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John O Idoko
Department of Pure and Industrial Chemistry, Bayero University, Kano- Nigeria

King O Ijege
Department of Applied Science, Kaduna Polytechnic Kaduna-Nigeria

Mohammed S Suleiman
Kaduna State Environmental Protection Authority, Kaduna-Nigeria

Halima Uba
Kaduna State Environmental Protection Authority, Kaduna-Nigeria

Correspondence
John O Idoko
Department of Pure and Industrial Chemistry, Bayero University, Kano- Nigeria

Lead toxicity and removal: A review

John O Idoko, King O Ijege, Mohammed S Suleiman and Halima Uba

Abstract
Lead poisoning has been recognized as a major public health risk, particularly in developing countries. Though various occupational and public health measures have been undertaken in order to control lead exposure, cases of lead poisoning are still reported. Exposure to lead produces various deleterious effects on the cardiovascular, renal, nervous system; reproductive health and effect on bone and other critical organs mainly through increased oxidative stress. These alterations play a prominent role in disease manifestations. Modulation of cellular metabolism for protection against reactive oxygen species (ROS), and has been used as a therapeutic strategy against lead poisoning. This review provides a comprehensive account of recent updates describing health effects of lead exposure, relevant biomarkers and mechanisms involved in lead toxicity, and possible removal from the environment via adsorption mechanism, as this technique updates the readers about recent advances in lead remediation.

Keywords: Lead toxicity, Encephalopathy, Reactive oxygen species, Adsorption, Remediation

1. Introduction
Lead is one of the earliest metals discovered by the human race. Unique properties of lead, like softness, high malleability, ductility, low melting point and resistance to corrosion, have resulted in its widespread usage in different industries like automobiles, paint, ceramics, plastics, *etc.* [1]. This in turn has led to a manifold rise in the occurrence of free lead in biological systems and the inert environment. Lead is regarded as a potent occupational toxin and its toxicological manifestations are well known. The non-biodegradable nature of lead is the prime reason for its prolonged persistence in the environment [1-3]. Human exposure to lead occurs through various sources like leaded gasoline, industrial processes such as lead smelting and coal combustion, lead-based paints, lead containing pipes or lead-based solder in water supply systems, battery recycling, grids and bearings, etc. Although lead toxicity is a highly explored and comprehensively published topic, complete control, removal and prevention over lead exposure is still far from being achieved [4-7]. There is no such level of lead that appears to be necessary or beneficial to the body and no "safe" level of exposure to lead has been found. Lead toxicity is a particularly insidious hazard with the potential of causing irreversible health effects. It is known to interfere with a number of body functions and it is primarily affecting the central nervous, hematopoietic, hepatic and renal system producing serious disorders [8]. Acute toxicity is related to occupational exposure and is quite uncommon. Chronic toxicity on the other hand is much more common and occurs at blood lead levels of about 40–60 ug/dL. It can be much more severe if not treated in time and is characterized by persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma [9, 10]. The aim of the present article is to summarize current knowledge regarding the risks this widespread pollutant may pose to human health and to derive possible and suitable methods for its removal from the environment. The review will be focused on the cardiovascular effect, renal effect, nervous system, reproductive health effect and effect on bone the critical organs for which dose-response relationships are the best documented. These target organs can be monitored using well-validated exposure and effect biomarkers. The review will also address some of the issues that complicate the risk assessment of lead and in particular the inconsistencies between the critical exposure levels derived in industrial workers and in the general population with much lower exposures to environmental lead [11].

2. Risk assessment/exposure routes
Lead is a common environmental pollutant. Causes of environmental contamination include industrial use of lead, such as is found in facilities that process lead-acid batteries or produce

lead wire or pipes, and metal recycling and foundries [12]. Children living near facilities that process lead, such as lead smelters, have been found to have unusually high blood lead levels. In August 2009, parents rioted in China after lead poisoning was found in nearly 2000 children living near zinc and manganese smelters [13]. Lead exposure can occur from contact with lead in air, household dust, soil, water, and commercial products. Leaded gasoline has also been linked to increases in lead pollution. Some research has suggested a link between leaded gasoline and crime rates [14].

