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Synthetic estrogens, their presence in aquatic ecosystems and effects on biota

Synthetic estrogens are endocrine disrupting compounds that might be in water bodies and, consequently, interfere in hormonal, metabolic and reproductive functions of organisms exposed. This study aims to analyze the international scientific literature about those chemicals through a systematic and narrative review. The investigated estrogens were 17a-ethinylestradiol (EE2), Mestranol (MeEE2), Diethylstilbestrol (DES) and Dienestrol (DNS), which are widely present in pharmaceuticals, consumed and disposed in the environment. For this review, only scientific papers, published from 1990 to 2019, were considered. They were collected in ScienceDirect, PubMed and Scielo online platforms. Introductory information about the compounds, such as their chemical characteristics and use in society were described, as their occurrence in aquatic ecosystems and effects on biota, reported by environmental assessments and ecotoxicological tests, respectively. According to this study, China is the major contributor in quantitative terms, counting 21 articles about synthetic estrogens. Some hormones demonstrated to be more investigated than others; moreover, the increasing of research about those emerging contaminants was noticed. Additionally, Brazilian water bodies revealed to have the highest concentrations, which should encourage critical thinking on its insufficient environmental management. The study also highlights the importance of scientific research expansion and its implementation on truly effective public policies for aquatic ecosystem conservation.

Keywords: Disruptor; Endocrine; Environment; Pollution; Hormone.

Estrógenos sintéticos, sua presença em ecossistemas aquáticos e efeitos na biota

Estrógenos sintéticos são disruptores endócrinos que podem estar presentes em corpos d'água e, consequentemente, interferir em funções hormonais, metabólicas e reprodutivas de organismos expostos. Este estudo busca analisar a literatura científica internacional sobre tais compostos através de uma revisão narrativa e sistemática. Os estrógenos investigados foram 17a-etinilestradiol (EE2), Mestranol (MeEE2), Dietilestilbestrol (DES) e Dienestrol (DNS), que estão amplamente presentes em fármacos, sendo consumidos e dispostos no ambiente. Para esta revisão, apenas artigos científicos, publicados entre 1990 e 2019 foram considerados, tendo sido coletados nas plataformas online ScienceDirect, PubMed e Scielo. Informações introdutórias sobre os compostos, como características químicas e uso em sociedade foram descritas, assim como sua ocorrência em ecossistemas aquáticos e efeitos na biota, reportados por monitoramentos ambientais e testes ecotoxicológicos, respectivamente. De acordo com o presente estudo, a China se mostrou como maior contribuinte em termos quantitativos, somando 21 artigos sobre estrógenos sintéticos. Alguns hormônios demonstraram ser mais investigados do que outros e o aumento de pesquisas a respeito destes contaminantes emergentes foi notado. Além disso, os corpos d'água brasileiros revelaram ter as maiores concentrações, o que deve encorajar uma reflexão crítica sobre sua gestão ambiental insuficiente. O estudo também destaca a importância da expansão de pesquisas científicas e sua implementação em políticas públicas realmente efetivas na conservação de ecossistemas aquáticos.

Palavras-chave: Disruptor; Endócrino; Poluição; Ambiental; Hormônio.

Topic: **Química Agrícola e Ambiental**

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INTRODUCTION

Environmental pollution is a great concern in contemporary society. It affects populations' health and quality of life, besides being one of the major contributors to species extinction alongside habitat destruction and introduction of invasive organisms (BAIRD, 2008; PRIMACK et al., 2001). Pollution's magnitude reflects on water resources, affected by municipal and industrial wastewater discharges. Despite the required treatment, effluents might still contain harmful chemicals such as endocrine disrupting compounds (EDCs) (FERREIRA, 2013; REIS FILHO et al., 2007).

Defined as exogenous substances that cause adverse health effects on an intact organism, or its progeny, consequent to changes in endocrine functions (EC, 1996), endocrine disrupting compounds comprise a wide range of chemicals, including steroid hormones, derived from cholesterol (ADEEL et al., 2017), and synthetic composites, capable of mimicking or inhibiting estrogen and testosterone action (KIYAMA et al., 2015). Synthetic hormones, which are called environmental estrogens and androgens too, have a wide application in society, including menopause treatment, contraception and livestock growth promotion (ALBERO et al., 2013), which contributes to their availability in ecosystems and biota exposure. What environmental impacts do those compounds have? Answering that requires comprehension of hormones physiological actions.

