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Review Article

The Presence of 17 Beta-Estradiol in the Environment: Health Effects and Increasing Environmental Concerns

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Abstract

Endocrine-disrupting compounds (EDCs) as active biological compounds can pose a threat to the environment through acute and chronic toxicity in organisms, accumulation in the ecosystem, and loss of habitats and biodiversity. They also have a range of possible adverse effects on environmental and ecological health. Estradiol, as one of the natural estrogenic hormones released by the humans and livestock, may exert endocrine-disrupting effects on the nanogram-per-liter range and cause serious problems for the aquatic organisms and animals in many aquatic systems. Various studies have reported the presence of synthetic estrogens such as 17 alpha-ethinyl estradiol (EE2) and natural estrogens including 17 beta-estradiol (E2) in wastewater sludge, surface water, river bed sediment, and also digested and activated sludge. The aim of the present study was to review and evaluate the endocrine disrupting compounds especially 17 beta-estradiol, as a representative of estrogen hormones present in the environment and their disturbing effects on humans and wildlife.

Keywords: Endocrine-disrupting compounds, 17 beta-estradiol, Health effects

Introduction

The endocrine-disrupting compounds (EDCs) as a group of xenobiotic-based chemicals with an external source are involved in mimicking or inhibition of normal functions of endocrine systems in animals and humans, including synthesis, secretion, and transport of the hormones or binding to them.[1] In addition, these compounds interfere with normal functions of the hormones which are responsible for maintaining the balance, reproduction, development, and natural behaviors.[2] The EDCs as active biological compounds can pose a threat to the environment resulting in acute and chronic toxicity in organisms, accumulation in the ecosystem, and loss of habitats and biodiversity. They also have a range of possible adverse effects on environmental and ecological health.[3] The EDCs include pesticides (e.g., atrazine & DDT) organochlorine compounds and stable organo-halogens (e.g., dioxin, furan, and bromine anti-inflammation), alkylphenols (e.g., nonyl phenol and octylphenol), heavy metals (e.g., mercury, cadmium, and lead), phytoestrogens (flavonoids and lignans), and synthetic and natural hormones, namely, 17 beta-estradiol and 17 alpha-ethinylestradiol. Furthermore, some pharmaceuticals and personal care products (PPCPs) that are suspected to have harmful effects in the endocrine system have been classified as the EDCs.[4]

Therefore, the EDCs mainly include natural or synthetic hormones and their metabolites. A number of common EDCs which have been the focus of many studies are as follows: natural estrogens such as estrone (E1), 17-beta-estradiol (E2), and steriole (E3); the synthetic estrogen like 17-alpha-ethinyl estradiol (EE2); and industrial chemicals such as bisphenol and nanyl-phenols.[3]

Estradiol, as one of the natural estrogenic hormones released by humans and livestock, may exert the endocrine-disrupting effect on nanogram-per-liter range and cause serious problems for the aquatic organisms and animals in many aquatic systems.[5] Some effects associated with EDCs exposure in animals include reducing the hatching rate in birds, fish, and turtles, creating female traits in male fish, problems in the reproductive system of fish, reptiles, birds, and mammals as well as changes in the mammalian immune system. These effects, in some cases, can lead to the population decline.[4]

In many aquatic animals, these compounds cause disturbances in the reproductive system including reduced sperm motility and their number as well as delayed spermatogenesis.[6] The reported effects of EDCs in humans include (*a*) reduced sperm count, (*b*) increased incidence of breast cancers, (*c*) increased incidence of testicular and prostate cancers, and (*d*) endometriosis.[4] Since steroids act at the molecular level by binding and activating intracellular steroid receptors of their own even very low concentrations of steroids in the environment can affect the physiology of the normal cells, and this is a fact that is associated with human immunity and health.[7] Various studies have reported the presence of synthetic estrogens such as 17 alpha-ethinyl estradiol (EE2) and natural estrogens like 17 beta-estradiol (E2) in wastewater sludge, surface water, river bed sediment, and also digested and activated sludge. This is due to the incomplete and inadequate removal of these estrogens in sewage treatment plants (STPs). Generally, in urban sewage treatment systems, there are no specific units designed to remove the EDC, therefore it seems that the removal of estradiol by urban wastewater treatment plants is inadequate.[3,5,8]

The present study sought to review and evaluate the endocrine disrupting compounds, especially 17 beta-estradiol, as a representative of estrogen hormones available in the environment and their disturbing effects on humans and wildlife.

