

## REVIEW ARTICLE

# LEAD EXPOSURE AND ENVIRONMENTAL HEALTH

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### Summary

Lead (Pb), which is widely used in industry, is a common element found in low concentrations in the Earth's crust. Lead has been used since prehistoric times. As a highly toxic heavy metal, the pollution and exposure risks of lead are of widespread concern for human health. This environmental contaminant causing irreversible health effects mainly in children. Especially children under the age of six are most at risk for lead poisoning. Lead toxicity causes hematological, gastrointestinal, and neurological dysfunction. Symptoms are usually noted with blood lead greater than 2  $\mu\text{mol/litre}$ . Severe or prolonged exposure may also cause chronic nephropathy, hypertension, and reproductive impairment. Lead inhibits some enzymes, alters cellular calcium metabolism, stimulates synthesis of binding proteins in kidney, brain, and bone, and slows down nerve conduction. The emission sources and pathological effects of lead are discussed.

*Key words: lead; lead toxicity; lead poisoning; environmental exposure; epidemiologic studies*

## INTRODUCTION

Lead (Pb) is the most abundant of the heavy metals in the Earth's crust. It has been used since prehistoric times, and has become widely distributed and mobilized in the environment. Continuous increase in the amount of lead in the environment is associated with the discovery of organic lead compounds. Highly toxic alkyllead compounds such as tetrame-

thyl and tetraethyl lead (Patočka, 2008) have been used for nearly 60 years as antiknock additives in gasoline (Thomas, 1995). Before the ban on the use of lead in gasoline, only in United States, the emission from the internal combustion engine totals about 200,000 tons/yr and were the largest single factor in the redistribution of Pb from natural sources to biological systems (Goyer and Rhyne, 1973). However, the amount of Pb in the environment is still high, and both occupational and environmental exposures to Pb remain a serious problem in many developing and industrializing countries, as well as in some developed countries (Zheng et al., 2013a,b; Min and Min, 2015; Monnot et al., 2015). In most developed countries, however, introduction of Pb into the human environment has decreased in recent years, largely due to public health campaigns and

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a decline in its commercial usage, particularly in petrol (Tong et al., 2000; Etchevers et al., 2015). Acute lead poisoning has become rare in such countries, but chronic exposure to low levels of the metal is still a public health issue, especially among some minorities and socioeconomically disadvantaged groups. In developing countries, awareness of the public health impact of exposure to lead is growing but relatively few of these countries have introduced policies and regulations for significantly combating the problem (Needleman, 2004). The article concerns potential harmful effects of exposure to lead. Although the occurrence of severe lead poisoning has receded in several countries, occupational exposure resulting in moderate and clinically symptomatic toxicity is still common. An earlier and precise characterization of an individual response is obligatory in order to assess the possible risks for human health. The article discusses information in the literature on natural and anthropogenic sources of Pb in environment, human exposure sources, entry paths of lead into the body and its fate, toxic effects of lead on the human organism.

## **LEAD IN ENVIRONMENT AND HUMAN EXPOSURE SOURCES**

While in historical times was Pb in the environment, mostly of natural origin, from the 60<sup>s</sup> to the 70<sup>s</sup> of the last century has become prevalent lead anthropogenic origin (Zaborska, 2014). Lead emitted from various natural and anthropogenic sources have the ability to accumulate in tissues of living organisms. The non biodegradable nature of lead is the prime reason for its prolonged persistence in the environment. Human exposure to lead occurs through various sources. The widespread occurrence of lead in the environment is primarily a result of anthropogenic activities. With the decline in combustion of leaded fuel and the phasing out of lead in pipes and paints, industrial emissions from mining, smelting or recycling are the predominant source of environmental lead (Datko-Williams et al., 2014). The phenomenon of accumulation of metal in the body is harmful and undesirable. The ability of plants to accumulate heavy metals from the individual elements of the environment has been used in biomonitoring of pollution (Szczygłowska et al., 2014). Leaves and roots of vegetables have particular predisposition for accumulating toxic metals such as lead and cadmium and therefore can be used for biomonitoring of the environment, mainly as a tool

for assessing the extent of soil contamination (Naveed et al., 2010).