Estrogen and progesterone are endogenous hormones that promote development and operation of female reproductive system, involved in the metabolism of lipids, minerals, carbohydrates and proteins. They have important functions in men as well, determining effects on bones, spermatogenesis and behaviour (LOOSE et al., 2010). Likewise, testosterone plays important roles in men such as the development of reproductive tissues, regulation of bone and muscles mass (WEIN, 2013). The effects of endocrine disruptors relate to hormone biosynthesis, metabolism, transport and mechanism of action on both receptor and post-receptor levels (HAMPL et al., 2016). Hence, EDCs have become a frequently discussed topic in research papers that evaluate their presence in natural water bodies and whether they influence wildlife (LIU et al., 2020; HUANG et al., 2019; DORABAWILA et al., 2005; IWANOWICZ et al., 2016; ANNAMALAI et al., 2015; BERTIN et al., 2020).

Despite the wide assessment of natural hormones, synthetic estrogens as 17α-ethinylestradiol (EE2), Mestranol (MeEE2), Diethylstilbestrol (DES) and Dienestrol (DNS) are targets of investigations as well, held in numerous countries from most continents. Thus, they became relevant objects of international studies (ARMSTRONG et al., 2016; ORN et al., 2016; UIRAPONG, 2017; POJANA et al., 2007; LEI et al., 2009; DAMKJAER et al., 2018).

In view of these considerations, this paper aims to review the current knowledge about the above-cited synthetic hormones, focusing on their occurrence in aquatic ecosystems and their effects on biota, reported by international scientific papers.

MATERIALS AND METHODS

The analysis of international scientific literature was held through ScienceDirect, PubMed and Scielo (Scientific Electronic Library Online) platforms using a combination of key words (Table 1). Only scientific papers about 17α-ethinylestradiol, Mestranol, Diethylstilbestrol and Dienestrol published from 1990 to 2019 were considered for the systematic review. The pollutants investigation simply considered the environmental perspective of field researches. Therefore, reviews, descriptive studies of analytical methods and clinical assays regarding other aspects of the composites were not selected.

Table 1: Key words used for paper browse.

COMPOUND	PLATFORM	SUBJECT	
		Occurrence in aquatic ecosystems	**Effects on biota**
EE2	ScienceDirect	Ethinylestradiol, occurrence, sediment	Ethinylestradiol, effects, biota
	PubMed	Ethinylestradiol, occurrence, sediment	Ethinylestradiol, effects, biota
	Scielo	Ethinylestradiol	Ethinylestradiol
MeEE2	ScienceDirect	Mestranol, occurrence, environment	Mestranol, effects, organism
	PubMed	Mestranol, occurrence, environment	Mestranol, effects
	Scielo	Mestranol	Mestranol
DES	ScienceDirect	Diethylstilbestrol, occurrence, sediment, water	Diethylstilbestrol, effects, ecotoxicology
	PubMed	Diethylstilbestrol, occurrence, sediment, water	Diethylstilbestrol, effects, ecotoxicology
	Scielo	Diethylstilbestrol	Diethylstilbestrol
DNS	ScienceDirect	Dienestrol, environment	Dienestrol, effects
	PubMed	Dienestrol	Dienestrol
	Scielo	Dienestrol	Dienestrol

Additionally, an introductory research was elaborated to support a deeper discussion about the contaminants. Its data sources include papers, monographs and official reports from renowned institutes and authorities. Moreover, PubChem and Drugbank websites were consulted for chemical information. The opening section concerns the pollutants' characteristics and use in society and it is followed by the systematic review itself, which is a critical examination of studies about synthetic hormones, especially their presence in nature along the years and potential harms in wildlife. Considering the review, we expect to evaluate science courses, to discuss possible gaps in our current knowledge about EDCs and future perspectives for it as well.

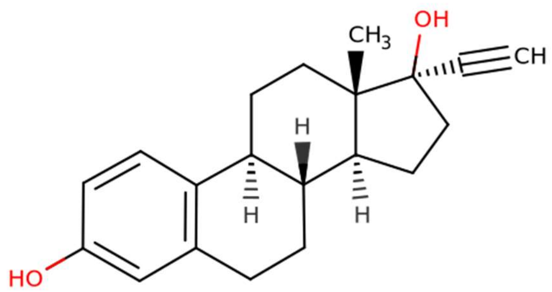
RESULTS AND DISCUSSION

Recognition of human activities that contribute to endocrine disrupting compounds availability in nature is important to understand synthetic estrogens sources. However, because of the high amount of EDCs, a direct and more specific analysis was considered more suitable for this work. Consequently, the next sections contain separate and specific information about 17α-ethinylestradiol, Mestranol, Diethylstilbestrol and Dienestrol. Their entry in society and their characteristics are presented with the support of a simpler review (the introductory research previously cited), then their occurrence in aquatic ecosystems and their effects on biota, which are the focus of this paper, are accompanied by the number of identified and selected records.

