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Endocrine Disruptors in Aquatic Environment: Effects and Consequences on the Biodiversity of Fish and Amphibian Species

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Abstract

Endocrine Disruptors (EDs) are synthetic or natural chemical compounds of exogenous origin that can cause serious health damage, in the growth and reproduction of animals when released into the aquatic environment through anthropic activities. Taking into account the current impact of pollutants on aquatic biodiversity in the last years, this study aims to systematically review the relevant literature on currently known EDs, focusing on their sources, their effects, and consequences on the aquatic biota, with emphasis to fish and amphibians. About 70% of the analyzed studies report that sewage represents the major source of EDs contamination to the water environment, and more than 90% of these contaminants are associated with interference in the sexual differentiation of aquatic animals, infertility, and reduction of sperm production. In addition, the main effects caused by EDs in fish include abnormalities in the reproductive system of animals (47%), induction of vitellogenin (VTG) synthesis (20%) and mortality of the species (13%). In amphibians, the main effects caused by EDs include changes in hormonal activity (physiological functions) during the embryonic development (11%), causing changes in anatomy (33%) and behavior (11%), leading to a reduction in reproductive success (11%), as well as gonadal abnormalities (22%), hermaphroditism (33%) and other alterations in the reproductive system (45%). Finally, this report calls attention to the importance to the rational use of these substances, as well as to encourage scientific research that shows the real seriousness of these contaminations on the decline of fish and amphibian populations, showing mediating and mitigating solutions to their impacts.

Keywords: endocrine disruption, hormonal changes, pollutants, aquatic biota, aquatic ecotoxicology

1. Introduction

The compounds that pose a risk to the proper functioning of the endocrine system include endocrine modulators and endocrine disruptors (EDs) (Lyche et al., 2013). In endocrine modulation, the clinical symptoms observed in individuals are milder and reversible, while the effects of endocrine disruptors are more serious and not Always reversible, and may lead to death (Moraes et al., 2008). In this case, EDs are synthetic or natural chemical compounds of exogenous origin, which can not only cause damage to health but can also affect animal growth and reproduction (Reis Filho et al., 2007; Moraes et al., 2008).

Drugs, synthetic hormones, natural steroids, chemical industrial products, pesticides, fire retardants, perfluorinated compounds, among others, are examples of EDs due to their characteristic deleterious effects. Furthermore, some of them are also considered to be Persistent Organic Pollutants (POPs) for the reason that they are resistant to environmental degradation through biological, chemical, and/or photolytic processes (Bila and Dezotti, 2007; Reis Filho et al., 2007; Loutchanwoot et al., 2013; Lyche et al., 2013).

Although EDs have been studied for some time, attention has been currently focused on these substances due to new findings on the severity and variety of damages that they can cause to human and animal health as well as biodiversity impairment (Meyer et al., 1999; Lee et al., 2015). Effects such as, for example, interference on the animals' sexual differentiation, resulting in the feminization of males or vice versa, besides damage to their fertility (Moraes et al., 2008; Biancardi et al., 2012). In cases of animals exposed to EDs where the effects are not so intense as to make them infertile, disturbances can be observed to their offspring or to other individuals in the population (Lyche et al., 2013). In addition, some EDs may function as cancer inducers (Bila and Dezotti, 2007).

Therefore, EDs can interfere with the organisms' metabolic pathways due to the similarity between their chemical structure and that of endogenous hormones. It can manifest their action at different points of hormonal functioning, ranging from the production of hormones to its excretion and biotransformation, enabling the triggering of adverse responses and alteration of cellular function (Confort and Silva, 2013).

Consequently, these substances bind to one or more types of cellular receptors (e.g., in sexual reversal, there may be involvement of the estrogen receptor) and elicit agonist or antagonistic responses (Crain et al., 2000). Thus, because they possess a chemical similarity with endogenous hormones, EDs can associate with the proteins that carry the hormones, altering hormonal metabolism and, subsequently, deregulating the endocrine system (Moraes et al., 2008).

