

Lead Toxicity, Antioxidant Defense and Environment

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1 Introduction

Environmental and occupational exposure to a large number of chemicals occurs at various stages throughout human life. Many of these are devoid of toxicity, but some could pose a significant health risk, i.e. the exposure to environmental xenobiotic metals as lead, mercury (Sinicropi et al. 2010a; Carocci et al. 2014), cadmium, etc. In particular, lead has long been a widespread public concern (Basha and Reddy 2010). Lead is one of the earliest heavy metals discovered by men. Due to its unique properties, as low melting point, softness, malleability, ductility, and resistance to corrosion, men have used lead for the last 5000 years in a wide range of applications.

Ancient civilizations have used the lead for the manufacture of kitchen utensils and decorative articles, in plumbing, tableware, and other products since the Roman Empire. It has been utilized in pipes, pigments and paints, construction materials, glass, ceramics, too. Successively, lead has been used as anti-knock fuel additive, in lead-acid batteries, electronic components, and to a lesser extent in ammunition, cable coverings, some paints and ceramics, and in soldering in the food canning industries. It has even been used in some medicines and cosmetics.

The non-biodegradable nature of lead is the reason for its prolonged persistence in the soil, air, and drinking water. The use of lead in pipes, paints, and gasoline additives resulted in large amounts of lead entering the environment. It is a multimedia pollutant, since the human exposure occurs via inhaled air, dust, food and drinking water. However, lead has no known biological function in humans.

In the last 30 years, this metal has been reduced or eliminated in most gasoline and paints with a concurrent drop of blood lead levels of adults and children. However, there are still lead sources near incinerators and smelters, and in poor city areas where peeling Pb-based paint is a source of exposure to children.

Lead accumulates in bone, with clearance half times of approximately two to three decades from cortical bone (e.g., tibia), where it can be measured using X-ray fluorescence. It can contribute to blood lead levels, although the latter are primarily influenced by new external exposure. Blood lead level is the best available estimate of recent dose, while tibia lead is an estimate of lifetime retained cumulative dose (Somervaille et al. 1988; Gulson 2000).

After its accumulation in the bone, lead is released over time especially during periods of bone demineralization such as pregnancy, lactation and postmenopause. Therefore, mobilization of lead from bone can occur in physiological or pathological situations, entailing an increased bone turnover or demineralization as, for instance, in osteoporosis, bone fracture, pregnancy, hyperthyroidism, bone cancer, and chemotherapy (Silbergeld et al. 1988; Silbergeld 1991).

Acute toxicity is related to occupational intense exposure of short duration reaching blood lead levels of 100–120 µg/dl. On the other hand, chronic toxicity is much more common and occurs after repeated exposure over a prolonged period, blood lead levels being of 40–60 µg/dl. If not treated in time, persistent vomiting,

encephalopathy, lethargy, convulsions, delirium, and coma can occur (Flora et al. 2006; Pearce 2007).

Numerous studies regarding the toxicology of lead have shown it to be a potent neurotoxicant, especially during nervous system development (Feldman et al. 1980). High levels lead exposure in adults and children has been associated with deficits in memory and in intellectual functioning (Arvig et al. 1980; Baghurst et al. 1992; Baker 1982; Baker et al. 1984), attention and concentration (Arvig et al. 1980; Stollery et al. 1989), speed and psychomotor performance (Arvig et al. 1980; Stollery et al. 1991). Lead has also well-known effects on the cardiovascular (Vaziri 2002), renal (Gonick 2002), reproductive (Bellinger 2005) and immune (Dietert and Piepenbrink 2006) systems, as well as bones and teeth (Hu et al. 1998) and it has been also identified as a probable human carcinogen (Silbergeld 2003; van Wijngaarden and Dosemeci 2006). Epidemiologic studies suggest an association of inorganic lead exposure to lung, stomach and, to a lesser extent, kidney and brain cancer (Steenland and Boffetta 2000; International Agency for Research in Cancer, IARC 2006).

Lead is known to disrupt dopaminergic function in experimental studies; it seems also to induce oxidative stress (Ercal et al. 2001), which is a candidate hypothesis for the etiology of Parkinson, Alzheimer and other neurodegenerative age-related diseases.

2 Chemical Form and Properties of Lead

Lead (Pb) is a bluish gray heavy metal (atomic weight 207.2), that occurs naturally in various mineral forms in the earth's crust. Metallic lead is resistant to corrosion, because, when it is exposed to air or water, thin films of lead compounds (oxides and carbonates) are formed and protect this metal from further attacks. It has been widely used for centuries because it is readily shaped, molded, and resistant to corrosion. Lead can exist in three forms: metallic, inorganic, and organic. Lead in the environment rarely occurs in its elemental state, but rather in its oxidation state (Pb^{2+}) in various ores throughout the earth. The phasing out of leaded gasoline for transportation vehicles between 1973 and 1995 and the removal of lead from paint by 1978 have resulted in substantial lowering of mean blood lead levels. However, because lead is a persistent metal, it is still present in the environment, water, soil, and dust (Patrick 2006).

In this regard, the work by Patterson in 1956 (Patterson 1956), who determined the age of the Earth by a uranium-lead isotopic data method, needs to be mentioned. Using a Canyon Diablo meteorite, Patterson was able to make an accurate measurement, calculating that the Earth was 4.55 billion years old. But in this study he discovered a disturbing and constant presence of lead in the atmosphere mainly due to tetraethyl lead used as an anti-knock gasoline. Thanks to the ongoing commitment of Patterson, tetraethyl lead, first in the United States and later in the rest of the world, was eliminated from gasoline. The presence of lead in the blood of human

beings has considerably diminished; but in any case, the human beings today have about 625 times more lead in his body than people did 100–120 years ago.