Estradiol Health Effects

Some pesticides, industrial products, plastics, and natural chemicals disrupt the activity of the endocrine system. These materials, which are known as the EDCs, may have adverse health effects on all the organisms.[7,9]

Generally speaking, the action of the EDCs is mediated through the following mechanisms: (1) Aromatase inhibitor, (2) Agonist and antagonist of the estrogen receptor, (3) Agonist and antagonist of the androgen receptor, (4) Aryl hydrocarbon receptor antagonist, (5) Interactions with binding proteins, and (6) Involvement in metabolism of hormone.[10] The EDCs mimic the activity of natural estrogen hormone and act through the activation of the estrogen receptor which consequently disturbs the normal function of this hormonal system through mimicking, modulation, or antagonistic activity.[9] The effects of these compounds on humans and other organisms are discussed in the following sections.

Effects of Endocrine Disrupting Compounds in Humans

Human beings are exposed to the EDCs through contaminated water and food, air inhalation, and skin absorption, of which the consumption of contaminated food is the most common way. The health consequences of these compounds on human include infertility, certain types of cancers, changes in serum level of testosterone hormone, reduced sperm count, preterm birth and intrauterine growth restriction, genitourinary disorders including hypospadias, cryptorchidism, decreased fetal testosterone level, decreased sperm quality and quantity, decreased male fertility, recurrent abortion, polycystic ovary syndrome, genital anomalies, testicular cancer, birth weight loss, prostate and breast cancers, endometriosis, infertility, early puberty, obesity, and menstrual dysfunction.[11,12] Some of the EDCs have been identified in the ovarian follicular fluid (i.e., a fluid that provides the growth and maturation environment for the oocyte). Jarrell et al in their study, examined the presence of the EDCs in follicular fluids and serum of woman undergone *in vitro* fertilization in three local clinics. Their results showed that contamination with EDCs had several effects on the rate and time of first splitting in the germ cells.[13]

In another study performed in the of Granada University Hospital to evaluate the effects of the estrogen on the environment, the increased risk of genital anomalies (i.e., hypospadias and cryptorchidism) was confirmed.[14]

Effects of EDCs on Animals

Mammals

The disturbing effects of the EDCs on mammals include cryptorchidism, masculinization, implantation failure, decreased fecundity, sterility, population decline, hermaphroditism, decreased testosterone, skull lesions, obstruction and stenosis of the uterus, decreased immunity, pathological disorders, and the developing of female traits in male.[15,16]

Disorders in Birds

The deleterious effects of the EDCs in birds also include the egg shell thinning, feminization, decreased hatching rate, goiter, decreased reproductive performance, increased dead in chicks, abnormal thyroid function, and changes in immune function.[15,16]

Disorders in Amphibians and Reptiles

Decreased hatching rate, feminization, metamorphosis, skin lesions, abnormal gonads in males and females, and abnormal levels of sex steroid are a number of disorders that can be observed in the amphibians and reptiles.

The development of female traits in male fish, the abnormal thyroid function, and a decrease in successful hatching are the adverse effects of EDCs in fish.[15,16]

In a study conducted in the Netherlands, fertile eggs from the juvenile Zebrafish were exposed to 17 beta-estradiol through synthetic wastewater or freshly discharged wastewater from the treatment plants. The results demonstrated the clear and obvious feminization in these animals. In this study, the highest concentrations of VTG (yolk protein vitellogenin) and also the highest prevalence of ovo-testis were observed in fish living in the Dommel River near the location of wastewater treatment plant discharge. In general, for The Netherlands, the estrogen effects on fish were a potential threat to the fish in the local aquatic environments while these effects were lower in big waters, potentially due to the dilution of estrogens in these areas. High concentrations of plasma vitellogenin and increased prevalence of ovo-testis in *Abramis brama* (bream) were observed in a small river receiving significant amounts of wastewater from a large wastewater treatment plant. No significant estrogenic effects were found in male flounder fish (*Platichthys flesus*) in an open sea. The prevalence of feminization was higher in male fish in a small local surface water which was heavily influenced by sources of disturbing hormonal compounds.[17]