Some of these compounds that act as EDs are called persistent organochlorine pesticides and are known to resist chemical, physical, biological and photochemical degradation. They undergo slow degradation and persist in the environment for long periods of time, which leads to the compromise of whole food chains through trophic magnification. In addition, some EDs are lipophilic compounds, which can accumulate in the adipose tissue of animals, persisting in organisms for many years (Mrema et al., 2013). Even at very low doses, some EDs may have deleterious effects on exposed organisms (Bila and Dezotti, 2007).

One of the most studied EDs is dichlorodiphenyltrichloroethane (DDT), which was already heavily used as an insecticide in the second half of the 20th century, but is now banned in many countries. One of the metabolites of DDT, p, p'- dichlorodiphenyldichlorethylene (DDE), is commonly found in human body fluids and has a negative effect on chromosome integrity of human spermatozoa in *in vitro* experiments (Tavares et al., 2013).

There are reports about the feminization of the reproductive tract of male fish of the species (*Rutilus rutilus* Linnaeus, 1758) found in rivers of the United Kingdom. It has been shown that this feminization was related to the presence of estrogenic compounds that were released into rivers through domestic sewage, and that the EDs effects were irreversible (Rodgers-Gray et al., 2001). In another study, it was reported that exposure of zebrafish females (*Danio rerio* Hamilton, 1822) to POPs had a suppressive effect on ovarian follicle development. There was not only a decrease in egg production compared to control females but also decreased the viability of eggs produced (Lyche et al., 2013).

The main objective of this study is to present the main EDs existing in the aquatic environment, and their main consequences in the aquatic biota, with emphasis on fish and amphibians, as well as emphasize worldwide research on this subject. Reviews like this are important because can facilitate the conservation efforts and give power to the protection and management strategies. This study can be used both in general ecological and management perspective.

2. Material and Methods

The research is based on a systematic review, which is a type of research with a well- defined question, aiming to identify, select, evaluate and synthesize the available relevant evidence (Galvão and Pereira, 2014). Hence, we present in this study the main approaches discussed by other authors (between 1990-2017) who worked with Endocrine Disruptors (EDs) problem in relation to the aquatic biota of fish and amphibians.

In this case, according to Galvão and Pereira (2014), the work in question predicted the following steps: (1) elaboration of the research question *("What are the main effects of endocrine disruptors on aquatic biota with an emphasis on fish and amphibians?"*); (2) literature search; (3) selection of articles; (4) data extraction; (5) methodological quality assessment; (6) data synthesis (meta-analysis); (7) evaluation of evidence quality; and (8) writing and publication of results.

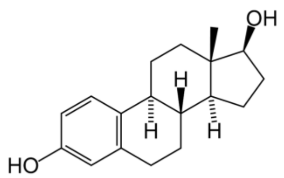
To conduct this systematic review, we used the following electronic research databases: Scopus®, Google® Scholar, PUBMED® and Science Direct®, with the combination of proper keywords during the search ("*endocrine disruptors*" and "*aquatic environment*"; "*endocrine* *disruptors*” and “*fish*”; “*endocrine disruptors*” and “*amphibian*”). Here, over 67 articles spanning the last 30 years are reviewed with following objectives: (i) to evaluate current EDs problems for aquatic biota (43 articles) and (ii) the effects of DEs to fish and amphibians biota (24 articles).

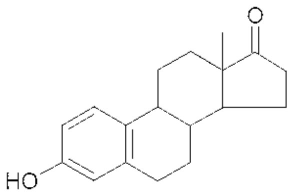
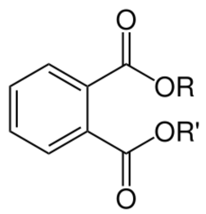
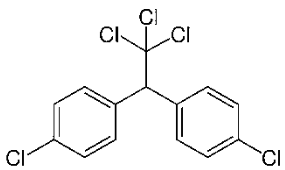
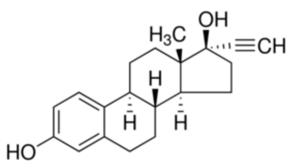
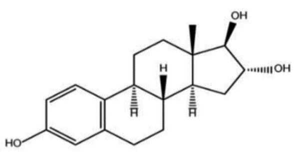
3. Results and Discussion