2.1 Occupational exposure

In adults, occupational exposure is the main cause of lead poisoning. People can be exposed when working in facilities that produce a variety of lead-containing products; these include radiation shields, ammunition, certain surgical equipment, developing dental x-ray films prior to digital x-rays (each film packet had a lead liner to prevent the radiation from going through), fetal monitors, plumbing, circuit boards, jet engines, and ceramic glazes [15]. In addition, lead miners and smelters, plumbers and fitters, auto mechanics, glass manufacturers, construction workers, battery manufacturers and recyclers, firing range instructors, and plastic manufacturers are at risk for lead exposure [16]. Other occupations that present lead exposure risks include welding, manufacture of rubber, printing, zinc and copper smelting, processing of ore, combustion of solid waste, and production of paints and pigments [17]. Parents who are exposed to lead in the workplace can bring lead dust home on clothes or skin and expose their children [18].

2.2 Food

Lead may be found in food when food is grown in soil that is high in lead, airborne lead contaminates the crops, animals eat lead in their diet, or lead enters the food either from what it was stored or cooked in [19-20]

2.3 Paint

Some lead compounds are colorful and are used widely in paints, and lead paint is a major route of lead exposure in children [21]. A study conducted in 1998–2000 found that 38 million housing units in the US had lead-based paint, down from a 1990 estimate of 64 million. Deteriorating lead paint can produce dangerous lead levels in household dust and soil [22]. Deteriorating lead paint and lead-containing household dust are the main causes of chronic lead poisoning [23]. The lead breaks down into the dust and since children are more prone to crawling on the floor, it is easily ingested. Many young children display pica, eating things that are not food. Even a small amount of a lead-containing product such as a paint chip or a sip of glaze can contain tens or hundreds of milligrams of lead [24]. Eating chips of lead paint presents a particular hazard to children, generally producing more severe poisoning than occurs from dust. Because removing lead paint from dwellings, e.g. by sanding or torching creates lead-containing dust and fumes, it is generally safer to seal the lead paint under new paint (excepting moveable windows and doors, which create paint dust when operated) [25]. Alternately, special precautions must be taken if the lead paint is to be removed. In oil painting it was once common for colours such as yellow or white to be made with lead carbonate. Lead white oil colour was the main white of oil painters until superseded by compounds containing zinc or titanium in the mid-20th century. It is speculated that the painter Caravaggio and possibly Francisco Goya and Vincent Van Gogh had lead poisoning due to overexposure or carelessness when handling this colour [26].

2.4 Water

Lead from the atmosphere or soil can end up in groundwater and surface water [27]. It is also potentially in drinking water, e.g. from plumbing and fixtures that are either made of lead or have lead solder [28]. Since acidic water breaks down lead in plumbing more readily, chemicals can be added to municipal water to increase the pH and thus reduce the corrosivity of the public water supply. Chloramines, which were adopted as a substitute for chlorine disinfectants due to fewer health concerns, increase corrosiveness. In the US, 14–20% of total lead exposure is attributed to drinking water [29]. In 2004, a team of seven reporters from The Washington Post discovered high levels of lead in the drinking water in Washington, D.C. and won an award for investigative reporting for a series of articles about this contamination. In the Flint water crisis, a switch to a more corrosive municipal water source elevated lead levels in drinking water in domestic tap water [30]. In Australia, collecting rainwater from roof runoff used as potable water may contain lead if there are lead contaminants on the roof or in the storage tank. The Australian Drinking Water Guidelines allow a maximum of .01 mg/L lead in water [31].