In the majority of adults, chronic lead poisoning comes from exposures to work places and can occur in numerous work settings, such as manufacturing, lead smelting and refinement, or it may be caused by use of batteries, pigments, solder, ammunitions, paint, car radiators, cable and wires, and certain cosmetics (Brodkin et al. 2007). Diagnosis of lead toxicity has traditionally based on significantly elevated blood lead levels. These are an indicator of circulating lead that discloses variation in recent external lead exposure as well as of lead that has been mobilized by tissue stores (mostly bones). Lead levels in tibia and patella provide an indication of cumulative dose over decades (particularly cortical tissue in tibia) as well as the largest pool of lead in the body that is available for mobilization into blood. The latter phenomenon is heightened at times of high bone resorption (e.g. during pregnancy, aging, postmenopause) (Hu et al. 2007).

Inorganic lead is absorbed from the respiratory or gastrointestinal tract but not through the skin. Approximately 90 % of the total body burden is stored in bone and the remainder is in blood stream and soft tissue (Philip and Gerson 1994). Gastrointestinal absorption varies depending on nutritional status and age. Iron is believed to impair lead uptake in the gut, while iron deficiency is associated with increased blood lead concentrations in children. Lead exposure in pregnant animals usually occurs through the oral route. It known that absorption of this metal increase during pregnancy. Lead crosses the placenta and it accumulates in the fetus. Accumulation of lead occurs in the fetal brain owing to lack of blood-brain barrier (BBB). Lead also accumulates in the placenta in times of fetal stress (Gupta 2012).

Once absorbed, the circulating lead is bound to erythrocytes for approximately 30–35 %, while only 1 % of absorbed lead is found in plasma and serum and it is dispersed into the soft tissues of liver, renal cortex, aorta, brain, lungs, spleen, where it accumulates as $Pb_3(PO_4)_2$ in the following 4–6 weeks (Begovic et al. 2008). Lead is primarily excreted via the kidneys, while a small amount is excreted in feces and with sweat (Sinicropi et al. 2010b). The most common symptom of acute inorganic lead poisoning is gastrointestinal colic; chronic exposure to Pb^{2+} produce damage to hematopoietic, nervous, gastrointestinal and renal systems.

The effects of lead exposure are a health concern for all humans, but especially during early childhood because children are most at risk. Exposure to excessive amounts of inorganic lead during the toddler years may produce lasting adverse effects upon brain function. Maximal ingestion of lead occurs at an age when major changes are occurring in the density of brain synaptic connections.

Organolead compounds, as tetramethyllead and tetraethyllead are readily absorbed by inhalation and through the skin as well as by gastrointestinal tract. Tetraethyllead is metabolized to triethyllead, and this demethylated compound is excreted with the urine. Tetraethyllead and its metabolites are toxic especially for the brain. Toxicity appears with headache, restlessness, nervousness, and anxiety (Beattie et al. 1972); severe symptoms including convulsion, delirium, coma, abdominal pain and peripheral neuropathy. The neurotoxic

effects of organolead compounds are associated with urinary lead concentrations higher than 30 mg/l (Macintyre 1994). In 2004, IARC classified lead and inorganic lead as probable human carcinogens (IARC group 2A), while organic lead remained unclassifiable.

3 Lead and Environment

Lead occurs naturally in the environment. It is rarely found in its elemental form but occurs in the Earth's crust primarily as the mineral galena (PbS), and to a lesser extent as anglesite (PbSO_4) and cerussite (PbCO_3). Lead minerals are found in association with zinc, copper, and iron sulfides as well as gold, silver, bismuth, and antimony minerals. It also occurs as a trace element in coal, oil, and wood.

Lead released from natural sources, such as volcanoes, windblown dust, and erosion, are minor compared with anthropogenic sources. In the air, lead is in the form of particles and is removed by rain or gravitational settling. The solubility of lead compounds in water is a function of pH, hardness, salinity, and the presence of humic material. Solubility is highest in soft and acidic water. The sink for lead is the soil and sediment. Because it is strongly adsorbed to soil, it generally is retained in the upper layers of soil and does not leach appreciably into the subsoil and groundwater.

Anthropogenic sources of lead include the mining and smelting of ore, manufacture of lead-containing products, combustion of coal and oil, and waste incineration. Many anthropogenic sources of lead, most notably leaded gasoline, lead-based paint, lead solder in food cans, lead-arsenate pesticides have been eliminated or strictly regulated due to lead's persistence and toxicity. Because lead does not degrade, these former uses leave their legacy as higher concentrations of lead in the environment.

Lead occurs naturally in the environment on account from human activities and it continues to be a significant public health problem in developing countries (Tong and McMichael 1999; Grant and Davis 1989), where there are considerable variations in the sources and pathways of exposure (Environmental Protection Agency, EPA 1986).

Exposure attributable to miscellaneous sources may be even more significant than universal exposure associated with leaded petrol, especially for people living in poverty (IPCS 1995, Environmental health criteria 165).

Exposure to lead from lead mining (Ajumobi et al. 2014), smelting of lead ores, as well as other ores (zinc, copper, iron, gold (Dooyema et al. 2012) and silver) in which lead is by-product or contaminant, battery factories and cottage industries is a significant environmental hazard in developing countries. Electrical utilities release into the atmosphere lead in flue gas from the burning fuels, such as coal, in which this element is a contaminant. As a result of human activity, environmental levels of lead increased more than 100-fold over the past three centuries.

The greatest increase occurred in the past century between the years 1950–2000 and reflected increasing worldwide use of tetraethyl lead and tetramethyl lead as gasoline additives to increase octane rating. Since gasoline additives have been banned, the level of lead in the atmosphere has dropped dramatically. Tetraethyl and tetramethyl lead, once added to gasoline, are no longer present in significant quantities in air. In fact, exposed to sunlight, they decompose rapidly to trialkyl and dialkyl lead compounds and to lead oxides by direct photolysis, and reacting with hydroxyl radicals and ozone. But it is necessary to emphasize that in the winter tetraethyl and tetramethyl lead have half-lives of up to several days since the atmospheric hydroxyl radicals concentration is lower than in summer (DeJonghe and Adams 1986).

