General Introduction
Metals and metal compounds are natural constituents of all ecosystems, moving between atmosphere, hydrosphere, lithosphere, and biosphere (Bargagli, 2000). Their distribution in the environment is a result of natural processes (volcanoes, erosion, spring water, bacterial activity) and anthropogenic activities (fossil fuel combustion, industrial and agricultural processes) (Florea et al., 2004). While, compounds containing Cd, Cu, Cr, Hg, Ni, Pb, and Zn are industrially produced, metallic derivatives containing Cu, Co, As, Sb, Zn, Cd, Au, Cl, C and Pb, are also used in home activities (Fergusson and Kim, 1991; Abdulla and Chmielnicka, 1990). Therefore, metal compounds are also increasingly introduced in the environment and could finally accumulate in biotic systems (Nordberg et al., 1985; Han et al., 2002). Exposure to toxic metals remains a widespread occupational and environmental problem in the world. Due to their widespread use in human activities such as industry, agriculture and even as medicine, numerous health risks may be associated with exposure to these substances.

Metals, when present in our body are capable of causing serious health problems, by interfering with, our normal body functions. Some of these metals are useful to the body in low concentrations like copper, Fe and nickel but are toxic at high concentrations. Other metals like aluminum, beryllium, Cd, Pb and mercury have no biological functions and are highly toxic disrupting bodily functions to a large extent by accumulating in vital organs and glands in the human body such as in the heart, brain, kidney, bone and liver. They also displace vital nutritional minerals from their proper place in the body to provide biological functions, e.g., Pb or Cd displaces Ca in an enzyme reaction disrupting the enzyme reaction to a large extent. As their impact in the body, is at such basic levels that they are the causal factors in multiple health problems. Metals cause genotoxicity as they affect the DNA and immunotoxicity as they are major irritants to the body. The genomic instability by these metals induces cancer (Leonord et al., 1948).

There are 35 metals that concern us because of occupational or residential exposure; 23 of these are the heavy elements or "heavy metals": antimony,
arsenic, bismuth, Cd, cerium, chromium, cobalt, copper, gallium, gold, Fe, Pb, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium, and Zn (Glanze, 1996). Interestingly, small amounts of these elements are common in our environment and diet and are actually necessary for good health, but large amounts of any of them may cause acute or chronic toxicity (poisoning). Heavy metal toxicity can result in damaged or reduced mental and central nervous function, lower energy levels, and damage to blood composition, lungs, kidneys, liver, and other vital organs. Long-term exposure may result in slowly progressing physical, muscular, and neurological degenerative processes that mimic Alzheimer's disease, Parkinson's disease, muscular dystrophy, and multiple sclerosis. Allergies are not uncommon and repeated long-term contact with some metals or their compounds may even cause cancer (International Occupational Safety and Health Information Centre, 1999).

A heavy metal is a member of an ill-defined subset of elements that exhibit metallic properties, which would mainly include the transition metals, some metalloids, lanthanides, and actinides (Duffus, 2002). Heavy metals occur naturally in the ecosystem with large variations in concentration. In modern times, anthropogenic sources of heavy metals, i.e. pollution, have been introduced to the ecosystem. Waste-derived fuels are especially prone to contain heavy metals so they should be a central concern in a consideration of their use. Living organisms require varying amounts of "heavy metals." Fe, cobalt, copper, manganese, molybdenum, and Zn are required by humans. Excessive levels can be damaging to the organism. Other heavy metals such as mercury, plutonium, and Pb are toxic metals that have no known vital or beneficial effect on organisms and their accumulation over time in the bodies of animals can cause serious illness (Lane et al., 2000).

Heavy metal pollution can arise from many sources but most commonly arises from the purification of metals, e.g., the smelting of copper and the preparation of nuclear fuels. Electroplating is the primary source of chromium and Cd. Through precipitation of their compounds or by ion exchange into soils and
mud, heavy metal pollutants can localize and lay dormant. Unlike organic pollutants, heavy metals do not decay and thus pose a different kind of challenge for remediation. One of the largest problems associated with the persistence of heavy metals is the potential for bioaccumulation and bio magnification causing heavier exposure for some organisms than is present in the environment alone. Coastal fish (such as the smooth toadfish) and seabirds (such as the Atlantic Puffin) are often monitored for the presence of such contaminants (Hogan, 2010).

COMMONLY ENCOUNTERED TOXIC HEAVY METALS

Arsenic

Arsenic is the most common cause of acute heavy metal poisoning in adults and is number 1 on the ATSDR's "Top 20 List." Arsenic is released into the environment by the smelting process of Cu, Zn, and Pb, as well as by the manufacturing of chemicals and glasses. Arsine gas is a common byproduct produced by the manufacturing of pesticides that contain arsenic. Arsenic may also be found in water supplies worldwide, leading to exposure of shellfish, cod, and haddock. Other sources are paints, rat poisoning, fungicides, and wood preservatives. Target organs are the blood, skin, kidneys, central nervous and digestive systems (Roberts, 1999; ATSDR ToxFAQs for Arsenic).

Lead

Pb is number 2 on the ATSDR's "Top 20 List." Pb accounts for most of the cases of pediatric heavy metal poisoning (Roberts, 1999). It is a very soft metal and was used in pipes, drains, and soldering materials for many years. Millions of homes built before 1940 still contain Pb (e.g., in painted surfaces), leading to chronic exposure from weathering, flaking, chalking and dust. Every year, industry produces about 2.5 million tons of Pb throughout the world. Most of this Pb is used for batteries. The remainder is used for cable coverings, plumbing, and ammunition and fuel additives. Other uses are as paint pigments and in PVC plastics, x-ray shielding, crystal glass production and pesticides. Target organs are the bones, brain, blood, kidneys, and thyroid gland.
Mercury

Number 3 on ATSDR's "Top 20 List" is mercury. Mercury is generated naturally in the environment from the degassing of the earth's crust, volcanic emissions. It exists in three forms: elemental mercury, organic and inorganic mercury. Mining operations, chloralkali plants, and paper industries are significant producers of mercury (Goyer, 1996). Atmospheric mercury is dispersed across the globe by winds and returns to the earth in rainfall, accumulating in aquatic food chains and fish in lakes (Clarkson, 1990). Mercury compounds were added to paints and in fungicides until 1990. These compounds are now banned; however, old paint supplies and surfaces painted with these old supplies still exist. Mercury continues to be used in thermometers, thermostats, and dental amalgam. Medicines, such as mercurochrome and Merthiolate are still available. Algaecides and childhood vaccines are also potential sources. Inhalation is the most frequent cause of exposure to mercury. The organic form is readily absorbed in the gastrointestinal tract (90-100%); lesser, but still significant amounts of inorganic mercury are absorbed in the gastrointestinal tract (7-15%). Target organs are the brain and kidneys (Roberts, 1999; ATSDR ToxFAQs for Mercury).