Similarly, in another study carried out in England it was revealed that the level of VTG in male flounder fish was significant in several estuaries (delta) (e.g., Tees, Mersey, & Tyne) industrialized during 1996-1996. The reduced concentration of VTG with low levels of estrogen contamination near the Howdon wastewater treatment plant was probably due to the secondary wastewater treatment processes implemented in this area. Finally, the development of male and female sexual organs (ovo-testis) was observed in male flounder fish, at a low but stable concentration.[18]

In a research aimed to determine the quality of the gametes in wild intersex roach (*Rutilus rutilus*), the sperm parameters, fertilization success, and the ability to produce live fishes were evaluated. The results showed that sperm motility in addition to its ability in fertilizing eggs and production of live fish in bisexual fish were decreased compared to normal male fish. The results also indicated that a mixture of the EDCs discharged to the aquatic environment could be a threat to the reproductive health of the males.[19] The findings of different studies have demonstrated the presence of the EDCs in aquatic environments which may affect the health of the aquatic organisms.

Physicochemical Properties of Estradiol

Estradiol has a tetracyclic network consisting of a phenolic ring, two cyclohexanes, and a cyclopentane. It also contains a hydroxyl group in C17 (carbon 17), which can be either downward or upward C17 on the molecular surface (Figure 1).[3] Estradiol has a log K_{ow} of 3.94[20] and is considered as a moderate hydrophobic, which tends toward the organic phase. The vapor pressure of 2.3×10^{-10} reflects its low volatility (Table 1).[3,21] From the whole hormones, the natural compounds of E1, (17 beta-estradiol & 17α-estradiol) and synthetic EE2 (ethinyl estradiol) have been identified as the strongest representatives of the EDCs. Estradiol and ethinyl estradiol are the strongest estrogenic compounds.[3]

The Fate of Estradiol in the Environment

The presence of estrogenic compounds in the environment is a serious concern, since these compounds may interfere with human, livestock, and wildlife reproduction. Besides, they have adverse effects on the health of all types of organisms.[7,21] The chemical partitioning coefficient of the estrogen (log K_{ow}) suggests that these compounds could significantly be absorbed by the precipitates and sludge. The log K_{ow} for 17 beta-estradiol is about 3.94-4.1. If pollutants are adsorbed by activated sludge particles, then they could accumulate in the sludge of the wastewater treatment plant. In this case, the use of digested sludge, as fertilizer, in the agricultural lands may cause soil and groundwater pollution. In the cases that contaminants are dissolved or are along with organic solvents or even with stable and unstable colloids, they can easily transport through the wastewater treatment plants.[22] The EDCs, in addition to being absorbed by the suspended solids, may disperse through being absorbed by non-polar lipids and lipids. After dehydration and digestion of sludge and then, its application as agricultural fertilizer, these compounds could enter the food chain.[23]

These compounds are released in aqueous environments by sewage, resulting in contamination of the receiving water sources or even raw water sources of the DWTPs (drinking water treatment plant) and WWTPs (wastewater in wastewater treatment plants) which are known as the main carriers of the EDCs in aquatic environments.[3]

The 17 beta-estradiol has been identified and observed in many aquatic environments. It causes serious problems in the aquatic organisms and animals. Although more than 90% of the 17 beta-estradiol can be removed through the activated sludge treatment system, estradiol is still considered as one of the main causes of wastewater estrogenic activity in a large number of wastewater treatment plants.[5]

In various environmental studies, estrogens and other steroids have been identified in seawater, lake and rivers water, and in different regions. According to one study in China, the total estrogen level in the Chile and Shenzhen reservoirs was measured within the range of 3-11 ng/L with an average level of 7 ng/L. This level (observed in 4 rivers in Shenzhen) was in the range of 47-90 ng/L with an average level of 60.25 ng/L. In addition, in the seawater near the wastewater discharge sites, the estrogen level was measured about 260 to 300 ng/L with an average level of 287 ng/L. Estrogen was more concentrated near the sewage discharge sites.[7] A wide-scale study was conducted in the Netherlands to evaluate the presence of some estrogenic compounds in the surface water, sediments, fauna (living plants and animals in a certain region), wastewater, rainwater, as well as their corresponding effects on fish. In this study, the compounds like natural and synthetic hormones, phthalates, alkylphenols, and bisphenol A were investigated. The results showed that almost all the selected esters were present in the aquatic environments. Natural steroid hormones were present in all the untreated wastewater samples and the results of this study confirmed the development of female traits in male fish.[17]