In parallel with enforcement of the reduction of lead gasoline in Italy, Annibaldi and coauthors (2009) have studied the lead content of Adriatic seawater. In the years from 2000 to 2004, seawater was collected systematically at three sites along the coast line close to the city of Ancona. The results show that the lead content in seawater diminished from a median value of 0.25 nmol/L in 2000–2001 to 0.12 nmol/L in 2003–2004. This decrease has been correlated to the concurrent decrease of lead in gasoline in Italy with a reduction of lead emission in atmosphere.

Lead is also released into the air during burning coal and oil. In fact, in the last 15–20 years the total lead emission from electric steam increased due to the increased demand for electric power and an increased use of coal and natural gas as fuel sources to generate electricity. Burning these sources of energy recklessly, the level of CO₂ and thus global warming due to greenhouse effect have increased considerably.

Once small lead particles get into the atmosphere, they can travel long distances about 10 km from emission sources (Berndtsson 1993), before to fall by rain to land or into surface of rivers, lakes and sea. Sources of lead in dust and in soil include not only lead that falls to the ground from the air, but also weathering and chipping of lead-based paint from buildings and bridges. Higher levels of lead in soil are found near roadways (Nielsen 1984). Once lead falls onto soil, it sticks strongly to soil particles for many years in the upper layer of soil. Small amounts of lead may enter in rivers, lakes and sea when the soil particles are moved by rain water, or when lead is released by acidic water.

The fate of lead in soil is affected by the absorption at mineral interfaces and the formation of relatively stable organic-metal complexes or chelates with soil organic matter. This process is dependent on factor such as soil pH, soil type, organic matter content of soil, and cation exchange capacity (Reddy et al. 1995). Most lead is strongly retained in soil and very little is transported through runoff to surface of water. Clays, silts, iron and manganese oxides, and soil organic matter may bind lead electrostatically as cation exchange resin, as well as chemically for specific adsorption (Reed et al. 1995).

The amount of soluble lead in surface water depends upon the pH of the water and the concentration of dissolved salts. Equilibrium calculations show that at pH 5.4 the solubility of lead is about 30 µg/L in hard water and approximately 500 µg/L in soft water. Sulfate ions, if present in soft water, decrease the lead concentration through

the formation of insoluble lead sulfate. The lead carbonate limits the amount of soluble lead considering also the partial pressure of CO₂, pH and temperature (Environmental Protection Agency, EPA 1986).

Plants and animals may bioconcentrate lead and the high lead concentrations are found in aquatic and terrestrial organisms. This occurs when these living beings have habitats near lead mining and smelting, areas affected by high automobile and truck traffic, sewage sludge and spoil disposable areas, sites where dredging have occurred, and in urban and industrialized areas (McGrath et al. 1994). Lead may be present on plant surfaces on account of atmosphere deposition; but its presence in internal plant tissues indicates biological uptake from the soil and leaf surface. Lead may be taken up in edible vegetables and fruits from the soil via the root system, by direct foliar uptake and translocation within the plant. As already mentioned, the amount of lead in soil, that is bioavailable to a vegetable plants, depends on factor such as cation exchange capacity, pH of soil, amount of organic matter present and type of fertilizer added to the soil (Holmgren et al. 1993).

Uptake of lead in animals may occur on account of inhalation of contaminated ambient air or ingestion of contaminated plants. However, lead is not biomagnified in aquatic or terrestrial food chains, as for other metals, for example mercury. In aquatic organisms, lead levels are usually highest in benthic organisms and algae, and lowest in upper trophic level predators as carnivorous fishes (Tulasi et al. 1992). Lead is toxic to all aquatic biotic component, and organisms higher up in the food chain may experience lead poisoning by ingestion of food contaminated with lead. Depuration is relatively rapid; in the case of rainbow trout exposed to tetramethyl lead the half-life values of depuration are about 35–45 h (Eisler 1988).

4 Lead Effect on Health

4.1 *Effect on the Nervous System*

Both central and peripheral nervous systems (CNS and PNS, respectively) appear to be the most sensitive targets for lead induced toxicity (Cory-Slechta 1996). While PNS is more affected in adults, the effect of lead on CNS is more pronounced in children (Bellinger 2004; Brent 2006). Once in the brain, lead-induced damage in the prefrontal cerebral cortex, hippocampus, and cerebellum can lead to a variety of neurological disorders, such as brain damage, mental retardation, behavioral problems, nerve damage, and possibly Alzheimer's disease, Parkinson's disease, and schizophrenia. Lead toxicity leads to encephalopathy with a progressive degeneration of certain regions of brain, the major symptoms including dullness, loss of memory, hallucinations, headache, poor attention span, and irritability.

At very high levels lead exposure, severe manifestations occur with delirium, convulsion and coma (Flora et al. 2006). Lead has negative effect especially on the developing nervous system of the fetuses and young children, which absorbs a higher fraction of this metal. The level of systematically circulating lead that has

access to the brain of children is significantly higher as compared to adult subjects (Needleman 2004). At low levels exposure, children may appear inactive, hyperactive and irritable; moreover, IQ and concentration ability are significantly lowered. In the presence of greater lead levels, children show growth retardation, decreased intelligence, short-term memory and hearing loss. At last, at higher levels, children suffer permanent brain damage and even death (Cleveland et al. 2008). Besides, repercussions on the nervous system have been observed involving reduced motor activity, due to the loss of the insulating layer of myelin; in this way, a weakening of the nerve signal occurs, causing muscular weakness, especially of the exterior muscles, fatigue and lack of muscular coordination (Sanders et al. 2009).

