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Recent Toxicity Study of Lead on Different Body System

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Sunita Bhardwaj, Amit Chaudhary, Shilpi Kashyap*, Chinu Sharma

Abhilashi University, Mandi, Himachal Pradesh, India.

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ABSTRACT

Lead poisoning and lead toxicity is a major effect on the body part and the various body systems. Generally, it produces a distinctive effect on the body, and it also involves the main toxic effect to the body which undergoes the process such as acute toxicity study (produce toxic or harmful effect on the body for a short period) and chronic toxicity study (produce toxic or harmful effect on the body for a long period) respectively. Each toxicity study provides us a wide range of knowledge about the harmful effect of any substance on the body. Here we discussed the various mechanisms of lead toxicity/poisoning. Lead regard as a potent occupational toxin and its manifestation are well known. Lead is biodegradable. Lead poisoning occurred due to human exposure. The lead--poisoning affect various systems and this review provides a very complete account of toxicity which describing health effects of the lead of human exposure and a various harmful effect of lead toxicity in a various body system.

INTRODUCTION

Toxicity the degree at which any substance may be poison or toxin that can cause the harmful effect on human or animals [1]. In an organism acute toxicity involves the harmful effect through a single or term exposure. Toxicity having mainly four general major types which has been discussed below [2].

- ❖ Acute toxicity
- ❖ Subacute toxicity
- ❖ Chronic toxicity
- ❖ Subchronic toxicity

Acute toxicity:

Acute toxicity may be defined as the toxicity which is produced by any pharmaceutical product [3], when it administered in one or more doses form during a period which is not exceeding 24hr.Generally the does form are given to a small groups of animals and the animals are observed for mortality and the LD50 dose is then calculated (the dose required to kill the 50% of the population). [4]

Sub acute toxicity:

Subacute toxicity may be defined as the study which is conducted to determine organs which is affected by the different dose form levels and this study will access the nature of toxic dose form under the more realistic situation than the acute toxicity studies. [5]

Chronic toxicity:

Chronic toxicity may be defined as the ability of any substance or mixture of any substance which does harmful effect due to the continuous exposure or due to the extended period, which also be sometime lasting stage for the entire life of the exposed organism these effects referred as Chronic toxicity respectively.[6]

Subchronic toxicity:

The subchronic toxicity may be defined as the ability of toxic substance which cause effects more than one year but this effect less than the lifetime of the exposed organism referred as Subchronic toxicity respectively [7].

Lead Toxicity

Distinctive properties of lead, like softness, high physical property, ductility, low freezing point and resistance to corrosion, have resulted widespread usages in numerous industries like cars, paint, ceramics, plastics, etc [8]. This successively has LED to a manifold is within the incidence of free lead in biological systems and also the inert surroundings. Lead is regarded as a potent occupational toxin and toxicological manifestation are well known [9]. The non biodegradable nature of lead is the prime reason for its prolonged persistence in the environment [10]. Human exposure to lead occurs through various sources like leaded gasoline, industrial processes such as lead smelt and. Lead is thought to be a potent activity poison and its toxicologic manifestations square measure documented [11]. The non perishable nature of lead is that the prime reason for its prolonged persistence within the setting [12]. Human exposure to guide happens through varied sources like gasoline, industrial processes like lead smelting and coal combustion[13], lead based paints, lead containing pipes or lead based sold in water system systems [14], battery use, grids and bearings, etc. though lead toxicity may be an extremely explore and comprehensively revealed topic [15],complete management and over lead exposure remains far away from being achieved. There is no such level of lead that seems to being necessary or helpful to the body and not “safe” level of exposure to guide has been found [16].Lead toxicity may be a not ably insidious hazard with the potential of inflicting irreversible health effects [17]. It better known to interfere with variety of body functions and it's primarily moving the central nervous, haematopoietic, viscous and urinary organ system manufacturing serious disorders [18]. Acute toxicity is said to activity exposure and is kind of uncommon [19]. Chronic toxicity on the opposite hand is far additional common and happens at blood lead levels of concerning 60ug/dL [20].It is way more severe treated in time and is characterised by persistent ejection, neurological disease, lethargy, delirium, convulsions and coma [21].

Main causes of lead toxicity:

Lead is a metal that occurs naturally in the earth crust, but human activity [22]. Burn fossil fuels and manufacturing [23] has caused it to become more widespread. Lead was also once used in paint and gasoline and still used in batteries, solder, pipes, pottery, roof materials and cosmetics [24].

Lead in paint

Lead based paints for homes, children and household furniture have been banned in the United States since 1978 [25]. Most lead poisoning in children results from eating chips of deteriorating lead-based paint.

