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Lead Poisoning - A Global Issue of Great Concern of Modern Times

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Abstract: *Lead is a non-essential, public health toxin. The entry of this silent poison into the ecosystem has become an issue of great concern at the global level. However, deliberate efforts are undertaken by several governmental and non-governmental organizations to deal with the problem. The ongoing lead poisoning issues can be tackled with ease only through proper countrywide lead awareness campaigns and legislation of strategies and policies in association with lead safety and prevention. By following safe work practices and consumption of healthy diet, the toxic manifestations of lead could be minimized. This review highlights some of the health issues with reference to the current lead exposure status and strategies that can be implemented to assess lead poisoning.*

Keywords: ***Lead Poisoning; Fetal Lead Exposure, Occupational Exposure, Chelation, Nutrition.***

1. Introduction

Lead is a naturally-occurring toxic heavy metal, ubiquitously found in the environment as a consequence of human anthropogenic activities. It is one of the world's most serious public health toxin and ranked second in the 2015 ATSDR hazardous substance priority list after arsenic [1]. The first decade of the 20th century documented lead poisoning as a clinical entity with acute, subacute and chronic devastating consequences for the health of children and adults worldwide [2]. Currently subclinical lead poisoning is a major public health concern at the global level. The cumulative effects of lead on multiple body systems viz., hematologic, gastrointestinal, cardiovascular, renal, central and peripheral nervous system, reproductive and immune systems are well known. According to WHO, more than 120 million people are overexposed to lead globally and about 99 percent of the cases reside in developing countries [3]. It has been observed that lead exposure accounts for 1,43,000 deaths per year with the highest number in developing countries [4]. Based on the epidemiological and experimental data, the International Agency for Research on Cancer (IARC) has classified inorganic lead compounds as probable (Group 2A) carcinogens to human beings. The Agency for Toxic Substances and Disease Registry Completed Exposure Pathway Site Count Report has considered Arsenic, Cadmium, Chromium and Lead as the top four metals in site frequency count [5]. Most of the developed nations have made efforts to reduce lead poisoning by implementing guidelines for both environmental and occupational settings. This has enabled them to comprehensively monitor and document the status of lead poisoning in their population which eventually has brought down the lead reference levels from 10 µg/dl to 2 µg/dl. However, in few developing countries, lead poisoning issues continue to persist and can be tackled only through proper countrywide awareness and education. To accomplish this, there is a need to evaluate the impact of lead on health and environment at the regional level. As per the current global standards, the reference lead levels in blood is <2 µg/dl, in atmospheric air is <1.5 μgm^{-3} and in paints is <90 ppm. This may not be applicable to developing countries where lead based activities are extensive and do not adhere to rules and regulations as implemented due to unsustainable economic reasons. Thus it would be a rationally challenging task to set the permissible levels for different geographical regions as the nature of lead contamination and the extent of lead exposure is different for different areas. This can be achieved by initially identifying the primary sources of exposure followed by developing effective remediation plans for medical monitoring and treatment and finally spreading the awareness of lead prevention and care [6].

Heavy duty industrial activities mobilize lead through air, soil, and water eventually accumulating throughout the food chain. Decades of research have implicated a direct/ or indirect link of blood lead levels with anemia, osteoporosis, hypertension, cardiovascular disease and neurobehavioral defects like ADHD (Attention Deficit Hypertensive Disorder) [7]-[12]. In the following section we will focus on the sources and metabolism of lead. Although the major source of lead exposure i.e., from gasoline and paint declined over the years, the incidence of lead poisoning cases especially children through the ingestion of paint chips, spices, cultural or ceremonial powders and

occupationally exposed workers due to unsafe work practices continue to rise. This calls for the need to create public awareness through community involvement, conducting free blood lead test campaigns and organizing lead conference meetings.

2. Sources of Lead

Lead is a soft, heavy metal with low melting point, resistance to corrosion, is highly malleable, ductile and a poor conductor of electricity. It is easily mined and smelted. Its low cost and easy workability has made it a very useful metal and is widely used in the industrial sector in applications such as in the manufacture of lead acid storage batteries, production of ammunition, metal products such as lead sheets, pipes, few brass and bronze products, in surgical and medical equipments like radiation shields which are used for protection against X-rays, electronic parts of ultrasound machines, lead solders of circuit boards of television sets, radio, computers, mobile phones, calculators and other electronic items [13], [14]. Lead is widely distributed in the environment and is present virtually in air (15%), water (20%), dust, soil and food (65%) [15], [16]. The largest source of anthropogenic lead emission has been the use of leaded gasoline. Organic additives viz., tetraethyl lead, added to gasoline as an antiknock agent is a major source of lead getting into air [17]. Once it enters the body, tetraethyl lead is converted to tetramethyl lead and inorganic lead. Most cases of lead poisoning are caused by inorganic lead. By the end of 1995, the Environmental Protection Agency (EPA) banned the addition of lead in gasoline; still however, other sources of lead emissions such as those from industries involved in iron and steel production; lead acid storage battery manufacturing, burning or weathering of lead painted surfaces, cigarette smoke or naturally from volcanoes and erosions remain. Lead is non-biodegradable and can persist in the air and soil for a very long time in turn serving as a continuing source of lead exposure. Lead particles may also adhere to leaves and other parts of the plant; hence, animals which live and graze in such contaminated areas will have high amounts of lead in their body. The meat and milk from these animals may also serve as a source of lead for humans. The amount of lead in food crops depends on the concentration of lead in soil. The contamination of food by lead is found to be highest near mines and smelters. Processed food or drinks can also be contaminated with lead if they are stored in lead-soldered cans, ceramics with lead glazes, pottery vessels and crystal glass wares. Lead leaches from the container especially when the food content is acidic. It is estimated that the average daily intake of lead in adults is 300 µg from food and beverages [18]. During the Greco-Roman period, lead lined vessels were used to prepare wines and food to enhance the flavor and prevent from further spoilage. A high amount of lead is also detected in paints, traditional/folk medicines, mineral supplements, some spices, and cosmetics [19]-[22]. A mixture of lead and tin used for recoating the inner surface of brass utensils - described as “tinning” is widely practiced in India and is another source of lead exposure. The use of tobacco and alcoholic beverages and leaching of lead from microwavable plastic wares made with lead-containing pigments are also sources of lead [23], [24].