4.2 Effect on the Hematopoietic System

Lead affects the hematopoietic system by inhibiting the synthesis of hemoglobin, acting directly on three key enzymes involved in the heme synthesis (Fig. 1) and, ultimately, leading to anemia. Lead affects the heme synthesis pathway by

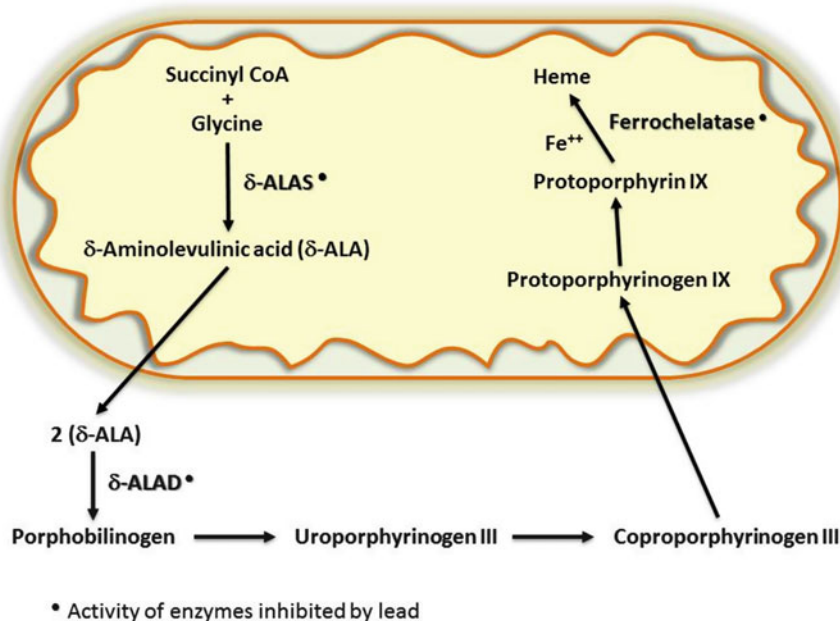


Fig. 1 Inhibition of lead in the heme biosynthetic pathway. The initial and final steps of heme synthesis take place in the mitochondria, while the intermediate steps develop in the cytoplasm. δ -ALAS: δ -aminolevulinic acid synthase; δ -ALAD: δ -aminolevulinic acid dehydratase; Succinyl CoA: Succinyl Coenzyme A

downregulating the three key enzymes in a dose dependent manner. The mitochondrial enzyme δ -aminolevulinic acid synthase (δ -ALAS) catalyzes the synthesis of δ -aminolevulinic acid (δ -ALA), starting from glycine and succinyl CoA (an intermediate of tricarboxylic acid cycle or Krebs cycle). Porphobilinogen is produced from two δ -ALA molecules, in the presence of the cytosolic enzyme δ -aminolevulinic acid dehydratase (δ -ALAD). Finally, the mitochondrial enzyme ferrochelatase catalyzes the insertion of a ferrous ion (Fe^{2+}) into protoporphyrin IX to form heme (Piomelli 2002).

δ -ALAD is a crucial enzyme in lead toxicity (Fig. 1); its inhibition decreases heme production and increases the quantity of δ -ALA that can be found in blood and urine of subjects with lead exposure (Bechara 1996). Heme synthesis does not decrease until the activity of δ -ALAD is inhibited by 80–90 %, which occurs at a blood lead concentration of about 55 $\mu\text{g}/\text{dl}$ (Ahamed et al. 2005). It has also been shown that δ -ALA, when accumulating during lead exposure, autoxidizes with the resulting conversion of oxyhemoglobin to methemoglobin (Monteiro et al. 1986).

Ferrochelatase inhibition by lead allows the substitution of iron by zinc producing zinc protoporphyrin (ZPP). Thus, the concentration of ZPP increases and its presence can be used as an indicator of lead exposure level (Jangid et al. 2012). Inhibition of ferrochelatase results in increased excretion in urine of coproporphyrinogen and accumulation of protoporphyrin in erythrocytes.

Lead also reduces the life span of erythrocytes in the bloodstream. Erythrocytes bind about 98–99 % of the lead in the bloodstream and this metal has a destabilizing effect on cellular membranes. In red blood cells (RBC) lead causes a decrease of cell membrane fluidity and an increase of erythrocyte hemolysis rate and this is associated to anemia (Vij 2009). Hemolysis is the final result of ROS-generated lipid peroxidation in the RBC membranes and in all cellular membranes. Lead can also bind directly to phospholipids (particularly to phosphatidylcholine) in the RBC membranes, reducing their levels.

4.3 Effect on the Reproductive System

Lead interferes with the reproductive system. In a scientific study, semen quality from 100 workers occupationally exposed to variable quantities of lead was compared with the quality of about 150 volunteers with no exposure to lead (Telisman et al. 1990). Average level of lead in the blood of workers control was 10.7 $\mu\text{g}/\text{dl}$ (range 6.7–20.8 $\mu\text{g}/\text{dl}$), while that of exposed workers was 37.1 $\mu\text{g}/\text{dl}$ (range 11.7–104.0 $\mu\text{g}/\text{dl}$). The presence of higher amounts of lead in the blood of exposed workers compared to control workers (about 3.5 times) reduced the volume of ejaculation, semen density, total sperm number and motility, and increased the percentage of pathological spermatozoa (Goyer 1993). Other effects of high levels of blood lead include reduced libido, abnormal spermatogenesis, chromosomal damage, infertility and changes in serum testosterone. Moreover,

during a study on men without occupational exposure to lead, it was demonstrated that high levels of lead in semen reduce the sperm count, contributing to its infertility (Wu et al. 2012).