Cadmium

Cd is a byproduct of the mining and smelting of Pb and Zn and is number 7 on ATSDR's "Top 20 list." It is used in nickel-Cd batteries, PVC plastics, and paint pigments. It can be found in soils because insecticides, fungicides, sludge, and commercial fertilizers that are used in agriculture. Cd may be found in reservoirs containing shellfish. Cigarettes also contain Cd. Lesser-known sources of exposure are dental alloys, electroplating, motor oil, and exhaust. Inhalation accounts for 15-50% of absorption through the respiratory systems; 2-7% of ingested Cd is absorbed in the gastrointestinal system. Target organs are the liver, placenta, kidneys, lungs, brain, and bones (Roberts, 1999; ATSDR ToxFAQs for Cd).
Aluminum

Although aluminum is not a heavy metal (specific gravity of 2.55-2.80), it makes up about 8% of the surface of the earth and is the third most abundant element (ATSDR ToxFAQs for Aluminum). It is readily available for human ingestion through the use of food additives, antacids, buffered aspirin, astringents, nasal sprays, and antiperspirants; from drinking water; from automobile exhaust and tobacco smoke; and from using aluminum foil, aluminum cookware, cans, ceramics, and fireworks. Target organs for aluminum are the central nervous system, kidney and digestive system (ATSDR ToxFAQs for Aluminum).

Lead

Chemical properties of Pb:

Atomic number: 82

Atomic mass: 207.2g.mol$^{-1}$

Density: 11.34 g.cm$^{-3}$ at 20°C

Melting point: 327°C

Boiling point: 1755°C

Isotopes: 13

Aside from smoke, Pb is probably the oldest human made atmospheric and occupational toxin, dating back at least 8000 years to the first Pb smelting furnaces (Elsinger 1996). Pb is one of the oldest known and most widely studied occupational and environmental toxins (Gidlow, 2004). Pb was widely used for more than 5000 years because this metal is corrosion resistant, dense, ductile and malleable. Therefore it was deployed for building materials, water pipes, ammunition, ceramic glazers, glass and crystals, paints, protective coatings, acid storage batteries, gasoline additives, cosmetics (face powders, lipstick, mascara, etc.), spermicidal (e.g. for birth control), and as a wine preservative (stops
fermentation). Due to its wide use, humans are exposed to Pb derivatives and have a daily Pb intake by food, drinking water and by inhalation.

**Uses of Pb**

The principal consumption of Pb is for the Pb-acid storage battery in which grid or plate is made of Pb.

Pb Sheet is used in the building industry for flashings or weathering to prevent water penetration & for roofing and cladding. By virtue of its resistance to chemical corrosion, Pb sheet also finds use for the lining of chemical treatment baths, acid plants and storage vessels. The high density of Pb sheet makes it a very effective material for sound insulation purpose. Pb clad steel has also found use in radiation shielding.

Pb pipes due to its corrosion resistant properties are used for carriage of corrosive chemicals at chemical plants. Also Pb pipe of appropriate composition is still extruded for cutting into short length 'sleeves' for use in the jointing of Pb sheathed cables.

Pb is used extensively in paints, although recently the use of Pb in paints has been drastically curtailed to eliminate or reduce health hazards.

Because of its high ductility, good extrusion ability, relatively low temperature & excellent proven corrosion resistance when in contact with a wide range of industrial and marine environments, soils and chemicals, Pb alloys are used extensively as sheathing materials for high voltage power cables.

Pb is used in ammunition of Pb bullets, which are commonly used in sport shooting with small arms. Pb forms alloys with many metals. Pb is used to make bearings, solder, antifriction metals, and type metal.
Exposure routes:

Pb is a common environmental pollutant (Ragan et al., 2009). Causes of environmental contamination include industrial use of Pb, found in plants that process Pb-acid batteries or produce Pb wire or pipes, and metal recycling and foundries (Manay et al., 2008). Children living near facilities that process Pb, such as smelters, has been found to have unusually high blood Pb levels (Sanborn et al., 2002). Pb exposure can occur from air, household dust, soil, water, and commercial products (Rossi, 2008).

Occupational exposure

In adults, occupational exposure is the main cause of Pb poisoning (Needleman, 2004). People can be exposed when working in facilities that produce a variety of Pb-containing products; like radiation shields, ammunition,
certain surgical equipment, fetal monitors, plumbing, circuit boards, jet engines, and ceramic glazes (Patrik, 2006). In addition, Pb miners and smelters, plumbers and fitters, auto mechanics, glass manufacturers, construction workers, battery manufacturers and recyclers, firing range instructors, and plastic manufacturers are at risk for Pb exposure (Sanborn, 2002). Other occupations that present Pb exposure risks include welding, manufacture of rubber, printing, Zn and copper smelting, processing of ore, combustion of solid waste, and production of paints and pigments (Dart et al., 2004). Parents who are exposed to Pb in the workplace can bring Pb dust home on clothes or skin and expose their children (Dart et al., 2004).

Absorption and distribution of Pb

Pb absorbed by the GIT comes from the intake of the Pb in food, beverages and soil or dust in case of older children and adults and in occupational exposure population mostly from atmospheric air (WHO, 1995). In adults, about 35–40% of inhaled Pb dust is deposited in the lungs, and about 95% of that goes into the bloodstream (Merrill et al., 2007). Of ingested inorganic Pb, about 15% is absorbed, but this percentage is higher in children, pregnant women, and people with deficiencies of Ca, Zn, or Fe (Karri et al., 2008). Children and infants may absorb about 50% of ingested Pb (Grant, 2009).

