



Review

Endocrine-Disrupting Compounds: An Overview on Their Occurrence in the Aquatic Environment and Human Exposure

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Abstract: Endocrine-disrupting compounds (EDCs) as emerging contaminants have accumulated in the aquatic environment at concentration levels that have been determined to be significant to humans and animals. Several compounds belong to this family, from natural substances (hormones such as estrone, 17 β -estradiol, and estriol) to synthetic chemicals, especially pesticides, pharmaceuticals, and plastic-derived compounds (phthalates, bisphenol A). In this review, we discuss recent works regarding EDC occurrence in the aquatic compartment, strengths and limitations of current analytical methods used for their detection, treatment technologies for their removal from water, and the health issues that they can trigger in humans. Nowadays, many EDCs have been identified in significant amounts in different water matrices including drinking water, thus increasing the possibility of entering the food chain. Several studies correlate human exposure to high concentrations of EDCs with serious effects such as infertility, thyroid dysfunction, early puberty, endometriosis, diabetes, and obesity. Although our intention is not to explain all disorders related to EDCs exposure, this review aims to guide future research towards a deeper knowledge of EDCs' contamination and accumulation in water, highlighting their toxicity and exposure risks to humans.

Keywords: emerging contaminants; organic contaminants; endocrine disruptor; water environment



Citation: Pironti, C.; Ricciardi, M.; Proto, A.; Bianco, P.M.; Montano, L.; Motta, O. Endocrine-Disrupting Compounds: An Overview on Their Occurrence in the Aquatic Environment and Human Exposure. *Water* **2021**, *13*, 1347. <https://doi.org/10.3390/w13101347>

Academic Editors: Heiko L. Schoenfuss and Anu Kumar

Received: 23 February 2021

Accepted: 11 May 2021

Published: 12 May 2021

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1. Introduction

Human activities have introduced a large number of contaminants of emerging concern (CECs) into the environment on a global scale. This category refers to any chemical discovered in the water cycle that had not previously been detected, and so is not yet regulated by an agency, and often presents at very low concentration levels [1–7]. CECs include a wide class of different types of organic and inorganic chemical compounds such as disinfection byproducts [8], endocrine disruptors [9–11], industrial chemicals, natural toxins, persistent organic pollutants (POPs), brominated flame retardants (BFRs), lifestyle compounds such as caffeine, and artificial sweeteners, pesticides, pharmaceuticals and personal care products (PPCPs), which have the potential to harm biota and humans [12–15].

Among them, endocrine-disrupting compounds (EDCs), also called endocrine-disrupting chemicals, or simply endocrine disruptors, are xenobiotics compounds mainly present in manufactured products such as children's toys, plastic bottles, polyvinylchloride pipes, detergents, toothpaste, and cosmetics [16,17]. These chemicals can bind to the body's

endocrine receptors to activate, block, or alter natural hormone synthesis and degradation which occur through a plethora of mechanisms resulting in a “false” lack or abnormal hormonal signals that can increase or inhibit normal endocrine function [18,19]. The term endocrine disruptor was first introduced by Colborn in 1991 [20] and subsequently, the International Programme on Chemical Safety (IPCS) of United Nations Environment Programme (UNEP) and World Health Organization (WHO) in 2002 and 2012 [21], defined it as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations” and a potential chemical endocrine disruptor as “an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations” [22]. During the last years, there have been many modifications to this definition, but we chose to use the original for this review. In fact, this definition is the commonly accepted one for a substance with endocrine-disrupting properties both by the scientific community and by regulatory bodies around the world [23–25]. Based on this approach, a chemical must have a demonstrated adverse effect related by a proof of causality to an endocrine disruption mode-of-action to be defined as an endocrine disruptor. As a consequence, in screening and testing chemicals for the endocrine activity or disruption, it is important to use concentrations that maximize the possibility to find a true endocrine effect, and at the same time avoid doses that cause generalized stress endocrine responses or indirect toxicities [26].

The group of molecules identified as endocrine disruptors is highly heterogeneous and can be divided into synthetic chemicals (from anthropogenic activities e.g., 17 α -ethinylestradiol (EE2), pesticides e.g., atrazine, phthalates, alkylphenol ethoxylate surfactants, nonylphenol (NP), dioxins, coplanar polychlorinated biphenyls (PCBs), parabens hydroxybenzoate derivatives, bisphenol A (BPA), polycyclic aromatic hydrocarbons (PAHs), organotins) used as industrial solvents/lubricants, plasticizers, pharmaceutical agents, and flame retardants, and natural substances (e.g., estrone (E1), 17 β -estradiol (E2), and estriol (E3); natural androgens e.g., testosterone; phytosteroids e.g., β -sitosterol; isoflavonoids e.g., daidzeine) [18,27–31]. The chemical structures of the commonly recognized EDCs are shown in Figure 1.

The most frequently studied endocrine disruptors are pesticides, bisphenols, phthalates, synthetic and natural hormones, and polychlorinated biphenyls [32–34]. They are generally found in the order of nanograms to micrograms per liter (ng/L and μ g/L) in the environment and can be identified in water using chemical analytical methods, like high-performance liquid chromatography and gas chromatography with mass spectroscopy, and biological methods or biosensors [35,36]. Commonly used pesticides acting as EDCs include organophosphorus pesticides (OPPs), organochlorine pesticides (OCPs) and herbicides such as chlorotriazine (CTs) and glyphosate [37]. OPPs are widely employed in agriculture (e.g., chlorpyrifos with 45,000 tons produced in 2016) and their residues in all food products and related environments need to be estimated in order to assess the risks of human exposure [38]. Atrazine is one of the most popular CTs herbicides used for many years and, together with other dangerous EDCs (equally banned in most countries) is again detected in surface and underground water all over the world [39]. Although the use of synthetic pesticides in agriculture has helped to increase food production, there is a great cost to human health, the environment, and its resources. Another widespread contaminant acting as EDC is bisphenol A, an artificial estrogen found in many hard plastics and hygiene products. It has been used to enhance the rapid growth of cattle and poultry and as an estrogen replacement for women [40].