It has been recognized that women with severe lead intoxication are more susceptible to prolonged and abnormal menstruations, infertility, miscarriage, still-birth, premature membrane rupture, pregnancy hypertension and premature delivery (Flora et al. 2011). Besides, during pregnancy, direct influence of lead on the developmental stages of fetus has also been reported (Saleh et al. 2009). Moreover, the transfer of lead through the placenta into the mother milk makes the blood lead levels of the mothers and infants usually similar (Dart et al. 2004).

4.4 Effect on the Kidney

Lead can cause acute and chronic nephropathies. Lead is absorbed by the proximal tubular cells of the renal tubules, where it binds to specific lead-binding proteins. In presence of acute lead nephrotoxicity, these lead-protein complexes are observed as typical intracellular inclusion bodies. They do not secrete proteins in urine, but generates an abnormal excretion of glucose, phosphates and aminoacids, a combination known as Fanconi's syndrome.

On the other hand, chronic lead nephropathy is much more severe and causes irrevocable morphological and functional changes, such as glomerular and tubulointerstitial changes accompanied by hypertension, hyperuricemia and renal breakdown (Rastogi 2008).

Lead accumulates in the kidney mitochondria and causes both structural and functional alterations. These effects include mitochondrial swelling and inhibition of respiratory chain function and oxidative phosphorylation for ATP production. Consequently, energy-dependent processes, including tubular transport, are impaired.

4.5 Effect on the Bone

It is well recognized that lead has effect on bone metabolism. It accumulates in human body primarily in the bones (Silbergeld et al. 1993; Renner 2010). Lead is stored in two bone compartments: the exchangeable lead is present at the surface of bone and the non-exchangeable lead is located deeply in the cortical bone. Lead in bone can be mobilized during different physiological and pathological states. These conditions include endocrine status, age, osteoporosis, and maternal age during pregnancy and lactation (Silbergeld 1991).

5 Molecular Mechanism of Lead Toxicity: Oxidative Stress and Cation Action

Oxidative stress represents an imbalance between the production of free radicals and the cells ability to detoxify the extremely reactive intermediates or to repair the resulting damage (Flora et al. 2011). Oxidative stress occurs as a consequence of two different and related pathways: the generation of reactive oxygen species (ROS), like hydroperoxides (HO_2^-), singlet oxygen and hydrogen peroxide (H_2O_2); and the direct depletion of antioxidant reserves (Ercal et al. 2001; Flora 2002). In any biological system where ROS production increases, antioxidant reserves are depleted.

The tripeptide glutathione (GSH, γ -glutamylcysteinylglycine) is the most important antioxidant in cells; glutathione has a sulfhydryl group ($-\text{SH}$), present in cysteine residue, and is found in millimolar concentrations in mammalian tissues. Glutathione exists in two forms: reduced GSH and oxidized glutathione disulfide (GSSG) forms. Glutathione in the reduced state acts as an important antioxidant for quenching free radicals, donating reducing equivalent to ROS and makes them stable. In the redox reaction, GSH readily combines with another molecule of GSH and forms oxidized GSSG in the presence of the enzyme glutathione peroxidase (GPx). In turn, GSH can be restored from GSSG by the enzyme glutathione reductase (GR). Under normal conditions, 90 % of total glutathione exists in cells as reduced form GSH, and about 10 % as oxidized form GSSG; on the contrary, under oxidative stress, the GSSG concentration is much higher than that of GSH (Mates 2000; Flora et al. 2012). Lead covalently interacts with $-\text{SH}$ groups of glutathione and antioxidant enzymes, inactivating them.

Lead inactivates not only GR, but also GPx, and glutathione-S-transferase, which further depress the glutathione levels (Hunaiti et al. 1995; Kasperczyk et al. 2004; Ahamed and Siddiqui 2007). Other important antioxidant enzymes inhibited by lead include superoxide dismutase (SOD) and catalase (CAT). Moreover, lead can also takes the place of the zinc ion, which acts as an important cofactor, in the catalytic site of various antioxidant enzymes, inhibiting them (Flora et al. 2007). Lead toxicity arises also on account of its ability to substitute other monovalent and divalent cations (Na^+ , Ca^{2+} , Mg^{2+} , Fe^{2+}), affecting fundamental and important biological functions of the body (Lidsky and Schneider 2003). These fundamental cellular processes include cellular signaling, cell adhesion, apoptosis, enzyme regulation, and release and uptake of neurotransmitters (choline, dopamine and GABA) (Bressler et al. 1999; Garza et al. 2006). The ability of lead to pass through the BBB is due in large part to its ability to substitute calcium ions. At the molecular level, lead interferes with the regulatory action of calcium on cell functions and disrupts many intracellular biological activities. After replacing calcium ions, lead contributes to neurological deficits and becomes able to cross the BBB at an appreciable rate. After crossing the BBB, lead accumulates in astroglial cell, containing lead binding proteins; the immature astroglial cells are

also damaged from lead, which may prevent the formation of myelin sheath (Bressler et al. 1999).

The developmental reorganization of synapses is in part mediated by protein kinases, and these enzymes are particularly sensitive to stimulation by lead. By inappropriately activating specific protein kinases, lead poisoning may disrupt the development of neural networks without producing overt pathological alterations. Protein kinases appear to regulate the development of brain capillaries and the expression of the BBB properties. Stimulation of protein kinase by lead may disrupt barrier development and alter the precise regulation of the neuronal environment that is required for normal brain function (Goldstein 1990).

