



Revista de Gestão Costeira Integrada -
Journal of Integrated Coastal Zone
Management

E-ISSN: 1646-8872

rgci.editor@gmail.com

Associação Portuguesa dos Recursos
Hídricos

Cotrim, Gabriel; Fahning, Cristiane S.; da Rocha, Gisele O.; Hatje, Vanessa
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Revista de Gestão Costeira Integrada - Journal of Integrated Coastal Zone Management,
vol. 16, núm. 3, septiembre, 2016, pp. 299-326
Associação Portuguesa dos Recursos Hídricos
Lisboa, Portugal

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Endocrine disruptors: strategies for determination and occurrence in marine environments *

Gabriel Cotrim^{a, @}, Cristiane S. Fahning^b, Gisele O. da Rocha^{a,b,c,d}, Vanessa Hatje^{a,b,c,d}

ABSTRACT

Research examining the occurrence of endocrine disruptors (ED) in the marine environment has substantially increased. These contaminants have been observed in several environmental compartments and matrices, and they may cause severe adverse effects in humans and ecosystems. In this study more than 240 papers investigating the analytical developments regarding the analysis on ED in environmental matrices and the occurrence of these compounds were critically evaluated. Modern sample preparation procedures aiming the use of minimal sample manipulation, minimal amount of solvents and energy according to the Green Chemistry principles are widely used. The ED in marine environments occurs in trace concentrations and their quantification still represents a challenge. The effects of these contaminants in marine ecosystems are poorly understood. However, due to their large use, it is predicted that new analytical developments to deal with ED contamination will promote a large increase in the number of scientific publications in the near future. Regulations and mitigation measures for the presence of these contaminants in the environment are still scarce and need to be quickly implemented to reduce potential future adverse effects on ecosystem services of coastal environments.

Keywords: Emerging contaminants; Endocrine disruptors; Contamination; Sample preparation; Environmental analysis

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* Submission: 29 JAN 2016; Peer review: 11 MAR 2016; Revised: 16 JUL 2016; Accepted: 10 AUG 2016; Available on-line: 26 SEP 2016

RESUMO

Pesquisas que examinam a ocorrência de interferentes endócrinos (IE) no ambiente marinho têm aumentado substancialmente. Estes contaminantes podem causar efeitos adversos em seres humanos e nos ecossistemas e têm sido observados em vários compartimentos e matrizes ambientais. Neste estudo, mais de 240 trabalhos que relataram o desenvolvimento analítico de IE em diversas matrizes e a ocorrência destes compostos no ambiente marinho foram criticamente avaliados. Procedimentos de preparo de amostra, visando a mínima manipulação, a mínima quantidade de solventes e energia de acordo com os princípios de Química Verde estão sendo amplamente utilizados. Os IE em ambientes marinhos ocorrem em concentrações traço e sua quantificação ainda representa um grande desafio. Como resultado, os efeitos desses contaminantes em ecossistemas marinhos ainda são mal compreendidos. No entanto, devido ao amplo uso destes compostos é previsto que novos desenvolvimentos analíticos para a determinação de IE irão promover um grande aumento no número de publicações científicas no futuro. Regulações e medidas mitigadoras para a ocorrência destes contaminantes ainda são bastante reduzida e precisam ser rapidamente implementadas para reduzir os futuros potenciais efeitos adversos nos serviços ecossistêmicos dos ecossistemas costeiros.

1. Introduction

The lifestyle adopted by humans in the modern society has favored the occurrence of continuous physical, chemical and biological changes in the environment. The contamination of water bodies due to the presence of domestic and industrial wastewater, water runoff and agricultural activities stand out among the major human impacts on the coastal zones. Thousands of substances (e.g., pharmaceuticals, personal care products, surfactants, nanomaterials, metals, phthalates, and hydrocarbons, among others), which have allegedly subsidized the improvement of the quality of human life and ensured the growth of activities such as aquaculture and agriculture, are produced and released in the environment.

The development of new analytical techniques of separation, identification and quantification of substances (e.g., high performance liquid chromatography (HPLC) coupled to mass spectroscopy, among others) has allowed the identification of a large number of compounds in samples of water, air, sediments and biological tissues so far unknown (Locatelli *et al.*, 2016; Casatta *et al.*, 2015; Emnet *et al.*, 2015; Benjamin *et al.*, 2015; Cai *et al.*, 2012a, 2012b; Bartolomé *et al.* 2010; Richardson & Ternes, 2011; Rubio & Pérez-Bendito, 2009). The sensitivity of many analytical techniques has improved, reducing the limits of detection from parts per million to parts per trillion and, in some cases, to parts per quadrillion (Huerta *et al.*, 2015; Bhandari *et al.*, 2009). As a result, the potential for studying traces of contaminants in the environment, especially in complex matrices, such as seawater, has also increased. The substantial improvement in analytical sensitivity enabled the detection of a series of compounds known, generically, as emerging contaminants (EC). Emerging contaminants can be defined as a class of natural or synthetic chemicals, or any group of microorganisms that are not naturally found in the environment (Richardson & Ternes, 2011; EPA, 1997). In general, the ECs are present

unknown toxicity, large industrial production and they are ubiquitous in the environment (Birch *et al.*, 2015; De la Cruz *et al.*, 2012; Deblonde *et al.*, 2011; Bhandari *et al.*, 2009). ECs are not necessarily new compounds, they are input in environment for several years. However, the identification and quantification of these compounds was only possible after the development of new analytical techniques that allows detection of trace and ultratrace concentrations.

Among the emerging contaminants, a number of compounds have been receiving special attention from the scientific community, due to their potential capacity of interfering with the functioning of the endocrine system of organisms. The literature uses several names for these compounds: xenobiotics, pseudo-estrogens, pseudo-androgens, endocrine disruptors (ED), and interfering endocrines (Lisboa *et al.*, 2013; Menzies *et al.*, 2013; Grassi *et al.*, 2013; Ghiselli & Jardim, 2007; Lathers, 2002; Kardinaal *et al.*, 1997). Many of them are not degraded or broken down by any biochemical and/or natural photochemical pathways and may also undergo bioaccumulation and/or biomagnification (Colin *et al.*, 2016). In this paper, this group of compounds will be referred to as endocrine disruptors.

Several contaminants, both organics and inorganics, have their ecotoxicological profiles and modes of action well determined. As a result decision makers can plan accordingly in order to regulate their use, minimize adverse effects for the provision of ecosystems services or even ban some compounds. The literature has already showed examples of the positive effect of such regulations in contamination levels in the environment. For instance, Sutton *et al.* (2014) observed declines in Polybrominated compounds in sediment and biota of San Francisco Bay. However, for most of the EDs dealt in this manuscript it still is necessary a better knowledge and understanding of the environmental cycles and toxicity in order to subsidize the development of regulations and management practices.

2. Importance and relevance of endocrine disruptors

The United States Environmental Protection Agency (U.S. EPA) defines endocrine disruptors as exogenous agents that interfere with the synthesis, secretion, transport, binding, action or elimination of hormones that are responsible for reproduction, development, behavior and maintenance of body homeostasis (EPA, 1997). Although there are multiple mechanisms of action of endocrine disruptors in biota, the vast majority of the observed disturbances are attributed to the functioning of the gonads, responsible for secondary sexual characteristics, and the development and functioning of sexual organs (Gu *et al.*, 2016; Gavrilescu *et al.*, 2015; Christiansen *et al.*, 2012; Boisen *et al.*, 2005; Lintelmann *et al.*, 2003; Toppari *et al.*, 2001; Paulozzi, 1999).

In humans, EDs may cause serious problems such as precocious puberty (Buttke *et al.*, 2012), testicular (Huyghe *et al.*, 2003), breast (Lee & Choi, 2013; Macon & Fenton, 2013), and prostate cancers (Bedia *et al.*, 2015; Prins, 2008), gynecomastia (irregular breast growing in men) (Vandenberg *et al.*, 2013), tract disorders in the male reproductive system such as cryptorchidism (irregular descent of the testicles from the abdominal cavity) (Main *et al.*, 2010; Toppari *et al.*, 2001), hypospadias (congenital malformation of the urinary meatus) (Thorup *et al.*, 2014; Main *et al.*, 2010; Boisen *et al.*, 2005; Toppari *et al.*, 2001; Paulozzi, 1999) low count and poor quality semen (Paoli *et al.*, 2015; Jouannet *et al.*, 2001). It is estimated that more than 87,000 commercialized chemicals need to be tested in order to determine their potential influence on the endocrine system of humans and biota (EPA, 1997).

It has been known that EDs can be either natural and/or synthetic compounds, originated through domestic and industrial uses (Gravilescu *et al.*, 2015; Nurulnadia *et al.*, 2014; Diamanti-Kandarakis *et al.*, 2009; Pojana *et al.*, 2004). Natural ED compounds of known effect include steroidal hormones such as estrogen, progesterone and testosterone, produced by both humans and animals. In addition, there are also the phytosterols, which are natural substances present in several plants that also possess hormonal activity. In turn, synthetic compounds include artificial hormones (contraceptives or additives used in animal food) as well as the xenosteroids, substances produced for use in the industry, agriculture and in the manufacture of several products (Li *et al.*, 2014; Kinani *et al.*, 2008; Ghiselli & Jardim, 2007; Birkett & Lester, 2003).

The most commonly known or classified as ED xenosteroids are the alkylphenols polyethoxylated (APEOs), organotin compounds, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), phthalates, polybrominated flame retardants (PBFRs), dioxins, furans, pesticides, and pharmaceutical

and personal care products (PPCPs), among others (Richardson & Ternes, 2014; Tan *et al.*, 2007b; Lintelmann *et al.*, 2003). The EDs can be grouped according to their chemical characteristics and utilization (Table 1).

