HUMAN BIOLOGY AND PUBLIC HEALTH JOURNAL OF THE AUXOLOGICAL SOCIETY

ISSN 2748-9957 | Vol. 3 2022 | pp. 1–11

The toxic effect of lead on human health – A review

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Citation:

Mandal, G./Mandal (Nandi), A./Chakraborty, A. (2022). The toxic effect of lead on human health, Human Biology and Public Health 3. https://doi.org/10.52905/hbph2022.3.45.

Received: 2022-07-31
Accepted: 2022-10-10
Published: 2023-03-10

Conflicts of interest:

There are no conflicts of interest.

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Keywords:

lead, lead-induced toxicity, blood lead levels, neurotoxicity, reactive oxygen species

Abstract

Increasing amounts of anthropogenic contaminants have heavily polluted the atmosphere. This is one of the global environmental problems. Deposition of atmospheric contaminants on the earth's surface brings potential risks to human health. This review aims to identify risks posed by lead in the atmosphere and its impact on human health. Lead is one of the most dangerous toxic metals found in the earth's crust. The lead-induced toxicity through oxidative stress mechanisms includes the effect of lead on membranes, DNA, and antioxidant defense systems of the cells. It affects various target sites including lungs, blood vessels, brain, testes, and liver. Acute exposure to high doses of lead is not the only source of lead-based neurotoxicity. Acute low-dose exposure also produces measurable effects on the nervous system. The most severe neurological effect of lead exposure is lead encephalopathy, a response to very high doses of lead that results in the development of irritability, headache, attention deficits, memory loss, mental dullness, and hallucinations. Lead exposure has effects on neuropsychological functioning that vary across the lifespan. Lead causes a number of adverse effects also on the reproductive system in both men and women, such as decreased libido, chromosomal damage, and impairment of spermatogenesis. Lead can cross the placenta and impairs the development of the fetus due to its interference with the calcium metabolism. Lead-exposed women are at risk of various complications during pregnancy, including spontaneous abortion. This article reviews the nature, cause, and importance of environmental exposure to lead and emphasizes requirements for future policy responses and interventions.

Take-home message for students Lead is one of the most dangerous toxic metals. It is neurotoxic and also affects many other tissues including lungs, liver, blood vessels, and the reproductive system. Lead-exposed women are at risk of various complications during pregnancy, including spontaneous abortion.

Introduction

Lead (Pb) is one of the most dangerous toxic metals found in the earth's crust. Due to its special physio-chemic properties, it is non-biodegradable in nature and, hence, its accumulation increases in the global environment (Mahaffey, 1990). Pb can enter the human body by direct contact or through air, water, and soil. Lead toxicity in humans occurs through lead-related occupations like leaded gasoline, mining, lead smelting, boat building, lead acid battery recycling, lead-based painting, book printing, etc. The adverse effects of lead exposure on human health have been recognized (Flora et al., 2012; Vaziri and Sica, 2004). Lead poisoning in children experiencing non-occupational exposure has been a matter of serious concern for a long time (Kosnett, 2007). Though its use has been fully stopped by the government in many countries, it is still used today in many industries like car repair, smelting, battery manufacturing, recycling, etc. However, the working environment in the lead industry, especially in developed countries, has been much improved (Flora et al., 2012; Nevin, 2007; Rossi, 2008).

The lead-induced toxicity through oxidative stress mechanisms includes the effect of lead on membranes, DNA, and antioxidant defense systems of the cells. Its effects on various target sites including lungs, blood vessels, brain, testes, and liver depend on the dose of lead exposure (Hsu and Guo, 2002). The production of Reactive Oxygen Species (ROS) is considered a plausible mechanism for the adverse effects of lead. Accumulation of lead in the cells severely affects the mitochondria and alters their normal function by inducing oxidative stress. This is one of the main reasons for the reduction of cellular antidefense mechanisms (Ahamed and Siddiqui, 2007; Lockitch, 1993).

Lead poisoning affects almost every organ of the body. Of all the organ systems, the nervous system is the most vulnerable to lead poisoning. The impact of higher concentrations of lead on children is greater than that on adults. This is why lead toxicity in childhood is of prime importance in the developing countries with often high lead levels in the environment.