2.5 Lead-containing products

Lead can be found in products such as kohl, an ancient cosmetic from the Middle East, South Asia, and parts of Africa that has many names; and from some toys [32]. In 2007, millions of toys made in China were recalled from multiple countries owing to safety hazards including lead paint Vinyl mini-blinds, found especially in older housing and may contain lead. Lead is commonly incorporated into herbal remedies such as Indian Ayurvedic preparations and remedies of Chinese origin [33]. There are also risks of elevated blood lead levels caused by folk remedies like *azarcon* and *greta*, which each contain about 95% lead. Ingestion of metallic lead, such as small lead fishing lures, increases blood lead levels and can be fatal. Ingestion of lead-contaminated food is also a threat [34-35]. Ceramic glaze often contains lead, and dishes that have been improperly fired can leach the metal into food, potentially causing severe poisoning in some places, the solder in cans used for food contains lead. When manufacturing medical instruments and hardware, solder containing lead may be present. People who eat animals hunted with lead bullets may be at risk for lead exposure Bullets lodged in the body rarely cause significant levels of lead, but bullets lodged in the joints are the exception, as they deteriorate and release lead into the body over time [36-38]. In May 2015, Indian food safety regulators in the state of Uttar Pradesh found that samples of Maggi 2 Minute Noodles contained lead up to 17 times beyond permissible limits. On 3 June 2015, New Delhi Government banned the sale of Maggi noodles in New Delhi stores for 15 days because it was found to contain lead beyond the permissible limit [39]. The Gujarat FDA on June 4, 2015 banned the noodles for 30 days after 27 out of 39 samples were detected with objectionable levels of metallic lead, among other things Some India's biggest retailers like Future Group, Big Bazaar, Easyday and Nilgiris have imposed a nationwide ban on Maggi noodles. Many other states too have banned Maggi noodles [4]

2.1.0 Bullets

Contact with ammunition is a source of lead exposure. As of 2013, lead-based ammunition production is the second largest

annual use of lead in the US, accounting for over 60,000 metric tons consumed in 2012 [41-42], second only to the manufacture of storage batteries. The Environmental Protection Agency (EPA) does not regulate lead, as a matter of law. Lead birdshot is banned in some areas, but this is primarily for the benefit of the birds and their predators, rather than humans. Non-lead alternatives include steel, tungsten-nickel-iron, bismuth-tin, and tungsten-polymer [43]. Because game animals can be shot using lead bullets, the potential for lead ingestion from game meat consumption has been studied clinically and epidemiologically. In a recent study conducted by the CDC, a cohort from North Dakota was enrolled and asked to self-report historical consumption of game meat, and participation in other activities that could cause lead exposure. The study found that participants' age, sex, housing age, current hobbies with potential for lead exposure, and game consumption were all associated with blood lead level (PbB) [44]. This study has been cited by popular media as simple evidence that hunting increases exposure to lead poisoning, prompting the University of Illinois Extension to release a statement that there is no such risk. Concerning the CDC report, the authors' conclusion in a related Epi-AID Trip report notes the small increase associated with game consumption in the study, and urges interpretation with respect to environmental context [45]. While this study suggests that consumption of wild game meat can adversely affect PbB, no participant had PbB higher than the CDC recommended threshold of 10μg/dl—the level at which CDC recommends case management; and the geometric mean PbB among this study population (1.17μg/dl) was lower than the overall population geometric mean PbB in the United States (1.60 μg/dl) [46]. The clinical significance of low PbB in this sample population and the small quantitative increase of 0.30μg/dl in PbB associated with wild game consumption should be interpreted in the context of naturally occurring PbB. Copper-jacketed, lead-based bullets are more economical to produce and use than lead or any other material. Alternative materials are available such as steel, copper, and tungsten, but alternatives are universally less effective and/or more expensive. However, the biggest impediment to using the vast majority of alternatives relates to current laws in the United States pertaining to armor-piercing rounds [47]. Laws and regulations relating to armor-piercing ammunition expressly prohibit the use of brass, bronze, steel, tungsten, and nearly every metallic alternative in any bullet that can be shot by a handgun, which at this time is nearly every caliber smaller than 50BMG (including the popular. 223 Remington, .308 Winchester and 30-06 to name just a few). Some lead-based bullets are resistant to fragmentation, offering hunters the ability to clean game animals with negligible risk of including lead fragments in prepared meat [48]. Other bullets are prone to fragmentation and exacerbate the risk of lead ingestion from prepared meat. In practice, use of a non-fragmenting bullet and proper cleaning of the game animal's wound can eliminate the risk of lead ingestion from eating game; however, isolating such practice to experimentally determine its association with blood lead levels in study is difficult. Bismuth is an element used as a lead-replacement for shotgun pellets used in waterfowl hunting although shotshells made from bismuth are nearly ten times the cost of lead [49-50].

