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Heavy metal toxicity in animals: A review

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Abstract
Heavy metals like lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) are grouped in environmental pollutants that may alter homeostasis in the body. These metals can damage the cells through different mechanisms, including direct damage of cell membrane and damage of certain organelles, altering signal transduction pathway or affecting the intracellular enzymatic system. The toxicity depends on various factors which include nutritional status of the animals, age, sex, route of exposure, amount, tissue distribution, accumulation and excretion. They cause toxicity by promoting the production of oxidative stress and reactive oxidative species at molecular level. They may cause inhibition of enzymes, inhibition protein synthesis, changes in nucleic acid functioning and changes in cell membrane permeability. Industrial progress, industrialization, urbanization and agricultural production have become permanent resources of heavy metals in environment. Therefore, an attention should be paid to understanding the problems and its amelioration in animals

Keywords: Animals, arsenic, cadmium, lead, mercury.

Introduction
Heavy metals are naturally occurring elements that have a high atomic weight and density, at least five times greater than that of water and is toxic, highly toxic or poisonous at low concentrations. A heavy metal is a member of an ill-defined subset of elements that exhibit metallic properties, which would mainly include the transition metals, some metalloids, lanthanides, and actinides. They are commonly known as toxic metal. Heavy metals are widely dispersed in the environment. "Environmental Protection Agency" (EPA), the 'Agency for Toxic Substances and Disease Registry' (ATSDR) in Atlanta, Georgia (a part of the U.S. Department of Health and Human Services) reported that in a 'Priority List for 2001' called the 'Top 20 Hazardous Substances', As, Pb and Hg are at the 1st, 2nd and 3rd position, respectively in the list; while Cd is at the 7th place. Therefore, the "elements/heavy metals", viz., As, Cd, Pb and Hg are considered most toxic to the humans, animals and environment [1]. Heavy metals concentrations in animal and their product may increase very fast [2]. Their ecosystem accumulation (water-soil-plant-animal) makes them very toxic and leads to undesirable consequences for live organisms [3]. These heavy metals produce reactive oxygen species and bring many changes in the repair mechanism of DNA. Depending upon its chemical form, heavy metal (s) cause toxicity or harm the body even if its concentration is very small. Increased concentrations of heavy metals in body of domestic animals result in decreased production, reproduction problems, immunity decline and occurrence of cancerous and teratogenic diseases [4].

Lead toxicity in animals
Pollution of the environment with lead is a world-wide problem. Lead has been added to petrol as an anti knocking agent in order to improve fuel performance and reduce wear on vehicle engines. Since this time, leaded petrol has been reported to cause more lead exposures than any other source worldwide [5]. In periodic table lead is situated at group 14A (IVth). It is a bluish or silvery grey soft metal with atomic number 82; atomic weight 207.19; specific gravity 11.34, melting point 327.5 ^{0}C and boiling point 1740 ^{0}C. During the 1970s, health impacts associated with lead emissions from vehicles became a widely discussed issue. Many studies have reported that environmental lead emissions have resulted in significant health effects to the central nervous system, haem-synthesis, reproductive system, as well as psychological and neurobehavioral functions, and may even increase the risk of cancer [6]. Manufacturing processes, incineration of refuse and combustion of coal, are also the other sources which contribute to lead occurrence in the atmosphere; hence it is not surprising that

lead levels are highest in area of intense industrialization[7].
Lead is toxic to the blood and the nervous, urinary, gastric and genital systems. Furthermore, it is also implicated in causing carcinogenesis, mutagenesis and teratogenesis in experimental animals [8]. Accumulation of lead in the organism produces damaging effects in the hematopoetical, hematic, renal and gastrointestinal systems [9]. In case of males, it gets accumulated in testes, epididymis, vas deferens and seminal vesicle. It deteriorates the spermatogenesis and steroidogenesis activity by detaching the germinal cell layer from basal membrane and also causes atrophy of Leydig cells [10]. It reduces the density of seminal plasma with significant decline in certain constituents like fructose and succinic dehydrogenase. It can also cause spontaneous abortions and fetal anomalies in case of rabbit and sheep. Lead treatment to *in-vitro* cultured human ovarian granulosa cells retrieved during IVF showed reduction in mRNA and protein levels of both P450 aromatase and estrogen receptor [8].

