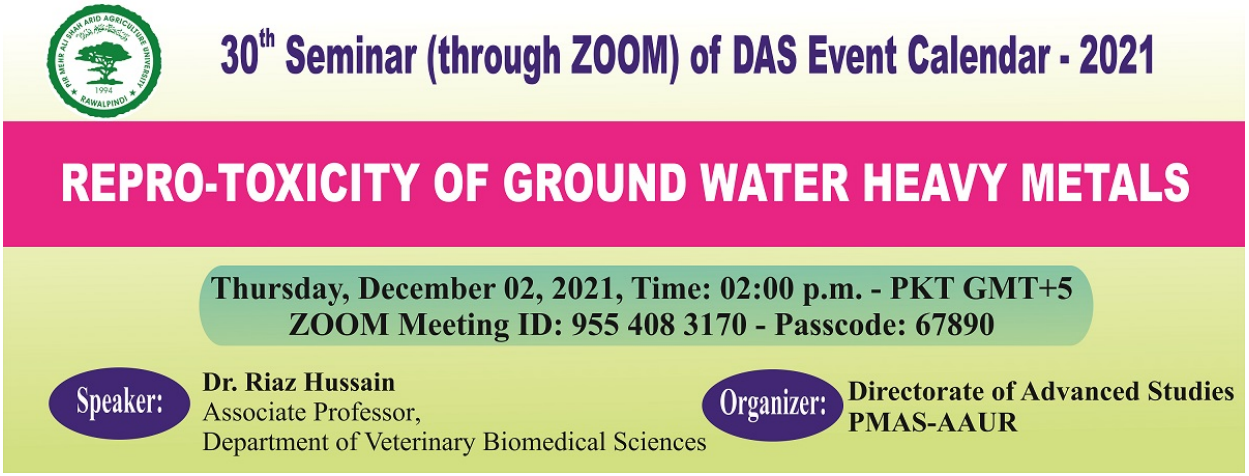
DIRECTORATE OF ADVANCED STUDIES
EVENT CATALOGUE
2021

30TH SEMINAR OF DAS EVENTS CALENDAR – 2021

REPRO-TOXICITY OF GROUND WATER HEAVY METALS



ACTIVITIES

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Introduction

- Metals are naturally existing in ecosystem
- Heavy metals are defined as any metallic chemical element that has a relatively high density above 5 g/cm3
- Biological essential metals : Copper (Cu), nickel (Ni), iron (Fe), Zinc (Zn), manganese (Mn)(Tolerable at low concentrations but toxic at high level)
- Non-essential heavy metals : Arsenic (As), Lead (Pb), mercury (Hg), cadmium (Cd), Chromium (Cr), and tin (Sn) (Toxic at low concentrations)

(Duffus, 2002, Fergusson, 1990)

- Metals found all over the earth including atmosphere, earth crust, water bodies, and accumulate in biological organisms including plants and animals
- Distributed in environment through volcanic eruptions, spring waters, erosion and through anthropogenic activities (fossil fuel combustion, industrial processes waste water effluents, agricultural activities etc)
- These heavy metals bio-accumulate in living organisms and human body, compartmentalized into body cells, tissue biding to proteins, nucleic acids and disrupting cellular functions

(Monisha et al., 2014)

- Water, air and food (main sources of heavy metals for life on earth)
- Ground water (major source of toxic heavy metals)
- water pollution has approved as Global threat to human and animal health
- Bacteriological and chemical contamination of drinking ground water reported Globally

(Sharaf et al., 2020; Ghaffar et al., 2020; Malik et al., 2010)