Phytosterols are substances with estrogenic and androgenic activities (Hwang *et al.*, 2006) found in plants such as soybean, wheat, rice, carrots, beans, potatoes, cherries and apples (Richardson & Ternes, 2014; Richardson, 2002). The main representatives of this class of EDs are isoflavones (genistein, daidzein, biochanin A, formononetin, equol, and demetilangolensine, among others), lignans (enterodiol, enterolactone, secoisolariciresinol, and metaresinol, among others), and coumestans (coumestrol) (Clapauch *et al.*, 2002). Although the capacity of the endocrine interference of phytosterols is low, between one and two orders of magnitude smaller than estradiol (Bovee *et al.*, 2004), some studies have reported the presence of these compounds in water bodies at levels that may cause endocrine disruption (Ribeiro *et al.*, 2009; Kuster *et al.*, 2009).

Pesticides belong to a class of EDs with a several representatives. Although the use of various pesticides has been prohibited in different countries, residues of these compounds are still present in the environment, as in the case of DDT and its metabolites. This reflects the high persistence and lipophilic properties of these substances (Garcia-Jares *et al.*, 2009). The main compounds used as pesticides that can behave as EDs are DDT, DDT metabolites (i.e., DDE and DDD), methoxychlor, chlorinated cyclodiene, vinclozolin, linuron and diuron, among others (Mnif *et al.*, 2011; Čeh & Majdič, 2010; Lintelmann *et al.*, 2003). Each of these compounds has distinct effects on the endocrine systems of organisms. For instance, the herbicide diuron is capable of inhibiting the androgens (Thibaut & Porte, 2004) while the DDT metabolites mimic the action of estrogens (Bulayeva & Watson, 2004). However the possibilities and pathways of pesticides may cause disturbance in endocrine systems as well as their endpoints in individuals still is not well understood (Ventura *et al.*, 2016; Monteagudo *et al.*, 2016; Marx-Stoelting *et al.*, 2014).

PAHs are generated in the processes of incomplete combustion or pyrolysis of organic matter (e.g., coal, oil, gas and wood) and traditionally have been used as tracers of burning fuels (Santos *et al.*, 2016; Sun *et al.*, 2013; Da Rocha, *et al.*, 2009) and oil refineries (Bayat *et al.*, 2015; Zrafi-nouira *et al.*, 2010). Antiestrogenic effects of PAHs have been reported in the literature for mollusks from contaminated areas (Gagné *et al.*, 2002). Weiss *et al.* (2009) suggested that the PAHs contribute to the anti-androgenic activity of sediments in rivers.

Another group of EDs that has received attention is the PCBs, which are compounds resulted from the addition

Table 1. Main classes of endocrine disruptors and use.

<i>Group</i>	<i>Main Species</i>	<i>Application and/or source</i>
Estrogen hormones ^{a,b}	Estrone (E1) 17 β -estradiol (E2) Estril (E3) 17 α -ethynylestradiol (EE2)	Natural estrogens (human or animal production) Synthetic estrogen (contraceptives)
Phthalates ^{b,c}	Dimethyl phthalate (DMP), Diethyl phthalate (DEP), Di-n-buthyl phthalate (DnBP), Diisobuthyl phthalate (DiBP), Di(2-ethylhexyl) phthalate (DEHP) Di-n-octyl phthalate (DnOP)	Plasticizers in polymers. Additives in pesticides, paints, cosmetics, floor coverings, ceilings, or insulators in electrical devices, among others
Alkylphenols (APs) ^b	APEO 4-n-nonylphenol (4-n-NP) 4-tert-nonylphenol (4-t-NP) 4-n-octylphenol (4-n-OP) 4-tert-octylphenol (4-t-OP) Bisphenol A (BPA)	Detergents, paints, propellants in pesticides, personal care products, plasticizers, elastomers, polymerization of acrylic and vinyl acetate
Phytosterols (phytoestrogens and fitoandrogens) ^b	Isoflavones (Genistein) Lignans (Metairesinol)	Soybean Linseed and wheat
Pesticides ^b	dichloro-diphenyl-dichloroethane (DDD) dichloro-diphenyl-trichloroethane (DDT) dichloro-diphenyl-dichloroethene (DDE) Methoxychlorine Linuron Diuron	Insecticides. Use banned in most countries Insecticide DDT substitute Herbicides
PAHs ^b	Anthracene Benzo(a)pyrene Phenantrene Fluoranthene Naphthalene Pyrene	Incomplete combustion of organic matter (coal, oil, petroleum, wood) Burning of fossil fuels
PCBs ^{b,d}	Addition of chlorine atoms to phenylbenzene or biphenyl. Several species	Plasticizers, pesticides, disinfectants, capacitor and transformer fluid, among other
PBFRs ^{b,e}	Several species	For Avoiding the easy fire ignition in electrical and electronic equipment
Organotin compounds ^f	Monobutyltin Dibutyltin Tributyltin	Antifouling used on boats, buoys, refrigeration system, dock, etc.; wood preservatives; disinfectant.
Dioxins ^{b,g}	2,3,7,8- tetrachlorodibenzo-p-dioxin	Byproducts of reactions: Synthesis of chlorine, Production of hydrocarbons
Furans ^{b,g}	2,3,7,8-tetrachlorodibenzofuran	Pyrolysis and incomplete combustion of organic material in the presence of chlorine

^aBeausse, 2004; ^bBirkett *et al.*, 2003; ^cGómez-Hens & Aguilar-Caballo, 2003; ^dCarpenter, 2006; ^eEriksson *et al.*, 2001;^fLintelmann *et al.*, 2003; ^gAssunção & Pesquero, 1999.

of chlorine atoms to the biphenyl molecule. PCBs were used as dielectric fluids in large transformers and capacitors, plasticizers, heat fluids, hydraulic lubricants, paints, and adhesives, among other applications (Anezaki & Nakano, 2015; Liu *et al.*, 2015; Pocar *et al.*, 2003). Although many countries have banned the production of PCBs in the 1970s and 1980s, it is believed that about 10^8 kg of PCBs are still spread out in the environment, mainly due to their persistent characteristics (Anezaki & Nakano, 2015; Scheringer *et al.*, 2009; Boyle *et al.*, 1992). There are evidences that PCBs inhibit estrogen activity, effectively increasing the bioavailability of estrogen in the body (Kester *et al.*, 2000) and, therefore, disturbing the functions controlled by this hormone. Together with PCBs, PBFRs are part of the halogenated organic compounds group, which are considered or accepted to be EDs. Although some studies have reported the endocrine disrupting potential of these compounds, there are no restrictions regarding their production and/or use (Richardson & Ternes, 2015; Kabir *et al.*, 2015; Mankidy *et al.*, 2013a; Gerecke *et al.*, 2008; Trachsel, 2008; Darnerud, 2008; Vos *et al.*, 2003; Legle & Brouwer, 2003). Besides those EDs already described, estrogenic hormones, alkylphenols (APs), bisphenol A (BPA) and phthalates are noteworthy for having high capacity of endocrine interference, yet they are of concern due to the large industrial production, and consumption on a global scale. Thus, these groups of substances will be discussed in more detail in this text.

2.1. Estrogenic Hormones

Estrogens are hormones that take part of a larger group of substances, the steroids. Figure 1 illustrates the structure of these substances which have an arrangement derived from the cyclopent[α]phenanthrene molecule (Moss, 1989). Estrogens are liposoluble, and this characteristic allows them to pass through the cell membranes, thus transmitting information by coupling themselves to intracellular receptors (Tata, 2005). Natural estrogens are responsible for female secondary characteristics, for the development of the male reproductive system, for processes associated with growth, metabolism, reproduction, development, besides acting in the maintenance of bones, cardiovascular and central nervous systems (Hampl *et al.*, 2016; Tata, 2005; Shimada *et al.*, 2001).

Estrogens have a tetracyclic structure arranged in a phenol, two cyclohexanes, and a cyclopentane condensed ring. Estrogens structures are differentiated from each other by the functional groups attached to carbons C16 and C17 (Figure 1) (Moss, 1989). Estrone (E1) and estradiol present a carbonyl group and a hydroxyl group, respectively, bonded to the carbon C17 of the tetracyclic structure (Table 2).

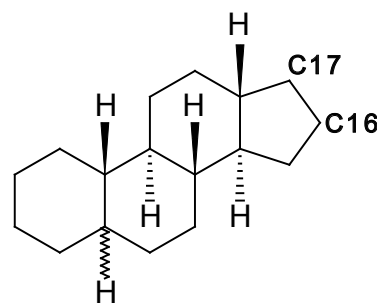


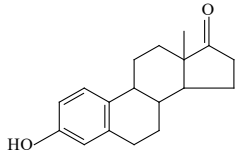
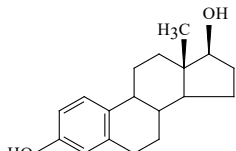
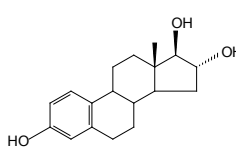
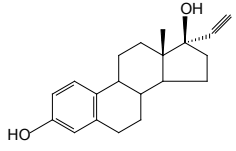
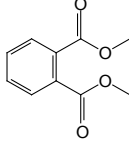
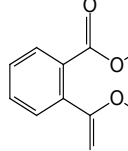
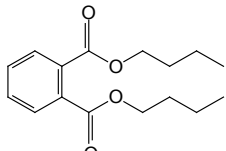
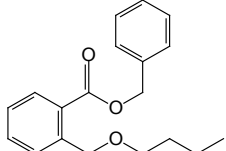
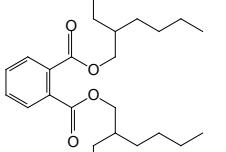
Figure 1. Cyclopent[α]phenanthrene.