Cadmium toxicity in animals

Pure Cd is a soft, silver-white metal. Its atomic number is 48 and atomic weight 112.4, electro negativity 1.7, ionization potential 8.993, oxidation state +2**,** density 8.64 g/cm3, melting point 320.9°C and boiling point 765°C at 100 kPa. It occurs in mineral forms combined with oxygen (Cd oxide), chlorine (Cd chloride) or sulphur (Cd sulfate, Cd sulfide) [11]. It is a metal that belongs together with zinc and Hg, to group IIb in the Periodic Table. There are two main sources of Cd in the environment *i.e.* natural and anthropogenic. In nature, it is mainly present as sulphide ore (greenokite) and carbonate ore (otavite) in association with zinc ores. Its other source in nature is volcanic activity. Among the anthropogenic sources, mining of zinc and other metals, incineration and combustion of coal and oil etc, are the major sources of increased Cd levels in the environment.
The first ever record of acute Cd toxicity has been made from Belgium [12]. Its toxicity contributes to a large number of health problems, including some of the major killer diseases like heart disease, cancer and diabetes. However, the most devastating natural toxicity occurred as a result of Cd contaminated water by Komioka mine in the inhabitants of Zinzu river basin in Japan, called as Itai-Itai disease. It was characterized by pseudofractures of bone, osteomalacia and renal dysfunction [13] (WHO, 1992). Cd constitutes 0.000011% of earth crust. However, in heavily polluted soil its concentration may reach up to 69 mg per kg [14]. Fresh water contains varying concentration ranging from 0.0002-0.15mg/L of Cd [15]. In India, higher concentration of Cd in water was reported in Baroda and Bombay [16].
Farm animals may have an access to Cd through water, soil, contaminated vegetation by industrial and automobile emission. Cd is widely distributed in various types of foodstuffs. Leafy vegetables like spinach, staples such as potatoes and grain foods exhibit relatively high values ranging from 30 to 150 ppb. Peanuts, soybeans and sunflower seeds also exhibit naturally high values of Cd with seemingly no adverse health effects. Meat and fish normally contain lower Cd contents ranging from 5 to 40 ppb. Animal offal's such as kidney and liver can exhibit extraordinarily high Cd values, up to 1000 ppb, as these are the organs in animals where Cd accumulate [13]. The Cd content of feedstuffs may vary widely with the agricultural practices followed in the particular area such as use of phosphate fertilizer, sewage sludge and manure application, the types of crops grown, and atmospheric Cd deposition from natural or anthropogenic sources. Cd concentration in milk of cattle exposed to Cd is higher than the non-exposed animals[17].indicating public health hazard. Half life of Cd is around 30 yrs, so it can store in the body for longer periods. Gastrointestinal absorption of Cd is about 5-8% and it will be enhanced in absence of calcium and iron in feed and by low protein diets.
Low dietary calcium stimulates synthesis of calcium binding protein, which enhances Cd absorption. Absorbed Cd is excreted in urine; gastrointestinal excretion, particularly in bile as glutathione complex. Cd excretion in urine increases proportionally with body burden [11]. Cd is transported through blood by binding to red blood cells and high molecular weight protein in plasma, particularly albumin. In liver Cd induces synthesis of metallothionenin (MT) and then stored either in liver as Cd- MT complex or transported via blood to kidney, where it accumulates and may induce renal toxicity.
The form of Cd and the route of exposure can greatly affect the absorption and distribution of Cd in various target tissues. Cd - metallothionein complex may have different toxic profile and is found in relatively high concentration in organs like liver and kidney. Numerous studies have reported the death of humans and animals upon acute inhalation of Cd. [18] reported the death of rats, mice, rabbits, guinea pigs, dogs and monkeys on acute inhalation of Cd oxide fumes and also reported that the mortality rate apparently being proportional directly to the duration of exposure and the concentration of Cd in inhaled fumes. It has been found that in acute exposures, the relatively more soluble Cd chloride, Cd oxide fume, and Cd carbonate compounds are more toxic than the relatively less soluble like Cd sulphide [19].
Inappetence is a common sign of chronic Cd toxicity. Dietary intake of Cd at the dose rate of 15, 30, and 60 ppm for 137 days caused decrease in feed intake in cattle, which was due to reduced rumen micro flora[20]. Calves given Cd in their diet shows decreased feed intake and body weight gain. [21] Reported that sheep supplemented with Cd ate less feed than the control groups. Experimentally induced Cd toxicity was found to reduce feed intake in cattle, which may be due to hyperkeratosis of fore
Cattle that grazed near Cd contaminated areas and zinc processing plants showed anemia and subnormal hemoglobin and PCV values. Calves fed with Cd for 6wks showed decreased erythrocyte count, progressive decrease in Haemoglobin (Hb) concentration, erythrocyte, neutrophill and monocyte counts. Cd deposited in various organs interferes with normal cell metabolisms, leading to abnormal function of those organs. It causes formation of free radicals like hydroxyl radicals, peroxides radicals in the body, which produces oxidative stress in animals. It not only causes decrease in production of animals but also causes various disease conditions in animals. In Cd toxicity there is an increase in concentration of various antioxidant enzymes like catalase, superoxide dismutase (SOD), lipid peroxidation and glutathione peroxidase in animal body [22].
Cd causes an altered immune response of animals, which varies considerably upon dose and species of animals. Cd toxicity causes immune suppression in animals and makes the host susceptible to various bacterial and viral infections [23]. It reduces antibody titer in chicken. It reduces antibody forming cells particularly IgG in mice fed with Cd chloride for 10wks. It also reduces number of spleen cells. It decreases haemagglutination (HA) titer values in animals. It reduces T-

lymphocyte proliferation leading to decrease cell mediated immunity in animals.

