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A REVIEW ON POTENTIAL EFFECTS OF ENDOCRINE DISRUPTORS ON VARIOUS ORGANISMS

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ABSTRACT

DDT which belongs to the category of endocrine disruptor chemicals is a persistent organochlorine and can bioaccumulate in the food chain leading to a drastic population decline in birds. The effect of Endocrine Disrupting Chemicals (EDCs) and scientific basis behind endocrine disruption has been a matter of discussion in various environmental issues- related programs of WHO and UNEP. It clearly emphasizes that EDC can alter the health of human beings and also wildlife and it will be a major threat shortly too. Endocrine disorders have also been detected in a variety of wild vertebrate species. Endocrine disruption in fish is happened to be one of the well-flourished areas in research. Studies have shown that high concentrations of vitellogenin were found in male fish caged in wastewater treatment plants in the 1990s. Most of the studies on endocrine-disrupting chemicals were focused on vertebrates, the action and mechanism of endocrine-disrupting chemicals on invertebrates is still an unexplored area except a few major works. The effect of xenoestrogens on organisms is of great concern to scientists all over the world. However, it is quite sad that work done in this field in our country is meagre when compared to other countries. This calls for proper and well-documented research in this field.

Keywords: Endocrine disruptors; feminization; xenoestrogens; organochlorine; endocrine-disrupting chemicals; vitellogenin.

1. INTRODUCTION

The last century has witnessed a drastic increase in the standard of living all over the world. This boom has been brought about by scientific and technological progress which was initiated in the mid-1950s. The actual number of chemicals on the global market is still unknown, although 143,835 have been

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preregistered by the European Union (EU) regulation REACH (Registration, Evaluation, and Authorization, Restriction of Chemicals). These chemicals are diverse and are originated from basic compounds which include pesticides, pharmaceuticals' and beauty products [1]. Some of these chemicals are beneficial to society while some are harmful to entire organisms. The effect of organochlorine pesticides (DDT) was well documented in Rachel Carson's Silent Spring. The book which came out in 1962 brought the issue of pollution and wildlife health to the forefront of public, media and political attention.

DDT which belongs to the category of endocrine disruptor chemicals is a persistent organochlorine and can bioaccumulate in the food chain leading to a drastic population decline in birds (Carson, 1962). In the early 1990s, a group of scientists in the United States started a consortium about chemicals that have a potential ability to induce adverse effects on the endocrine systems of both humans and wildlife. The outcomes of the consortium, the "Wingspread Consensus Statement," triggered further programs in both the USA and Europe. "Our Stolen Future" by Theo Colborn, Dumanoski and Myers published in 1996 urged the regulatory bodies to take serious actions on synthetic chemicals and environmental contaminants acting as EDC. The waves generated by the Wingspread Consensus Statement, The Stolen Future, and Silent Spring have awakened the ill effects of endocrine disruptor chemicals in India. It is just over a recent decade that the ability of certain chemicals to interfere with the endocrine system of humans and wildlife has been perceived. These chemicals are collectively referred to as Endocrine disruptor chemicals and according to the US Environmental Protection Agency, an endocrine-disrupting chemical is defined as "an exogenous agent that disrupts the production, release, transport, metabolism, binding, action, or elimination of endogenous hormones that are responsible for the maintenance of homeostasis and the regulation of developmental activities" [2]. As evidence from research work on the effect of endocrine disruption, some countries have set up monitoring protocols to analyze suspected endocrine disruptors, and the Endocrine disruptor Screening program by US environmental protection agency is globally accepted one. The effect of EDCs and scientific basis behind endocrine disruption has been a matter of discussion in various environmental issues related programs of WHO and UNEP. It clearly emphasizes that EDC can alter the health of human beings and also wildlife and it will be a major threat shortly too. Hence an authentic scientific data is needed to validate the potential effects of EDC's upon human life, fish and wildlife as a whole.

2. ENDOCRINE SYSTEM

It is necessary to comprehend the various functions of the endocrine system to understand the scientific basis of EDC's. An endocrine system is a network of ductless glands that secretes hormones into the blood and regulates various metabolic and physiological activities of the body. The precursors of hormones are amino acids, cholesterol or phospholipids and they travel through the blood and act upon distant target organs, tissues, and cells [3]. The hormones are classified into three major categories by synthesis and action. Hormones that act upon the same cells are known as autocrine hormones. Hormones that are synthesized proximate to their site of action are known as paracrine hormones. Hormones that are synthesized by endocrine glands and transported via the blood to target cells to act upon the appropriate receptors are known as Endocrine hormones.