The three-dimensional arrangement of the hydroxyl group attached to the C17 in the estradiol originates the 17β -estradiol (E2) or the 17α -estradiol. In turn, estriol (E3) presents two hydroxyls, one is connected to the C16 and the other to the C17; while the 17α -ethynylestradiol (EE2), a synthetic estrogen used in many contraceptives and therapeutic agents, presents an ethynyl group bonded to the C17. All these estrogens have very low vapor pressures, ranging between 2.3×10^{-10} and 6.7×10^{-15} mmHg (Table 2), responsible for the low volatility of these compounds. The partition coefficients of estrogens between octanol and water ($\text{Log } K_{ow}$) are high, ranging between 2.81 and 4.15 (Lu, 2009).

The E1, E2 and E3 are produced mostly by ovaries and are the main natural estrogens. These estrogens, together with the synthetic hormone EE2, have been detected in domestic wastewater and effluents from wastewater treatment plants (WWTP) (Xu *et al.*, 2012; Behera *et al.*, 2011; Quednow & Püttmann, 2008; Tan *et al.*, 2007a; Tan *et al.*, 2007b) that are discharged in superficial water bodies (Lisboa *et al.*, 2013; Noppe *et al.*, 2007). Although most of the estrogen is excreted in their inactive form, the action of bacteria transforms them into biologically active compounds that are capable of producing adverse effects (Zheng *et al.*, 2012; D'Ascenzo *et al.*, 2003; Panter *et al.*, 1999; Belfroid *et al.*, 1999). Many studies have shown that these estrogens, in concentration as low as few ng L^{-1} , may have adverse effects on the reproductive systems of biota and humans (Luzio *et al.*, 2016; Palanza *et al.*, 2016; Salvador *et al.*, 2007; Kuster *et al.*, 2004; Grist *et al.*, 2003). Human exposure to high concentrations of estrogens can cause various disorders such as gynecomastia, libido decrease, impotence, and sperm counting decrease. In addition to direct effects on the reproductive system, these estrogens and/or their metabolites may cause breast, prostate, and/or ovary cancers (Palanza *et al.*, 2016; Frye *et al.*, 2011; Xu *et al.*, 2007; Xu *et al.*, 2005).

The estrogenic hormones are compounds with the highest interference potential in the endocrine system (Ghiselli & Jardim, 2007; Aksglaede *et al.*, 2006; Reis Filho *et al.*, 2006. Laws *et al.*, 2000). Although they have relatively short half-lives, when compared to other

Table 2. Physicochemical properties of steroids and phthalates.

Compound	Molar mass ^a	Solubility ^b	Vapor pressure ^c	Log K _{ow} ^d	Chemical structure
Estrone (E1)	270.4	13	2.3×10^{-10}	3.43	
17 β -estradiol (E2)	272.4	13	2.3×10^{-10}	3.94	
Estriol (E3)	288.4	13	6.7×10^{-15}	2.81	
17 α -ethynylestradiol (EE2)	296.4	4.8	4.5×10^{-11}	4.15	
Dimethyl phthalate (DMP)	194	7,273	0.258	1.41	
Diethyl phthalate (DEP)	222	808	6.95×10^{-2}	2.35	
Di-n-butyl phthalate (DnBP)	278	9.9	5.16×10^{-3}	4.22	
Butylbenzyl phthalate (BBP)	312	0.93	1.27×10^{-3}	5.22	
Di(2-ethylhexyl) phthalate (DEHP)	391	2.09×10^{-3}	3.65×10^{-5}	7.7	

Adapted from Lu, 2009. ^aMolar mass (g mol⁻¹); ^bSolubility in water (mg L⁻¹ at 20 °C); ^cVapor pressure (mmHg); ^d Octanol / water partition coefficient

organic compounds (e.g. pesticides, PCBs and PAHs), estrogens are introduced into the environment in a continuous and large scale way (Johnson & Williams, 2004) and thus becoming a pseudopersistent pollutant. Therefore, estrogens are potential sources of a large number of adverse effects in the environment. For instance, fish cultivated in waters contaminated by estrogenic hormones have shown altered hormone levels and anatomical changes in the reproduction organs (Luzio *et al.*, 2016; Volkova *et al.*, 2015; Dziewieczynski & Buckman, 2013; Larsson & Förlin, 2002). It was also observed a total reversion of male to female sex in medaka fish (*Oryzias latipes*), when exposed to natural estrogens in concentration of 140 ng L⁻¹ (Hirai *et al.*, 2006).

2.2. Alkylphenols and Bisphenol A

Alkylphenols (APs) and Bisphenol A (BPA) are the endocrine disrupting substances most intensively studied. The APs are substances formed by a phenol group attached to a carbon chain (Table 3). APs, including nonylphenols (NPs) and octylphenols (OPs) are used directly in the production of a large range of products or can be originated from the degradation of APEO (Funakoshi & Kasuya, 2009). APEOs and APs belong to a class of non-ionic surfactants used in the production of phenolic resins, detergents, adhesives, paper, plastic additives, acrylic, vinyl acetate, emulsifiers, wetting agents, spermicides, among other applications (Hotta *et al.*, 2010; David *et al.*, 2009; Isidori *et al.*, 2006; Tsuda *et al.*, 2000).

NPs and OPs are names given to a large number of isomer compounds with structural formulas C₁₅H₂₄O and C₁₄H₂₂O, respectively. In the context of endocrine disruptors, the most studied NPs and OPs are the 4-n-nonylphenol (4-n-NP), 4-tert-nonylphenol (4-t-NP), 4-n-octylphenol (4-n-OP), and the 4-tert-octyl-phenol (4-t-OP) (Koniecko *et al.*, 2014; Quednow & Püttmann, 2008; Loos *et al.*, 2008; Tsuda *et al.*, 2000).

The effects of APs in humans are still unknown. However, their endocrine disrupting potential has already been established in laboratory experiments by the high multiplication of breast cancer cells, which are sensitive to estrogens (Kabir *et al.*, 2015; Soto *et al.*, 1995; Soto *et al.*, 1991). Indeed, manipulative experiments with mice have shown an increase in the endometrial mitotic index when single doses of 20 and 50 mg of NP were administered (Soto *et al.*, 1991). Kurihara *et al.*, (2007) showed that NPs present in sediments of Tokyo Bay induced the production of vitellogenin (VTG) in male and young fish.

Oehlmann *et al.* (2000) described the enlargement of accessory sex glands, the stimulation of oocytes in females and a reduction in length of penis and prostate in males of the gastropod *Lapillus nucella* exposed to

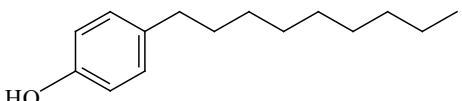
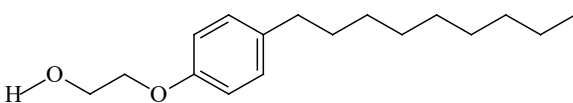
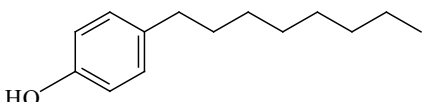
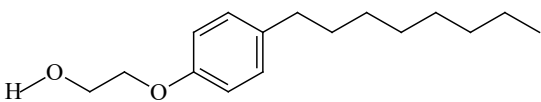
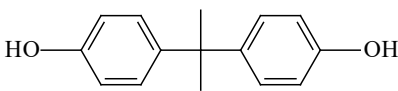
OP. The main sources of APs for the environment are the domestic, industrial and WWTP effluents (Bergé *et al.*, 2014; Richardson & Ternes, 2014; Solé *et al.*, 2000; EPA, 1997). APs can also be released into the marine environment due to fossil fuel activities, such as the release of water produced in oil rigs (Boitsov *et al.*, 2007).

In WWTP and in the environment, APEOs may only be partially degraded microbiologically, which may generate shorter chain APs (e.g., NPs, OPs and mono-, di-, and tri- etoxylated APs) that are more persistent (David *et al.*, 2009; Zhang *et al.*, 2008; Ying *et al.*, 2002a; Renner *et al.*, 1997). In general, compounds originated from the degradation of APEOs present higher estrogenic activity, are more insoluble in water and have lower coefficients of octanol/water (K_{ow}) (Table 3). As a result, they are more lipophilic and susceptible to accumulation in fauna and humans (Gu *et al.*, 2016; Casatta *et al.*, 2015; Nurulnadia *et al.*, 2014; Bouzas *et al.*, 2011; Basheer *et al.*, 2004; Ying *et al.*, 2002a).

Bisphenol is a generic name given to a group of hydroxylated diphenylalkanes, being the bisphenol A (BPA) the main substance of this group (Perez *et al.*, 1998). BPA is used in various applications, such as the production of polymers (e.g., polyvinyl chloride - PVC), epoxy resins, polyester resins, polycarbonates, fungicides, antioxidants, flame retardants, and resin for dental filling (Frye *et al.*, 2011; Yi *et al.*, 2010; Lintelmann *et al.*, 2003). Additionally, BPA is used in plastic films and packaging, routinely used into food packages. This is a fact of concern given the known ability of BPA to migrate from the packaging to the food (Gu *et al.*, 2016; Casatta *et al.*, 2015; Emnet *et al.*, 2014; Nurulnadia *et al.*, 2014; Fasano *et al.*, 2012; Bouzas *et al.*, 2011; Basheer *et al.*, 2004). In some countries, such as Canada, USA, France, and more recently in Brazil, BPA has been banned from use in children utensils and toys (ANVISA, RDC 41/2011; Lintelmann *et al.*, 2003).