Water pipes and imported canned goods

Lead pipes, brass plumbing fixtures and copper pipes soldered release lead particles into the tap water and lead solder in food cans [26], banned in the United States, is still used in some countries [27].

Other sources of lead exposure:

Lead sometimes can also be found in:

- **Soil:**

Lead contaminated so still a major problem around high ways and in some urban settings [28]. Some so close to walls of older houses contains lead [29].

- **House hold dust:**

Household dust can contain lead from lead paint chips or from contaminated soil brought in from outside [30].

- **Pottery:**

Glazes found on some ceramics [31], china and porcelain can contain lead that can leach into food served or stored in the pottery [32].

- **Toys:**

Lead is sometimes found in toys and other products which are produced abroad [33].

- **Cosmetics:**

An eye cosmetic from Nigeria has been linked to lead poisoning [34].

- **Herbal or folk remedies:**

Lead poisoning has been linked to great and azarcon [35], traditional medicines, as well as some from India, China and other countries [36].

Symptoms:

Initially, lead poisoning can be hard to detect people who seem healthy can have high blood levels of lead [37]. Signs and symptoms usually don't appear until dangerous amounts have accumulated [38].

Lead poisoning symptoms in children:

Signs and symptoms of lead poisoning in children include:

- Developmental delay
- Learning difficulties
- Irritability
- Loss of appetite
- Weight loss
- Sluggishness and fatigue
- Abdominal pain
- Vomiting
- Constipation
- Hearing loss

- Seizures
- Eating things, such as paint chips, that aren't food [39].

Lead poisoning symptoms in newborns:

Baby sex posed to lead before birth might:

- Baby born prematurely
- Have lower birth weight
- Have slowed growth [40]

Lead poisoning symptoms in adults:

Although children are primarily at risk, lead poisoning is also dangerous for adults. Signs and symptoms in adults might include:

- High blood pressure
- Joint and muscle pain
- Difficult with memory concentration
- Headache
- Abdominal pain
- Mood disorders
- Reduce dispermi count and sperm.
- Miscarriage, is till birth premature birth pregnant women.[41]

Disadvantages of lead toxicity:

- Heavy metal toxicity.
- Two, both highly toxic developing the brain and nervous system too. [42]
- Exposure to others. [43]

- Prenatal exposure. [44]

Mechanism of lead toxicity:

Lead toxicity mechanism based on two types of class:

1. **Main mechanism of lead toxicity**
2. **Ionic mechanism of toxicity**

1. Main Mechanism of toxicity:-

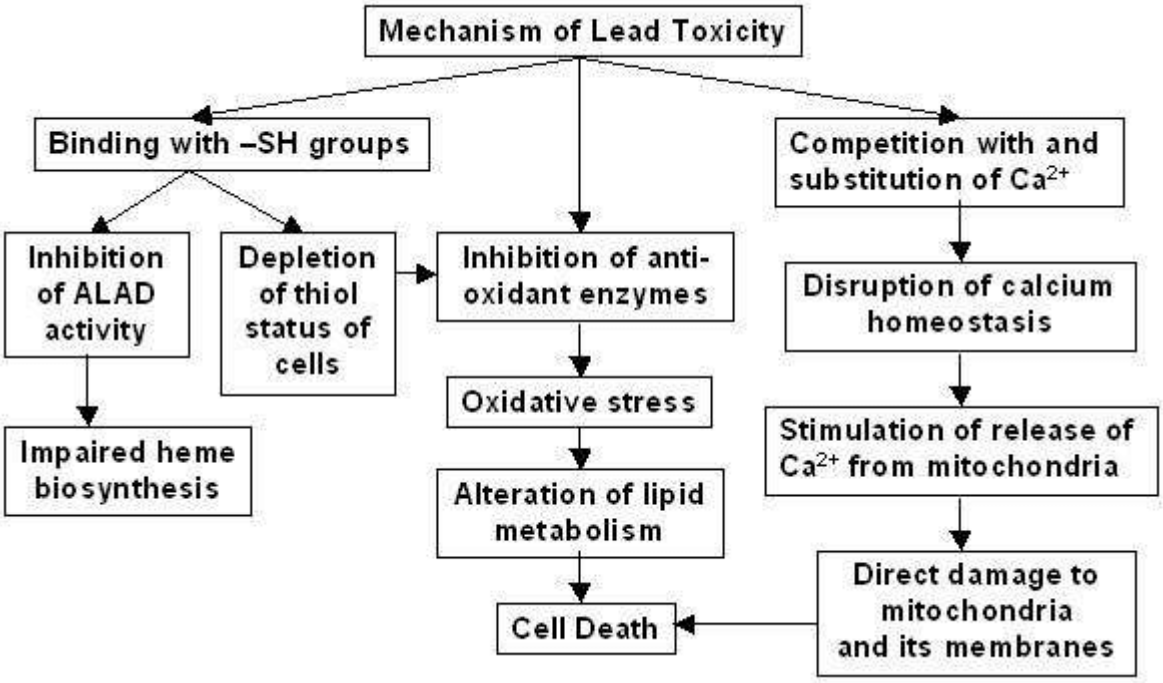

Figure No. 1: Mechanism of toxicity

The major mechanism of lead toxicity is due to increased generation of reactive oxygen species (ROS) and interference with generation of antioxidants [45]. Lead causes the generation of ROS like hydroperoxide, hydrogen peroxide, and singlet oxygen [46]. ROS are stabilized by glutathione in the body [47].

2. Ionic mechanism toxicity:

Ionic mechanism is based up on the action for lead mainly arises due to its ability to substitute other bivalent cations like Ca2+, Mg2+, Fe2+ and monovalent cations like Na+

(though bivalent cations are more readily substituted), affecting various fundamental biological processes of the body [48]. Significant effects have been found on various fundamental cellular processes like intra and intercellular signaling, cell adhesion, protein folding and maturation, apoptosis, ionic transportation, enzyme regulation, release of neurotransmitters, *etc* [49]. The ionic mechanism contributes principally to neurological deficits, as lead, after replacing calcium ions, becomes competent to cross the blood brain barrier (BBB) at an appreciable rate [50]. After crossing the BBB, lead accumulates in astroglial cells (containing lead binding proteins) [51]. The Toxic effects of lead are more pronounced in the developing nervous system comprising immature astroglial cells that lack lead binding proteins. Lead easily damages the immature astroglial cells and obstructs the formation of myelin sheath, both factors involved in the development of BBB [52].Lead,even molar concentration, can replace calcium, thereby affecting key neurotransmitters like protein kinase C, which regulates long term neural excitation and memory storage. It also affects the sodium ion concentration, which is also responsible for numerous vital biological activities like generation of action potential in the excitatory tissues form the purpose of cell to cell communication, uptake of neurotransmitters (choline, dopamine and GABA) and regulation of uptake and retention of calcium by synaptosomes [53]. This interaction between lead and sodium seriously impairs the normal functioning of the fore mentioned sodium dependent processes [54].

Lead poisoning:

Lead poisoning is a type of metal **poisoning** caused by **lead** in the body. The brain is the most sensitive [55]. Symptoms may include abdominal pain, constipation, headaches, irritability, memory problems, inability to have children, and tingling in the hands and feet [56].

Causes: Exposure to lead via contaminated air.

Symptoms: Intellectual disability.

Types of lead poisoning:

Table No. 1: Types of lead poisoning

Types	Exposure	Lead level(ug/dl)	Clinical symptoms
Acute poisoning	Intense exposure of short duration	100-120	Muscle pain, Fatigue, abdominal pain, headache, vomiting, seizure & coma
Chronic poisoning	Repeated low-level exposure over a prolonged period.	40-60	Persistent vomiting, encephalopathy, lethargy, delirium, convulsion & coma

Toxic effect of lead on various body systems:

1. Effect on the Nervous System
2. Cardio vascular Effects
3. Renal Effects
4. Reproductive Health Effects
5. Effect on Bone
6. Effect on the Hematopoietic System
7. Effect of lead on GSH metabolism[57]

1. Effect on the Nervous System:

Compared to different organ systems, the system seems to be the sensitive and chief target for lead elicited toxicity [58]. The central system and therefore the peripheral system become affected on lead expose.The consequences on the peripheral system in adults whereas the central system is additional prominently affected in youngsters [59].

Neurological disease (a progressive degeneration of sure elements of the brain) may be a directicon sequence of lead exposure and therefore the major symptoms include [60]:

- Dullness
- Irritability
- Poor span
- Headache
- Muscular tremor
- Loss of memory and hallucinations [61].

Additional severe manifestations occur at high exposures such as:

- Lack of coordination
- Convulsions, paralysis
- Coma and neurological disorder [62].

Fetuses and youngsters are particularly at risk of the neurologic effects of lead because the developing system absorbs a better fraction of lead. The proportion of systematically current lead gaining access to the brain of is considerably higher as compared to adults [63]. Youngsters could seem inattentive, active and irritable even at low lead exposure [64]. Youngsters with bigger lead levels could also be affected with:-

- Delayed growth,
- Diminished intelligence,
- Remember
- Hearing disorder.

