Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

Journal of Entomology and Zoology Studies

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2018; 6(6): 27-30

Received: 04-09-2018
Accepted: 06-10-2018

Ranjeet Verma
Department of Animal Reproduction, Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India

Kennady Vijayalakshmy
Department of Veterinary Physiology, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, India

Vikas Chaudhiry
Senior Research Fellow, Central Institute for Research on Buffaloes, Hisar, Haryana, India

Correspondence
Kennady Vijayalakshmy
Department of Veterinary Physiology, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, India

Detrimental impacts of heavy metals on animal reproduction: A review

Ranjeet Verma, Kennady Vijayalakshmy and Vikas Chaudhiry

Abstract
Lead, cadmium, mercury and arsenic are often referred to as "heavy metals" and are highly toxic to animals and human. The indiscriminate human activities like rapid industrialization, overgrowing urbanization and environmental manipulation have drastically altered the biogeochemical cycles. Aggregation with polluted water tends to pollute the agricultural soil and the crops that grow in this soil will be having a more heavy metal accumulation. These crops that have been used by animal for grazing or feed purpose will be accumulated with heavy metals that can reach the animal body, in other ways heavy metals can directly reach the animal body by means of drinking contaminated water. Prolonged exposure to heavy metals such as lead, mercury, cadmium and arsenic causes deleterious health effects in animals. Heavy metal primarily affects the liver, kidney, brain and other body systems. Lead, mercury, arsenic and cadmium are the most common heavy metals that are found in industrial and domestic wastages. With exposure to heavy metals, reproductive system shows the chronic type of toxicity and produces cellular impairments at both structural and functional level. It could cause impairment in steroidogenesis, hormonal regulation, gametogenic process, affect leydig cells and spermatogenesis in males and granulosa cells, theca cells in females; placental growth, pregnancy rate and development of fetus in females. Animals that are reared near the area that are having extreme level of heavy metals contamination are highly prone to infertility problems.

Keywords: Heavy metals, toxicity, steroidogenesis, infertility, reproduction

Introduction
The heavy metals are a heterogeneous group of elements that are having more than 5g cm^3 specific weight and atomic weight greater than sodium (22.99). They act as a cumulative poison for living creatures. They enter into an animal body either through inhalation; ingestion or absorption (direct contacts) and they develop the carcinogenicity, mutagenicity, embryotoxicity, hepatotoxicity and renal toxicity. The heavy metals are mostly present in soil and aquatic ecosystem rather than atmosphere.

Classification of Heavy metal
Essential: Copper, Zinc, Cobalt, Chromium, Manganese and Iron (up to threshold level)
Non-essential: Barium, Lithium and Zirconium
Less toxic: Selenium and Aluminium
Highly toxic: Mercury, Cadmium and Lead

Source of contamination
Heavy metal enters in the environment by means of natural and anthropogenic sources. In natural way, they originates during the origin of earth and it is distributed all over the earth may or may not be evenly. In other hand, anthropogenic activities such as rapid industrialization, overgrowing urbanization and environment manipulation split heavy metals into the environment. The accumulation of heavy metals through emissions from the rapidly expanding industrial areas, mine tailings and disposal of high metal wastes etc. contaminates the soil and water.
The sources of heavy metals are leaded gasoline, battery plant, refinery, smelter, fuel combustion, lead-based paints, lead-soldered food cans, lead plumbing pipes, automobile exhaust (tetraethyl lead) refinery, plastic, paints, antiseptic, scientific instruments, photography, fuel combustion, tannery, smelter, battery crushing unit, mining, electroplating, pigments (Cadmium yellow), plastics, pesticides, wood preservative, glass/copper smelters,

glass/copper smelters, coal combustion, land application of fertilizers, animal manures, sewage sludge, pesticides, waste water irrigation, spillage of petrochemicals and Uranium mining etc. Heavy metal enters into the animal body by indirect means like eating or grazing of contaminated fodder, drinking contaminated water and sometimes respiration with polluted air. Heavy metals may enter into plant tissue by means of crop production in polluted soils or irrigation with contaminated water.

