



EXPOSURE AND ASSOCIATED HEALTH RISK OF ENDOCRINE DISRUPTION COMPOUNDS

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ABSTRACT

Endocrine-disrupting chemicals (EDC) are an inevitable environmental pollutant due to their wide range of applications in the industrial sector. Deliberate or unkempt disposal of materials containing EDCs has also significantly contributed to its ecological exposure. Several natural and synthetic chemicals are recognized EDCs which at low doses are capable of eliciting abnormal responses in the body, this is a threat to life for both human and animal health. Due to the hormone-like nature of most of the EDCs, they have the ability to disrupt the hormone signaling pathways leading to alteration of typical functioning of the endocrine system. These will eventually results in dysfunctions in key life processes such as growth and reproduction. Owing to serious health issues attached to EDC exposure in the ecosystem, continuous research is ongoing and inevitable for excellent conclusions, proper documentation, and formulation of regulatory policies toward maintaining a healthy ecosystem. The buildup of endocrine disruptors in organisms can be through the food chain, which may negatively impact ecosystems and organisms at low concentrations. This review discusses the sources, possible mechanisms of action and summarizes the adverse health effects of endocrine disruptors, as well as makes recommendations to alleviate the effects of the EDCs and their negative impact on animals and human health.

Keywords: *Ecosystem, Endocrine disrupting chemicals (EDC), Food chain, Policies, Pollutant*

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INTRODUCTION

In the last 20 years, enormous research articles that address the environmental occurrence, ecological effects, and associated health risks of endocrine-disrupting chemicals (EDC) have been published (Encarnaç o *et al.*, 2019; Vandenberg, 2019; Bertin *et al.*, 2020). Recent investigations by Kasonga *et al.* (2021) led to the conclusion that EDCs are recognized as a key threat not only to human health but also to animal health. Endocrine-disrupting chemicals (EDCs) consist of enormous amounts of chemicals, which include naturally occurring or man-made substances or chemicals, that modify the endocrine systems and affect the development and reproduction of humans and animals (Gong *et al.*, 2017; Jin *et al.*, 2019). Due to the effect of the endocrine system on organs, such as metabolism, growth, development, reproduction among others, EDCs have an intense systemic impact on the body.

The Endocrine Society defines EDCs as “a non-natural (exogenous) chemical that obstructs hormone action” (Gore *et al.*, 2015; G lvez-Ontiveros *et al.*, 2020). “Therefore, an endocrine disruptor is an exogenous substance, chemical, or mixture that modifies the endocrine system functions and subsequently triggers unfavorable health effects in an organism, its offspring, or subpopulation” (Magnusson and Persson, 2015). Hence, in humans and animals, the major source of exposure to EDC through food intake.

Endocrine disruptors (ED) ability to impede the normal activity of the endocrine system results in unfavorable health conditions, including abnormalities of the metabolic, cardiovascular, skeletal, neurological, and immune systems (Schug *et al.*, 2011). They routinely gain access to the food chain via several route, for example, food, water, drugs, and air, among others. In 2015, 323 million tons of chemicals were produced within the 28 member states of the European Union, however, 205 million tons were considered unsafe and dangerous to health (Encarnaç o *et al.*, 2019). With increasing industrialization, more chemical agents belonging to the family of EDCs are being produced and consequently find their way into the environment through industrial products such as food, personal care products, cosmetics, and pharmaceuticals.

When used as insecticides, these compounds may enter the food chain directly, or they may be discharged from metal-containing food packaging. The purpose of this review is to contribute to existing knowledge of associated environmental effects on animals. In this review, several peer-reviewed studies on the effects of EDC in animals, and scientifically validated mechanisms of action are discussed. This compilation of data on EDCs is intended to support an understanding of the consequences of environmental occurrence, exposure, and bioaccumulation in food animals.

