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LEAD AS A DEVELOPMENTAL TOXICANT: A REVIEW

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ABSTRACT: A toxic substance is one which can produce its adverse effects in biological systems by interfering with their structure and function, which may lead to mortality. From the biological point of view, it can be consider that no chemical is either completely safe or harmful .The safe or harmful nature of toxic substance depends on the doses, duration and the time when animal is exposed to the particular toxic substance. Susceptibility to toxicant often depends on developmental stage. There are critical period of development during pre and postnatal time and a particular structure or function will be most sensitive to disturbance during its critical period. Developmental toxicants are agents that cause adverse effects on the development of new progeny. Recently the developmental toxicology has become an increasingly significant area of toxicology and encompasses the study of hazard and risk associated with exposure to toxicants during pre and postnatal development. It has been expanded by the U.S Environmental Protection Agency to include effects on the developmental process in the course of the time of puberty, i.e., until the completion of all developmental processes. Although considerable progress has been made in determination of causation, the etiology of the majority of birth defects is unknown or only poorly established. The present review is an effort to learn much more about the toxicant and their mechanisms involved in eliciting congenital defects. The attention has been focused on the genetic and environmental factors and their interactions involved in triggering such mechanisms.

INTRODUCTION:

Lead: Developmental Toxicant: Lead is known to be one of the most toxic environmental and industrial pollutants. Its industrial applications were developed based on its unique chemical and physical properties.

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Lead is a ubiquitous toxic heavy metal and, unlike organic compounds, it is not biodegradable and has a very long biological half-life. In spite of many studies, the mechanism of its toxicity has not yet been well elucidated and in contrast to other metals, there is no effective therapy for its poisoning.

Lead has been extensively used since ancient times, and the history of public exposure to lead in food and drink is extensive. Lead poisoning was common in Roman times because of the use of lead in water pipes and in wine containers. Lead poisoning became common among industrial

workers in the 19th and 20th centuries, when workers were exposed to lead in smelting, painting, plumbing, printing, and many other industrial activities. Following the advent of motor vehicles at the beginning of the 20th century and the introduction of leaded gasoline, environmental lead contamination substantially increased.

Lead appears on the FDA's list of poisonous and deleterious substances which was established to control levels of contaminants in human food and animal feed [1]. Lead has been identified as a contaminant in at least 1,026 of the National Priorities List (NPL) sites and is currently ranked first on the priority list of Hazardous substances [2].

RECOGNIZED DEVELOPMENTAL TOXICANTS:

Chemical Name	CAS Registry Number (or EDF Substance ID)	Reference(s)
Lead	7439-92-1	P65
Lead acetate	301-04-2	P65-MC

Proposition 65 includes lead as developmental and reproductive toxicants, but not its compounds. Environmental Defense lists lead compounds as recognized developmental and reproductive toxicants based on the inclusion of their elemental forms on the Proposition 65 list. This analysis includes lead compounds in our list of developmental and reproductive toxicants.

Substances Reported to TRI in 2004 with Known or Suspected Health Effects

Chemical Name	Carcinogen	Developmental Toxicant	Reproductive Toxicant
Lead	R	R	R
Lead compounds	R	R	R

R= Recognized S= Suspected

The biological half-life of lead is extremely difficult to estimate [6]. The half-life of lead in erythrocytes is 35 days; in soft tissues (kidney, liver, and nervous tissue) the half-life is 40 days; the half-life in bone is 20 to 30 years [7].

Effects of Lead on development: Environmental lead toxicity is an old but persistent public health problem throughout the world. The population most sensitive to lead exposure from various sources is pregnant women and children[8]. As far as the exposure to environmental elements is concerned, attention has been directed to study the exposure to lead, and since its health effects may begin during exposure in uterus, the study of maternal exposure is of significance [9].

Developmental toxicants are agents that ground their adverse effects on the development. Effects can include birth defects, low birth weight, morphological, structural, histopathological, biological dysfunctions, or behavioral deficits. Maternal exposure to toxic chemicals during pregnancy can disrupt the development or even cause the death of the fetus. Exposure of pregnant females to lead lowers birth weight and can cause severe brain damage in offspring. While developmental toxicity usually results from prenatal exposures to toxicants experienced by the mother, it can also result from paternal exposures.

For example, serious toxic effects of lead on the fetus are well established and prenatal exposure is a major cause of childhood lead poisoning [10]. Preterm delivery, congenital abnormalities and decrease in growth stature have all been associated with prenatal lead exposure. Early postnatal contact with toxicants can also affect normal development. Our experimental results suggest that during pre-differentiation stage, the embryonic cells multiply and differentiate at high rates so that the embryo is more susceptible to teratogenic agents, which will either cause death of the embryo or produce no apparent effect on the embryo [11].

