JKIMSU, (2012), Vol. 1 (1) 6-23
ISSN 2231-4261

REVIEW ARTICLE

Future of Lead Chelation – Distribution and Treatment

Venkatesh Thuppil and Vasuki S Kaushik*
National Referral Centre for Lead Poisoning in India, Bangalore, 560034, (Karnataka), India

Abstract:

Lead is the major environmental toxin resulting in the ill health and deleterious effect on almost all organs in the human body in a slow and effective manner. The best treatment for lead poisoning is chelation therapy which is next only to prevention. The authors describe the disruption of homeostasis of the human body by lead in various tissues like blood, bones, liver, kidneys and brain; and the ability of lead to enter the cell using calcium channels and calcium receptors like Ca^{++} dependant K^{+} ion channels, transient receptor potential channels, T-tubules, calmodulin receptors, inositol trisphosphate receptors and ryanodine receptors. We report a few novel chelating agents like ionophores, decadentate ligands, picolinate ligands, octadentate ligand, allicin, thiamine, that show good potential for being used in chelation therapy. Future of lead poisoning is a challenge to all and it needs to be meticulously studies to have an economic and health approach.

Key Words:

Ca^{++} dependant K^{+} ion channels, Transient receptor potential channels · T-tubules, Calmodulin receptors, Inositol trisphosphate receptor, Ryanodine receptors, Ionophores, Decadentate ligands, Picolinate ligands, Octadentate ligand, Allicin, Thiamine

Introduction:

Lead is an element that is described to be purely toxic to all forms of life. Elements like manganese, selenium, nickel and molybdenum, although toxic at high levels, are actually required nutrients at lower levels. In the case of lead, no nutritional value or positive biological effect has been shown at even the lowest concentrations. Exposure to lead can produce a wide range of adverse health effects to all age groups. Both adults and children can suffer from the effects of lead poisoning, but childhood lead poisoning is much more frequent and severe because the damage done is irreversible. Despite an overall decrease in human exposure to lead in recent years, the potential for high intake of lead still exists in millions of homes and in many occupational places [1-5]. In India by the efforts of The National Referral Center for Lead Poisoning (NRCLP), there is a growing awareness of the health threat posed by lead, which has stimulated increased efforts to develop a detailed characterization of the biological behaviour of lead in humans. In order to effectively treat lead poisoning, one must understand the distribution of lead in different tissues, calcium channels and calcium receptors the lead uses to gain entry into a cell. This review paper covers the above mentioned aspects and some novel chelating agents that show potential in chelation therapy for lead poisoning.

Distribution of lead in different tissue

Lead enters the human body by inhalation, ingestion and skin absorption [6]. On entering the body, lead gains access to the circulatory

system. From here, it can move into various tissues [7]. An attempt to trace the movement of lead in blood, bones, liver, kidneys and brain is done in this review paper.

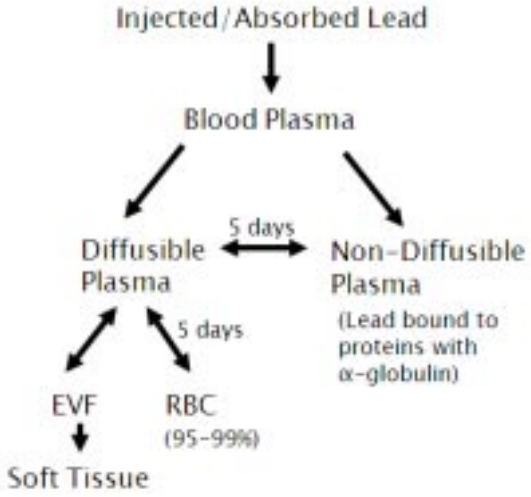
The total body burden of lead can be determined only by measuring the blood lead levels which is measured in micrograms of lead per deciliter of blood (ìg/dl). The US Centers for Disease Control and Prevention and the World Health Organization state that a blood lead level of 10 ìg/dl or above is a cause for concern; however, lead may impair development and have harmful health effects even at lower levels, and there is no known safe exposure level [8, 9]. The blood lead level is measured using Anodic Stripping Voltammetry (ASV) which is a sensitive and reproducible method for analysis of trace metal ions and Graphite Furnace Atomic Absorption Spectrometry (GFAAS) [10,11]. The Food and Drug Administration (FDA) has approved a portable blood lead analyzers called Lead Care II which is on par with GFAAS and ASV.

Blood (Fig. 1):

The pathways of lead in the blood first begin in the blood plasma. Under steady state most of the plasma lead is present bound to proteins with á-globulin [12, 13]. Blood plasma is classified into two distinct components, diffusible blood plasma and non-diffusible blood plasma [14, 15]. There is a gradual shift of a large portion of lead from diffusible to non-diffusible plasma protein. Lead absorbed into blood is said to be present in the diffusible plasma. From the diffusible plasma, part of the lead moves into RBCs and the other part moves into soft-tissues via extra vascular fluid [12, 13, 16]. A small portion of lead from diffusible plasma also moves into the protein bound non-diffusible plasma, which slowly returns back lead to the diffusible plasma to be replaced at a half-time of 5 days [16-19]. The maximum plasma lead is present in the non-diffusible plasma. Total plasma may contain less than 2% of blood lead.

RBC receives one-fourth of lead form diffusible plasma and RBC returns lead to diffusible blood plasma at a half-time of 5 days. [17, 19] RBC has high affinity for lead and contains 95-99% of entire blood lead. One-third of the lead absorbed by the body reaches the blood in 2-3 minutes of which three-fourth of blood lead is present in RBC [19-23]. Over the next week, lead is lost from the RBC with a net half-time of 15-20 days.