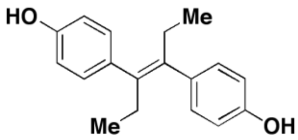
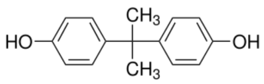
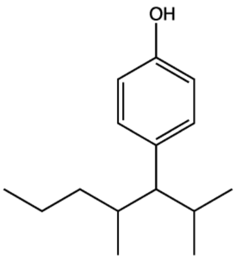
3.1 Endocrine Disruptors in the Aquatic System

Endocrine disruptors (EDs) are characterized as micropollutants (Muller et al., 2008), and are commonly discharged into the aquatic environment through anthropic activities (Abreumota et al., 2014; Venturini et al., 2015). In general, sewage represents the largest source of contamination of pollutants to the water environment (Cordeiro et al., 2008). This contamination causes serious public health problems and negative impacts on aquatic fauna and flora, besides inducing ecosystem imbalance (Pratt et al., 2008). Several substances have the characteristic of affecting the animals’ endocrine system (Bila and Dezotti, 2007), and these endocrine disrupting substances have two classifications: (a) natural, produced by plants and animals (phytoestrogens and estrogens); or (b) synthetic, man-made substances used in the manufacture of oral contraceptives, in hormone replacement, as a feed additive in the diet of several animals (Ghiselli and Jardim, 2007), for use in industry and agriculture, socalled xenoestrogens (Behera et al., 2011). Some examples of synthetic substances are alkylphenols, pesticides, phthalates, polychlorinated biphenyls, bisphenol A and drugs (Table 1).

Table 1. List of substances classified as Endocrine Disruptors (EDs) and their main route of transmission.

Substance/Chemical Structure	**Characteristics/ Path of Contamination to the Water Bodies**	**Author**
17β-estradiol (E2) 	Natural estrogen, related to the development of female sexual characteristics and reproduction, used for the manufacture of oral contraceptives and in cases of hormone replacement/excreted in the feces and urine of humans and/or inadequately dumped into the environment (in the form of a drug), arriving to water bodies through sewage networks.	Ikehata et al., (2006).
Estrone (E1)	Natural estrogen/excreted in the feces and urine of humans and/or dumped into the environment, reaching water bodies	Ikehata et al., (2006).

	through sewage networks.	
Phthalates 	Synthetic Substance, xenoestrogen, compounds with oxygen, generated through industrial activity/reach the water bodies through inappropriate disposal of industrial solid waste and through sewage networks.	Ghiselli and Jardim (2007); Bila and Dezotti (2007); Reis Filho et al. (2006).
DDT (2,2 bis-p-chlorophenyl -1,1,1-trichloroethane) 	Synthetic Substance, xenoestrogen, used as a pesticide in agriculture/contaminate water by improper disposal of solid waste and through surface runoff of the substance that is leached to water bodies.	Ghiselli and Jardim (2007); Bila and Dezotti (2007); Reis Filho et al. (2006).
17α-Ethinylestradiol (EE2) 	Synthetic estrogen, used as contraceptive/ are found in surface water through inappropriate disposal of drugs in the natural environment and excreted through urine and feces.	Bila and Dezotti, (2007).
Estriol (E3) 	Natural estrogen/excreted through urine and feces, being released into the sewer.	Bila and Dezotti, (2007).
Diethylstilbestrol	Synthetic estrogen/inadequately discarded in water and in the environment and	Kuster et al.,

(DES) 	excreted through urine and feces.	(2009).
Bisphenol A (BPA) 	Xenoestrogen, produced by industry, widely found in the environment/reach water bodies through the inappropriate disposal of industrial solid waste and also through sewage networks.	Aquino et al., (2013).
Nonylphenol (NP) 	Xenoestrogen, produced by industry, widely found in the environment/reach water bodies through the inappropriate disposal of industrial solid waste and also through sewage networks.	Aquino et al., (2013).

Urban effluents are considered the main form of entry of EDs into water bodies and are normally discarded in the environment through excretion of humans and other animals (Diniz et al., 2010), of untreated sewage or with primary treatment in bodies of water (Sodré et al., 2010) and the inadequate disposal of drug residues in dumpsites and landfills. These drugs contain resistant EDs molecules, and when excreted in the urine, feces and/or in the original form are difficult to eliminate and may persist in the environment (D'Ascenzo et al., 2003).