SOURCES AND USES OF EDCs

EDCs can be naturally occurring or man-made. The most common EDCs are:

Hormones/Organic compounds: Phytoestrogens/plant hormones such as genistein, mycoestrogen, flavones, daidzein, chalcone, coumestrol, goitrin, and xenoestrogens/synthetic hormones such /as 17-alpha ethinylestradiol, alkyl phenols, dihydroepiandrosterone, perfluorooctonic acid (PFOA), diethylstilbestrol, and ethynilestradiol (EE2) (Gaddafi *et al.*, 2021).

Pharmaceutical agents: these include fungicides (Vinclozolin), organochlorine insecticides (endosulfan, chlordecone), herbicides (Atrazine), and other pesticides with phenol derivatives (Gaddafi *et al.*, 2021).

Other endocrine disruption chemicals: Diglycidylmethacrylate, bisphenol A (BPA), polychlorinated biphenyls (PCBs), styrene, and polybrominated diphenyl ethers (PBDEs). Phthalates, and Dichlorodiphenyltrichloroethane (DDT) (Chang *et al.*, 2022).

Metals: Certain metals have been discovered to cause endocrine disruptions, such as mercury, cadmium, lead, arsenic, zinc, and manganese (Chang *et al.*, 2022).

POSSIBLE MECHANISM OF ACTION OF EDCs

EDCs frequently disrupt the endocrine system by mimicking natural hormones, opposing their action, or altering their production, metabolism, and transport across cell membranes, even though they typically exhibit a much lower affinity for hormone receptors than do native ligands (Predieri *et al.*, 2022). EDCs have the ability to initiate epigenetic modification in hormone-secreting or responsive cells (Predieri *et al.*, 2022). The majority of the observed negative effects of EDCs are related to their interaction with nuclear receptors, such as the nuclear hormone receptor (NHRs) superfamily members, which act as transcriptional regulators in the cell nucleus (Figure 1).

NHRs are a group of ligand-activated proteins that operate as transcription factors in the nucleus to transactivate or inhibit the expression of genes. Without the ligand, NHRs are found in the cytoplasm or cell nucleus, where they are part of a complex with co-repressors and/or chaperones (coRe). The disassembly of the repressive complex, the activation of transcriptional co-activators (coAct), and the dimerization of the receptor are all caused by interactions between the NHRs activation domain and hormone. Retinoid X receptor and NHRs either homodimerize or heterodimerize, which ultimately causes transcription of NHRs' target genes (Gore *et al.*, 2015; Combarrous and Nguyen, 2019). EDCs can bind to NHRs inappropriately and operate as agonists or antagonists, increasing gene expression or inhibiting receptor activation, respectively, leading to undesirable biological effects.

Regulation of EDCs has over the past ten years concentrated on substances that affect the so-called "EATS pathway," in which the most active NHRs are the estrogen receptors (ER), adrenergic receptors, thyroid hormone receptors (ThR), glucocorticoid receptors (GR), mineralocorticoid receptors (MR), and progesterone receptors (PR) (Predieri *et al.*, 2022; Toporova and Balaguer, 2020). Hence, EDCs with EATS modalities are primarily linked to development, metabolism, and reproduction (sex steroid hormones and steroidogenesis) (thyroid hormone) (Toporova and Balaguer, 2020; Predieri *et al.*, 2022).

There are additional mechanisms of action involving the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor that controls the expression of numerous genes, including the members of the cytochrome P450 (CYP)-1 gene family (Predieri *et al.*, 2022); despite the majority of studies concentrating on ER, AR, and ThR and their mechanistic pathways (Rothhammer and Quintana, 2019; Predieri *et al.*, 2022). As AhR's transcriptional activity resembles that of NHRs, it is currently regarded as an endocrine disruptor target along with other EATS receptors (Doan *et al.*, 2020). To be more specific, the non-activated AhR protein is tethered to a chaperone complex in the cytosol, and upon ligand-mediated activation; the AhR translocates into the cell nucleus and forms a heterodimer with the widely distributed aryl hydrocarbon receptor nuclear translocator (ARNT). The AhR-ARNT complex recruits transcriptional coAct to specific DNA sequences known as xenobiotic response elements (XRE) in the promoter region of target genes, activating the transcription of these genes (Predieri *et al.*, 2022). When first discovered, AhR was the major target of toxic dioxins, however, it is now known that AhR also responds to other EDCs (Denison and Faber 2017).