### **Air**

In general, background levels of aluminum in the atmosphere in present are low, typically ranging from about 0.005 to 0.18  $\mu\text{g}/\text{m}^3$ . Much higher levels are routinely observed in urban and industrial locations. Concentrations of lead in air depend on a number of factors, including proximity to roads and point sources. Annual geometric mean concentrations measured at more than 100 stations across Canada declined steadily from 0.74  $\mu\text{g}/\text{m}^3$  in 1973 to 0.10  $\mu\text{g}/\text{m}^3$  in 1989 (EPS, 1981, 1989), reflecting the decrease in the use of lead additives in petrol. Typical quarterly averages for urban areas without significant point sources in the USA in 1987 were in the range 0.1–0.3  $\mu\text{g}/\text{m}^3$ ; in the vicinity of major point sources, such as lead smelters and battery plants, air levels typically ranged from 0.3 to 4.0  $\mu\text{g}/\text{m}^3$  (EPA, 1986). Levels at three locations in Barcelona (Spain) during the winter of 1985 ranged from 0.9 to 2.5  $\mu\text{g}/\text{m}^3$  (Tomas et al., 1989), presumably reflecting heavy use of leaded petrol. The overall means in London and in a rural area of Suffolk in 1984–85 were 0.50  $\mu\text{g}/\text{m}^3$  (range 0.23–0.82) and 0.10  $\mu\text{g}/\text{m}^3$  (range 0.05–0.17), respectively (Strehlow and Barltrop, 1987). Levels of lead in 1983 in the Norwegian Arctic, an area remote from urban influences, varied between 0.1–0.3 and 0.3–9.0  $\text{ng}/\text{m}^3$  (Pacyna AND Ottar, 1985). If an average concentration in air of 0.2  $\mu\text{g}/\text{m}^3$  is assumed, the intake of lead from air can be calculated to range from 0.5  $\mu\text{g}/\text{day}$  for an infant to 4  $\mu\text{g}/\text{day}$  for an adult (WHO, 1996).

### **Water**

Water supply systems and drinking water inaccessibility in developing countries is a global problem. About 884 million people in the world still do not get their drinking water from approved sources, and almost all of these people are in developing regions (WHO/UNCEF, 2010). Poor drinking water often contains besides bacteria also dangerous chemical substances, especially heavy metals. Heavy metals exist as natural constituents of the earth crust and are persistent environmental contaminants, because they cannot be degraded or destroyed. Whilst these elements occur naturally they are often bound up in inert compounds. However, their concentrations have increased several-fold as a result of anthropogenic activities.

With the decline in atmospheric emissions of lead since the introduction of legislative restricting use in fuels, water has assumed new importance as the largest controllable source of lead exposure (Wilker et al., 2011). Lead is present in tapwater to some extent as a result of its dissolution from natural sources but primarily from household plumbing systems in which the pipes, solder, fittings, or service connections to homes contain lead.

In 1989, a lead levels in drinking-water in the USA found the geometric mean to be 2.8 µg/litre (Levin et al., 1989). The median level of lead in drinking-water samples collected in five Canadian cities was 2.0 µg/litre (Dabeka et al., 1987). Later study in Ontario (Canada) found that the average concentration of lead in water actually consumed over a one-week sampling period was in the range 1.1–30.7 µg/litre, with a median level of 4.8 µg/litre (NHW, 1992). In Glasgow (Scotland), where the water was known to be in lead pipes, even in the 90s of last century lead concentration in about 40% of the samples exceeded 100 µg/litre (Sherlock and Quinn, 1986). The problem of the presence of lead in drinking water, however, still remains. As shown by a recent study from the Virginia, USA, the analysis of 2,146 samples submitted by private system homeowners, almost 20% of first draw samples submitted contained lead concentrations above the United States Environmental Protection Agency action level of 15 µg/litre (Pieper et al., 2015). This value is higher than the maximum permissible concentration of 5 µg/litre in drinking-water, when the total intake of lead from this source can be calculated to range from 3.8 µg/day for an infant to 10 µg/day for an adult.

## **Food**

Daily dietary lead intake, were 26 µg/day in Sweden (Slorach et al., 1991), 66 µg/day in Finland (Varo and Kovistoinen, 1980), and 23 µg/day for a 2-year-old in the USA (Gundarson, 1988). Estimates obtained from diet studies are in the same range and include a mean dietary intake for all food and drink of about 40 µg/day for mothers and 30 µg/day for children aged 5–7 years in England (Strehlow and Barltrop, 1987) and 53.8 µg/day (0.8 µg/kg of body weight per day) for the intake of lead from food for adolescents and adults in Canada (Dabeka et al., 1987). In the 90s of the last century lead intakes for adults were 90 µg/day in Belgium, 24 µg/day in Sweden, and 177 µg/day in Mexico (Anonymous, 1985). In some countries, dietary intakes as high

as 500 µg/day have been reported (Galal-Gorchev, 1991).