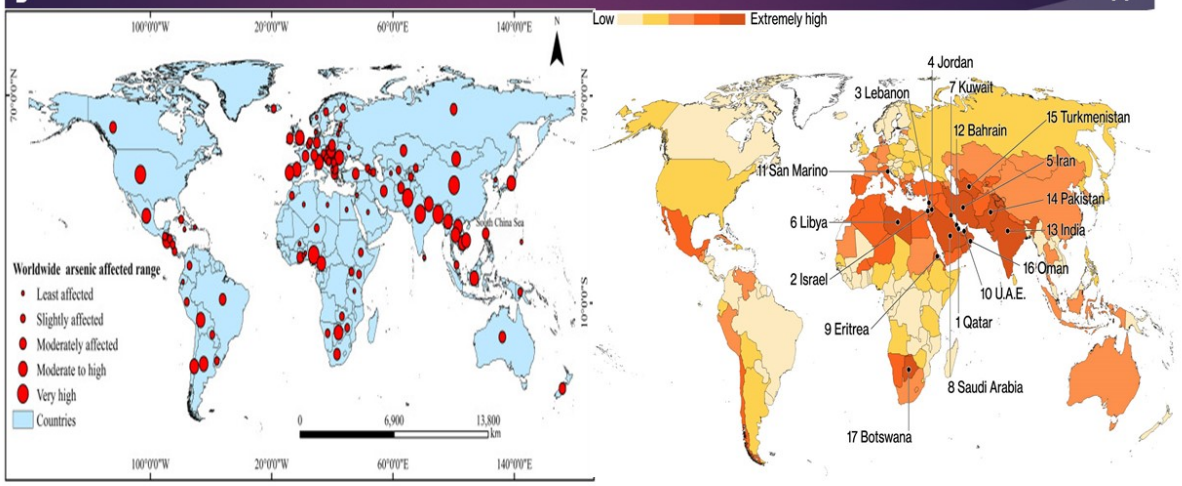


Fig: Global water crisis and ground water heavy metal contamination (Ali *et al.*, 2019; theryf.org., 2020)

- Swift industrialization and overwhelming civilization, results into heavy metal toxicity which impose Global health hazard threat
- Heavy metals (strong biological poisons) (Continual nature & accumulation)
- Heavy metal contaminated food and water is major source of reproductive disorders
- Heavy metal poisoning reported as massive epidemic in most of the Globe and particularly in Pakistan due to ground water contamination and toxicity

(Malik et al., 2010; Sohail et al., 2019; Naz et al., 2020; Imran et al., 2020)

Water Quality Status in Pakistan

- Geographical information system and water quality index studies of bore wells and open wells of Rawalpindi and Islamabad revealed more than 50% samples were poor in quality for drinking due to bacteriological and anthropogenic contaminations
- High amount of Calcium, Lime stone and magnesium carbonate reported in I-9 and G-10 sectors in Islamabad
- In most areas of **Punjab (Faisalabad, Rawalpindi, Lahore, Villages of South Punjab, Kasur, Gujranwala, Multan, Bahawalpur, Sheikhupura**) ground water reported as intensively contaminated with WHO and PEPA standards for bacteriological and heavy metal contaminations

- Districts **Banu, Swabi, Narangi, and Haripur of Khyber Pakhtunkhwa** (KP) water quality reported as poor and below the quality parameters of WHO however in most areas the water quality is within range set by WHO (**Jamrud, Landikotal, Khyber agency, Kohat, Lachi, Nagar Valley**)
- In four cities of **Baluchistan (Ziarat, Loralai, Quetta and Khuzdar)** the water quality is badly contaminated with microorganisms and heavy metals
- Contamination and water shortage is a major problem in many cities of **Sindh (Karachi , Khairpur, Hyderabad, Sukkur and Larkanna, Theta**)
- Sewerage water mixing, chemical pollution (industrial effluents, textile dyes, pesticides, nitrogenous fertilizers) contaminants

(Azhar, 1996; Zulfiqar et al., 2016; Hussain et al., 2020)