3. Effects on human

3.1 Cardiovascular Effects

Both chronic and acute lead poisoning causes cardiac and vascular damage with potentially lethal consequences including hypertension and cardiovascular disease [51]. Low level lead exposure can contribute to hypertension in both animals and humans [52]. Other major disorders include ischemic coronary heart disease, cerebrovascular accidents and peripheral vascular disease. Although evidence of causal relationship of lead exposure and hypertension was reported, it applies only in cases of cardiovascular outcomes of lead toxicity [53].

3.2 Renal Effects

Renal dysfunction occurs mostly at high levels of lead exposure (>60 μg/dL) but damage at lower levels has also been reported (~10 μg/dL) [54]. Renal functional abnormality can be of two types: acute nephropathy and chronic nephropathy. Acute nephropathy is characterized functionally by an impaired tubular transport mechanism and morphologically by the appearance of degenerative changes in the tubular epithelium along with the occurrence of nuclear inclusion bodies containing lead protein complexes [55]. It does not cause protein to appear in the urine but can give rise to abnormal excretion of glucose, phosphates and amino acids, a combination referred to as Fanconi's syndrome [56]. Chronic nephropathy on the other hand, is much more severe and can lead to irreversible functional and morphological changes. It is characterized by glomerular and tubulointerstitial changes, resulting in renal breakdown, hypertension and hyperuricemia [57].

3.3 Effect on the Nervous System

Compared to other organ systems, the nervous system appears to be the most sensitive and chief target for lead induced toxicity [58]. Both the central nervous system and the peripheral nervous system become affected on lead exposure. The effects on the peripheral nervous system are more pronounced in adults while the central nervous system is more prominently affected in children [59-60]. Encephalopathy (a progressive degeneration of certain parts of the brain) is a direct consequence of lead exposure and the major symptoms include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory and hallucinations. More severe manifestations occur at very high exposures and include delirium, lack of coordination, convulsions, paralysis, coma and ataxia [61]. Fetuses and young children are especially vulnerable to the neurological effects of lead as the developing nervous system absorbs a higher fraction of lead. The proportion of systemically circulating lead gaining access to the brain of children is significantly higher as compared to adults [62]. Children may appear inattentive, hyperactive and irritable even at low lead exposure. Children with greater lead levels may be affected with delayed growth, decreased intelligence, short-term memory and hearing loss. At higher levels, lead can cause permanent brain damage and even death [63]. There is evidence suggesting that low level lead exposure significantly affects intelligent Quotients (IQs) along with behavior, concentration ability and attentiveness of the child. Repercussions of lead exposure on the peripheral nervous system have also been observed in the form of peripheral neuropathy, involving reduced motor activity due to loss of myelin sheath which insulates the nerves, thus seriously impairing the transduction of nerve impulses, causing muscular weakness, especially of the exterior muscles, fatigue and lack of muscular co-ordination [64].

3.5 Reproductive Health Effects

Lead causes a number of adverse effects on the reproductive system in both men and women. Common effects seen in men

include: reduced libido, abnormal spermatogenesis (reduced motility and number), chromosomal damage, infertility, abnormal prostatic function and changes in serum testosterone. Women on the other hand, are more susceptible to infertility, miscarriage, premature membrane rupture, pre-eclampsia, pregnancy hypertension and premature delivery [65]. Moreover, during the gestation period, direct influence of lead on the developmental stages of the fetus has also been reported [66].