In 2013, the World Health Organization highlighted that exposure to these chemicals is an issue of concern for wildlife and humans and that decision-makers need to take action to regulate human and environmental exposure to these chemicals [21].

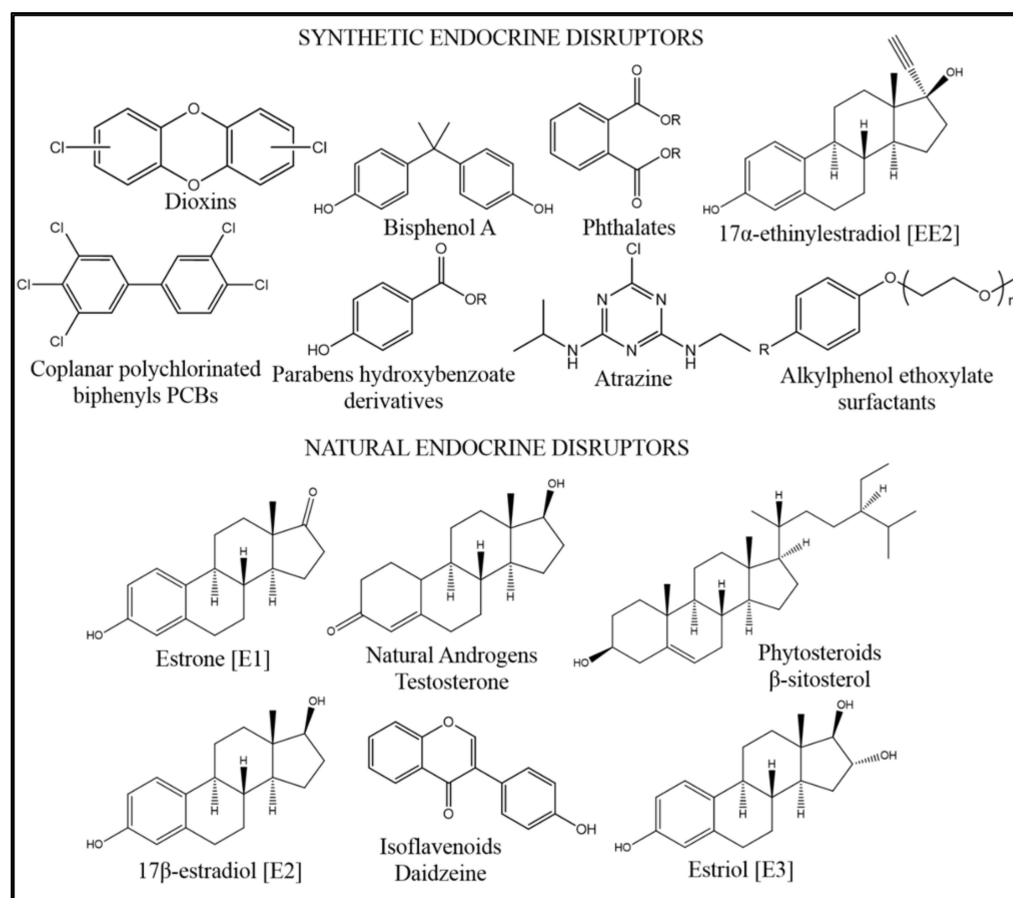


Figure 1. Structure of common synthetic and natural endocrine disruptors.

EDCs can reach the aquatic environment through different pathways, e.g., wastewater discharge and release of pesticide residues from agricultural activities. Fish and wildlife can be directly exposed, and humans may become exposed through the intake of contaminated water and sea products. These substances, like CECs, are not easily removed from water through conventional treatment processes offered by water or sewage treatment plants. Thus, advanced removal technologies could represent more appropriate removal pathways. Owing to the diverse physicochemical properties of the endocrine disruptors, several processes can be applied as treatment technologies and obtain different removal efficiencies [41]. Data from ecological studies, animal models, clinical observations in humans, and epidemiological studies agree that endocrine-disrupting chemicals are significant for wildlife and human health [42,43].

Ultimately, EDCs are widespread in the environment and the increase of some effects such as diabetes, obesity, cognition deficits, neurodegenerative diseases, early puberty, thyroid dysfunction, heart diseases, and infertility have been hypothesized by some scientists to be linked to human exposure to these substances [44]. However, this relationship is highly debated in the literature and some authors have shown that links between EDCs and human health effects are weak to modest, so it needs to be further evaluated in future studies. Due to the increasing interest in this topic, this review reports an overview of the most important EDCs discovered in water, animals, and human exposure to them, analytical methods for their detection, and technologies useful to remove these compounds from waterbodies.

2. The Methodological Approach of the Review

In this review, the authors attempt to discuss the presence of EDCs in the aquatic compartment with particular attention to possible consequences due to human exposure

to these compounds. Based on the scientific literature related to endocrine disruptors, this review has four main aims: (1) to summarize contamination and accumulation of emerging organic contaminants such as EDCs in water; (2) to outline and discuss the analytical methods used to assess EDC concentration, technical considerations and limitations; (3) to describe treatment technologies for the removal of these compounds from water environments; (4) to delineate the urgency and seriousness of EDC occurrence in water by emphasizing the different interactions with humans and health implications. The keywords “organic contaminants”, “environment”, “endocrine disruptor”, “emerging contaminants”, and “water” were selected individually or jointly to search for relevant information on the Web of Science, Scopus, and Google Scholar. Key literature published between 2004 and 2021 (up to January) were assimilated and analyzed.

3. EDCs in the Aquatic Environment

3.1. Contamination Sources and Paths into the Environment

Endocrine-disrupting compounds are involved in the water compartment contamination [45–47] of both surface water and groundwater [48], the marine environment [49–52], wastewater [53–56], and rivers and lakes [57–60]. In the last few years, EDCs reached the aquatic environment through various routes such as pharmaceutical and hospital waste disposal, wastewater treatment plants, leaching of chemicals used in industrial and household items (detergents and personal care products), and release of pesticide residues from agricultural activities (see Figure 2).