As well as urban effluents, effluents generated by industry (plastic manufacturing) and agricultural activities (livestock confinement, use of animal manure and sludge from sewage treatment plants such as compost and soil fertilizer, and the use of hormones such as food supplements in livestock and aquaculture) (Orlando et al., 2004; Young et al., 2004), are also considered important pathways of EDs contamination in the aquatic environment (Kuster et al., 2004, Orlando et al., 2004) (Figure 1).

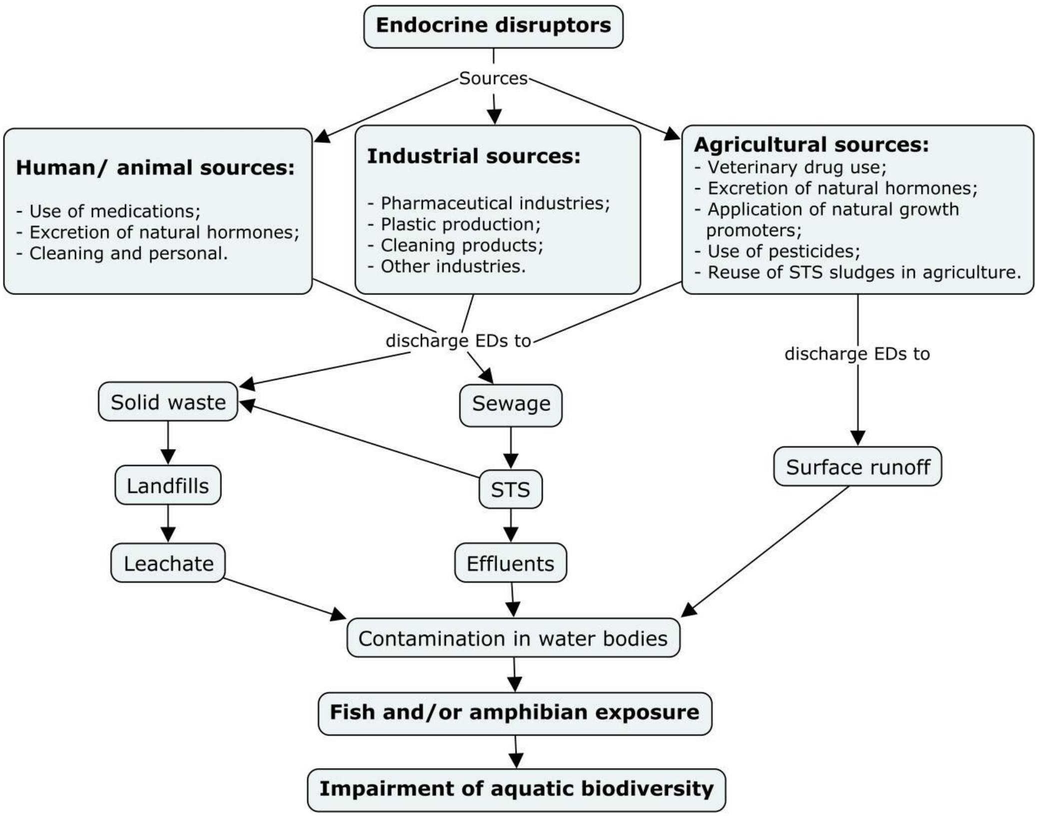


Figure 1: Routes of contamination of water bodies and exposure of fish and/or amphibian to substances characterized as endocrine disruptors (STS = Sewage Treatment Station; EDs = Endocrine disruptors) (Adapted from Aquino et al., 2013).

Among the synthetic substances, pesticides are classified as being the largest group of EDs. Traces of various pesticides have been found in bodies of water, soil and food, which can cause drastic changes in the diversity and dynamics of various aquatic animals, as well as causing serious damage to humans (Bila and Dezotti, 2007).

3.2 Effects of Endocrine Disrupters in Fish

The effects of EDs on the environment depend not only on their concentrations but also on other factors, such as lipophilicity, persistence, bioaccumulation, exposure time, biotransformation and excretion mechanisms (Bila and Dezotti, 2007). Due to these factors, fish become one of the animals most directly affected by these contaminants. The aquatic risk caused by EDs can lead to changes in the community, reducing the most sensitive species and increasing the most resistant, with the consequent loss of biodiversity (Palma et al., 2014).