17α-ethinylestradiol

Initially commercialized as an oral contraceptive in the 1960s, 17α-ethinylestradiol (EE2) is currently used to treat menopause symptoms, for hormone therapy in female with hypogonadism and to increase livestock productivity too (DHONT, 2010; LUCENA, 2013; ARIS et al., 2014). 17α-ethinylestradiol has been present in oral contraceptives (OCs) with varied doses over the years. Nowadays, they typically contain from 15 to 35 µg of EE2 (HAMPSON, 2020). United Nations estimate that 842 million women of reproductive age use modern methods of contraception, whereas 151 million consume pills, mostly in Europe, The Caribbean, Northern and Latin America, and Oceania (UN, 2019). Its widespread use contributes for EE2 presence in ecosystems, since natural expelling through wastewater discharges and runoff follows their ingestion.

Lipolytic nature of the compound reinforces its low solubility in water, which is indicated as 4.8 mg/L at 20ºC (LAI et al., 2000). Similar to natural hormone estradiol, 17α-ethinylestradiol chemical formula is $C_{20}H_{24}O_2$ (Picture 1). It is soluble in ethanol and its reported log K_{ow} ranges from 3.67 (KOVACEVIC et al., 2019) to 4.15 (REN et al., 2017). Its molecular weight is 296.40.



Picture 1: 17α-ethinylestradiol.

Considering the above-mentioned chemical traits, chemical analysis of EE2, which is a hydrophobic organic compound, is mainly directed to sedimentary compartments. That is the motive of 'sediment' being one of the key words used in this review. It is where we expect to find the contaminants, considering their presence in the ecosystem.

17α-ethinylestradiol in aquatic ecosystems

Inspection at ScienceDirect, PubMed and Scielo led to 504, 27 and 38 articles, respectively. Analysis of the synthetic hormone presence in organisms as replicates and papers that did not contemplate studies in natural ecosystems were disregarded. Moreover, investigations held in wastewater treatment plants were not considered either. Accordingly, 17 articles were appropriate for this review (Table 2).

The revised studies took place in China (nine studies), Brazil (6), Italy (1) and Malaysia (1). Concentration of 17α-ethinylestradiol ranged from not detected to 4.073 ng/L. The lowest level was registered as 0.3 ng/L in a Chinese river (Liu et al., 2015), while the highest one was in Brazilian waters (Montagner, Jardim, 2011). Most of the researches occurred in rivers (eleven studies), followed by estuaries

(4), a bay (1), a lake (1) and a mangrove (1) environment.

Table 2: Presence of Ethinylestradiol in aquatic ecosystems.

COUNTRY	MATRIX	CONCENTRATION	AUTHORS
Brazil	Water	17 – 4073	MONTAGNER et al., (2011)
	Sediment	0.45 – 129.78	FROEHNER et al. (2012)
	Sediment	70.28	PIMENTEL et al. (2016)
	Sediment	20 ± 6.2 – 86.3 ± 25.6	PUSCEDDU et al. (2019)
	Sediment	91.04 – 321.71	SANTOS et al. (2019)
	Sediment	90.92 ± 8.32	MORAIS et al. (2019)
China	Water	ND – 0.52	LI et al. (2013)
	Water	ND – 206.5	HUANG et al. (2013)
	Sediment	ND – 21.2	
	Water	0.3 – 5.9	LIU et al. (2015)
	Water	ND – 43.93	YANG et al. (2015)
	Sediment	ND – 33.38	
	Water	4.09 – 16.85	WANG, ZHU (2017)
	Water	1.14 – 2.39	WANG et al. (2017)
	Sediment	1.06 – 2,19	
	Sediment	8.2 – 16.9	LIU et al. (2018)
	Water	ND – 17.112	TAN et al. (2018)
	Sediment	ND – 17.9	
	Water	0.391 – 0.523	ASHFAQ et al. (2019)
Italy	Water	ND – 34	POJANA et al. (2007)
	Sediment	12 – 41	
Malaysia	Water	ND – 0.005	PRAVEENA et al. (2019)
	Sediment	ND – 0.329E-4	

In spite of EE2 intense use in society (probably it is the most used synthetic estrogen), it can be observed the small percentage of successful results during papers browsing. Perhaps, the use of more scientific platforms for this review would be necessary. Another possibility is to assume that the number of diagnosis of EE2 concentrations in aquatic environments is not proportional to its presence in daily life.