Hormones have various functions in the human body in controlling physiological and developmental processes. Some are crucial in the normal development of an organism and cause irreversible changes to morphological structures [4]. The secondary sexual characters are linked to the hypothalamic-pituitary-gonad axis, which plays an important role in the reproductive cycle [5]. The endocrine system works through the feedback mechanism. For example, insulin plays a pivotal role in metabolism and glucose storage. Insulin is secreted by the pancreas in response to plasma glucose level, it inhibits glucose production by the liver and promotes uptake and converts to glycogen. The reduction of glucose is a negative feedback mechanism on the pancreas to subside insulin secretion; this regulation helps an organism to maintain homeostasis [6]. During stressful conditions, the glucocorticoid cortisol is released, which enhances gluconeogenesis and lipolysis to get over increased metabolic needs [7]. Various endocrine disorders have been detected in humans, wildlife, etc. which can affect the development of the organism. For example, congenital hypothyroidism may be a reason for neurological damage, including intellectual deficits and cretinism, if it is not cured in the early stage [8]. The deficiency of the enzyme 5α-reductase, which converts testosterone to 5 α -dihydrotestosterone (DHT), can cause poorly-developed external genitalia, micropenis, prostate hypoplasia, reduced spermatogenesis and scarce facial and body hair [9]. Hormones bind to specific receptors, elicit signal transduction and mediate hormonal responses [10]. Hormone receptors are seen on either cell membranes or within the cell cytoplasm or nucleus. Hydrophilic hormones, such as hypothalamic and pituitary hormones, are lipid insoluble hormones and they

cannot pass through the cell membrane. Hence they bind to receptors on the cell membrane and induce or inhibit the actions of the second messenger system. It induces a cascade of protein phosphorylations, producing transcription factors to enhance the hormone to regulate transcription in response to genes, whereas, lipophilic hormones, such as sex steroids can pass through the cell membrane and bind to the intracellular receptors. The hormone-receptor complex functions as a transcription factor by binding to a hormone response element on the DNA within the nucleus of a cell to activate transcription [10]. The genomic responses take much time to synthesize and accumulate the protein [11]. There is a large number of evidence which suggests that lipophilic steroid hormones can also act upon receptors in the membrane to induce fast responses [12]. EDCs are extremely distinct that comprise synthetic chemicals utilized as PCBs, plastics, plasticizers, Triclosan, pesticides, fungicides, phytoestrogens, pharmaceutical agents, and certain industrial or commercial products [13]. These chemicals can enter the aquatic environment through effluent discharge or storm-water runoff. The major transport of EDCs to the aquatic environment is by industrial and municipal wastewater discharge into the rivers, streams, and surface waters [14[, (Luo 2014). Industrial effluents have been recognized as the principal source of EDCs to the aquatic environment (Bhargava, *et al.* 2017), [15]. The exposure to EDCs is normally distinct and generally diffused all over the environment. Globally, EDCs have noticeable toxicities in humans as well as in wildlife [16], (Saxena and Bharagava 2017).