## **Street Dust**

Street dust is a recurring problem in many countries. The elemental composition, patterns of distribution and possible sources of street dust are not common to all urban environments, but vary according to the peculiarities of each city (de Miguel et al., 1997). The results of numerous studies have shown that street dust and soil samples from the urban and industrial area represents a source of compounds with potential health risk (Calvillo et al., 2015). Street dust contained significant levels of the heavy metals (Christoforidis and Stamatis, 2009; Lu et al., 2014; Acosta et al., 2015) and lead is present in high concentration (Zhou et al., 2015). The data for Pb seem to prove that the gradual shift from leaded to unleaded petrol as fuel for automobiles has resulted in an almost proportional reduction in the concentration of Pb in dust particles under 100 µm (Zhao et al., 2015).

## **House Dust**

House dust has been recognized as an important contributor to Pb exposure of children in many countries (Zheng et al., 2013a). Studies of this kind were carried out for example in Greece (Demetriades et al., 2010; Argyraki, 2014), Canada (MacLean et al., 2011; Rasmussen et al., 2011, 2013), Japan (Yoshinaga et al., 2014), China (Li et al., 2014; Bi et al., 2015; Lin et al., 2015), Tunis (Ghorbel et al., 2014), Pakistan (Eqani et al., 2016) and many other countries and especially in the areas of industrial production and high concentrations of dust in the air (Parajuli et al., 2015). Such country is especially China, which recently became an industrial superpower.

The concentrations of Pb in 477 house dust samples collected from twenty eight areas throughout China varied from 12 to 2510 mg/kg, with a median concentration of 42 mg/kg. The median Pb concentrations in different geographical areas ranged from 16 (Zhangjiakou, Hebei) to 195 mg/kg (Loudi, Hunan). No correlations were found between the house dust Pb concentrations and the age of houses, as well as house decoration materials. Whereas outdoor soil, coal combustion, and site specific pollution may be potential Pb sources (Bi et al. 2015). In the study of Li et al. (2014) house dust samples from 15 Chinese cities varied from 25 to 738 mg of Pb/kg.

The similar values of Pb content in house dust of 100 Japanese residences also reached Yoshinaga and coworkers (2014) when measured median concentration of 49.1 mg Pb/kg. High concentrations of Pb in house dust was measured in some industrial areas of Greece. Argyraki (2014) measured values up to 7,000 mg/kg in house dust samples. In another study (Demetriades et al., 2010), the measured values of Pb in house dust were from 418 to 18,600 mg/kg. Consequently, children in the neighbourhoods with a large amount of metallurgical processing wastes have high blood-Pb concentrations (5.98-60.49 µg/100 ml; median 17.83 µg/100 ml; n = 235).

The results of all studies show that the source of interior dust lead was primarily from soil (Laidlaw et al., 2014). There are also reveal that the risk from oral exposure is much higher than the risk from inhalation and dermal contact with house dust. (Zheng et al., 2013b).

#### **Other sources**

External occupational factors significantly increasing mean levels of BLL were tobacco, consumption of some beverages (wine, coffee, tea, and/or tap water), raw vegetables, housing characteristics (built prior to 1948, Pb piping in the home) and do-it-yourself or leisure activities (paint stripping or rifle shooting) (Tagne-Fotzso et al., 2016).

Significant source of lead in humans consumption may be various beauty products. Recent reports describing the presence of lead in lipsticks have suggested that, under ordinary use, the potential amount of Pb exposure is harmful (Hepp et al., 2009). Lead content in lipstick and other consumer products has become an increasing concern. In 2010, the United States Food and Drug Administration tested 400 lipstick samples and found a maximum Pb concentration of 7.19 ppm (Monnot et al., 2015).

### **KINETICS AND METABOLISM IN HUMANS**

**Absorption** of metal can be highly variable in human populations because it is influenced by a variety of factors that include the chemical form of the metal, environmental matrix in which the ingested metal is contained, gastrointestinal tract contents, diet, nutritional status, age, and, in some cases, genotype (Diamond et al., 1997). Most of the current population is relatively little threatened by lead,

however, chronic lead exposure and an understanding of its effects is of great significance to the population's health.

The absorption of particulate lead following inhalation involves the deposition of airborne lead particle in the respiratory tract and the absorption and clearance from the respiratory tract into the circulation (IPCS, 1995). Approximately 35 - 50 % of inhaled lead of particle size less than 1 µm is deposited in the lower respiratory tract, primarily in the alveolar tract, and 50 - 70 % of an inhaled dose is absorbed (ATSDR, 2007). Higher deposition rates may occur with larger particles but this occurs in the upper respiratory tract and absorption occurs via the ingestion route. Smaller particles of lead, such as those generated in exhaust fumes, are almost completely (>90 %) absorbed (IPCS, 1995).