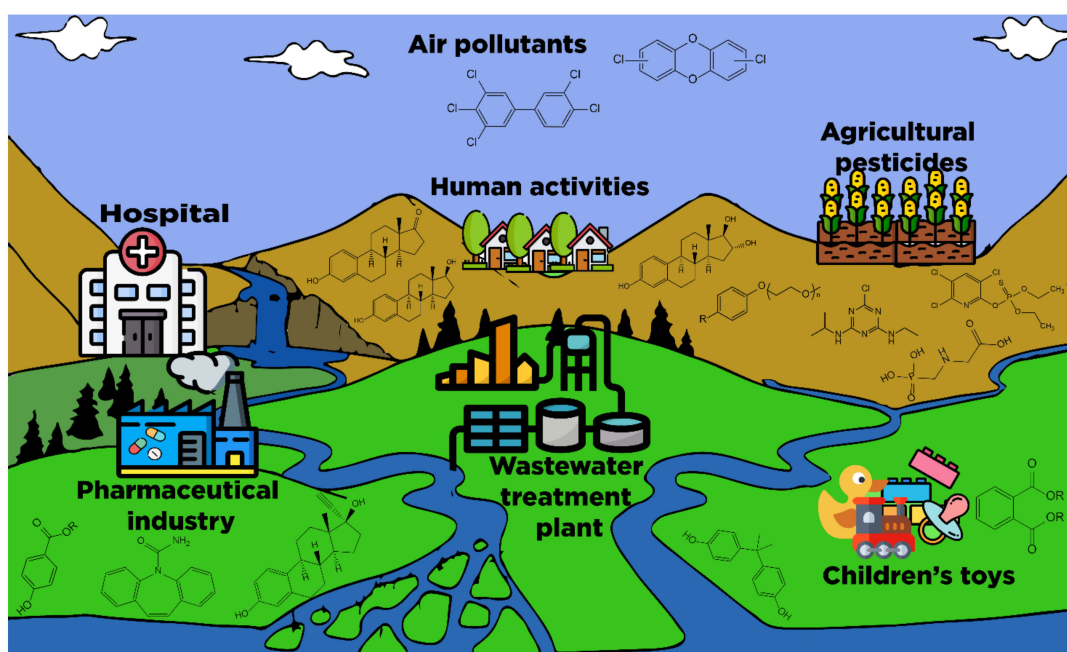


Figure 2. Sources of endocrine disruptors in the aquatic compartment.

Water is a dynamic system and not a static location for accumulating contaminants, so in order to assess contamination issues some distribution mechanisms must be taken into account including sorption to sediments that can result as a long-term source. Flow in the natural water cycle is dominated by rain events. Precipitation leaches contaminants from buildings, streets, land surfaces, and agricultural fields (e.g., pesticides) or improperly disposed wastes and transports them into surface waters of local rivers, lakes, and reservoirs [61]. So rainwater runoff has also been identified as a source for contaminants [62]. In some cases, stormwater is conveyed in combined sewer systems that collect rainwater runoff, domestic sewage, and industrial wastewater [63]. During very rainy periods, the wastewater volume in these sewer systems can exceed their capacity, so excess wastewater

(containing not only storm water but also untreated human and industrial waste, and toxic materials) is discharged into the surface water of nearby streams, rivers, or other water bodies as combined sewer overflows. Typically, water discarded by households and commercial users, collected in the sewer system, is treated by wastewater treatment plants in order to be discharged into surface waters. Furthermore, excess surface water and runoff (both due to the rain) are percolated into aquifers, bodies of permeable rock which can contain or transmit groundwater, and withdrawn during dry periods, increasing water reliability, protecting water quality, and providing treatment. In cities that rely on groundwater for their drinking water supply, aquifers are used in bank filtration to purify surface water [64]. Surface water and groundwater transport across the water cycle can provide natural water purification, often referred to as natural attenuation, e.g., processes such as dilution, sorption, volatilization, and chemical or biological degradation. In these ways, contaminant concentrations could be attenuated below the detection limits [61]. A considerable amount of pollutants are released from sewer leakages into the sewer-shed's groundwater [65]. EDCs as pesticides reach the soil from rainwater or irrigation water washing and then they can infiltrate into ground and surface waters [61]. Moreover, contaminants not totally removed by wastewater treatment, and so present in treated wastewater, are released into the receiving surface waters, resulting in long-term chronic exposure of the aquatic ecosystem [66].

EDCs' presence in the environments and their consequent exposure risk have been analyzed only in recent years thanks to the application of appropriate and sensitive methods for their detection. The application of advanced chromatography and mass spectrometry technologies to environmental analysis has allowed the determination of a broader range and a more comprehensive assessment of environmental contaminants [67].

In a recent review, Gonsioroski et al. [68] described the common endocrine-disrupting chemicals present in aquatic environments and their effects on the reproductive system. The review highlighted that chemical contamination in water has originated from byproducts formed during water disinfection processes, release from industry and livestock activity, or therapeutic drugs released into sewage including disinfection byproducts, fluorinated compounds, bisphenol A, phthalates, pesticides, and estrogens. Several studies reported the formation of EDCs during drinking water treatments and the association between exposure and increased risk of cancer development and adverse reproductive outcomes [69–73].

3.2. Occurrence in Water

In the following subsection, we describe the occurrence and abundance of EDCs in different water matrices, starting from freshwater and estuaries to seawater, wastewater, and also drinking water. All the data analyzed are summarized in Table 1.

Table 1. Concentrations of main EDCs in different water matrices.

