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Human Health Effects from Exposure to Lead: A Review of the Current Literature

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Abstract: Low-level chronic exposure to heavy metals can go undetected for years accumulating in the human body which in turn can impact virtually any organ system. Lead is of particular concern given its prevalence, toxicological effects at low concentrations, and persistence in the body. In order to adequately regulate lead concentrations in food, water, air and consumer products, it is important to understand the relevant toxicodynamics and minimum risk levels at which deleterious effects are observed. An excellent resource is the lead toxicological profile published by the U.S. Center for Disease Control (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) in cooperation with the U.S. Environmental Protection Agency (EPA). This peer-reviewed profile identifies and reviews published literature that describes human health effects, toxicokinetics, chemical and physical properties, and potential for human exposure. Since the release of that monograph in August of 2020, over 200 additional research papers have been published on the impact of lead exposure as it pertains to genotoxicity, cytotoxicity, neurological and cardiovascular effects to name a few. The purpose of this report is to review the published research since the release of the last ATSDR lead toxicology profile in order to present the most current studies relative to lead toxicodynamics, associated concentration levels, and potential areas for continuing research.

Keywords: Lead, Heavy Metals, Toxicity, Toxicodynamics, Review

1. Introduction

Metals are unique as toxicants in that they are ubiquitous and many can be both essential for human physiology as well as toxic when present at elevated concentrations. Whereas acute exposure such as an occupational accident primarily affects the respiratory system or gastrointestinal tract, low-level chronic exposure may go undetected for years resulting in bioaccumulation which can impact virtually any organ system. It is for these reasons, that heavy metals have been referred to as "silent killers" and oftentimes go undetected until a public health issue arises. Examples include the recent concerns in the U. S. regarding elevated heavy metal concentrations in baby food [1] and in cannabis and hemp derived products [2].

In order to adequately regulate metals concentrations in consumer products, it is important to understand the relevant toxicodynamics and minimum risk levels at which deleterious effects are observed. An excellent series of resources are the toxicological profiles published by the Center for Disease Control (CDC) Agency for Toxic Substances and Disease Registry (ATSDR). These are comprehensive monographs for substances on the ATSDR priority list which are categorized (levels 1 – 4) based upon degree of toxicity, frequency of occurrence at hazardous waste sites, and potential for human exposure. Level 1 toxicants include arsenic, mercury, cadmium and lead. Lead, in particular, is an element of primary concern with over 200 research papers published on the mechanism of lead toxicity since the last ATSDR lead profile was published in 2020. The primary purpose for this report is to review the published research since the release of the last ATSDR lead toxicology profile in order to present the most current studies relative to lead toxicodynamics, associated concentration levels, and to highlight potential areas for continuing research.

2. Exposure and Toxicokinetics

Lead (Pb) is a blueish white highly corrosive metal found widely distributed through our environment as a result of various anthropogenic activities. It can be found in various chemical states, does not readily decompose and is easily transferred continuously through water, air and soil by different chemical and physical processes [3, 4]. Exposure and/or toxicity is usually quantified by internal metrics, primarily blood-lead (PbB) concentrations usually expressed in terms of µg/dL. The effects of lead have been widely documented with concentrations as minute as 5µg/dL being the lowest at which adverse effects can manifest especially in infants [5, 6]. High levels of PbB have been found in males as compared to females with higher levels of lead also associated with the use of tobacco products and alcohol consumption [7, 8].

The toxicokinetics i.e., absorption, distribution, metabolism and excretion of lead, has been studied extensively using various models. Absorption of inorganic lead in the respiratory tract is achieved when lead is in sub-micron sizes with much larger particles cleared towards the oropharynx and swallowed. Gastrointestinal absorption usually occurs in the duodenum and is dependent on a number of factors such as age (with children generally absorbing much larger amounts than adults), diet, nutrition and the chemical nature of lead and the medium in which it was ingested. Dermal absorption may occur, however it is an inefficient means of absorption compared to respiratory and gastrointestinal absorption. Distribution of lead in the body is heavily route-dependent with the majority of total body lead burden concentrated in the bones. Lead in blood is primarily found in the red blood cells and can be increased by conditions such as pregnancy, lactation, menopause and osteoporosis which result in bone resorption [9, 10]. Excretion of lead occurs primarily in urine and feces regardless of the route of exposure and may also be excreted in sweat, saliva, hair, nails, breast-milk and seminal fluid in minor quantities. Elimination of lead is multiphasic and can occur between 1 week to as long as 2 years depending on the age and history of exposure. Elimination from bones can take up to 2 decades demonstrating the potential for lead to accumulate in the body.