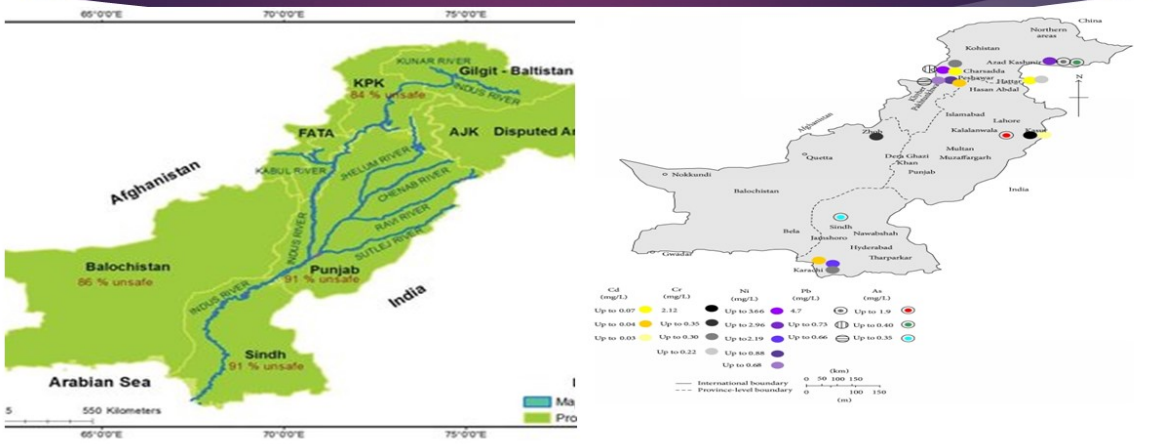


Fig: Ground water contamination status in Pakistan (Raza *et al.*, 2017; Waseem *et al.*, 2016)

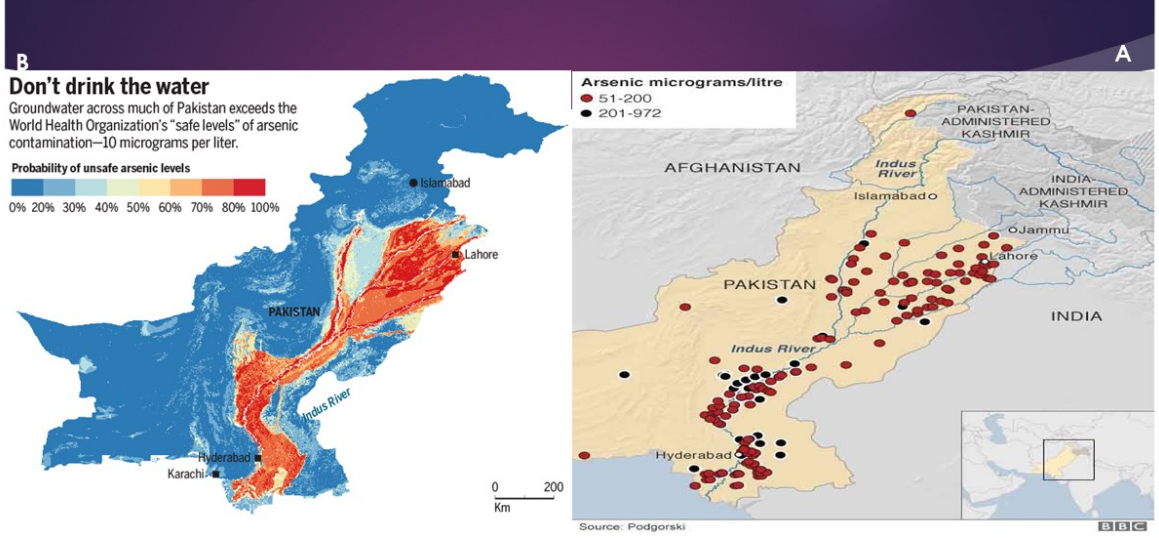


Fig: Ground water contamination status in Pakistan (bbc.com 2016; science.org. 2017)

- Heavy metal groundwater contamination and toxicity has lead to a massive epidemic of heavy metal poisoning in many countries of the world
- Studies conducted by Pakistan Council of Research in Water Resources (PCRWR)
- Approximately 60 million people are drinking ground water with elevated conc. of heavy metals above WHO standards (arsenic 0.01 mg/liter, cadmium 0.003 mg/liter, lead 0.01 mg/liter)
- Heavy metal toxicity may lead to developmental, teratogenic, carcinogenic, genotoxic, nervous and reproductive disorders in human and animal species (Jarup, 2003)