3. TIMELINE FOR ENDOCRINE DISRUPTORS

The understanding of endocrine disruptor chemicals has been achieved only in recent decades. Reproductive problems were reported in female sheep, and cows grazed on pastures containing red clover (*Trifolium pretense*) species [17], later it was found the presence of estrogenic compounds such as coumestrol [18]. A concern about DDT in the environment was published in Silent Spring by Rachel Carson. It was about health-related problems such as eggshell thinning in birds, population decline, skewed sex ratio, etc. Carson pointed out the ability of certain organochlorines that can affect the reproductive system. Unfortunately, the mechanism of endocrine disruption was not clear. Studies have shown that environmental contaminants in Lake Michigan adversely affected the successful hatching of herring gulls [19]. In the mid-1960s presence of synthetic and natural hormones was marked in the wastewater treatment plants in the US (Sumpter, 1995). The first study on the impact of EDCs was followed by vaginal cancer in daughters of mother who had consumed synthetic estrogen by named DES during the trimester period of pregnancy in order to prevent miscarriage [20] Studies have shown that around 2000 people got poisoned by hormonally active PCBs and PCDFs in Japan [21]. Studies have shown that even low–dosage of PCBs caused neurodevelopmental and reproductive effects [22]. In 1976, the accidental release of tetrachlorodibenzo-p-dioxin (TCDD) from a pressure tank in Seveso, Italy, caused various developmental and reproductive effects to the population [23], (Eskenazi *et al.,* 2000). In 1981, Imposex in molluscan was observed following the exposure to tributyltin. It was the first well-documented effect of EDC on wildlife [24]. In 1991, a group of scientists found that xenobiotic chemicals could disrupt the endocrine system thereby causing serious effects in wildlife and humans [25]. The term endocrine disruptor was first coined in the world wingspread conference. Studies on plastics in the laboratory found that it has leaching estrogenic property which can alter endocrine physiology (Soto *et al.,* 2006). A study was carried out to link the relationship between environmental estrogens and male reproductive problems and found declining sperm counts [26,27]. In 1995, the National Academy of Sciences and National Research Council conducted a study on Hormone-Related Toxicants in the Environment [28]. Awareness of endocrine disruption has widened to another level following the release of the book by Theo Colborn and co-authors Dumanoski and Myers, the central focus of the book was on how anthropogenic chemicals have been altering the development, behaviour, physiology, and ultimately well-being and survival of entire population [29]. Demasculinization of alligators in Lake Apopka has been reported in the same year [30]. Also in 1996, the endocrine disruption in fish of North American wastewater is also reported for the first time [31]. These reports helped to strengthen the fact that endocrine disruptors are a major threat to the entire population. The first European workshop on the effects of EDCs on human health and wildlife was conducted in Weybridge, UK 1996. Studies conducted on mice have shown that BPA mimics natural sex hormone estrogen [32]. Later widespread occurrence of intersex fish in British rivers was reported due to exposure to STP effluents [33]. Low levels of exposure of atrazine to frog led to demasculinization [34]. In 2004, studies showed that long-term exposure to Ethinyl estradiol caused reproductive failure in zebrafish [35]. Later years studies on genes' activity, altering phenotype expression, were observed due to the effect of endocrine disruptor chemicals [36]. In 2009, the Endocrine Society came across global concerns of endocrine disruptor chemicals [16]. The American Medical Association has put forward new

policies to decrease the public's exposure to EDCs in 2011 [37]. In late 2012, a group of scientists developed a tiered protocol for endocrine disruption (TiPED) to find out potentially harmful chemicals early in the development [38]. In early 2013, WHO/UNEP published a report on the State of the Science of Endocrine Disrupting Chemicals – 2012. (WHO/UNEP 2013). The expanding knowledge of functional and structural data has incorporated for the analysis of the potential interactions of known EDCs to different targets using docking or more demanding approaches [*e.g.*, molecular dynamics) [11].

4. MAJOR TIMELINE FOR ENDOCRINE DISRUPTORS

1958 – Endocrinologist Roy Hertz for the first time proposed that certain chemicals found in cattle feed could mimic hormone activity in the human body.
1960 - Intersex patterns observed in wildlife studies.
1962 - Rachel Carson's "Silent Spring" published.
1969 - National Institute of Environmental Health Sciences established.
1970 - Environmental Protection Agency established.
1971 - Effects of Diethylstilbestrol (DES) observed in human beings.
1972 - EPA banned DDT.
1977 - EPA banned PCBs.
1979 - Effects of estrogens in the environment studied.
1995 - EPA meeting on Endocrine Disrupting Chemicals conducted.
1996 - Endocrine Disruptor Screening Programme (EDSTAC) launched.
1996 - "Our Stolen Future" by Colborn and Mayers published.
1998 - International Conference on Endocrine Disruptors held at Kyoto.
1999 - US government issued the first proposal on Endocrine Disruptor Chemical research.
1999 - NRC reported hormonally active agents in the environment.
2002 - World Health Organization globally assessed the state of the science of Endocrine Disruptors.
2005 - Gordon Research Conference on Environmental Endocrine Disruptors conducted.
2007 - Copenhagen Workshop on Endocrine Disruptors conducted.
2008 - World Health Organization assessed the state of the science of Endocrine Disrupting Chemicals.
2009 - Endocrine Society released a statement on Endocrine Disrupting Chemicals.
2012 - Tiered Protocol for Endocrine Disruption (TiEPD) has been put forward.
2013 - European Food Safety Authority released a statement on Endocrine Disruptors.
2014 - Copenhagen based Nordic Council of ministers released a report on Endocrine Disruptors on the male reproductive system.
2015 - Endocrine Society released the statement on the EDC's in the European Union.
2016 - European Union proposed criteria to identify EDC's.
2017 - First International Chemicals Management (SAICM) meeting held in Brazil.
2018 - Environmental Endocrine Disruptors Conference held at Switzerland.

