CRITICAL REVIEW ON THE IMPACT OF EDCs ON REPRODUCTIVE DISORDERS IN HUMANS

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Abstract: Endocrine-disrupting chemicals (EDCs) are substances in our environment, food, and consumer products that interfere with hormone biosynthesis, metabolism, homeostasis and reproduction. The aims of present study are to broadly assess and summarise existing data on the presence any substances that have or may have, endocrine disrupting potential of relevance to human health. The present study also aimed to maintain up dated knowledge of the potential EDC exposure to wildlife and human health.
This review explores the literature that deals with the major occurring EDCs in the atmosphere including pesticides and plastics. An extensive search approach was developed to identify literature using search terms like EDCs, xenoestrogens, hormone disruptors for identifying EDC related articles and reviews. Information was obtained through searches of SCOPUS (includes Medline & Embase) and CSA Illumina (Aqualine, Biological Sciences, Environment Abstracts, Environment Science and Pollution Management, Medline, Risk Abstracts, Toxline, Water Resources Abstracts) from year 2006 onwards.
Results clearly indicated that endocrine disruptors (EDCs) have effects on male and female reproduction, breast development and cancer, neuroendocrinology, metabolism and cardiovascular endocrinology. Results from animal models, human clinical observations, and epidemiological studies join to connect EDCs as a significant concern to public health. The mechanisms of EDCs involve divergent pathways that are highly conserved in wildlife and humans. It is recommended that the database of evidence generated through this review study should be periodically reviewed, since the available information on a number of substances identified here is expected to increase. In conclusions, we found that, the risk posed by mixtures of EDCs was fairly complicated in nature and it is suggested that a more detailed investigation is required on exposure assessment. We also observed a number of noticeable gaps in current knowledge and suggestions were made for further research to address the problems related to EDC.

Key words: endocrine disruptors, human health, and xenoestrogens.

Introduction: The issue of endocrine disruptors (or Endocrine Disrupting Chemicals, EDCs) became the spotlight of media attention throughout the world in 1990s when Theo Colborn [1]coined the term *endocrine disruptor* at the Wingspread Conference Centre in Wisconsin. She confirmed that environmental chemicals disrupt the growth and development of the endocrine system, and that effects are often permanent. Since 1995, the endocrine-disruptor hypothesis has encouraged new scientific studies that address several relevant issues.
Endocrine disrupting chemicals (EDCs) are chemicals that are present in daily products (drinking water, plastics, cosmetics, pesticides). They are capable to interact with the endocrine systems of living organisms and cause serious health and environmental impacts [2,3] (Diamanti-Kandarakis, E et al, 2009, Vandenberg, L.N., et al, 2012). Although the endocrine disruption has been disputed by Grady D [4] (2010), but work sessions from 1992 to 1999 have produced agreement statements from scientists regarding the risk from endocrine disruptors ([5,6,7,8] Bern HA et al, 1992, Bantle J,et al, 1995, Benson WH et al, 1997, Brock J et al, 1999). The research of endocrine disruption began with study on the health of wildlife in and around the Great Lakes of North America (For nearly 30 years, Dr. Theo Colborn [1] (1927–2014) dedicated herself to studying the harmful effects of endocrine- disrupting chemicals on wildlife, humans, and the environment. It is remarkable to note that after 25 years of progress in this science, several prestigious and professional societies have called today for precautionary measures to avoid exposure to endocrine disrupting chemicals. [9,10] (Gore et al. 2015; Zoeller et al. 2012).It is assumed that prenatal or early postnatal exposure to these endocrine disruptors could result in permanent and irreversible damage to both wildlife and humans[11] (Stephen safe, 2000).
Recently much media and public interest keep on focusing on Endocrine disrupting chemicals (EDCs) and the quality of food and drinking water. Hence, it has become a topic of debate, and raised the concern among scientists, physicians, regulators, and the public. Therefore, it is necessary to maintain up-to-date knowledge of the potential for EDC exposure to occur. Hence, the present study is aimed to broadly assess and summarise existing data on the substances that have, or may have, endocrine disrupting potential of relevance to wildlife and human health.
Methodology: A widespread search approach was developed to identify literature relating to the presence of EDCs in food and drinking water sources. Relevant information was obtained from peer

reviewed published manuscripts, reports, and books. A detailed set of search terms like EDC, xenoestrogens, hormone disruptors were used as the basis for identifying articles and reviews. Published literature was obtained through searches of SCOPUS (includes Medline & Embase) and CSA Illumina (Aqualine, Biological Sciences, Environment Abstracts, Environment Science and Pollution Management, Medline, Risk Abstracts, Toxline, Water Resources Abstracts) from year 2006 onwards. The output of these searches was subjected to detailed consideration by expert risk assessors and toxicologists. Basic information was then taken out on the nature of the substance and its status as a potential EDC.