The estrogenic potency of BPA is 10⁻³ to 10⁻⁵ times smaller than that of estradiol (Lintelmann *et al.*, 2003; Milligan *et al.*, 1998). However, its estrogenic capacity can be amplified due to its wide release and large persistence in the environment. The first evidence of estrogenic activity of BPA was reported in the late 1930s (Dodds & Lawson, 1938; Dodds & Lawson, 1936). Overtime, various toxicological studies confirmed the estrogenic behavior of bisphenol A (Xu *et al.*, 2015; Mandich *et al.*, 2007). Vandenberg *et al.* (2010) have examined 80 biomonitoring studies of BPA in tissues and fluids of humans, focusing on individuals exposed to BPA through the environment, or by non-occupational exposure. Levels of BPA between 2 to 150 ng L⁻¹ were detected in children, teenagers and adults blood and urine samples. Those results suggest that this substance is possibly causing adverse effects in human health.

Table 3. Physicochemical properties of Alkylphenols, alkylphenols polyethoxylated e Bisphenol A.

Compound	Molar mass ^a	Solubility ^b	Log K _{ow} ^c	Chemical structure
4-n-Nonylphenol (4-n-NP)	220	5.43	4.48	
4-t-Nonylphenol (4-t-NP)	220	-	-	
Nonylphenol monoethoxylated	264	3.02	4.17	
Nonylphenol diethoxylated	308	3.38	4.21	
Nonylphenol polyethoxylated	-	-	-	
4-n-Octylphenol (4-n-OP)	206	12.6	4.12	
4-t-Octylphenol (4-t-OP)	206	-	-	
Octylphenol monoethoxylated	250	8.00	4.10	
Octylphenol diethoxylated	294	13.2	4.00	
Octylphenol polyethoxylated	-	-	-	
Bisphenol A	228	120	3.30	

Adapted from Ying *et al.*, 2002a. ^amole mass (g mol⁻¹); ^bSolubility in water (mg L⁻¹ at 20 ° C); ^cCoefficient of octanol/water partition.

Experimental tests with biota showed that the action of BPA in mice may be associated to changes in the development of the mammary gland tissues (Lee *et al.*, 2015; Vandenberg *et al.*, 2007; Muñoz-de-Toro *et al.*, 2005; Markey *et al.*, 2001), behavioral disorders and premature sexual maturation (Talsness *et al.*, 2009). Ortiz-Zarragoitia & Cajaraville (2005) reported the reabsorption of gametes in both genders of mussel

Mytilus edulis, also as a result of exposure to BPA. Biological effects such as the increase synthesis of VTG, the inhibition of gonad growth, the increase of liver metabolism and the bioaccumulation of steroidal and phenolic EDs were assessed in high-back crucian carp (*Carassius auratus*) exposed to WWTP effluents (Liu *et al.*, 2012).

The presence of BPA as well as APs in the environment are caused by leaching processes of materials with them in the constitution (Wang & Schnute, 2010). These compounds have been detected in several environmental compartments such as air, water, soil, sediment, and biota (Salgueiro-González *et al.*, 2015; Nurulnadia *et al.*, 2014; Jakimska *et al.*, 2013; Maggioni *et al.*, 2013; Bach *et al.*, 2012). Due to its higher water solubility when compared to AP and phthalates, and its relatively high $\log K_{ow}$ value (Table 3) it may be predicted that BPA has a wide distribution in the aquatic environment (Sun *et al.*, 2012; Cunha *et al.*, 2012). This hypothesis, however, needs to be further investigated.

2.3. Phthalates

Phthalates or phthalic acid esters are synthetic compounds that have been used in industrial activities since the 1930s. Their application includes plasticizers in polymers and additives for various products such as insecticides, paints, packaging, cosmetics, floor coverings, ceilings, clothing, and/or electrical insulating compounds additives (Net *et al.*, 2015; Mankidy *et al.*, 2013b; Li *et al.*, 2008; Horn *et al.*, 2004; Sumpter, 1998). The most commonly used phthalates are dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), diisobutyl phthalate (DiBP), di(2-ethylhexyl) phthalate (DEHP) and butylbenzyl phthalate (BBP). A quarter of the whole world production of phthalate is represented by DEHPs, which is employed in the production of PVC (Net *et al.*, 2015; Dargnat *et al.*, 2009).

Although Brazil does not prohibit the use of phthalates in products such as cosmetics and food packaging, the World Health Organization (WHO) warns about the possible health problems caused by these compounds (WHO, 2012). Phthalates, especially DnBP, BBP and DEHP, have high values of $\log K_{ow}$ (Table 2), characteristic of lipophilic compounds, which allows the accumulation of these compounds in the organic matter present in soils and sediments (Benjamin *et al.*, 2015; Net *et al.*, 2015; Gavala *et al.*, 2003).

The interfering nature of phthalates has been reported in a number of studies both *in vivo* and *in vitro* (Benjamin *et al.*, 2015; Romani *et al.*, 2014; Mankidy *et al.*, 2013; Hashimoto *et al.*, 2003; Picard *et al.*, 2001; Körner *et al.*, 1999). Phthalates became the subject of much concern once they are suspected to cause premature puberty (Tsai *et al.*, 2016; Zhang *et al.*, 2015; Fisher & Eugter, 2014; Colón *et al.*, 2000).

In humans, phthalates can affect not only the endocrine and reproductive systems, but also may cause respiratory and dermatological problems (Pérez-Feás *et al.*, 2011). In rodents, the exposure of males in the intrauterine period to DnBP, BBP and DEHP results in a series of reproductive abnormalities, such as damage to testicles (Foster, 2006;

Gray *et al.*, 2006; Foster *et al.*, 2001). Other studies have shown carcinogenic effects and feminization in mice and fish even at low concentrations of phthalates (Benjamin *et al.*, 2015; Valton *et al.*, 2014; Martino-Andrade & Chahoud, 2010; Larsen *et al.*, 2002).

In the environment, phthalates can suffer natural degradation (Benjamin *et al.*, 2015; Liang *et al.*, 2008). According to ecotoxicological models for mammals, fish and arthropods the degradation products of DEHP, such as 2-ethylhexanol and 2-ethylhexanal, present more toxicity than the original compound (Benjamin *et al.*, 2015; Horn *et al.*, 2004; Nalli *et al.*, 2002). Therefore, environmental studies should take into account the presence and toxicity of both the original compounds and their metabolites.

The main routes of intake of phthalates in humans are inhalation associated with atmospheric particulate matter, direct contact with materials composed with phthalates and the ingestion of contaminated food (Net *et al.*, 2015; Gärtner *et al.*, 2009; Rudel *et al.*, 2003). The addition of phthalates to food is not common. However, the food contact to its package or even with plastic utensils used during food processing may generate food contamination. The phthalates, which are used as plasticizers, are not chemically bound to the polymer matrix, so they can be quickly released to the environment during their production, use and disposal (Net *et al.*, 2015; Sax, 2010; Heudorf *et al.*, 2007; Fromme *et al.*, 2002). Considering the relatively high vapor pressures, when compared to other organic compounds (Table 2), phthalates can be volatilized into the atmosphere and be transferred to other environment compartments during their life cycle (Net *et al.*, 2015; Xie *et al.*, 2007).

3. Analytical techniques employed in the determination of EDs in the environment

Techniques for sample preparation

The development of new procedures for sample preparation should aim for simplification, automation, economy, minimal sample manipulation, minimal use of solvents and energy, according to the principles of the Green Chemistry (Huerta *et al.*, 2015; Yan & Wang, 2013; Farré *et al.*, 2010).

The determination of organic contaminants such as EDs in environmental samples is always challenging, not only due to the very low concentrations of analytes but also due to the complexity and diversity of sample matrices. Matrix effects may have negative impacts to important analytical parameters (e.g., limit of detection (LOD), limit of quantification (LOQ), linearity, accuracy and precision), making the direct analysis of environmental samples very difficult (Farré *et al.*, 2012; Wu *et al.*, 2010). Therefore, the pretreatment of environmental samples,

especially for matrices such as coastal and ocean waters that have high salinities, is a real necessity. This step, nevertheless, usually takes up to 70-90 % of the analysis time (Zuloaga *et al.*, 2012).

Sample preparation for the determination and quantification of organic compounds are based on three main steps: extraction, clean up and pre-concentration. The extraction step is a procedure performed to separate the analytes from the sample matrix. In the clean up step the possible interferences in the analysis, which difficult to identify and quantify the compounds of interest, are removed. EDs in environmental samples are usually present at concentration levels below the LOD of most analytical methods. Consequently, the pre-concentration it is a crucial step to improve detectability and to meet LOD and LOQ of analytical methods.