Plausible mechanisms of inorganic lead carcinogenicity include direct DNA damage, clastogenicity, or inhibition of DNA synthesis or repair. Since lead may generate ROS, it may cause oxidative damage to DNA, it can replace zinc in several proteins that function as transcriptional regulators, including protamines. Lead further reduces the binding of these proteins to recognition elements in genomic DNA, which suggests an epigenetic involvement of lead in altered gene expression. These events may be of particular relevance in transplacental exposures (Silbergeld et al. 2000). It has also been demonstrated that the ingestion of lead acetate may induce significant stimulation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities; moreover, total soluble protein and albumin contents of plasma are significantly decreased, the cholinesterase activity is inhibited, while the activities of alkaline and acid phosphates and lactate dehydrogenase are stimulated. Pb^{2+} ingestion reduce the contents of hemoglobin and RBC count of intoxicated rat's blood and the plasma levels of triiodothyronine (T3), thyroxine (T4) and white blood cells (WBC) count decrease (Ibrahim et al. 2012).

6 The Role of Antioxidants in Protecting Lead-Induced Oxidative Stress

Preventive measures are preferred over the treatment regimens, considering that once lead enters the body it is almost impossible to remove it completely or to reverse the harmful effects.

The oxidative stress stimulated by lead is a state that involves free radicals generation with decreasing of the antioxidant reserves and at the same time hampering the ability of the body to annihilate the negative effects of free radicals (Fig. 2). Free radicals generate a series of chain reactions that induce lipid peroxidation with cell membrane disruption, oxidation of proteins and nucleic acids DNA and RNA with cancer formation. The phospholipids of cell membranes, including RBC membranes, being constituted by polyunsaturated fatty acids with two or more double bonds, are more susceptible to oxidative stress induced by lead. In this peroxidation process, lead could affect the activity of membrane enzymes, endo- and exocytosis and signal transducing processes (Adonaylo and Oteiza 1999).

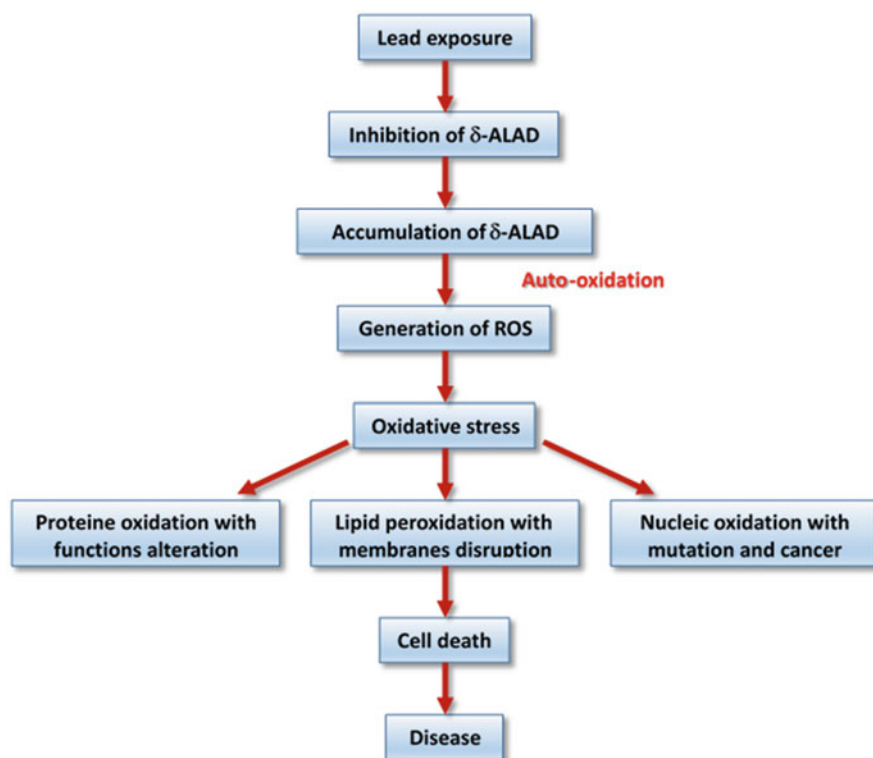


Fig. 2 Possible mechanism for lead-induced oxidative stress and cell death

Many authors suggested that administration of various antioxidants could prevent and cure the toxic effects of lead that causes the generation of free radicals in the body. They have the ability to scavenge ROS at molecular level and chelate lead ions, thereby reversing the toxic effects (Garcia and Gonzalez 2008).

The aforementioned enzymatic antioxidants, as SOD, CAT and GPx, are endogenously produced in the cells, whereas non-enzymatic antioxidants, like carotenoids, flavonoids, polyphenols, vitamins (vit B, vit C, vit E) are present in our daily food as fruits, vegetables, nuts, grains, meats and milk (Flora 2009). The non-enzymatic antioxidants are taken through the diet or in the form of supplements to maintain the homeostasis between free radicals and antioxidants.

6.1 Flavonoids and Polyphenols

Flavonoids are naturally polyphenolic compounds which represent the main constituents of fruits, vegetables, plant derived beverages (red wine and tea) and chocolate (Youdim et al. 2002). Flavonoids play an important role in plants, mainly

protecting them against external pathogens, ultra-violet light, or heat. Flavonoids are responsible for the red, purple, and blue color of fruits and flowers, and play a role in pollination by attracting insects.

In human beings, these compounds, like other antioxidants, can cure or prevent oxidative stress by chelating active metal ions and also by terminating the free radical chain reaction (Terao 2009). The flavonoids ability to act as antioxidants depends on their molecular structure, characterized by two or more aromatic rings with at least one or more hydroxyl groups apiece and conjugated electrons giving also metal chelating properties (Heim et al. 2002; Wolfe and Liu 2008).

Quercetin is a ubiquitously distributed flavonoid present in fruit, vegetable and tea. The hydroxyl groups together with the carbonyl group donate electrons by undergoing resonance and stabilize free radicals, thus inhibiting lipid peroxidation. Quercetin chelates lead by forming a coordination bond between this metal and its ortho-phenolic groups (Fig. 3).