Gastrointestinal absorption of lead is affected by physicochemical characteristics of the lead particles and by physiological factors including age, fasting, nutritional calcium and iron status and pregnancy (Rabinowitz et al., 1980; Taylor et al., 2013). In adults without occupational exposure, and in older children, lead absorbed by the gastrointestinal tract comes mainly from the intake of lead from food, drink and soil/dust (Lin-Fu, 1973; Zhang et al., 2016). In adults, approximately 5 - 15 % of ingested lead is absorbed in the gut whereas, in children and infants, absorption may be as high as 40 % (Zhang et al., 2016).

Dermal absorption of inorganic lead compounds is generally quite low. The absorption of lead through the skin during the normal use of lead containing products has been estimated to be 0.06 % (ATSDR, 2007). PbO can pass through the skin with a median penetration of 2.9 ng/cm<sup>2</sup>. The cleaning procedure using liquid soap significantly increased skin penetration with a median value of 23.6 ng/cm<sup>2</sup>, whereas the new experimental cleanser only marginally increased penetration (7.1 ng/cm<sup>2</sup>) (Filon et al., 2006).

#### **Accumulation**

The main lead storage site in the body is the bone. The toxicologic significance of this fact has been clarified only recently (Beier et al., 2015; Wong et al., 2015). Bone accumulates lead throughout most of the human life span but, at the same time, lead is mobilised from bone by remodelling. In adults, approximately 90 % of the total body burden of lead found in bones (Brito et al., 2014). However, in children, only 70 % of the body burden is found

in the bones, but the concentration increases with age (Barry, 1981). Following chronic exposure, lead becomes deposited, in the form of insoluble lead phosphate, in areas of the skeleton that are rapidly growing, such as the radius, tibia and femur (Barbosa et al., 2005).

Under certain circumstances the bone lead is readily mobilised to blood, the effect of which is most apparent in people with a history of occupational exposure and older people. Mobilisation of lead from bone to the more bioavailable blood compartment is of importance in pregnant women and nursing mothers (Song et al., 2012). Pregnant women are particularly susceptible to toxic effects associated with Pb exposure. Pb accumulates in a bone tissue and is rapidly mobilized from bones during pregnancy and transferred via the placenta from the mother to the developing fetus (Rezende et al., 2010).

### **Excretion**

Faecal excretion is a basic means of detoxification upon ingestion of Pb-contaminated feed (Čadková et al., 2013). Experiments on laboratory animals showed that the excretion of lead can accelerate the use of some substances, eg. high doses of ascorbic acid (Lihm et al., 2013) or hormone melatonin (Hernández-Plata et al., 2015).

Suitable antidote of lead poisoning are some chelating agents. The chelating agents containing vicinal thioether groups, for example 4,5-dicarboxy-3,6-dithiooctanedioic acid (DMSA), disodium-3,6-dithia-1,8-octanediol-4,5 dicarboxylate (DMES) or 2,9 diamino- 5,6 dicarboxy-4,7-dithiadecanedioic acid (DCSA) are very effective, however, none of them could decrease brain Pb (Tandon et al., 1988). The efficacy of DMSA was evaluated in workers occupationally exposed to lead (Pb blood level >50 µg/dL). Ten men were given 600 mg of DMSA peroral daily, for five days. The Pb concentrations of whole blood and urine were determined throughout therapy. DMSA therapy had no influence on hepatic, hematologic, or renal functions and was effective in decreasing the concentration of blood Pb in all the subjects without adverse drug reactions (Torres-Alanis et al., 2002).

### **MECHANISM OF TOXICITY**

Lead is probably the most extensively studied heavy metal. Studies carried out in this field have

reported the presence of various cellular, intracellular and molecular mechanisms behind the toxicological manifestations caused by lead in the body (Bosch and O'Neill, 2016; Clemens and Ma, 2016; Wu et al., 2016).

Oxidative stress has been reported as a major mechanism of lead induced toxicity. Oxidative stress represents an imbalance between the production of free radicals and the biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Two different pathways of Pb toxicity mechanisms operative simultaneously; first comes the generation of reactive oxygen species (ROS), like hydroperoxides, singlet oxygen and hydrogen peroxide, and second, the antioxidant reserves become depleted (Flora et al., 2011).