Water Matrix	EDC Type	Analytical Method	Concentration (ng/L)	Country	[REF]
Freshwater	Lamivudine	HPLC-MS-MS	167,100	Kenya	[74]
	Paracetamol	HPLC-MS-MS	106,970	Kenya	[74]
		HPLC-MS-MS	1289	Spain	[74]
	Naproxen	HPLC-MS-MS	59,300	South Africa	[74]
	Sulfamethoxazole	HPLC-MS-MS	53,828	Mozambique	[74]
	Ibuprofen	HPLC-MS-MS	17,600	South Africa	[74]
		HPLC-MS-MS	1440	Spain	[74]
	Zidovudine	HPLC-MS-MS	17,410	Kenya	[74]
	Ciprofloxacin	HPLC-MS-MS	14,331	South Africa	[74]
	Trimethoprim	HPLC-MS-MS	11,383	Kenya	[74]
	Valsartan	HPLC-MS-MS	6260	Spain	[74]
	Caffeine	HPLC-MS-MS	5928	Spain	[74]
	Erythromycin	HPLC-MS-MS	5300	Croatia	[74]

Table 1. Cont.

Water Matrix	EDC Type	Analytical Method	Concentration (ng/L)	Country	[REF]
Freshwater	Metformin	HPLC-MS-MS	3100	Germany	[74]
	Carbamazepine-10,11-epoxide	HPLC-MS-MS	1670	Spain	[74]
	Sulfadimidine				
	Azithromycin	HPLC-MS-MS	1500	Croatia	[74]
	Sulfadiazine	HPLC-MS-MS	1100	Croatia	[74]
	Progesterone	HPLC-MS-MS	1000	Croatia	[74]
	Testosterone	HPLC-MS-MS	0.23–13.7	Hungary	[74]
	E1	HPLC-MS-MS	2.6–3	Italy	[74]
		HPLC-MS-MS	0.1–69	Europe	[74]
	E3	ELISA	1.5–7.2	Portugal	[60]
		HPLC-MS-MS	45,550	South Africa	[74]
		HPLC-MS-MS	2.38	France	[74]
	E2	HPLC-DAD	510–45,500	Africa	[75]
		HPLC-MS-MS	0.33–5	Hungary	[74]
		HPLC-MS-MS	15,700	South Africa	[74]
	EE2	ELISA	0.8–1.7	Portugal	[60]
		ELISA	0.3–0.5	Portugal	[60]
	BPA	HPLC-DAD	3310–15,700	Africa	[75]
	Octylphenol	HPLC-MS-MS	22–146	Spain	[76]
	NP	HPLC-MS-MS	0.98–43.7	Spain	[76]
Alkylphenols	HPLC-MS-MS	30–337	Spain	[76]	
	HPLC-MS-MS	600–1070	Portugal	[60]	
	HPLC-MS-MS	233–8200	Portugal	[77]	
	HPLC-MS-MS	0.1–37.2	Serbia	[78]	
Seawater	BPA	GC-MS	10.6–52.3	Greece	[52]
		HPLC-MS	1.1–17	Portugal	[77]
		GC-MS	249	Portugal	[77]
		LC-MS-MS	0–5.7	Portugal	[77]
		HPLC-MS-MS	0.98–43.7	China	[79]
		GC-MS	17–776	Germany	[80]
		LC-MS-MS	0–5.7	Germany	[81]
	NP	HPLC-MS	4100	Spain	[82]
		GC-MS	22–201	Greece	[52]
		LC-MS	210	Spain	[83]
		HPLC-MS	29–78	Portugal	[77]
		GC-MS	0.3–221	Germany	[80]
		LC-MS-MS	1.3–21.3	Germany	[81]
	E1	HPLC-MS-MS	1.43	China	[79]
		LC-MS-MS	1.1	China	[84]
	E2	LC-MS-MS	0.7	China	[84]
EE2	LC-MS-MS	0.6	China	[84]	
Wastewater	Nordiazepam	HPLC-MS-MS	0.6	Greece	[56]
	Carbamazepine	HPLC-MS-MS	6822	Greece	[56]
	9-OH risperidone	HPLC-MS-MS	0.4	Greece	[56]
	Alkylphenols	HPLC-MS-MS	1.1–78.3	Serbia	[78]
	BPA	HPLC-MS-MS	6.8	Serbia	[78]
	NP	HPLC-MS-MS	4.9	Serbia	[78]
	Octylphenol	HPLC-MS-MS	1.9	Serbia	[78]
	Diclofenac	LC-MS-MS	4869	Greece	[85]
	Indomethacine	LC-MS-MS	297	Greece	[85]
	Ketoprofen	LC-MS-MS	793	Greece	[85]
	Meloxicam	LC-MS-MS	648	Greece	[85]
	Naproxen	LC-MS-MS	3581	Greece	[85]
	Nimesulide	LC-MS-MS	2452	Greece	[85]
	Paracetamol	LC-MS-MS	27.7	Greece	[85]
	Phenazone	LC-MS-MS	44.9	Greece	[85]
Piroxicam	LC-MS-MS	1192	Greece	[85]	

Table 1. Cont.