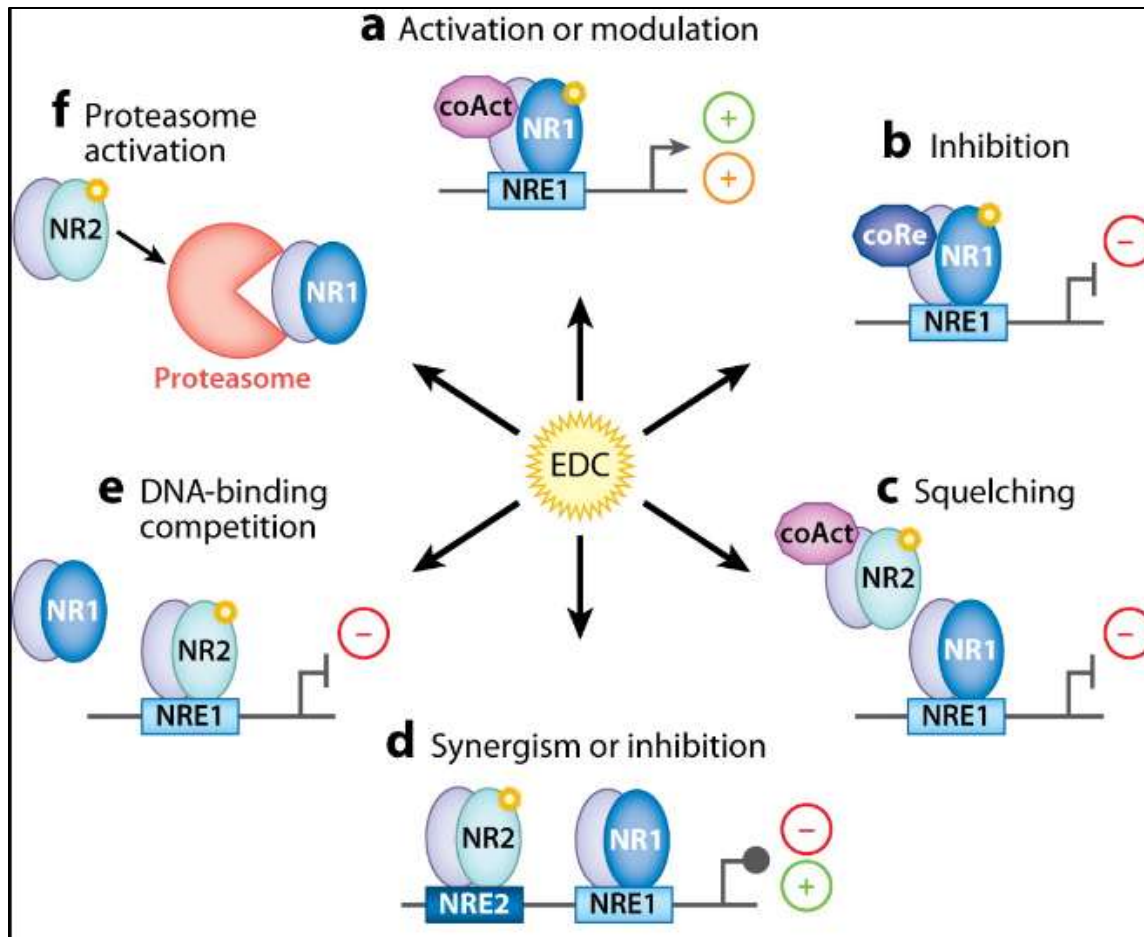


Figure 1- Endocrine-disrupting chemicals disturb nuclear receptor signaling through several mechanisms

Source: (Casals-Casas and Desvergne, 2011)

The NHRs and AhR signaling are primarily involved in EDC mechanisms of action (Predieri *et al.*, 2022), some of which are briefly described below.