At higher levels, lead will cause permanent brain injury and even death there is proof suggesting that low level lead exposure considerably affects IQ in conjunction with behavior, concentration ability and attentiveness [65]. Lead exposure on the peripheral system has additionally been ascertained within the variety of peripheral pathology, involving reduced motor activity so seriously impairing the [66]:

- Transduction of nerve impulses,
- Causing muscular weakness,
- Particularly of the muscles, fatigue and lack of muscular coordination [67].

2. Effect on Cardiovascular System:

Both chronic and acute illness causes viscus and tube shape distructure injury with doubtless fatal consequences together with high blood pressure and upset [68].Low level lead exposure will contribute to high blood pressure in each animals and humans. Different major disorders include such as:

- Anaemia coronary heart condition
- Vas accidents and peripheral tube-shaped structure illness [69]. Though proof of causative relationship of lead exposure and high blood pressure was reportable,it applies only in cases of cardio vascular outcomes of lead toxicity [70].

3. Effect on Renal system:

Renal disfunction happens principally at high levels of lead exposure (>60 µg/dL) however harm at lower levels has additionally been according (~10µg/dL)[71]. Urinary organ useful abnormality will be of 2 types:

❖ Acute uropathy

❖ Chronic uropathy. [72]

❖ **Acute uropathy:**

Acute uropathy is characterized functionally by associate degree impaired hollow transport mechanism and morphologically by the looks of chronic changes within the hollow epithelial tissue at the side of the prevalence of nuclear inclusion bodies containing lead macromolecule complexes and the result is [73]:

- It doesn't cause macromolecule to seem within the excrement however will bring about to abnormal excretion of glucose, phosphates and amino acids [74]:

❖ **Chronic uropathy:**

Chronic uropathy on the other hand, is far severe and might result in irreversible purposeful and morphological changes [75]. It is characterised by capillary and tubul interstitial changes which leading to urinary organ breakdown, high blood pressure and hyperuricemia are respectively [76].

4. Effect on reproductive system:

Generally Lead causes variety of adverse effects on the genital system in each men and girls [77]. The Common effects seen in male include:

- Reduced sexual desire,
- Abnormal gametogenesis (reduced motility and number),
- Body injury,
- Physiological condition,
- Abnormal endocrine operate and changes in liquid body substance androgen. In female includes are unit additional liable to physiological condition [78].
- Miscarriage[79],
- Premature membrane rupture,
- Preeclampsia, gestation cardiovascular disease and premature delivery throughout the gestation, direct influence of lead on the organic process stages of the foetus has additionally been according [80].

5. Effect on Bone:

The primary site of lead storage with in the human body area unit bones .The area unit-2 compartments in bones wherever lead is believed to keep. [81]. The exchangeable pool gift at the surface of bone and also the non exchangeable pool settled deeper within the plant tissue bone and the lead will enter into plasma comfortable from the exchangeable pool however will leave the non exchangeable pool and move to the surface only if bone is actively being reabsorbed [82]. Stable lead atom methodology showed that bones contribute around 70% of

lead free into blood in adults. In adults [83], 95% of the lead is keep in bones and distinction to seventieth in children, leading to higher concentration of lead in soft tissues in children [84]. The storage and also the mobilization of lead in bones depend on many factors such as dose/rate of lead exposure, age, pregnancy, gestation and race [85].

6. Effect on the Hematopoietic System:

Lead directly affects the organic process system through restraining the synthesis of haemoglobin by inhibiting numerous key enzymes concerned within the haemitin synthesis pathway [86]. It conjointly reduced the generation of current erythrocytes by increasing the fragility of cell membranes. The combined aftermath of those two processes results in anemia [87], Anemia caused on account of unwellness may be of two types: anaemia [88], that is related to acute high level lead exposure, and frank anemia, that is caused only if the blood lead level is considerably elevated for prolonged periods [89]. Lead considerably affects the haemitin synthesis pathway in very dose dependent manner by down regulating three key enzymes within the synthesis of haemitin [90].