Fig. 1: Schematic representation of the distribution of lead in blood



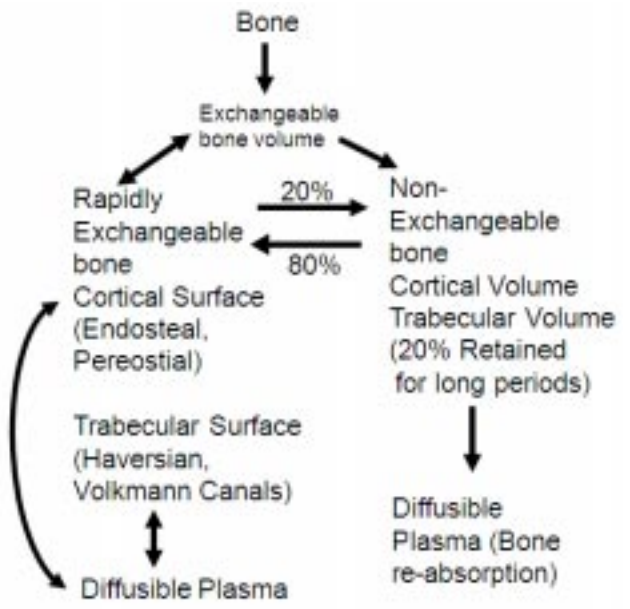
Lead moves from diffusible plasma to Extra Vascular Fluid (EVF) which in turn moves to the retention sites in the tissues in a time and concentration dependant process [14,15]. This movement of lead is treated as if it passed directly from the diffusible plasma to the retention sites in the tissue and therefore, in

effect, is regarded as passing instantaneously through the EVF [13, 16]. The EVF is three times the size of plasma pool and therefore, the EVF contains three times as much lead as diffusible plasma [18, 19].

Bone (Fig. 2):

There is a quantitatively similar behaviour between lead and alkaline earth metals like calcium to a great extent with regard to bone [18]. The model of lead distribution in bone proposed: 1) Bone is divided into four primary parts: cortical surface, cortical volume, trabecular surface, and trabecular volume. 2) The rapidly exchangeable material in bone is assumed to reside on bone surfaces, meaning endosteal and periosteal surfaces of cortical bone, surfaces of Haversian and Volkmann canals, surfaces of resorption cavities, and surfaces of trabecular bone. Bone surfaces do not include the surfaces of lacunae or canaliculi and should not be confused with the surfaces of the sub-microscopic bone crystals. 3) The more slowly exchangeable material in bone is assumed to reside in bone volume. 4) Long term loss from bone is associated primarily with bone resorption which occurs under hormonal influence in pregnant and lactating mothers [23, 24]. Cortical and trabecular bone volume are each viewed as consisting of two pools, referred to as the exchangeable and non-exchangeable pools respectively. The exchangeable bone volume pool is known to contain calcium like substances moving from bone surface to bone volume and are assumed to leave this pool with an element of specific half time [25-27]. Part of the lead leaving the exchangeable bone volume returns to the exchangeable bone surface and the other part enters the non-exchangeable bone volume from which the lead is removed to the diffusible plasma by bone resorption [28]. Rabinowitz suggested that not all bone lead is equally exchangeable with blood but has varying degrees of accessibility until penetrating the crystal surface, after which it becomes firmly buried and must await osteoclastic turnover [29]. The concentration of lead is initially much higher in trabecular than cortical bone. There is four times as much cortical bone as trabecular bone by mass in the skeletal system and the rate of transfer of lead from diffusible plasma to trabecular surface is five-fourth times higher than that in cortical surface [25]. It is interesting to note that 20% of lead entering bone volume is retained for a long period of time. Around 20% of lead leaving the exchangeable bone volume moves to non-exchangeable bone volume and 80% of that returns to the bone surface [28].

Fig. 2: Schematic representation of distribution of lead in bone

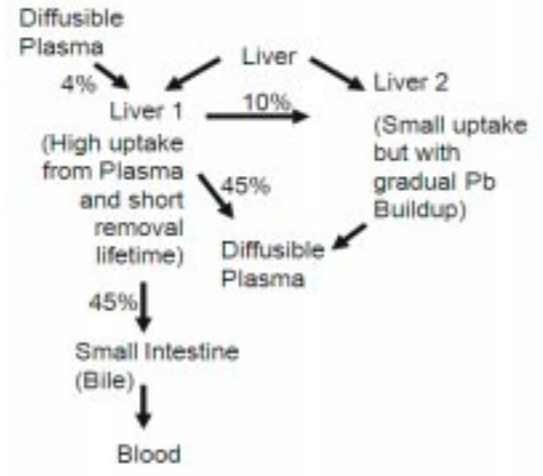


Liver (Fig. 3):

The liver is known to rapidly accumulate 10-15% of systemic lead on absorption and loses most of the lead within a week [30-34]. This is a time bound activity which is important in understanding the process of lead chelation. Liver is viewed as consisting of 2 compartments: Liver 1 which has high lead uptake from plasma and short half-time, Liver 2 which has low lead uptake but with high retention time it gradually builds up lead content over time [35,36].

Of all the lead entering the liver from the diffusible plasma, around 4% gets deposited in liver 1 and the removal half-time from liver 1 is 10 days. 45% of the lead from liver 1 enters the small intestine as biliary secretions, another 45% returns to the diffusible plasma and 10% of the lead in liver 1 is transferred to liver 2 where it is stored for a long time where the removal half-time is about 1 year. All the lead leaving the diffusible plasma is assumed to return to the diffusible plasma over time. Liver may contain 2-3% of total body lead [37, 38].

Fig. 3: Schematic representation of distribution of lead in liver

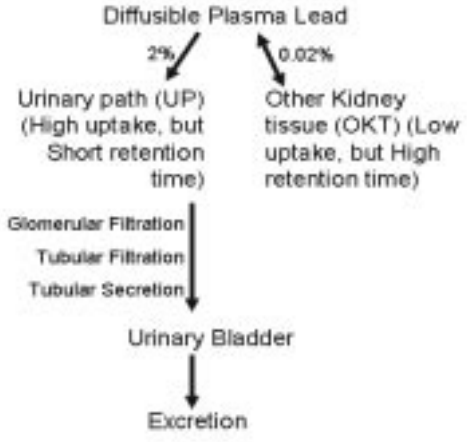


Kidney (Fig. 4):

15-20% of lead from the exchangeable blood plasma enters the kidney within 1-2 hours. A substantial amount of the lead that enters the kidney is excreted as urine or reabsorbed into the blood within a few hours [39, 40]. Comparison of the decline of renal and hepatic activity over the first two months indicates a half-time in the kidneys that would be roughly one-half of that in the liver [41]. The kidney is viewed as containing two compartments, urinary path and the other kidney tissue. The urinary path has relatively high lead deposition but short retention time. The other kidney tissue has relatively low lead deposition but high retention time.

Both these compartments receive lead from the blood plasma. Lead in the urinary path compartment moves to the urinary bladder. Lead goes through glomerular filtration, tubular absorption and tubular secretion after which it is excreted [42]. Around 2% of plasma lead is said to enter the urinary path compartment and 0.02% of plasma lead enters the other kidney tissue which has tenacious lead retention ability. The removal half-time from the other kidney tissue to the diffusible plasma is about 1 year.