Infants and young children are very sensitive even to low levels of lead exposure which may result in lowered IQ, learning deficiencies, and behavioral problems. Long-term exposure of adults can result in decreased cognitive performance which is used to measure the functions of the nervous systems (Strayer and Rubin, 2008). The central nervous system cannot adequately perform when the Blood Lead Levels (BLLs) rise above a certain value. This leads to encephalopathy and edema that mainly affect the cerebellum. Excessive exposure to lead can disturb other body functions like the cardiovascular, the hematological, and the reproductive systems (Pal et al., 2015; Rao et al., 2014).

This review aims to identify the risk posed by lead in the atmosphere and its impact on human health. It reviews the literature on different aspects of lead toxicity including some recent updates. It shows the vulnerable section of the human population who are more at risk, with special regard to the effects of lead toxicity on children, their growth and development, and on human reproductive health as well as on the aged section of the human population who are at risk for dementia and related illnesses.

Lead toxicity

Lead toxicity is termed as "Plumbism" or "Saturnism". It is known to cause acute, chronic, and sub-clinical toxicity.

Acute toxicity: Acute lead poisoning is uncommon. It results from inhalation of large quantities of lead due to occupational exposure among industrial workers and in children through ingestion of large oral doses, e.g. from the lead-based paint industry. The clinical symptoms of acute lead poisoning are: metallic taste, abdominal pain, vomiting, diarrhea, oliguria, and anemia (Ahamed and Siddiqui, 2007).

Chronic toxicity: Chronic lead poisoning is very common and can be described in three stages of progression: I) The early stage is characterized by loss of appetite, weight loss, fatigue, weakness, vomiting, constipation, lead lines of gums, and anemia; II) The second stage is marked by intermittent vomiting, irritability, nervousness, tremors, and sensory disturbance in the extremities; III) The severe stage of toxicity is characterized by persistent vomiting, encephalopathy, lethargy, convulsions, and coma (Nelson et al., 2019).

Sub-clinical toxicity: Chronically low levels of lead exposure particularly through the environment do often not result in the overt manifestation of toxic symptoms but lead to chronic, slow, progressive, and usually irreversible intoxication of the hematopoietic, the nervous, the renal, the gastrointestinal, and the reproductive system (Flora et al., 2012).

Effects of lead poisoning

Severe effects of lead toxicity have been reported throughout human history. Lead poisoning leads to drastic reductions in fertility and reproduction, and can cause anemia, dementia, impairments of the respiratory system, diabetes, and other illnesses. Lead poisoning increases mortality rates. Occasional lead poisoning was found to be caused by lead salts used in pottery glazes leached by acidic fruit juices. Since the beginning of the 20th century, numerous studies have suggested that the fall of the Roman Empire was partially due to chronic exposure to lead (Büsselberg et al., 1993; Cohen et al., 1981; Kazantzis, 1989). It was argued (Cilliers and Retief, 2014) that the production of lead had reached its peak in ancient Rome. Lead acetate was used as a sweetener of wine. Its prolonged use was considered to have caused dementia to many Roman emperors and may have also affected the Roman leadership. It was found that toxic effects on blood cells of rats caused by lead nitrate were alleviated by sodium selenite (Baş et al., 2015). The authors also showed that effects of lead nitrate were more harmful in diabetic than in non-diabetic rats. Oxidative stress was studied by low-level lead exposure in first grade Uruguayan children, suggesting potentially adverse effects on oxidative stress (Roy et al., 2015). An impaired respiratory function was observed in workers exposed to lead with elevated blood lead and zinc protoporphyrin concentration (Jurdziak et al., 2015).

Effects on the hematopoietic system

Lead has a high probability to bind to red blood cells. It directly disturbs the hematological system through limiting the synthesis of hemoglobin by hindering different key compounds involved in the heme synthesis. It increases the fragility of cell membranes as a result of which the life span of circulating erythrocytes decreases (Cornelis et al., 2005; Guidotti et al., 2008). Lead exposure alters the enzymatic activity of three key enzymes which are involved in the heme synthesis pathway

in dose-dependent manners. δ-aminolevulinic acid dehydratase (ALAD) has a catalytic effect to form porphobilinogen from δ-aminolevulinic acid (ALA) and a mitochondrial enzyme aminolevulinic acid synthetase (ALAS) that catalyzes the formation of aminolevulinic acid (ALA); finally ferrochelatase, a mitochondrial enzyme which acts as a catalyzer to insert iron into protoporphyrin. Lead toxicity impairs the hemoglobin synthesis pathway through mutant expression of genes encoding δ-aminolevulinic acid dehydratase, δ-aminolevulinic acid, and ferrochelatase (Piomelli, 2002).