The main body compartments that store Pb are the blood, soft tissues, and bone; the half-life of Pb in these tissues is measured in weeks for blood, months for soft tissues, and years for bone (Karri et al., 2008). Pb in the bones, teeth, hair, and nails is bound tightly and not available to other tissues, and is generally thought not to be harmful (Rubin, 2008). In adults, 94% of absorbed Pb is deposited in the bones and teeth, but children only store 70% in this manner, a fact which may partially account for the more serious health effects on children (Barbosa et al., 2005). The estimated half-life of Pb in bone is 20 to 30 years, and bone can introduce Pb into the bloodstream long after the initial exposure is gone (Patrick, 2006). The half-life of Pb in the blood in men is about 40 days, but it
may be longer in children and pregnant women, whose bones are undergoing remodeling, which allows the Pb to be continuously re-introduced into the bloodstream (Barbosa et al., 2005). Many other tissues store Pb, but those with the highest concentrations (other than blood, bone, and teeth) are the brain, spleen, kidneys, liver, and lungs (Dart et al., 2004). It is removed from the body very slowly, mainly through urine (Pearson et al., 2003). Smaller amounts of Pb are also eliminated through the feces, and very small amounts in hair, nails, and sweat (Kosnett, 2006).

Figure 2. Conceptual diagram of the movement of environmental Pb into and through the human body. Data from the U.S.E.P.A.

**Health effects of Pb**

Unlike most chemicals for which health impacts of low level doses are still uncertain, exposure to Pb, even at very low levels, is highly toxic (Sillbergeld, 1994). Although 10 micrograms of Pb per 1 deciliter of blood is generally used as the level above which health impacts are known to be
substantial, scientists have not yet identified a level below which no adverse effects of Pb occur (Schwartz, 1994). Several studies have found detectable learning problems in children whose blood Pb levels are as low as 5 – 10 micrograms per deciliter (Sillbergeld, 1995).

Pb is particularly toxic to the brain, kidneys, reproductive system, and cardiovascular system. Exposures can cause impairments in intellectual functioning, kidney damage, infertility, miscarriage, and hypertension (Silbergeld, 1996). Pb is a special hazard for young children. Several studies have shown that Pb exposures can significantly reduce the IQ of school aged children; some estimates suggest that every 10 micrograms per deciliter increase in Pb levels in the blood is associated with a 1-5 points decrease in the IQ of exposed children (Goyer, 1996). Pb exposures have also been associated with aggressive behavior, delinquency, and attention disorders in boys between the ages of 7 and 11 (Needleman et al., 1996). In adults, Pb exposure has been related to increased blood pressure and hypertension, conditions known to increase the risk of cardiovascular disease.

Pb is a poisonous metal that can damage nervous connections (especially in young children) and cause blood and brain disorders. Pb poisoning typically results from ingestion of food or water contaminated with Pb; but may also occur after accidental ingestion of contaminated soil, dust, or Pb based paint (ATSDR). Long-term exposure to Pb or its salts (especially soluble salts or the strong oxidant PbO2) can cause nephropathy, and colic-like abdominal pains. The effects of Pb are the same whether it enters the body through breathing or swallowing. Pb can affect almost every organ and system in the body. The main target for Pb toxicity is the nervous system, both in adults and children. Long-term exposure of adults can result in decreased performance in some tests that measure functions of the nervous system. It may also cause weakness in fingers, wrists, or ankles. Pb exposure also causes small increases in blood pressure, particularly in middle-aged and older people and can cause anemia. Exposure to high Pb levels can severely damage the brain and kidneys in adults or children and ultimately cause
death. In pregnant women, high levels of exposure to Pb may cause miscarriage. Chronic, high-level exposures have shown to reduce fertility in males (Golub, 2005). High blood levels are associated with delayed puberty in girls (Schoeters et al., 2008). Pb has been shown to permanently reduce the cognitive capacity of children at extremely low levels of exposure (Needleman et al., 1990).

Effects of Pb on Enzymes

The primary cause of Pb toxicity is its interference with a variety of enzymes due to the fact that it binds to sulphydryl groups found on many enzymes (Pearson, 2003). Part of Pb toxicity results from its ability to mimic other metals that take part in biological processes, which act as cofactors in many enzymatic reactions, displacing them at the enzymes on which they act (Dart et al., 2004).

Pb is able to bind to and interact with many of the same enzymes as these metals but, due to its differing chemistry, does not properly function as a cofactor, thus interfering with the enzyme's ability to catalyze its normal reactions. Among the essential metals with which Pb interacts are Ca, Fe, and Zn (Kosnett, 2006).

One of the main causes for the pathology of Pb is that it interferes with the activity of an essential enzyme called δ-aminolevulinic acid dehydratase, or ALAD, which is important in the biosynthesis of heme, the cofactor found in hemoglobin (Patrick, 2006). Pb also inhibits the enzyme ferrochelatase, another enzyme involved in the formation of heme. Ferrochelatase catalyzes the joining of protoporphyrin and Fe\(^{2+}\) to form heme. Pb's interference with heme synthesis results in production of Zn protoporphyrin and the development of anemia (Mycyk, 2005). Another effect of Pb's interference with heme synthesis is the buildup of heme precursors, such as aminolevulinic acid, which may be directly or indirectly harmful to neurons (Kosnett, 2005).

Renal system

Kidney damage occurs with exposure to high levels of Pb, and evidence suggests that lower levels can damage kidneys as well (Grant, 2009). The toxic
effect of Pb causes nephropathy and may cause Fanconi syndrome, in which the proximal tubular function of the kidney is impaired (Rubin et al., 2009). Long-term exposure at levels lower than those that cause Pb nephropathy have also been reported as nephrotoxic in patients from developed countries that had chronic kidney disease or were at risk because of hypertension or diabetes mellitus (Ekong et al., 2006). Pb poisoning inhibits excretion of the waste product urate and causes a predisposition for gout, in which urate builds up. This condition is known as saturnine gout (Wright et al., 1984; Lin 1994; Shadick et al., 2000).

Reproductive system

Pb affects both the male and female reproductive systems. In men, when blood Pb levels exceed 40μg/dL, sperm count is reduced and changes occur in volume of sperm, their motility, and their morphology (Grant, 2009). A pregnant woman's elevated blood Pb level can lead to miscarriage, prematurity, low birth weight, and problems with development during childhood (Cleveland, 2008). Pb is able to pass through the placenta and into breast milk, and blood Pb levels in mothers and infants are usually similar (Dart et al., 2004). A foetus may be poisoned in utero if Pb from the mother's bones is subsequently mobilized by the changes in metabolism due to pregnancy; increased Ca intake in pregnancy may help mitigate this phenomenon (Bellinger, 2005).