### **EFFECTS ON HUMANS**

Lead is a cumulative general poison, infants, children up to 6 years of age, the fetus, and pregnant women being the most susceptible to adverse health effects. Its effects on the central nervous system can be especially dangerous (Patočka and Černý, 2003; Kasten-Jolly et al., 2011). Acute or chronic lead exposure may cause reversible or even permanent damages in human beings. Occupational lead poisoning is still a health issue, particularly in developing countries. Environmental lead exposure is a global health concern in children. Lead exposure and lead poisoning are pediatric public health risks. Studies have shown that no level of lead is considered safe, and the emphasis has shifted to primary prevention of lead exposure. Despite the focus on primary prevention (Schnur et al., 2014). Lead is highly toxic to children, causing intellectual and behavioral deficits, hyperactivity, fine motor function deficits, decreased intelligence quotient, alteration of hand-eye coordination, and problems in reaction time. Children's exposure to Pb occurs mainly through ingestion of contaminated food, water and soil (Koyashiki et al., 2010).

#### **Acute exposure**

Overt signs of acute intoxication include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, and loss of memory, encephalopathy occurring at blood lead levels of 100–120 µg/dl in adults and 80–100 µg/dl in children (EPA, 1986).



Two cases of acute lead poisoning due to occupational exposure to lead were described by Ogawa et al. (2008). The patients were engaged in stripping off antirust compounds including Pb from a bridge and re-painting it at the same work place. Both patients exhibited colic, arthralgia, and anemia. Blood lead levels were 73.1 µg/dL and 96.3 µg/dL. Intravenous CaEDTA chelation therapy was therefore performed. After chelation, blood lead levels decreased and symptoms gradually disappeared.

### **Chronic exposure**

Signs of chronic lead toxicity, including tiredness, sleeplessness, irritability, headaches, joint pain, and gastrointestinal symptoms, may appear in adults at blood lead levels of 50–80 µg/dl. After 1–2 years of exposure, muscle weakness, gastrointestinal symptoms, lower scores on psychometric tests, disturbances in mood, and symptoms of peripheral neuropathy were observed in occupationally exposed populations at blood lead levels of 40–60 µg/dl (EPA, 1986). Lead causes health problems such as toxicity of the liver, kidneys, hematopoietic system, and nervous system. Having a carcinogenic risk as well, the IARC classifies inorganic lead compounds as probably carcinogenic to humans (Group 2A). Occupational lead poisonings have decreased due to the efforts to reduce the lead concentrations in the working environment (Kim et al., 2015).

Urban children remain disproportionately at risk of having higher blood lead levels than their suburban counterparts. Soils have been identified as a source of chronic Pb exposure to children, but the spatial scale of the source-recipient relationship is not well characterized. The results show that while there is not a direct relationship between soil Pb and children's blood lead levels, resuspension of locally sourced soil is occurring based on the interior Pb accumulation (Morrison et al., 2013). May be, that the negative effect of lead exposure on human health can be greatly exacerbated in urban children due to high concentrations of polycyclic aromatic hydrocarbons (PAHs) (Xu et al., 2015).

### **Pregnant women exposure**

Exposure of an embryo or fetus in utero to lead increases the possibility of premature birth and low birth weight (Taylor et al., 2015). As the body size of children is smaller than that of adults and lead is more quickly absorbed, they are more vulnerable to lead poisoning. Common symptoms occurring

in children include a loss of appetite, stomach ache, vomiting, learning disabilities, behavioral problems, and anemia (Landrigan et al., 2002). Because lead can be stored in bones for decades and mobilized to the blood when calcium needs increase in pregnancy, women and their children can be at risk for lead-related complications like anemia, gestational hypertension, preterm labor, low birth weight, and developmental delays without any identifiable current exposure (Manton et al., 2003; Alba et al., 2012).

## **BIOMARKERS OF LEAD EXPOSURE**

The symptoms of lead poisoning do not appear instantly. Therefore appropriate selection and measurement of lead biomarkers of exposure are critically important for health care management purposes, public health decision making, and primary prevention synthesis. Therefore, when lead poisoning is suspected, basic information should be determined through a medical interview that takes into consideration the symptoms reported by the patient, current medical history, and the surrounding environment or diet that could be associated with lead exposure. The biomarkers for identification of genetic susceptibility to a particular disease are useful to identify individuals who are at risk for lead poisoning (Shaik et al., 2014). After a basic medical interview and examination, the lead concentrations are measured in the blood, hair, urine, and saliva. After confirming the presence of lead poisoning, the most important priority when observing progression is measuring the blood lead levels. During the last decades, new methods and medications have been advocated for the prevention and treatment of lead poisoning (Kianoush et al., 2015).