Arsenic toxicity in animals

Arsenic occurs in many minerals, usually in combination with sulphur and other metals. Its atomic number is 33 and atomic weight 74.92, electro negativity 2.18, ionization potential 8.993, density 5.72 g/cm3. Arsenic level in the environment is increasing due to natural as well as anthropogenic reasons. Exposure to as contaminated water, food/feed leads to its accumulation in plants and/or animal tissues affecting their normal metabolism, particularly dysfunction of liver and kidney in the animals. The affliction by as is attributed to depletion of sulfhydryl groups, oxidative stress, liver and renal toxicity, leading to alterations in blood biochemical profile and in histology. Intensity of toxicity of as depends upon many factors like its dose, valence state and compound of As, as its different compounds differ in their absorption and metabolism in the body. Organic compounds of as are less toxic than their inorganic counterparts, mostly owing to their better absorption and difference in metabolism. The trivalent forms are more toxic than the pentavalent ones. Among the trivalent forms, As trioxide and sodium arsenite are the most common As compounds used in agriculture and many industrial formulations.

The clinical signs observed decreased body weight and feed intake, dullness, open mouth breathing, increased thirst, ruffled feathers, pale comb, skin irritation and watery diarrhea in animals [24]. As responsible for the generation of reactive oxygen species (ROS) (intracellular peroxide, hydrogen peroxide, superoxide anion radicals, and hydroxyl free radicals), reactive nitrogen species (RNS), which provoke proinflammatory cytokines, profibrogenic cytokines, and assault mitochondrial respiratory chain which create obstacle in the antioxidant defence system further lead cellular DNA and protein marred. As exposure results in impairment of glucose metabolism, insulin secretion in pancreatic β-cells, altered gene expressions and signal transduction, and affects insulin stimulated glucose uptake in adipocytes or skeletal muscle cells. As toxicity causes abnormalities in glucose metabolism through an increase in oxidative stress. As inhibits glucose transporters present in the cell membrane, alters expression of genes involved in glucose metabolism, transcription factors and inflammatory cytokines which stimulate oxidative stress [25]. Acute symptoms of as toxicity include staggering gait, collapse and paralysis. Arsenic poisoning is usually acute with major action on gastro-intestinal tract and cardio-vascular system. Symptoms include watery diarrhoea, colic pain, dehydration, skeletal muscle cramps, convulsions and death with in 24hours. Inorganic forms of As causes irritation to lung, stomach and intestine, skin disturbances, and decreased formation of RBCs and WBCs. Very high concentrations of inorganic As can cause infertility, skin disturbances, decreased resistance to infections, heart disruptions, brain damage and death. The acute LD_{50} (oral) of as ranges from 10-300 mg/kg. As trioxide intoxication causes increased level of serum creatinine by enhanced formation of metabolic waste product of muscle metabolism. Phosphocreatine which presents in muscle undergoes spontaneous cyclization with loss of inorganic phosphorus to form creatine. Creatine is converted to creatinine by non-enzymatic and irreversible process. Arsenic has affinity for thiol groups of various proteins which are found in cell membrane of muscles. So As damages the cells and so on release of enzyme CPK. CPK is responsible for the conversion of phosphocreatine into creatine [26].

Mercury toxicity in animals

In periodic table Mercury (Hg) is placed at group 12th (III B) and 6th periods. At room temperature it is found in liquid state. Its atomic number is 80, atomic weight is 200.59, melting point: 234.32 k, boiling point: 629.88 k (356.73°c or 674.11°f) and density is 13.53 gm/cm3. It enters into the animal body as like Lead**.** Its toxicity depends on its chemical form. Methyl Hg is found to be more hazardous than metallic form of Hg. Young ruminants are more susceptible to Hg poisoning rather than old ruminants and non-ruminants (Horse and Pig).

Industrial wastes and sewage water form the chloroalkali industry are a major source of Hg pollution. The symptoms of toxicosis in most species of animals include in coordination of movement, visual aberration and decline in awareness Minimata disease is characterized by symptoms of fatigue, loss of memory and concentration, tremors' constriction of visual field, cortical blindness *etc*. occurs due to toxicity of Hg [27]. The animal consumed high Hg containing vegetation will be affected and will suffer from alopecia, neuropathy, visual and gastrointestinal tract disorder. It hampers synthesis of hemoglobin molecule by replacing iron leading to non binding of oxygen and hence no oxygen transportation will occur.

It also acts as a spermatotoxic, steroid toxic and fetotoxic agent. In male, it changes the functional activity of growing testicular tissue such as depletion and clogging of spermatogenic cells. It can also deteriorate semen quality by production of vacuolated elongated spermatid, dispositional acrosome and pyknotic nuclei. It affects the membrane bound hydrolysis that causes the progressive degeneration of peritubular membrane. It has been reported that Hg exposure is highly responsible for cryptorchidism in male animal's. However, chronic exposure causes anemia, liver and kidney damage, hyperpigmentation and keratosis. It also affects the process of meiosis and post-meiotic stages of spermatogenesis. Acute exposure can cause rapid and extensive disruption of spermatogenesis in mice.

Conclusion

Heavy metal enters in animal either from direct or indirect sources affect the liver, kidney and nervous system. Chronic exposure of the heavy metals causes the steroid genic dysfunction, fetal abnormality and reproductive failure.

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