Exposure to lead has a more profound effect on ALAD production. Its inhibition occurs due to the accumulation of aminolevulinic acid which is detectable in plasma at BLLs of 10μg/dl. The inhibitory effects of lead first occur at BLLs of 10–20μg/dl, but heme synthesis is not hampered until the activity of ALAD is inhibited by 80–90%. This occurs when the BLLs reach 55μg/dl. The inhibition of ALAD has been clinically used to understand the degree of lead poisoning (Ahamed and Siddiqui, 2007). Increased excretion of coproporphyrin in the urine and protoporphyrin accumulation in erythrocytes occurs when the ferrochelatase is inhibited. Iron is then substituted by zinc in the porphyrin ring and forms zinc protoporphyrin (ZPP) which increases in the human body. Thus, heme production gets interrupted via the heme synthesis pathway due to the collective inhibition of these key enzymes.

Effects of lead on the nervous system

Neurotoxicity describes neuro-physiological changes caused by an exposure to toxic agents which may result in cognitive changes, memory disorders, and changes in mood or psychological disturbance. Neurotoxicity from heavy metals including lead, arsenic, and mercury is most commonly studied in two groups: acute exposure and chronic exposure. Acute exposure often involves nausea, headache, and cognitive changes. In chronic exposure, neuro-degeneration and psychiatric manifestations are more prevalent. Psychiatric manifestations may include anxiety and depression. Chronic exposure may also result in prolonged fatigue and decreased cognitive functions (Caban-Holt et al., 2005; Han et al., 2011; Mason et al., 2014).

Compared to other organ systems, the nervous system appears to be the most sensitive and the chief target for lead-induced toxicity. Both the central nervous system and the peripheral nervous system become affected by lead exposure. The effects on the peripheral nervous system are more pronounced in adults, while the central nervous system is more prominently affected in children (Bellinger, 2008; Brent, 2006).

Acute high-dose exposure to lead is not the only source of lead-based neurotoxicity. Acute low-dose exposure may also produce measurable effects on the nervous system. The most severe neurological effect of lead exposure is lead encephalopathy, a response to very high doses of lead that results in the development of irritability, headache, attention deficit, memory loss, mental dullness, and hallucinations (Kumar et al., 1987).

The brain is the most sensitive organ to lead exposure (Cleveland et al., 2008). In a child's developing brain, synapse formation in the cerebral cortex is greatly affected. Lead also interferes with the development of neurotransmitters and the organization of ion channels (Liu et al., 2007). Lead poisoning causes loss of neuron myelin sheath

and reduction in the number of neurons. It interferes with neurotransmission and decreases neuronal growth. The brain of adults exposed to increased lead levels during childhood shows a decreased volume, especially in the prefrontal cortex on MRI (Cleveland et al., 2008). Lead is able to pass through the endothelial cells of the blood–brain barrier and interferes with synapse formation, because it can substitute for calcium ions and be taken up by calcium-ATPase pumps. There is apparently no lower threshold to the dose–response relationship below which lead exposure is treated as safe (Meyer et al., 2003). BLLs lower than 5μg/dl were found to be associated with reduced academic performance (Bellinger, 2008; Needleman et al., 1990). Increased BLLs are also associated with a decrease in cognitive performance and psychiatric conditions like depression and anxiety (Jacobs et al., 2002). An increase in BLLs from 50 to some 100μg/dl was found to be associated with more severe conditions like permanent impairment of central nervous system functions (Bellinger, 2004). High lead levels in the air seem to cause aggressive and violent behavior, for example the highest murder rates were found in countries with high levels of lead in the air (Needleman, 2004). One study hypothesized that lead exposure explains 65% to 90% of the variation in violent crime rates in the US (Kosnett, 2007). Another study showed a strong association between preschool BLLs and subsequent crime rate trends over several decades in nine countries (Nevin, 2007).

The hippocampus is a part of the brain involved in learning and memory. The main reasons for lead interfering with learning particularly in children is that it damages the cells within the hippocampus. In rats exposed to lead, structural damages, such as irregular nuclei and denaturation of myelin, were reported (Mycyk et al., 2005). Lead interferes with the release of neurotransmitters (Needleman, 2004), thereby disrupting intercellular communication. The main target of lead toxicity appears to be an inhibition of the N-methyl-D-aspartate (NMDA) receptor, thus interfering with glutamatergic neurotransmission, which is important for learning and memory. Lead was found to be involved in the apoptosis of brain cells in animal studies (Needleman, 2004).