Lead (Pb)

In periodic table Lead is situated at group 14 (IVthA) 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. It enters into the animal body by indirect sources. It gets accumulated in the liver, kidney, brain and bone. Its half-life is around 1–2 month in blood, but it is upto 20–30 years in case of bone. In acute poisoning cases, fatality rate is upto 100%. Only chronic exposure affects the reproductive system of animals. 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. It reduces the density of seminal plasma with significant decline in certain constituents like fructose and succinic dehydrogenase. The low fructose content reduces the succinic dehydrogenase and alkaline phosphatase activity that further develop semen abnormalities such as azoospermia, asthenozoospermia, teratozoospermia and morphologically abnormal sperm (mainly, the tail abnormality) [1]. It also inhibits certain membrane bound enzymes, like, 5¢-nucleotidase, ATPase and alkaline phosphatase in the testicular tissues. It interferes only with those enzymes that are having (−SH) group or with the intervening redox systems and tissue respiration [2]. In Sertoli and Leydig cells, it impedes the enzymatic activity by inhibiting gonadotropin receptors, StAR, p450 side chain cleavage, 3-HSD (3-hydroxysteroid dehydrogenase), and P450c17 that are necessary for the conversion of progesterone into testosterone.

In case of females, steroidogenesis activity is hindered in the same way as like males. *In-vivo* exposure of lead in case of cynomolgus monkey, suppressed circulating luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol without affecting progesterone, causing overt signs of menstrual irregularity [3]. The prenatal and neonatal exposure to lead suppressed ovarian homogenate-4 androgen production, whereas 5-reduced androgens were increased in rat. In mice, there is no change noticed in antral follicles but there is a decrease in primordial follicles and increased growing and atretic follicles [4]. But some studies experienced a significant reduction in the number of ovarian primordial follicles. It can also cause spontaneous abortions and fetal anomalies in case of rabbit and sheep [5]. 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 [4]. It also targeted the steroid genic acute regulatory protein (StAR) that mediates the transfer of cholesterol into mitochondria [6].

Mercury (Hg)

In periodic table mercury is placed at group 12th (III B) and 6th periods. At room temperature it is found in 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) and Density: 13.5336 gm/cm^3. It enters into the animal body as like Lead**.** Its toxicity depends on its chemical form, methyl mercury is found to be more hazardous than metallic form of mercury. It alters the activity of enzymes that are having (–SH) group [5]. Selenium and Vitamin E help in protecting against mercuric toxicity by their antagonistic mechanism. Chronic exposures to mercury cause neuro-degeneration, behavioral changes and ultimately end up in death. Large-scale mercury poisoning has occurred in Minamata and Niigata in Japan and Iraq by industrial or inadvertent introduction of mercury into the food chain.

In animals, reproductive toxicity may be developed after chronic exposure but sometimes it is even acute. Young ruminants are more susceptible to mercury poisoning rather than old ruminants and non-ruminants (Horse and Pig) [7]. 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 [8]. It can also deteriorate semen quality by production of vacuolated elongated spermatid, dispositional acrosome and pyknotic nuclei [8]. It affects the membrane bound hydrolysis that causes the progressive degeneration of peritubular membrane. It has been reported that mercury exposure is highly responsible for cryptorchidism in the Florida panther [9]. The intraperitoneal injection of mercury for 90 days in male rat and mice causes consistent changes in testicular steroidogenesis by suppressing various steps in steroidogenesis along with decreased testosterone and LH level [10]. Oral exposure to mercuric chloride can suppress the testosterone level and it can increase the testicular cholesterol level [11]. It may be because of the block in biosynthetic conversion of sex steroid hormones such as testosterone. Another possibility is that mercury act as an estrogenic mimic on the testes which inhibits androgen production and it also causes accumulation of cholesterol, because it up regulates the high-density lipoprotein (HDL) receptor and scavenger receptor class B, type I (SR-BI).