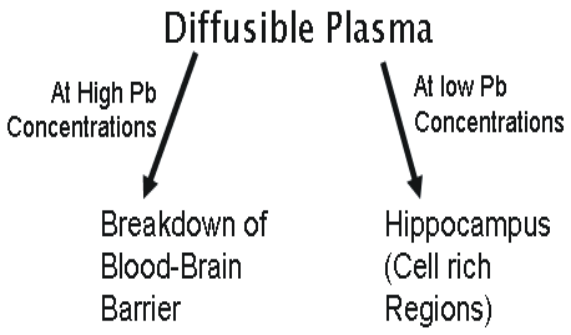
Fig. 4: Schematic representation of distribution of lead in kidney



Brain (Fig. 5):

The brain was treated as a single compartment, but now treated as distinct compartments. This organ is extremely sensitive to lead toxin. Lead is distributed unevenly in the brain, which depends on the amount of lead exposure. At low levels, the lead concentration in different regions of the brain is significantly correlated with the potassium concentrations, indicating that lead is mostly accumulated in the cell rich parts of the brain like the hippocampus [43-45]. Lead that enters the cell gets accumulated in the mitochondria and in calcium rich centers. At very high concentrations of lead, there is change in blood-brain barrier and lead enters neuronal tissue. In young children with high lead poisoning, sometimes the lead concentration in the brain even exceeds that of liver and kidneys. The brain has low lead uptake capacity, but it has high tenacious lead retention capacity [46]. The brain can accumulate up to 0.1% of body lead with a half-time of 2 years for children and up to 0.15% in adults with a half-time of 6 months.

Fig. 5: Schematic representation of distribution of lead in brain



Lead entering a cell:

Lead shows the ability to mimic calcium and the accumulation of lead is generally seen in the area where calcium concentrations are high. This lead to the discovery that lead enters a cell through calcium channels & calcium receptors which are found abundantly throughout the surface of every cell in every tissue.

Ca^{++} dependent K^{+} channel:

Calcium activated potassium channels are a family of ion channels which are activated by voltage or intracellular Ca^{++} ion [47]. They are present in all types of cells where they are involved in a multitude of physiological functions. They are tetrameric integral membrane proteins forming transmembrane aqueous pores through which K^{+} specifically permeates. The most fundamental task carried out by all K^{+} ion channels is to catalyze the rapid permeation of K^{+} ions while rejecting biologically abundant potential competitors like Na^{+}, Ca^{++}, Mg^{++} [47-49]. This process is called membrane hyperpolarization. Through these channels Pb^{++} may also gain entry into a cell where they cause disruption in normal functioning. These channels are essential for many biological processes such as smooth muscle contraction and neurotransmitter release. When Pb^{++} gains entry, all these biological processes may get affected.

Transient Receptor Potential Channels:

Transient Receptor Potential (TRP) Channels is a group of channels present on the plasma membrane of all types of cells. These receptors are essential for the biological

sensory processes like pain, hot, cold, pressure, taste and vision. These channels are non-selectively permeable to cations like sodium, calcium, magnesium [50]. Transient Receptor Potential Vanilloid (TRPV) is a family of transient receptor channels which are selectively permeable to calcium and magnesium over sodium. TRPV ion channels are tetrameric in structure and are either homo-tetrameric or hetero-tetrameric [49-51]. Pb^{++} ions also gain entry into a cell through the TRP receptors which then accumulate in the mitochondria and other cell organelles to hamper the biological functioning of the cell and eventually cause cell death.

T-tubules:

These are deep invaginations of the sarcolemma which is the plasma membrane in the skeletal and cardiac tissue cells. They allow propagation of action potential to the cell interior allowing spatially and temporally synchronous Ca^{++} release throughout the cell. T-tubules are not simple invaginations; many of the key proteins involved in excitation-contraction coupling are located predominantly at the t-tubules, which suggests that they play a specialized and important role in Ca^{++} handling and excitation-contraction coupling [52]. The sarcolemma invaginates perpendicular to the length of the muscle and skeletal fiber to form what is called a T-tubule. At these invaginations, the sarcolemma is studded with a large number of calcium channels. It is physiologically important for excitation-contraction coupling that the T-tubules are positioned close to the terminal cisternae of the sarcoplasmic reticulum as the triad or diad arrangement (T-tubule association with cisterne) allows physical and functional contact by voltage dependent calcium channels. So, an action potential along the sarcolemma causes calcium channels to open in the terminal cisternae/ sarcoplasmic reticulum which enables calcium to move from the sarcoplasmic reticulum into the cytoplasm and the intracellular calcium concentration to increase. Lead ion gains entry onto the cell through the same calcium channels that the calcium ion uses.

T-tubules are the major sites for the coupling of excitation and contraction, which is the process whereby the spreading depolarization is converted into force production by muscle fibers. The calcium channels in the T-tubules activate in response to the electrical stimulation; their opening allows calcium to flow down its electrochemical gradient and into the cell. Activation of the channel also causes a mechanical interaction between it and calcium-release channels located on the adjacent sarcoplasmic reticulum membrane. In skeletal muscle, the influx of calcium through the calcium channel on the T-tubule contributes little to excitation-contraction coupling, whereas it is crucial to the proper function of cardiac muscle. Conversely, the mechanical interaction between the T-tubule's calcium channel and the calcium-release channel is critical to proper skeletal muscle contraction, whereas it contributes little to the contraction of cardiac muscle [53, 54].

Calmodulin Receptors:

Calmodulin (CaM) is a ubiquitous calcium

binding protein expressed in eukaryotic cells. These can bind to and regulate a multitude of different protein targets, thereby affecting many different cellular functions such as inflammation, metabolism, apoptosis, muscle contraction, intracellular movement, short-term and long-term memory, nerve growth and the immune response. Many of the proteins that CaM binds are unable to bind calcium themselves, and as such use CaM as a calcium sensor and signal transducer. CaM can also make use of the calcium stores in the endoplasmic reticulum, and the sarcoplasmic reticulum [55-57]. CaM undergoes a conformational change upon binding to calcium, which enables it to bind to specific proteins for a specific response. CaM can bind up to four calcium ions, and can undergo post-translational modifications, such as phosphorylation, acetylation, methylation and proteolytic cleavage, each of which can potentially modulate its actions [57]. Increased calcium concentrations lead to calcium binding by regulatory proteins, which can turn the calcium signal into a biological response. There are many such regulatory proteins that bind calcium, which together form an intricate network of feedback loops to control the location, amount and effect of calcium influx. Calmodulin is one such calcium-binding protein that is considered a major transducer of calcium signals [55-57]. If lead binds to calmodulin instead of calcium, then all the above mentioned vital biological process are hampered.