Results and Discussion: We retrieved 992 journal citations and were reviewed by our research scholar team to assess their potential relevance. Out of 209 articles reviewed, 125 published articles confirmed the presence of EDC in drinking water. About thirty-five of these chemicals were expected to have highest (worst case) concentrations. The level of the threat posed by intake was determined by establishing the margin of safety (MOS) between this intake and standard value.Although a number of investigations on laboratory animals showed certain chemicals have potential endocrine disrupting activities, but enough data is not available on their endocrine disrupting effects in humans through dietary exposure. International and national authorities are in the process of screening potential EDCs for setting research and management priority.

EDCs in Food*:* Most food packaging materials and processing utensils are made of plastics, or they contain polymeric layers which are in direct contact with food like a laminate or coating. Polymeric laminates, plastics, and coatings are complex chemical mixtures. Understanding the leaching of chemicals from plastic-type food contact materials (FCM) into food is an important task of food packaging risk assessment [12] (Muncke, J., 2011). Due to the complex chemistry of polymers numerous unidentified substances can be incorporated in the final plastics material and potentially transfer into thefood [13] (Grob, K, 2002). Currently 10 ppb is the threshold leaching level from food packaging to ignite the adverse effects [14] (Muncke, 2009).

EDCs in drinking water:Besides food, humans and animals can be exposed to EDCs by the consumption of drinking water. However, at present the exact concentrations of endocrine disrupting chemicals in drinking water and thus the consumed quantities are currently uncertain[15] (Wenzel, A., et al, 2003).The sources of EDCs in the environment are varied but are for the most part related to human activities[16] (Fatta-Kassinos, D et al, 2011). The primary sources for release of EDCs into surface and groundwater are discharges from municipal wastewater treatment plants, industrial activities, leaky drains, and limited animal feeding operations [17,18] (Drewes and Shore 2001; Kim and Carlson 2006). As a consequence, the occurrence level of EDCs and PPCPs in drinking water sources primarily depends upon the degree of wastewater impact in the watershed. Additional factors affecting occurrence are usage pattern for different compounds as well as prescription practices for pharmaceuticals, which can vary with region; per-capita water consumption, which can result in different levels of dilution; and substitution and phase-out programs for specific chemicals. These variable factors explain why the occurrence pattern of currently detected compounds is not static.

In order to compile information on the occurrence of trace organic compounds of interest in secondary or tertiary treated wastewater effluents, more than 1,000 references reporting occurrence in studies across the globe were screened. This comprehensive review considered only articles that were peer-reviewed and reported both analytical methods employed and detailed experimental conditions. Based on the findings of this survey, pharmaceutical residues, antibiotics, steroid hormones, and fragrances are the most commonly reported trace organic compounds currently observed to occur in secondary and tertiary treated municipal effluents as well as in surface water and groundwater receiving these wastewater discharges. Most studies considered in this report show occurrence of certain compounds in source water receiving various degrees of wastewater discharge, which likely explains the rather wide range of concentrations reported for individual compounds. Although the exact degree of impact is mostly unknown, the reported concentrations usually increase significantly with closer proximity to the point of discharge. The highest concentrations are usually observed in recycled water used for planned indirect potable reuse applications. Dilution with non-impacted source water and photolysis and biodegradation processes can frequently reduce concentrations close to or below the detection limits. In general, median concentrations reported for the compounds of interest in receiving streams are significantly lower than those observed in treated wastewater effluents. Due to differences in prescription practices and per-capita water consumption, certain pharmaceutical residues are present in lower concentrations in source waters in the U.S. as compared to Europe. Steroid hormones usually occur in source waters in Europe and North America at similar concentrations, frequently close or below the detection limits employed in the studies.

The mechanism of action: Most endocrine disrupting chemicals (EDCs) present in food and water are often unintentionally taken up but

sometimes they are intentionally taken up like phytoestrogens. The Environmental Protection Agency (EPA) considers them as potential endocrine disruptors.

Hormones are proteins/ peptides, lipids or amino acid derivatives which act on receptors to cause reactions within the respective receptive cells. Each cell of the body is in one way or another coordinated by hormones. Therefore, hormones exert innumerable effects on the organism of animals and humans[19] (Wuttke, W et al, 2010). Most EDCs may interact with the steroid or amino acid derived (thyroid) hormones [20,21] (Fisher, J.S., 2004, Molehin, D et al, 2016).

The mechanisms by which EDCs operate in the body are quite complex because EDCs are not natural ligands and do not interact with hormone receptors with the same specificity and affinity. Yet, EDCs can interfere with those endogenous systems mainly on estrogen receptors (ER) and, to a lesser extent, antiandrogenic and thyroid effects [9] (Gore, A.C et al, 2015).

EDCs also act on enzymes involved in steroid metabolism and protein/peptide synthesis. They affect intracellular signaling processes and cell proliferation, growth, and death [20,22,] (Fisher, J.S., 2004, Craig, Z.R, et al, 2011). Hundreds of published papers showing that EDC exposures affect expression of genes and proteins in different cells[23,24,25] (Kazeto, Y et al,2004, Jin, Y.et al,2010, Roepke, T.A et al,2016).