Nervous system

The nervous system is the primary target for the low levels of Pb-exposure and the developing brain appears to be especially vulnerable to Pb-neurotoxicity (Kuhlmann et al., 1977; Zawia et al., 1998; Reddy and Zawia, 2000; Chetty et al., 2001; Basha et al., 2003; Devi et al., 2005). Pb affects the peripheral nervous system (especially motor nerves) and the central nervous system (Dart et al., 2004). Peripheral nervous system effects are more prominent in adults and central nervous system effects are more prominent in children (Bellinger, 2004). Pb causes the axons of nerve cells to degenerate and lose their myelin coats (Dart
et al., 2004). Pb is a highly neurotoxic agent that causes functional and structural abnormalities in the brain (Struzynska et al., 2002).

The brain is most sensitive to Pb exposure (Cecil et al., 2004). Pb poisoning interferes with the normal development of a child's brain and nervous system; therefore children are at greater risk of Pb neurotoxicity than adults (Sanders et al., 2009). In the developing brain, Pb interferes with synapse formation in the cerebral cortex, neurochemical development (including that of neurotransmitters), and organization of ion channels (Mycyk et al., 2005). It causes loss of neurons' myelin sheaths, reduces number of neurons, interferes with neurotransmission, and decreases neuronal growth (Pearson et al., 2003).

Pb exposure in young children has been linked to learning disabilities (Meyer et al., 2003), and children with blood Pb concentrations greater than 10 μg/dL are in danger of developmental disabilities (Brunton et al., 2003). Increased blood Pb level in children has been correlated with decreases in intelligence, nonverbal reasoning, short-term memory, attention, reading and arithmetic ability, fine motor skills, emotional regulation, and social engagement (Cleveland et al., 2008). The effect of Pb on children's cognitive abilities takes place at very low levels. Blood Pb levels below 10 μg/dL have been reported to be associated with lower IQ and behavior problems such as aggression; in proportion with blood Pb levels (Guidotti et al., 2007). High blood Pb levels in adults are also associated with decreases in cognitive performance and with psychiatric symptoms such as depression and anxiety (Shih et al., 2007).

Pb exposure in children is also correlated with neuropsychiatric disorders such as attention deficit hyperactivity disorder and antisocial behavior (Bellinger, 2008). Elevated Pb levels in children are correlated with higher scores on aggression and delinquency measures (Needleman, 2004). A correlation has also been found between prenatal and early childhood Pb exposure and violent crime in adulthood (Cleveland et al., 2008).
Pb interferes with the release of neurotransmitters, chemicals used by neurons to send signals to other cells (Dart 2004; Needleman 2004). It interferes with the release of glutamate, a neurotransmitter important in many functions including learning, by blocking NMDA receptors. The targeting of NMDA receptors is thought to be one of the main causes for Pb's toxicity to neurons (Xu et al., 2009). A Johns Hopkins report found that in addition to inhibiting the NMDA receptor, Pb exposure decreased the amount of the gene for the receptor in part of the brain. In addition, Pb has been found in animal studies to cause programmed cell death in brain cells (Needleman, 2004).

**Cardiovascular system**

Evidence suggests that Pb exposure is associated with high blood pressure, and studies have also found connections between Pb exposure and coronary heart disease, heart rate variability, and death from stroke (Navasacien, 2007). People who have been exposed to higher concentrations of Pb may be at a higher risk for cardiac autonomic dysfunction (Park et al., 2008).

Chronic Pb exposure has been linked to serious, sometimes lethal disturbances in cardiac rhythmicity and contractile function (Harlan et al., 1985; Pirkle et al., 1985; Khera et al., 1980). The experimental findings that have been reported suggest that Pb acts at multiple sites within the cardiovascular system. These findings include direct effects on the excitability and contractility of the heart (Kopp et al., 1980; Prentice et al., 1985), vascular sites of action affecting the compliance and contractility of vascular smooth muscle (Webb et al., 1981; Tomera et al., 1986) and possibly sites of action within the central nervous system affecting blood pressure regulation (Iannaccone et al., 1981). Myocarditis (Kline et al., 1960), electro cardio graphic abnormalities (Silver et al., 1968), altered heart rate activity (Stofen et al., 1974), slowed ventricular systole (Dimitrova et al., 1972), hypertension (Bertel et al., 1978; Boscolo et al., 1981; Kirkby et al., 1985) and vascular degeneration (Stofen et al., 1974) have all been among the reported cardiovascular aberrations detected in humans chronically and acutely.
exposed to toxic Pb levels. Electro cardio graphic abnormalities, including sinus bradycardia, multi focal ventricular escape beats, T-wave inversion, left bundle branch block (LBBB), first degree heart block and ectopic atrial rhythms have all reported in conjunction with chronic Pb poisoning (Read et al., 1952; Kline et al., 1960; Myerson et al., 1963; Silver et al., 1968; Dimitrova et al., 1972; Stofen et al., 1974).

In general, administration of Pb, most commonly as the acetate salt, to experimental animals has been shown to induce myocarditis, degenerative structural and biochemical changes affecting the musculature of the heart and vasculature, hypertension, hypercholesterolemia, increased arterial plaque deposition, electrocardiographic disturbances, accentuated catecholamine arrhythmogenicity, altered contractile responsiveness of the myocardium to inotropic stimulation, and increased vascular reactivity to adrenergic agonists (Williams et al., 1977; Perry et al., 1978; Revis et al., 1980; Webb et al., 1981; Iannaccone et al., 1981; Kopp et al., 1980; Evis et al., 1985).

**Effects on the Blood-forming System**

Pb impairs the synthesis (formation) of a substance called "heme" which is extremely important to human life because it carries oxygen to tissues of the body. Pb interferes with the production of this substance at several different steps. Pb exposed persons can develop anemia. In adults, anemia is usually seen in severe chronic Pb poisoning and blood Pb levels of 70 μg/dL and higher is usually found.

Pb has a more severe effect on the blood-forming system in Fe deficient people. Generally young children and women of child bearing age are much more likely to be Fe deficient than are adult men. Because the combination of Fe deficiency and Pb exposure cause more severe effects on the blood forming system than either condition alone, women and children tend to show more severe effects. These occur at lower blood Pb levels in women and children than in men (Gulson et al., 1995).
Haematological effects:

Pb inhibits the body's ability to make hemoglobin by interfering with several enzymatic steps in the heme pathway. Specifically, Pb decreases heme biosynthesis by inhibiting δ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase activity. Ferrochelatase, which catalyzes the insertion of Fe into protoporphyrin IX, is quite sensitive to Pb. A decrease in the activity of this enzyme results in an increase of the substrate, erythrocyte protoporphyrin (EP), in the red blood cells (also found in the form of ZPP—bound to Zn rather than to Fe). Also associated with Pb exposure is an increase in blood and plasma δ-aminolevulinic acid (ALA) and free erythrocyte protoporphyrins (FEP) (ATSDR 1999). EPA estimated the threshold BLL for a decrease in hemoglobin to be 50μg/dL for occupationally exposed adults and approximately 40μg/dL for children, although other studies have indicated a lower threshold (e.g., 25μg/dL) for children. (ATSDR 1999)

Pb can induce two types of anemia, often accompanied by basophilic stippling of the erythrocytes (ATSDR 1999). Acute high-level Pb exposure has been associated with hemolytic anemia. Frank anemia is not an early manifestation of Pb exposure and is evident only when the BLL is significantly elevated for prolonged periods. In chronic Pb exposure, Pb induces anemia by both interfering with heme biosynthesis and by diminishing red blood cell survival. The anemia of Pb intoxication is hypochromic and normo- or microcytic with associated reticulocytosis. The heme synthesis pathway, on which Pb has an effect, is involved in many other processes in the body including neural, renal, endocrine, and hepatic pathways (ATSDR, 1999).