Inositol Trisphosphate Receptor:

Inositol trisphosphate receptor (InsP3) is involved in the regulation of numerous processes, including transepithelial transport, learning and memory, muscle contraction, membrane trafficking, synaptic transmission, secretion, motility, membrane excitability, gene expression, cell division, and apoptosis. It involves the activation of phospholipase C. This phospholipase C hydrolyzes the membrane lipid phosphatidylinositol 4, 5-bisphosphate, generating inositol 1, 4, 5-trisphosphate (InsP3). InsP3 diffuses in the cytoplasm and binds to its receptor (InsP3R), which is an intracellular ligand-gated Ca^{++} release channel localized primarily in the endoplasmic reticulum (ER) membrane. The ER is the major Ca^{++} storage organelle in most cells [58]. Upon binding InsP3, the InsP3R is gated open, providing a pathway for Ca^{++} to diffuse down this electrochemical gradient from the ER lumen to cytoplasm [59]. Pb^{++} when present in the medium can also diffuse down this electro-chemical gradient and enter the cytoplasm. The distribution and concentrations of Ca^{++} binding proteins and the release channels, as well as the complex properties of the release channels, enable InsP3R-mediated Ca^{++} ion signals to have diverse spatial and temporal properties that can be exploited by cells, making this signaling system remarkably robust. Consequently, despite its expression in probably all cells in the body, this signaling system can provide specific signals that regulate diverse cell physiological processes [58-60].

Ryanodine Receptor:

These are a class of intracellular calcium channels seen in muscles and neurons. Ryanodine Receptor (RyR) corresponds to the Sarcoplasmic Reticulum (SR) Ca^{++} channel, but also seen on other organelles. The channel in the RyR is a cation-selective channel with low cation selectivity with Ca^{++} having high permeability, but, Pb^{++} ions can use the same calcium ion channel [61]. The RyR mediates the efflux of Ca^{++} from the SR or other intracellular stores. It has a central role in excitation-contraction coupling between sarcolemmal depolarization and SR Ca^{++} release. The sarcolemmal depolarization produces a conformational change in the dihydropyridine receptor that is transmitted to the RyR and this induces the release of Ca^{++} from the SR. Alternatively, excitation-contraction coupling might be mediated by a process known as Ca^{++} induced Ca^{++} release. As the SR channel is activated by an increase in cyosolic Ca^{++} ions, the sarcolemmal Ca^{++} current could induce further release of Ca^{++} from the SR. This process may be favoured by the existence of Ca^{++} gradients in the cytosol, because Ca^{++} ions entering the cell through the dihydropyridine receptor seem to have preferential access to the RyR [61, 62].

Chelating agents:

Chelating agents are divided into Prophylactic chelators and Therapeutic chelators. Prophylactic chelators are mainly used as a preventive treatment using natural chelating agents to avoid lead poisoning. Therapeutic chelating agents are used as treatment using synthetic chelating agents or derivatives of natural chelating agents which are used after the conformation of the diagnosis of lead poisoning. There is continuous development in the field of chelation therapy; therefore there is a constant change in the dosage and mode of administration of these chelating agents. For example, administration of $CaNa_2EDTA$ as rectal suppositories has been successful in decreasing lead concentration in the brain and prostrate [63]. Prophylactic chelators are mostly naturally available, garlic, cloves and cilantro leaves consumed raw, chlorella, single celled green algae is also known to reduce lead content in the body [64,65,66]. Vitamin C, tea and Indian gooseberry mainly act as antioxidants which help in combating the reactive oxygen species generated due to lead poisoning [67, 68, 69]

New chelating agents:

Today the best treatment for lead poisoning is chelation therapy. Over the years many chelating agents have been used successfully to treat lead poisoning. For example, $CaNa_2EDTA$, Succimer (meso-DMSA) Dimercaprol (BAL), Unithiol (DMPS), D- penicillamine (DPA) and many more. In this review paper, we cover the new and emerging lead chelating agents, most of which are still under study. These show good potential to be used in chelation therapy to treat lead poisoning.

Ionophores:

Chelating agents bind to plasma lead but cannot cross the cell membranes where the total body lead burden lies. Some ionophores have been shown to transport lead across the

cell membrane providing a novel method for reducing body burden of lead [70,71]. Pyrithione (N-hydroxypyridine-2-thione), a zinc ionophore along with some 8-hydroxyquinoline derivatives has been found to reduce lead content in erythrocytes. Water soluble Sodium pyrithione was found to reduce lead in whole blood without partitioning into the erythrocytes [71]. Monensin, a sodium ionophore is found to be selective in transporting Pb (II) into model phospholipid bilayer vesicles, while it does not transport other divalent cations. Administration of monensin, in combination with the chelating agent DMSA, produce reduced lead levels in liver, kidney, brain, femur, heart, and skeletal muscle. This occurrs while the levels of endogenous metals such as Ca(II), Mg(II), and Zn(II) were relatively unchanged. Salinomycin, and Lasalocid are other ionophores. They have also shown to reduce body lead burden. Ionophores may prove useful in mobilizing lead into the extra cellular spaces, thereby improving the efficiency of chelation therapy using DMSA [72].

Macrocyclic decadentate ligands:

Chelation of heavy-metals using macrocyclic decadentate N,N-Bis[(6-carboxy-2-pyridil) methyl]-1,13-diaza-18 crown 6. This ligand is found to be highly suited for the complexation of large metal ions like Pb (II) and Sr (II) in aqueous solution. This results in very high Pb (II) /Ca (II) and Pb (II) / Zn(II) selectivity and the highest Sr (II) / Ca(II) selectivity reported so far. The Pb(II) ion is endocyclically coordinated, being directly bound to the 10 donor atoms of the ligand. The structure of the complex observed is the so-called hemidirected compound, in which the Pb(II) lone pair is stereochemically active. It shows promise for application in chelation treatment of metal intoxication by Pb(II) and Sr(II) [73].