3. Lead Susceptibility

The most vulnerable population exposed to the toxic effects of lead include growing fetus, young children, pregnant women and occupationally exposed workers. Some of the common sources of lead which pregnant women and children are exposed to include chipping paint dust, contaminated food and water, traditional medications, toys and jewelry. An elevated blood lead level in pregnant women is a health concern for both mother and child. Lead in the bloodstream of a pregnant woman can easily cross the placental barrier into the fetal blood-brain barrier and cause irreversible neural damage thereby affecting cognitive development [25], [26]. Chronic lead exposure in pregnant women can lead to miscarriage, reduced birth weight and length, gestational hypertension, preeclampsia, congenital malformations and impaired neurodevelopment [25], [27]. The skeletal bone store is a major contributor to maternal blood lead. Lead is prenatally transferred via breast milk posing additional risk to the growing fetus [28]. Studies have reported an inverse relationship between the maternal blood lead levels and neonatal behavioral neurological assessment scores [29], [30]. Further blood lead levels as low as 5 µg/dl during the first trimester of pregnancy can affect the developing fetus and might serve as a window of possibility to detect vulnerability of lead to newborn behaviors [31]. Although the maternal blood lead level is on average 30 % higher than infants, most studies reveal that about one quarter of the infants blood lead is higher than their mothers [32]. This is in agreement with reports which show that umbilical cord blood concentrations are higher than maternal blood lead concentrations by a factor of 1.3 [33]. This variation in cord blood lead levels can be explained by maternal factors like age and parity, nutrition, alcohol consumption during late pregnancy, hemoglobin, blood pressure and caesarean section delivery [32], [34]-[36]. Hence, a long-term control of maternal lead exposure and proper management of pregnancy and diet is necessary to minimize fetal lead exposure. Toddlers and children below six years are easily accessible to lead by their pronounced hand-mouth behavior (pica habit). A meta-analysis by Needleman HL et al (1990) documented a strong link between low lead exposure and intellectual deficit in children. Another associated entity is the dose (blood lead or tooth lead) and response (teachers ratings of classroom behavior and reaction time under varying intervals of delay) of a child [37]. Such dose-response studies revealed that persistent childhood lead poisoning can significantly affect

the academic performance rating from high school to graduate level eventually making them less confident and socially insecure [38]. Furthermore, it has been hypothesized that childhood lead exposure may even have an impact on adult crime, unemployment rate, alcohol consumption, and effective abortion rate and population age distribution [39]. Moderately high level lead exposure is associated with aggressivity, impulsivity, ADHD, and lower IQ.

Occupational lead exposure in developing countries is entirely unregulated with no monitoring of exposure putting workers at risk of lead poisoning [40]. Some of the heavy risk jobs associated with lead include smelting or casting lead, removing lead coatings, heating, machining or spraying and making of lead products [41]-[44]. The major route of exposure for workers is inhalation and ingestion of lead dust and fumes. According to the US Occupational Safety and Health Administration (OSHA) lead standards (1993), a lead exposed worker may attain a blood lead level of 40 µg/dl during their work life time [45]. Few case study reports has documented non-symptoms among workers exposed to hazardous levels of lead such as nausea, abdominal pain, constipation, lack of appetite, wrist drop, tingling and numbness in fingers and hands, headache, depression, memory impairment, wrist drop, sleep disturbances and decreased libido [46]. In addition, male workers showed abnormal sperm morphology and decreased sperm count at blood lead levels <40µg/dl [47]-[49]. Neurotoxic effects of lead is induced in workers at blood lead levels <18 µg/dl which is higher than the critical level of lead neurotoxicity in children [45]. Workers are prone to the ill effects of lead when subjected to unsafe work practices which include not wearing suitable personal protective equipments (PPE), working in a contaminated environment or not regularly monitoring and assessing the overall health of the individual. Eating, drinking or smoking in lead-contaminated surroundings is also an additional source of exposure to lead. Lead dust deposited on workers body, clothes and shoes can be passed on to their family members. Human beings, animals, and plants existing in the vicinity of lead-based industries which use and discard lead into the surroundings are at higher risk for the exposure of lead [50]. Hence, by following safe work practices, exposed workers can prevent this occupational and environmental health hazard.

4. Biotransformation (Absorption, Deposition, Metabolism and Excretion) of Lead

The principle routes of lead exposure are via inhalation, ingestion and dermal absorption. About 99 % of lead accumulates in the erythrocytes out of which 80 % binds to aminolevulinate dehydratase, a cytosolic enzyme of the heme pathway and the rest binds to hemoglobin. 1 % of lead accumulates in the plasma which eventually gets distributed to soft tissues such as the liver, renal cortex, aorta, brain, lungs, spleen, teeth and bones of which the liver is the largest repository for lead followed by the kidney cortex and medulla [51], [52]. A study was conducted on 32 long-term exposed lead smelters and the concentrations of lead in major soft tissues were assessed and it was found to be in the order of liver, kidney, lungs and brain, indicating that liver is a chief target organ for lead [53]. Lead exhibits a domino effect. As a consequence of the impact of lead on the hematopoietic system and reducing heme body pool, several other systems such as the gastrointestinal, cardiovascular, nervous, the immune system, and reproductive system are affected. The half-life of lead in blood is 30-35 days; in soft tissues- about 40 days and in bone for more than 25 years. It has been observed that a large portion of absorbed lead is incorporated in the skeleton accounting for more than 90% of total lead body burden; this enables us to identify individuals who are exposed to chronic levels of lead over a long period of time [54]. Blood lead levels reflects recent lead exposure while tibia or patella bone lead represents retained cumulative lead dose. When the total lead body burden remains heavy, the blood lead levels will fall significantly. But at times of heightened bone turnover i.e., during pregnancy, lactation, menopause, physiological stress, hyperthyroidism, renal disease, advanced ageing and all that which are exacerbated by calcium deficiency, the circulating lead levels reach peak values. One of the predominant channels of lead entry into the human body is by inhalation in the form of lead dust aerosols. Approximately 30-50 % of inhaled lead of particle size less than 1 µm is deposited in the lower alveolar tract and about 50-70 % of it is absorbed into the circulation [55]. The gastrointestinal absorption of lead is highest in children than in adults. About 5 -15 % of dietary lead is absorbed and less than 5 % of it is retained in adults while in children and infants, the absorption rate is as high as 30-40 % making them more sensitive to lead poisoning [56], [57]. In the case of adults, the absorption rate varies depending on the physiological state of exposure and the chemical property of the ingested lead. Lead is excreted by the kidneys or through biliary clearance. A study reports that about 60 % of lead is retained in the body and 40 % of it is excreted. Data from human studies however, report that about 50-60 % of lead is excreted on a short term basis than when in a steady state condition with respect to intake and output. Other areas of the body prone to lead deposition include hair, nails, sweat, saliva and breast milk secretions. There is a need to explicitly understand the relationship between speciation of lead and metabolic toxicity outcomes in order to improve lead risk assessment [58].