Sample preparation techniques are specific for each sample type. Solid phase extraction (SPE), for instance, has been the preferred technique in studies of EDs in liquid samples (Anumol e Snyder, 2015; Melo e Brito, 2014; Richardson & Ternes, 2014; Lisboa *et al.*, 2013; Zhang *et al.*, 2012; Richardson, 2012; Saravanabhavan *et al.*, 2009; Fatoki & Noma, 2001). The SPE technique applied to aqueous samples has the advantage of aggregating three steps, i.e., extraction, clean up and preconcentration, in a single stage. In addition, SPE offers a wide variety of solid phases for extraction, resulting in different types of interactions with the analytes and, then, wide applicability. Another advantage of SPE is the possibility of automation, which facilitates its use in environmental studies when it is necessary to process a large number of samples. However, SPE has limitations, such as the blocking of the extraction phase pores by the matrix components, several operational steps, and analytical variations among extraction cartridges (Richardson & Ternes, 2014; Queiroz & Lanças, 2005; Lisboa *et al.*, 2013). Even with these limitations, the SPE has been the extraction procedure most used in EDs studies. Shan *et al.* (2014) analyzed BPA, 4-n-OP and 4-n-NP in tap and bottled water using SPE C18 with minimum detectable concentrations of 0.75-1.0 ng L⁻¹ and the recoveries ranged from 87.0 % to 106.9%. Zhang *et al.* (2012) used C18 as stationary phase in SPE and found limits of determination for OP, NP, E1, E2, E3, EE2 and BPA in wastewater below 0.8 ng L⁻¹, with recoveries higher than 80%. Ribeiro *et al.* (2009) investigated the presence of estradiol, estrogen, 17 α -ethinylestradiol, bisphenol A, 4-octylphenol, 4-nonylphenol in estuarine waters, using Oasis HLB cartridges and found BPA concentrations up to 800 ng L⁻¹.

In the case of solid samples, such as suspended particulate matter, sediment and biota, the most used sample preparation procedures are microwave assisted extraction (MAE) (Vega-Morales *et al.*, 2013; Liu *et al.*, 2012; Dévier *et al.*, 2010), ultrasound assisted

extraction (UAE) (Huerta *et al.*, 2015; Yu *et al.*, 2011; Sánchez-Avila *et al.*, 2011) and pressurized liquid extraction (PLE) (Salgueiro-Gonzales *et al.*, 2014; Ma *et al.*, 2013; Jakimska *et al.*, 2013). They have been the main alternatives to replace the extractions traditionally performed by Soxhlet (Bossio *et al.*, 2008; Wang *et al.*, 2007). Both soxhlet and liquid liquid extraction (LLE) extractions use large amounts of solvents, generate a large amount of organic residues, are time consuming and also difficult to automate. These factors decrease their analytical speed, and make them unattractive for the preparation of a large number of samples, as required in monitoring programs. Due to the large complexity of the solid matrices, such as sediment, soil or animal tissues, it is necessary to perform clean up steps. These procedures are intended to minimize or eliminate the impurities that may cause equipment damage or even interfere with the determination. Additionally, after their first step extraction, those solid sample extracts obtained by MAE, UAE and PLE are further cleaned up using mainly the SPE technique. The main strategy used to perform the clean up in solid samples is the SPE with C18 and/or florisil cartridges (Zhang *et al.*, 2012; Arditoglou & Voutsas, 2008a; Braga *et al.*, 2005).

Yu *et al.* (2011) have used the UAE for the extraction of hormones, BPA and personal care products and have quantified them by ultra high performance liquid chromatography coupled with tandem mass spectrometry. The analytes were extracted for 15 minutes with a mixture of acetonitrile/water, centrifuged and cleaned up with C18 cartridges. The method was applied to sludge and sediment samples with recoveries ranging between 63 % and 119 % and LOQs between 0.1 and 3 ng g⁻¹, for the sludge samples, and from 0.02 to 0.5 ng g⁻¹, for sediments. Matějčíček (2011) has developed a method for extraction of estrogens in sediments based on MAE. The samples were extracted with a mixture of methanol/water for 10 minutes, filtered and determined by HPLC. Recoveries ranged 99-110 % and limits of detection were 90 ng g⁻¹ (E2), 180 ng g⁻¹ (E1), and 250 ng g⁻¹ (EE2). Ma *et al.* (2013) have optimized a method on GC-MS combined with PLE for the determination of six phthalates in soil samples. The LOQs of the proposed method ranged from 0.02 to 0.29 μ g g⁻¹ and recoveries varied between 90 and 110%.

The LOD and recoveries reported in the literature for MAE, PLE and UAE are very variable depending on the sample size, solvent volumes and equipments used. However, these techniques offer several benefits compared to traditional Soxhlet technique, for instance relatively fast extraction, reduced solvent consumption, and a smaller amount of sample handling.

Methods for ED analysis

The HPLC and gas chromatography (GC) are the most commonly analytical techniques used for the determination of persistent organic pollutants (POP), EDs, and ECs in environmental samples. GC and liquid chromatography (LC) are powerful separation techniques and should be combined with highly sensitivity detectors for enabling the analytes determination. EDs are analyzed mainly by liquid chromatography with ultraviolet, fluorescence, and/or mass spectrometry detectors or by GC with mass spectrometry detector (Huerta *et al.*, 2016; Birch *et al.*, 2015; Emnet *et al.*, 2015; Zhang *et al.*, 2014; Selvaraj *et al.*, 2014; Melo & Brito, 2014; Lisboa *et al.*, 2013; Villar-Navarro *et al.*, 2013; Ribeiro *et al.*, 2009; Bossio *et al.*, 2008; Xie *et al.*, 2007; Fatoki & Noma, 2001; Khim *et al.*, 1999). The coupling of a chromatograph with mass spectrometer combines the advantages of the chromatography technique (which are high selectivity and separation efficiency) with the advantages of mass spectrometry (*e.g.* structural information and high selectivity) (Vekey, 2001).

GC is a relatively inexpensive, rapid and reproducible technique for a large number of compounds in environmental samples. The GC presents high resolution and the possibility to be coupled to selective and sensitive detectors such as mass spectrometry (MS) and electron capture detector (ECD), among other possibilities. However, GC is a technique that mainly requires analytes to be volatile or semi-volatile, thermally stable and non-polar in order to facilitate the maximum number of successive interactions between the analyte and the stationary phase, reducing the height and increasing the number of theoretical plates (H and N , respectively). Although polar-bonded phase columns are commercially available, in general, studies mostly use DB-1 (100% polysiloxane) or DB-5 (95% polysiloxane and 5% phenyl) columns since they present higher robustness and better reproducibility and repeatability. For the analyses of PAHs, several pesticides, phthalates and PCBs, among others, the GC can be used without the need of analyte modification. However, the determination of hormones, antibiotics and other drugs, APs and bisphenol A, among other EDs by GC requires the use of a derivatization step (Farajzadeh *et al.*, 2014; Wu *et al.*, 2010) in order to prevent those analyte adsorption and decomposition in the column or in the injector, resulting in non-reproducible peak areas or heights and shapes. Moreover, the purpose of derivatization is also the improvement of LOD and selectivity (Farajzadeh *et al.*, 2014). Derivatization is a transformation the chemical compound into a specific product with characteristics with features that allow its determination.

On the other hand, a growing number of studies has been done using LC, coupled to diode array detectors

(DAD), with fluorescence detectors (FLD) and/or of mass spectrometer detectors (Huerta *et al.*, 2015; Torres *et al.*, 2015; Valdés *et al.*, 2015; Anumol e Snyder, 2015; Salgueiro-Gonzales *et al.*, 2014; Melo e Brito, 2014; Ammann *et al.*, 2014; Lisboa *et al.*, 2013; Zhang *et al.*, 2012; Jardim *et al.*, 2012; Matějček, 2011; Labadie & Hill, 2007; Ferguson *et al.*, 2000; Khim *et al.*, 1999). A good advantage of the liquid chromatography is that derivatization is mostly unnecessary. In this way, a relatively complicated and time-consuming derivatization procedure, which may lead to an underestimation of ED concentrations and possibly contamination of samples, is then eliminated. Another interesting LC advantage is its applicability for the determination of polar organic pollutants, thermolabile substances and/or those easily decomposed, and, hence cannot be analyzable by GC systems.

The best technique (GC or LC) and the best detector (DAD, FLD, flame ionization (FID), ECD or MS) for the determination of EDs in environmental samples will depend on the study goals, the type of matrix to be studied, and the physicochemical characteristics of the analytes. It also should be taken into account the following parameters: sensitivity, number of samples, availability of instrumentation, costs and the analyst skills. Liquid and gas chromatography are complementary techniques, and both have interesting innovations in order to achieve LOD in the range of few ng L⁻¹.

The recent advances in LC, GC, types of columns, detectors (especially for mass spectrometers), the interface chromatograph-detector and their speed of data acquisition have been providing significant improvements in the separation of complex samples in short analyses, with little use of solvent and good selectivity and sensitivity. With this, the current and future trend is to find EDs and ECs at even lower concentrations levels in an increasing number of matrices and places around the world. It is also expected that studies are likely to switch focus, *i.e.*, from descriptive studies of EDs occurrence in several environmental compartments towards processes studies. These changes will subsidize a better understanding in the processes controlling transformations, transport, fate and interactions between environmental compartments. Ecological, (eco)toxicological and human health risk assessments will contribute even further for the evaluation of behavior and possible adverse effects of ED inputs into the ecosystems.

4. Occurrence of EDs in marine environment

The origins of EDs in the aquatic environment are highly variable and are often attributed to human activity. In general, coastal environments, such as estuaries, bays and mangroves, serve as major receptors of domestic, industrial, hospital, agricultural, and aquaculture

effluents. Submarine outfalls, port and ship activities, surface runoffs are also important sources of EDs. The relative inefficiency of conventional WWTP in the complete removal of EDs makes them one of the most important sources of these compounds to water bodies (Deblonde *et al.* 2011; Pal *et al.*, 2010; Santos *et al.*, 2010; Kuster *et al.*, 2009).

Once in the environment, EDs may undertake different pathways: (i) distribution between environmental compartments, such as water, air, soil, sediment, suspended particulate matter and biota, (ii) degradation and subsequent transport and distribution of their metabolites in the environment, (iii) bioaccumulation and/or biomagnification (Lintelmann, 2003).