Picolinate ligand:

Picolinate ligand designed to accommodate the Pb(II) ion pair leading to high stability and selectivity. The crystal structure of the lead complexes of the diprotonated and monoprotonated tripodal ligand coordinate the lead in an asymmetrical way leaving a gap in the coordination sphere to accommodate the lead lone pair. The geometry of the dipodal ligand is designed to accommodate the lead lone pair in the structure of the complex. The donor atoms of the ligand occupy only a quarter of the coordination sphere, reducing the sterical interaction between the lead lone pair with respect to the tripodal complexes. As a result, in the lead structures of dipodal complexes all the ligand donor atoms are strongly bound to the metal ion leading to increased stability. A remarkable increase in the Pb/Ca selectivity is observed for dipodal ligand compared to tripodal ligand, making the dipodal ligand a good candidate for application as lead chelating agent [74].

Octadentate ligands:

Chelation of heavy-metals using octadentate ligands containing pyridine carboxylate and pyridil pendants. The coordination properties toward Cd(II), Pb(II), Ca(II), and Zn(II) of a new octadentate ligand (py-H2bcpe) based on a ethane-1,2-diamine unit containing two picolinate and two pyridyl pendants. This ligand

shows good Pb(II)/Ca(II) and Cd(II)/Ca(II) selectivities., which increases complexation with the heavy metal. This ligand can be considered as a new structural framework for the design of novel Cd(II) and Pb(II) extracting agents. The stabilities of the Cd(II) and Pb(II) complexes are higher than those of the corresponding EDTA analogues. The Zn(II) complex is six-coordinated, while the Pb(II) complexes are eight-coordinated [75].

Allicin:

Allicin [2-Propene-1-sulfinothioic acid S-2-propenyl ester] is an active compound present in Garlic which reduces lead toxicity in the body [76]. The high permeability of the compound enhances intercellular interactions. It does not induce leakage, fusion or aggregation of membrane. Crude garlic (Allium sativum) extracts contain antioxidants that combat against the Reactive Oxygen Species (ROS) generated because of lead. The antioxidant activity of garlic is attributed to biologically active lipophilic sulfur-bearing compounds such as allicin, S-allyl-cysteine (SAC), diallyl-di-sulphde (DADS), and diallyl-sulphde (DAS) and these compounds can easily permeate through phospholipid membranes and reduce intracellular lead [64,77,78]. Allicin treatment reduced lead retention in both blood and tissues. It is known to reduce blood, liver, kidney, bone and ovary lead considerably. The reduction of lead concentration in blood and tissues is dose dependant. There are also reports of reduced zinc concentration in the liver. Garlic extracts also have anticarcinogenic, hypolipidemic, hypoglycemic, antiathero-sclerotic, antibacterial and antifungal properties [79].

Thiamine:

Thiamine considerably reduces ovary lead content. Lead interacts with the pyrimidine ring of thiamine, leading to its solubilization and thereby prevention of its accumulation and clearance form tissues at physiological pH. The mechanism by which this occurs is speculated to be lead chelation. However, the exact nature of the interaction is not very clear [80]. A combination treatment of Thiamine and Ascorbic acid (Vitamin C) has been effective in reducing lead induced inhibition of delta amino leavilinic acid dehydratase in blood and also effective in inhibition of uptake of lead by kidneys, liver and blood. The order of effectiveness is Thiamine > Ascorbic acid > Thiamine + Ascorbic acid. However, the ALAD levels in blood show improvement in the presence of Ascorbic acid [81]. Thiamine is also known to reduce lead content form blood, kidney and bone. Interestingly, thiamine appears to prevent accumulation of lead in bone during treatment [67]. Thiamine also increases urinary excretion of lead.

Table-1: Therapeutic chelating agents used to treat lead poisoning

Chelating Agent	Minimum blood Lead levels(µg/dL) required for usage of drug	Dosage	Duration	Mode of application	Contraindications
Dimercaprol (BAL)	50 – 60	4mg/ kg. Every 4 hours for 48 hours. Then every 6 hours for 48 hours. Then every 6 – 12 hours for 7 days [82, 83].	11 Days	Intramuscular injection [82,83].	Instances of hepatic and renal insufficiency with the exception of post arsenical jaundice. Known hypersensitivity to peanuts [84].
Dimercapto-succinic acid (DMSA)	45-60	10mg/kg every 8hours for 5 days. Then every 12 hours for 2 weeks [85, 86].	19 Days	Orally [86]	Not given to patients with advanced hepatic or renal failure. Hypersensitivity to the drug [85]
Dimercapto-propane sulfonate (DMPS)	45-55	10 - 30 mg/kg BW per day, administered as 6 to 8 individual doses of 3-5 mg/kg, every 3-4 hours [87]	Treatment is continued until the heavy metal concentrations in the blood and urine are below the limit values [87]	Intravenous [87]	Not used in the presence of hypersensitivity to DMPS or its salts. Special care is required on injection of DMPS in patients with allergic asthma symptoms [87]
D-Penicillamine	50-60	20–30 mg/kg daily [83]	Till heavy metal concentrations are below the limit values [83,88,89]	Orally [88,89]	Not administered during Pregnancy, lactation, Caution is advised if there is a prior evidence of Cystinuria, Wilson's disease, Lupus erythematosus, Thrombocytopenia, agranulocytosis [83,88,89]
Ethylenediamine tetraacetic acid (calcium disodium versante) ($CaNa_2$-EDTA)	25 - 45	25 – 75mg/ kg/ day Should not exceed a total dose of 500 mg/ kg [89-91]	5 Days [89-91]	Intramuscular injection, intravenous infusion, oral or rectal suppositories [63, 89-91]	Anuria, Active renal disease, Hepatitis [91]

N-Acetyl-L-Cysteine (NAC)	45 - 50	600-1500 mg daily in 3 divided doses. However, doses of 70-140 mg/kg per day may be used to treat acetaminophen poisoning [92].	No limit as it is also an amino acid supplement	Orally [92]	Not administered to patients with organ transplant. Caution is advised in presence of stomach ulcers [92]

Conclusion:

The growing population and rapidly changing environmental conditions result in the higher usage of lead in various sectors and the possible exposure to living organisms results in growing environmental pollution. The usage of lead in day to day life has increased and the existing high concentrations of lead in the environment are gaining entry into the human system through various means. As awareness about lead and its harmful effects is so less among people, the symptoms of lead poisoning are misunderstood and misdiagnosed and misinterpreted. Some of the traditional medications of different cultures have been found to contain lead. This is a cause of worry as most people in the rural and some people in the urban areas are still dependant on the traditional folk medications. It is our responsibility as researchers to educate the general population and health care provides on this life threatening issue and take some important steps for the betterment of society. This sense of responsibility has led a lot of researchers to explore the new horizons in search of effective chelating agents to combat lead poisoning. This has led to the discovery and development of so many new lead chelating agents, some of which have been documented in this review paper. When awareness is not taken seriously and prevention fails, specific and targeted chelation is required. This is the future of chelation therapy where small, specific and targeted medications are required which will be a faster and safer means of chelation. Is it possible to develop drugs which act as carriers to deliver chelating agents to specific organs and act in a way where there is no re-distribution of the chelated lead to other organs!