In females, it can cause fetotoxicity that it can easily cross the placenta and blood brain barrier that causes the neuronal dysfunction. It can also cause the spontaneous abortion and fetal malformation in animals [7]. In hamster, subcutaneous mercuric chloride treatment disrupts estrus cycles, suppresses follicular maturation, reduces plasma and luteal progesterone levels, and it may also disrupt hypothalamus-pituitary gonadotropin secretion. In rat, mercury causes lengthening of estrous cycle and morphological changes in the corpus luteum [1]. It also stimulates the estrogen receptor-dependent transcription and increases the proliferation of MCF-7 cells [12]. Mercury can also behave as an estrogen mimic [7].

Cadmium (Cd)

Pure cadmium is a soft, silver-white metal. It is situated in periodic table at group 12th (ÎÌB) and 5th periods The physical property of cadmium include atomic number 48, atomic weight 112.411, electro-negativity 1.5, crystal ionic radius (Principal valence state) 0.97, ionization potential 8.993, oxidation state +2, Electron configuration Kr 4d1 5S2, Density 8.64 g/cm3, Melting point 320.9°C and Boiling point 765°C at 100 kPa. 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). It enters into the animal body as like lead and gets accumulated in kidney and liver through chronic exposure. It interacts with other minerals such as Zinc, Iron, Copper and Selenium due to their chemical similarities and competing for their binding stage. It can also affect Calcium and Phosphorus metabolism in bones [13].

In male, it can cause testicular necrosis in case of rats [14]. Research with animal models like rat leydig cells, it is found that cadmium is highly toxic since it affects steroidogenesis. However at high concentrations >10 M steroidogenesis can coincide with cell death [15]. However, in another study by using rat Leydig cells by treating with 100-M Cadmium treatment it is found that it causes doubled testosterone production with no change in cell viability [16]. In contrast, subcutaneous injection of Cadmium to adult rats can cause a decline in plasma testosterone level [13]. These experiments suggest that the route of exposure to Cadmium is the deciding factor for stimulation or inhibition of testicular androgen production. Exposure to Cadmium through ingestion is also associated with increased testosterone and estradiol. It can also cause inhibition of DNA repair, decreased antioxidants, activates signal transduction or cellular damage [8] rather than acting through a specific receptor or mechanism to inhibit steroidogenesis as well as spermatogenesis at a specific spermatogenic stage and impairs the semen quality [13].

In case of females, it inhibits the process of steroidogenesis. Maternal exposure to high level of cadmium can lead to a significant increase in premature delivery probably by compromising placental function. Cadmium at high concentrations can inhibit placental progesterone synthesis and also suppresses the expression of the low-density lipoprotein receptor that is necessary to bring cholesterol substrate into the cells. Cadmium mediated reduction in progesterone production by the cultured human trophoblast cells indicated that the decline is not because of cell death or apoptosis. Rather, there is a specific block of P450 side chain cleavage expression and activity. This has been proven by blocking P450 side chain cleavage activity with amino-glutathamide and then by addition of pregnenolone, which was converted to progesterone by the unaffected activity of 3-HSD (3-hydroxysteroid dehydrogenase) [17]. The activity of placental 11-HSD (3-hydroxysteroid dehydrogenase) is critical to protect the fetus from maternal cortisol, which suppresses fetal growth by converting it into inactive cortisone. A recent reports describe that Cadmium at the concentrations <1-M reduces the activity of 11-HSD (3-hydroxysteroid dehydrogenase) type 2 and its expression in cultured human trophoblast cells [17]. It may also downre gulate 11-HSD (3-hydroxysteroid dehydrogenase) by mimicking the ability of estrogen to attenuate the expression of this placental enzyme. It can also contribute to risk of various major diseases later in life, particularly for the low birth weight fetus that was not protected from maternal cortisol. Cadmium of more than 5 Molar concentrations shows detrimental effect on reproduction [18]. However, at concentrations <5 Molar, Cadmium stimulates transcription of P450 side chain cleavage in porcine granulosa cells that results in greater progesterone production [11]. It may also act to stimulate gene transcription by its high-affinity displacement of calcium from its binding to calmodulin and by activation of protein kinase-C and second messenger pathways. The P450 side chain cleavage is the rate-limiting step for steroidogenesis. *In-vivo* treatment of rat ovaries with cadmium exhibited suppression of progesterone, testosterone, and estradiol production in culture [5]. It can also acts as an estrogen mimic [2].

