accumulation in human beings

Lead (Pb) is one of the ancient heavy metals used by human beings. From time immemorial, Pb has huge applications in the manufacturing of instruments and tools due to its splendid physical and chemical properties. Lead is used in the manufacture of boats, bearings, buildings, paints, lead batteries, automobiles, gasoline, pipes, ceramics, plastics, and in smelting, mining processes, and the arms industry. Studies have revealed that both adults and children are affected by lead toxicity. In the case of children, both internal and external tissues are soft, hence making them more susceptible (Ara and Usmani, 2015). Its malleability, ductility, corrosion resistance, low melting point, and abundant availability are the reasons lead is used till today, even though its accumulation is hazardous (Wani & Usmani, 2015). Being non-biodegradable in nature, the removal of lead from the environment is inevitable. Lead toxicity and lead accumulation in humans is one of the major health concerns. While occupational causes like dermal contact and inhalation contribute to the indirect intake of lead in humans, consumption of Pb contaminated food and water are direct sources of accumulation. Acute Pb toxicity leads to dysfunction of the kidney, reproductive system, and brain while chronic damages are caused to the CNS and PNS.

Lead also inhibits the synthesis of hemoglobin. Pregnant women with low calcium, iron or zinc levels are prone to the effects of lead accumulation (Kwong et al., 2004). Lead is a poisonous metal and disturbs the functions of almost every organ in the human body as depicted in Fig. 3. Common symptoms observed are behavioral changes, lowered IQ, slow learning in children, diarrhea, anemia, skin allergies, kidney malfunctioning and many more (Cerazy and Cottingham, 2010). Also the Pb interacts with mechanisms and functions of the male reproductive system and affects the sperm count (B. Quintanilla-Vega et al., 2000). Even low levels of Pb in the kidney cause chronic renal malfunctioning (Barbier et al., 2005). It is found that Pb interferes with the activities of several enzymes, delta-aminolevulinic acid dehydratase (ALAD), ferroxidase catalase, superoxide dismutase (SOD) and many more (On-

alaja, A. O., & Claudio, L., A.O. 2000). Lead-induced oxidative stress increases radical production damaging the cell membranes, cell functions and DNA (Hsu and Guo, 2002; Ahamed and Siddiqui, 2007).

#### 3.1. Effect of lead on the nervous system

Lead toxicity affects the nervous system drastically when compared to the other organ systems in the human body. Symptoms worsen and give rise to paralysis, coma, or even death (Gilani et al., 2015). Lead is considered to be a neurotoxin. The half-life of Pb in the brain is 2 to 3 years whereas in the blood it is 30 days. Encephalopathy is a condition where there is a progressive deterioration in the parts of the human brain, major manifestations of encephalopathy including headache, dullness, poor attention span, memory loss, and hallucinations within a few weeks of exposure (Karri et al., 2008; Arora et al., 2015).

Children are more likely to get affected by Pb toxicity in their developing stages than adults (Needleman, 2004). Pb toxicity in children is mostly asymptomatic, while children below 5 years show some symptoms like lethargy, abdominal cramps, vomiting, irritability, and loss of appetite. Epidemiological studies reveal that children with Blood Lead Level BPb (BPb - 'Biomarker' is a term used to measure the interactions between the biological system and an external environmental agent) less than 10 µg/dL are affected severely (Garza et al., 2006; Sander et al., 2009). Astrocytes, a type of glial cells in the brain, along with neurons and the extracellular matrix contain the physical Blood-Brain Barrier (BBB). As Pb<sup>2+</sup> ions easily substitute Ca<sup>2+</sup> ions, it crosses the BBB swiftly and accumulates in the brain cells (Florea et al., 2013). Joint F. A. O et al. performed experiments on the children's IQ. As Pb<sup>2+</sup> ions easily substitute Ca<sup>2+</sup> ions, it crosses the Blood-Brain-Barrier (BBB) swiftly and accumulates in the brain cells. Pb<sup>2+</sup> replaces Ca<sup>2+</sup> in Protein Kinase C (PKC) Enzyme assay, a calcium-dependent process, changes the behavior of endothelial brain cells and disrupts the functions of BBB (Joint F. A. O., & WHO Expert Committee on Food Additives, F.A.O. 2002). On testing the intelligence, it was found that IQ dropped by 3 points when BPb level increased from 10 µg/dL to 20 µg/dL and WHO con-



