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REVIEW ARTICLE

Adverse effect of Heavy metals in Animal Reproductive System- An overview

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ABSTRACT
The heavy metals predominantly include Pb, Hg, Cd, Cr, Cu, Zn, Mn, Ni, Ag, etc. The heavy metals, such As, Cd, Pb and Hg are considered most toxic to humans, animals, fishes and environment. Excessive concentrations of heavy metals are detrimental effect. All heavy metals, in spite some of them are essential micronutrients, have their toxic effects on living organisms via metabolic interference and mutagenesis. The heavy metals like Pb and Hg have significant toxic effects. The heavy metals are important pollutants for fishes, because these are not eliminated from aquatic systems by natural methods, such as organic pollutants, and are enriched in mineral organic substances. Occurrence of heavy metals differs in fishes, depending on their age, development and other physiological factors. Heavy metals can have toxic effects on different organs including animals. They can enter into water via drainage, atmosphere, soil erosion and all human activities by different ways. As the heavy metals concentrated more in the environment, they enter biogeochemical cycle causes toxicity.
Keywords: *Animals, environment, heavy metals, toxicity.*

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INTRODUCTION

Heavy metals constitute a very heterogeneous group of elements widely varied in their chemical properties and biological functions. The term "heavy metals" defined as those metals, which have specific weights more than 5g cm-3[1]. Heavy metals are kept under environmental pollutant category due to their toxic effects in plants, animals and human. Some of the heavy metals like arsenic (As), Cadmium (Cd), Lead (Pb), Mercury (Hg) are considered as cumulative poison. These heavy metals are persistence, accumulate and not metabolized in to other intermediate compounds and do not easily breakdown in environment. These metals are accumulating in food chain through uptake at primary producer level consumption at consumer level. Metals are entering the animal's body either through inhalation, ingestion or absorption (direct contacts). Heavy metals such as Cd, Ni, As, Pb and Hg pose a number of hazards to animals. These metals are also potent carcinogenic, mutagenic, embryotoxic, hepatotoxic and renal toxic. Co and zn serve either as cofactor as a activator biochemical reactions [2]. The high concentration intake of cadmium cause itai itai disease and mercury intake lead to minamita disease and other heavy metals cause poisoning due to drinking water contamination. Heavy metals have largest availability in soil and aquatic ecosystem and to relatively smaller proportion in atmosphere at particular vapors. Metal toxicity to plants varies with plants species, chemical form, soil composition, pH.

HEAVY METAL

The elements which have atomic weight greter than sodium (22.99) and specific gravity greater than 5g cm^3 (3).

Classification of Heavy metal:- Heavy metals can be classified into four major groups on their health importance basis :

Essential: These metal also called micronutrients [3] and are toxic when taken in excess [4,5] Eg Cu, Zn, CO, Cr, Mn and Fe .
Non essential: Ba, Li and Zr
Less toxic: Sn and Al
Highly toxic: Hg and Cd.
Some heavy metals are also called trace element due to their presence in trace (10mg Kg-1) or in ultratrace (1µg kg-1) quantities in the environment.

SOURCE OF CONTAMINATION
Heavy metals pollution can originate from natural as well as anthropogenic sources. Heavy metals enters in to animal body mainly through polluted soil, water and air. Heavy metals enters in to crops, fodders and others by in polluted soils or contaminated water used for the irrigation purpose that leads to deposition of heavy metals in to the plants grazing in contaminated area, ingestion of contaminated fodders, drinking of contaminated water, licking of leaded paints, batteries others leaded compounds
Activities such as mining and smelting leads to contamination of extensive areas of world maily Japan, Indonesia, and China mostly such as Cd, Cu and Zn [6] Cu and Pb in north Greece [7], Cu, Pb, Cu, Ni, Zn, and Cd in Austrilia [8] Cd, As, Pb and Hg were reported. In animal body, metals enter through animal's feeds, green fodder, drinking water and pharmaceutical medicines etc. Other sources are accidental access to limed field, mineral supplements with high content of trace metal and licking of painted surfaced containing metallic pigments.