Arsenic (As)

The abundance of arsenic in the Earth's crust is 1.5–3.0 mg/kg, making it the 20th most abundant element in the earth's crust. It is steel grey, very brittle, crystalline, semi metallic (metalloid) solid. It tarnishes in the air, and when heated rapidly oxidizes to arsenous oxide which has a garlic odour. Arsenic and its compounds are very poisonous. Upon heating arsenic and some minerals containing arsenic tends to sublime (transfers from the solid to the gaseous state, without passing through the liquid state). Chemical properties include atomic number 33 and relative atomic mass 74.92160. It is situated in the periodic table at group 15^{th} (5^{th}A) and 4^{th} periods. It is well known as a favored form of intentional poisoning and recognized for being developed by Paul Ehrlich as the first drug to cure syphilis. The most extensive environmental exposure to arsenic is mainly by means of contamination with drinking water. Since 1980s, the provision of arsenic-contaminated Artesian well water in Bangladesh has exposed an estimated 50–75 million people to very high levels of arsenic toxicity [19]. The arsenic-related carcinogenesis including skin, lung, urinary bladder, kidney, and liver is found in human as well animals. Arsenic enters into the animal body as like lead. Another common source of arsenic poisoning are certain fluids that are used for dipping and spraying of animal to control ectoparasites. Arsenic toxicity in cattle varies from gastrointestinal form to nervous form. Arsenic toxicity produces goiter in rats, thyroid antagonism in man and inhibited growth of rumen bacteria in pure culture as well as it reduces the fermentative activity in ruminants. Chronic toxicity of arsenic is mostly manifested in weight loss, capricious appetite, conjunctivitis and mucosal erythematic lesion including mouth ulceration and reduction in milk yield. Acute exposure causes abdominal cramping, hyperesthesia in extremities, abdominal patellar reflexes and abdominal electrocardiogram [20]. However, chronic exposure causes anemia, liver and kidney damage, hyperpigmentation and keratosis [8].

In males, Arsenic damages the Androgen binding protein (ABP) that gets secreted from the Sertoli cells which passes though the sertoli cells-lymphatic channels, and bind with androgens that are necessary to maintain their activity. It causes the steroid genic dysfunction in rats, leading to impairment of spermatogenesis [17]. 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 [17]. It reduces the gonadotropins, plasma estradiol, and decreases the activities of certain steroid genic enzymes, 3-hydroxysteroid dehydrogenase (HSD), and 17 HSD [14]. Arsenic poisoning causes testicular degeneration and interstitial cell hyperplasia in mice [8].

In case of females, Arsenic at very low concentrations even in (µmol) stimulates the proliferation of progesterone receptor pS2 and it can alter the mRNA expression of estrogen receptor [21]. It also causes the cystic hyperplasia of the uterus, which is often related to abnormal and prolonged estrogenic stimulation in mice.

Conclusion

The heavy metal enters in animal either from direct or indirect sources and it contaminates the food chain of ecosystem that

is dangerous for survival. Mostly of the heavy metals are targeted to affect the liver, kidney and nervous system. Chronic exposure of the reproductive system to heavy metals causes the steroid genic dysfunction, fetal abnormality and embryotoxicity. They can also act as an endocrine-disrupting substance that manipulates hormone and its receptor activity. Some heavy metals are highly associated with an estrogen mimicking action and it causes physiological dysfunction related to reproduction.