3. Human Health Effects

3.1. Infants and Children

Infants and children are of utmost concern since maternal transfer in utero and subsequent exposure through breastfeeding and/or environmental exposure can lead to lifelong decrement especially in neurological function [11-15]. Decrement in neurological function can range from reduced cognitive function, altered behavior and mood leading to difficulties in social interactions as well as altered neuromotor and neurosensory function and much higher doses may even result in alteration in nerve function and in some cases encephalopathy [16-19].

Reuben et al., [20] examined lead exposed children with follow-up psychometric test for over 3 decades to determine the impact of lead exposure on mental health and behavioral challenges. The study found a correlation between abnormal cognition and early childhood lead exposure as well as an association between children exposed to lead and higher levels of neuroticism and lower agreeableness and conscientiousness. Other studies have also found a significant association between reduced cognitive function and elevated lead levels in children [21-23].

There is also evidence of developmental deficiency in infants and children and studies have confirmed childhood lead exposure to be a precursor for a variety of hepatic conditions in later life [24]. Evidence from a cohort intergenerational study consisting of about 1400 mother-child pair by Wang et al., [25] found obesity and overweight childhood to be associated with maternal exposure to lead. Maternal exposure is also likely to cause elevated blood pressure in childhood and adolescence [26, 27]. Saheli et al., [28] found a link between maternal lead exposure and congenital heart disease (CHD) in children. The study found mothers of children born with CHD to have a significantly higher levels of lead compared to mothers of children with no CHD.

Rygiel et al. [29] assessed prenatal lead exposure and DNA methylation using umbilical cord blood collected within 12 hours of birth and maternal bone lead collected 1 month postpartum. There was a significant differential methylation at several sites presenting the likelihood of epigenetic modifications impacting child development. High levels of DNA methylation promotor - δ-Aminolaevulinic acid dehydratase (ALAD)- factors was found present in children with high lead exposure as compared to those with low exposure. The study also demonstrated a strong association between clinical symptoms of ALAD including anemia, body pains, memory loss and low intelligent quotient (IQ) [30, 31]. Linares et al., [32] also found iron-deficient anemic hematological parameters to be highly associated with blood lead concentrations in a study among Peruvian children.

Lead causes a number of biochemical changes in infants and children. Particularly pre- and postnatal lead exposure has been found to influence the development of immunological systems of children thereby impacting the proper function of cytokines and lymphocytes [33-35]. Rahman et al., [36] also established an association between PbB levels, total and free 25-hydroxyvitamin D levels (25(OH)D) and vitamin D binding proteins (VBP) – biomarkers for vitamin D status in children. Results showed a positive and negative correlational relationship between PbB levels and free and total 25 (OH)D and VBP, respectively.

There is also evidence of reduction of the levels of non-enzymatic antioxidant of biochemical components such as bilirubin, albumin and creatinine in children due to lead poisoning. This is indicative of oxidative hyperirritability and a much higher chance of development of neurological symptoms with some associated gastrointestinal disorder or developmental retardation [37].

3.2. Neurological

In adults, neurological effects following low levels of lead exposure are also encountered [38]. Waliszewska-Prosół et al., [39] examined brain activity in the form of Evoke Potential (EP) and its correlation with lead and other metals in an occupational study and compared the data with a control group. The study group showed changes in latency and amplitude of EP suggesting brain dysfunction.