- 30% of clean water in nature is groundwater
- 53% of the world populations use ground water as source of drinking water
- Human and animal body systems exposed to heavy metals through ingestion in the form of food and water
- In developing countries people depend on ground water and surface water sources for domestic use
- Bio-toxic heavy metals in crops and subsequent in food chain pose potential risk to human and animal health

Sources Ground Water Contamination

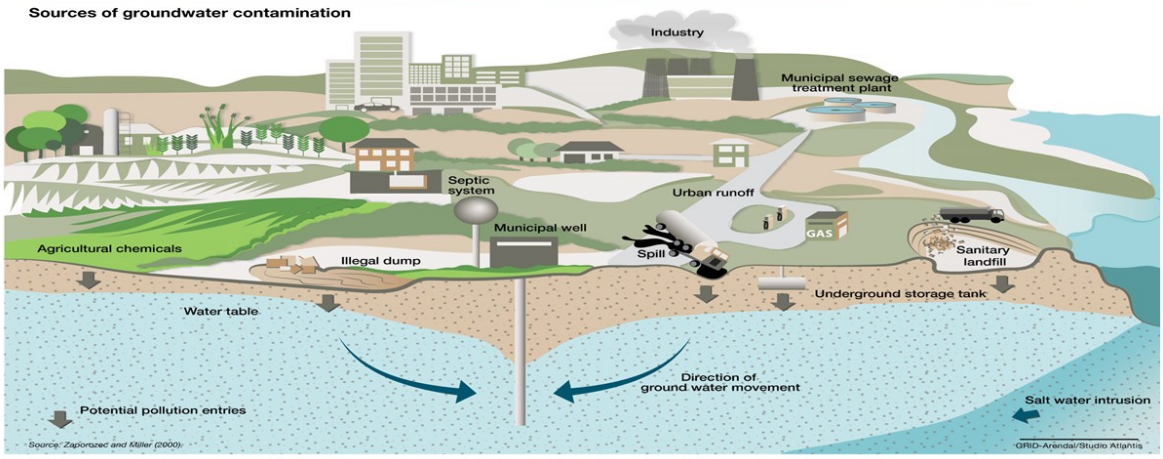


Fig: Sources of ground water contaminations (www.grida.no)

B A

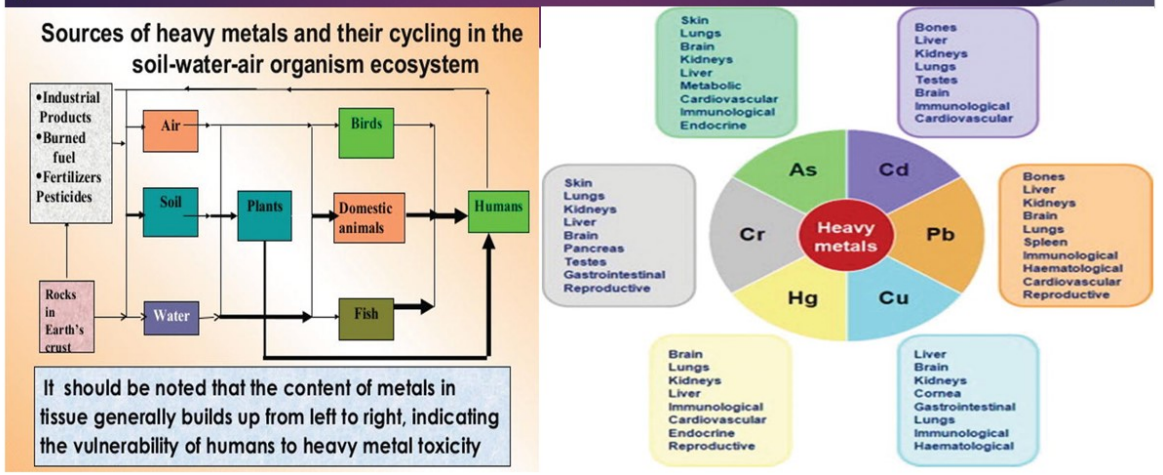


Fig: Heavy metal Sources, cycling and targeted vital organs (Masindi and Muedi, 2018)