I. δ-aminolevulinic acid dehydratase (ALAD),

II. Cytosolic accelerator that catalyzes the formation of porphobilinogen from δ-aminolevulinic acid (ALA), aminolevulinic acid synthetase (ALAS)[91],

III. Mitochondrial acceleratorm that catalyzes the formation of aminolevulinic acid (ALA)[92], The mitochondrial accelerator ferrochelatase that catalyzes the insertion of iron into protoporphyrin to make haem and the initial and final steps of haemitin synthesis occur within the mitochondria [93], whereas the intermediate steps ensue within the protoplasm. Lead inhibits the three same important enzymes of this pathway however its impaction ALAD is a lot of profound and its inhibition has been used clinically to determine the degree of unwellness [94]. Inhibition of ALAD leads to the buildup of amino levulinic acid, detectable within the plasma and excreta even at blood lead levels of but ten µg/dl. And ALAD inhibition initial note blood lead levels of 1020 µg/dl[95], haemitin biogenes doesn't decrease till the activity of ALAD inhibited by 90%, that happens at a way higher blood lead concentration of concerning fifty five µg/dl[96] . Inhibition of ferro chelatase leads to increased excretion of proporphyrin in excreta and accumulation of protoporphyrin in erythrocytes (EP)[97]. Moreover, inhibition of this accelerator leads to the substitution of by atomic number 30 within the pigmenting forming atomic number 30 protoporphyrin

(ZPP)[98].The concentration of ZPP so get increased, which may even be used as associate degree indicatorito observe the amount of lead exposure[99].Thus, the collective inhibition of those three key enzymes blocks the haemitin production via the haemitine synthesis pathway and the mechanism answerable for shortening the life cycle of erythrocytes isn't well understood[100].One in all the earliest determined haematological effects of lead disclosed stainability stipplings of red blood cells (presence of dense material in red blood cells), that is additionally a possible biomarker for the detection of unwellness [101]. These aggregates degradation product of RNA [102].

7. Effect of lead on GSH metabolism:

GSH can be regenerated from GSSG by the enzyme glutathione reductase [103].Under the normal conditions, 90% of the total glutathione content exists in reduced form (GSH) and around 10% is in the oxidized form (GSSG[104]). Under the conditions of oxidative stress, the concentration of GSSG is much higher than that of GSH [105]. Lead shows electron sharing capability that results in the formation of covalent attachments and these attachments are formed between the lead moiety and the sulphydryl groups present in antioxidant enzyme[106], which are the most susceptible targets for lead and which eventually get inactivated and lead inactivates glutathione by binding to sulphydryl groups presents in it[107].

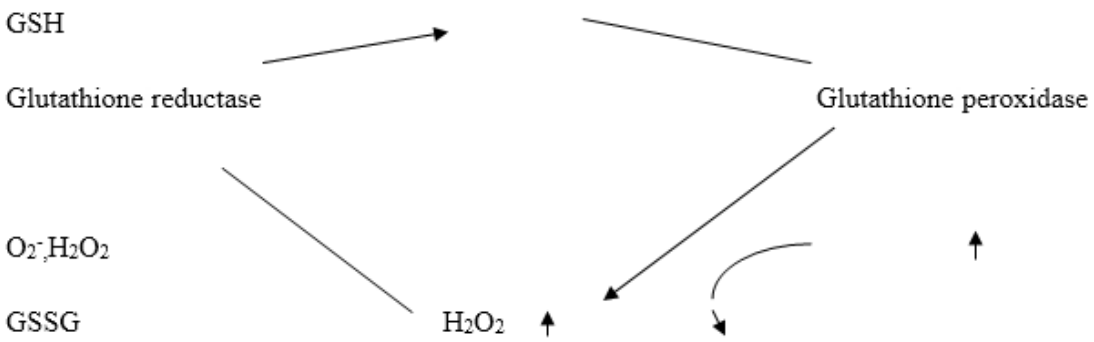

Figure No. 2: Effect on GSH metabolism.[108]

This all results in synthesis of GSH from cysteine via the γ glutamyl cycle, which is usually not effective in replenishing the supply of GSH and Similarly, lead inactivates enzymes like δ amino levulinic acid dehydratase (ALAD), glutathione reductase (GR), glutathione

peroxidase (GPX) and glutathione-S-transferase, which also further depresses the glutathione levels[109].

Notable antioxidant enzymes, rendered inactive by lead:

- Superioxide dismutase (SOD)
- Catalase (CAT).

Decrease in SOD concentration reduces the disposal of superoxide radical, whereas reduction in CAT impairs scavenging of superoxide radical (O2•) [99], I and apart from targeting the sulfhydryl groups, the lead can also replace the zinc ions that serve as important of actors for these antioxidant enzymes and inactivates them[110].

CONCLUSION:

Lead poisoning has been known to be mankind since the situation got aggravated since the 18th century during the industrial revolution .And it was the basic period when the various very important qualities of the lead poisoning were discovered. Although the lead has no biological function in the body but it has been found that when it enters in the body it causes several problems in the body and sometimes it causes death of the individuals. It has been found that it affects all over the body systems in the body syste like nervous system, cardiovascular system, skeletal system, haematopoitic system etc.

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