Every human, especially women, excrete estrogens through their bodies without using hormonal drugs.[24] The levels of estradiol hormone excreted by the women and men are about 2.3-259 and 1.6 μG/day, respectively,[21] which is a reason for the presence of this hormone in sewage. Consequently, these compounds could be transported to

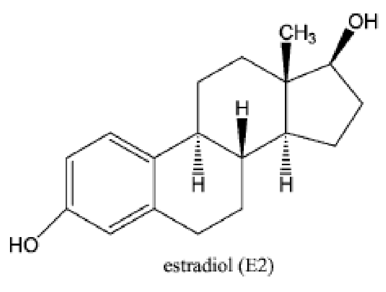

Figure 1. The Chemical Structure of Estradiol.

Table 1. Physicochemical Properties of Estradiol

Molecular Weight	Water Solubility (mg/L at 20°C)	Log K_{ow}	Vapour Pressure (mm Hg)
272.4	13	3.94	2.3×10^{-10}

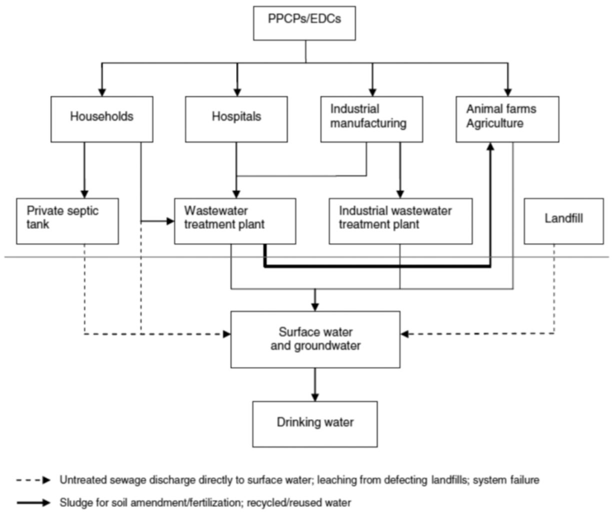

Figure 2. Occurrence of Endocrine Disrupting Compounds in the Environment.

STPs through sewage systems.

Many scientists and policymakers have placed great emphasis on this problem and attempted to find new biological systems for efficient removal of the steroid hormones- and other endocrine-disrupting chemicals.[7] Given that estrogens are highly hazardous compounds for the environment, they must be removed and decomposed through the process of sewage treatment using advanced equipment and facilities in order to protect aquatic organisms.[24]

Environmental Measurement of Steroid Hormones

Among the most important environmental components that must be considered regarding the presence of steroid hormones are surface waters, groundwater, and urban sewage. Awareness of the presence and concentration of these compounds is one of the requirements for environmental planning and management of water quality control. In the following sections, the recent studies and their most important results will be discussed.

The Concentration of Estradiol Measured in Different Types of Surface Water Samples

Several studies have been conducted around the world to measure the concentration of steroid hormones in the surface water, some of which are summarized in the following table for a variety of surface water samples (Table 2).

The Concentration of Estradiol Measured in Wastewater

The concentration of steroid hormones, especially the 17 beta-estradiol, has been measured in different types of wastewater, particularly in the influent of the treatment plants and in the effluent from the treatment plants in different countries. Measuring the concentration of estradiol in the hospital and industrial wastewater was less studied compared to the municipal wastewater. A summary of the results related to a number of these studies is presented in Tables 3 and 4.