5. EVIDENCE FOR ENDOCRINE DISRUPTION IN HUMANS AND ANIMALS

In the last few decades, increased studies on endocrinology and ecotoxicology have expanded the scope of endocrine disruption. There are increasing proofs for long-term impacts of EDCs, low dose effects, and the combined action of mixtures.

6. ENDOCRINE DISRUPTION IN HUMANS

DDT has been detected in human fat and milk; it was first reported in non-occupationally exposed mothers [39,40]. Studies have shown these chemicals have the ability to cross the placenta and have been detected in amniotic fluid, umbilical cord blood, etc (Woodruff *et al.,* 2011). Studies carried out in pregnant women detected the presence of certain chemicals such as PCBs, organochlorine pesticides, perfluorinated compounds, phenols, PBDEs, phthalates, polyaromatic hydrocarbons (PAHs), and perchlorate (Woodruff *et al.,* 2011). EDCs such as arsenic, bisphenol A, phthalates, PCBs act as a major cause of diabetes and metabolic dysfunction [41]. Exposure to EDCs can affect placental development and lead to abnormal development of the fetus [42]. There are numerous examples suggesting that EDCs can affect the immune system by stimulating autoimmune functions of the body [43]. A recent study shows that synergic actions of BPA and phytoestrogen can induce breast cancer in human beings [44]. Synergic effects of EDCs induces calcium response, reduction of phagocytosis, alterations in TNF-α, IL-1 β and IL-8 cytokine secretions and Reactive oxygen species [45]. Studies conducted on the animal, clinical observations, and also the epidemiological studies have shown that possible function in affecting reproductive systems, prostate, breast, lung, liver, thyroid, metabolism, and obesity [46].

7. ENDOCRINE DISRUPTION IN BIRDS

Reproductive failure and thinning of eggshell were observed in bald *eagles (Haliaeetus leucocephalus), brown pelicans (Pelecanus occidentalis), gulls (Larus occidental*is, *Larus argentatus*) exposed to DDE [47]. It was due to the effect of DDE which blocks the prostaglandin signaling that stimulates the eggshell gland to deposit calcium in the shell [47]. Environmental mercury pollution caused a serious problem to American white ibises (*Eudocimus Albus*) in south Florida that consumed methyl mercury [48]. Abnormal breeding behavior in gulls was observed at Scotch Bonnet Island in Lake Ontario and on Santa Barbara Island in southern California, on exposure to organochlorine pollutants [49]. The embryo of domestic fowl *G. domesticus* has been used as an alternative to mammalian bioassays for the analysis of EDCs on reproductive tissues (Jessl, 2018).

8. ENDOCRINE DISRUPTION IN WILD VERTEBRATES

Endocrine disorders have also been detected in a variety of wild vertebrate species. In Canada, the occurrence of intersex in two frog species has been observed with the presence of pesticides [50]. Intersex has also been reported in reptiles, such as red-bellied turtles (*Pseudemys nelsoni)* in the pesticide-contaminated Lake Apopka, Florida [30]. In mammals, true hermaphroditism has been discovered in a beluga whale *(Delphinapterus leucas),* with two testes and two ovaries, in the St Lawrence estuary, Canada (De Guise *et al.,* 1994). Thyroid disruption has been reported in marine mammals and linked to exposure to organochlorines, such as fibrosis of the thyroid gland in harbor porpoises (*Phocoena phocoena*) [51]. Similarly, lesions of the thyroid gland were found in beluga whales from St Lawrence estuary and Hudson's Bay, Canada, which were unique to these populations (Mikaelian *et al.,* 2000). Enlarged thyroid glands were observed in herring gulls at sites highly contaminated with PCBs in the Great Lakes, Canada, [52]. Furthermore, disruption to thyroid hormone, vitamin D, calcium and phosphate, which are linked to bone homeostasis, have been correlated with hepatic PCBs and DDT in Baltic grey seals. This is thought to be linked to bone abnormalities including skull lesions and reduced bone density [53]. Studies have shown that the amphibian population in the US has become feminized in the agricultural areas exposed to atrazine (Hayes *et al.,* 2002). EDCs affect endangered species whose existence is vulnerable to any reproductive disturbance [54].