Water Matrix	EDC Type	Analytical Method	Concentration (ng/L)	Country	[REF]
Wastewater	Ampicillin	LC-MS-MS	1805	Greece	[85]
	Ciproflaxacin	LC-MS-MS	591	Greece	[85]
	Erythromycin	LC-MS-MS	320	Greece	[85]
	Lincomycin	LC-MS-MS	281	Greece	[85]
	Metronidazole	LC-MS-MS	64.7	Greece	[85]
	Moxifloxacin	LC-MS-MS	773	Greece	[85]
	Sulfadiazine	LC-MS-MS	846	Greece	[85]
	Sulfamethoxazole	LC-MS-MS	507	Greece	[85]
	Trimethoprim	LC-MS-MS	200	Greece	[85]
	Fluvoxamine	LC-MS-MS	75.4	Greece	[85]
	Caffeine	LC-MS-MS	102–5597	Greece	[85]
	Cetirizine	LC-MS-MS	816	Greece	[85]
	Cimetidine	LC-MS-MS	1466	Greece	[85]
	Cinnarizine	LC-MS-MS	119	Greece	[85]
	Atenolol	LC-MS-MS	2346	Greece	[85]
	Furesomide	LC-MS-MS	15,320	Greece	[85]
	Parabens	LC-MS-MS	600	Greece	[85]
Drinking water	Alkylphenols	HPLC-MS-MS	0.4–7.9	Serbia	[78]
	BPA	HPLC-MS-MS	9.1	Serbia	[78]
	NP	HPLC-MS-MS	3.1	Serbia	[78]
	OP	HPLC-MS-MS	1.7	Serbia	[78]
	E1	HPLC-MS-MS	5.9	Serbia	[78]
	E2	HPLC-MS-MS	7.2	Serbia	[78]
	E3	HPLC-MS-MS	4.9	Serbia	[78]
	E1-3-sulfate	HPLC-MS-MS	4.4	Serbia	[78]
	E3-3-sulfate	HPLC-MS-MS	6.6	Serbia	[78]
	Total pesticides	GC-MS	39.3	Vietnam	[39]
	Trialkyl		0.94–16	Korea	[86]
	Phosphates	GC-MS			[86]
	Chloroalkyl		4.63–67.0	Korea	[86]
	Phosphates	GC-MS			
	BPA	HPLC-MS	140	Korea	[86]
	Phthalates	HPLC-MS	2–316	Taiwan	[87]
	Caffeine	HPLC-MS	10–22	Taiwan	[87]
	Erythromycin	HPLC-MS	11	Taiwan	[87]
	Acetaminophen	HPLC-MS	7	Taiwan	[87]
	Sulfamethoxazole	HPLC-MS	13	Taiwan	[87]
Gemfibrozil	HPLC-MS	17	Taiwan	[87]	
Ketoprofen	HPLC-MS	3	Taiwan	[87]	
Triclosan		8–103	Taiwan	[87]	

Abbreviations. HPLC-DAD: high-performance liquid chromatograph coupled to a diode array detector.

The occurrence of hormones in surface freshwater was reported in several African and European countries at different concentration levels. Estrone concentrations in the range of 0.1–69 ng/L were detected in France, the Czech Republic, Italy, Germany, Luxembourg, and Spain, whereas 0.23–13.7 ng/L of progesterone were reported in France and Hungary. Testosterone and estriol were instead found in concentrations of up to 3 ng/L and 2.38 ng/L respectively, in Italy and France and 17 β -estradiol was discovered in the concentration range of 0.33–5 ng/L in Hungary and Luxembourg [74]. The highest hormone levels were detected in Africa, where the discharge of untreated domestic and animal farm wastewater is common [74]. The African concentrations are from 3000 to 20,000 times higher than in Europe, with ranges of 3310–15,700 ng/L for 17 β -estradiol and 510–45,500 ng/L for estriol [75]. In Portugal, the presence of EDCs was investigated in different rivers (Minho, Ave, and Mondego) to evaluate their influence on the observed feminization phenomenon

in male fish. Concentrations of estrogens were lower in surface water samples from Minho than Ave or Mondego estuaries, with the estrone as the main estrogen, followed by 17β -estradiol and 17α -ethynylestradiol. By converting estrogen concentrations in 17α -ethynylestradiol equivalents, the contribution of estrogens was 1.3 ng/L, 3.5 ng/L, and 2.4 ng/L, respectively, for Minho, Ave, and Mondego estuaries stressing out a high risk for local aquatic species. The concentrations of alkylphenols and alkylphenol ethoxylates at both Minho and Mondego estuaries were 600 ng/L and 2700 ng/L respectively, lower than those detected at the Ave (1070 ng/L and 4855 ng/L). This study also shows that in Ave and Mondego estuaries the concentrations of industrial estrogens were excessive, and the amount detected may induce an endocrine disruption in aquatic organisms [60]. Several pharmaceutical and antifungal residues (e.g., sulfamethoxazole) were discovered in 18 out of the 20 collected samples in the Romanian territory of the Danube River at concentrations ranging from 2.5 to 30 ng/L [59,88]. The occurrence of alkylphenols and bisphenol A was also observed in five estuaries along the Northwest coastal area of Spain, with maximal concentrations of 337 ng/L for NP and 146 ng/L for BPA [76]. In Italy, the Higher Institute for Environmental Protection and Research (HIEPR) has identified several pesticides in surface and groundwater in the years 2017–2018. A higher percentage of detection was observed for surface water (25%) with respect to groundwater (15%) [89]. The substances that most often led to an overwhelming concern are the herbicide glyphosate and its metabolite aminomethylphosphonic acid (AMPA), metolachlor and its metabolite metolachlor-ESA, and the fungicides dimethomorph and azoxystrobin. The report from HIEPR highlighted the presence of a higher number of non-compliance cases in surface water (Figure 3) compared to the limits set by European legislation (2008/105/CE and 2013/39/UE) for these substances.

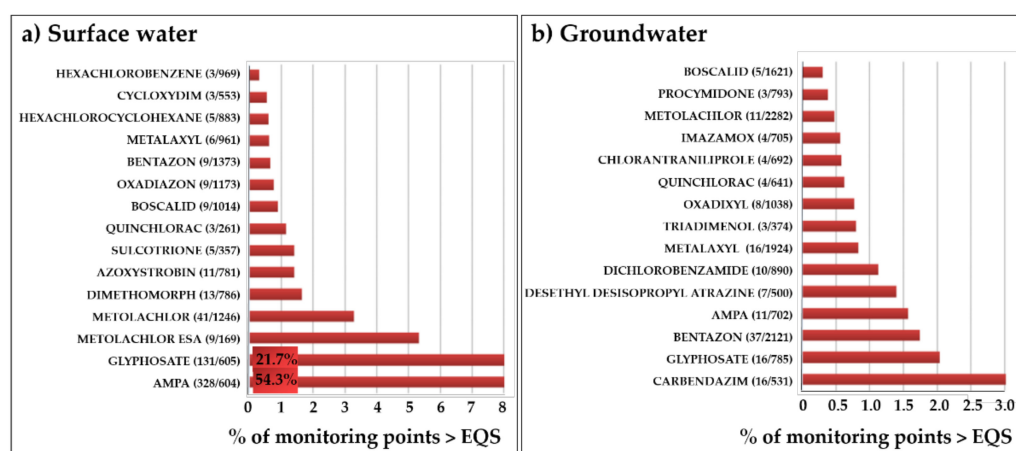


Figure 3. Most frequently detected substances above the environmental quality standard (EQS) at monitoring points in Italy, in 2018 for surface water (a) and groundwater (b).