The anemia that occurs in Pb poisoning results from two basic defects:

2. Impairment of heme synthesis.
Shortened of life span of RBC is thought to be due to increased mechanical fragility of cell membrane (Hernberge et al., 1967). Gautam and Chowdhury (1987) noticed that erythropoietic alteration in normal and splenectomized mature male rats treated with aqueous Pb acetate intra peritoneally at dosages of 4 and 6 mg/kg body weight over a period of 30 days. Changes in the morphology of erythrocytes revealed that Pb might increased the development of irregularly shaped blood cell, and the development of anemia resumed by a decrease in Hb, Bazzaz et al., (1989), noticed that the change in the morphology of erythrocytes revealed that Pb might increased the development of irregularly shaped blood cells and the development of anemia, and also reported that there is significant reduction of hemoglobin, packed cell volume, number of erythrocytes and leucocytes associated with significant increase in the number of monocytes were observed in case of Pb intoxication.

Exposure to Pb significantly decreases red blood cells count, hemoglobin level and haematocrit value of rats (Terayama, 1993). Goyer (1996) stated that the effects of Pb over exposure on heme synthesis have been thoroughly investigated and there is a consensus that adverse effects on Hb are associated with BLL values of 50μg/dL in adults. Anemia can result from both shortened red cells life span and impairment of heme synthesis. Kim et al., (2003), noticed that anemia accompanies Pb poisoning as a result of various inhibitory effects of Pb on heme biosynthesis. Pb also increases the rate of red blood cell destruction due to the profoundly depressed activities of erythrocyte pyrimidine 5-nucleotidase activities. Exposure to Pb at different doses in drinking water significantly decreases red blood cells count, hemoglobin concentration and haematocrit values of rabbits (Bersenyi, et al., 2003). Payton et al., (1994) found that early kidney damage is difficult to detect. However, a 10mg/dL increase in BLL has been associated with a 10.4 ml/minute decrease in renal creatinine clearance rate.

Hogan et al., (1992) pointed out that renal parameters showed modifications of blood urea nitrogen levels for both oral and intraperitoneal administered male wistar rats with Pb acetate for 4 weeks which can indicate a
prerenal uremia. This was supported by the significant increase of creatinine in the first week of Pb treatment by intra peritoneal injection. Daily oral administration of Pb acetate at dose of 40 mg/kg body weight caused significant increase in serum urea, uric acid, and creatinine of rabbits (Ashour, 2002).

Speich et al., (1983) noticed that elevation of amino transferases SGOT and SGPT in serum of experimental animals. In human cases both positive and negative finding have been reported by (Waldron, 1975; Tola and Nordmen, 1977). Aziz (2002) identified the biochemical changes in adult male domesticated rabbits following oral administration of Pb acetate at dose of 40 mg/kg body weight daily for 20 days. Data revealed that levels of serum AST and ALP were significantly increased. Sivaprasad et al., (2003) found that the activities of serum SGOT and SGPT were elevated in rats administered 2% Pb acetate drinking water for 5 weeks.

A growing amount of evidence indicates that cellular damage mediated by reactive oxygen species (ROS) may be involved in the pathology associated with Pb intoxication (Bechera, 1993). A strong correlation between blood Pb concentration and malondialdehyde levels in blood of Pb exposed workers was already reported (Jiun, 1994). In erythrocytes, from the workers exposed occupationally to Pb, the activities of the antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase were remarkably lower than the non-exposed workers (Monteiro et al., 1985). Heavy metal induced alteration of antioxidant enzyme activities and nucleic acids concentrations are also reported (Das et al., 2001).

Pb causes oxidative stress by inducing the generation of ROS, reducing the antioxidant defense system of cells via depleting glutathione, interfering with some essential metal, inhibiting sulphydryl dependent enzymes or antioxidant enzyme activities and/or increasing susceptibility of cells to oxidative attack by altering membrane integrity and fatty acid composition (Hande et al., 2000). The binding activity of Pb compounds with oxidative stress factors and with the
generation of reactive oxygen species, such as hydrogen peroxide and its interaction with different metals and also toxic activity of δ-aminolevulinic acid (ALA) are reported earlier (Ariza, 1998; Ding, 2000).

AGING:

Aging is inevitable, and is characteristically described as a time-dependent functional decline, leading to the cell's incapacity to withstand external and internal challenges. The consensus among researchers broadly views the concept of biological aging as an organism's failure to maintain homeostasis (Gutteridge, 1992). The free radical theory of aging (Harman, 1956) proposes that free radicals [specifically reactive oxygen species (ROS)], by-products of normal metabolism, cause oxidative damage to macromolecules, whose accumulation causes cellular dysfunction with age and eventually cell death. Many investigators believe that free radical damage to cellular molecules and organelles is the primary cause of aging of the organism (Semsei et al., 1991).

Over time, the free radical theory has been further refined to reflect the fact that mitochondria are at the same time major sources and targets of ROS (Miquel et al., 1980; Linnane et al., 1989). According to the mitochondrial theory of aging, ROS produced via mitochondrial respiration attack mitochondrial constituents. In particular, accumulation of oxidant-induced somatic mutations in mitochondrial DNA (mtDNA) is believed to be the underlying cause of the decline in physiological function with age (Trifunovic et al., 2004; Kujoth et al., 2005). Mitochondrial respiratory complex function may be altered as a result of mtDNA mutations, leading to increased ROS production and further damage to mtDNA, as well as other macromolecules (Lenaz et al., 2002).