Lead can readily cross the placenta; therefore, exposure of women to lead during pregnancy results in uptake by the fetus and they are at even greater risk. During development, the fetus is at the mercy of its mother. If the mother has high blood lead levels during pregnancy, the developing fetus will have the same. Lead freely crosses the placenta consequently; gestational lead poisoning is not only harmful to the women but also to the developing fetus [12]. Furthermore, since the physiological stress of pregnancy may result in mobilization of lead from maternal bone, fetal uptake of lead can occur from a mother who was exposed to lead before pregnancy, even if no lead exposure occurs during pregnancy [13].

Childhood lead poisoning is a worldwide problem. Although recent data continue to demonstrate a decline in the prevalence of elevated blood lead levels (BLL) in children in the industrialized world, lead remains a common, preventable, environmental health threat. Guidelines for developmental toxicity evaluation have been published by the US EPA [14]. This document provides specific guidance concerning the assessment of maternal toxicity in teratology and reproductive toxicity bioassays.

Children are more susceptible than adults to the adverse effects of lead exposure [15]. Children's unique physiology and behavior can influence the extent of their exposure. The physiological uptake rates of lead in children were higher than those in adults. In addition, children were rapidly growing, and their systems were not fully developed, which renders them more susceptible to the effects of lead. No safe blood lead level in children has been determined. Children were exposed to lead all through their lives. They can be exposed to lead in the womb if their mothers have lead in their bodies. Babies can swallow lead when they breast feed, or eat other food and drink water that contains lead. Babies and children can swallow and breathe lead in dirt, dust, or sand while they play on the floor or ground. These activities make it easier for children to be exposed to lead, in comparison to adults [16].

Poisoning by inorganic lead compounds presents as three main clinical pictures: chronic poisoning; acute poisoning; and asymptomatic poisoning, occurring during childhood. The dose of lead required to cause adverse effects is rarely, if ever, known. The lead blood level confirms a causal link between likely exposure and an effect [6]. The well-known toxicity of lead to many organs and systems is generally dose-dependent [17]. There is no evidence for a threshold below which lead has no adverse effects [18].

Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period. Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults.

For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight [19], the gastrointestinal absorption of lead is greater in infants and young children[20]. Since a substantial body of literature has demonstrated adverse effects of lead on the adult system in a variety of laboratory animals, but very little has been done in this area of developmental biology.

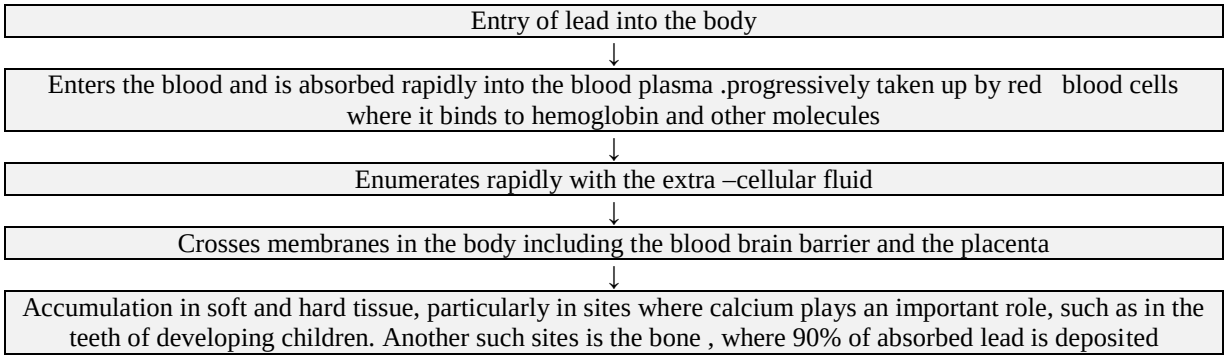
Absorption and distribution of Lead: The efficiency of lead absorption depends on the route of exposure, age, and nutritional status. Adult humans absorb about 10-15% of ingested lead, whereas children may absorb up to 50%, depending on whether lead is in the diet, dirt, or paint chips. More than 90% of lead particles deposited in the respiratory tract are absorbed into systemic circulation [13]. Lead absorbed into the body is distributed to three major compartments: blood, soft tissue, and bone. The largest compartment is the bone, which contains about 95% of the total body lead burden in adults and about 73% in children. The half-life of bone lead is more than 20 years. The concentration of blood lead changes rapidly with exposure, and its half-life of only 25-28 days are considerably shorter than that of bone lead. Blood lead is in equilibrium with lead in bone and soft tissue. The soft tissues that take up lead are liver, kidneys, brain, and muscle. Inorganic Lead is not metabolized in the body, but it may be conjugated with glutathione and excreted primarily in the urine [13, 21].