## **BIOMONITORING**

Biomonitoring is the use of biological responses to assess changes in the environment, generally changes due to anthropogenic causes. Biomonitoring programs may be qualitative, semi-quantitative, or quantitative. Biomonitoring is a valuable assessment tool that is receiving increased use in water quality monitoring programs of all types. Human exposure to Pb makes it necessary to monitor this element in the human body if the objective is to relate this heavy metal exposure to adverse health effects.

Biomonitoring projects on Pb and other heavy metal are being carried out on people living in the vicinity of industrial enterprises and municipal waste incinerators that release heavy metals into the environment. In order biomonitoring of lead in the environment may be used alone humans and Pb can be detected in blood, urine, or e.g. in hair, or may be used in plants or animals living in tested area. (Besser et al., 2007; Garçon et al., 2007; Reis et al., 2007; Liu et al., 2015; Molina-Villalba et al., 2015; Sánchez-Chardi et al., 2016).

## **TOXICOLOGY**

Lead poisoning has been recognized as a major public health risk, particularly in developing countries. Exposure to lead produces various deleterious effects on the hematopoietic, renal, reproductive and central nervous system, mainly through increased oxidative stress. These alterations play a prominent role in disease manifestations.

### **General toxicity**

The number of reports concerning the chemical toxicology of lead in the environment by natural as well as anthropogenic sources, have been increasing constantly. Lead is described as a classic chronic toxin (Sansar et al., 2011). Few adverse health effects are observed following acute exposure to relatively low levels. Effects observed following acute exposure to high levels of lead include GI disturbances, dullness, restlessness, irritability, poor attention span, headaches, hepatic and renal damage, hypertension, hallucinations, and encephalopathy (Mongolu and Sharp, 2013; Greig et al., 2014; Kumawat et al., 2014).

### **Neurotoxicity**

Compared to other organ systems, the nervous system appears to be the most sensitive and chief target for lead induced toxicity (Cory-Slechta, 1996). Both the central nervous system and the peripheral nervous system become affected on 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, 2004; Brent, 2006).

Knowledge of the neurotoxicity of lead has advanced in recent decades due to revelations re-

garding the mechanisms and cellular specificity of lead (Bressler et al., 1999; Garza et al., 2006). Potential mechanisms of lead-induced cognitive deficits have been investigated using cellular and animal models of learning and memory (Brown et al., 1971; Yang et al., 2003). New research provides convincing evidence that exposures to lead have adverse effects on the CNS, that environmental factors augment lead susceptibility, and that exposures in early life can cause neurodegeneration in later life (Lidsky and Schneider, 2003; Stewart et al., 2006).

In children, the most frequent neurotoxicological effect observed following acute exposure is encephalopathy, a progressive degeneration of certain parts of the brain, which is likely to occur at Pb blood concentrations of 80 – 100 µg/dL (Toto et al., 2012; Greig et al., 2014). In adults, encephalopathy may occur at Pb blood levels of 100 – 120 µg/dL (de Souza et al., 2013). Symptoms of lead induced encephalopathy include irritability, agitation, poor attention span, headache, confusion, ataxia, drowsiness, convulsions and coma (Ahmad et al., 2014; Qasim and Baloch, 2014). More severe manifestations occur at very high exposures and include delirium, lack of coordination, ataxia, convulsions, paralysis, and coma (Flora et al., 2006).

As the main target for lead toxicity is the CNS, the brain is the organ most studied in lead toxicity (Winder and Kitchen, 1984). Lead neurotoxicity occurs when the exposure to lead alters the normal activity of the CNS and causes damage to the CNS (Nava-Ruiz and Méndez-Armenta, 2013; Du et al., 2015). The direct neurotoxic actions of lead include apoptosis (programmed cell death), excitotoxicity affecting neurotransmitter storage and release and altering neurotransmitter receptors, mitochondria, second messengers, cerebrovascular endothelial cells, and both astroglia and oligodendroglia (Flora et al., 2012; Liu et al., 2013). 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 (Kazi et al., 2013). Most early studies concentrated on the neurocognitive effects of lead, but recently higher exposures have been associated with such morbidities as antisocial behavior, delinquency, and violence (Rapisarda et al., 2015; Reyes, 2015; Boutwell et al. 2016; Kloog and Portnov, 2016; Yoon and Ahn, 2016). Several hypotheses have been proposed to explain the mechanism of lead toxicity on the CNS (Amos-Kroohs et al., 2016; Carpenter et al., 2016).