It has been suggested by many authors that oxidative stress is a possible aging-accelerating factor (Matsuo et al., 1992). During the aging process, tissues are damaged to some extent due to the oxidative processes primarily caused by reactive oxygen species. According to the hypothesized central role of mitochondria in the aging process, tissues that exhibit a high rate of oxygen
consumption throughout an individual’s lifetime, such as the heart, may be especially prone to oxidative damage.

Figure 2. Proposed schematic representation of the steps that take place during aging.

Oxidative stress conditions lead to formation of O$_2$ and H$_2$O$_2$, which can oxidize cellular macromolecules mainly through the mediation of Fe. Normally, the oxidized proteins are degraded to the constituting amino acids, which are subsequently used for synthesis of new proteins. However, under conditions of elevated levels of H$_2$O$_2$ and/or Fe or decreased cellular degradation capacity, secondary oxidation of already oxidized proteins takes place and leads to formation of over-oxidized products that are not capable of further processing. The consequences of the formation of over-oxidation products are dual. First, they inhibit the cellular degradation systems, and secondly they progressively
accumulate inside the cells, thus compromising the cells’ structures and functions. These effects are especially apparent in terminally differentiated non-divided cells. It is proposed that regulated suppression of labile Fe levels may decrease the rate of accumulation of over-oxidized materials and in this way favourably influence the aging process.

THERAPEUTIC OVERVIEW

Chelation Therapy

Chelation is a chemical process that has applications in many areas, including medical treatment, environmental site rehabilitation, water purification, and so forth. In the medical environment, chelation is used to treat cardiovascular disease, heavy metal toxicity, and to remove metals that accumulate in body tissues because of genetic disorders (hemochromatosis). Chelation therapy, simply defined, is the process by which a molecule encircles and binds (attaches) to the metal and removes it from tissue (Smith, 2001). Depending on the drug used, chelating agents specific to the heavy metal involved are given orally, intramuscularly, or intravenously. Once the bound metal leaves the tissue, it enters the bloodstream, is filtered from the blood in the kidneys, and then is eliminated in the urine (Dupler 2001).

Chelating agents

(Dimercaprol)

BAL (British Anti Lewisite) is a chelating agent administered by injection in the treatment of acute poisoning by certain heavy metals (e.g., arsenic, Pb, mercury, gold, bismuth, and antimony). BAL has significant side effects that are frequent and include pain at the injection site, hypertension, tachycardia, abdominal pain, nausea, vomiting, headaches, burning sensation of the lips, excessive salivation, rhinorrhea, and tearing, fever, muscle pain, muscle spasms, a feeling of chest constriction, and profuse sweating. It is considered to be the most toxic of the chelating agents (Wentz, 2000).
DMSA (Di Mercapto Succinic Acid)

DMSA is an oral chelating agent and an analogue of BAL. DMSA is used in conjunction with or as an alternative to BAL for Pb and mercury toxicity. DMSA is less toxic than BAL, and it is sometimes substituted for BAL when the patient's condition improves. It is also used when intolerance to BAL develops. Although DMSA is similar to BAL, it has fewer and milder side effects (e.g., nausea, vomiting, diarrhea; rhinitis, cough, and rash). An interesting study on thiol chelating substances showed that DMSA was more effective than DMPS and SAMe (S-adenosyl methionine) in protecting mice from acute hepatic or renal toxicity caused by arsenic, and that all three substances were nontoxic to the liver or kidneys of mice (Tripathi et al., 1998).

DMPS (Di Mercapto Propane Sulfonate)

DMPS is another analogue of BAL. It has been shown to be less effective and to have more side effects than DMSA (Aaseth et al., 1995). DMPS is the drug of choice in Europe and Asia; however, the FDA has not approved DMPS for chelating purposes in the United States. It does, however, appear on the FDA list of drugs that appear to be safe. In the United States, DMPS is distributed to pharmacists in bulk form for compounding and dispensing in oral and injection forms (FDA, 1999; Marcus, 2001).

D-Penicillamine

D-penicillamine is an oral chelating agent used to treat heavy metal toxicity, particularly arsenic and mercury. Side effects are gastrointestinal intolerance, nausea and vomiting, and itchy skin (wheals). Contraindications are allergy to penicillin, possible interaction with other drugs (immunosuppressant, digoxin), severe blood disorders, kidney insufficiency, and pregnancy (USNML/NIH 2001d).

Deferoxamine
Deferoxamine is used to chelate Fe, especially in acute Fe poisoning in small children. It is also used to chelate aluminum. Common side effects are blurred vision, wheezing, rapid heartbeat, seizures, itching, skin rash, bluish skin, and redness and pain at the injection site (USNML/NIH 2001).

EDTA (Ethylene Diamin Tetra Acetic Acid, Edetate Disodium)

EDTA is one of the oldest chelating agents, came into prominence in the 1950s. Common side effects are gastrointestinal upset and headache. More serious side effects can include seizures, numbness or tingling in the hands and feet, irregular heartbeat, skin rashes and fever or chills (Ferner, 2001). EDTA is contraindicated in pregnancy and if there is kidney disease. It can also interact with insulin and heart medicines (USNML/NIH, 2001).

Antioxidants

Vitamin C: Vitamin C has long been recognized as having positive effects for the prevention of heart disease and some forms of cancer, improving immune function, maintaining healthy skin and blood vessels, accelerating healing, and reducing allergic reactions. A steady supply of vitamin C is vital to overall good health, because the human body cannot manufacture or store vitamin C. Therefore our requirements must be met from dietary sources, such as citrus fruit, vegetables, and supplements. Vitamin C is particularly beneficial for antioxidant protection for the lungs. It has been shown to protect the airways from inhaled (environmental) oxidants (Ghio et al., 1998). Additionally, researchers have shown that vitamin C can help reduce the harmful effects of Pb, aluminum, copper, silica, and radiation (Dhir et al., 1990; West et al., 1994; Ghio et al., 1998; Vij et al., 1998; Cai et al., 2001).

Vitamin E: Some of the benefits of vitamin E include synergy with vitamin A; reducing cellular aging; reducing the risk of Alzheimer's disease; protecting the nervous system; preventing abnormal blood clotting; lowering the risk of heart
disease (Pryor, 2000); protecting immune function; lowering the risk of certain cancers; and protecting the lungs from toxins and pollutants (West et al., 1994).