References:

1. Richard W, Leggett. An age-specific kinetic model of lead metabolism in humans. *Environmental Health Perspectives* 1993; 101(7): 598-616.
2. Geraldine M, Herman SD, Venkatesh T. Chronic lead poisoning in an adult battery worker. *Occup Med* 2003; 53: 476–478.
3. Warren MJ, Cooper JB, Wood SP, Shoolingin-Jordan PM. Lead poisoning, haem synthesis and 5-aminolevulinic acid dehydratase. Trends in Biochemical sciences 1998; 23: 217-221.
4. Ogata A, Sueta S, Tagawa M, Nihon Jinzo Gakkai Shi. Case of lead nephropathy due to chronic occupational lead exposure.

Nihon Jinzo Gakkai Shi 2011; 53(2): 207-211.
5. Callan AC, Hinwood AL. Exposures to lead. *Rev Environ Health* 2011; 26(1): 13-25.
6. Barltrop D, Meek F. Absorption of different lead compounds. *Postgraduate Medical Journal* 1975; 51: 805-809.
7. Rabinowitz MB, Wetherill GW, Kopple JD. Kinetic analysis of lead metabolism in healthy humans. *J Clin Invest* 1976; 58: 260-270.
8. Wright JP, Dietrich KN, Douglas Ris M, Hornung RW, Wessel SD, Lanphear BP *et al*. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med* 2008; 5(5): e101.
9. Raymond JS, Anderson R, Feingold M, Homa D, Brown MJ. Risk for elevated blood lead levels in 3- and 4-year-old children. Maternal and child health journal 2009; 13(1): 40-47.
10. Vishwanath P, Prashant A, Devanand D, Nayak N, D'souza V, T Venkatesh. Screening of school children for blood lead levels and attempts to reduce them by nonpharmacological means in a coastal city of India. *Indian J Med Sci* 2008; 62: 185-92.
11. Huo X, Peng L, Xu X, Zheng L, Qiu B, Qi Z *et al*. Elevated blood lead levels of children in guiyu, an electronic waste recycling town in China. *Environ Health Perspect* 2007; 115(7): 1113–1117.
12. Chamberlain AC, Heard MJ, Little P, Newton D, Wells AC, Wiffen RD. Investigations into lead from motor vehicles. AERE-R 9198. Oxon, UK: Harwell. 1978:151.
13. Heard MJ, Chamberlain AC. Uptake of lead by human skeleton and comparative metabolism of lead and alkaline earth elements. *Health Phys* 1984; 47:857-865.
14. Griffin RM, Matson WR. The assessment of individual variability to trace metal insult: low molecular-weight metal complexing agents as indicators of trace metal insult. *Am Ind Hyg Assoc* 1972; 33:373-377.
15. Booker DV, Chamberlain AC, Newton D, Stott ANB. Uptake of radioactive lead following inhalation and injection. *Br J Radiol* 1969; 42:457-466.
16. Wells AC, Venn JB, Heard MJ. Deposition in the lung and uptake to blood of motor exhaust labeled with Pb-203. In: Inhaled particles IV, Proceedings of a symposium of the British Occupational Hygiene Society, (Walton WH, McGovern B, eds). Oxford: Pergamon Press 1975; 175-189.
17. Stover BJ. Pb (ThB) tracer studies in adult beagle dogs. *Proc Soc Exp Biol Med* 1959; 100: 269-272.
18. Hursh JB, Suomela J. Absorption of Pb-212 from the gastrointestinal tract of man. *Acta Radiol Ther Phys Biol* 1968; 7: 108-120.
19. Morrow PE, Beiter H, Amato F, Gibb FR. Pulmonary retention of lead, an experimental study in man. *Environ Res* 1980; 21: 373-384.
20. Rabinowitz MB, Wetherill GW, Kopple JD. Studies of human lead metabolism by use of stable isotope tracers. *Environ Health Perspect* 1974; 7: 145-153.
21. Araki S, Aono H, Yokoyama K, Murata K.

Filterable plasma concentration, glomerular filtration, tubular balance, and renal clearance of heavy metals and organic substances in metal workers. *Arch Environ Health* 1986; 41: 216-221.