Al-Anabri et al., [40] investigated Type 2 diabetes mellitus patients and the potential neurological damage associated with exposure to lead. MRI results showed high brain hyperintensities in lead exposed diabetic patients with increasing levels of lead likely to cause more hyperintensities and consequently leading to cognitive malfunction. Current research study posits that low level lead exposure, even after the source of exposure has been eliminated is able to cause significant epigenetic alterations that underlies many neurodegenerative conditions [41, 42].

Lead exposure and toxicity has also been linked to long term effects on neurotransmitters and thyroid hormones thereby causing neurobehavioral changes, increasing psychopathologies and impairing dopaminergic and serotonergic systems and affecting the intelligence quotient especially of school going children [43-46]. Lead exposure has been documented to influence neurotransmitter status significantly which can potentially lead to many neuropathies including anxiety [47-50]. Cybulska et al., [51] advocates for the need to conduct studies to fully understand the possible relationship and mechanism of lead toxicity and anxiety as well as depression.

3.3. Cardiovascular

There is a myriad of cardiac related diseases that result from lead exposure. Lead exposure significantly increases the likelihood of blood pressure elevation especially when associated with other metals [52-54]. There are also reports that both systolic and diastolic blood pressure as well as white blood cell (WBC) counts and cholesterol levels were positively correlated with PbB levels in a dose-response manner [55, 56]. Park & Oh, [57] found smoking as one of the risk factors for high levels of PbB and other heavy metals which influence metabolic system such as systolic and diastolic pressure, waist circumference and triglyceride levels, impacting an individual's overall wellness. High levels of lead have been identified as a risk factor for obesity, diabetic vascular complications and coronary related diseases [58-60]. Recent studies suggest the association between lead exposure and obesity results from the bioaccumulation of lead in the adipose tissues thereby increasing bone marrow adiposity which is characterized by an increase in adipose size and number as seen in animal models. There is also evidence of lead exposure leading to an increase in cytosolic adipose accumulation, indicative of adipogenesis [61].

In a study by Meswari et al., [62] a case-control in Malaysia demonstrated that there is a significant association between blood lead and myocardial infarction even at concentrations as low as 5µg/dL. Kim et al., [63] also conducted a 20-year study assessing the association between PbB levels and coronary artery stenosis with results suggesting that PbB levels of less than 5µg/dL was associated with moderate to severe coronary artery stenosis in 94% of the asymptomatic participants. Obeng-Gyasi et al., [64] reported that the combined effects of lead exposure and chronic stress is twice as likely to cause cardiac mortality in persons exposed to lead than non-exposed persons.

Yu et al., [65] conducted a two-year study on the link between occupational lead exposure and heart rate variability – a risk factor for coronary heart disease. There was ternary increment in the levels of lead although this did not produce a corresponding dose-response relationship.

3.4. Hematological and Immunological

Hematological and immunological effects also result from exposure to lead where there is a decrease in the synthesis of heme through the inhibition of enzymes and perturbed immune system response, respectively [66-68]. Increase in PbB concentration can also likely lead to anemic conditions by reducing blood hemoglobin and erythrocytes. Peters et al., [69] confirmed that PbB levels influence anemic conditions in a dose-dependent manner by determining Red Blood Cell Width (RBCW) elevation and measured amounts of cadmium and lead. The study found an association although a weak one between elevated RBCW and lead especially in males. Yu Meng et al, [70] also investigated the linkage between lead exposure and hematotoxicity by determining the neutrophil to lymphocyte ratio (NLR) and the results showed a significant positive association. Lead exposure also induced genotoxicity, with an increase in NLR corresponding to increase in DNA damage.

Lead levels above 6µg/dL may have a significant dose-dependent effect on the percentage of plasmacytoid dendritic cells which in turn have stimulatory effects on T helper 1 cells. Corroboration was derived from studies on modulation of lead to assess this relationship [71, 72]. Furthermore, there is a significant established association between Hemoglobin A1c (HA1c) and lead exposure. HA1c is a diagnostic parameter in assessing diabetic status, this therefore suggests lead exposure as a potential risk for the development of diabetics [73, 74].