Effects of 17α-ethinylestradiol on biota

The effects of endocrine disrupting compounds have been observed in reptiles, birds and mammals (BHANDARI et al., 2015; OTTINGER et al., 2015). Experimental tests in animals, reported by scientific literature, cooperate in defining a certain chemical as an EDC, which can lead to those compounds regularization, for the benefit of public health (TOPPARI, 2019). Ecotoxicological tests involving EE2 demonstrated that it can be from twice (in humans) to five times (in some fish species) more relatable to estrogen receptor, compared to estradiol (ARIS et al., 2014). Furthermore, EE2 has a high potential of bioaccumulation in ichthyofauna (LIU et al., 2017). Fish are exposed to 17α-ethinylestradiol in contaminated environments and in aquaculture’s monosex populations such as tilapia’s (Oreochromis niloticus), even though 17β-estradiol is the preferred estrogen in sexual reversion induction (PANDIAN et al., 1995; HOGA et al., 2018).

Regarding human exposure to EE2, Salierno et al., (2009) presented degenerative effects as changes in reproductive behavior and development of secondary sexual characteristics in men. Moreover, contraindications of EE2 include carcinoma and neoplasia; although its carcinogenicity is not directly listed, 17α-ethinylestradiol constitute combined oral contraceptives, which are listed as carcinogenic to humans (group 1), according to International Agency for Research on Cancer (IARC, 1999).

Systematic search for ecotoxicological tests in biota involving EE2 led to 350 (ScienceDirect), 21 (PubMed) and 38 (Scielo) articles. Studies about bioaccumulation, risk assessments as reviews and tests using mixtures of EE2 and other contaminants were not considered. Thus, 11 scientific papers were selected.

Table 3: Effects of 17α-ethinylestradiol on biota.

TEST ORGANISM	C	REPORTED EFFECTS	A
Drosophila melanogaster	0.015% and 0.003%	Mortality; decrease in fertility; interference in gene expression	BOVIER et al. (2018)
L. catesbeianus	10 ng/L	Tachycardia	SALLA et al. (2016)
Salmo salar	0.04 nM – 0.4 nM	Increase in vitellogenin (VTG) levels; decrease in hepatic proteins levels and hormone receptors (estrogen α and GHR)	BREVES et al. (2018)
Pimephales promelas	0.5 ng/L	Inhibition of eggs production	RUNNALLS et al. (2015)
Chlorella vulgaris	0.1 mg/L	Increase in biomass; decrease in chlorophyll a levels	CZARNY et al. (2019)
Scenedesmus armatus			
Mytilus trossulus	50 ng/dm³	Gonadal regression and atresia	SKJAERLUND (1992)
Oreochromis mossambicus	120 mg/kg	Feminization; increase in gonadosomatic index (GSI) and muscle fat	LÁZARO-VELASCO et al. (2019)
Chironomus tentans	1.6 mg/L	Mortality and growth decrease	DUSSAULT et al. (2008)
Hyalella azteca	2.5 mg/L and 4.1 mg/L		
M. galloprovincialis	50 – 500 ng/L	Mortality and inhibition of gametes fertilization	CAPOLUPO et al., (2018)
P. lividus			
Peromyscus californicus	0.1 ppb	Changes in intestinal flora	JAVUREK et al. (2016)
Oreochromis niloticus	250, 500 and 1000 ng/L	Malformation, behaviour change, development of intersex fish	PASSOS NETO et al. (2019)

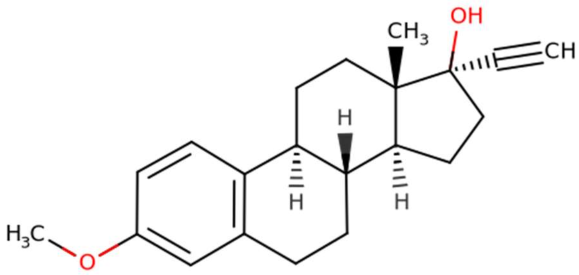
C = Concentration/ A = Author (s)

Insects, amphibian, fish, algae and marine invertebrates were submitted to ecotoxicological tests, while rats were tested in a toxicological assay. The concentrations of EE2 were varied, as the observed effects on organisms. Other studies mention change in social behaviors such as mating, increase in aggressiveness, induction to vitellogenin (VTG) production in male fish and inhibition of reproduction (VOLKOVA et al., 2015; CHEN et al., 2017; ZHA et al., 2008).

Comparing different studies when the doses and organisms are different is a limited approach, especially if the concentrations present in organisms that were exposed in ‘natural’ conditions are unknown. From the discharge of contaminants in water bodies to the estimation of toxic doses for aquatic living beings, there is a blank held by bioaccumulation and biomagnification processes. How exposed to EE2 is biota? Are the observed effects overwhelmed or underwhelmed? Do they reflect real circumstances?.