22. Simons TJB. Lead-calcium interactions and lead toxicity. In: Handbook of Experimental Pharmacology, Berlin: Springer-Verlag, 1988; 83: 509-525.
23. Leggett RW. A generic age-specific biokinetic model for calcium-like elements. *Radiat Prot Dosim* 1992; 41: 183-198.
24. International Commission on Radiological Protection. Alkaline earth metabolism in adult man. ICRP Publication 20. Oxford: Pergamon Press; 1973.
25. Norrdin RW, Arnold JS. Comparison of Ca accumulation in samples of trabecular and cortical bone and its retention in ribs, humerus, and femur. In: Bone histomorphometry Uee WSS, Parfitt AM, eds). Paris: Societe Nouvelle de Publications Medicales et Dentaires 1980; 499-500.
26. Batuman V, Wedeen RP, Bogden JD, Balestra DJ, Jones K, Schidlovsky G. Reducing bone lead content by chelation treatment in chronic lead poisoning: an in vivo x-ray fluorescence and bone biopsy study. *Environ Res* 1989; 48: 70-75.
27. Bobby R, Scott. Health Risk Evaluations for Ingestion Exposure of Humans to Polonium-210, Dose Response 2007; 5(2): 94–122.
28. Rabinowitz MB. Toxicokinetics of bone lead. *Environ Health Perspect* 1991; 91: 33-37.
29. Aub JC, Robb GP, Rossmeisl E. Significance of bone trabeculae in the treatment of lead poisoning. Lead studies XVII. *Am J Public Health* 1932; 22: 825-830.
30. Thomas PA, Fisenne I, Chorney D, Baweja AS, Tracy BL. Human absorption and retention of Polonium-210 from caribou meat, radiation protection dosimetry 2001; 97(3): 241-250.
31. Hamilton El, Minski MJ, Cleary JJ. The concentration and distribution of some stable elements in healthy human tissues from the United Kingdom. *Sci Total Environ* 1972; 1: 341-374.
32. Gross SB, Pfitzer EA, Yeager DW, Kehoe RA. Lead in human tissues. *Toxicol Appl Pharmacol* 1975; 32: 638-651.
33. Barry PSI. A comparison of concentrations of lead in human tissues. *Br J Ind Med* 1975; 32: 119-139.
34. Barry PSI. Concentrations of lead in tissues of children. *BrJ Ind Med* 1981; 38: 61-71.
35. Iyengar V, Woittiez J. Trace elements in human clinical specimens: Evaluation of literature data to identify reference values. *Clin Chem* 1988; 34: 474-481.
36. Ishihara N, Matsushiro T. Biliary and urinary excretion of metals in humans. *Arch Environ Health* 1986; 41: 324-330.
37. Quinlan GJ, Halliwell B, Christopher P, Moorhouse, John MC, Gutteridge. Action of lead(II) and aluminium(III) ions on iron-stimulated lipid peroxidation in liposomes, erythrocytes and rat liver microsomal fractions. *Biochimica et Biophysica Acta* (BBA) - Lipids and Lipid

Metabolism 1988; 962(2): 196-200.
38. Mallon RP. A metabolic model of lead kinetics based upon measured organ burdens during chronic exposure experiments with infant and juvenile baboons (dissertation). New York, New York University; 1983.
39. Victery W, Vander AJ, Mouw DR. Effect of acid-base status on renal excretion and accumulation of lead in dogs and rats. *Am J Physiol* 1979; 237: 398-407.
40. Keller CA, Doherty RA. Distribution and excretion of lead in young and adult female mice. *Environ Res* 1980; 21: 217-228.
41. Morgan A, Holmes A, Evans JC. Retention, distribution, and excretion of lead by the rat after intravenous injection. *Br J Ind Med* 1977; 34: 37-42.
42. Victery W, Vander AJ, Mouw DR. Renal handling of lead in dogs, stop-flow analysis. *Am J Physiol* 1979; 237: 408-414.
43. Grandjean P. Regional distribution of lead in human brains. *Toxicol Lett* 1978; 2: 65-69.
44. Dou C, Zhang J. Effects of lead on neurogenesis during zebrafish embryonic brain development. *J Hazard Mater*; 2011 [Epub ahead of print].
45. Petit TL, Alfano DP, LeBoutillier JC. Early lead exposure and the hippocampus, a review and recent advances. Neurotoxicology 1983; 4: 79-94.
46. Zoeger N, Streli C, Wobrauschek P, Jokubonis C, Pepponi G, Roschger P *et al*. Elemental mapping in slices of human brain by SR-ìXRF. JCPDS - International Centre for Diffraction Data, Advances in X-ray Analysis 2005; 48: 284-289.
47. Wu Y, Yang Y, Sheng Y, Jiang Y. Structure of the gating ring from the human large-conductance Ca2+-gated K+ channel. Nature 2010; 466: 393-397.
48. Miller C. An overview of potassium channel family. Genome Biology 2000; 1(4): Reviews0004.1–Reviews0004.5.
49. Jiang Y, Pico A, Cadene M, Chait BT, MacKinnon R. Structure of the RCK domain from the E. coli K1 channel and demonstration of its presence in the human BK channel. Cell Press 2001; 29: 593-601.
50. Clapham DE, Julius D, Montell C, Schultz G. Nomenclature and structure-function relationships of transient receptor potential channels. *Pharmacol* 2005; 57(4): 427–50.
51. Vennekens R, Owsianik G, Nilius B. Vanilloid transient receptor potential cation channels: an overview. *Curr Pharm* 2008; 14(1): 18–31.
52. Brette F, Orchard C. Resurgence of cardiac T-tubule research. Physiology 2007; 22: 167-173.
53. Brette F, Despa S, Bers DM, Orchard CH. Spatiotemporal characteristics of SR Ca2+ uptake and release in detubulated rat ventricular myocytes. *J Mol Cell Cardiol* 2005; 39: 804–812.
54. Hong TT, Smyth JW, Gao D, Chu KY, Vogan JM, Fong TS *et al*. BIN1 localizes the L-type calcium channel to cardiac T-tubules. *PLoS Biol* Feb 2010; 16; 8(2):e1000312.
55. Dutta S, Goodsell D. Calmodulin Structure, RSCB Protein Data Bank; 2003.
56. Yap KL, Kim J, Truong K, Sherman M, Yuan T, Ikura M. Calmodulin Target Database. *J Struct Funct Genomics*, Ontario Cancer