References

1. Davis BJ, Price HC, O'Connor RW, Fernando R, Rowland AS, Morgan DL. Mercury vapor and female reproductive toxicology. Toxicol Sci. 2001; 59:291-6.
2. Johnson MD, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G, *et al.* Cadmium mimics the *in vivo* effects of estrogen in the uterus and mammary gland. Nat Med. 2003; 9:1081-84.
3. Foster WG. Reproductive toxicity of chronic lead exposure in the female cynomolgus monkey. Reprod Toxicol. 1992; 6:123-31.
4. Taupeau C, Poupon J, Nome F, Lefevre B. Lead accumulation in the mouse ovary after treatment induced follicular atresia. Reprod Toxicol. 2001; 15:385-91.
5. Piasek M, Laskey JW. Acute cadmium exposure and ovarian steroidogenesis in cycling and pregnant rats. Reprod Toxicol. 1994; 8:495-507.
6. Srivastava V, Dearth RK, Hiney JK, Ramirez LM, Bratton GR, Dees WL. The effects of low-level Pb on steroidogenic acute regulatory protein (star) in the prepubertal rat ovary. Toxicol Lett. 2004; 77:35-40.
7. Choe SY, Kim SJ, Kim HG, Lee JH, Choi Y, Lee H, Kim Y. Evaluation of estrogeni city of major heavy metals. Sci Total Environ. 2003; 312:15-21.
8. Waalkes MP, Keefer LK, Diwan BA. Induction of proliferative lesions of the uterus, testes, and liver in Swiss mice given repeated injections of sodium arsenate: possible estrogenic mode of action. Toxicol Appl Pharmacol. 2000; 166:24-35.
9. Lafuente A, Marquez N, Perez-Lorenzo M, Pazo D, Esquifino AI. Pubertal and post pubertal cadmium exposure differentially affects the hypothalamic-pituitary-testicular axis function in the rat. Food Chem Toxicol. 2000; 38:913-23.
10. Ramalingam V, Vimaladevi V, Rajeswary S, Suryavathi V. Effect of mercuric chloride on circulating hormones in adult albino rats. J Environ Biol. 2003; 24:401-4.
11. Smida AD, Valderrame XP, Agostini MC, Furlan MA, Chedrese J. Cadmium stimulates transcription of the cytochrome P450 side chain cleavage gene in genetically modified stable porcine granulosa cells. Biol Reprod. 2004; 70:25-31.
12. Sukocheva OA, Yang Y, Gierthy JF, Seegal RF. Methyl mercury influences growth- related signaling in MCF-7 breast cancer cells. Environ Toxicol. 2005; 20:32-44.
13. Jurasovic J, Cvitkovic P, Pizent A, Colak B, Telisman S. Semen quality and reproductive endocrine function with regard to blood cadmium in Croation male subjects. Biometals. 2004; 17:735-43.
14. Chattopadhyay S, Ghosh S, Chaki S, Debnath J, Ghosh D. Effect of sodium arsenite on plasma levels of gonadotrophins and ovarian steroidogenesis in mature albino rats: duration-dependent response. J Toxicol Sci. 1999; 24:425-31.
15. Zeng X, Jin T, Zhou Y, Nordberg GF. Changes of serum sex hormone levels and MT mRNA expression in rats orally exposed to cadmium. Toxicol. 2003; 186:109-8.
16. Piasek M, Laskey JW. Effect of *in vitro* cadmium exposure on ovarian steroidogenesis in rats. J appl Toxicol. 1999; 19:211-17.
17. Kawai M, Swan KF, Green AE, Edwards DE, Anderson MB, Henson MC. Placental endocrine disruption induced by cadmium: effects on P450 cholesterol side-chain cleavage and hydroxysteroid dehydrogenase enzymes in cultured human trophoblasts. Biol Reprod. 2002; 67:178-83.
18. Paksy K, Rajczy K, Forgacs Z, Lazar P, Bernard A, Gati I, Kaali G. Effect of cadmium on morphology and steroidogenesis of cultured human ovarian granulosa cells. J Appl Toxicol 1997; 17:321–27.
19. Mandal BK, Suzuki KT. Arsenic round the world: a review. Talanta. 2002; 58:201-35.
20. Facemire CF, Gross TS, Guillette LJ Jr. Reproductive impairment in the Florida panther: nature or nurture. Environ Health Perspect. 1995; 103(Suppl 4):79-86.
21. Stoica A, Pentecost E, Martin MB. Effects of arsenite on estrogen receptor expression and activity in MCF-7 breast cancer cells. Endocrinology. 2000; 141:3595-602.