**Alpha-Lipoic Acid:** Alpha-lipoic acid is a potent free radical scavenger that has an ability to detoxify metals and regenerate other antioxidants, such as vitamins C and E, coenzyme Q10, and glutathione. Alpha-lipoic acid has also been used in the treatment of diabetes, heart disease, and other oxidant-related diseases. In a study by Gurer et al., (1999), lipoic acid improved the thiol capacity of cells by increasing glutathione levels and reducing malondialdehyde levels in Pb-exposed cells.

**Glutathione:** Glutathione is a tripeptide (chain of amino acids) that functions as a modulator of cellular homeostasis (the orderly status of cell life), including detoxification of oxyradicals and carcinogens. If glutathione is depleted, an organism can be predisposed to incur stress from pollutants (Ringwood et al., 2000). Glutathione and glutathione-related enzymes are important antioxidants. These enzymes appear to play an important role in detoxifying carcinogens (Chouchane et al., 2001; Lorico et al., 2002; Maiti et al., 2001). Glutathione status has also been shown to have an impact on the ability of the body to handle heavy metals such as Cd, Pb (Daggett et al., 1998; Wright et al., 1998), and mercury.

**Lactoferrin:** Lactoferrin, a natural component of cow and human milk, has well-documented antiviral, antimicrobial, anticancer, and immune modulating and enhancing effects. However, lactoferrin's best-known role is as an Fe-binding protein. Lactoferrin acts as an antioxidant, scavenging free Fe and helping to prevent uncontrolled Fe-based free radical reactions. Interestingly, although lactoferrin is both an Fe scavenger and donor (depending on the cellular environment), it has been found to scavenge or donate Fe appropriately depending on what the body needs at any given time. At normal physiological pH, lactoferrin binds tightly to Fe, diminishing oxidative stress to tissues (Brink, 2000).
Selenium and Zn: Deficiency of important antioxidant micronutrients like selenium and Zn, contributes to compromised immunity (Girodon et al., 1999) and lowered defense against free radicals (Porter et al., 1999; Schumacher 1999). Selenium and Zn act as cofactors of antioxidant enzymes to protect against oxygen free radicals produced during oxidative stress (Leung, 1998).

Herbs: Herbs and herbal extracts have been used for decades and studied for years, particularly in Europe and China (Huang, 1993). Many drugs commonly used in modern-day medicine have been derived either directly or indirectly from herbal origin. Herbs are often complexes (combined) to assist in blood purification and detoxification (e.g., dandelion root, yellow dock root, sarsparilla root, Echinacea, licorice root, etc.)

Garlic: Garlic has been valued for centuries for its medicinal properties. Research has shown that garlic can protect us from various pollutants and heavy metals (Cha, 1987). Some scientists speculate that garlic may protect against cancer by its ability to help the body to inactivate and eliminate cancer-causing substances without damage. The aged form of garlic (Kyolic) is organically grown and then harvested and aged to produce a mild, odour free garlic extract.

Essential Amino Acids: Amino acids are the basic chemical "building blocks" of life that are derived from dietary protein that is broken down into individual amino acids by the body. The body then reassembles the amino acids into new and vital structures that are essential to produce protein structures for genes, enzymes, hormones, body fluids, and neurotransmitters (Clayman, 1989). A deficiency in essential amino acids can negatively affect protein synthesis. Exposure to pollution, chemicals and agricultural pesticides are environmental sources that contribute to a deficiency of amino acids. L-cysteine and its acetylated form, N-acetyl-cysteine (NAC), act as antioxidants and liver protectants (Quig, 1998). When taking L-cysteine or NAC, administrating vitamin C will help to maintain their powerful free radical-suppressing effects.

Effect of nutrients on Pb toxicity
Calcium: Ca is one of the most important elements in the diet because it is a structural component of bones, teeth, and soft tissues and is essential in many of the body's metabolic processes. Approximately 99 percent of the body's Ca is stored in the bones and teeth (NIH, 2011). The rest of the Ca in the body has other important uses, such as some exocytosis, especially neurotransmitter release, and muscle contraction. On the cellular level, Ca is used to regulate the permeability and electrical properties of biological membranes (such as cell walls), which in turn control muscle and nerve functions, glandular secretions, and blood vessel dilation and contraction. Ca is also essential for proper blood clotting. The extracellular fluid (ECF) contains approximately 22.5 m mol, of which about 9 m mol is in the serum. Approximately 500 m mol of Ca is exchanged between bone and the ECF over a period of twenty-four hours (Marshall, 1995). Low Ca intake may also be a risk factor in the development of osteoporosis. In one meta-analysis, the authors found that fifty out of the fifty-two studies that they reviewed showed that Ca intake promoted better bone balance (Heaney, 2000).

Enhanced susceptibility to Pb intoxication in case of dietary Ca deficiency has been attributed to increased intestinal absorption (Mykkanen et al., 1981) and body Pb retention (Six et al., 1970). Ca and Pb compete for similar binding sites on intestinal mucosal proteins, which are important in the absorptive process. These shared binding sites on absorptive proteins would explain why sufficient dietary Ca decreases Pb absorption. A study by Six and Goyer (1970) has shown that rats fed a low Ca diet containing varying amounts of Pb had higher blood and tissue concentrations of Pb than rats fed a normal Ca diet. This study demonstrates that dietary Ca deficiency increases Pb concentration in critical organs. Other studies have also shown that absorption of Pb by the gastrointestinal tract is inversely related to dietary Ca (Farias et al., 1996).

Six and Goyer (1970) demonstrated that feeding a low Ca diet markedly increased the susceptibility of rats to the effects of Pb toxicity. The Pb-poisoned rats on the low Ca diet suffered elevated body burdens of Pb, more severe anemia, increased urinary excretion of δ-aminolevulinic acid, and a higher incidence of
renal intra nuclear inclusion bodies. A dose response study showed that rats fed a high Ca diet developed renal inclusion bodies only when they were given 200 mg Pb/ml of drinking water, whereas rats fed a low Ca diet developed inclusions when given as little as 12 μg Pb/ml (Mahaffey et al., 1973). Although the metabolic interrelationship of Pb and Ca has been the subject of numerous investigations, the mechanism by which low dietary Ca affects Pb metabolism is still not completely understood (Goyer, 1978). Barton et al., (1978) demonstrated that different levels of intra luminal Ca decreased the absorption of test doses of Pb from ligated loops of small intestine in a dose-related manner. The mechanism of this effect presumably was a competition between Pb and Ca for mucosal acceptor ligands. These results confirm those of Barltrop et al., (1976) who found that increased levels of Ca in perfusate media decreased the transfer of Pb across ligated gut loops. Meredith et al., (1977) showed that oral Ca administered immediately before Pb was highly effective in decreasing Pb absorption. Pb-Ca²⁺ interactions are of interest also in that a significant negative correlation has been reported between dietary Ca intake and the concentration of Pb in the blood of children (Rosen, sorrell 1977). Some nutrition surveys have indicated that certain population group of children exposed to Pb are likely to be deficient in Ca (Mahaffey, 1975). The Pb-Ca²⁺ relationship may also have implications with regard to the hypothesized public health hazards of drinking soft rather than hard water. The reversal effect of Pb due to Ca supplementation was observed in rats (Prasanthi et al., 2006). The reversal effect of Pb in Ca²⁺ supplemented rats is due to the competition between Pb and Ca²⁺ for gastrointestinal absorption and binding to active sites of the enzymes (Prasanthi et al., 2006).