1. **Direct activation of the classical NHRs:** Structurally, EDCs are similar to natural hormones, and can infiltrate the cell where some NHRs are kept dormant. NHR monomers dimerize upon binding to EDCs, bind to NHR response elements (NREs), and link with DNA sequences (Predieri *et al.*, 2022). Depending on the recruitment of co-Activators (coAct) or co-Repressor (coRe) to the target gene, the active dimer can either operate as an activator or a repressor of gene transcription.

2. **NHR signaling disruption:** EDCs can alter receptor performance by interfering with:

a. **Degradation of the receptor:** The ubiquitin (Ub)-proteasome pathway, which also appears to be dependent on the AhR, may control the degradation of NHRs. By directing NHRs to the Ub-ligase complex and promoting a decrease in some NHRs' levels, including AR and ER, the liganded AhR-ARNT heterodimer can suppress hormone-mediated transcription (Predieri *et al.*, 2022).

b. **CoAct recruitment:** Transcriptional coAct is necessary for both the NHRs' and the AhR's activity. It is hypothesized that AhR ligands may interfere with NHR signaling by competing with NHRs for a shared coAct (Predieri *et al.*, 2022).

c. **DNA-binding competition:** The liganded AhR-ARNT heterodimer attaches to sequences near unliganded NHRs binding sites, referred to as inhibitory xenobiotic response elements (iXREs), which have a slightly different constitution from xenobiotic response elements XREs. The active AhR can attach in this manner but is unable to initiate gene transcription (Predieri *et al.*, 2022).

3. **Hormone metabolism dysregulation:** The metabolism of xenobiotic and the catabolism of steroid hormones require enzymes that activate AhR induction. By regulating the expression of the CYP gene, which is involved in the synthesis of estrogen from cholesterol. AhR can modulate the circulating estradiol (E2) levels by regulating the gene expression of the CYP enzyme involved in estrogen synthesis from cholesterol (Predieri *et al.*, 2022). The enzyme aromatase (CYP19), which transforms androgens to 17-E2 via demethylation, is a direct AhR target gene and is susceptible to interference from many EDCs. As a result, enhanced steroid hormone breakdown and increased E2 synthesis may occur as a result of AhR activation by EDCs (Predieri *et al.*, 2022).

ENVIRONMENTAL IMPACT, BIOACCUMULATION, AND HEALTH IMPLICATIONS ON ANIMALS

Organisms' health depends on the right functioning of the endocrine system, therefore, its deregulation is related to the onset of many metabolic disorders. For several decades, studies have established that almost all metabolic diseases relate in some way to exposure to environmental chemicals (Maradonna and Carnevali, 2018). EDCs alter the adipose tissue, muscle, liver, pancreas, gastrointestinal system, brain homeostatic and hedonic pathways, which may enhance vulnerability to various conditions (Heindel *et al.*, 2017).

EDC has been reported to affect the reproductive systems of different animal species in different ways, such as altered spermatogenesis (Yeung *et al.*, 2011; Veeramachaneni, 2008), cryptorchidism (Virtanen and Adamsson, 2012), disturbed sexual behaviors (Frye *et al.*, 2012), and changed puberty onset (Magnusson and Ljungvall, 2013). The non-vegetarian populace is very susceptible to exposure to these endocrine-disrupting chemicals because of their solubility in lipids. These tend to build up in the animals' adipose tissues, leading to their bioaccumulation. The process of biomagnification further strengthened the bioaccumulation challenge because concentrations of EDCs intensify at higher trophic levels. There has been a report on biomagnification among various species of marine mammals. The EDs concentrations are estimated to be 100 times higher in aquatic birds than in the surrounding water because of biomagnification (Eram *et al.*, 2021).