The presence, behavior, ecotoxicity and the interfering effects of EDs have been reported for riverine environments (Gu *et al.*, 2016; Esteban *et al.*, 2016; Kabir *et al.*, 2015; Li *et al.*, 2014; Fu *et al.*, 2007; Fatoki & Noma, 2001,) while the effects and fate of EDs in the marine environments is still unknown. Coastal regions, in special estuaries, are dilution zones, where river water mixes with marine waters. In general, coastal waters have lower levels of contaminants than freshwaters, either due to distance from sources or to the occurrence of attenuation processes (i.e., dilution, sorption, precipitation and photooxidation). Tables 4, 5 and 6 shows a review of the occurrence of EDs studies in coastal environments, which will be discussed below.

Among the EDs discussed here, APs and BPA are the most studied EDs in marine environments. As previously discussed, APEOs, their degradation products (e.g., NPs and OPs), and BPA are synthetic and their presence in the environment is a result of human activity. Industrial and domestic effluents, WWTPs (effluents and sludge) as well as the application of pesticides are the main sources of APs, APEOs and BPA to the marine environment (Kabir *et al.*, 2015; Gravilescu *et al.*, 2015; Quednow & Püttmann, 2008; Soares *et al.*, 2008; Ying *et al.*, 2002a).

The high partition coefficients of NP, OP and BPA, according to $\log K_{ow}$ values of 4.48, 4.12, and 3.30, respectively, suggest that these compounds, when entering the aquatic environment they are sorbed in suspended particulate matter and sediments.

NP concentrations in saline waters (Table 4) range from 0.002 ng L⁻¹, in the sea of Japan (Kannan *et al.*, 1998), to 4100 ng L⁻¹, in the coast of Spain (Petrovic *et al.*, 2002). In turn, OP concentrations in water ranged from 0.013 ng L⁻¹, in the North Sea (Xie *et al.*, 2006), to 800 ng L⁻¹, in Singapore (Basheer *et al.*, 2004). The concentrations of NP are up to an order of magnitude above the concentrations of OP, probably due to the highest use of polyethoxylated nonylphenol (Isobe *et al.*, 2001). In general, the most contaminated areas are estuaries and coastal regions under the influence of industrial and domestic effluents and WWTP. In the

ocean, concentrations decrease abruptly with distance from the coast. In the North Sea waters, however, the concentrations of OP (0.013 to 3 ng L⁻¹) and NP (0.09 to 1.40 ng L⁻¹) increased with the distance from the coast (Xie *et al.*, 2006). The authors have suggested that atmospheric deposition of OP and NP, from the burning of aircraft fuels, was the main source.

In general, there is a negative correlation between the concentrations of OP and NP with salinity. This relationship is primarily due to dilution (physical mixing processes) with distance from the source. Studies also showed the influence of salinity on the distribution of AP and APEO (Li *et al.*, 2005; Ferguson *et al.*, 2001). Nevertheless, according to these studies the increase of salinity favors the removal and degradation processes of AP and PEA in the water column. This is the result of the salting out. This process results from the decrease in the solubility of organic compounds in water due to the effect of ionic strength on their activity coefficients but also represents these substances are going to be preferentially absorbed in environmental matrices with less polar nature as well as higher content of organic matter, such as SPM, sediments and biota. Furthermore, as a result of the reduced solubility, and high affinity for organic matter, it is expected that these compounds participate in processes of aggregation, flocculation and and the fate is usually the accumulation in sediments.

In sediments, concentrations of NPs (Table 5) ranged from 0.01 ng g⁻¹, in Morro Bay, California (Diehl *et al.*, 2012) to 32000 ng g⁻¹, in Auckland, New Zealand (Stewart *et al.*, 2014), while the concentrations of OPs ranged from 0.01 ng g⁻¹, in the estuary Urdaibai in Spain (Puy-Azurmendi *et al.*, 2010), to 179 ng g⁻¹, in Masan Bay, South Korea (Khim *et al.*, 1999). Similarly to the processes that occur in the water column, the concentration of APs in sediments decreases with increase distance from the coast, due to dilution processes.

The presence of organic matter is the main factor influencing on the accumulation of APs in sediments, mainly due to lipophilic characteristics of these compounds. Jonkers *et al.* (2003), found high correlations between organic carbon and concentrations of NP in sediments from Scheldt and Rhine estuaries. The accumulation and persistency of AP in estuarine sediments (Shang *et al.*, 1999) suggests that benthic macrofauna may be subject to long term exposition to these contaminants, potentially causing chronic effects in biota. The presence of AP in marine organisms (e.g. fish, oysters, squid, mussels, prawns, etc.) has been reported in several regions around the world (e.g., USA, Italy, Taiwan, Greece, Singapore and Japan) (Colin *et al.*, 2016; Casatta *et al.*, 2015; Emnet *et al.*, 2015; Lee *et al.*, 2015; Arditoglou & Voutsas, 2012; Bouzas *et al.*, 2011; Bartolomé *et al.*, 2010; Wang *et al.*, 2010; Kumar *et al.*, 2008; Ferrara *et al.*, 2008; Isobe *et al.*, 2007; Pojana

Table 4. Endocrine disruptors (BPA, AP and estrogens) in seawater (ng L⁻¹) around the world.

Site	BPA	E1	E2	E3	EE2	OP	NP
Todos os Santos Bay, Brazil ^a	<LOD-48.2	<LOD	<LOD-18.2	<LOD-37.9	<LOD	<LOD-134	<LOD
Morro Bay, United States ^b	-	-	-	-	-	-	100-900
La Coruña Beach, Spain ^c	35	-	-	-	-	175	70-199
Biscay Bay, Spain ^d	60-130	-	-	-	-	50-100	1110-1460
Southeast Coast of California, United States ^e	-	-	-	-	-	<LOD-42	<LOD-230
Thermaikos Gulf, Greece ^f	10.6-52.3	<LOD	<LOD	<LOD	<LOD	1.7-18.2	22-201
Northeast Coast, Spain ^g	7.1-35	-	-	-	-	3.8-39	29-712
Aveiro Coast, Portugal ^h	2.6-13	<LOD-0.5	<LOD-1.1	-	<LOD	-	15-98
Mondego Estuary, Portugal ⁱ	178-589	<LOD	<LOD	-	<LOD	<LOD	-
Halifax and St. John Port, Canada ^j	-	1.4-7.5	1.8	-	<LOD	-	-
Thessaloniki Coast, Greece ^k	25-59	-	-	-	-	8-29	181-915
Laguna Venice, Italy ^l	3.4-145	3.2-6.7	3.0-175	-	4.6-28	-	4.0-211
Scheldt Estuary, the Netherlands ^m	-	0.37-10	<LOD	<LOD	<LOD	-	-
Suruga Bay, Japan ⁿ	3.6-1070	<LOD-9.2	<LOD	-	<LOD	<LOD	28.2-276
Acushnet Estuary in Buzzards Bay, United States ^o	-	0.78-1.2	0.56-0.83	-	3.01-4.67	-	-
North Sea, German Creek ^p	-	-	-	-	-	0.013-3	0.09-1.4
North Sea ^q	-	-	-	-	-	0.013-0.3	0.09-1.4
Taiwan Coast ^r	-	-	-	-	-	61-66	290-370
Baltic Sea, German ^s	0.1-5.7	0.13-0.54	<LOD	<LOD	1.6-17.9	0.1-1.1	1.3-7.5
Singapore coast ^t	2-2470	-	-	-	-	10-800	290-370
Rhine Estuary, the Netherlands ^u	-	-	-	-	-	-	31-147
Scheldt Estuary, the Netherlands ^u	-	-	-	-	-	-	35-934
Coast of Spain, Mediterranean and Atlantic ^v	-	-	-	-	-	300	300-4100
North Sea, German Creek ^w	1.6-6	-	-	-	-	0.02-1.6	0.8-63
Jamaica Bay ^x	-	-	-	-	-	1.56-8.3	77.4-416
Jamaica Bay ^y	-	-	-	-	-	3.3	201
Japan Sea ^z	-	-	-	-	-	-	0.002-0.093
Pearl River Delta and coastal ^{aa}	10-227	<LOD-3,1	-	-	<LOD-1,56	-	11-234
Cape D'Aguilar Marine Reserve, Hong Kong ^{ab}	14,1-206,5	-	-	-	-	-	91.7- 473.9
Gulf of Gdansk, Southern Baltic ^{ac}	<LOD-713.9	-	-	-	-	<LOD - 834.8	<LOD-3659.6
Yangtze River Estuary, China ^{ad}	0.98-43.8	<LOD-1.43	<LOD	-	<LOD-0.11	-	-

^aLisboa *et al.*, 2013; ^bDiehl *et al.*, 2012; ^cSalgueiro-González *et al.*, 2012; ^dde los Ríos *et al.*, 2012; ^eVidal-Dorsch *et al.*, 2012; ^fArditsoglou & Voutsas, 2012; ^gSánchez-Avila *et al.*, 2011; ^hJonkers *et al.*, 2010; ⁱRibeiro *et al.*, 2009; ^jSaravanabhavan *et al.*, 2009; ^kArditsoglou & Voutsas, 2008b; ^lPojana *et al.*, 2007; ^mNoppe *et al.*, 2007; ⁿHashimoto *et al.*, 2007; ^oZuo *et al.*, 2006; ^pXie *et al.*, 2006; ^qEbinghaus & Xie, 2006; ^rCheng *et al.*, 2006; ^sBeck *et al.*, 2005; ^tBasheer *et al.*, 2004; ^uJonkers *et al.*, 2003; ^vPetrovic *et al.*, 2002; ^wHeemken *et al.*, 2001; ^xFerguson *et al.*, 2001; ^yFerguson *et al.*, 2000; ^zKannan *et al.*, 1998; ^{aa}Xu *et al.*, 2014; ^{ab}Xu *et al.*, 2015; ^{ac}Staniszewska *et al.*, 2015; ^{ad}Shi *et al.*, 2014.