LEAD (Pb):
In periodic table Pb situated at group 14 (IVth A) and period 6th. 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.It is a ubiquitous environmental contaminant and most common industrial metal that has become widespread in air, water and soil. The primary source of Pb are leaded gasoline, battery plant, refinery, smelter, fuel combustion, paints industry, lead-soldered food cans, Pb plumbing pipes and automobile exhaust where tetraethyl Pb acts as anti-knocking agent[9]. It enters in animal body through grazing in contaminated area, ingestion of contaminated fodders, drinking of contaminated water, licking of leaded paints, batteries others leaded compounds.
It behaves like calcium in body and accumulates in bone, liver, kidney, brain and other tissues. Its half-life in the blood is 1–2 months, but depending on exposure, it can accumulate in bone where its half-life is 20–30 years that is toxicity depends on the degree of exposure and produces the acute and chronic toxicity. In acute lead poisoning case fatality rate may go up to 100% but in chronic toxicity slightly less (10).
Reproductive system
In reproductive system toxicity occur mainly chronic type and it developed very extreme periods. It affects the reproductive system mainly through following ways
Lead toxicity in male
It mainly affects of the testicular function and steroidogenesis. Pb accumulates in male reproductive organs such as testes, epididymis, vas deferens and seminal vesicle. It detached the germinal cell layer from basal membrane, atrophy of leydig cells and produces low density of seminal plasma with significant decreased in certain constituents like, fructose and succinic dehydrogenase which impaired the male reproductive functional [11]. The low fructose content decreased the activity of succinic dehydrogenase and alkaline phosphatase in seminal plasma [12]. Ultimate decrease sperm concentration in semen [13]. It produces adverse effect on spermatogenesis & leads to morphological abnormalities of sperms (mainly, the tail abnormality) along with azoospermia, asthenozoospermia, teratozoospermia with inhibition of post-meiotic cells mainly pachytene spermatocyte stage [29]. In fact, there was an inverse relationship between lead concentration in blood and seminal plasma. The rate of fertilization decreases due to altered sperm function. The progesterone-dependent acrosome reaction of spermatozoa is mainly affected. It also inhibits both sertoli and leydig cell steroid production at every step of synthesis. Expression and or activity of gonadotrophin receptors, StAR, p450 side chain cleavage, 3-HSD, and P450c17, the enzyme that converts progesterone into testosterone.
Lead toxicity in female
It mainly affects the ovary and steroidogenesis . Pb exposure *in-vivo* in cynomolgus monkey suppressed circulating luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol without affecting progesterone or causing overt signs of menstrual irregularity (14). Prenatal and neonatal lead exposure resulted in suppressed rat ovarian homogenate-4 androgen production whereas 5-reduced androgens were increased [15]. There are some studies that examine changes in follicle populations after lead

exposure. For instance, mice exposed to lead in utero experienced a significant reduction in the number of ovarian primordial follicles [16]. Adult mice given lead by gavage for 60 days had significant changes in ovarian small, medium, and large follicle populations [17] but, in another study, lead was given by injection and there was no change in either antral follicles but decreased primordial follicles and increased growing and atretic follicles [18]. Accelerated elimination of ovarian follicles, common to the above reports, will ultimately lead to premature ovarian failure if the reduced follicle pool is the non-regenerating primordial follicles or disrupted cycles if the growing follicles are targeted. It also causes the spontaneous abortions & birth defects in rabbit and sheep [19].

Pb treatment of culture human ovarian granulosa cells retrieved during IVF reduces mRNA and protein levels of both P450 aromatase and estrogen receptor [18]. Female rats exposed to Pb in utero have decreased basal ovarian StAR, mRNA and protein but this is reversed by stimulating with gonadotrophins before collecting the ovaries. On the basis of these results, it was concluded that lead acts at the hypothalamic–pituitary level of the reproductive axis.