### **Neurological effects in infants and children**

Recent study of Liu et al., (2014a) demonstrate that fetal lead exposure as low as 5 µg/dL has an adverse effect on neurodevelopment, most expressed during the first trimester and best arrested by measuring maternal blood Pb levels. The collective evidence indicates that screening and intervention after the first trimester may be too late to prevent the fetal neurotoxic effects (Liu et al., 2014b). The precise mechanisms by which Pb exerts neurotoxic effects are not fully elucidated. In the study of Allen (2015) infants with elevated umbilical cord blood lead levels were associated with maternal demographic factors and country of origin. Maternal-specific exposure to lead products prior to or during pregnancy was associated with elevated umbilical cord blood lead levels. The evidence on neurological consequences of prenatal exposure to lead appears to reflect changes in cognitive impairment; however, it needs further study. Gąssowska et al. (2016) suggest that neurotoxic effect of Pb might be mediated, at least in part, by GSK-3β and CDK5-dependent Tau hyperphosphorylation, which may lead to the impairment of cytoskeleton stability and neuronal dysfunction.

### **Renal toxicity**

Acute exposure to lead can cause proximal renal tubular dysfunction with proteinuria, aminoaciduria, glycosuria, renal tubular acidosis and cellular casts (Chung et al., 2014; Trzeciakowski et al., 2014). Most effects are largely reversible (Garçon et al., 2007). Prominent inclusion bodies are visible in the cells of the proximal tubules at Pb blood concentrations of 40 – 80 µg/dL (Navarro-Moreno et al., 2009). Acute interstitial nephritis has also been reported at Pb blood concentrations of 40 – 80 µg/dL (Wedeen et al., 1979).

### **Cardiovascular toxicity**

Chronic and acute lead poisoning cause overt, clinical symptoms of cardiac and vascular damage with potentially lethal consequences. Morphological, biochemical, and functional derangements of the heart have all been described in patients following exposure to excessive lead levels (Kopp et al., 1988). Disturbances in cardiac electrical and mechanical activity and postmortem evidence of morphological and biochemical derangements of the myocardium have all been reported following excessive exposure to lead in humus (Flora et al., 2012). Acute exposure to lead leading to PbB concentrations of 48– 120 µg/dL

has been reported to cause hypertension (Gerald et al., 2016; Simões et al., 2016).

### **Reproductive and developmental toxicity**

A systematic literature search in the effect of lead on reproductive toxicity identified a total of 32 experimental studies in animals and 22 epidemiological studies, one case report on humans and five review articles or documents (Apostoli et al., 1998). Nevertheless, metals occur as mixtures in the environment and risk assessment procedures for metals currently lack a framework to incorporate chronic metal mixture toxicity (Nys et al., 2015).

Chronic exposure to lead causes adverse effects on both male and female reproductive functions. Several studies on rats and other rodents indicated that blood lead concentrations > 30-40 µg/dL were associated with impairment of spermatogenesis and reduced concentrations of androgens (Pandya et al., 2012; Anjum et al., 2015). However, other animal studies, mainly about histopathological, spermatozoal, and hormonal end points, indicated that certain species and strains were quite resistant to the reproductive toxicity of lead (Goyer, 1993). The human studies focused mainly on semen quality, endocrine function, and birth rates in occupationally exposed subjects, and showed that exposure to concentrations of inorganic lead > 40 µg/dL in blood impaired male reproductive function by reducing sperm count, volume, and density, or changing sperm motility and morphology (Pant et al., 2014; Telišman et al., 2007).

Occupational maternal exposure to lead resulting in Pb blood of ≥10 µg/dL is associated with an increased risk of spontaneous abortion, preterm delivery and low birth weight. There is evidence to suggest that the risk of spontaneous abortion may be increased at lower Pb blood concentrations. In one study, the risk of spontaneous abortion doubled at maternal Pb blood levels of 5 – 9 µg/dL (UKTIS, 2010).

The most critical effects of lead toxicity occur in children exposed during fetal and/or postnatal development (Liu et al., 2014). Evidence from numerous studies suggests that the higher the maternal concentration of lead, the greater the risk adverse neurodevelopmental effects in the child. Significant reductions in intellectual function have been reported in the offspring of mothers with Pb blood levels of < 10 µg/dL (Liu et al., 2014, 2015; Kashala-Abotnes et al., 2016).



### Gastrointestinal toxicity

Following acute lead exposure, gastrointestinal disorders such as abdominal cramps, diarrhoea with black stools, vomiting and anorexia are most commonly observed in adults at Pb blood concentrations of 100 – 200 µg/dL although effects have been observed at concentrations as low as 40 – 60 µg/dL (Lockitch, 1993; Shah et al, 2016).