5. Signs and Symptoms of Lead Poisoning

According to the Centers for Disease Control and Prevention, no symptom is the symptom of lead poisoning [59]. Several case studies have been reported of patients

with higher blood lead levels with no obvious and immediate signs and symptoms of lead poisoning. A study reporting high blood lead levels of 82.8 µg/dl in a lead acid battery worker with normal blood picture indicated that over time lead builds up in the body and the rate of lead retention may vary from individual to individual [60]. Lead is a subtle, slow acting toxin. Some of the early classical symptoms of lead poisoning include loss of appetite, abdominal pain, general fatigue, constipation, nausea, weight loss, arthralgia, memory problems, headache and insomnia [61]. These symptoms are commonly seen in other illnesses too; hence, accurate diagnosis of lead poisoning is a challenging task. The symptoms and onset of lead exposure may also vary due to individual toxic response variations. The actual symptom of lead poisoning however, becomes obvious in chronic exposed conditions. Some of the high dose exposure symptoms include intermittent abdominal cramps, frank anemia, appearance of blue line on the gingivodental gums, metallic taste in the mouth, neurological disturbances including headache, cataract, irritability, lethargy, convulsions, muscle weakness, ataxia, decreased fertility, tremors and paralysis of the motor muscles resulting in wrist drop and encephalopathy [62]. There are several factors which may influence an individual's susceptibility to lead toxicity such as age, gender, frequency of exposure, dosage bioaccumulation, genetic and epigenetic makeup; all of which collectively determines the individual's phenotypic response to lead metabolism (Figure 1).

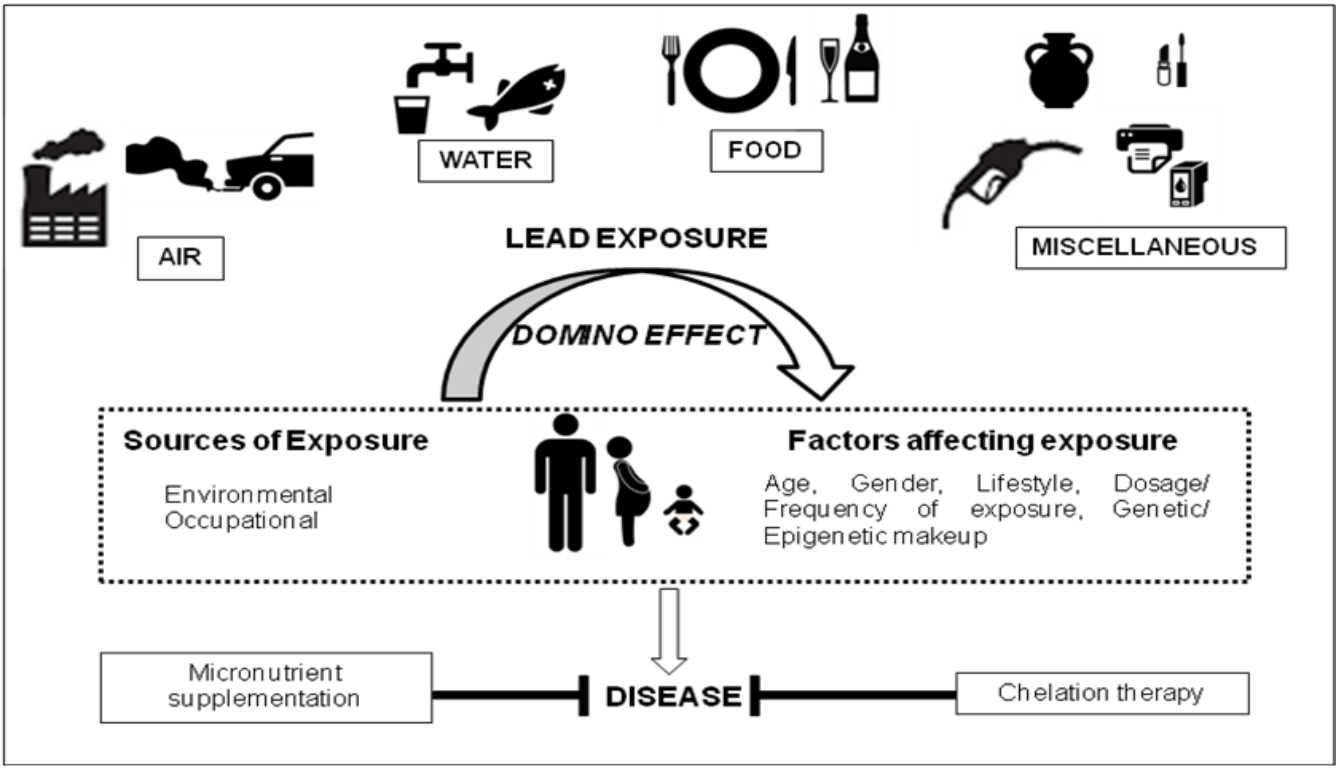


Figure 1: Factors Influencing Individual Susceptibility to Lead Exposure and Toxicity

Children are more susceptible to the adverse effects of lead exposure than adults. They spend more time crawling and playing on the ground and getting exposed to higher amounts of lead due to their hand-to- mouth activity and eating substances of no nutritive value (pica) such as house dust or soil from playgrounds contaminated with leaded paint and chewing painted window sills. Lead paint chips can be scattered and added to the household dust while renovating, remodeling and repainting. Lead exposure in children can also occur while using toys, cosmetics and unbranded medicine containing high amounts of lead in them. There is no placental barrier for lead; hence, the growing fetus is also at high risk of lead poisoning in cases when the pregnant mother is exposed to vulnerable amounts of lead. To support this fact, studies have reported a significant association between maternal bone lead and umbilical cord blood lead levels [63], [64]. The blood-brain barrier of the developing fetus is not fully matured until after its birth. Lead in the blood circulation crosses the developing blood brain barrier and may cause irreversible defects in brain functions later in early life. There is strong evidence in the literature suggesting that even at blood lead levels below 10 µg/dl, a child's mental and physical growth is affected leading to impairment of cognitive development and behavior deducing that there exists no safe level for lead in the body. In a cohort study of 1333 children followed from birth until 5-10 years of age, an inverse relationship was observed between blood lead concentration and full scale IQ score indicative that with increase in blood lead levels, the IQ score decreased by one unit. Childhood lead poisoning can result in brain damage leading to mental retardation, hyperactivity, attention deficit disorder, low IQ,

diminished academic performance and behavioral problems which make them socially insecure and violent with impaired speech and hearing ability [45]. Hence, it is necessary to prevent lead poisoning before it can cause irreversible damage in children. The risk of lead poisoning may not be great for adults as it is for children but continuous exposure can result in fatal consequences. The appearance of symptoms due to lead poisoning may vary from person to person and from region to region which may lead to a delay in diagnosis or misdiagnosis receiving only symptomatic treatment. Hence, there is an urge for risk exposure assessment and screening for lead exposure.