The biomagnification of EDCs in the food chain makes some researchers to conclude that disruption of the endocrine system is usually observed in species at the top of the trophic ladder, though this may not be true. The grazing of animals in fields near incineration plants can result in exposure to high concentrations of contaminants having endocrine-disrupting characteristics in the environment (Magnusson and Persson, 2015). There have been some reports in several farm animals showing endocrine disruption initiated by environmental pollutants, one such case is the report in cows that revealed increased age at first calving, and the heifers were exposed to drinking water that was in direct interaction with a sewage overflow (Magnusson and Persson 2015).

The American mink is an animal that is at the top of the food chain, alteration of the reproductive system has been observed to occur when their diets are high in fish from waters polluted with EDCs. Furthermore, decreased litter size

and increased offspring mortality have also been observed in mink feeding on fish from water polluted with organochlorines (Bursian *et al.*, 2013).

The exposure of animals to phytoestrogens results in sweet clover disease, which occurs due to the binding of genistein and formononetin both phytoestrogens, to the estrogen receptors. Phytoestrogens also modulate estrogen enzymes, which lead to uterine prolapse and embryonic death in sheep (Beck *et al.*, 2005). The use of growth enhancers in beef cattle, such as synthetic steroid hormones in certain countries, makes the effect of endocrine disruptors relatable in domestic animals. Farm animals are injected with hormones such as melengestrol acetate, zeranol, progesterone, testosterone propionate, estradiol, trenbolone acetate, and bovine somatotropin, as result, either more milk will be produced or the livestock's muscles will grow quickly (Eram *et al.*, 2021). Because these animals' adipose tissues store metabolically active metabolites or medication residues that are then released in their milk and ingested by humans, consumption of meat or dairy products from these animals may raise the risk of developing diseases like breast cancer (Nachman and Smith, 2015). However, aside from the use of growth promoters, leakage of endogenous endocrine active substances into the environment may also affect domestic animals. Large amounts of bioactive steroids have been obtained from the soil and run-off from larger feedlots, and this may affect animals feeding in such environment (Cavallin *et al.*, 2014; Magnusson and Persson, 2015).

Magnusson and Persson (2015) documented that the amount of endocrine-disrupting chemicals/ compounds found in pig manure might be of environmental interest. A watchful inference from this writing is that endocrine disruptors may be spread into the environment through manure from livestock activities and those using endocrine disruptors as growth promoters. Several experimental studies involving both sexes of domestic animals to investigate endocrine disruption revealed species parallels in effect, albeit some are different. The differences in effect observed in some species might be due to diversities in the endocrine disruptors' absorption from the intestines, their metabolism, signaling, and endocrine enzymes in the exposed species (Evans *et al.*, 2014; Krogenaes *et al.*, 2014; Corbel *et al.*, 2015; Gralen *et al.*, 2012).

Aspergillus flavus and *Aspergillus parasiticus* are fungi that produce Aflatoxin B1, and mycotoxins. It has been reported to invade food products such as maize and peanuts during storage after harvest (Corbel *et al.*, 2015). These toxin gets into the food supply chain when cows graze on vegetation or fodder already infested by these fungi, the toxin is then released in the milk (Eram *et al.*, 2021). When ingested, the toxin may lead to cancer and may harm a pregnant woman's endocrine system.