### Hepatotoxicity

Occupational and environmental exposure to lead can cause its absorption by the body and consequently exert toxic effects in the liver (Labudda, 2013). Hepatic damage has been reported following acute exposure by Pb in Wistar rats (Soliman et al., 2016).

### Endocrine toxicity

Occupational studies provide evidence for an association between high exposures to lead and changes in thyroid, pituitary, and testicular hormones. Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean Pb blood  $\geq$  40–60 µg/dL (Cullen et al., 1984). Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone, have been observed at Pb blood  $\geq$  30 – 40 µg/dL. Some data, mainly results of tests of hormonal stimulation tests, suggest that the changes in thyroid and testicular hormones are secondary to effects of lead on pituitary function (Ng et al., 1991).

### Hematotoxicity

Lead affects the hematopoietic system through restraining the synthesis of hemoglobin by inhibiting three key enzymes involved in the synthesis of heme. Cytosolic enzyme  $\delta$ -aminolevulinic acid dehydratase (ALAD), that catalyzes the formation of porphobilinogen from  $\delta$ -aminolevulinic acid (ALA), mitochondrial enzyme aminolevulinic acid synthetase (ALAS), that catalyzes the formation of ALA, and finally, the mitochondrial enzyme ferrochelatase that catalyzes the insertion of iron into protoporphyrin to form heme (Piomelli, 2002).

Lead also reduces the life span of circulating erythrocytes by increasing the fragility of cell membranes. The combination of these two processes leads

to anemia (Guidotti et al., 2008). Anemia caused on account of lead poisoning can be of two types: hemolytic anemia, which is associated with acute high-level lead exposure, and frank anemia, which is caused only when the blood lead level is significantly elevated for prolonged periods (Vij, 2009).

### Mutagenicity

Certain effects of lead on genetic material have been observed in simple organisms, and it appears that lead exposure *in vivo* or *in vitro* can induce light chromosomal aberrations such as gaps and fragments (Gerber et al., 1980). Under conditions of calcium deficiency, severe aberrations such as dicentric may also arise, but the data on man are controversial because lead is almost never the only potentially mutagenic agent to which people are exposed in an industrial environment (Deknudt and Gerber, 1979; Al-Qahtani et al., 2015). Nevertheless, the efficiency of lead in causing such aberrations appears low compared with that of other mutagenic agents so that genetic effects of lead do not appear of primary concern for human health. The risks to the developing human organism are difficult to evaluate owing to the large differences in lead metabolism between man and rodent, so studies on species resembling man are desirable.

### Carcinogenicity

Because millions of people worldwide are exposed to lead, both in the workplace and in general environment, its potential carcinogenicity is an important health problem. Although lead has been shown to be carcinogenic in laboratory animals (Tokar et al., 2010), epidemiological studies have been inconclusive, and the relationship between lead and human cancer is still unclear (Ilychova and Zaridze, 2015). No human study either of an epidemiological form or of a case report in industrial, agricultural or community medicine has proven that lead may cause cancer in man.

The Working Group of the International Agency for Research on Cancer (IARC) considered epidemiological evidence from occupational studies of highly-exposed workers. Cancers of the lung, stomach, kidney, brain and nervous system were evaluated. Based on the available data, the Working Group concluded that there is limited evidence for the carcinogenicity to humans following exposure to inorganic lead compounds (IARC, 2006).

## HUMAN HEALTH RISKS

To the questions the presence of lead in the environment and its impact on human health are devoted thousands of scientific studies. This topic remains important for comprehending the present status of human health and welfare. Multiple advances in science serve to refine our understanding about the extent of lead in the environment and the health effects it poses. The articles in this review provide a window into what is currently known about the topic and join tens of thousands of articles on the topic. They underscore recent advances and the global extent concerning the environmental and public health outcomes of lead exposure (Mielke, 2016; Mombo et al., 2016).

## CONCLUSIONS

Lead is toxic metal which has no known biological function in the body and once it enters the body, it is known to cause severe health effects that might be irreversible. It affects almost all the major organ systems of the body like hematopoietic, renal, cardiovascular, and nervous systems. Various molecular mechanisms have been proposed to explain the toxicological profile of lead and from these oxidative stress has been found to be more pronounced and much more severe. Lead causes generation of ROS which results in critical damage to various biomolecules like DNA, enzymes, proteins and membrane based lipids, while simultaneously it impairs the antioxidant defense system.

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