3.6 Effect on Bone

The primary sites of lead storage in the human body are bones [67]. There are two compartments in bones where lead is believed to be stored. The exchangeable pool present at the surface of bone and the non-exchangeable pool located deeper in the cortical bone. Lead can enter into plasma at ease from the exchangeable pool but can leave the non-exchangeable pool and move to the surface only when bone is actively being re-absorbed [68]. Stable lead isotope methodology showed that bones contribute around 40–70% of lead released into blood in adults. In adults, 85–95% of the lead is stored in bones, in contrast to 70% in children, resulting in higher concentration of lead in soft tissues in children. The storage and the mobilization of lead in bones depend on several factors, like dose/rate of lead exposure, age, pregnancy, gestation and race etc. [68].

3.7 Mechanism of toxicity

Lead is probably the most extensively studied heavy metal. Studies carried out in this field have reported the presence of various cellular, intracellular and molecular mechanisms behind the toxicological manifestations caused by lead in the body which include oxidative stress [68].

3.1.0 Oxidative stress

Oxidative stress represents an imbalance between the production of free radicals and the biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage [69]. It has been reported as a major mechanism of lead induced toxicity. Under the influence of lead, onset of oxidative stress occurs on account of two different pathways operative simultaneously; first comes the generation of reactive oxygen species (*ROS),* like hydroperoxides (HO_2), singlet oxygen and hydrogen peroxide (H_2O_2), and second, the antioxidant reserves become depleted [70]. The antioxidant defenses of the body come into play to nullify the generated ROS. The most important antioxidant found in cells is glutathione (GSH)**.** It is a tripeptide having sulfhydryl groups and is found in mammalian tissues in millimolar concentrations. It is an important antioxidant for quenching free radicals [71-73]. Glutathione exists in both reduced (GSH) and oxidized form (GSSG). The reduced state of glutathione donates reducing equivalents ($H^+ + e^-$) from its thiol groups present in cysteine residues to (ROS) and make them stable. After donating the electron, it readily combines with another molecule of glutathione and forms glutathione disulfide (GSSG) in the presence of the enzyme glutathione peroxidase (GP_X)**.** GSH can be regenerated from GSSG by the enzyme glutathione reductase (GR). Under normal conditions, 90% of the total glutathione content exists in reduced form (GSH) and around 10% is in the oxidized form (GSSG). Under conditions of oxidative stress, the concentration of GSSG is much higher than that of GSH [74].

3. Removal Mechanism

Out of the many methods of removal of this inorganic pollutant from the environment, most especially from water, waste waters, adsorption is the predominantly used method with high efficiency removal and less expensive [75-76]. Adsorption is widely used as an effective physical method of separation in order to eliminate or lowering the concentration of wide range of dissolved pollutants (Organic and inorganic) in an effluent. It is big news that activated carbon is a well-known adsorbent that could be used efficiently for removal of a broad spectrum of pollutants from air, soil and water [77]. Adsorbents are usually porous solids, and adsorption occurs mainly on the pore walls inside particles. Examples are activated carbon (adsorbs mainly organics and inorganics), silica gel and activated alumina (adsorbed moisture), zeolites and molecular sieves and synthetic resins. Among others, activated carbon is more efficient adsorbent for elimination of many pollutants (organic, inorganic, and biological) of concern in water and wastewater treatment [78]. In the recent years, it has been increasingly used for the prevention of environmental pollution and antipollution laws have increased the sales of activated carbon for control of air and water pollution [79]. Activated carbon is a broad-spectrum agent that effectively removes toxic and bio-refractive substances such as insecticides, herbicides, chlorinated hydrocarbons, heavy metal ions, and phenols, typically present in many water supplies [80]. Activated carbon, in fact is a microcrystalline, non-graphitic form of carbon with porous structure that has been processed to develop its internal porosity. Activated carbon has a high degree of porosity, an extensive surface area, and a high degree of surface reactivity. Its large specific surface area of (200 – 2000 m^2/g) is in fact the most important physical property of activated carbon which allows the physical adsorption of gases or vapors and dissolved or dispersed substances from liquids [80]. It has large number of very fine pores (microspores) which gives the activated carbon a large inner surface, which is the basis of its remarkable adsorption properties. Consequently, they are effective adsorbents for many pollutant compounds (organic, inorganic, microbial and biological) of concern in water and wastewater treatment [81].