Mestranol

Mestranol (MeEE2, Picture 2), whose chemical formula is $C_{21}H_{26}O_2$ ap]nd molecular weight is 310.42, is more persistent in environment and has greater resistance to biodegradation, compared to EE2 (URAIPONG et al., 2017; ADEEL et al., 2017). Its octanol/water partition coefficient (K_{ow}) is 4.61, while its solubility in water is 0.3 mg/L under 20 ºC (LAI et al., 2000).



Picture 2: Mestranol.

Mestranol is a prodrug, consumed in its inactive form and converted to EE2 through biotransformation processes in mammal's livers (URAIPONG et al., 2017). The first hormonal pill, called Enovid® was approved in 1960 in the United States. It had Mestranol (150 µg) and Norethynodrel (9.85 mg) in its composition. However, occurrence of side effects as nauseas, headaches and vomits motivated decrease in estrogen concentrations in pills (CHRISTIN-MAITRE, 2013). According to Food and Drug Administration's drugs data bank, smaller concentrations of MeEE2 and Norethynodrel in Enovid® reached 0.1 mg and 2.5 mg, respectively. Nonetheless, pills commercialization was interrupted (FDA, 2019).

Mestranol in aquatic ecosystems

Systematic search for international studies concerning Mestranol presence in water resources led to 199 (ScienceDirect), 12 (PubMed) results. Search on Scielo did not have any result. As in 17α-ethinylestradiol browse, studies done out of the determined period (1990-2019) as well as 'below limit detection' results were not considered. Thus, three articles were selected.

Table 4: Presence of Mestranol in aquatic ecosystems.

COUNTRY	MATRIX	CONCENTRATION	AUTHORS
Brazil	Sediment	801.6 ± 20.6	MORAIS et al. (2019)
	Sediment	119.24 – 301.99	SANTOS et al. (2019)
Serbia	Sediment	1.0 ± 0.1 – 77.5 ± 6.3	BUJAGIC et al. (2019)

Concentration in sediment (ng/g).

Two studies from Brazil reveal higher values of Mestranol in estuaries, compared to a Serbian investigation. The small number of identified articles can be interpreted as an indication that few inspections of MeEE2 in environment are made and/or this contaminant is less detected, which contrasts with 17α-ethinylestradiol. Additionally, it is possible that the key words or platforms used in this review were not adequate for Mestranol studies inquiry.

Analyzing two Brazilian academic studies, a dissertation and a thesis, we can observe high values of MeEE2 as well. Morais (2018) identified the contaminant ranging from 53.65 to 1960.98 ng/g in Jaguaribe River sediment, while Lima (2016) detected MeEE2 in another river, yet in the same Brazilian state. Acaraú River and Estuary had from 2.77 to 251.67 ng/g of Mestranol. Those studies are not in Table 3 because they were not identified through the systematic review, but previous literary investigation done by the authors.

Effects of Mestranol on biota

It is important to emphasize that studies concerning the effects of oral contraceptives were not considered for this review, since they contain more than one chemical. Moreover, studies about MeEE2 effects on drugs pharmacokinetics were disregarded either. Hence, systematic search for Mestranol effects on biota led to 228 (ScienceDirect) and 141 (PubMed) results, in which seven appropriate articles were selected.

Most of the studies found were toxicological tests done in the 1990s, with varied doses concentrations. Abas et al. (1994) highlight that administrated doses in rats are higher than Mestranol concentrations ingested by women who consumed Enovid. Still, it is crucial to remind the differences between long-term and short-term effects as ecotoxicological tests can indicate either acute or chronic effects. Clinical studies might be more efficient in demonstrating chronic effects of pharmaceutical consumed by patients or people from a certain sample frame.

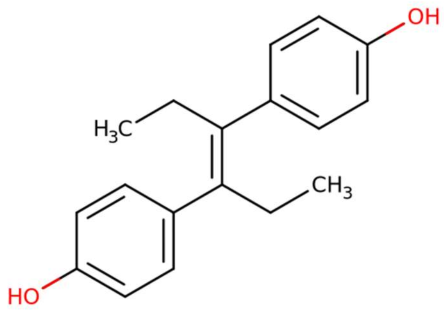
Table 5: Effects of Mestranol on biota.