Absorption of lead may increases during pregnancy. An increase in lead absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone lead), to the increase in PbB concentration that has been observed during the later half of pregnancy [22].

Absorbed lead is attracted to sulfur, nitrogen, and oxides. Its toxicity is elicited by inhibiting sulfhydryl-dependent enzymes. Most of the lead is sequestered in the bone, and the rest is distributed in the blood and soft tissues. Lead interferes with hematopoiesis at several steps. Lead exposure during gestation and lactation led to various hematological disorders in red blood cells of neonates [23].

This results in less heme synthesis and the accumulation of toxic products (eg, aminolevulinic acid, protoporphyrin). The half-life of lead in the soft tissues and blood is approximately 30-70 days. Conversely, lead deposits in the bones for several years. Lead is primarily excreted by glomerular filtration.

Lead is very similar chemically to calcium, so once in the body; it is handled as if it were calcium .The flow diagram below shows what happen in the body after an intake of lead:



Bone turnover and Calcium and Lead relationships during pregnancy and lactation: Pregnancy and lactation are times of physiologic stress during which bone turnover is accelerated[24]. Changes in blood lead during pregnancy and lactation are inexorably linked with changes in calcium. During pregnancy and lactation, there is increased demand for calcium for transport to the fetus. The maternal response to the demand for calcium theoretically can involve increased absorption of calcium from the intestine, greater calcium conservation by the kidneys, of greater bone turnover [25].

During pregnancy stores of lead deposited in bones over a lifetime may be mobilized and transferred to the more bio-available compartment of the maternal circulation with potential toxic effects on the fetus and mother [26]. This possibility of bone resorption during pregnancy is alarming in view of recent studies linking even lower levels of lead exposure with deficits in neurobehavioral function in infants [27]. The early 3rd trimester of pregnancy may constitute a critical period for subsequent intellectual child development during which lead exposure can produce lasting and possibly permanent effects [27, 28].

The period of fetal growth is often the stage of development at which an organism is most sensitive to toxic agents. However, fetal exposure cannot be directly measured during pregnancy in human research studies. Maternal measurements are the only exposure indices ethically available [29].

The tendency for the body to confuse lead for calcium accounts for the fact that lead is incorporated into developing bones and teeth. Lead, in the form in which it affects biological systems, has the same +2 charge and roughly the same size as calcium ions. Lead ions are also similar to zinc and iron ions. Lead ions take the place of calcium, zinc and iron ions in many overlapping biochemical pathways. By substituting for essential minerals, lead can do permanent and severe damage to humans and other animals.

Because it is an element, lead does not degrade or lose its toxic effect over time. Being toxic on such a basic level, it is important to note that there is no known level at which lead is safe [30]. There is no chemical or biological reason to expect there to be a safe level of lead. Lead ions can substitute for iron, zinc or other metal ions in the chemically active core of several enzymes, blocking the functioning of the enzyme.

Lead is a persistent and common environmental contaminant. Like other commonly found, persistent toxic metals--mercury, arsenic, and cadmium--lead damages cellular material and alters cellular genetics [31]. Lead is known to disrupt the normal biochemistry in the kidney, brain and bones by causing the excessive production of some proteins whose role is to bind specifically to other molecules [32]. Lead plays no positive role in human biochemistry. The body cannot break down lead to make it less dangerous.

The pathogenesis of lead toxicity is multifactorial, as lead directly interrupts enzyme activation, competitively inhibits trace mineral absorption, binds to sulfhydryl proteins (interrupting structural protein synthesis), alters calcium homeostasis, and lowers the level of available sulfhydryl antioxidant reserves in the body [33].

The mechanisms of lead-related pathologies, many of which are a direct result of the oxidant effect of lead on tissues and cellular components, may be mitigated by improving the cellular availability of antioxidants. N-acetylcysteine (NAC), zinc, vitamins B6, C and E, selenium, taurine, and alpha-lipoic acid have been shown, in a number of animal studies, to interrupt or minimize the damaging effects of lead and improve the effects of pharmaceutical chelating agents [31].