Moreover, the evolution of the EU legislation suggests a further reduction of the limits for many of these substances to increasingly guarantee a reduction in the risks associated with exposure. The new EQS (concentration thresholds below which no adverse impact on the medium occurs) to which reference will be made, in some cases, are extremely low and a considerable analytical effort will therefore be required in order to be sure to meet these limits [89].

Such hazardous presence of pollutants in estuaries indicates that terrestrial river input is an important source of EDCs to coastal and marine environments. Alkylphenols, alkylphenol ethoxylates and bisphenol A were detected in the seawater of Thermaikos Gulf, Northern Aegean Sea, Greece. Concentration ranges of 22–201 ng/L for NP and 10.6–52.3 ng/L for bisphenol A were observed, whereas steroid EDCs were not detected [52]. In Spain concentrations of NP up to 4100 ng/L have been measured near the Mediterranean coast [82], while lower concentrations were observed in the Catalanian

coast, i.e., 210 ng/L of NP [83]. In a Portuguese coastal area, the concentrations of BPA and NP were in the range of 1.1–17 ng/L and 29–78 ng/L, respectively [77]. In the North Sea, NP was detected at a concentration range of 0.3–221 ng/L and BPA up to 249 ng/L [80], while lower concentrations of NP (1.3–21.3 ng/L) and BPA (0–5.7 ng/L) were discovered in the Baltic Sea of Germany [81]. In China, concentration levels of 0.98–43.7 ng/L for BPA and of 1.43 ng/L for E1 were detected in the East China Sea water [79], whereas natural hormones as E1 and E2, as well as the synthetic EE2, were detected in surface water samples on the northern shelf of the South China Sea near the Pearl River Estuary at concentrations of 1.1 ng/L, 0.7 ng/L, and 0.6 ng/L, respectively [84]. In the case of BPA, one of the chemicals that is the subject of regulatory decisions all over the world, concentrations in North American and European fresh and marine surface waters and sediments were monitored over the years of 1996–2014 [90]. The 95th percentile concentrations of BPA in freshwater were 0.30 µg/L both for North America and Europe, whereas those in marine water were 0.024 µg/L and 0.15 µg/L, respectively. Notwithstanding the increased production of BPA and polycarbonate plastic over the sampling period, BPA concentrations for both North America and Europe have not changed significantly. Moreover, concentrations of BPA in all samples did not exceed the EU Predicted No Effect Concentrations (1.5 µg/L and 0.15 µg/L for freshwater and marine organisms, respectively).

EDCs' occurrence in wastewater was also investigated, with particular attention to the different contamination levels between effluent and influent of wastewater treatment plant (WWTP). For example, in Volos (Greece), pharmaceutical and personal care compounds belonging to classes (from antibiotics to disinfectants) were detected during a one year monitoring study on water samples collected from the influent and the effluent of a WWTP, reaching concentrations from 1 ng/L to 15,320 ng/L in the influents and between 18 ng/L and 9965 ng/L in the effluents [85], highlighting that most EDCs are not removed by the performed treatment. In addition, several pharmaceutical compounds were identified in samples from five WWTPs in Santorini (Aegean Sea, Greece) at concentrations of 0.6 ng/L for nordiazepam and 6822 ng/L for carbamazepine in the influent and a non-negligible amount (0.4 ng/L for 9-OH risperidone and 2200 ng/L for carbamazepine) in the effluent [56].

Moreover, some works reported in the literature investigated surface water, wastewater, and drinking water, discovering concentrations that may differ by also several orders of magnitude depending on water type. The concentration of 13 selected EDCs was monitored in untreated urban and industrial wastewater in Serbia with the aim to assess their impact on the Danube River basin and associated freshwaters employed as sources for drinking water [78]. Natural and synthetic estrogens were detected in surface and wastewater at concentrations ranging from 0.1 to 64.8 ng/L, but not in drinking water. In addition, total estrogenic activity surpassed the threshold of 1 ng/L of E2 in three surface water samples and over half of wastewater samples. Alkylphenols, instead, were present in concentration ranges of 1.1–78.3 ng/L in wastewater, 0.1–37.2 ng/L in surface water, and 0.4–7.9 ng/L in drinking water. Among all EDCs identified, bisphenol A was the most abundant in all water types, with detection frequencies of 84% in wastewater, 70% in surface water, and 57% in drinking water [78]. Recently, emerging pesticides (chlorpyrifos, carbendazim, atrazine, and some of their degradates) were detected in freshwater (lakes and rivers) and drinking water (tap and bottled water) in Vietnam. Concentration in lakes reached 86.7 ng/L for carbendazim and 49.3 ng/L for triazines, while in rivers triazines content increased to 164 ng/L. Furthermore, lower contamination was observed for drinking water with respect to freshwater with total pesticide concentrations of 39.3 ng/L and 3.54 ng/L found in tap water and bottled water respectively [39]. Very different concentration levels were instead observed for parabens in distinct water sources, in particular mg/L in the influents of WWTPs, µg/L in their effluents, and ng/L in drinking water [91].