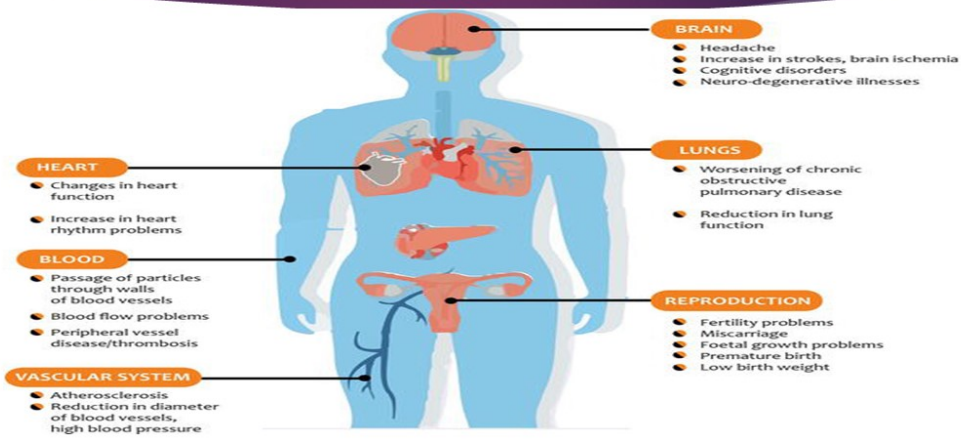
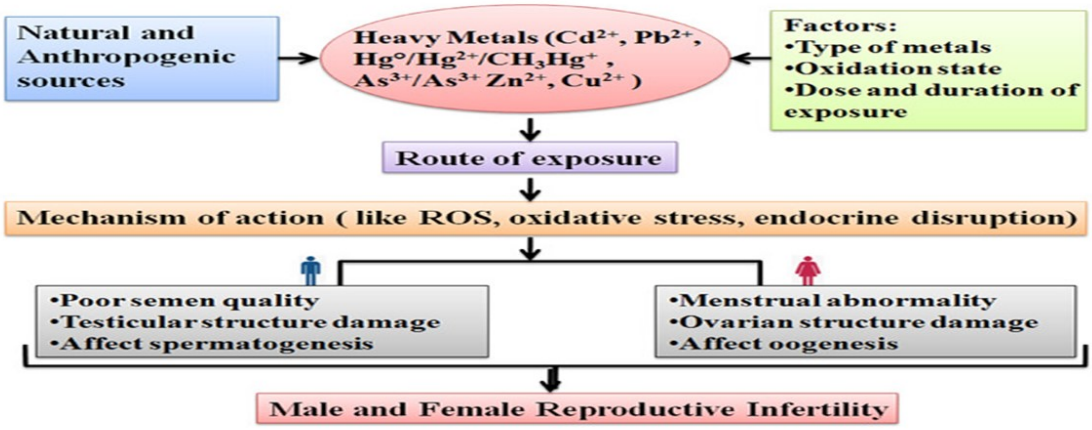


Fig: Heavy metal toxic effects

Heavy Metal Repro-toxicity

- Testes develop during early embryogenesis due to testis determining factors (SRY & related proteins and SOX9)
- Spermatogenesis (Pituitary hormones LH & FSH)under effect of GnRH of Hypothalamus)
- FSH ----Sertoli cells & LH-----Leydig cells (Testosterone & estradiol production)
- Testosterone-----major androgenic hormone in male----acts on Sertoli cells---to control spermatogenesis (Sertoli cells provide mechanical and nutritional support to germ cells during spermatogenesis & provide appropriate microenvironment through Sertoli cells blood-testis barrier)
- Estradiol stimulates spermatozoa motility and act as germ-cell survival factor