Neuropsychological effects of lead toxicity on children

Lead exposure has effects on neuropsychological functioning that vary across the lifespan. Fetuses and young children are especially vulnerable to the neurological effects of lead as the developing nervous system absorbs a higher fraction of lead. The proportion of systematically circulating lead gaining access to the brain of children is significantly higher than compared to adults (Needleman, 2004). At lower doses, children may develop lead encephalopathy (U.S. EPA, 1986). Children with greater lead levels may be affected by delayed growth, decreased intelligence, hearing impairment, and short-term memory loss (Cleveland et al., 2008).

Evidence suggests that lower levels of lead exposure significantly affect the IQ as well as behavior, concentration ability, and attentiveness of the child. Repercussions of lead exposure on the peripheral nervous system have also been observed, followed by peripheral neuropathy and reduced motor activity due to loss of myelin sheath. This insulates the nerves and seriously impairs the transduction of nerve impulses, with muscular weakness, fatigue of entension muscles , and lack of muscular coordination (Sanders et al., 2009).

Children with blood lead concentrations greater than 10μg/dl are at high risk for developmental disabilities (Brunton and Parker, 2007). The effect of lead on children's cognitive abilities takes place at very low levels (Park et al., 2008; Sanders et al., 2009; Xu et al., 2009). However, it is yet to determine the lower margin of the threshold value of lead (Meyer et al., 2003). BLLs lower than 5μg/dl were found to be associated with reduced academic performance (Bellinger, 2004; Needleman et al., 1990). BLLs below 10μg/dl were reported to be associated with lower IQ levels and behavior problems such as aggression (Guidotti et al., 2008). Between BLLs of 5 and 35μg/dl, an IQ decrease of 2 to 4 points for each μg/dl increase was reported in children (Brunton and Parker, 2007). Increased BLLs are also associated with a decrease in cognitive performance and psychiatric conditions like depression and anxiety (Jacobs et al., 2002). Increased lead exposure in children is associated with an increase in neuropsychiatric disorders like antisocial behavior (Sanders et al., 2009). Prenatal and early childhood exposure correlates with violent crimes in adulthood (Nevin, 2007).

Effects of lead on the growth and development of children

Relatively low BLLs show adverse effects on human health,especially on childhood growth and development (Bellinger, 2004). Infants with BLLs greater than or equal to 15 mg/dl have a higher risk of a low birth weight. Maternal BLLs showed an inverse association with weight gain in infants. Exclusively breastfed infants showed decreased weight with increased maternal BLL (Sanín et al., 2001). The most common symptoms of lead toxicity in children are anorexia, lethargy, vomiting, and abdominal pain. Even passive smoking in children brings about a greater exposure to lead (Kaji et al., 1997). Children should always be protected from the risk of lead pollution as this has adverse effect on their intellectual and physical growth.

Effects on the reproductive system

Lead causes a number of adverse effects on the reproductive system in both men and women. Exposure to lead has been associated with several reproductive dysfunctions in men, such as decreased libido, chromosomal damage, and impairment of spermatogenesis (Zhang et al., 2021). Hosni and others reported that lead exposure reduces sperm count and affects sperm morphology (Hosni et al., 2013).

Lead impairs the majority of the endocrine glands. Serum testosterone levels decreased and steroid-binding globulin levels increased in lead smelting workers (Erfurth et al., 2001; Gulson et al., 2003; Rodamilans et al., 1988; Tuppurainen et al., 1988). Concentrations of FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone) were higher among lead battery workers when compared with controls, indicating testicular damage and altered testicular functions (Doumouchtsis et al., 2009; Nigg et al., 2016; Rodamilans et al., 1988; Tuppurainen et al., 1988). BLLs appeared higher in patients who were suffering from prostate cancer (Siddiqui et al., 2002).

Lead exposure can alter the reproductive hormonal axis and hormonal control of spermatogenesis instead of directlyaffecting the seminiferous tubules of the testes (Ng et al., 1991). Yet, the blood–testis barrier acts as a protector for testis cells against

the detrimental effect of lead (El-Zohairy et al., 1996; Xu et al., 1993).

Occupational exposure to lead is more common in males than females. Females are usually not directly exposed to lead but rather contaminated through clothes, shoes, and working instruments that are taken home by their cohabitants who work in places where lead is used. Lead exposure may also occur when using cosmetics (Al-Saleh et al., 2009; Kaličanin and Velimirović, 2016). Women are at greatest risk of suffering lead related health problems at their reproductive age.