The main effects caused by endocrine disrupters have been reported in fish, including abnormalities in the reproductive system of animals, induction of vitellogenin (VTG) synthesis in fish plasma and effects on human health, such as reduction in sperm production and increase of the incidence of some types of cancer (Bila and Dezotti, 2007). According to the European Union (EU), endocrine disrupters can: directly damage and change the function of an endocrine organ; interact with a receptor for hormones or, change the metabolism of a hormone in an endocrine organ.

Among the main sources, domestic effluents are sources of estrogenic substances in the aquatic environment. Research has shown that 17β-estradiol natural estrogens together with 17α-ethinylestradiol are responsible for most of the estrogenic activity detected, these substances are excreted in the sewage and, most of them are not treated or are not completely removed in the treatment plant, followed by surfactants of nonylphenol polyethoxylates (NPEOx) and nonylphenol (NP) as the main degradation product (Solé et al., 2000; Reis Filho et al., 2007; Bila and Dezotti, 2007).

The major contaminants and consequences of ED in fish are summarized in Table 2. The production of fertile eggs of *Pomatoschistus minutus* (Pallas, 1770) was reduced by 90% when exposed to a concentration of 6 ng l^{-1} of 17α-ethinylestradiol (Robinson et al., 2003). On the other hand, Thorpe et al. (2003) in an experiment with juvenile zebrafish, *Danio rerio* (Hamilton, 1822), exposed to concentrations of 100 ng/L of 17β-estradiol, for a period of 21 days, detected reproductive damages such as feminization of the reproductive tube, thus showing how much damage, these hormones can do to fish.

Table 2. Types of contaminants, fish species, consequences, type of environment and place of study of reviewed works.

Contaminant	**Species**	**Effects**	**Type of environment**	**Place of study**	**Author**
17β-estradiol	*Oryzias latipes* (Temminck & Schlegel 1846)	Hermaphroditism	Marine	USA	Hartley et al., 1998.
Metais pesados	*Oncorhynchus mykiss* (Walbaum, 1792)	Disorders of cortisol synthesis	River	Canada	Leblond etb al., 1999.
17β-estradiol	*Cyprinodon variegatus* (Lacepède, 1803)	Induction of VTG synthesis in blood	Marine	USA	Folmar et al., 2000.
17β-estradiol	*Pimephales promelas* (Rafinesque, 1820)	Changes in gonad weight	River	United Kingdom	Panter et al., 2000.
Nonilfenol polietoxilado nonilfenol	*Cyprinus carpio* (Linnaeus, 1758)	Induction of VTG synthesis	River	Spain	Solé et al., 2000.
Octilfenol	*Oryzias latipes* (Temminck & Schlegel 1846)	Reproductive effects	Marine	Germany	Knörr e Braunbeck, 2002.
17α-etinil sintético	*Pomatoschistus minutus* (Pallas, 1770)	Late maturation, and low egg fecundity	Estuary	United Kingdom	Robinson et al., 2002.
17a-etinilestradiol	*Pimephales promelas* (Rafinesque, 1820)	Mortality of the species	River	Switzerland	Schmid et al., 2002.
17β-estradiol	*Danio rerio* (Hamilton, 1822)	Feminization of the reproductive tube	River	United Kingdom	Thorpe et al., 2003.
Metais pesados	*Xiphias gladius* (Linnaeus, 1758)	Induction of VTG synthesis	Marine	Italy	Fossi et al., 2004.

17α-etinilestradiol	*Pimephales promelas* (Linnaeus 1757)	Changes in reproductive behavior	River	USA	Salierno e Kane, 2009.
Monocrotofós e profenofos	*Oreochromis niloticus* (Linnaeus 1757)	Mortality of the species	River	Camarões	Vroumsia et al., 2014.
Pesticidas organoclorados e esteroides	*Oreochromis niloticus* (Linnaeus 1757)	Thyroid disorder	River	Brazil	Duarte e Borges, 2015.
Nonilfenol	*Zacco ornitorrinco* (Temminck & Schlegel, 1846)	Decreased in reproduction	River	Taiwan	Lee et al., 2015.
17β-estradiol	*Betta splendens* (Regan, 1910)	Change in mating behavior	River	Brazil	Santos et al., 2016.