Iron: Fe is one of the important nutrients as it is necessary for oxygen transport in the blood. It is the major nutrient present in hemoglobin. Other important proteins in the body that contain heme groups (and therefore contain Fe) include myoglobin, which takes oxygen from hemoglobin and allows the oxygen to diffuse throughout the muscle cells, and the cytochromes, which supply the body with its energy currency. Other proteins, such as those needed for DNA synthesis and cell division, also rely on Fe. Furthermore, Fe is used to help produce the
connective tissues in our body, some of the neurotransmitters in our brain, and to maintain the immune system. Hence, Fe is necessary for allowing the cells that need oxygen to obtain O₂, for supplying the body with a reliable source of energy, and for maintaining several other important structures and systems in the body (Lippard et al., 1994).

Increased Fe intake has also been suggested as one part of a multi-tiered approach to lessening Pb toxicity (CDC, 1997). Nutritional Fe deficiency and Fe deficiency during periods of rapid growth, such as infancy, in laboratory animals also enhance Pb absorption and promotes Pb toxicity. This is more evidence for concern that pregnant women and young children may be more susceptible to dietary Pb (Mahaffey, 1995). A negative relationship between dietary Fe intake and blood Pb levels was also found in a study of preschool children (Hammad et al., 1996). Several hematopoietic effects were noted in the Fe-deficient Pb-poisoned rats such as depressed hematocrits, elevated reticulocyte counts and a more severe hypochromic, microcytic anemia. The mechanism by which Fe deficiency potentiates Pb toxicity is not clear, but there are several metabolic pathways in which Fe/Pb interaction could occur. The effects of Pb and Fe on the heme biosynthetic pathways have been extensively investigated and characterized. Pb inhibits two major enzymes of the heme biosynthetic pathway: δ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase. Also, Kaplan et al., (1975) suggested that these two metals might compete directly for specific erythrocyte binding sites (Kaplan et al., 1975). Vanderkooi and Landesberg (1977) found that cytochrome C isolated from liver mitochondria of Pb intoxicated rats lacked Fe. Recently, Ragan has demonstrated a five-fold increase in the absorption of Pb in rats when body-Fe stores were reduced but before frank Fe deficiency was manifested (Ragan et al., 1977). The possible practical implications of Fe deficiency in human Pb poisoning have been commented upon several times (Lin-Fu et al., 1973), for the children that are most apt to be exposed to Pb are also likely to suffer from Fe deficiency.
**Zinc:** Zn has traditionally identified in biological literature as a trace element. The total Zn concentration in plasma is about 15μM, of which 3 to 5μM is tightly bound to α₂-Macroglobulin. The remainder is exchangeable about 9 to 11μM bound to albumin and 1μM to transferrin, only about 0.15μM is bound to low molecular weight components mainly to cysteine and histidine (Harris and Keen, 1989). Zn⁺² is a component of many enzymes and in many cells is bound to a storage protein, metallothionein.

Zn influences both tissue accumulation of Pb and susceptibility to Pb toxicity, particularly the inhibitory effects of Pb on δ-ALAD (Mahaffey 1995; Lauwerys et al., 1983; Victrey et al., 1987). Studies show that as dietary Zn increases, Pb absorption and its subsequent toxicity decrease, indicating that Zn exerts its effect on Pb in the gastrointestinal tract. A definitive study reported that as dietary Zn increased, the severity of Pb toxicity in the rat decreased (Cerklewski and Forbes, 1976). This antagonistic effect of Zn on Pb was thought to be due to its interference in Pb absorption since Zn did not affect urinary Pb excretion and injected Zn had no effect on Pb toxicity. These authors felt that the effect of Zn on Pb absorption was not likely due to formation of a Zn-Pb complex of low solubility. Rather, they hypothesized that Zn and Pb competed for similar binding sites on a metallothionein-like protein in the intestine responsible for metal transport.

Interactions between Zn and Pb are possible beyond the level of the gastrointestinal tract, however, since Zn added in vitro or given in vivo has been shown to activate the enzyme δ-aminolevulinic acid dehydratase and to prevent the inhibition of this enzyme by Pb (Haeger-aronson 1976, Finelli 1975). The enzyme δ aminolevulinic acid dehydratase (ALAD), involved in an early stage of heme synthesis, is dependent upon dietary Zn for its very synthesis (Finelli et al., 1974). It is itself a Zn metalloenzyme which is inactivated with exposure to Pb, and its activity can be restored both in vivo and in vitro by Zn (Abdulla and Haeger-Aronsen, 1974; Finelli et al., 1975). Thus disturbed heme synthesis could be restored by Zn.
Most epidemiological and experimental research describe the negative influence of Pb on neurological, behavioral, gastrointestinal, hematological, reproductive and immune systems (Reddy et al., 2003; El-Nekeety et al., 2009) and less documented on cardiovascular system. Even at low concentrations of blood levels significantly increase the risk of heart attacks, strokes and cardiovascular mortality (Menke et al., 2006). The toxic metal, Pb can target the cardiovascular system in a variety of ways, ranging from hemorrhagic injury to subtle pathogenic remodeling and metabolic changes. Chronic low level Pb exposure has been linked to hypertension and other cardiovascular disturbances in both clinical and experimental studies. In general, it can be concluded that Pb over a wide range of exposure intensities can induce significant changes in the function of the cardiovascular system. Blood parameters are probably the more rapid and detectable variations under stress and are useful in assessing the health conditions. Nutrient metals like Ca, Fe and Zn play an important role in reducing the Pb toxicity. Since the nutrient metals play an important role in the treatment of Pb poisoning, the present study was therefore aimed at investigating the potential of Ca, Fe and Zn nutrient metal mixture in countering Pb induced toxicity in the cardiovascular system of rats in age dependent manner.