Lead absorbed by inhalation enters the blood stream, accumulates in the bones, and is considered to represent approximately 95% of the total body burden (Barry and Mossman, 1970; Rădulescu and Lundgren, 2019). Calcium demands increase during pregnancy. Lead stored in the bone replaces calcium due to similar chemical characteristics and analogous metabolic pathways. Lead then recirculates in the blood and becomes an endogenous source of exposure (Gulson et al., 2016, 2003; Potula and Kaye, 2005; Rădulescu and Lundgren, 2019). Lead crosses the placenta and impairs the development of the fetus by interference with calcium metabolism (Gundacker and Hengstschläger, 2012; Wang et al., 2009; Zhang et al., 2015; Zhu et al., 2010). Lead-exposed women are at risk for various pregnancy complications including spontaneous abortion (Hertz-Picciotto, 2000), pregnancyhypertension (Vigeh et al., 2004), intrauterine growthrestrictions (Srivastava et al., 2001), lowbirthweight (Zhang et al., 2015; Zhu et al., 2010), premature rupture of membranes (Huang et al., 2018; Vigeh et al., 2010), and preterm delivery (Taylor et al., 2015).

Cardiovascular effects

Lead affects peripheral vascular resistance, cardiac output, and heart rate (Vaziri and Sica, 2004). Both chronic and acute types of lead exposure may lead to cardiovascular dysfunction and damages with potentially lethal consequences including hypertension (Flora et al., 2012). Even low BLLs can contribute to hypertension (Kim et al., 2015).

Diagnostic symptoms of lead toxicity

Symptons in children include delayed development, weight loss, lack of appetite, irritability, abdominal pain, vomiting, hearing loss, fatigue and so on. Where as among the adults symptoms include high blood pressure, joint and muscle pain, lack of concentration, headache, abdominal pain, reduced sperm count and abnormal sperm among men, miscarriage, stillbirth or premature birth among pregnant women.

Proper and early diagnosis, medical history, and determination of clinical symptoms are very important to prevent lead poisoning (Nevin, 2007). With the help of clinical diagnosis, involvement of proper staff, toxicologists, and medical specialists, diagnosis and treatment of lead toxicity can be better controlled and reduced. Non-invasive X-ray by fluorescence may reveal the total body burden of lead (Grant, 2020).

Prevention of lead toxicity

Lead toxicity is preventable and the best way to do so is by avoiding exposure to lead (Rossi, 2008). Simple practices like frequent washing of hands, eating only after proper cleaning of hands, and drinking water after purification can prevent lead

toxicity. Avoiding the use of leaded household objects like curtain blinds, jewelry, and house pipes can help prevent exposure to lead. Children should always be protected from lead poisoning. Anti-oxidants can also help to prevent lead toxicity (Flora et al., 2012).

Conclusion

Lead appears to be the most prominent and harmful of all heavy metal poisons. Since ancient times, lead has been used and its toxic effects have been well documented all over the world. Children and adults when exposed to lead related sites are at high risk of health impairment. Lead is toxic for the digestive, the nervous, the respiratory, the skeletal, and the reproductive system. Lead hampers the activities of various enzymes and disrupts DNA transcription. Lead has no physiological role and even small amounts are toxic. Lead toxicity can be reversed and reduced by a number of techniques and procedures, but preventing lead exposure remains the best. Hence, awareness and education about pollution and lead toxicity are important measures for parents so that they can educate their children about preventive measures to avoid accidental lead poisoning. Areas of lead pollution should be identified and measures should be taken to reduce the pollution. Public health measures are needed and should aim for the reduction and prevention of exposure to lead. This can be achieved by reducing or rather minimizing the use of this metal and its compounds. Various countries have already taken measures for reducing lead exposure. The major areas addressed by these measures are:

1. Populations at high risk of lead exposure are to be identified and monitored.
2. Exposure to lead in workplaces is to be identified and controlled.
3. Awareness and understanding of lead exposure have to be spread among people.
4. Emphasis is to be increased on adequate nutrition, health care, and other social conditions that may help controlling the effects of lead.
5. Lead additives in fuels have to be either removed or reduced as much as possible.
6. Lead-based paints have to be phased out.
7. Use of lead in food containers is to be eliminated.
8. Lead used in traditional medicines and cosmetics is to be identified, reduced, and eliminated.
9. Lead dissolved in water has to be treated.

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