Table 5. Endocrine disruptors (BPA, AP and estrogens) in marine sediments (ng g⁻¹).

Site	BPA	E1	E2	E3	EE2	OP	NP
Abra and Urdaibai Estuary, Spain ^a	<LOD-0.04	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD-0.2
Morro Bay, United States ^b	-	-	-	-	-	-	0.01-157
Biscay Bay, Santander Coast, Spain ^c	4-59	-	-	-	-	9-14	150-210
Thermaikos Golf, Greece ^d	7.2-39	<LOD	<LOD	<LOD	<LOD	6.0-25	223-2695
Northeast Coast, Spain ^e	-	-	-	-	-	38-39	79-521
South-central Coast, Chile ^f	-	0.06-4.61	0.06-16.81	0.01-53.21	4.18-48.14	-	-
Urdaibai Estuary, Spain ^g	0.01-43	<LOD	<LOD	<LOD	<LOD	0.01-0.03	154-264
Northeast Coast, China ^h	-	-	-	-	-	-	8.8-1000
Yangtze Estuary, China ⁱ	0.72-13.2	-	-	-	-	-	1.56-35.8
Xiamen Bay, China ^j	1.7-121.9	1.1-7.4	1.0-2.4	<LOD	0.9-2.2	1.4-24.0	12.9-1160.0
Thessaloniki, Greece ^k	17	<LOD	<LOD	<LOD	<LOD	8	266
Masan Bay, Japan ^l	-	-	-	-	-	-	92-557
Savannah Estuary, United States ^m	-	-	-	-	-	0.86-6.9	4.1-18
Laguna Venice, Italy ⁿ	3.4-145	<LOD	<LOD	-	12-41	-	47-192
Tóquio Bay, Japan ^o	-	0.05-3.6	<LOD-0.59	-	-	-	-
Taiwan Coast ^p	-	-	-	-	-	27-49	130-190
Yeongil Bay, Korea ^q	<LOD-191	-	-	-	-	<LOD-24.3	<LOD-1430
East Coast of Sidney, Australia ^r	-	0.16-1.17	0.22-2.48	-	0.05-0.5	-	-
Califórnia Coast, United States ^s	-	<LOD-0.6	0.16-0.45	-	-	1.9-8.2	122-3200
Rhine Estuary, the Netherlands ^t	-	-	-	-	-	-	1.5-92.2
Scheldt Estuary, the Netherlands ^t	-	-	-	-	-	-	0.4-1080
Spain Coast, Mediteranean and Atlantic Ocean ^u	-	-	-	-	-	17-145	18-1050
Tóquio Bay, Japan ^v	-	-	-	-	-	6-10	120-640
Jamaica Bay ^w	-	-	-	-	-	<LOD-45	6.99-13700
Jamaica Bay ^x	-	-	-	-	-	8.1	846
Masan Bay, South Korea ^y	2.7-50.3	-	-	-	-	4-179	113-3890
Auckland, New Zealand ^z	<LOD-145	<LOD-2.2	<LOD-1.0	-	<LOD	<LOD-135	<LOD-32000
Gulf of Gdansk (Baltic Sea) ^{aa}	-	-	-	-	-	<LOD-48.88	<LOD-249.08
Yellow Sea ^{ab}	-	-	-	-	-	0.8-9.3	349.5-1642.8
East China Sea ^{ab}	-	-	-	-	-	0.7-11.1	31.3-1423.7
Cape D'Aguilar Marine Reserve, Hong Kong ^{ac}	60,8-265,9	-	-	-	-	-	527,3-800,0
Yangtze River Estuary, China ^{ad}	<LOD-7.87	<LOD-1.92	<LOD-0.30	-	<LOD-0.72	-	-

LOD=limit of detection. ^aPuy-Azurmendi *et al.*, 2013; ^bDiehl *et al.*, 2012; ^cde los Ríos *et al.*, 2012; ^dArditsoglou & Voutsas, 2012; ^eSánchez-Avila *et al.*, 2011; ^fBertin *et al.*, 2011; ^gPuy-Azurmendi *et al.*, 2010; ^hWang *et al.*, 2010; ⁱBian *et al.*, 2010; ^jZhang *et al.*, 2009; ^kArditsoglou & Voutsas, 2008b; ^lLi *et al.*, 2008; ^mKumar *et al.*, 2008; ⁿPojana *et al.*, 2007; ^oIsobe *et al.*, 2006; ^pCheng *et al.*, 2006; ^qKoh *et al.*, 2006; ^rBraga *et al.*, 2005; ^sSchlenk *et al.*, 2005; ^tJonkers *et al.*, 2003; ^uPetrovic *et al.*, 2002; ^vIsobe *et al.*, 2001; ^wFerguson *et al.*, 2001; ^xFerguson *et al.*, 2000; ^yKhim *et al.*, 1999; ^zStewart *et al.*, 2014; ^{aa}Konieczko *et al.*, 2014; ^{ab}Duan *et al.*, 2014; ^{ac}Xu *et al.*, 2015; ^{ad}Shi *et al.*, 2014

Table 6. Phthalates in sediments (ng g⁻¹) and water (ng L⁻¹)

Site	Sample	DMP	DEP	DBP	DEHP	BBP	DnOP
Abra and Urdaibai Estuary, Spain ^a	Sediment	<LOD	<LOD-6218	<LOD-1010	688-2530	-	-
Biscay Bay, Santander Coast, Spain ^b	Water	<LOD	3330-37360	4450-5960	7080-85360	-	-
	Sediment	<LOD	170-7670	630-1040	1120-15190	-	-
Southeastern California Coast, United States ^c	Water	-	-	-	-	-	<LOD-85
Northeastern Coast, Spain ^d	Water	9.4-21	43-4482	-	4.6-138	2.6-658	-
	Sediment	12-26	22-4317	-	1.9-107	12-3297	-
Urdaibai Estuary, Spain ^e	Sediment	<LOD	908-6377	466-1168	346-4376	-	-
Cantábria Coast, Spain ^f	Sediment	<LOD	<LOD	<LOD	190-2800	<LOD	
Kavala Coast, Greece ^g	Water	-	-	370-700	600-1300	300-6000	-
Arctic Sea, Norway ^h	Water	0.013-0.312	0.008-0.795	0.0002-0.048	0.024-3.330	-	-
North Sea ⁱ	Water	<LOD-0.68	0.03-4.0	0.45-6.6	<LOD-5.3	<LOD-0.26	-
Elizabeth Port and East London, South Africa ^j	Water	500-350800	4400-398300	700-1028100	2100-2306800	-	-
Auckland, New Zealand ^k	Sediment	<LOD	<LOD	<LOD	<LOD-11500	<LOD-1600	<LOD
Anzali wetlands, Iran ^l	Sediment	-	-	0.12-19.02	0.25-43.12	-	-

LOD – Detection limit. ^aPuy-Azurmendi *et al.*, 2013; ^bde los Ríos *et al.*, 2012; ^cVidal-Dorsch *et al.*, 2012; ^dSánchez-Avila *et al.*, 2011; ^ePuy-Azurmendi *et al.*, 2010; ^fAntizar-Ladislao, 2009; ^gGrigoriadou *et al.*, 2008; ^hXie *et al.*, 2007; ⁱEbinghaus & Xie, 2006; ^jFatoki & Noma, 2001; ^kStewart *et al.*, 2014; ^lHassanzadeh *et al.*, 2014

et al., 2007; Cheng *et al.*, 2006; Basheer *et al.*, 2004). NPs concentrations ranged from 1.2 ng g⁻¹ in oysters, at Savannah, USA (Kumar *et al.*, 2008), to 7600 ng g⁻¹ in mussels and oysters from the northeastern coast of China (Wang *et al.*, 2010a). Concentrations of OPs ranged from 0.2 ng g⁻¹, in anchovies in the Tyrrhenian Sea (Ferrara *et al.*, 2008), to 1460 ng g⁻¹, in oysters collected on the coast of Taiwan (Cheng *et al.*, 2006). In many studies a significant relationship between the concentrations of NP and OP in biota and in the water column was not observed (Tsuda *et al.*, 2000). The absence of this correlation is not only associated with the high water dynamics, but also to the fact that the concentration of biological tissues reflects the contamination exposure integrated over the animal lifetime.

OP concentrations were positively correlated with NP concentrations in oysters that inhabit the Taiwan Coast. This was similar to that found between OP and NP in the marine gastropod *Thais clavigera*, which is a predator of oysters *Crassostrea gigas*, from the same region. Cheng *et al.* (2006), by analyzing these two trophic levels, suggested that there was biomagnification of NP and OP. Studies of biomagnification of EDs, nevertheless, are

still scarce and efforts should be made to understand the mechanisms associated to the transfer and accumulation of contaminants trophic levels.

In the studies reviewed, concentrations of NPs in sediments and biota were always higher than the concentrations of OP, similarly to the observed in water. Moreover, NP present higher lipophilicity (log K_{ow} NP > log K_{ow} OP), therefore it is accumulated in higher proportion in sediments and biota when compared to OP. Concentrations of OP and NP in coastal sediments are much lower than concentrations found in rivers. Fu *et al.* (2007) have reported concentrations of NP up to 31704 ng g⁻¹ in rivers that flow into the bay of Jiaozhou, China. In turn, for marine environments the NP values were below 14000 ng g⁻¹ (Gu *et al.*, 2016; Isolbe *et al.*, 2007; Pojana *et al.*, 2007; Ferguson *et al.*, 2001). Attenuation due to dilution and degradation processes is possibly the main reason for the differences in the concentrations observed between riverine and marine environments.