6. Biomonitoring of Lead

There are two main populations at risk of lead exposure-children between 9 months to 3 years of age and adults working in lead contamination sites. While medically evaluating a lead poisoned case, a physician needs to be well informed of the point source of lead exposure. There are several ways to assess lead burden in an individual. The lead level in the blood reflects recent acute lead exposure while the bone represents long term chronic exposure. For instant and appropriate clinical decision, the best screening and diagnostic tool appear to be the estimation of blood lead levels. A number of analytical methods are available to determine the concentration of lead from various kinds of samples. Some of the approved methods include Atomic Absorption Spectroscopy (AAS), Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Anodic Stripping Voltammetry (ASV). The choice of method depends on the setting and resources available in the laboratory [65]. In this era of technology, conventional laboratory testing has advanced so much that analysis of lead has become digitalized to on-the-spot testing. Magellan diagnostics, a medical device company developed the Lead Care^{R} II portable unit (ASV technology) which determines the blood lead levels in just three minutes using a finger prick. This methodology is approved as a CLIA (Clinical Laboratory Improvement Assessment) waived test. It is cost effective with low error rate and found to improve health outcomes. This portable point-of-care blood lead analyzer can be transported to rural or remote areas to widen the assessment of lead testing outside the laboratory setting. In addition this technology evidently eliminates the use of vacutainers and also the need to transport samples to the laboratory for testing hence saving time [66]. Table 1 illustrates the strengths and limitations of the current approved analytical methods for the estimation of lead.

Table 1: Analytical Techniques Available for Estimation Lead

METHOD	PRINCIPLE	STRENGTHS	LIMITATIONS	SAMPLE TYPE
Flame Atomic Absorption Spectrometry (FAAS)	• Flame method • Sample undergoes nebulization followed by atomization. • Uses acetylene- air/ nitrous oxide-acetylene-air fuel-oxidant mixtures in the order of 2000-3000^{0}c.	• High sample throughput • Typically takes 3-10 seconds to determine a single element. • The limit of detection for a sample amount of 50-100 µl blood is 10-30 µg/dl. Generally, the limit of detection is between 1ppm for transition metals to 10 ppb for alkali metals. • It can be fitted with an autosampler for detection from a large number of samples.	• Requires specific light sources, optical parameters and flame gases for different elements. • Limit of detection depends on the sample amount. • Skilled technician • Instrument cannot be left unattended. • Technically not sensitive enough to atomize the entire sample amount. • Relatively little interference.	• Whole blood • Plasma/serum • Hair • Nails • Tissues • Water samples from contaminated water sources. • Soil
Graphite Furnace/ Electrothermal Atomic Absorption Spectrometry (GFAAS/ETAAS)	• Non-flame method • Sample undergoes nebulization followed by atomization. • Uses electrically heated graphite tube to vaporize and atomize at temperatures up to 3000^{0}c.	• It is reliable, accurate and safe. • Typically requires two to three minutes for each sample. • 10-50µl blood sample is required for analysis with a limit of detection in the order of 1-2 µg/dl. Generally, the limit of detection is between 100mg/kg to 1mg/kg. • This method is very sensitive enabling measurement of blood lead concentrations as low as 0.1µg/dl. • It can be fitted with an autosampler for detection from a large number of samples.	• Expensive • Low sample throughput • Skilled technician • Requires long time for analysis. • Large spectral interferences than FAAS	
Lead Care^{R}II	• CLIA- waived point-of-care blood lead analysis	• Cost effective • Portable • Requires two drops of blood on a fingerstick.	• Expensive • Low sample throughput • Requires very less time for analysis	Only whole blood

		• Two mandatory tests can be performed simultaneously- for blood lead and hemoglobin. • Results are immediately available • Any employee of a laboratory under a CLIA certificate of waiver can perform this test. • Parents can no longer feel traumatic in checking their child's blood lead level		

7. Health Issues of Lead Poisoning

Today we are experiencing lead contamination in our daily lives- in our food, water, medicines, cosmetics, paint and printing ink. Lead poisoning is an unavoidable environmental and global health problem yet it is entirely preventable. The US FDA (Food and Drug Administration) has recommended a maximum level of 0.1 ppm lead in candies and other food items [67], [68]. Elimination of lead from gasoline was one of the greatest achievements of all time. Nichani V et al (2006) observed that the percentage of children blood lead levels >10 µg/dl dropped from 61.8 % to 33.2 % during the post lead gasoline era [69]. After lead in petrol, the major source of lead poisoning is from house paints. Paints and paint dust are a major source of lead poisoning in children. In 1914, US documented the first case of pediatric death linked to lead based paints [70], [71]. WHO reported that 99 % of children affected by high lead exposure live in low- or middle-income countries with an estimated 1,43,000 deaths occurring each year due to lead poisoning of which lead paint exposure is a major contributor [72]. By 1978, US banned the use of paints containing more than 600 ppm lead for homes, children's toys and household furniture. But this continues to be a problem in developing countries around the world due to lack of regulations implemented for lead content in paints. Clarke CS et al (2000) investigated paint samples from India, China, Malaysia and Singapore and observed that the first three countries exceeded the regulatory standards of 600 ppm with median lead levels of 16,720 ppm, 3,280 ppm, 21,300 ppm respectively while the fourth showed lower concentrations with median lead level of 9 ppm [73]. Adebamowo EO et al (2007) on the other hand observed that 96% of the collected Nigerian paint samples with median lead level of 15,800 ppm spiked the recommended level compared to the Asian study [74]. Similarly in a study by Lin GZ et al (2009), the lead levels in paint samples from 24 kindergarten and primary schools in Guangzhou, China exceeded the regulatory limit [75]. Toxic Link, a non-governmental Indian organization claims that while small scale paint manufacturers continued adding lead to paints the brands representing 60-70 % of the market share followed stringent regulations [76], [77].To promulgate public awareness about hazardous lead paint at the global level, the Global Alliance to Eliminate Lead Paint (GAELP) was convened by WHO and UNEP (United Nations Environment Programme) with an aim to phase out the manufacture and sale of paints containing lead and reducing the risk of lead poisoning [72]. The US congress suggested lowering the lead content in paints to 90 ppm. In addition to housing, lead-based paints are applied to idols associated to various forms of rituals and traditions. It is estimated that a 2 kg idol may have 6-8 gm of lead [78]. These idols are immersed in water bodies making it unfit for aquatic life and domestic purposes. Currently, substitutes for lead pigments are encouraged and made readily available which may consequently eliminate the global use of lead-based paints. In households where old plumbing is used and in areas where water is of low alkalinity, lead tends to leach into the water lines contaminating drinking water. Lead pipes are now replaced with copper pipes fitted with lead free solders containing not more than 0.2 % lead [55]. Several South Asian and Indian communities are at risk of lead poisoning through the use of culture-specific non-paint lead sources such as imported utensils, cosmetics such as kohl, surma and henna (a dye prepared from henna plant *sp*. Lawsonia), spices, ceremonial powders like kumkum, sindoor (a powder applied on a woman's scalp as a sign of marriage) sandalwood and ayurvedic medicines [22]. A number of studies have shown that children exposed to cosmetics containing lead like surma or kohl were subjected to high blood lead levels consequently putting them at increased risk of cosmetic plumbism. A comparative study of blood lead levels between children using surma and controls revealed a significant association between surma users and high blood lead concentrations [79]. Cristiane GL et al (2015) observed that children of Boston area exposed to imported ceremonial powders and spices containing high lead content showed higher lead levels in the blood including high zinc protoporphyrin and low hemoglobin levels [22]. The ancient ayurvedic system of medicine has been practiced for a very long time and still remains a skeptical issue. There has been case studies' reporting association of lead with the consumption of ayurvedic medicines. Saper et al (2004) observed that 20 % of ayurvedic medications sold in Boston area stores contained high concentration of lead, arsenic and mercury above daily metal ingestion permissible limits [80]. Further he observed that about 20 % of US and Indian manufactured ayurvedic medicines sold over the internet contained detectable levels of lead, mercury and arsenic hence putting the users at risk

of heavy metal toxicity. The current US law governing the dietary supplements produced and sold domestically (DSHEA) has made it mandatory to test all imported dietary supplements including ayurvedic medicines for toxic heavy metals [81].