Mechanisms of Lead toxicity:

The effect of Lead on oxidant/antioxidant balance: Lead Binds to Glutathione and Sulfhydryl-Containing Enzymes. Lead toxicity leads to free radical damage via two separate, although related, pathways:

(1) The generation of reactive oxygen species (ROS), including hydroperoxides, singlet oxygen, and hydrogen peroxide, and

(2) The direct depletion of antioxidant reserves [33]. In any biological system where ROS production increases, antioxidant reserves are depleted. In this situation, the negative effects on the human system's ability to deal with increased oxidant stress occur via independent pathways.

One of the effects of lead exposure is on glutathione metabolism. Glutathione is a cysteine-based molecule produced in the interior compartment of the lymphocyte. More than 90 percent of non-tissue sulfur in the human body is found in the tripeptide glutathione. In addition to acting as an important antioxidant for quenching free radicals, glutathione is a substrate responsible for the metabolism of specific drugs and toxins through glutathione conjugation in the liver [34].

The sulfhydryl complex of glutathione also directly binds to toxic metals that have a high affinity for sulfhydryl groups. Mercury, arsenic, and lead effectively inactivate the glutathione molecule so it is unavailable as an antioxidant or as a substrate in liver metabolism [35]. Lead also binds to enzymes that have functional sulfhydryl groups, rendering them nonfunctional and further contributing to impairment in oxidative balance [36].

Lead generates Reactive Oxygen Species (ROS): Erythrocytes have a high affinity for lead, binding 99 percent of the lead in the bloodstream. Lead has a destabilizing effect on cellular membranes, and in red blood cells (RBC) the effect decreases cell membrane fluidity and increases the rate of erythrocyte hemolysis. Hemolysis appears to be the end result of ROS-generated lipid peroxidation in the RBC membrane [37]. Lead can also bind directly to phosphatidylcholine in the RBC membrane, leading to a decrease in phospholipid levels [38].

Hypochromic or normochromic anemia is a hallmark of lead exposure; it results from ROS generation and subsequent erythrocyte hemolysis [33, 39]. Lead is considered, along with silver, mercury, and copper, to be a strong hemolytic agent, able to cause erythrocyte destruction through the formation of lipid peroxides in cell membranes [40]. In addition to membrane peroxidation, lead exposure causes hemoglobin oxidation, which can also cause RBC hemolysis. The mechanism responsible for this reaction is lead-induced inhibition of ALAD. ALAD is the enzyme most sensitive to lead's toxic effects--depressed heme formation [41].

Lead-induced oxidative stress has been identified as the primary contributory agent in the pathogenesis of lead poisoning. Oxidative stress has also been implicated in specific organs with lead-associated injury, including liver, kidney and brain tissue. ROS generated as a result of lead exposure have been identified in lung, endothelial tissue, testes, sperm, liver and brain [42]. The reactive oxygen species generated by lead is responsible for the ovarian dysfunction affecting the female reproduction [43]. The ovarian follicle is the functional unit of the ovary. It contains the oocyte that may eventually ovulate, undergo fertilization and form an embryo. It also provides the steroid and protein hormones required for maintenance of the ovarian cycle, the secondary sex characteristics and preparation of the uterus for implantation [44].

Lead acetate administrated during gestation and lactation adversely affects developing testis [45].

Production of antioxidants and free radicals in the body is theoretically balanced. When conditions favor free radical production, a state known as oxidative stress occurs. This can happen when either production of radicals is increased or antioxidant defenses are impaired. Cells can tolerate some degree of oxidative stress and typically respond by increasing the synthesis of antioxidants. Prolonged oxidative stress can result in oxidative damage to tissues [46]. Taking antioxidant without complete understanding of their effects may disrupt this balance.

Heavy metal toxicity may in fact be the real root cause of most health disorders and diseases today. Heavy metal ions produce large quantities of free radical compounds which destroy lipids, proteins, and DNA in the cellular system. Two-thirds (45–75%) of lead in blood, however, comes from long-term tissue stores and this is especially true for newborn infants and pregnant women. Several data suggest that for lead the main toxic event is prenatal exposure: therefore we should focus our attention on maternal lead stores and whenever possible avoid their mobilization during pregnancy. In this regard we should design appropriate studies to confirm whether dietary supplementations can reduce bone resorption and lead mobilization during pregnancy [47].

CONCLUSION: The role of environmental insults in diseases process is highly defined; however the risk of pre and postnatal abnormalities due to exposure to heavy metal lead early in life is not adequately addressed. Exposure to chemical agents at critical periods of development may cause some permanent change in the functioning of various vital systems in organism. It is not surprising to see an extensive response due to exposure to chemical agent early in life as the organ systems are more vulnerable to chemical insults during developmental stages.

This article summarizes the association of early life exposure to environmental agent and late life abnormalities with an emphasis on developmental exposure to lead.

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