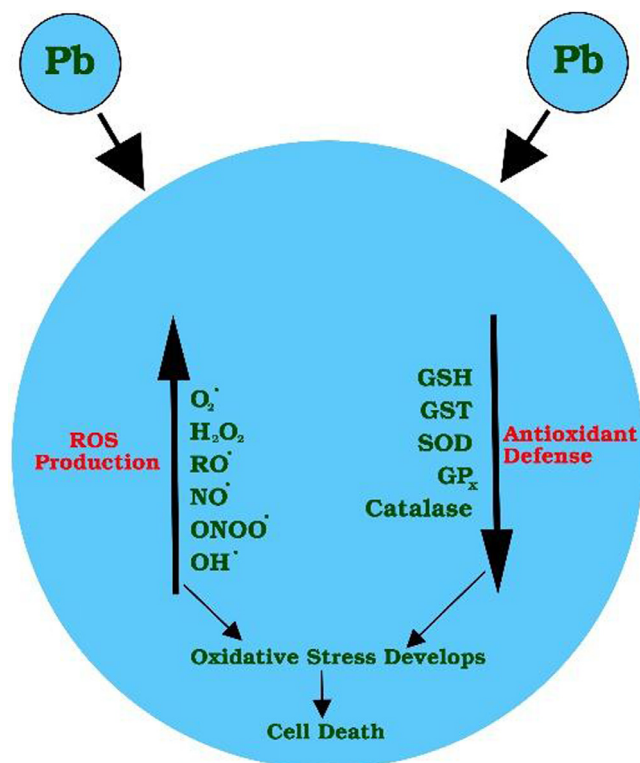


Fig. 2. The mechanism underlying the development of oxidative stress in a cell on lead exposure.

cluded that for every 10  $\mu\text{g}/\text{dL}$  increase in BPb levels, IQ decreases by 1–5 points (Bellinger et al., 2005, Reuben et al., 2017). Lanphear et al. examined 4853 children of NHANES(III) (National Health and Nutrition Examination Survey – it is a program that is designed to assess the health and nutrition of adults and children in the US) and conducted

psychometric tests for them (Lanphear et al., 2000). He disclosed that the mean BPb level was 1.8–1.9  $\mu\text{g}/\text{dL}$  and also found that children had neural development, linguistic and processing problems, decrement in the memory power, and difficulty in comprehension of visuospatial skills (Rogan et al., 2001). Stokes et al. in their research studies stated that occupational exposure is a major source of Pb accumulation in adults and affects the PNS.

Silbergeld et al. proposed that there can be two types of neurotoxicity:

- (1) Neurodevelopmental Pb that disturbs the functions of CNS.
- (2) Neuropharmacological Pb intrudes and alters the ionic mechanisms of the neurotransmitters.

Observations state that high BPb concentrations  $>4 \mu\text{M}$  result in acute Encephalopathy, Apoptosis, dysfunction of the Blood-Brain Barrier (BBB), and severe conditions leading to hemorrhage and schizophrenia (Ishaq et al., 2021). Tetraethyl lead (TEL) is a powerful neurotoxin and an additive in motor fuel and 25 workers died in 1925 due to long-time exposure to Pb.  $\text{Pb}^{2+}$  also can replace  $\text{Ca}^{2+}$  ions, thus increasing the  $\text{Pb}^{2+}$  concentration in the cells. Even nanomolar concentrations of  $\text{Pb}^{2+}$  disturb the mitochondrial functions and kill brain cells via apoptosis (Yang et al., 2014). This state is initiated when the mitochondria dysfunctions. Mitochondrial dysfunction is caused by the increase in intercellular  $\text{Ca}^{2+}$  ions or by the accumulation of  $\text{Pb}^{2+}$  ions.  $\text{Pb}^{2+}$  ions disrupt  $\text{Ca}^{2+}$  homeostasis leading to higher  $\text{Ca}^{2+}$  ions in cells.