Heavy Metal Repro-toxicity



Heavy Metal Repro-toxicity

- **Lead (Pb)** absorbed through GIT, lungs and skin (organic)
- After absorption it distributed throughout body (bones, teeth, liver, lung, brain, spleen) major accumulation occurs in Bone
- Can cross blood-brain barrier and placental barrier and hence developing fetus
- Excretion is very slow, 90% bound to RBC,s , having high affinity for sulfhydryl groups (SH) and hence it impairs zinc-dependent enzymes like gamma-aminolevulinic acid dehydratase (ALAD) which involve in haem synthesis, cytochrome synthesis, **steroid metabolism**, **membrane integrity**, metabolite synthesis of Vitamin D in renal tubular cells

(Sahni, 2011)

Heavy Metal Repro-toxicity

- **Mercury (Hg)** occurs in three forms Elemental mercury is oxidized in air, inhaled and rapidly distributed in body, organic mercury is lipo-soluble and well absorbed through GIT, lungs and skin, can cross placenta and into breast milk
- Develop into monomethylmercury cation and dimethyl mercury , enters food chain
- Binds to SH of membrane proteins, may lead to anuria, anemia
- **Cadmium (Cd)**: tobacco smoke and ground water are important sources
- Transported in blood bound to metallothionine, very slow excretion , effect brain, kidneys, liver and reproductive organs
- Binds to sulfhydryl groups, displacing other metals from metalloenzymes, disrupting those enzymes, competes with calcium for binding sites on regulatory proteins, having lipid peroxidation potential and human carcinogen

Heavy Metal Repro-toxicity

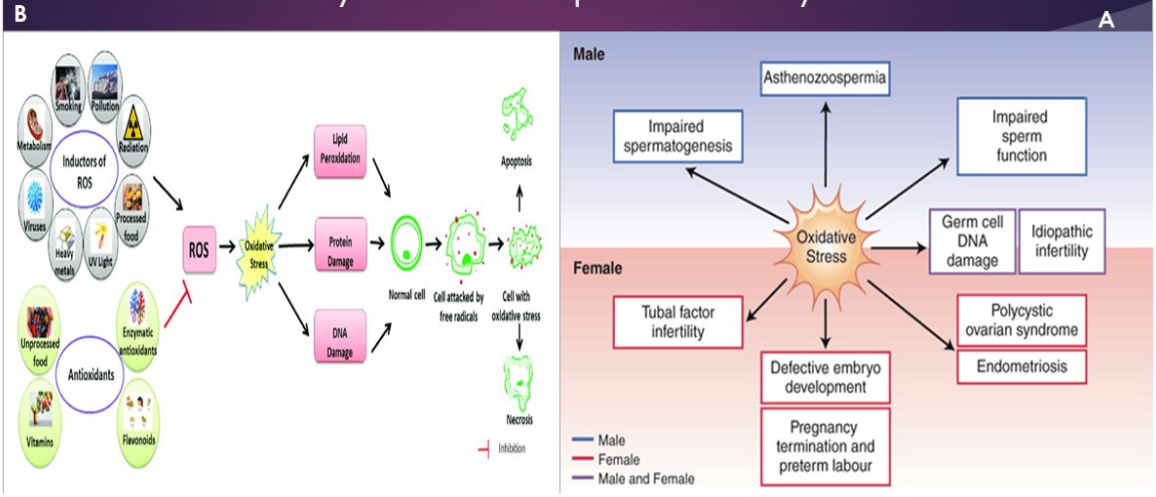
- **Arsenic (As)**: absorbed through GIT and Pulmonary route, accumulate in keratin-rich tissues like nails, hairs, skin, distributed throughout body binds to sulfhydryl groups of tissue proteins or enzymes leading to inhibition of enzymatic systems
- Affects energy transduction reactions like Krebs cycle and oxidative phosphorylation, and inhibition of ATP production, oxidative stress and steroidogenic hormonal disruption and infertility
- **Endocrine disrupting effects of heavy metals:**
- Reproductive toxicants---chemicals, agents or physical conditions that impair the ability of male or female fertility
- In male ---toxicants interact with reproductive function to impair the function of testes to produce viable sperm