Institute, University of Toronto 2008; 1: 8-14.
57. Anita Lewit-Bentley, Réty S. EF-hand calcium-binding proteins. Current Opinion in Structural Biology 2000; 10(6) (1): 637-643.
58. Bosanac I, Alattia JR, Mal TK, Chan J, Talarico S, Tong FK *et al*. Structure of the inositol 1,4,5-trisphosphate receptor binding core in complex with its ligand. Nature 2000; 420(6916): 696-700.
59. Foskett JK, White C, Cheung KH, Mak DO. Inositol trisphosphate receptor Ca2+ release channels. *Physiol Rev* 2007; 87(2): 593-658.
60. Bosanac I, Yamazaki H, Matsu-Ura T, Michikawa T, Mikoshiba K, Ikura M. Crystal structure of the ligand binding suppressor domain of type 1 inositol 1,4,5-trisphosphate receptor. *Mol Cell* 2005; 17(2): 193-203.
61. Wang YX, Zheng YM, Mei QB, Wang QS, Collier ML, Fleischer S *et al*. FKBP12.6 and cADPR regulation of Ca2+ release in smooth muscle cells. *Am J Physiol Cell Physiol* 2004; 286: C538–C546.
62. Zucchib R, Testoni SR. The sarcoplasmic reticulum Ca2+ channel/Ryanodine receptor: modulation by endogenous effectors, drugs and disease states. The American Society for Pharmacology and Experimental Therapeutics 1997; Volume 49.
63. Ellithorpe R, Mazur P, Gum G, Button G, Le BSJ, Ernest H. Pfadenhauer *et al*. Comparison of the absorption, brain and prostate distribution, and elimination of $CaNa_2$ EDTA of rectal chelation suppositories to intravenous administration. Journal of the American Nutraceutical Association 2007; Vol. 10, No. 2.
64. Sharma A, Sharma V, Kansal L. Amelioration of lead-induced hepatotoxicity by Allium sativum in swiss albino mice. *Libyan J Med* 2010; 5: 4621.
65. Aga M, Iwaki K, Ueda Y, Ushio S, Masaki N, Fukuda S *et al*. Preventive effect of *Coriandrum sativum* (Chinese parsley) on localized lead deposition in ICR mice, *J Ethnopharmacol* 2001; 77(2-3):203-208.
66. Mary LS, Queiroz, Rodrigues APO, Bincoletto C, Figueirêdo CAV, Malacrida S. Protective effects of *Chlorella vulgaris* in lead-exposed mice infected with listeria monocytogenes. International Immunopharmacology 2003; 3(6): 889-900.
67. Flora SJS, Tandon SK. Perventive and therapeutic effects of thiamine, Ascorbic acid and theis combination in lead intoxication. *Acta Pharmacologica et Toxicologica*, Life Sciences 1986; 58(5): 374-378.
68. Gurer H, Ercal N. Can antioxidants be beneficial in the treatment of lead poisoning? Free Radical Biology and Medicine 2000; 29(10): 927-945.
69. Devasagayam TPA, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: current status and future prospects. JAPI 2004; 52: 794-804.
70. Lind SE, Park JS, Drexler JW. Pyrithione and 8-hydroxyquinoline transports lead across erythrocyte membranes. Translational Research 2009; 154(3): 153-159.

71. Gregory SE. Heavy metal ion transport utilizing natural and synthetic ionophores, The Ohio State University 2007:130.
72. Hamidinia SA, Erdahl WL, Chapman CJ, Steinbaugh GE, Taylor RW, Pfeiffer DR. Monensin improves the effectiveness of meso dimercaptosuccinate when used to treat lead intoxication in rats. *Environ Health Perspect* 2005; 114: 484-493.
73. Ferreiro's-Marti'nez R, Esteban-Go'mez D, Andre's de Blas, Platas-Iglesias C, Rodri'guez-Blas T. Macrocyclic receptor showing extremely high Sr(II)/Ca(II) and Pb(II)/Ca(II) selectivities with potential application in chelation treatment of metal intoxication. *Inorg Chem* 2011; 50(8): 3772–3784.
74. Pellissier A, Bretonnière Y, Chatterton N, Pécaut J, Delangle P, Mazzanti M. Relating: A new picolinate ligand designed to accommodate the Pb(ii) structural and thermodynamic effects of the Pb(ii) lone pair lone pair leads to high stability and selectivity. *Inorg Chem* 2007; 46(9): 3714–3725.
75. Ferreiro's-Marti'nez R, Esteban-Go'mez D, Andre's de Blas, Platas-Iglesias C, Rodri'guez-Blas T. Selective chelation of Cd(II) and Pb(II) versus Ca(II) and Zn(II) by using octadentate ligands containing pyridinecarboxylate and pyridyl pendants. *Inorg Chem* 2009; 48(23): 10976–10987.
76. Najar-Nezhad V, Aslani MR, Balali-Mood M. Evaluation of Allicin for the treatment of experimentally induced subacute lead poisoning in sheep. Biological Trace Element Research 2011; 8: 8185-8189.
77. Aslani MR, Najarnezhad V, Mohri M, Azad M. The effect of Allicin on blood and tissue lead content in mice. Comparative Clinical Pathology 2010; 20: 121-125.
78. Miron T, Rabinkov A, Mirelman D, Wilchek M, Weiner L. The mode of action of Allicin: Its ready permeability through phospholipid membranes may contribute to its biological activity. *Biochimica et Biophysica Acta* (BBA) – Biomembranes 2000; 1463(1): 20-30.
79. Shahsavani D, Baghshani H, Alishahi E. The impact of allicin on lead-induced oxidative damage in selected organs of the common carp (*Cyprinus Carpio*). Comparative Clinical Pathology 2011; 142: 572-580.
80. Vahid N, Mohammad R A, Mehdi B. The therapeutic potential of thiamine for treatment of experimentally induced subacute lead poisoning in sheep. *Comp Clin Pathol* 2010; 19: 69-73.
81. Reddy SY, Pullakhandam R, Kumar BD. Thiamine reduces tissue lead levels in rats: mechanism of interaction. Biometals 2011; 23: 247-253.
82. Committee on Drugs, American Academy of Pediatrics. Treatment guidelines for lead exposure in children. Pediatrics 1995; 96: 155-60.
83. McEvoy GK, *ed*. Dimercaprol. Bethesda, MD: American Society of Health-System Pharmacists. AHFS Drug Information 2007.
84. BAL in Oil (dimercaprol) injection prescribing information. Decatur, IL 2006; Rev 07-10.
85. Succimer capsules prescribing information.

Seymour, IN; 2007, Rev 05-10
86. Henretig FM. Lead. In: Flomenbaum NE, Goldfrank LR, Hoffman RS *et al*, eds. 8th edition. New York: McGraw-Hill 2006: 1308-1324
87. Ruprecht J. (RS)-2,3-Bis(sulfanyl) propane-1-sulfonic acid, 1 H_2O sodium salt, Scientific Product Monograph, 7th Edition 2008.
88. Penicillamine capsules prescribing information. Whitehouse Station, NJ 2004.
89. Penicillamine tablets prescribing information. Somerset, NJ. 2003.
90. Calcium disodium Versenate (edetate calcium disodium injection) prescribing information. Lake Forest, IL 2004.
91. Howland, MA. Edetate Calcium Disodium ($CaNa_2$ EDTA). In: Flomenbaum NE, Goldfrank LR, Hoffman RS *et al*, eds. Goldfrank's toxicologic emergencies. 8th edition. New York: McGraw-Hill 2006: 1331-1333.
92. Alternative medicine Review 2000; 5(5): 467-471.

**Corresponding Author: Dr. Venkatesh Thuppil National Referral Centre for Lead Poisoning in India, John Nagara Post, Koramangala, Bangalore - 560034*
Email: venkatesh.thuppil@gmail.com Cell No. - 093412424300