### 3.2. Effect of lead on the skeletal system-Bone

Lead exposure from both occupational and environmental sources causes an increase in levels of lead in the bone matrix throughout childhood and most of adulthood. The major  $\text{Pb}^{2+}$  concentration is detected in the bone tissues of human beings which can be seen in Fig. 4. In a case study, it has been reported that a woman with acute lead toxicity was diagnosed with abdominal and knee pain, neurological symptoms, hypertension, chronic kidney disease, and anemia with basophilic stippling. It was observed that, compared to her previous pregnancy, lead levels in her body tripled in her subsequent one. This increase in blood

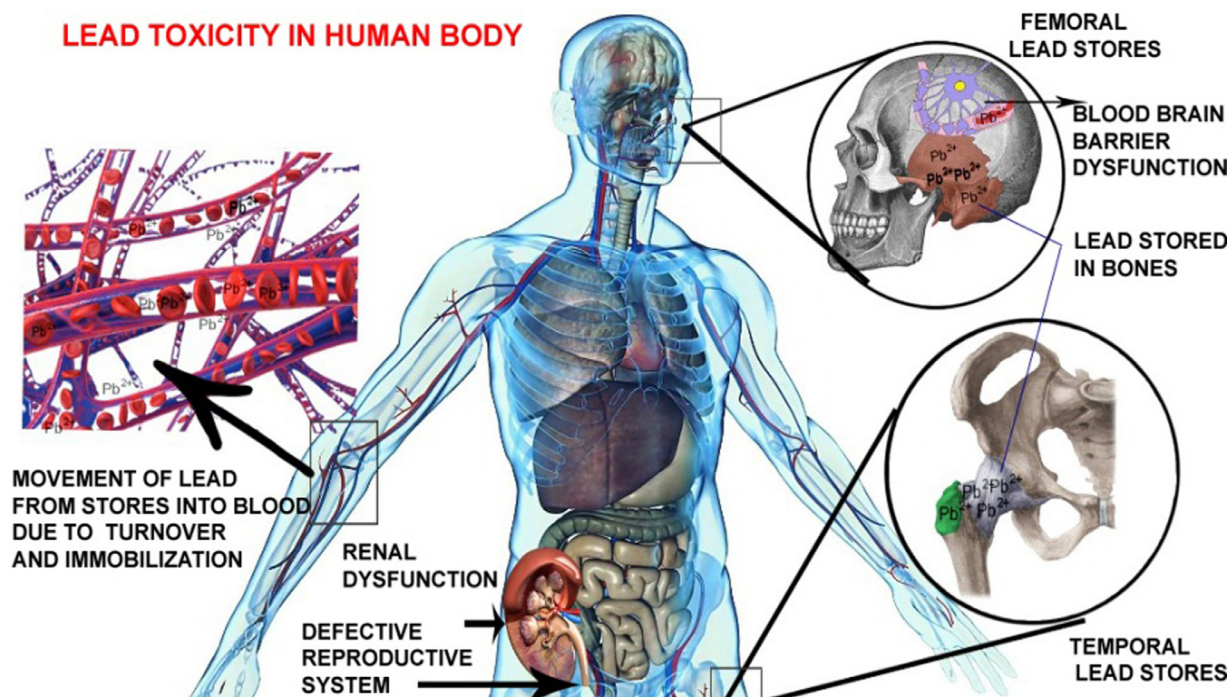


Fig. 3. Diagrammatic representation of lead accumulation in the major organs.