Lead acts as an Endocrine-Disrupting Chemical in Animals

The Pb probably direct effects on the hypothalamic–pituitary–ovarian axis and leads to delay in body growth and decreased body size. The lead treatments delayed the age of vaginal opening, first estrus and disrupted estrous cycling associated with suppressed serum levels of insulin-like growth factor-1 (IGF-1), a liver hormone involved in growth and reproduction. Moreover, lead affected hormones and responsiveness of all levels of the hypothalamic–pituitary–ovarian axis. Dietary Pb may delay the onset of puberty in female mice, and rats [20], although by contrast, very low levels of dietary Pb, 0.02 ppm, were associated with a marked and significant acceleration of puberty in mice.

MERCURY (Hg)

In the periodic table mercury situated at group 12^{th} (IIB) and 6^{th} periods. At room temperature it found as liquid state. Its Atomic Number: 80, Atomic Weight: 200.59, melting point: 234.32 K (-38.83°C or -37.89°F), boiling point: 629.88 K (356.73°C or 674.11°F), density: 13.5336 grams per cubic centimeter. Primary source of mercury are oil refinery, plastic and paints, antiseptic, scientific instruments, photography, fuel combustion. Industrial wastes and sewage water from the chloroalkali industry are a major source of mercury pollution. It enters in animal body. Grazing in mercury contaminated area, ingestion of mercury contaminated fodders, and use of sewage water for drinking or irrigation purpose. The toxicity of mercury depends on its chemical form methyl mercury being the most hazardous metal and stable form of mercury that has been attributed to the suffering of most avian, animal and humans. Depending on its chemical form mercury can be very toxic. It acts as spermatotoxic, steroidotoxic and fetotoxic agent. High exposure leads to neurodegeneration, behavioral changes, and death. It also causes the structural and functional disintegration of those enzymes which has (–SH) group, due to its high affinity towards the enzyme's (SH) group [21, 22]. Large-scale Hg poisonings have occurred in Minamata and Nigata in Japan, and Iraq by industrial or inadvertent introduction of Hg into the food chain [23].

Reproductive system

In animals reproductive toxicity developed mainly chronic type but some time it may occur acutely. Young ruminants more susceptible than Horse and Pig [26].

Mercury toxicity in male

In male animal it acts as spermatotoxic and steroidotoxic agents that cause the structural and functional change of testicular tissue, depletion and clogging of spermatogenic cells and abnormal semen quality with pyknotic nuclei and vacuolated elongated spermatid along with dispositioning of acrosome [28]. It also affects the membrane bound hydrolytic enzymes resulted in sharp decrease of these enzymes, co-related with progressive degeneration of peritubular membrane**.** In wildlife, it has been reported that Hg exposure has been responsible for increased cryptorchidism in the Florida panther as a result of exposure through bioaccumulation [25].

The intraperitoneal injection of mercury for 90 days in male rats or mice reveals consistent changes in the reproductive system such as testicular steroidogenesis suppressed at the 3-βHSD synthetic step with a significant decrease in serum testosterone and LH [27].Oral exposure of rats to mercuric chloride for 45 days resulted in suppressed testosterone and increased testicular cholesterol [30]. There is increased cholesterol due to the block of biosynthetic conversion to sex steroid hormones such as testosterone. Another possibility is that Hg as mimics the effect of estrogen on the testes which is to both inhibit androgen production and cause accumulation of cholesterol probably because of up regulation of the high-density lipoprotein (HDL) receptor, scavenger receptor class B, type I (SR-BI).

Mercury toxicity in female

Animal exposed to mercury, leads to reproductive dysfunction associated with estrous disorders, subfecundity, adverse pregnancy outcomes and compromised fertility. In female animal, it acts as fetotoxic agents and easily crosses the placenta and blood brain barriers that leads to neuronal, pregnancy dysfunction that may causes the spontaneous abortion and fetus malformation [26].

In hamster, subcutaneous mercuric chloride treatment disrupts estrous cycles, suppresses follicular maturation, reduces plasma and luteal progesterone levels, and disruption of hypothalamus-pituitary gonadotrophin secretion. The estrous cycle was lengthened and morphological changes in the corpora lutea, but ovulation, implantation or maintenance of first pregnancy was unchanged [24].