Heavy Metal Repro-toxicity

- Heavy metals acts as toxicants and results into decreased fertility in term of sperm counts and quality, congenital malformations and testicular cancer
- These toxicants act mainly through dysregulation of hormonal signaling on the hypothalamus-pituitary- gonadal axis and induction of **oxidative stress** and infertility
- Damage Androgen binding proteins (ABP), steroidogenic dysfunction leading to impairment of spermatogenesis, Impair meiosis and post-meiotic stages of spermatogenesis, testicular degeneration and interstitial cell hyperplasia

(Verma *et al.*, 2018; Waalkes, *et al.*, 2000)

Heavy Metal Repro-toxicity



Heavy Metal Repro-toxicity

- **Endocrine toxicity of heavy metals on Hypothalamus-pituitary complex;**
- Hypothalamus secret GnRH ---stimulate production of FSH & LH from Pituitary glands
- Regulated by neurotransmitters (biogenic amines and amino acids)
- Heavy metals act as modulators of these neurotransmitters and alters biogenic amines synthesis
- Increase norepinephrine conc. and decrease dopamine conc. in anterior hypothalamus, Cd also induces oxidative stress and apoptosis in cortical neurons and impair GnRH synthesis / release
- Inhibit gonadotrophins hormones and decrease in spermatozoa number

(Yang *et al.*, 2013)

Heavy Metal Repro-toxicity

- Alters the morphology of Sertoli and Leydig cells
- Lead to Leydig cell tumor
- Inhibit testicular steroidogenic enzymes (3-beta-hydroxysteroid dehydrogenase and 17-beta-hydroxysteroid dehydrogenase, leading to reduction of plasma testosterone
- Reduction in testes weight, inhibition of sperm motility, and induction of oxidative stress and hence male infertility
- Prostate tumor, azospermia and testicular dysfunction

(Yang *et al.*, 2013)

Heavy Metal Repro-toxicity

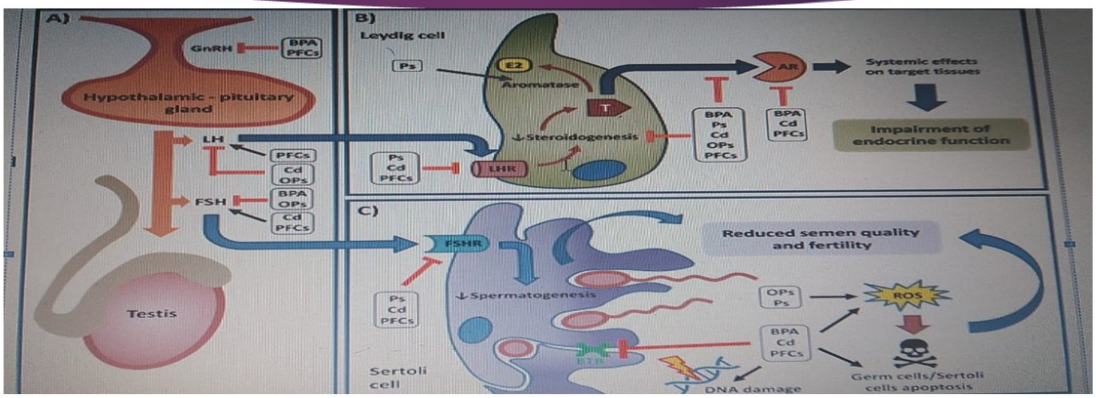


Fig: Schematic representation of endocrine disruptors effects on male fertility
PFC,s : Perfluoroalkyl compound, Ops; Organophosphate pesticides, BPA: Bisphenol (Nisio & Foresta, 2019)