Liu and coworkers studied the protective mechanism of quercetin against lead-induced injuries of liver (Liu et al. 2010a, 2013) and kidney (Liu et al. 2010b, 2012). They found that quercetin significantly decreased the malondialdehyde (MDA), H_2O_2 , and ROS levels and lowered the GSH/GSSG ratio in the liver and kidney of lead-treated rats. Furthermore, this bioflavonoid markedly restored Cu/Zn SOD, CAT and GPx activities and decreased DNA oxidative damage and apoptosis in the liver and kidney of lead-treated rats.

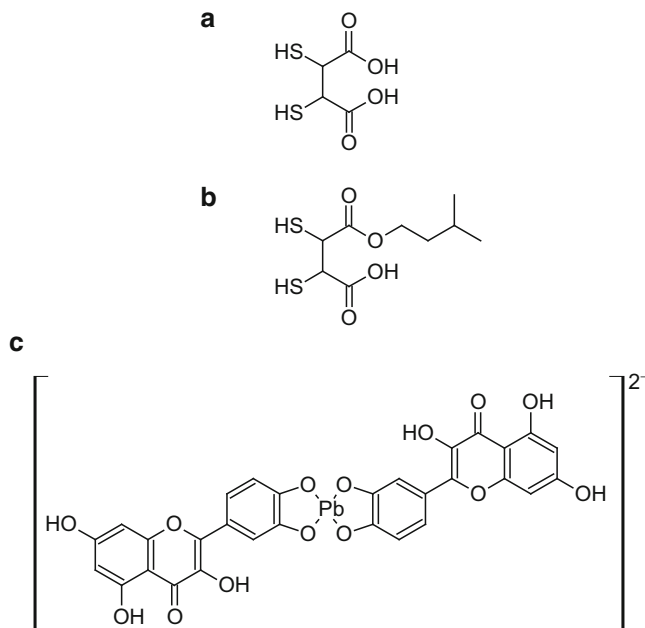


Fig. 3 Chemical structure of chelating agents: (a) meso-2,3-dimercaptosuccinic acid (DMSA); (b) monoisoamyl ester of DMSA (MiADMSA); (c) quercetin-Pb complex

Curcumin, a yellow polyphenolic compound, is the active component of tumeric, which possesses multiple activities, including antioxidant properties, radical scavenging and metal chelating in lead toxicity (Agarwal et al. 2010; Singh and Sankhla 2010). Shukla et al. (2003) reported the protective effect of curcumin against lead-induced neurotoxicity in rats. Exposure of rats to lead caused an increase in lipid peroxidation and a decrease in the level of reduced GSH, and in SOD and CAT activities in cerebellum, corpus striatum, hippocampus and frontal cortex as compared to controls. Treatment with curcumin caused in brain regions of the treated rats a significant decrease in lipid peroxidation and an important increase in reduced GSH level and SOD and CAT activities. Daniel et al. (2004) pointed out the chelation properties of curcumin, reducing lead level in rat brain. However, its extremely low aqueous-solubility and rapid intestinal and hepatic metabolism, which result in poor systemic bioavailability, restrict its oral use.

6.2 Vitamins

Vitamin B6 (pyridoxine) and vitamin B1 (thiamine) are the prosthetic groups of the coenzymes pyridoxal 5'-phosphate and thiamine pyrophosphate; these vitamins are essential in the treatment of the deleterious effects of lead toxicity. Vitamin B6 indirectly acts as an antioxidant stimulating the synthesis of GSH and as a chelator agent (Ahamed and Siddiqui 2007). A diet rich in pyridoxine in lead-exposed rats improved δ -ALAD activity (Tandon et al. 1987); in addition, levels of lead in blood, kidney and liver were reduced after this particular diet. McGowan (1989) found that rats treated with lead and nourished with diet deficient in pyridine have significantly lower levels of GSH compared to lead-exposed rats and fed with normal levels of vitamin B6.

It has been reported that vitamin B1 exerts protective effect against lead toxicity. Senapati et al. (2000) reported the protective effect of thiamine hydrochloride on lead induced endogenous lipid peroxidation in liver and kidney of rats with an important decrement in the level of this metal.

Vitamin C is the most thoroughly studied vitamin in the prevention of lead induced oxidative stress. Its capability of quenching ROS together with metal chelation makes the ascorbic acid a potential detoxifying agent for lead (Tariq 2007).

Vitamin C (ascorbic acid) fortified with silymarin has been shown to reduce the toxic effect of acute lead poisoning on rat liver (Shalan et al. 2005). The combination of ascorbic acid with silymarin restored the activity of liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (γ GT) after a lead induced damage. Combined treatment of lead-exposed animals with vitamin C and silymarin showed marked improvement of the biochemical, molecular and histopathological findings.

In rat liver supplementation of ascorbic acid and thiamine nullified the oxidative stress in a concentration dependent manner and protected DNA from damage

induced by lead (Wang et al. 2007). In addition, Shan and coworkers (2009) reported that ascorbic acid and thiamine showed defensive results against the toxic effects of lead on testes of mice.

Vitamin E (α -tocopherol), a fat soluble vitamin, possess powerful antioxidative properties and in the membrane prevents lipid peroxidation by blocking the free radical chain reaction. Some authors (Sajitha et al. 2010) reported that α -tocopherol given to rats counteracted the harmful effect of lead by scavenging free radicals and preventing oxidative stress. δ -ALAD inhibition induced by lead in the erythrocytes is reversed by vitamin E treatment (Rendón-Ramírez et al. 2007).

Lead has been shown to decrease RBC membrane flexibility and to increase RBC fragility with risk for hemolysis (Levander et al. 1977). Vitamin E was shown to prevent RBC membrane damage on account of lead toxicity by lowering lipidic peroxide levels and increasing the activity of the enzymes SOD and catalase (Chaurasia and Kar 1997).