9. ENDOCRINE DISRUPTION IN FISH

Endocrine disruption in fish is happened to be one of the well-flourished areas in research. Studies have shown that high concentrations of vitellogenin were found in male fish caged in wastewater treatment plants in the 1990s. This was due to the feminization responses of fish under the influence of effluents in waste treatment plants [55]. Further studies on common roach *Rutilus rutilus* in rivers in the UK also identified vitellogenin, (egg yolk precursor exclusively present in female fish) induction in males, which varied between sites and concentration of effluents [56]. Many works have been shown worldwide on the unusual occurrence of intersex in male fish, characterized by testicular and ovarian germlines [33]. Feminization in male fish *Oncorhynchus mykiss* was observed when it was exposed to effluent discharge [55]. On the contrary to that masculinization in female fish was reviewed by Mattehesion et al. [57]. Several studies have shown that the relationship between sex ratio and reproductive success is species-specific and also a response to endocrine disruptor chemicals varies according to species [58]. The effects of EDCs on wildlife of many banned chemicals with endocrine activity are usually higher than those produced by current-use chemicals, with the exception of ethinylestradiol and other estrogens detected in sewage effluents, which are generating widespread impacts on fish populations [57]. In fish, exposure to both estrogenic and androgenic EDCs in wastewater and pulp mill effluents can modify steroid production, affect the development of intersex gonads, and influence of the sexually dimorphic phenotypes [33]. The zebrafish exposed to nitrated benzenes showed an increase in the hepatosomatic index and a decrease in the gonadosomatic index [59]. Zebrafish exposed to xenoestrogens showed vitellogenin induction, altered sex hormones [59]. Sex ratios of fishes were varied on exposure to endocrine disruptor chemicals [60].

10. ENDOCRINE DISRUPTION IN AMPHIBIANS

Studies have shown that the amphibian population declines due to EDC exposure [61]. Studies showed that exposure to EDs as a major factor in the amphibian population decline through metabolism disruption [62]. Amphibians in the montane riparian zones in the Neotropics face population decline due to the exposure of EDCs [63]. In amphibians, the main effects induced by EDs exposure involve variations in hormonal activity during embryonic development, alterations in anatomy, and behavior, reduction in reproductive success, gonadal abnormalities,

hermaphroditism and alterations in the reproductive system [64].

11. ENDOCRINE DISRUPTION IN INVERTEBRATES

Most of the studies on endocrine-disrupting chemicals were focused on vertebrates, the action and mechanism of endocrine-disrupting chemicals on invertebrates is still an unexplored area except a few major works. The development of male gonads in female marine gastropods on the exposure to tributyltin (TBT) has been reported [65]. The insecticide organochlorine l, l, l-trichloro-2,2-bis[4-chlorophenyl]ethane (DDT), caused a significant reduction in fecundity of the snail *Lymneae stagnalis* [66]. The wildlife population is seriously affected by exposure to endocrine-disrupting chemicals [67]. The Organization for Economic Co-operation and Development has come up with new testing policies to identify the potential effects of endocrine disruptors. Major demerit related to the study of the action of endocrine disruptors in invertebrates is their poorly developed hormone system when compared to the complex system of vertebrates [68]. Oehlmann *et al*. [69] reported the effect of organotin on molluscans leading to imposex. A similar study reported the presence of intersex in lobster (*Homarus americans*) collected from Nova Scotia, Canada [70]. The implication of RXR and E75 in hormonal regulation of female reproductive cycles in *Gamarus fossarum* and their sensitivity towards EDCs makes them as a suitable biomarker Gouveia et al. [71]. Studies have found that EDC naproxen could modulate sex hormones in water fleas and fishes using H295R cell assay [72].

12. CONCLUSION

The brief report on the effects of different endocrine disruptor chemicals summarized above clearly shows how the entire population has been facing a threat. As an increasing number of compounds are known to act as endocrine disruptors, the scientific world has a keen interest to work on the factors affecting endocrine disruptor chemicals. The deleterious effects of endocrine disruptor chemicals on endocrine system have been detailed with supporting evidence. However, long-term studies are needed to hypothesize the relationship between Endocrine disrupting chemicals and their actions.. The aim of the studies should be mainly focused on the detection of the substance, mechanism of action, the significant relationship between the substance and its effects upon organisms. The effect of xenoestrogens on organisms is of great concern to researchers all over the world. However, it is quite sad that work done in this field in our country is meagre when compared to other countries, which calls for proper and well-documented research in this field.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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