Currently, the ongoing world's deadliest acute lead poisoning crisis is observed in Zamfara state of Northern Nigeria due to illegal and unsafe mining and ore processing activities. It has been considered one of the worst lead poisoning epidemics in modern history. This has caused serious environmental contamination costing the lives of many including new borns and young children. Comprehensive and sustained efforts have been executed in these lead contaminated sites by non-governmental authorities to provide point of medical care and health education mainly in environmental remediation and in following safe mining practices [82]. In another public crisis few years ago, the Ernst and Gallo glass production company was sued for introducing hazardous lead, arsenic, selenium and cadmium dust during the wine bottle manufacturing process. Eventually when these wine bottles were kept in long term storage, lead leached from the glass into the wine preparation contaminating the wines [83]. Likewise there are various forms of lead poisoning issues occurring around the globe for which governmental and non-governmental organizations need to consider, anticipate and execute immediate action to protect the environment from further lead contamination. Although it is not completely liable to eliminate an important metal like lead from the environment it is only through increased vigilance and control that we can reduce the exposure and risks associated to lead poisoning.

8. Lead Safety Guidelines for Individuals Working in Industries

Individuals who work as lead acid battery manufacturers, electronic soldering workers, paint and ceramic glazing personnel, workers in lead mines and hobbyists using lead for various purposes are found to be at the highest lead poisoning risk due to lack of awareness and inadequate training [43]. Parents who work in such occupational setting need to take necessary precautions to avoid taking home lead which may be deposited on their body, clothes and shoes. Given below are some of the guidelines to avoid lead exposure.

- Changing over to work uniform prior to entering work premises in a lead-free chamber. The changed clothes to be packed in polyethene cover and stored in a lead-free area.
- Wearing quality tested PPE such as gloves, head gear, masks equipped with PARP's (full powered air purifying respirators), aprons, safety glasses and boots.
- Washing hands and face thoroughly before eating or drinking.
- Eating and drinking only in areas free of lead dust and fumes.
- Wet cleaning and vacuuming are generally safer rather than stirring up lead-containing dust with dry sweeping or blowing.
- Taking a shower and changing over to clean clothes and shoes/boots before going home.

- Laundering clothes at work. If they have to be taken home, it should be washed and dried separately.
- Using disposable cotton ear plugs to prevent any lead dust getting into the inner ear.
- Cutting and cleaning nails more frequently to ensure that no lead dust get deposited under the nail bed.

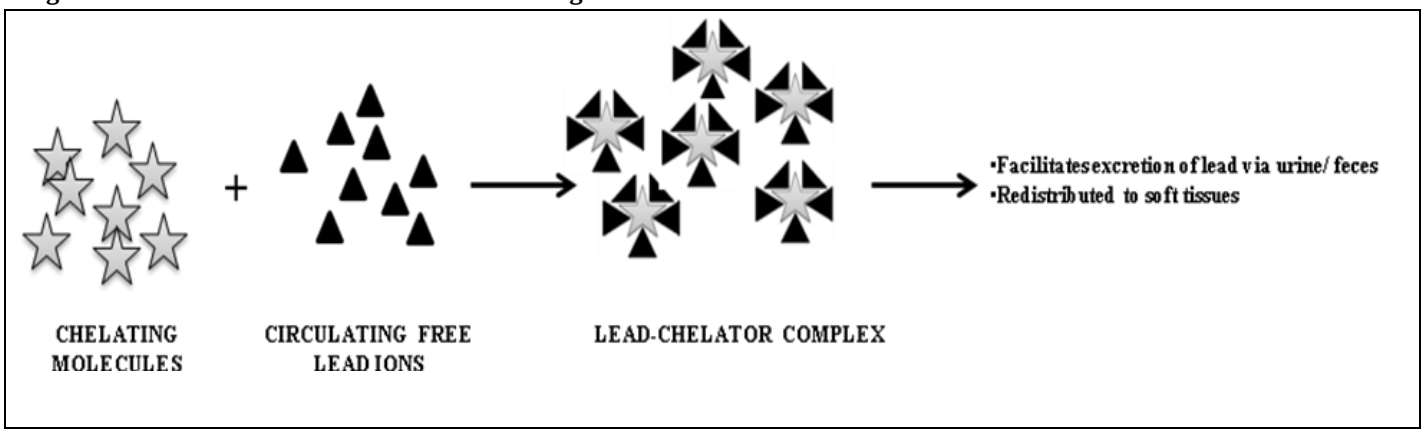
According to OSHA standards, it is mandatory that industries with permissible airborne lead levels above 30 $\mu g/m^3$ and over a time weighted average of 8 hours monitor the blood lead levels of workers regularly every three months with free medical surveillance [84]. Workers must be well informed about the ill-effects of lead poisoning and safe work practices to be followed. It is estimated that between 0.5-1.5 million workers are exposed to workplace lead each year [85]. Similarly, in large scale industries prior to assigning employers to high exposure trigger tasks, he/she must be educated about the sources of lead exposure, health hazards associated to lead, methods to reduce exposure and most importantly knowledge about the awareness of existence of employers rights under the lead standard guidelines. If the blood lead level exceeds 50 µg/dl, workers will be recommended for chelation therapy unless he/she is removed from the point source of exposure and does not return to the same job environment. Thus, by following simple safety measures, the risk of lead poisoning in workers can be reduced.

9. Management of Lead Poisoning

9.1 Chelation Therapy

For several decades, the most practiced strategy to fight lead poisoning is chelation therapy which involves the use of chemical chelators. The choice of chelators depends on the blood lead concentration, clinical symptoms and environmental lead burden [86]. Studies have shown that sulfhydryl or sulfur containing chelating agents are effective scavengers of heavy metals [87]. They typically bind the metal at two or more sites and preferably get excreted as a complex. This lead:chelator complex tend to remain in the tissue where they bind or get redistributed along with endogenous essential metals to other tissues as depicted in figure 2.