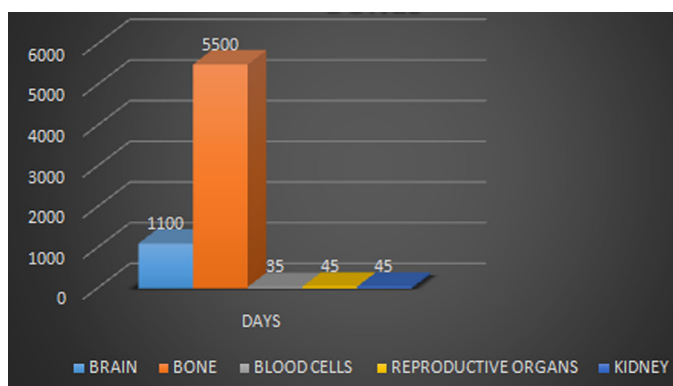


Fig. 4. The half-life of lead in bones.

lead concentration was likely due to the skeletal mobilization without any new lead exposure. This acute lead toxicity traced is due to mobilization and redistribution of lead from the bone by pathophysiological and physiological conditions. The subject had a serious failure in her neurologic, renal, orthopedic, hematologic, and gastrointestinal systems and her reproductive system (Riess & Halm, Matthias 2007). It was reported that occupational exposure to lead decreased the calcitriol formation resulting in lowered absorption of phosphorous and calcium at the renal and intestinal tracts. It was observed that the total serum calcium levels and serum ionized calcium levels decreased by 14–21% in all the study groups and similarly the serum phosphorous levels were also decreased by 14–19%. It was also reported that this increased lead exposure showed a slight elevation in systolic (7–13%) and diastolic (5–17%) pressure (Dongre et al., NN 2013; Rodríguez & Mandalunis, J. 2018). It is reported that lead affects osteoblasts, osteoclasts, and chondrocytes, and increases the risk of osteoporosis. Women undergoing menopause are at a higher risk of experiencing osteoporosis. Moreover, Pb exposed individuals suffer a serious fracture and recover at a very slow rate in comparison with non-exposed individuals (Carmouche et al., 2005).

### 3.3. Effect of lead on the reproductive system

The reproductive system of both males and females are affected by increased BPb levels. Studies reveal that pregnant women tend to have greater complications due lead accumulations (Vigeh et al., M. 2010). Men with BPb levels greater than 25 µg/dL experience reduced sperm mobility, fertility, sperm count, and abnormal sperm morphology. On the other hand, women with 10 µg/dL BPb level face complications like preterm birth, low birth weight, infertility, miscarriage, neural defects in early childhood, and maternal hypertension (van Straaten, J. 2000). BPb level in the range 10–15 µg/dL in women of childbearing age directly affects the developing fetus. Generally, women who give birth after 30–35 years are more vulnerable to having Pb in their breast milk (Bellinger, D.C. 2005; Shannon, M. 2003). Assent et al. studied the sperm count of lead workers. His studies reported Teratospermia (genetic damage to sperm), Hypospermia (low sperm count), and chromosomal aberrations (Telişman et al., 2007). Protamine (HP2) is a Zn protein that protects the sperm DNA. Pb tends to replace this Zn and causes sperm DNA damage (Quintanilla-Vega et al., 2000). It has also been observed that the fetus has 19% more BPb level than the mother at the time of birth (Cleveland et al., 2008). At 12 weeks of the gestation period, the lead easily crosses the placenta (Hatzidaki et al., 2005). A fetus accumulates about 30 g of calcium into the fetal skeleton during the gestation period. During the bone resorption, a bone lead that has been accumulated for years is transferred to the fetal circulations through the placenta. (Téllez-Rojó, M.M. 2004)