TEST ORGANISM	C	REPORTED EFFECTS	A
Rabbits	1.5 mg	Portal fibrosis with biliary ploriferation	SKAJAERLUND (1994)
Rats	112 µg/kg of feed	Higher arterial pressure	ABAS et al., (1994)
	0.2 mg/kg diet	Increase in percentage of liver occupied by Altered Hepatic Foci (AHF) expressing Placental Glutathione S- Transferase (PGST)	DRAGAN et al., (1996)
	0.2 ppm	Increase in the amount of diploid hepatocytes (evidence of carcinogeny)	DRAGAN et al. (1998)
	0.5 to 10 mg/kg of body weight	Increase in the expression of splenic-macrophage FcγRs	GOMES et al. (2001)
Female Rats Hepatocytes	3 µM	Co-mitogenic effects	NI et al., (1994)
Mytillus galloprovincialis	0.1 µM	Increase in lysosomal enzyme release	CANESI et al. (2007)
Salmonella typhimurium	1 – 10 mg/dish	Inhibition of bacterial growth and stimulation of chromatid sisters sisters	DHILLON et al. (1994)
Human lymphocytes	1 – 100 µg/ml		

C = Concentration/ A = Author (s)

Diethylstilbestrol

Diethylstilbestrol (DES) (Picture 3) is a pharmaceutical compound whose chemical formula is $C_{18}H_{20}O_2$ and octanol/water partition coefficient (K_{ow}) is 5.07. It is hydrophobic and its solubility in water is 12 mg/L, under 20 ºC.



Picture 3: Diethylstilbestrol.

Diethylstilbestrol was synthetized in 1938, when it was widely used as an oral estrogen due to its affinity with estrogen receptors. DES was prescribed to pregnant women from 1940 to 1971 with the aim of preventing miscarriage and other complications during pregnancy (LOOSE et al., 2010). Women, via pills without standardized doses, injections, suppositories and creams, globally ingested that pharmaceutical (JISHI et al., 2017). Nowadays, it is known that women who were exposed to DES present higher risks to have subfertility, premature menopause and pregnancy complications. Furthermore, the daughters of those women have more chances to acquire adenocarcinoma than the ones whose mothers were not exposed to Diethylstilbestrol (BJORKMAN et al., 2018). Approximately five to ten millions of American women either consumed DES during pregnancy or were exposed to it in the uterus (GIUSTI et al., 1995).

Moreover, Diethylstilbestrol was used to increase livestock weight in the 1950s and for poultry castration in the 1970s (MCLACHLAN, 2016). It is still used in cattle raising and aquiculture in many parts of the world (ADEDEJI et al., 2012). In spite of its prohibition in some countries, DES remains in society, even in daily products as milk (WEI et al., 2018).

Diethylstilbestrol in aquatic ecosystems

Systematic search concerning Diethylstilbestrol presence in water bodies lead to 400 (ScienceDirect), 7 (PubMed) and 21 (Scielo) results, in which 12 articles were selected. The studies selected are most from China (8 papers), followed by Brazil (2), Italy (1) and Spain (1).

Table 6: Presence of Diethylstilbestrol in aquatic ecosystems.

COUNTRY	MATRIX	CONCENTRATION	AUTHORS
Brazil	Sediment	304.07 ± 15.54	MORAIS et al. (2019)
	Sediment	11.85 – 207.38	SANTOS et al. (2019)
China	Water	ND – 8.51	LEI et al. (2009)
	Sediment	ND – 4.51	
	Sediment	1.25 ± 0.17 – 8.79 ± 1.28	ZHANG (2009)
	Water	ND – 10	JIN et al. (2013)
	Sediment	ND – 6	
	Suspended particles	ND – 6	
	Water	ND – 2.15	RAO et al. (2013)
	Water	5.65	LIU et al. (2017)
	Water	0.72 – 2.01	WANG et al. (2017b)
	Sediment	1.53 – 3.57	
	Water	ND – 9.6	LUO et al. (2019)
	Water	12.05	XU et al. (2019)
Italy	Sediment	ND – 63	POJANA et al. (2007)
Spain	Sediment	ND – 0.32	GORGA et al. (2015)

Concentration in water (ng/L), sediment and suspended particles (ng/g). ND = not detected.

Similar to investigations about 17α-ethinylestradiol and Mestranol, the highest concentrations are observed in Brazilian aquatic ecosystems, which can be related to the sewage treatment methods adopted in Brazil and weather the activities responsible for the estrogen discharges are more intense in Brazilian territory than others.

Effects of Diethylstilbestrol on biota

Browse for studies about Diethylstilbestrol effects on organisms resulted in 181 (ScienceDirect), 12

(PubMed) and 21 (Scielo) articles, but only 15 were adequate for this review.

Table 7: Effects of Diethylstilbestrol in biota.