Figure 2: Ionic interaction of Lead and Chelating Molecules



Consequently, the endogenous metal pool gets exhausted spiking the blood lead levels. To avoid such downsides, chelation therapy is planned and performed in phases of an initial five day treatment followed by a short period of no treatment or lesser dose (ideally 10-20 mg/kg/day) before the next course of pretreatment, so that during the non-treatment period the body's endogenous metal levels can be restored through proper dietary supplementation [88]. Chelation therapy is principally administered via oral, intravenous, intramuscular or rectal routes and the routing is decided depending on the extent of lead poisoning. Children and adults with blood lead levels >10 µg dL^{-1} and ≥45 µg dL^{-1} respectively must undergo this treatment for further evaluation of lead toxicity [86], [89]. An optimal chelating agent is characterized by high water solubility, greater affinity, low toxicity, ability to reach the sites of metal storage, compete with natural chelators and penetrate cell membranes, a capacity to form non-toxic complexes and rapid elimination from the system; above all it should be affordable, safe and easily administered without any side effects [86], [90]. Some of the chelators used to date for lead poisoning treatment include calcium disodium EDTA (Ca Na_2 EDTA), meso- 2, 3 dimercaptosuccinic acid (DMSA), 2, 3-Dimercapto-1-propane sulfonic acid (DMPS) or Dimercaprol trade named as British Antilewisite (BAL) and D-penicillamine, but not all are effective in serving the purpose; only few which are approved by the US FDA are prescribed for treatment [89]. In medical practice, there are two forms of EDTA used for chelation therapy- calcium disodium EDTA and disodium EDTA. Ca Na_2 EDTA exchanges calcium for lead and was found to be effective in lowering lead levels while Na_2 EDTA on the other hand chelates metals including both essential and non-essential. A 2006 Morbidity and Mortality Weekly Report affirmed that three patients died after receiving Na_2 EDTA from the effects of severe hypocalcaemia. Controversies like these relating to the safety and efficacy of EDTA chelation therapy arose due to the possible clinical side effects it presents especially for cardiovascular diseases. Hence, FDA approved only Ca Na_2 EDTA and recommends it for any kind of heavy metal poisoning. Although this agent is medically preferred most of the time, utmost care in planning of doses is necessary as EDTA itself is a non-specific metal chelating agent which can lead to redundant depletion of endogenous metal stores with minor side effects. D-penicillamine is another chelating agent that is shown to have optimistic chelating properties for lead when administered orally. A study reported that administration of oral D-penicillamine reduced the blood lead levels of a male worker from 106.5 µg/dl to 35 µg/dl with improvement in complete blood picture [91]. Several studies have shown that the therapeutic efficiency of chelation can be increased by the combined administration of chelators rather than administration with monochelators. Tandon et al. (1994) showed that combined administration of Ca Na_2EDTA and DMSA was more efficient than Ca Na_2EDTA and DMPS. It consequently enhanced urinary and fecal excretion of lead; restored the ALAD (δ-aminolevulinate dehydratase) activity, reduced the lead burden in tissues and increased the blood zinc protoporphyrin levels but did not reduce the brain lead levels. When lead gains entry into the cell, it interacts with multiple signaling pathways via disruption of the membrane by lipid peroxidation and other oxidative stress mechanisms [92]. Similarly, Flora et al. (1997) reported rapid excretion of lead and restoration of biochemical parameters except neurotoxicity when administered with calcium EDTA and DMSA [93]. Chelation therapy has its limitations. It can only halt the further progress of neuropsychological effects of lead but fails to reverse the damages occurred. So far no remedy is available to reverse this damage; hence, prevention is the only way out. In contrast to this, there are several reports on the use of chelators in connection with thiol group containing antioxidants. Antioxidants have shown a strong role in reducing oxidative stress from lead exposure and in improving the prooxidant/ antioxidant balance of the cells. This administration has shown to produce synergistic and beneficial effects than just treatment with chelators alone. A study by Flora et al. (2004) showed that taurine, a sulfur containing amino acid when coadministered with DMSA in lead treated male rats, the biochemical alterations indicative of oxidative stress caused by lead was reversed [94]. Similarly, they showed that the therapeutic chelating potency increased when succimer is coadministered with

sulfur containing antioxidants such as N-acetylcysteine, lipoic acid, and liposomal glutathione, consequently reversing oxidative stress and reducing lead levels [95]. Chelation therapy is recommended only to chronic lead poisoning cases due to severe compromising side effects it can cause such as in the redistribution of lead from blood to soft tissues and leaching of lead from skeleton (osteoporosis) into circulation during high bone turnover rate. Chelation is thus a risky therapy with very limited success rate. However, research in metal chelation to confer safe methods of chelating lead out of the system without disturbing the endogenous metal pool may need to be implemented with constant efforts to design ligands/ analogues of currently available chelators that specifically bind to lead. Table 2 illustrates the dosage regimen of chelators for adult lead poisoned cases.

Table 2: Dosage Regimen of Chelators used for Adult Lead Poisoning

Chelating agent	FDA Approval	Route of administration	Administration dose	Reported side effects	Mode of action
Dimercaprol (British Anti-Lewisite)	Yes	Intramuscular (IM)	• Initial IM dose- 4mg/kg. • Repeat administration of same dose after 4 hrs. • Then combine same dose with EDTA for 3-5 days. • If BLL rebounds, continue treatment with just EDTA.	• Nausea • Vomiting • Headache • Tachycardia • Burning sensation of lip, mouth and throat • Conjunctivitis • Lacrimination • Blepharal spasm • Rhinorrhea • Salivation.	The thiol group of dimercaprol forms a complex with lead and is excreted in the urine.
Calcium disodium EDTA	Yes	Intravenous (IV)	1000mg/m^2 body surface area/ day	• Dizziness • Headache • mild nausea • acute renal failure • mild elevation of hepatic transaminases • hypotension • cardiac arrhythmias • Allergic reaction at the site of administration.	An analogue of dimercaprol; it binds to lead ions with high specificity to form water-soluble complexes which is readily excreted via kidneys.
DMSA (Dimercaptosuccinic acid/Chemet/ Succimer)	No	Oral (O)	• 1st course: 10mg/kg orally every 8 hours for 5 days. • 2nd course: 10mg/kg orally every 12 hours for 14 days.	• Diarrhoea • Nausea • Vomiting • loss of appetite • Mild elevation of hepatic transaminase • Allergic reaction	A water soluble analogue of dimercaprol; it increases urinary excretion of lead.
DMPS (meso2,3-Dimercaptopropane-1-sulfonate)	No	Oral (O) Intramuscular (IM) Intravenous (IV)	• **Oral**: 50-100 mg every 6-8 hours or 5 mg/kg in 2- 4 doses.	• Dizziness • Weakness	A water soluble analogue of dimercaprol