In order to evaluate human exposure to endocrine disruptors, the difference between wastewater concentrations and environmental concentrations of contaminants must be taken into account. Considering the results discussed above, humans are potentially

exposed to EDCs daily through drinking water intake. In fact, several EDCs have been identified in the treated drinking water supply worldwide [86,87,92], particularly in tap water in the concentration range of 0.2–5510 ng/L, with a maximum concentration (28,000 ng/L) detected in drinking water from the wells in India. Currently, the impact on human health derived from drinking water is considered negligible but the effects of long-term exposure (accumulation of EDCs also in mixtures up to the concentration of mg/L) are of concern [93]. Among EDCs all over the world, only a few of them have been regulated in the national drinking water standards, in particular BPA in Europe, the USA and Japan, NP in Japan, phthalates in China, Japan, and the USA, and E2 in Japan. Moreover, in some cases chlorination byproducts are more potent than their parent compounds, so chlorinated EDCs should also be taken into account in future drinking water regulations [94]. Greater scientific efforts should be devoted to monitoring EDCs in drinking water and the development of epidemiological studies in order to ensure safe access to drinking water.

In conclusion, endocrine disruptor compounds were detected in water environments all over the world in concentrations from ng/L to mg/L depending on the nature of the compound. Higher concentrations were discovered for chemicals from anthropogenic activities such as bisphenol A, nonylphenol, and phthalates, whereas natural hormones such E2 were detected at lower concentrations even if their activity is much higher than those of synthetic EDCs.

3.3. Analytical Methodologies for EDC Detection

The physical and chemical properties of EDCs influence instrument techniques, such as sensitivity and/or selectivity. An important parameter useful to compare the analytical methods is the limits of detection (LOD), calculated from the lowest analyte concentration producing a peak that could be reliably distinguished from the noise. So we reported the typical values of LODs for the most representative compounds for EDCs class i.e., bisphenol A (BPA), nonylphenol (NP), and 17 β -estradiol (E2) achieved from the different analytical methods present in the literature. The main analytical techniques used for EDC detection are summarized in Table 2 with their strengths and limitations.

Table 2. Comparison of the main analytical methods for EDC detection.

Analytical Techniques	Advantages	Limitations
Enzyme-linked immunosorbent assay (ELISA)	<ul style="list-style-type: none"> – Identification and quantification – Selective and reproducible – NP (LOD of 6 ng/L [95]), BPA (LOD range 30–80 ng/L [96]), and hormones with good sensitivity (LOD of 0.2–5 ng/L for E2), accuracy and precision 	<ul style="list-style-type: none"> – Use of bioantibodies that are unstable – Time consuming
Liquid chromatography methods	<ul style="list-style-type: none"> – Selective and reproducible – Small sample amounts – Limited sample preparation-Identification of a multi-class EDCs – LOD 5.7 ng/L for BPA, 2.7 ng/L for NP, and 3.3 ng/L for E2 	<ul style="list-style-type: none"> – High cost – Require expert analysts – Time consuming – Byproducts
Gas chromatography-mass spectrometry (GC-MS)	<ul style="list-style-type: none"> – Identification of organic pollutants – Quantification of small amounts in mass concentration – Suitable for biological matrices and environmental screening – LODs values: 1.5 ng/L for BPA, 0.3 ng/L for NP, and 0.1 ng/L for E2 	<ul style="list-style-type: none"> – Requires an expert operator – Time consuming – Derivatization step for non-volatile compounds and polar molecules – Interferences into the sample

Table 2. Cont.

Analytical Techniques	Advantages	Limitations
High-resolution gas chromatography-negative chemical ionization-mass spectrometry (HRGC-NCI-MS)	<ul style="list-style-type: none"> – Identification of EDC with quickness, accuracy, and high sensitivity – Identification of compounds with functional groups such as phenolic compounds – Identification of complex chemical components – Suitable for mixtures – LOD value: 0.02 ng/L for BPA, 0.05 ng/L for NP, and 0.1 ng/L for E2 	<ul style="list-style-type: none"> – Complex to use and expensive – Derivatization treatment – Time consuming

Gas chromatography coupled with a mass spectrometry detector (GC-MS) is one of the most powerful techniques for the separation and identification of organic pollutants, however, in the case of non-volatile compounds and polar molecules with one or more functional groups such as hydroxyl or carboxyl substituents (as is the case with the majority of EDCs), a derivatization step is often required before GC analysis. The derivatization step changes the properties of target molecules for better chromatographic separation and higher sensitivity of instrumental detection and prevents sample thermal decomposition. So, a disadvantage of the GC-MS analysis compared to liquid chromatography is the need for preparation sample processes that are often time consuming and may also introduce new interferences into the sample [97,98]. Recently, high-resolution gas chromatography-negative chemical ionization-mass spectrometry (HRGC-NCI-MS) was reported as an enhanced useful method to measure estrogens in the water sources thanks to the advantages related to the quickness, accuracy, and identification of complex chemical components [99]. Negative chemical ionization (NCI) is a soft ionization technique that provides high sensitivity and selectivity for compounds containing electronegative atoms or functional groups such as phenolic compounds [100]. Moreover, by introducing an electronegative group through derivatization, a large number of chemicals can be accurately and sensitively quantified using this approach. In the literature, the following rank order of methods for estrogen detection based on a number of studies has been reported: high-resolution gas chromatography-negative chemical ionization-mass spectrometry (HRGC-NCI-MS) (34.8%) > high-pressure liquid chromatography (HPLC) (30.5%) > liquid chromatography-high resolution mass spectrometry (LC-HRMS) (17.5%) > enzyme-linked immunosorbent assay (ELISA) (9.2%) > gas chromatography-mass spectrometry (GC-MS) (4%)~liquid chromatography-mass spectrometry (LC-MS) (4%) [101]. The HRGC-NCI-MS method is able to reach a LOD of nanograms per liter (ng/L) or slightly below (0.02 ng/L for BPA, 0.05 ng/L for NP, and 0.1 ng/L for E2) [102], which is very important in the case of phenols and steroids presents in the water at concentrations of ng/L and pg/L respectively.