Mercury acts as estrogen mimics

Mercuric chloride stimulated both estrogen receptor-dependent transcription and increased proliferation of MCF-7 cells. The study of the methyl mercury impact on MCF-7 cells was performed by [31]. In this, instead of measuring increased number of MCF-7 cells. Multicellular foci form in response to estrogen agonists and are proportional to hormone dose or concentration. A very narrow concentration range, 0.5×10−7 to 1×10−6 M, of methyl mercury stimulated MCF-7 cell foci formation but did not reach the maximum response elicited by estradiol, indicating that Hg is a weak estrogen mimic. Hg exhibited estrogen receptor agonist–antagonist properties depending on concentration. Methyl mercury reacts with sulfhydryls and could interact with protein thiol groups such as those located in the ligand-binding domain of the estrogen receptor to stimulate MCF-7 cell proliferation.

CADMIUM (Cd)

Pure cadmium is a soft, silver-white metal. It situated in periodic table group 12^{th} (IIB) and 5^{th} periods The physical property of Cd is atomic number 48, atomic weight 112.411, electro-negativity 1.5, crystal ionic radius (Principal valence state) 0.97, ionisation potential 8.993, oxidation state +2, Electron configuration Kr 4d1 5S2 density 8.64 g/cm^3, melting point 320.9°C and boiling point 765°C at 100 kPa. The source of Cd are tannery, smelter, battery crushing unit, mining, electroplating, pigments (Cd yellow), plastics, water foods, water pipes and coal burning. It enters in animal body through grazing in contaminated area, ingestion of contaminated fodders, drinking of contaminated water and use of sewage water for irrigation purpose. It is interact with numbers of minerals mainly Zn, Fe, Cu and Se due to chemical similarities and competition for binding stage [32]. It is also reported that Cd can affected Ca, P and bone metabolism in both animals and human exposed to Cd in environment [33]. Cadmium is very slowly excreted from the body so it accumulates with time.

Reproductive system

It is usually found as a mineral combined with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulphur (cadmium sulphate, cadmium sulphide). Cd is a toxic to virtually every system in the animal body.

Cadmium toxicity in male

The toxic effects of Cd on the testes, as first reported by Laskey [34] testicular necrosis was induced by Cadmium which leads to impaired fertility. A study conducted by Laskey and Phelps , (34) in rat Leydig cells, 100-M Cd treatment doubled testosterone production with no change in cell viability. *In-vitro* observation of increased testosterone in the presence of Cd, chronic Cd oral exposure resulted in increased plasma testosterone in rats [34]. The increase in plasma testosterone was not evident until after more than 1-month exposure to Cd in the drinking water. At the same time, there is an increase in testicular weight. In contrast, Cd given by subcutaneous injection to adult rats caused a decrease in plasma testosterone [37].

These experiments suggest that the route of exposure to Cd affects whether it stimulates or inhibits testicular androgen production. Cd exposure through ingestion also is associated with increased testosterone and estradiol. It also inhibits of DNA repair, decreased antioxidants, activates signal transduction, or cell damage [38] rather than acting through a specific receptor or mechanism to inhibit steroidogenesis as well as spermatogenesis at a specific spermatogenic stage and finally reduces semen quality [39].

Cadmium toxicity in female

In animal cadmium mainly affects the estrous cycle, pregnancy and the fetus. It inhibits the Steroidogenic activity in ovary that leads to abnormal cyclicity. Maternal exposure to high levels of Cd has led to a significant increase in premature delivery possibly by compromising placental function. There are enhanced concentrations of cadmium in follicular fluid and placentae of infected that are correlated with lower progesterone. Cd at high concentrations inhibits placental progesterone synthesis and expression of the low-density lipoprotein receptor that is needed to bring cholesterol substrate into the cells. Placental 11-HSD activity is critical to protect the fetus from maternal cortisol, which suppresses fetal

growth, by converting it to inactive cortisone. Mutation or reduced expression of 11-HSD is associated with fetal growth. Cd accumulates in the placenta. A recently report describes that Cd at <1-M reduces 11-HSD type 2 activity and expression in cultured human trophoblast cells [40]. Cd's effect unique because it was not mimicked by other metal divalent cations such as Zn, Mg or Mn.