The toxicity of fipronil in fish varies by species (Pan-Uk, 2007). In a study carried out by Pan-Uk (2007), this substance is highly toxic to *Lepomis macrochirus* (Rafinesque, 1819) when it reaches an LC_{50} (Median Lethal Concentration) of 85 μg/L and *Oreochromis niloticus* (Linnaeus, 1757) reaching of 42 μg/L, and less toxic to *Oncorhynchus mykiss* (Walbaum, 1792) and *Cyprinus carpio* (Linnaeus, 1758), which became toxic only at concentrations of 248 and 430 μg/L, respectively. In the larval stage of *Oncorhynchus mykiss* exposed to concentrations higher than 6.6 μg/L, it affects the growth of the species.

Heavy metals are important EDs, in the research conducted by Fossi et al. (2004), to know the effects of organochlorines and heavy metals (Hg, Cd, and Pb) on swordfish specimens, they analyzed vitellogenin (VTG) and zone radiate proteins (ZRP). In this research, we found that VTG and ZRP were dramatically induced in some adult male specimens. Levels of heavy metals in the liver were in the following ranges: Hg 1-22, Cd 1-28 and Pb 0-1.6 ppm, indicating potential reproductive changes in these fish.

Research has been carried out with the intention of detecting EDs in the environment, in which those with interaction with the aquatic environment are highlighted. It is observed that a great effort has been made, mainly by more developed countries and that has many factories and chemical industries, to determine which substances can be classified as EDs and what their consequences are, whether for biota or environmental health.

3.3 Effects of Endocrine Disrupters in Anuran Amphibians

Hayes and coworkers (2003) showed that exposure to endocrine disrupting chemicals (EDCs) changes hormonal activity (physiological functions) during embryonic development and is responsible for changes in the anatomy, behavior and reproductive system of amphibians.

Agrochemicals or pesticides used in agriculture are associated with the population decline of anurans (Davidson and Knapp, 2007), as well as in gonadal abnormalities, hermaphroditism, changes in reproductive organs, among others (Hayes et al., 2002; McCoy et al., 2008).

In the study conducted by McCoy et al. (2008), the testicular function of anuran amphibians inhabiting environments contaminated with pesticides was compromised. In addition, there was a change in the life cycle of anurans, leading to reproductive abnormalities and consequently to population decline.

Atrazine® is an endocrine disruptor that has rarely been studied in amphibians. Its effect on *Xenopus laevis* (Daudin, 1802) was the loss of male characteristics, such as the feminized larynx development, reduction of testosterone, reduction of sperm production, drop in fertility and reduction of reproductive glands in species exposed (Hayes et al., 2002). McCoy et al. (2008) evaluated the activity and reproductive success of anurans correlating with steroid concentrations (17β-estradiol) and secondary sexual traits (Testosterona). Consequently, reproductive success in populations of anurans exposed to these agents would be reduced due to the reproductive abnormalities brought to them.

Heavy metals are a type of EDs studied for causing infertility and congenital malformation in fish and amphibians, especially cadmium that can be found easily in batteries, pesticides, galvanizing, pigment production and the processing of rubbers discarded in domestic and industrial waste or aquatic ecosystems (Lee et al., 2010).

The release of household effluents directly into the water bodies without previous treatment contains large amounts of 17α-ethinylestradiol (Hoffmann and Kloas, 2012) and Flutamide (antiandrogenic drugs) (Gregório, 2015) excreted by humans that may interfere with male sex hormones of anurans, in the secondary sexual characteristics, such as singing (Behrends et al., 2010) and the nuptial callus or sponge and serum levels of testosterone (Wyk et al., 2003).

As for the harmful effects of EDs on the analyzed taxa, according to Table 3 only two authors reported that there were no adverse effects on metamorphosis and sexual differentiation (Oka et al., 2008), and showed no morphological and histological changes in amphibian gonads (Murphy et al, 2006). Other studies (Hayes et al., 2002; Hayes et al., 2003; McCoy et al., 2008; Hoffmann and Kloas, 2012) found gonadal changes, hermaphroditism, and suggested that EDs are responsible for population decline in this group.