### 3.4. Effect of lead on the hematopoietic system

Lead directly affects the hematological system at very low BPb levels-10 µg/dL. It restrains the synthesis of hemoglobin by the inhibition of important enzymes involved in heme synthesis and reduces the life span of erythrocytes by the destabilization and increasing fragility of its cell membrane. This directly results in anemia and high blood Pb levels lead to Frank's anemia (iron deficiency anemia) (Ameen et al., 2009). Acute lead exposure leads to hemolytic anemia, where the red blood cells are destroyed as fast as they are made (Guidotti et al., 2008). A key enzyme for the synthesis of heme is  $\delta$ -aminolevulinic acid dehydratase (ALAD).  $\delta$ -ALAD, a cytoplasmic enzyme rich in SH groups, is the enzyme that catalyzes the formation of porphobilinogen from  $\delta$ -aminolevulinic acid (ALA). Nikkanen et al. in their studies demonstrated that  $\delta$ -ALAD is inhibited when the BPb levels are as low as 5 µg/dL and leads to behavioral changes and childhood lead encephalopathy. The inhibition of  $\delta$ -ALAD results in the accumulation of  $\delta$ -ALA in the plasma and excess of  $\delta$ -ALA leads to severe neurological effects (Dehari-Zeka et al., 2020).  $\delta$ -ALA in urine is also used as an indicator for lead exposure among industrial workers. Ferrochelatase is another mitochondrial enzyme that catalyzes the incorporation of iron (Fe<sup>2+</sup>) into the porphyrin ring. Lead toxicity inhibits this enzyme and in case of low availability Fe<sup>2+</sup>, Zn<sup>2+</sup> is substituted and also interferes with the trans-mitochondrial transport of iron (Jangid et al., 2012). More than 90% of Pb in the blood is bound to the RBC keeping plasma lead concentrations constant at 2–3 µg/dL even when BPb concentration is 10–150 µg/dL (Mrugesh et al., 2011; Patrick, 2006). These lead to decrease in hemoglobin in human beings, followed by anemia, weight loss, complications during pregnancy, kidney malfunctioning, and cancer in severe cases are some direct effects.

### 3.5. Effect of lead on the renal system

The mechanism of lead nephrotoxicity, renal cancer-role of the lead binding protein, adverse effect of low level environmental and chronic lead exposure in neurotoxicity, renal toxicity, renal cancer, renal dysfunction, and other complications were reported (Assi et al., 2016). Jia, et al. reported the mechanism of lead nephrotoxicity and formation of inclusion bodies such as lead-protein complex due to accumulation of lead in proximal renal tubular lining cells with cause proximal tubular dysfunction (Jia et al., Q. 2012). The effect of lead in nephrotoxicity was reported to be occurring in three stages, primarily reversible or acute nephropathy, next stage is chronic nephropathy and the final stage is the renal tubular cell neoplasia or adenocarcinoma (Flora et al., 2012). Clinical manifestation includes a decrease in energy-dependent transport functions, including glycosuria, aminoaciduria, and changes in specific ion transport (Niemann and Serkova, 2007). Reduced glomerular filtration rate, decreased inulin clearance, and decreased maximal reabsorption of glucose are also observed in chronic nephropathy (Wang et al., 2002). Lead can bind with proteins and creates the risk of renal cancer. Kidney-specific proteins act as receptors and facilitate interactions with DNA in renal proximal tubular cells, the altered gene results in cancer (Silbergeld et al., 2000). Lead exposure also influenced renal plasma excretion and plasma renin activity. Lead poisoning in mitochondria creates deficiency of ATP, this reduces the reabsorption of sodium, an important process of kidney and increased renal excretion of sodium is observed (Marsden, P.A. 2003). Patients with acute and chronic renal injury were observed with excretion of more than 600 µg of lead over 72 h after an EDTA-mobilization test (Fontanellas et al., A 2002). Almost 99% of blood lead bounded to zinc-dependent delta-aminolaevulinic acid dehydratase (ALAD) are stored in erythrocytes, since ALAD is inhibited this reflects in suppression of the heme synthesis (Siddarth et al., M 2018).

A study collected workers' renal biopsies and analyzed for various parameters like inclusion bodies glomeruli filtrate rate, the plasma concentration of urinary excretion of ALA, renal excretion of lead, and lead-induced nephropathy. The samples with acute exposure showed the presence of nuclear inclusion bodies in the proximal tubular lining and

greater urinary excretion of lead and the biopsy samples with chronic exposure showed peritubular fibrosis (Karimooy et al., H.N. 2010).