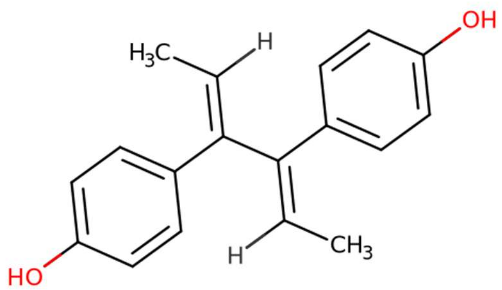
TEST ORGANISM	C	REPORTED EFFECTS	A
Uca pugilator	5 mg/L	Decrease in enzyme activity (cytobiase)	ZOU et al. (1999)
Ictalurus punctatus hepatocytes	From 10 pM to 100 nM	Increase in VTG production	MONTEVERDI et al. (1999)
Caenorhabditis elegans	0.5 mg/L	Gene induction	REICHERT et al. (2005)
Daphnia magna	0.5 mg/L	Decrease in fecundity	BRENNAN et al. (2006)
	500 µg/L	Decrease in fecundity, ecdysis frequency and metabolic changes of steroids	CLUBBS et al. (2007)
	100 µg/L	Growth inhibition	KASHIAN et al. (2004)
Carassius auratus	10 µg/L	Increase in estrone and estradiol levels, decrease in androgenic levels	YANG et al. (2008)
Rats	0.05 µg/kg	Chromosomal mutation	FUCIC et al. (2009)
Anodonta cygnea	0.75 µM	Inhibition of ion exchange in epithelial mantle	ALVES et al. (2013)
Oreochromis niloticus	100 – 400 mg/kg	Mortality, feminization and Decrease in growth and GSI	MARÍN-RAMÍREZ et al. (2016)
Oryzias latipes	10 – 1000 ng/L	Increase in mortality, incubation time and GSI; abdominal swelling	LEI et al. (2016)

C = Concentration / A = Author (s)

It is possible to observe a greater diversity of animals tested for Diethylstilbestrol than Mestranol. Besides a study involving rats, another one with human cells and at last a nematode experiment, all ecotoxicological tests were held with aquatic organisms, which includes fish, crabs, plankton and mussels.

Dienestrol

Dienestrol (Picture 4) (DNS) is a product of DES dehydrogenation. It was previously used to treat vaginal atrophy in women after menopause period (SCHREIBER et al., 2019). Its chemical formula is $C_{18}H_{18}O_2$, its solubility in water is 3 mg/L under 37 ºC and its Log Kow is 5.64 (YUAN et al., 2015).



Picture 4: Dienestrol.

Dienestrol in aquatic ecosystems

Most of the papers found during this review were analysis of Dienestrol in dairy products and studies of chemical methods to detect it. Additionally, papers concerning DNS presence in animals were not considered. Therefore, the review about Dienestrol occurrence in water bodies lead to one (Scielo), 162 (ScienceDirect) and 119 (PubMed) results, in which one article was selected. A Brazilian paper evaluated DNS presence in a mangrove-estuary environment. Its concentration in sediment varied from not detected to 56.17 ng/g (SANTOS et al., 2019).

The small amount of studies about Dienestrol can be interpreted as a consequence of it being a product of Diethylstilbestrol, which is more investigated. It is noticeable that DNS investigations are recent ones, if we consider the identified papers cited on the following section too.

Effects of Dienestrol on biota

Screening for papers about Dienestrol effects on organisms resulted in one (Scielo), 283 (ScienceDirect) and 119 studies on PubMed. However, four studies were considered appropriate for this review.

Table 8: Effects of Dienestrol.

TEST ORGANISM	C	REPORTED EFFECTS	A
Rats	0,0037; 0,037 and 0,37 mg/kg/day	Testicular atrophy	FROEHNER et al. (2012)
	50 and 3,12 µg/kg/day	Abortion and decrease in sperm progressive molility	SCHREIBER et al. (2019)
	75 and 50 µg/kg bw/day	Abortion	GONZÁLEZ et al. (2018)
Yeast cells	10 µM - 156 nM	Constitutive Androstane Receptor (CAR) agonistic effect	KAMATA et al. (2018)

C = Concentration / A = Author (s)

Rats and yeast cells resistance to the estrogen was analyzed. Rats from different studies (SCHREIBER et al., 2019; GONZALEZ et al., 2018) had one common reported effect, which is abortion, as a common concentration of 50 µg/kg/day. We would like to highlight a detected study that reports the incidence of mammal tumors in rats (INANO et al., 1993). Nonetheless, we did not considered it because the paper does not specify the dose concentration administrated. Moreover, epithelial cysts smaller than 1.5 mm were observed rats treated with 15 mg of Dienestrol dissolved in sterile water 1.3 and 1.7 ml for five to seven months (SILVA et al., 1998).