The BPA concentrations (Table 4) in seawater ranged from 0.1 ng L⁻¹ in the Eastern Baltic Sea, Germany (Beck *et al.*, 2005), to 2470 ng L⁻¹ in waters from Singapore coast

(Basheer *et al.*, 2004). The BPA concentration is mainly attributed to industrial activity and the WWTP effluents. As a result, it was observed a decreasing gradient of BPA concentration with the distance increase from the sources. This variation in the BPA concentrations has been mainly attributed to dilution and degradation processes. It is estimated that BPA present half-life between 2.5 - 4 days in marine waters (Heemken *et al.*, 2001). Thus BPA molecules that are not sorbed and transferred to sediment may be rapidly degraded.

In sediments, BPA ranged from 0.01 ng g⁻¹, in sediments from Urdaibai estuary, Spain (Puy-Azurmendi *et al.*, 2010), to 266 ng g⁻¹ in sediments of Cape D'Aguilar Marine Reserve, Hong Kong (Xu *et al.*, 2015). There are few studies describing the presence of BPA in marine organisms, among these, a study with mussels reported BPA concentrations ranging from 0.54 ng g⁻¹ and 213 ng g⁻¹ (Isobe *et al.*, 2007). AP and BPA concentrations in mussels are generally higher than those obtained for fish since they feed on suspended material and accumulate large amounts of contaminants (Basheer *et al.*, 2004), including trace metals and PHA.

Unlike the AP, the BPA concentrations in sediment and biota were, in many cases, lower than its concentrations in water. This pattern can be explained by the lower lipophilicity of BPA compared to AP, and its high solubility. It seems like that these compounds degrade before reaching the sediments (Gu *et al.*, 2016; Casatta *et al.*, 2015; Emnet *et al.*, 2015; Miège *et al.*, 2012; Bouzas *et al.*, 2011; Isolbe *et al.*, 2007; Pojana *et al.*, 2007; Cheng *et al.*, 2006; Heemken *et al.*, 2001).

E1, E2, E3 and EE2 are the most studied hormones, primarily because of their large inputs in the environment and their high endocrine disruption potential. The concentrations of E1 in water, sediment and mussels range from 0.13 ng L⁻¹ (Beck *et al.*, 2005) to 52 ng L⁻¹ (Noppe *et al.*, 2007), 0.05 ng g⁻¹ (Isobe *et al.*, 2006) to 7.4 ng g⁻¹, (Zhang *et al.*, 2009) and 0.2 ng g⁻¹ to 0.4 ng g⁻¹ (Saravanabhavan *et al.*, 2009), respectively. The E2 in water and sediment was found at concentrations ranging from 0.56 ng L⁻¹ (Zuo *et al.*, 2006) to 175 ng L⁻¹ (Pojana *et al.*, 2007), and 0.06 ng g⁻¹ to 16.8 ng g⁻¹ (Bertin *et al.*, 2011) respectively, while E2 has not been detected in organisms. Among the studied hormones, the synthetic EE2 is the only one that has exclusively anthropogenic sources. EE2 in water, sediment and biota was found in concentrations ranging from 1.6 ng L⁻¹ (Beck *et al.*, 2005) to 28 ng L⁻¹ (Pojana *et al.*, 2007), 0.05 ng g⁻¹ (Braga *et al.*, 2005) to 48 ng g⁻¹ (Bertin *et al.*, 2011), and 7.2 ng g⁻¹ to 38 ng g⁻¹ (Pojana *et al.*, 2007), respectively. On the other hand, E3 was only identified in sediments of the south-central coast of Chile (Bertin *et al.*, 2011) ranging from 0.01 ng g⁻¹ to 53.2 ng g⁻¹.

Estrogenic hormones are released into the environment in their inactive conjugated forms (*i.e.* glucuronic or

sulfate acid). However, they are rapidly transformed in their interfering forms through the activity of microorganisms present in environment (Ying *et al.*, 2002b). Like other EDs, estrogens are presented in relatively low concentrations in the marine environment, due to dilution and/or attenuation processes.

High concentrations of estrogens were not found in the sediments, possibly due to their relatively fast degradation before the occurrence of other processes such as sorption, flocculation and/or deposition. Bowman *et al.*, (2003) reported half-lives from 2.8 to 3 days for E1 and E2. However EE2, with slower degradation rate than natural hormones (Braga *et al.*, 2005), has the potential to accumulate and to present high concentrations in sediments. Evaluations of estrogenic hormones in marine biota showed very low concentrations, reflecting the concentrations observed in environment (Gu *et al.*, 2016; Emnet *et al.*, 2015; Casatta *et al.*, 2015; Miège *et al.*, 2012; Bouzas *et al.*, 2011; Saravanabhavan *et al.*, 2009; Pojana *et al.*, 2007; Isolbe *et al.*, 2007; Cheng *et al.*, 2006).

Table 6 presents the occurrence of phthalates in water and sediment from coastal regions. The highest concentrations of phthalates were found in areas near large harbors, quite possibly due to effluents and plastic waste originating from them (Fatoki & Noma, 2001). Urban and industrial effluents from neighboring regions may also have been important sources of phthalates in these regions. As for the other studied EDs, salinity and content of organic matter in the water influence the transfer of phthalates to sediments (Mackintosh *et al.*, 2006) or biota (Cheng *et al.*, 2013; Bartolomé *et al.*, 2010; Dagnat *et al.*, 2009). In general, with increasing salinity the balance between the concentrations of phthalates in the sediment and water may be affected. Phthalates can be mobilized and transferred between compartments, besides being degraded through biological processes. The biodegradation processes occur with higher intensity in aerobic conditions. In the anoxic environments biodegradation processes are minimized (Fromme *et al.*, 2002). Similarly to other classes of contaminants, phthalates can be stored in anoxic sediments for a long period of time and in medium to large temporal scales sediments may be remobilized and they may act as a source of contaminants.

5. Conclusions

A large variety of emerging contaminants, and among them, those ones which are likely to cause endocrine disruption in some level, are emitted by ever-growing and diverse man-made sources, effectively spreading themselves out to every environmental compartment throughout the globe. The limited knowledge about the chemistry, transport, toxicity and fate of endocrine disruptors, associated to its wide use in anthropogenic

activities have promoted a growing interest in the development of analytical methods and its applications to study the distribution and behavior of these contaminants in the environment. Yet, probably the quantity of new compounds considered “emerging” or “endocrine disruptors” which has been recently synthesized, developed, and released for use by industrial, pharmaceutical, agricultural, and aquicultural sectors are continuously increasing, and faster than analysis systems and analytical methods are possibly progressing. This happens, in part, in order to benefit humanity for increasing its well being conditions, but it also happens for creating substitute molecules for those ones being banned of use because are considered nocive for the environment, biota and/or human beings. However, an important portion of the problem is associated with the accelerated development and registry of new substances without a proper study of their cycle of life (which includes environmental risk evaluation and the development of degradation and removal processes for them), which is time-consuming and cost-effective. So, it is quite possible these new substances are going to be accumulated in the environment soon after they started to be utilized. In spite the recent advances in Analytical Chemistry regarding sample preparation and detection systems for the study of EDs, it is believed that a large amount of micropollutants remain unidentified and undetected in the environment. If they persist unknown, it is quite possible that identification of sources, transport and fate of these contaminants are underestimated or not existent at all. And, therefore, subsidizing the development of regulatory measures, source control and decision-making to promote the sustainable management of ecosystems and the preservation of the environment and human health is delayed or biased.

Studies around the world indicated that estuaries and coastal regions under the influence of domestic or industrial and WWTP effluents have increasing levels of EDs, and hence this topic needs to be addressed. However, the number of these studies is still very incipient to produce a good diagnosis of the real situation of these contaminants in marine environments. If on one hand this data reflects the relative novelty of this subject, on the other hand the major impediments to the development of this topic is the complexity of marine waters (*i.e.*, high ionic strength, dissolved organic matter and high content of dissolved salts, which are in general the main interfering species in chemical analysis) and the low concentration levels of EDs. These factors represent significant challenges for the coming years. Additionally, it is well accepted conventional water-treatment systems are inefficient to remove EDs from their inffluents, which eventually are realeased to superficial waters and then reaching estuarine and coastal regions. In this way, it becomes necessary the development of new and more efficient water treatment systems, possibly employing

advanced oxidative methods or biodegradation by microorganisms (such as bacteria, fungi, enzymes, yeasts, and/or genetically modified organisms) able to break ED molecules down. If new and more adequate WWTP systems are developed, lower levels of residual EDs in the effluents would be reached. In this way, it is possible to a substancial lower amount of EDs could reach coastal areas resulting in the decrease of contamination levels, what could facilitate the management of those areas. In the same direction, the development and application of mitigation and/or remediation of affected areas would alliviate the environmental pressure in regard to EDs to the already impacted regions. New and more studies are needed in these research areas.

It is also urgent the acquisition of robust databases through long-term investigations about EDs behavior and distribution in different compartments and how they participate in food chain in order to access their possible bioaccumulation and/or biomagnification among different trophic levels. The real understanding of ED effects in the aquatic environment is far from understood. In addition, studies about the possible adverse human health effects of endocrine disruptors are scarce. Until robust analytical procedures, with high selectivity and sensitivity could be developed to the analysis of a large number of samples, as it is required in monitoring studies, the behavior of these contaminants in the environment as well as their fate and effects in biota may not be fully understood. Indeed, cause-effect manipulative studies and ecotoxicology tests are still in an embrionary stage of development, and represent a major challenge.

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