Table 3. Types of contaminants, frogs anuran species, consequences, type of environment and place of study of revised works.

Contaminants	**Species**	**Consequences**	**Type of environments**	**Study site**	**Authors**
Atrazine	*Xenopus laevis* (Daudin, 1802)	Reduction of the size of the larynx and hermaphroditism	Terrestrial and aquatic	Berkeley and Nasco	Hayes et al., 2002
Atrazine	*Rana pipiens* (Schreber, 1782)	Hermaphroditism and gonadal abnormalities retarded	Terrestrial and aquatic	United States	Hayes et al., 2003
Atrazine	*R. catesbeiana*; *R. pipiens* e *Rana clamitans* (Latreille, 1801)	No morphological changes and histological in gonads	Terrestrial and aquatic	Michigan, Kalamazoo	Murphy et al, 2006
Pesticidas Testosterona 17β-estradiol	*Bufo marinus* (Linnaeus, 1758)	Hermaphroditism and gonadal abnormalities	Terrestrial and aquatic	Flórida	McCoy et al., 2008
Atrazine	*Xenopus laevis* (Daudin, 1802)	No adverse effects on metamorphosis and sexual differentiation	Artificial	Hiroshima, Japan	Oka et al., 2008
Cadmium 17β-estradiol	*Rana catesbeiana* (Shaw, 1802)	Oxidative stress in hepatocytes and vitellogenin in males	Terrestrial and aquatic	Japan	Lee, et al., 2010
17α-ethinylestradiol	*Xenopus laevis* (Daudin, 1802)	Changes in mating behavior and reducing reproductive success	Freshwater	Berlin, Germany	Hoffmann e Kloas, 2012

17β-estradiol	*Rhinella schneideri* (Werner, 1894)	Changes in espermatogêneses, Oogenesis Bidderiana, and responsiveness of hepatic pigments	Terrestrial and Aquatic	São José do Rio Preto, Brazil	Freitas, 2013
Flutamide	*Rhinella schneideri* (Werner, 1894)	Increase of espermatogônias, reduction of sperm, interference in the morphology of the reproductive organs and the liver	Terrestrial, aquatic and artificial	São José do Rio Preto, Talhado and Mirassol, Brazil	Gregório, 2015

The variety of reproductive modes and parental care is a notable feature in amphibians (Duellman and Trueb, 1994; Haddad, 1991) that are derived from morphological, physiological and behavioral characteristics (Pombal Júnior and Haddad, 2005). These taxa are considered important environmental indicators because they control some populations of vertebrates and invertebrates (Pough et al., 2003), and are excellent indicators of environments preserved and/or strongly changed by anthropic activity. Endocrine disruptors are one of the main aspects responsible for the reduction of populational density or even extinction (Silvano and Segala, 2007), hermaphroditism (Hayes et al., 2003; McCoy et al., 2008), changes in the reproductive behavior (Hoffmann and Kloas, 2012), changes in the histology and morphology of reproductive gonads (Hayes et al., 2003; McCoy et al., 2008; Freitas, 2013; Gregório, 2015).

4. Concluding Remarks

A large number of these substances, in addition to technical requirements and costs to measure them in organisms and in the environment, makes it difficult to determine the actual concentration of these elements and quantification of harm to the organisms. Consequently, investments in further studies are needed to uncover the real effects of these contaminants in the food chain, especially on the impacts of EDs on human health.

It is known that developing organisms exposed to EDs may undergo changes in sexual differentiation, leading to the feminization of males and vice versa. Adult individuals, on the other hand, may suffer damage to fertility such as loss of semen quality or reduced development of ovarian follicles. Also, due to biomagnification, humans and other animals can be targeted by these EDs indirectly, either through the contaminated waters or through the trophic chain.

It is therefore increasingly important to study EDs and to make decisions about them, as they can cause serious damage to the environment and wildlife through contamination of bodies of water, as well as human health. In addition, water is one of the main vehicles for the spread of toxic substances, such as agricultural pesticides. Even communities that are geographically distant from the sites of use of these substances are also affected by them, and it is important to realize that, when contamination occurs in a collection of water bodies, an entire food chain may be compromised.

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