3.5. Cytotoxicity

Some studies have established an association between cancer and lead exposure albeit these results are inconsistent and based upon limited data. Lead has been known to cause mitochondrial damage through the generation of reactive oxygen species. Gao et al., [75] investigated the association between endoplasmic reticulum stress and mitophagy. The results demonstrated significant decrease in mitochondrial proteins and the detection of ER stress- related proteins in a dose-dependent manner.

Metryka et al., [76] demonstrated low levels of lead can affect the viability of cells in an in vitro experiment where

monocytes and macrophages were induced with lead ranging from 1.25µg/dL to 10µg/dL. The study also showed a dose-dependent increase in the number of early and late apoptotic cells after incubating for up to 48 hours.

Attafi et al., [77] investigated the role of Nuclear Factor kappa B(NF-kB) and Aryl hydrocarbon Receptors (AhR) in lead induced lung toxicity. The study used human lung cancer A549 cells and reported lead exposures to cause an up-regulation of apoptotic genes and subsequent increase in oxidative stress through the generation of reactive oxygen species. The study also reported an inhibition of NF- kB and AhR either chemically or genetically diminishes lead induced oxidative stress and apoptosis. Further experiments by Wei et al., [78] in an occupational cohort study found lung toxicity to be caused by moderate to high doses of lead. *"The high levels of oxidative stress may be as a result of decreased expression of NQO1 – an enzyme necessary for the reduction of ROS as observed in lead exposed individuals"*. Rhee et al., [79] in a separate study found a significant association between high PbB and increased lung cancer mortality to be more prevalent in females than in males.

Ho et al., [80] found synergistic activity between lead and cigarette smoking in 267 lead workers as measured thiobarbituric acid reactive substances (TBARS) values correlate positively with the ratios of oxidized low-density lipoproteins to low density lipoproteins.

Angiogenesis – a means of generating or forming new blood vessels- a process critical for the transport of essential molecules and nutrients thus has a significant health implication whether at high or low rates in humans. Current body of research indicate an association between lead exposure and angiogenesis promoting factors, however less is understood about the mechanisms involved [81].

3.6. Genotoxicity

Lead exposure results in the generation of oxidative stress and reactive species that affect metabolic functions particularly influencing the activity of δ-Aminolaevulinic acid dehydratase in blood and 8-hydroxyl-2-deoxygenase concentration in urine and damaging DNA as well (Ibrahem et al, 2020; Fu & Xi, 2020) [82, 83]. Ono & Horiguchi., [84] studied the relationship between PbB and (delta Aminoluvinic acid) urinary ALA-U levels in lead workers in Japan. The authors propose 1 mg/L -independent of smoking- as the biologically acceptable level of ALA-U instead of the formerly established 5mg/L.

Another study in Jodpur, India examined lead exposure and DNA damage as well as gene repair in 100 occupationally exposed individuals by determining 8-OHdG and quantitatively determining RT-PCR of repair genes. Comparing results from non-occupational samples show significant differences as well as confirming association with oxidative stress, DNA damage and alteration in repair of DNA [85, 86].

Ochoa-Martínez et al., [87] also undertook scientific studies to investigate the association between lead exposure and its associated changes observed in microRNA levels expression. Conclusions drawn from the study shows lead exposure significantly contributes to epigenetic alterations which is associated with a number of health implications including cancer and cardiovascular injury among others [88-90].

3.7. Reproductive

Reproductive effects of exposure to lead in males are much more documented than in females. Damage to sperm including low sperm count, decreased mobility or viability and deformed sperm as well as alterations in production of reproductive hormones may occur in males with severity of the effects increasing with increasing PbB levels. Semen mobility has been demonstrated to be significantly reduced by low levels of lead (5-10 µg/dL) and thus affecting fertility [91-93].

Lead from sampled urine has been found to be inversely related to testosterone and the follicle stimulating hormones and interestingly positively correlates with progesterone and estrogen [94, 95]. Mitra et al., [96] examined the physiological and microscopic parameters and conducted a hypo-osmotic swelling test to assess the integrity of semen samples. In another study, Wu et al., [97] found high levels of PbB to be associated with high serum prostate specific antigen (an indicator of prostate cancer) in males over 40 years. These studies confirms that lead exposure affects male reproductive health.