Vitamin E in combination with other antioxidant agents is more effective than its individual administration. Flora and coauthors (2003) studied the positive effects of naturally occurring antioxidants like vitamin C and vitamin E either alone or in combination with thiol chelators as meso-2,3-dimercaptosuccinic acid (DMSA) or monoisoamyl ester of DMSA (MiADMSA), on parameters indicative of oxidative stress in various organs (liver, kidney, brain and blood) of lead-exposed rats. The obtained results suggest that vitamin C and vitamin E administered during chelation with DMSA or MiADMSA were significantly beneficial in reducing oxidative stress. In fact, these thiol chelators (DMSA and MiADMSA) have two sulfhydryl (-SH) groups in the structure (Fig. 3) that can be useful in complexing lead and scavenging free radicals. This combination (vitamin and chelating agents) is more effective than the vitamin and the chelating agents alone, due to the fact that vitamin does not have lead chelating property but can consistently prevent oxidative stress.

Chelating agents form a complex with the toxic lead ion and these complexes, that show low toxicity, are easily eliminated from the body through the excretory system. An ideal chelating agent has to possess characteristics like great affinity for the toxic metal, that has to be chelated (in our case the lead), high water solubility, ability to cross cell membranes, possibility to oral administration and low metabolism. The uptake can be accomplished by passing through the phospholipid bilayers of the cellular membrane as an uncharged molecule or by utilizing a protein transport system embedded in the membrane.

6.3 Antioxidants Availability and Nanoparticles

There are several lines of evidence from *in vitro* and *in vivo* studies suggesting that antioxidants encapsulated in nanoparticles have a great potential in the prevention and treatment of various diseases. The major drawback in the usefulness of antioxidants appears to be due to poor solubility in aqueous solvents, poor absorption,

poor bioavailability and rapid metabolism. To cancel these negative causes and to improve antioxidants usefulness numerous approaches have been undertaken, involving the use of nanoparticles, liposomes and phospholipid complex (Anand et al. 2007).

Lipid systems of nanoencapsulation enhance the antioxidants usefulness by improving their solubility and bioavailability and by preventing unwanted interactions with other food components. Liposome technology presents exciting opportunities in encapsulation and controlled release of antioxidants, as well as enhanced bioavailability and stability.

Mozafari and coauthors (2006, 2008) reported the use of liposomes as carrier vehicles of nutrients, enzymes, drugs, and food antimicrobials, because of their small size, biodegradability, hydrophobic and hydrophilic characters, and low toxicity. Results from several studies demonstrate that liposomes have the potential to enhance drug penetration, improve therapeutic effectiveness, and reduce serious side effects. Liposomes are tiny vesicles of spherical shape (usually between 100 and 1000 nm in diameter) containing water, artificially prepared and composed by phospholipids bilayers as the cellular membranes. Liposomes are prepared by sonication and are composed of phospholipids enriched of phosphatidylcholine and phosphatidylethanolamine. Phospholipids are amphiphilic with long hydrocarbon tails of the molecule being hydrophobic, while its polar head is hydrophilic.

The phospholipids have hydrophilic heads pointing outside, while the hydrophobic tails of both lipid bilayers point inside interacting with each other. Also the inside of the liposomes is water soluble and can contain soluble drugs, enzymes, nutrients and biomolecules. The outer phospholipids membranes can be covalently modified with charged molecules; in this way the liposomes may be more easily conveyed at the target cells.

Excellent results were obtained encapsulating curcumin in liposomes. Although curcumin, encapsulated into liposomes, is more bioactive and bioavailable, *in vivo* studies are yet necessary to confirm these properties (Gandhi et al. 2011).

7 Summary

Humans have used lead since early history for over 4000–5000 years for the most different applications. So lead poisoning has been known to men, but the situation worsened in the 18th century with the industrial revolution. In the last century the levels of lead in the human body increased because levels in the atmosphere increased due to the presence of this metal in the exhaust gases of cars powered by gasoline added with tetraethyl lead. Nowadays, the level of lead in our body is going down because it was banned from gasoline, however it is still present in many manufactured products and therefore produces deleterious toxic effects.

Lead released to the atmosphere partitions to surface water, soil and sediment. Organolead compounds (tetraethyl and tetramethyl lead) are transformed in the atmosphere by photodegradation and reaction with ozone to alkyl lead, oxides and

carbonates; instead, in surface water organolead compounds are transformed by photolysis and hydrolysis. Anyhow, properties such as pH, oxygen content and salinity are necessary to fully understand the chemical transformation and the environmental fate of lead in soil and water.

It is important to stress that lead exposure induces generation of free radicals and ROS, resulting in oxidative damage to various biomolecules like nucleic acids (DNA and RNA), proteins and enzymes, and membranes based phospholipids, impairing at the same time the antioxidant defense system. In human beings, lead has no biological functions and once it enters the body, it causes severe irreversible health effects and it affects important systems as nervous, hematopoietic, reproductive and renal and so on.

Antioxidants, specifically vitamins (B₁, B₆, C and E) have been shown to lower ROS generated cellular damage. They have the ability to scavenge ROS and chelate lead ions, reversing the toxic effects. These antioxidants were also reported to provide an elevated therapeutic impact when administered with thiol chelators DSMSA and MiADMSA. These beneficial effects were accompanied by more pronounced urinary lead elimination and tissue lead depletion.

The biggest drawback in the case of antioxidants is their poor bioavailability due to low solubility and rapid clearance. Novel approaches to overcome the problem of low bioavailability of these antioxidants include the formulation of nanoparticles, liposomes and micelles. Compared to conventional methods, this approach reduces the dosage of antioxidants to maintain the therapeutic level in the body. Further experiments are needed to show the effects of nutrients on cells of animals and men that undergo the lead exposure.

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