### 3.6. Effect of lead on the cardiovascular system

Lead also affects the cardiovascular system and has a significant impact on the human heart. Besides inducing increased blood pressure and hypertension, it has been observed that exposure to high levels of lead is also associated with increased risks of stroke, peripheral arterial disease, coronary heart disease, and cardiovascular functional abnormalities such as left ventricular hypertrophy and alterations in the cardiac rhythm (Lustberg & Silbergeld, M. 2002; Menke et al., 2006; Navas-Acien et al., A. 2004; Schober et al., 2006). Another study demonstrated the positive association between blood lead levels and total peripheral resistance, reduced cardiac output, and reduced stroke volume in response to acute stress in children (9 to 11 years) when the blood lead level was below 10 µg/dL (Gump et al., 2011). At the blood lead level >5 µg/dL, the percentage of adults above the threshold of systolic blood pressure elevates as the age group increases. A report on steel factory workers in Poland revealed a significantly higher left ventricle mass and lower ejection fraction when the results were compared to the administrative workers of the same factory (Kasperczyk et al., 2005). The workers who were in contact with higher concentrations of lead had developed weakened diastolic functions when compared with the workers who were not exposed to lead (Beck & Steinmetz, B. 2005). Lead can also escalate the release of pro-inflammatory cytokines by stimulating the endothelial and peripheral mononuclear cells in humans (Nawrot et al., 2002). Inflammatory cytokines cause an increase in endothelial inflammation along with cardiovascular damage (Cao et al., 2015). Lead has the potential to play a role in arterial stiffness and the mechanism of involvement of metals in cardiovascular pathology has been studied. Pre-school children who are exposed to e-waste show a positive response to future cardiovascular diseases, as the elevated blood lead level is associated with the heightened vascular endothelial inflammation (Zheng et al., 2019). Thus the effect of lead on the cardiovascular systems is first noticed when there is an increase in blood pressure. However, this becomes apparent when the blood lead level crosses the threshold level of 5 µg/dL (Navas-Acien et al., 2007).

### 3.7. Effect of lead on the saliva, hair, nail, and tooth

#### 3.7.1. Lead in saliva

Some reports indicate the presence of lead in the salivary glands which can be seen in the saliva at high concentrations (Thaweboon et al., 2005). In a study conducted by Thaweboon et al. on a population residing in a highly lead-contaminated area, he noticed that the salivary lead levels were higher in the affected population than in the reference population. However, the lead levels in the saliva were much lower than the ones present in the blood. This may be because the lead levels in the saliva are proportional to the diffusible lead present in the blood rather than the lead present in the whole of the blood.

#### 3.7.2. Lead in hair

Correlation between blood lead levels and hair has been previously reported in occupationally exposed workers (Ahmad et al., 2018). Concentrations of lead in hair cannot be used to monitor the environmental exposure of lead, this makes hair an ineffective biological indicator (Mehra et al., 2011)

#### 3.7.3. Lead in nail

Nail is also a point of excretion of lead. The concentration of lead found in the nail is higher than that found in the hair in occupationally exposed workers and the concentration of lead in nails depends on the age of the subject (Mehra and Juneja, 2004; Nowak & Chmielnicka, B. 2000). However, it does not depend on the sex of the subject (Roudshkin & Axelsson, I. 2000).

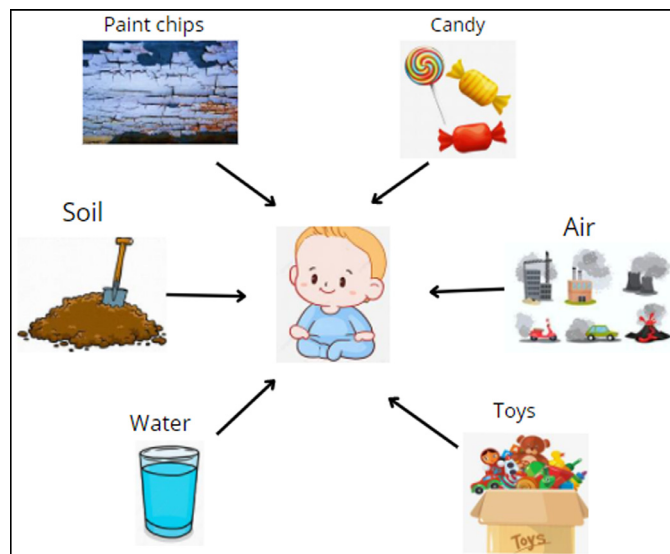


Fig. 5. The most common sources of Lead exposure in children can be found in their homes.