Increased infertility, spontaneous abortion, increased pre-term birth, disturbed reproductive hormonal secretions and early onset of menopause are usually characteristic of lead exposure in females (Jin et al, 2013; Khanam et al, 2021; Turker 2013; Tartaglione et al, 2020) [98-101]. A study by Upson et al., [102] investigated the association between the use of depot medroxyprogesterone acetate (DMA), a contraceptive for women and blood levels and reported higher levels of lead present in women using DMA as compared to non-users. *"This likely results from increased bone resorption that occurs with the use of DMA permitting increased blood lead from lead stored in bones"*.

Lead exposure has been found to cause preeclampsia in women even in non-occupational settings suggesting that environmental and low levels of Lead exposure is likely to cause complications during pregnancy [103, 104]. M. G. Kim et al., [105] also in a 5-year study found a relationship between endometriosis, a chronic inflammatory condition that can result in infertility and low levels of lead among females occupationally exposed.

3.8. Renal

Renal damage and a decreased renal function are observed as effects from exposure to lead. Enzymuria, proteinuria, impaired transport of anions and molecules and a decreased glomerular filtration rate are usually found when lead is present in even minute amounts and can result in nephrotoxicity when the levels of exposure are much higher. High amount of Lead exposure has also been linked with

elevated levels of creatinine and low levels of creatinine clearance indicating renal damage [106, 107]. Cabral et al., [108] in a study found evidence indicating necrosis of the cells of the proximal and distal tubules in individuals exposed to lead and cadmium. This greatly affects the integrity of the kidneys with subsequent exposures capable of causing a great score of nephropathies. Lead can generate reactive species in tubular and glomerular cells leading a cascade of reactions that ultimately damages the structural and functional integrity of the renal system in exposed persons [109-111].

3.9. Other Toxic Effects

Lead exposure demonstrates an inverse correlation with prestin levels -a protein associated with auditory function. However further evidence is needed in this area taken into account noise pollution levels [112, 113].

High bone turnover rates or resorption has been associated with high levels of PbB especially in persons with vitamin D deficiency, diabetics and the elderly. Also, diabetics with a deficiency in vitamin D are at a much greater risk with even minute environmental exposures [114, 115].

Evidence from research indicates lead exposure can cause several dental diseases such as Burton's line, periodontitis, fluorosis, enamel and gingival defects, and tooth loss and pocket formation especially in children. These result via a number of degenerative mechanisms including salivary secretion, interaction with bone-seeking elements and oxidative stress. It can also interfere with oral inflammatory parameters, increase gut microbiota and influence mineralization [116, 117].

Lead exposure also influences the normal functioning of the microbiota present in the gut/intestine and may lead to a number of pathologic states such as gastrointestinal distress, obesity, cardiovascular diseases, neurological impairment and cancer. This is evidenced by many documented animal and human study models and experiments respectively [118-121].

Other health effects that result from the exposure to lead affects different organ systems producing respiratory, hepatic, musculoskeletal, ocular and endocrine effect [122-126].

4. Conclusion and Recommendations

Lead continues to be a focus for toxicological research given its prevalence and broad toxicodynamic effects. As the emerging economies of developing countries continue to grow, so does the impact of lead contamination resulting from industrial activity in those parts of the world. In addition, advances in epigenomics research have opened the door to a better understanding of how lead alone, or in concert with other metals, impact cell regulation such as the methylation cycle. Below is a summary of several areas that were identified as opportunities for continued research:

Cybulska et al., 2021 advocates for the need to conduct studies to fully understand the possible relationship and mechanism of lead toxicity and anxiety as well as depression.

The association between cancer and lead exposure needs to be further investigated as the results of previous studies are inconsistent and based upon limited data sets.

Similarly, the mechanisms involved in the association between lead exposure and angiogenesis promoting factors are not well understood.

Further investigation is needed into the mechanism by which lead exposure contributes to epigenetic alterations leading to cancer and cardiovascular injury among others.

The inverse correlation of lead concentration with prestin levels and auditory function requires further understanding.

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