3.1.0 Applications of Activated Carbon (AC)

Applications of Activated Carbon are enormous. It is use for gasoline vapor emission control canisters in automobile. Activated carbon can act as a filter material in air cleaning filters for removal of gases and vapors in the industrial environment [82]. Especially impregnated grades are used in cigarette filters to absorb some of the harmful components of tobacco, and as the catalyst or carrier of catalytically active substances [82-84]. Heavy metal ions such as mercury, lead and cadmium in drinking waters are very dangerous even in trace amount, and adsorption method for removing these ions can be essential for water and waste water contaminated by heavy poisonous metal ions. For example lead, cadmium, mercuric ions all are very toxic and carcinogenic. Lead is also a cumulative metabolic poison, acting as a mutagen when adsorbed in excessive amounts. These ions cannot be removed from water with classic physical or chemical treatments completely. Activated carbon can be used for removal of poisonous heavy metal ions from aqueous solutions. Adsorption in this case is due to the surface complex formation between the metal ions and the acidic surface functional group of the adsorbent. Since activated carbon is a hydrophobic adsorbent, so it seems to be not a good candidate for adsorption of simple inorganic ions from polar aqueous solution; however, it is possible to improve the rate of adsorption of heavy metal ions by pretreatment of activated carbon with some suitable chemical reagents.

Sorption improvement is based on simple chemical reactions that are common in chemistry such as acid-base or neutralization, complex formation, redox, precipitation, hydrolysis and catalytic reactions [85]. For example if activated carbon is impregnated by molecule, ions and chelating agents that can combine with transition metal ions to form precipitation, complex or chalets, they can improve adsorption of metal cations significantly. For more illustration, the adsorption of mercury ion is also increased in acidic solutions and also when treated with surface sulphurized activated carborn. Highly colored waste streams such as result from dying operations can be cleaned-up by activated carbon. Its first use came into prominence through its use as an adsorbent for certain poisonous gases in gas masks in World War 1.

3.1.2 Formation of Active Carbon

Any carboneous materials (animal, plant, or mineral origin) with high concentration of carbon can be simply changed into activated carbon (using both chemical or gas activation methods), The most common raw materials are wood, charcoal, nut shells, fruit pits, brown and bituminous coals, lignite, peat, bone and paper mill waste (lignin), synthetic polymers like PVC, are used for manufacturing of activated carbon [86-87]. Activated carbons are commonly prepared by two basic processes: (i) Physical or gas activation method, and (ii) Chemical activation. The choice of activation method is also depending upon the starting material and whether a low or high density, powdered or granular carbon is desired. In gas activation method the raw material with less than 25% moisture, is carbonized first at 350 - 500 ^{o}C to eliminate the bulk of the volatile matter and then the carbon is subjected to oxidizing gases usually carbon dioxide or steam at 800-1000 ^{o}C or and with air at low temperature, for selective oxidation [88].

4. Conclusions

Adsorption process is a powerful technique that can be used for efficient removal or uptake of lead and some toxic materials from gas and liquid phases. Activated charcoal is one of the most important adsorbent that can be employed for these purposes. The use of activated carbon is perhaps the best broadspectrum control technology available at present moment. It is also quite possible to increase the amount of adsorption of inorganics by impregnating the activated carbon with suitable chemicals. The selection of impregnating material should be so that it encourages the adsorption via usual chemical reactions (e.g. neutralization, redox, hydrolysis, precipitation and catalytic reactions). Among the many factors affecting sorption or removal of toxic materials from aqueous solutions, the pH effect is the most prominent especially in the case of inorganics such as (lead), weak organic acid and bases which their dissociation is highly pH dependent.

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