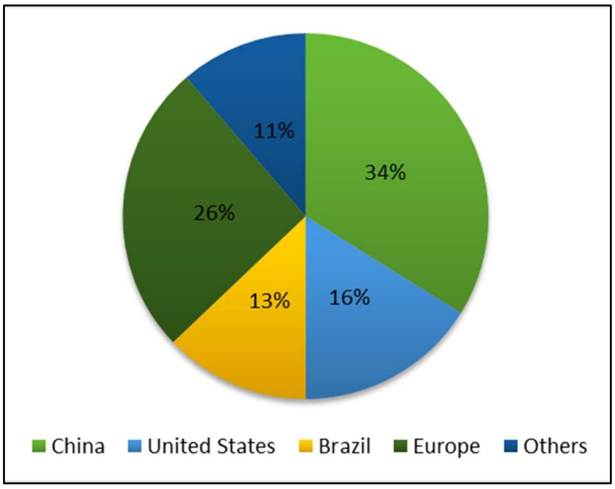
An overall view

Considering the review concerning 17α-ethinylestradiol, Mestranol, Diethylstilbestrol and Dienestrol, some aspects of our current knowledge about synthetic estrogens can be discussed. According to systematic investigation, held through 62 papers collected in ScienceDirect, PubMed and Scielo, most studies were developed by scientists located in China (21), followed by The United States (10) and Brazil (8).

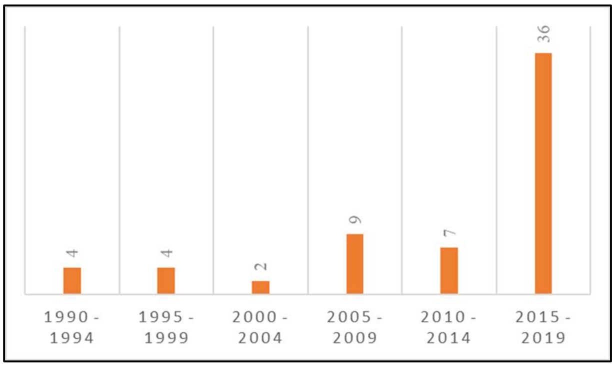
European studies were mainly developed by Spain (4), Italy (3) and Poland (2). The United Kingdom, Austria, Germany, Croatia, Scotland, Portugal, Mexico, Japan, Malaysia, India and Canada had one paper each. There were three studies whose research teams were composed by scientists with different affiliations. Those partnerships were between Spain and Italy; Brazil and Mexico; Sweden and The United States. Developed countries are majorly present in the rank, which is expected, considering the high cost of emerging contaminants analysis and the fact that investment in Science is not equal around the globe.

Moreover, despite endocrine disrupting chemicals being a raising topic, it might not be seen as a priority to countries that are still dealing with challenges that are more basic. Nevertheless, one Latin

American country stands out for having contributed to more studies than it would be predicted by stereotypes. Brazilian papers were published from 2011 to 2019 (half of them in 2019), which can be seen as a prospecting period for its scientific community. After all, studies about synthetic hormones are recent since that topic is an emerging one. The Graphic 2 shows the distribution of the papers browsed along the years.



Graphic 1: Countries representativeness on reviewed studies.



Graphic 2: Number of reviewed studies per period.

It is possible to observe that most of the papers investigated were published from 2015 to 2019, corresponding to 36 papers. This shows that although endocrine disruptors are a discussed theme since the 1990s, the world seems to be still crawling towards a complete understanding of synthetic estrogens as a concrete environmental problem.

CONCLUSIONS

Synthetic estrogens are important study objects, whose investigation can be divergent. The superiority of contaminants as 17α-ethinylestradiol and Diethylstilbestrol, in quantitative terms, could be observed since they were more investigated than their metabolites. Secondly, the relevance of China, United States and Brazil to research about the compounds is clear.

Finally, the highest concentrations of the contaminants were majorly in Brazilian waters, which reveals not only insufficient methods of effluents treatment, but also the need of implementation of more effective ones. Effects observed in organisms exposed are varied and concerning. Furthermore, the repercussion of ecotoxicological tests results was also questioned, once the doses administrated can be incompatible to real levels. Therefore, it is necessary to consider the complexity of interactions between the xenobiotic and wildlife.

Hence, to discuss Environmental Pollution as Environmental Science is to evaluate economic, social, natural and political backgrounds. Synthetic estrogens have gained recognition as prospective concerns for the current and future generations. They started to be studied in the previous decades, but they are not entirely dealt with in practical terms. Their ubiquitous presence seems to be invisible to people outside of Academia. Scientific community's role might be knowledge creation. However, what comes next? Managers of natural resources as citizens must be aware of emerging issues, which requires wide and equal scientific divulgation. Consequently, true commitment to solving emerging challenges should not be faced as an option, but as a duty.

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