9.2 Nutritional Intervention

A safe approach to fighting lead poisoning is the consumption of a balanced nutritive diet; nutritional well being and diet provides resistance and alters the susceptibility to toxic substances including heavy metals, drugs, pesticides and carcinogens. Nutrients sustain expression of the genetic program of an individual [96], [97]. This is further supported by the rising concept of nutritional epigenetics where certain bioactive food components modify gene expression at the transcriptional level. Some of the nutrients that regulate expression include vitamin B12, vitamin B6, riboflavin, methionine, choline and betaine. As of now literatures on lead toxicity is flooding with studies where micronutrients are administered in appropriate doses to lead poisoned rats consequently, reversing lead induced biochemical effects indicating a significant role of gene-diet interactions in toxicology. In India, while the primary prevention of lead poisoning through policy and public health decision makers is implemented, clinicians or industrial hygienists need to focus on secondary prevention through nutritional supplementation to reduce the effects of lead exposure. There is strong evidence that various dietary factors can influence the gastrointestinal absorption of lead [98]. As stated by the famous Greek philosopher Hippocrates- "Let food be thy medicine and medicine be thy food", there are several food sources that reduce the absorption and

reabsorption of lead and detoxify the body naturally [99]. The three ways by which micronutrients can absorb lead from the gut include-

1. Binding of dietary micronutrients to lead to form a complex, making it unavailable for absorption.
2. Interaction of this complex with cellular processes that regulate lead absorption.
3. Modification in metabolic status of tissues with an affinity for absorbed lead.

Figure 3 illustrates the mechanism of lead and micronutrients interaction. Studies have shown that chief nutrients like calcium, iron, and vitamin-C and to a lesser degree- phosphorus and zinc reduce lead levels [100]. Individuals consuming diet deficient of micronutrients will become predisposed to toxicity of lead [101]. Depending on the severity of lead exposure and nutritional balance of an individual, the dietary intake must be planned; hence, there is a need to implement nutrition interventional strategies for lead poisoned individuals. Moreover, the ability of micronutrients to modulate the toxicity of lead is a challenging area due to variations in the body metabolism.

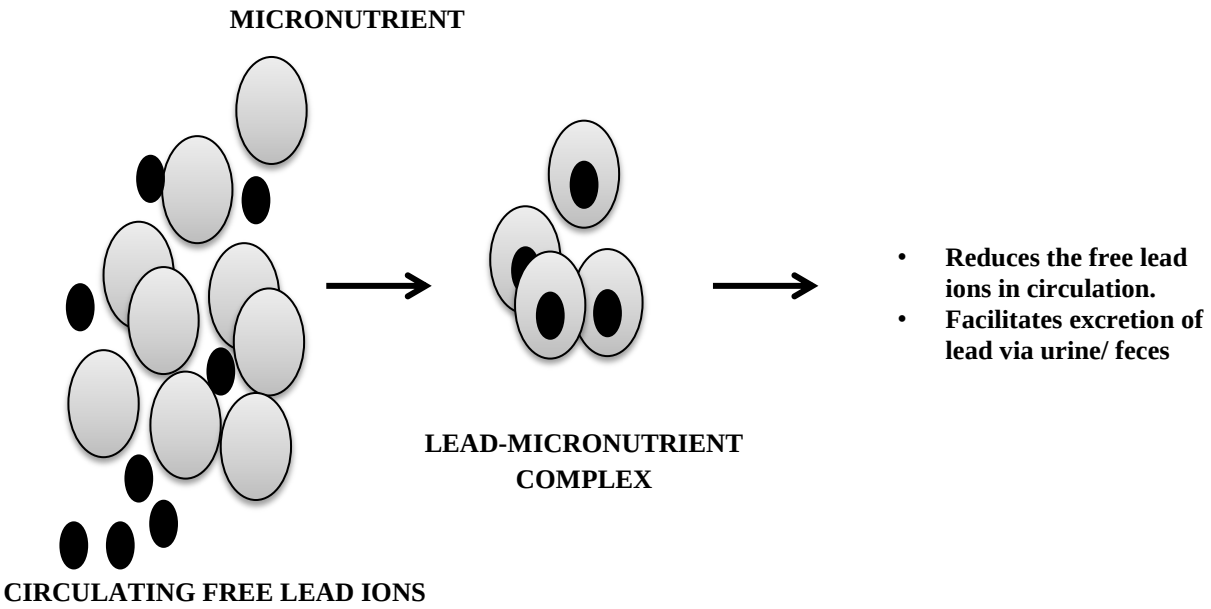


Figure 3: Lead- Micronutrient Interaction

9.2.1 Vitamin-C

Vitamin C or ascorbate, known for its antioxidant properties essentially neutralizes the free radical damage inflicted on various organs and tissues during oxidative stress [102]. It is an antiscorbutic, essential for normal growth and development. Some of the sources enriched with vitamin C include citrus fruits like orange, lemon, grapes, strawberry, gooseberry (amla) and kiwi fruit and vegetables like broccoli, spinach, tomatoes, and baked potatoes. Vitamin C exhibits metal chelation property with a similar potency to that of EDTA. Lead forms soluble complexes with ascorbic acid to form poorly ionizable lead ascorbate due to which the concentration of free lead ions reduces and its precipitation into the bone is delayed enhancing excretion of lead and reduced lead body burden [103]. Its antiabsorption property enables it to increase the availability of iron by reducing ferric iron to ferrous iron in the duodenum to compete with lead for intestinal absorption. It functionally protects ALAD, the most targeted enzyme of the heme synthesis hence, preventing anemia. In a follow-up study of 34 chronically lead exposed workers, vitamin C administration improved the blood picture and the overall health. In another study it was observed that the ascorbate and blood lead levels were inversely related suggesting that ascorbate imparts a protective effect against lead poisoning and reverses the pathological impact of chronic lead poisoning [104], [105].

9.2.2 Vitamin-E

Vitamin E or α- tocopherol, protects the cell membranes from oxidative stress by interacting with free radicals and terminating the chain of lipid peroxidation [106]. Animal observational studies have shown that vitamin E can improve the stability of red blood cell membranes signifying its potential role in eradicating lead induced anemic conditions [100]. Some of the food sources that contain vitamin E include eggs, cereals, leafy vegetables such as spinach, nuts and its oils, vegetable oil, olive oil, wheat germ oil and whole grains. Azab et al. (2013) showed that sesame seed oil which is a good source of vitamin E and mono/ polyunsaturated fatty acids exhibit a protective action

against lead acetate induced hemato-biochemical toxicity in mice models [107].