Heavy Metal Repro-toxicity

- Disruption of the ubiquitin-proteosome system, results apoptosis in the cells
- Inhibited proliferation of Sertoli cells and caused oxidative stress through stimulation of lipid peroxidation and antioxidant enzymes inhibition (superoxide dismutase and glutathione peroxidase) and DNA damage, vacuolated Sertoli cells, abnormal sperm cells
- Inhibits testicular steroidogenesis through reduction of StAR protein expression and inhibition of FSH release
- Induces attrition of placental telomere- alters stability of genome and chromosome integrity- leads to deleterious effects on developing fetuses

(Renu *et al*., 2018)

Heavy Metal Repro-toxicity

- Exposure lead to breast cancer, endometriosis, endometrial cancer, menstrual disorders, abortions, stillbirths, and pre-term deliveries
- Endocrine disrupting chemical mimic or block endocrine actions, interfere with receptor binding steroidogenesis and metabolism of hormones
- Disrupt and impair hormonal secretions (LH & FSH) and receptor bindings , ovarian oocyte yield, decreased ovarian weight, decrease in healthy follicle number, and increased atresia
- Decreased uterine size, reduced uterine epithelial cells, less endometrial glands and thinner myometrial wall
- Downregulated mRNA expression and protein levels of estrogen receptor 1 (ER alpha) and reduced expression of vascular endothelial growth factor in endometrium (Chatterjee & Chatterji, 2010)

Heavy Metal Repro-toxicity

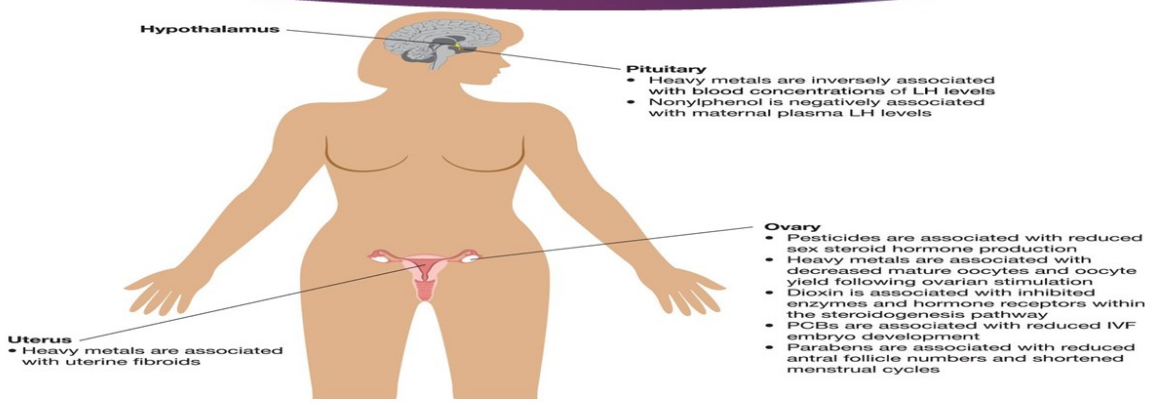


Fig: Heavy metal female repro-toxicity

Heavy Metal Repro-toxicity

- Alterations of steroidogenesis, delayed puberty, pregnancy loss, disorders of menstrual cycle, premature birth, reduced birth weight
- Impedes progesterone synthesis by inhibiting expression of steroidogenic acute regulatory protein StAR and cytochrome P450 cholesterol side chain enzyme P450scc
- Miscarriages / spontaneous abortions due to suppression of pregnancy hormone
- Through placenta enters into fetal circulation thereby blocking nutrients and blood flow resulting into growth retardation

(Sharma et al., 2014)

Conclusion

- Heavy metals are ubiquitous and represent a serious threat to human health and life on earth
- Heavy metal enters in Human or animal body either from direct or indirect sources and contaminates the food chain of ecosystem that dangerous for survival
- Target vital organs (liver, kidney, nervous and reproductive system)
- Chronic exposure causes steroidogenic dysfunction, fetal abnormality and embryotoxicity
- Act as endocrine-disrupting substance
- Associated with Estrogen mimicking action and reproductive physiological dysfunction