Various species of *Fusarium* for instance *F. tricinctum*, *F. moniliforme*, *F. roseum*, *F. oxysporum* and *F. sporotrichioides* produce the mycoestrogen known as Zearalenone (ZEA). When hay and maize are stored in humid and warm conditions, they can get infected by fungi, leading to a high concentration of Zearalenone production (Zinedine *et al.*, 2007). Through its interactions with estrogen receptors, ZEA and its metabolites, such as zearalenol (ZOL), have demonstrated estrogenicity, even though it has a non-steroidal structure, it is capable of binding to both estrogen receptors and hence eliciting functional and morphological alterations in the reproductive system. ZEA also interacts with the endocrine enzyme systems. It has been observed in farm animals like pigs that exposure to ZEA affects organs that are dependent on estrogen, triggering alteration in vaginal growth, resulting in vaginal prolapse, pseudopregnancy, abortions, and stillbirths (Fink-Gremmels and Malekinejad, 2007; Zinedine *et al.*, 2007). The reason why different species respond differently to ZEA is thought to be variations in their hydroxylation systems. Prepubescent gilts are known to be extremely sensitive to ZEA, but there are also reports that prepubescent heifers

may experience enlargement of the mammary glands and consequent infertility. It is important to know that with a shift to a warmer and more humid climate, there may be a higher chance of cereals becoming more frequently contaminated with ZEA (Van Der Fels-Klerx *et al.*, 2012). *Fusarium* also produces other mycotoxins such as trichothecenes and fumonisins, which can interact with ZEA and cause health problems (Eram *et al.*, 2021).

Several EDCs have been established to contaminate the water bodies, these include agriculture inputs, industrial and municipal wastewater, personal care products, and pharmaceutical products. Recently, the pollution of aquatic ecosystems with EDCs has become a major threat to public health. Numerous natural hormones (estrone (E1), 17 β -estradiol (E2), and estriol (E3)) and man-made chemicals (bisphenol A (BPA), 4-nonylphenol (NP), and alkyl phenols) have been recognized as chief contaminants present in the effluents produced by several industries (Stasinakis *et al.*, 2010). EDC exposure can have long-term negative consequences on aquatic creatures, including growth inhibition, mortality, and reproductive toxicity. Some of the toxic effects associated with BPA in aquatic organisms are changes in the level of vitellogenin and sex hormones such as testosterone, and estrogen in fish (Hatef *et al.*, 2012; Villeneuve *et al.*, 2012). Furthermore, BPA exposure leads to reduced sperm mobility and density in brown trout (*Salmo trutta*) and reduced production of sperm in the fathead minnow (*Pimephales promelas*) (Jung *et al.*, 2020). Studies have also shown that 4-nonylphenol can disrupt sex steroid synthesis, result in gonad abnormalities such as intersex gonads, raise the vitellogenin levels in the serum of male fish liver, and could lead to modifications in the control of genes coding for vital steroidogenic proteins (Sayed and Ismail, 2016); 4-nonylphenol (4-NP) is capable of distorting the concentration of follicle-stimulating and luteinizing hormones (Sayed *et al.*, 2012). Moreover, histological alterations in the gonad, hepatocytes, gills, and kidney structure following exposure to 4-nonylphenol (4-NP), these negative impacts of nonylphenol (NP) have been investigated in catfish *Clarias gariepinus* as a toxicological model (Sayed and Ismail, 2016).

CONCLUSION

Although we currently know more about the processes by which EDCs work and the significance of the critical windows of exposure. As a result of latent effects that may manifest at later ages, it is still challenging to evaluate the effects of animal exposure to EDCs. Although there is strong evidence that EDCs play a pathogenic role in animals and humans.

RECOMMENDATION

It is recommended that exposure to EDCs is kept to the barest minimum, this can be done by keeping endocrine-disrupting chemicals out of our environment.

It is therefore essential that polluted environments be cleaned up using natural techniques like bioremediation to get rid of environmental pollutants from the ecosystem. EDCs most likely have a supplementary impact, therefore, any improvement is beneficial. Making one minute improvement is preferable to worrying about factors that are beyond your control.

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CONFLICTS OF INTERESTS

All authors declare that there is no competing financial interest or personal relationship with other people or organizations that could inappropriately influence the reported work in this manuscript.

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