The possible mechanisms of action of endocrine disrupters may be of following types:

a) Acting as an oestrogen binding and activating the oestrogen receptor,
b) Acting as an anti-oestrogen. Binding but not activating the oestrogen receptor,
c) Binding other receptors,
d) Modifying the metabolism of natural hormones,
e) activate enzymes which speed up the metabolism of hormones, so disrupting their natural state,
f) Modifying the number of hormone receptors in a cell,
g) Modifying the production of natural hormones.

Endocrine disruption and Reproductive health*:* Most EDCs obstruct with reproduction. They act as either agonists or competitors of the steroidal sex hormones. A number of EDCs interfere with the daily need of coping with internal or environmental stress and other adverse events.But the time and duration of exposure of EDCs in the various stages of development of an organism is very vital for the harmful effects. It is key to both human and animals disease because there are critical developmental periods during which there may be increased vulnerability to environmental endocrine disruptors [2,26,27] (Diamanti-Kandarakis, E.et al, 2009, Fenton, S.E. and Birnbaum, L.S., 2015, Zama, A.M., et al, 2016).Exposure to EDCs during the critical period of development may result in a permanent change of function or sensitivity to stimulatory and inhibitory signals.

But exposure in middle age may be balanced for by normal homeostatic mechanisms and may therefore not result in any significant or detectable effects. Exposure to the same level of an endocrine signal during different life history stages or during different seasons may produce different effects. Even exposure to the same level of an endocrine signal during different life history stages or during different seasons may produce different effects [28,29,30] (Kavlock, R.J et al, 1996,Zoeller, R.T.et al, 2012,Gore AC, et al, 2015, Bourguignon, J.Pet al, 2016). Because of crosscommunication between different components of the endocrine systems, effects may occur unpredictably in target tissues other than the system predicted.

Most EDCs interfere with steroidal signaling. Few EDCs either inhibit synthesis or interfere with the metabolism of sex steroids. But most of EDCs with adverse effects on reproduction bind either to the estrogen receptors (ERs) or to the androgen receptor (AR) and may either stimulate or inhibit the transcriptional or post-transcriptional mechanisms[20,31,32] (Fisher, et al, 2004, Shanle, E.K. and Xu, W., 2010, Craig, Z.R., et al, 2011).Through these mechanisms, EDCs may interfere with fundamental sex steroid effects on the brain, the pituitary gland, the gonads and the accessory sex organs.

Pollutants (with pesticides, fungicides or herbicides) present in surface water are also of great concern since most of them have relatively strong antiandrogenic effects [2] (Diamanti-Kandarakis, E, et al, 2009). These substances may also enter the human and animal through food chain and may cause adverse effects. In addition, the antiandrogenic substances can even directly contaminate our daily food. EDCs like estrogens and antiandrogenic compounds in surface waters have profound effects on aquatic life. Feminisation or demasculinisations of molluscs, arthropods and fish have been reported in polluted lakes or rivers [33,34] (Guillette LJ et al, 2007, Crain D.A,et al, 2008).

Hypospadias and cryptorchidism*:*Sexual differentiation and reproductive functioning in males are critically dependent on a balanced ratio of androgen and estrogen. Cryptorchidism is a condition in which one or both testicles have not descended and remains in scrotum while hypospadias happens when the urethral opening is dislocated. Both of these responses have been observed in male offspring of rodents exposed EDC compounds [35] (Fernandez, M.F etal, 2007). Carbone, P., et al (2006)

[36] found a connection between pesticides use and Cryptorchidism and hypospadias in the Sicilian district of Ragusa. Vryheid, M., et al (2003)[37] found risk of hypospadias in relation to maternal occupational exposure. Recently Fernández, M.F.et al, (2016) [38] confirmed that Bisphenol A and other phenols in human placenta induced cryptorchidism or hypospadias in children. These reports suggest a possible link between the exposure to EDCs and reproductive health. Jeng, H.A., (2014)[39] suggested that decreased male reproductive capacity may be associated to exposure to endocrine disruptors and pointed out that some studies reported increases in hypospadias and cryptorchidism in male infants[40] (Hauser, P.,et al,2015).

Conclusions: This review mainly presented the recent progress in scientific data from epidemiology studies on the associations between EDCs and male reproductive health. It also highlighted our understanding of possible mechanisms associated with the effects of EDCs on male reproductive health. Though different EDCs may be released into the environment untreated municipal and industrial waste water is found to be main source for EDCs. Thus, a huge number of endocrine disrupting effects may be anticipated when combinations of endocrine disruptors are polluting our environment and are incorporated by plants or animals that are part of our food chain. There is an urgent need to develop methods to better study mixtures of endocrine disruptors at different levels and how they may act additively or synergistically, or even antagonistically.Obviously, more work is necessary for a better understanding of the effects of endocrine disruptors in humans.

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