Cd may downregulate 11-HSD by mimicking the ability of estrogen to attenuate the expression of this placental enzyme and contribute to risk of major diseases later in life, particularly for the low birth weight fetus that was not protected from maternal cortisol. For instance, in human granulosa cells collected during in-*vitro* fertilization (IVF) procedures, Cd>16-M inhibited progesterone production (41). However, at concentrations <5-M, Cd stimulates transcription of P450 side chain cleavage in porcine granulosa cells that results in greater progesterone production [42].

Cd may act to stimulate gene transcription by its high-affinity displacement of calcium from its binding to calmodulin and activation of protein kinase-C and second messenger pathways. P450 side chain cleavage is the rate-limiting step for steroidogenesis. Thus cadmium's ability to either stimulate or suppress this enzyme could have a profound impact in all steroidogenic tissues. In primary ovarian cell cultures from either cycling or pregnant rats placental tissue, Cd at concentrations >100-M suppressed progesterone and testosterone production. In addition, in vivo cadmium treated rat ovaries exhibited suppressed progesterone, testosterone, and estradiol production in culture [43].

Cadmium acts as a Metalloestrogen

Cadmium acts as estrogen mimic [13], showed by female rats injected with cadmium experienced earlier puberty onset, increased uterine weight, and enhanced mammary development. Cd treatment induced estrogen-regulated genes such as progesterone receptor and complement component C3. It also promoted mammary gland development with an increase in the formation of side branches and alveolar buds. In utero exposure of female offspring resulted in their reaching puberty earlier and an increase in epithelial area and number of terminal end buds in the mammary glands. Importantly the effect of cadmium on uterine weight, mammary gland density, and progesterone receptor expression in uterus and mammary gland was blocked by co-administration of the antiestrogen ICI-182, ICI-780 [13].The reversibility of these Cd induced effects by an antiestrogen is the most robust in supporting the conclusion that Cd is an endocrine disrupting chemical and a putative metalloestrogen. Evidence for Cd interaction with the estrogen receptor is the best characterized of all the heavy metals (Pb, Hg, As).

The specific nature of Cd interaction with the estrogen receptor. Low concentrations of Cd activate the estrogen receptor by interacting non-competitively with the hormone-binding domain to block the binding of estradiol. The binding domain of specific amino acids engaged by Cd are cysteines, glutamic acid, and histidine. Cd binds both estrogen receptor and androgen receptor, and in many tissues of reproductive system. The metal exposure could lead to different responses depending on the relative localization and activation of the two steroid receptors in various tissues.

ARSENIC (As)

It is steel grey, very brittle, crystalline, semi metallic (metalloid) solid. It tarnishes in air and when heated rapidly oxidizes to arsenous oxide which has a garlic odour. Arsenic and its compounds are very poisonous. Upon heating As and some minerals containing arsenic, it sublimes (transfers from the solid to the gaseous state, without passing through the liquid state). Its atomic number 33, relative atomic mass 74.92160. It situated in the periodic table at group 15^{th} (5^{th}A) and 4^{th} periods. The abundance of arsenic in the earth's crust is 1.5–3.0 mg/kg, making it the 20^{th} most abundant element in the earth's crust. It is famous as a favored form of intentional poisoning.

The primary source of As are pesticides, wood preservative, glass, Cu smelters, coal combustion, and uranium mining. The most common source of as poisoning is exposure to environment and drinking water. For instance, since the 1980s, the provision of arsenic-contaminated Artesian well water in Bangladesh has exposed an estimated 50–75 million people to very high levels of As [44]. As also causes carcinogenesis mainly skin, lung, urinary bladder, kidney, and liver. It enters in animal body through grazing in contaminated area, ingestion of contaminated fodders, drinking of contaminated water and use of sewage water for irrigation purpose.