Domestic Studies

There exist a number of Iranian studies which have been

Table 2. Concentration of 17 Beta Estradiol Measured in Surface Water Samples

Measured Concentration	Unit	Type of Sampling Locations	Country	Ref
Lake Mead: ND[a] – 2670 Detroit river: ND-1290	(pg/L)	Eight sites in the Trenton channel of the Detroit river, 5 sites in lake Mead (Michigan)	USA	25
Ebre River (Tortosa): ND Ebre River: ND Industrial port of Tarragona: 0.1 Marina (Salou): ND Coast (Salou): ND Ebre Delta (irrigation canal): ND	(µg/L)	Freshwater samples from Ebre River (in the Ebre Delta and Tortosa), and an irrigation canal of the Ebre Delta, and seawater samples from the marina and coast of Salou and the industrial port of Tarragona	Spain	26
<0.3- 5.5	(ng/L)	11 surface water samples of coastal estuarine and freshwater locations	The Netherlands	27
0.05-0.8	(ng/L)	Colorado River, Sacramento River Delta, engineered Wetland(California)	USA	28
Rainwater: <1.5 Surface water: <0.8-1	(ng/L)	Rainwater, surface water (freshwater locations Vrouwenzand in Lake IJssel, the saltwater tidal inlet Hammen in the Eastern Scheldt and the North Sea near Noordwijk)	The Netherlands	17
n.d	(µg/L)	15 German rivers and streams	German	29
1.4 – 3.2	(ng/L)	River	France	30
n.d - 7.1	(ng/L)	River water samples from Thames	Britain	31
2–6	(ng/L)	River	Italy	32
Rivers: ND - 3677.4 Estuaries: ND - 28.8 Lake : ND – 27.7	(ng/L)	Rivers , estuaries and lake	Malaysia	33
Tamagawa River: 0.6 - 1.0 Lake Kasumigaura: below the detection limit	(ng/L)	Tamagawa River, Lake Kasumigaura	Japan (Tokyo, Ibaraki)	34
ND	(ng/L)	St. Lawrence River	Canadian	35
ND – 74.4	(ng/L)	River water	China	36

[a] Not determined.

performed to measure the estradiol concentration. These studies are conducted in cities including Ahwaz, Hamedan, and Tehran. Table 5 summarizes the results of these studies.

Estradiol Removal from Wastewater

Wastewater filtration using a sand filter or microfiltration eliminates approximately 70% of the hormones from the secondary effluent while the advanced treatment method, using the reverse osmosis, eliminates more than 95% of the hormones.[28]

Clouzot et al showed successful use of adapted activated sludge for ethinyl estradiol biodegradation (11% increase in removing ethinylestradiol). In this study, the total removal of ethinyl estradiol was estimated to be 99% (absorption + biological degradation).[44]

In the same vein, Liu and Liu investigated the effect of radiation power induced by UV-light and UV-vis lights (high-pressure mercury lamp) on chemical the decomposition of two estrogens, that is, 17 beta-estradiol and sterone in high-concentration aqueous solutions. They showed that chemical decomposition, due to radiation power, caused a breakdown in both estrogens. A UV disinfection lamp (ls254 nm, 30 W) and a high-pressure mercury lamp (l0365 nm, 125 W) were used for E2 and E1, respectively.[45]

In a study performed by Yoon et al, the adsorption of 3 estrogenic compounds (bisphenol A (BPA), 17β-estradiol (E2), and 17α-ethynyl estradiol (EE2) on several powdered activated carbons (PAC) was investigated. This study showed Using powdered activated carbons (PAC) to remove more than 99% of these three compounds from raw drinking waters is effective.[46]

In a study performed by Mai et al, photodegradation of 17b-estradiol (E2) in aqueous solution with titanium dioxide (TiO2) was investigated. The result showed that the degradation of E2 increased with increasing concentration of TiO2.[47]

In a study performed by Yaping and Jiangyong, from a-FeOOHR and H2O2 was used for photodegradation 17 bestradiol (E2), the result showed that high removal efficiency of E2 by a-FeOOHR in aqueous solutions.[48]

In a study conducted by Ouellette et al a polymer was employed to absorb the EDCs. The results showed that the Hytrel polymer could absorb a large amount of EDCs. Moreover, the results of the partitioning coefficient determination demonstrated the high affinity of EDCs to absorb by the polymer.[6]

In addition, in another study, an enriched microbial environment which was adapted for two-phase bioreactors was used to biodegrade the EDCs. The results demonstrated that the bacteria were able to decompose the estrone, estradiol, and estriol. Moreover, the findings of this study confirmed the significant potential of the TPPB (two-phase partitioning bioreactor) for decomposition of highly dilute disruptive compounds present in wastewater.[49]

Similarly, in a study, the TPPB operated as a biotrickling filter was used to remove styrene vapor. Industrial silicone oil was used as a non-aqueous phase in a 2-phase bioreactor. This study showed that the 2-phase partitioning bioreactor as the biotrickling had better removing function compared to biotrickling as a control.[50]

Presence of Hormonal Contraceptive Pills and Other Estrogens in Water and Wastewater

In the United States, 13 million women use hormonal contraceptives pills to protect their health and prevent unwanted pregnancies. A review of the literature by the researchers shows that contraceptive pills (estrogen-based hormonal contraceptive pills) are one of the main causes of