#### 3.7.4. Lead in tooth

Teeth tend to accumulate lead over a long period. The accumulation of lead in children in their teeth occurs even before the tooth eruption (Asaduzzaman et al., 2017). The lead concentration in the carious teeth is 33% higher than the non-carious teeth. Hence the carious molar is an efficient pathway for the contamination of lead. Also, it has been recorded that the carious and molar teeth of boys are a better contamination path for lead. This shows an increased tooth lead concentration in boys than in girls (Arruda-Neto et al., 2009).

## 4. Prevention and treatment of lead accumulation in human beings

The most successful and vital treatment is chelation therapy. It is a clinical intervention where chelating agents are administered, which in turn binds  $Pb^{2+}$  and removes it from the tissues via urine in case of acute exposure (Hao et al., 2013). Calcium disodium ethylene diamine tetraacetic acid ( $CaNa_2EDTA$ ) is one of the best chelators. Succimer (2,3 meso-dimercaptosuccinic acid or DMSA), an oral chelating agent, is preferred for mild and asymptomatic cases (Cao et al., 2015). They form stable water-soluble complexes and reduce lead levels in blood, brain, and kidney immediately. They are dosed at 350 mg/m<sup>2</sup> and given thrice a day for five days (Batoool et al., 2017). Then it is reduced to twice per day for 14 days. DMSA being an antioxidant significantly depletes Pb-induced oxidative stress and apoptosis (Obeng-Gyasi, 2019). The most common sources of lead exposure in children and adults illustrated by Taina Litwak have been depicted in Fig. 5 that can be highly avoided. The best treatment available to quickly reduce the blood lead level is chelation therapy (Kumar et al., 2017). Since  $Pb^{2+}$  is toxic and finds no application in the human body, it has to be completely eliminated. This is possible only by replacing the existing  $Pb^{2+}$  ions by  $Ca^{2+}$  ions which are useful. This is because  $Pb^{2+}$  ions replace  $Ca^{2+}$  ions in important sites and causes severe damages that have been discussed above. Only chelation therapy fits this condition. Brought into clinical use in 1950 as antidote for lead toxicity, much research has been done since the early chelating agent that is, EDTA. Chelation therapy is sought out as it can drastically clean out the blood lead levels and  $Pb^{2+}$  ions can be easily removed from the body by urine. (Aaseth et al., 2015). Never the less, since the chelating agents cause side effects, their usage is limited to severe cases of over exposure of heavy metals (Kushwaha et al., 2018).



## 5. Conclusion

Lead poisoning affects most organs in both children and adults. So knowing the therapy is really important. Preventing exposure to lead is the primary therapy. Keeping in mind that once lead enters the body, it cannot be totally removed, dietary supplements and medical therapies may help lower the quantity of Pb stored in various organs and help eliminate Pb from organ tissues. Also, lead buildup in bones does not directly cause difficulties, but the immobile bone deposits cause major pregnancy issues. They produce renal tubular cell destruction, nephropathy, and renal inefficiency. Low BPb (5 g/dL) causes hypertension and vascular endothelial inflammation. The effects of lead in nails, hair, teeth, and saliva are unknown since they are much lower than in blood. Lead disrupts ionic processes and causes oxidative stress, causing enzyme and protein malfunction. While micronutrients like Ca, Zn, and Fe cannot entirely eliminate lead from the body, they may lower its level. Natural antioxidants, vitamins (flavonoids) scavenge ROS. Early detection of lead poisoning and continuous monitoring of BPb levels may prevent significant consequences. Preventing direct exposure and keeping sufficient diet prevents Pb<sup>2+</sup> buildup in tissues.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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