The organo arsenicals in food are one of the most poisoning in livestock now a days because of the displacement of arsenic form almost all phases of farming activities. The common of source of As is in fluid used for dipping and spraying of animal to control ecto-parasites. As toxicity in cattle varies from gastrointestinal to nervous system. As were killer including sodium or sodium arsenate, Arsenic pentaoxide and monosodium or disodium acid. It toxicity produces goiter in rats, thyroid antagonism in man and inhibited the growth of rumen bacteria in pure culture as well as reduces the fermentative activity. Chronic arsenic toxicity is mostly manifested in weight loss, capricious appetite, conjunctively

and mucosal erythematic lesion including mouth ulceration and reduce milk yield. Acute toxic effects include abdominal cramping, hyperesthesia in extremities, abdominal patellar reflexes and abdominal electrocardiogram [45]. However, chronic poisoning of as causes anemia, liver and kidney damage, hyper pigmentation and keratosis i.e. skin damage [46].

Reproductive system

Inorganic arsenic in the forms +3 (arsenite) or +5 charges are the most often encountered forms of As and are most readily absorbed from the gastrointestinal tract; therefore, these forms cause the greatest number of health problems in human as well as animals. Then deposited in different parts of body and produces the reproductive problems.

Arsenic toxicity in male

As damage the Androgen binding protein (ABP) secreted from sertoli cells bind with androgens and maintain their activity. It causes the steroidogenic dysfunction leading to impairment of spermatogenesis in rat (48). It mainly effects in the processes of meiosis and post-meiotic stages of spermatogenesis and acute exposure causes rapid and extensive disruption of spermatogenesis in mice [47]. It also reduces the gonadotrophins, plasma estradiol, and decreases the activities of these steroidogenic enzymes, 3 HSD and 17 HSD (47). Testicular degeneration and interstitial cell hyperplasia also seen in mice [50].

Adult rats that consume drinking water with arsenite at 5 mg/kg of body weight per day 6 days a week for 4 weeks have reproductive tract abnormalities such as suppression of gonadotrophins and testicular androgen, and germ cell degeneration all effects similar to those induced by estrogen agonists [51]. The degenerative problems could have resulted from arsenic chemical toxicity. The experiments conducted by Waalkes in mice that were injected with sodium arsenate at 0.5 mg/kg i.v. once a week for 20 weeks, males had testicular interstitial cell hyperplasia and tubular degeneration that probably resulted from the interstitial cell hyperplasia [51]**.**

Arsenic toxicity in female

Arsenite at low concentrations (μmol) stimulates the proliferation of progesterone receptor, pS2, and decreased estrogen receptor mRNA expression [52]. The antiestrogen ICI-182, ICI-780 or fluvestrant blocked the effects of arsenite indicating the dependence on the estrogen receptor. Arsenate injections given in female mice caused cystic hyperplasia of the uterus, which is often related to abnormally high, prolonged estrogenic stimulation. Again, as these changes were unexpected, there was no attempt to determine the dependence on the estrogen receptor by using an antiestrogen to block the changes in the male and female reproductive tissues. As levels at 0.4 ppm/day given daily in drinking water to rats results in reduced gonadotrophins, plasma estradiol and decreased activities of these steroidogenic enzymes, 3-HSD and 17-HSD. At the same time there was no change in body weight, but ovarian, uterine and vaginal weights were significantly reduced.

CONCLUSION

The heavy metals, such as As, Cd, Pb and Hg are most toxic to all human beings, animals, fishes. Although some heavy metals are essential for animals, plants and several other organisms. However excess levels of heavy metals cause severe toxicity. The Pb and Hg cause severe toxicity in all. Animals are not the exception and they may also be highly polluted with heavy metals, leading to serious problems and ill-effects. The heavy metals can have toxic effects on different organs. They can enter into water via drainage, atmosphere, soil erosion and all human activities by different ways. With increasing heavy metals in the environment, these elements enter the biogeochemical cycle leading to toxicity in animals, including fishes.

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