Table 3. Estradiol Concentration in Wastewater

Influent	Effluent	Ref.
	<0.1- 4.05 ng/L	28
	ND-3660 pg/L	25
(Untreated) municipal wastewater: 17-150 ng/L	<0.8 ng/L	17
German : average: 0.015 µg/L Brazil: average: 0.021 µg/L	German: Maximum:0.003 µg/L Canadian: Maximum:0.064 µg/L	29
11.1±1.7- 17.4±1.7 ng/L	4.5±1.0 – 8.6±0.9 ng/L	30
	0.3 – 2.5 ng/L	34
	1.6 (Median) – 15 (Maximum) ng/L	37
10–31 ng/L	3–8 ng/L	32
ND-66.9 ng/L	ND-26.7 ng/L	35
	1.6 – 7.4 ng/L	31
Min: < 5.0- 30.4	< 5.0–7.6	38

Table 4. Estradiol Concentration in Domestic, Industrial, and Hospital Wastewater

Domestic, Industrial Hospital Wastewater	Reference
Domestic: n.a-12 ng/L Industrial: <0.4- 1.8 ng/L	27
Industrial: 0.8-54	17
2.7 ± 0.1 - 48.0 ± 6.0 ng/L	39
Influent: ND -16.9± 9.1 ng/L Effluent: ND-2.5± 0.4 ng/L	40

Table 5. Estradiol Concentration in Iran (ng/L)

Wastewater	River	Dam	Groundwater	Urban Drinking Water	Industrial Wastewater	Slaughterhouse Wastewater	References, City
35	Surface water :10	Ekbatan Dam :7	0.3	0.01			41, Hamadan
Municipal wastewater: 57.46	Karun River: ND - 13.7			2.96	70.6	70.6 ± 16.98	42, Ahvaz
1.02–8							43, Tehran

the presence of estrogens in the waterways. The researchers concluded that contraceptive pills import the small amounts of synthetic estrogens into the waterways and that ethinyl estradiol is present in a small amount in drinking water. The University of California, San Francisco (UCSF) has pointed to several other sources of the EDCs in water including natural and synthetic estrogen released from the livestock like lactating cows in which hormones are used to increase milk production, synthetic estrogens in crop fertilizers, and several unknown industrial chemicals including plastic additives like bisphenol A. Industrial chemicals compounds may enter the waterways either through runoff from the chemical industries or through disposal of products at the landfills. Chemical compounds presented in the drugs, for instance, anticonvulsants and antidepressants play a similar role as the estrogens (they mimic the action of the estrogen) in the environment. Therefore, women who use contraceptives are not the only source of estrogen entry into the waterways. Usually, during their pregnancy women excrete a large amount of estrogen. Everyone (men and women) is releasing the estrogen that is dispersed through the sewage. While Ethinylestradiol is chemically stronger than other estrogenic compounds, it is less administered by the women as contraceptive pills compared to other mentioned sources. For instance, the number of veterinary estrogens given to lactating cows in the United States was 5 times higher than that of the ethinylestradiol used by women as the contraceptive pills.[51]

Estradiol Measurement Methods

Methods to measure the estradiol concentration include gas chromatography–mass spectrometry (GC-Mass), high-performance liquid chromatography (HPLC), enzyme-linked immunosorbent assay (ELISA), and gas chromatography/tandem mass spectrometry.

The ELISA can provide an alternative method to determine the amount of the estrogen hormones. This method is simple, inexpensive, and very sensitive. Furthermore, the kits related to this method are easily available.[1]

Discussion and Conclusion

Estrogen hormones like estradiol enter the environment through wastewater as well as humans or animals and thus threaten the health of humans and wildlife. These compounds have been measured in urban, industrial and hospital swage, surface waters, or even in groundwater in various quantities. The presence of these compounds in the aquatic environments and exposure of aquatic organisms to these compounds has emerged some concerns. Moreover, considering the absorption of estradiol and other estrogenic hormones on sludge, their entry into the environment and chain food through sludge as well as health problems and environmental concerns related to these compounds, some evaluation should be conducted for continuous measurement of these compounds, removing the EDCs from wastewater and preventing their entry into the environment.

Ethical Approval

Not applicable.

Conflict of Interest Disclosures

None.

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