9.2.3 Calcium

Pathways involving calcium as the sole signaling molecule represents a sensitive target for lead. Due to similar divalent character lead competes with higher affinity for calcium channels/ pumps of the plasma membrane such as calmoldulin, protein kinase C (PKC) and calcium dependent

K^+ channels [101], [108], [109]. The cellular effects as a consequence of lead-calcium interactions are well described in literature. Ca^{2+} mediated cellular processes including vitamin D synthesis and inhibition, Ca^{2+} second messenger system, Ca^{2+} homeostasis and Ca^{2+} regulating proteins is affected by lead. Dietary Ca^{2+} levels are replenished from food sources like milk, yoghurt, cheese, vegetables and fish meat. Six and Goyer (1970) observed that rats fed with low calcium diet increased the lead body burden resulting in anemia, excretion of ALA (δ-aminolevulinate), appearance of intranuclear inclusion bodies in renal tubular cells and aminoaciduria [110]. Ettinger et al. (2007) observed that calcium supplementation during pregnancy and lactation suppressed lead levels [111]. Hence dietary Ca^{2+} supplementation constitutes an important secondary prevention to reduce circulating lead levels and protect the growing fetus from lead exposure. However, Ca^{2+} must not be prescribed for mild or moderate lead poisoned individuals who are dietarily Ca^{2+} sufficient as it may result in hypercalcaemic condition. Thus a constant level of dietary calcium is essential to compete with lead released during high bone turnover to reduce brain and organ toxicity [96].

9.2.4 Iron

Iron is important in determining an individual's ability to resist the toxic effects of lead. A majority of iron is bound to hemoglobin which is necessary for the transportation of oxygen to various tissues. Some of the rich sources of iron include lean meat, sea food, nuts, sunflower seeds, beans, whole grains, dark leafy vegetables, dark chocolate and tofu. Lead inhibits ferrochelatase (FECH), the last enzyme involved in the heme synthesis. Ferrochelatase catalyzes the insertion of iron (Fe^{2+}) into the porphyrin ring of protoporphyrin IX molecule to form heme. This enzyme is sensitive to the effects of lead particularly during iron deficient conditions leading to accumulation of porphyrin molecules, very low hemoglobin content and anemia [100]. Good levels of iron in the body can help decrease lead induced brain and kidney damage avoiding the impact of lead induced anemia [100], [112]. A handful of studies have revealed that iron deficiency and iron overloading disease (hemochromatosis) which is a proven cause of anemia may have a significant impact on the circulating blood lead levels and also on the cumulative lead body burden [113].

9.2.5 Zinc

Zinc does not have much impact on reducing lead levels as iron or calcium but when combined with other supplemental amino acids like lysine it aids in clearing of lead [100], [114]. It is an antioxidant and a constituent of free radical scavengers essential for proper brain development and function. Studies have shown that zinc deficiency during development caused permanent malformation of the brain. Some of the important food sources of zinc include oysters, wheat germ, cocoa, crab, seeds, nuts, beef, dates, eggs and blue cheese. Dietary zinc decreases lead absorption and its toxicity, indicating that zinc competes with lead for gastrointestinal uptake; studies have also indicated that a good level of zinc can modify lead toxicity in reproduction [115]-[117]. Zinc administration in lead poisoned cases has shown to reduce the excretion of ALA (δ- aminolevulinate) and iron protoporphyrin levels in urine. In lead exposed iron deficient conditions, zinc protoporphyrin levels increase suggesting that zinc has a limiting role in chelating lead.

9.2.6 Phosphorus

Phosphorus is another nutrient of interest found in large quantities in dairy products, meat, fish, soft drinks, beans, nuts and whole grains. The number of studies on the protective effect of phosphorus on lead toxicity is very limited. Studies have shown that animals fed with phosphorus deficient diet increased the lead retention. However, when fed in combination with calcium in diet, the gastrointestinal absorption of lead decreased indicating a partial involvement of phosphorus in sequestering lead [100], [101].

9.2.7 Selenium

Selenium is another micronutrient of concern that in trace amounts is beneficial to reduce lead levels. It serves as a cofactor for the antioxidant metalloenzyme glutathione peroxidase which chiefly aid in recycling glutathione, reducing lipid peroxidation and protecting DNA, RNA and proteins from oxidative damage. Some of the food sources of selenium include skin of sardines, raw cow or goat's milk, raw cheese and yoghurts, fermented milk drink (kefir), mustards of all kinds, garlic, onion and lentils, arrowroot powder and sunflower seeds and nuts. Selenium is known to form inactive selenium-lead complexes which consequently reduce the free lead ions in the body [118]. A comparative study was performed on lead poisoned vitamin-E deficient rats and it was observed that excess dietary selenium showed partial protection against lead poisoning [119]. Tandon et al. (1992) on the other hand showed that administration of selenium with effective chelating drugs namely Ca Na_2 EDTA and calcium trisodium diethylenetriamine penta acetic acid (Ca Na_3 DTPA) only slightly enhanced lead mobilization than when administered with drug alone indicating that selenium is not a potent chelator of lead [120]. In addition, a high dietary

supplementation of selenium can put an individual at high risk of selenium poisoning [100], [121].

9.2.8 Organosulphur compounds

A diet rich in sulfur containing amino acids such as N-acetylcysteine and methionine help in the generation of antioxidants glutathione in the body and food sources include soybeans, beef, lamb, sunflowers seeds, chicken, oats, pork, fish, cheese, eggs, legumes, and wheat. Other active substances such as allecin (or diallyl thiosulfinate) from garlic, an organosulfur compound known to chelate heavy metals including lead [122], [123]; a mice study shows that cucurmin (chemically diferuloylmethane), a compound from organically grown turmeric have protective effects on lead induced neurotoxicity [124]; β-carotene from carrots and other natural food sources such as bananas, pineapple, oranges, oats, tomato, rice, barley and sweet corn enhances melatonin production and protects tissues from lead induced free radical damage [125], [126].The healthy medicinal herb, cilantro is another remedy for lead poisoning. Animal studies with cilantro have shown to reduce the amount of lead accumulated in bones of lead exposed mice and removes lead settled in kidney tissues, decreases the urinary excretion of ALA and inhibition of ALAD [99], [127]. As long as MMND is avoided, lead poisoning can be fought easily and prevented.

10. Conclusion

Since the potential health hazards of lead poisoning is rising in India, continuous efforts are required to deal with the problem. Any developing country like India can manage this preventable environmental health hazard only through proper countrywide awareness and education. Phasing out of lead based products such as paints, ceramics, pipes and plumbing materials and eliminating the practice of adding lead to spices, cosmetics, traditional medicines and banning of items containing high amount of lead might reduce lead exposure. Employers working in the lead based industries should get their blood lead levels tested at least every two months by any one of the CDC approved methods. Lead poisoning is 100% preventable and treatable. If the problem is diagnosed in early stages, it may require simple treatment or environmental interventions to identify and eliminate the potential sources of lead exposure. If ignored, it becomes chronic and may require a longer course of chelation therapy. By following safe work practices and consuming good nutrition with adequate supply of micronutrients, natural antioxidants, use of vitamins, essential minerals and sulfur containing food like garlic, onions, cauliflower, cabbage, broccoli, egg yolk in the diet, exposure to lead can be reduced and the individual will develop better resistance to lead toxicity. Through this paper we would like to convey that in this global sea of information, let us all stand together and work as an organization to eradicate the use of lead from our paints, medicines, food products, cosmetics, gasoline and be the voice of hope for those who are at high risk of lead exposure.

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