Liquid chromatography methods (HPLC, LC-HRMS, and LC-MS), instead, eliminate the need for the derivatization step, which requires skillful analysts to obtain optimum results. However, the high capital cost involved for sophisticated instruments such as LC-tandem mass spectrometry (LC-MS-MS) makes the GC-MS an excellent alternative (typical LODs values: 1.5 ng/L for BPA, 0.3 ng/L for NP, and 0.1 ng/L for E2 [103]) for researchers with hands-on experience and skill in handling samples, providing comparable sensitivity and selectivity to the LC-MS [104]. Some works demonstrated that LC-MS-MS can examine and monitor a variety of organic pollutants consisting of a multi-class of EDCs compared to other chromatograms like HPLC and GC-MS. Due to the instrumental sensitivity and accuracy, LC-MS-MS permits identifying and quantifying the multi-class of targeted EDCs in environmental samples (LODs values: 5.7 ng/L for BPA, 2.7 ng/L for NP, and 3.3 ng/L for E2) that are expected to have a very low concentration (10–1000 ng/L) [105].

Furthermore, LC-MS combined with multiple reaction monitoring analysis is a sensitive tool for the qualitative and quantitative determination of the target analytes [106].

Although the above discussed chromatography techniques can identify and quantify EDCs with high sensitivity and accuracy, they also require expensive equipment, skilled technicians, and time-consuming sample preparation procedures [93–95]. For these reasons, alternative immuno-analytical methods for rapid detection of EDCs such as enzyme-linked immunosorbent assay (ELISA) and immunosensors were developed in the last years [107]. The ELISA method was successfully employed for the quantification of nonylphenol (LOD of 6 ng/L [95]), bisphenol A (LOD range 30–80 ng/L [96]), and hormones with good sensitivity (LOD of 0.2–5 ng/L for E2), accuracy (mean recovery 96%), and precision (RSD 7–10) [108]. These immuno-analytical methodologies have high sensitivity, cost effectiveness and simplification but employ bioantibodies that are unstable and require a long time to be prepared [109]. These disadvantages have been overcome by many researchers through synthesizing antibody alternatives able to imitate the molecular recognition characteristics of bioantibodies. For example, a sensitive plasmonic biomimetic-ELISA (PBELISA) method, which involves the use of molecularly imprinted polymers film as recognition elements and catalase-mediated growth of AuNPs as signal generation strategy, was recently reported in the literature for the detection of BPA [110]. This method has several remarkable advantages including time saving and cost effectiveness, and shows excellent selectivity and sensitivity for BPA with a LOD of 6.20 ng/L, making it suitable for the detection of trace BPA residues in real samples. However, the detection of BPA through ELISA is specially challenging because this method is less specific than others due to the fact that it can also detect other bisphenols [111,112].

In conclusion, both chromatographic techniques (GC-MS and LC-MS) and immuno-analytical methods (ELISA) were extensively reported in the literature for the detection of EDCs in water matrices. In recent years the development of advanced analytical methodologies (e.g., HRGC-NCI-MS, LC-MS-MS, and PBELISA) have allowed reaching very low LOD for several EDCs (lower than ng/L) making their monitoring easier, but with a consequent increase of the cost of instrumentation and qualified personnel.

3.4. Removal of EDCs from Water

Current water and wastewater treatment technologies, including flocculation, chemical coagulation, precipitation, adsorption, membrane, and activated sludge processes, provide only the reduction of endocrine disruptor concentrations. In order to reach their total removal from waters, advanced processes need to be employed, thus minimizing the health issues that these compounds can cause even at low concentrations (below the LOAEL). Owing to the diverse physicochemical properties of the endocrine disruptors, several processes can be applied as treatment technologies, obtaining distinct removal efficiencies [41]. Different methods, like biosorption, adsorption, advanced oxidation, membrane filtration, and biodegradation, have been investigated as suitable treatment pathways [113–116] for the removal of EDCs, mainly bisphenol A, phthalates, natural and synthetic estrogens (estrone, 17 α -ethynylestradiol, 17 β -estradiol), parabens, alkylphenols, and pharmaceuticals.

Thanks to its exceptional characteristics such as great efficiency, low operative and maintenance costs, and no relevant byproduct generation, adsorption is one of the most employed processes for EDC removal from water. Several compounds such as clays [117], zeolites [118], biochars, bioadsorbents, metal-organic frameworks [119], graphene oxide [120], carbon nanotubes [121], and industrial waste have been studied as novel non-conventional adsorbents in alternative to the more expensive activated carbon (the most used material for micro-contaminant removal) in order to make the adsorption process for the treatment of endocrine disruptors more sustainable [122–124]. In this context, bioadsorbents can be considered as green and economical alternatives to commonly used carbon-based adsorbents thanks to the fact that they are available and abundant in nature. Consequently, biosorption methodology was widely used in drinking water and industrial wastewater

treatment [125,126] because it is easy to apply, inexpensive, low energy consuming, and gives safe byproducts [55,127]. The most employed biosorbents are fungi, yeast, bacteria, algae, chitosan, wood, bio-polymers, and wastes of agriculture materials that are usually more selective than conventional adsorbents [128,129]. The possible use of a sulfonated derivative of coffee waste (CW-SO₃H) as a convenient and effective biosorbent for the removal of BPA from an aqueous solution has been reported in the literature with the aim to obtain a biosorbent to clean contaminated water and reduce coffee waste at the same time [130]. CW-SO₃H has shown good properties such as a calculated biosorption capacity of 270 mg/g for the removal of BPA, about five times higher than the commercially available activated carbon. Moreover, bean (*Phaseolus vulgaris*) husk biomass residual wastes were recently employed to obtain activated carbon in the presence of orthophosphoric acid, reaching optimum results in the sequestration of ibuprofen (IBP) from aqueous solution at pH of 4.75 with a maximum monolayer adsorptive capacity of 50.00 mg/g at 50 °C [131].

Membrane filtration (microfiltration, ultrafiltration, nanofiltration, and reverse osmosis), instead, take advantage of the particular physicochemical characteristics of the material from which membrane is made to successfully reject a wide spectrum of endocrine disruptors [132–134]. Ultrafiltration removal efficiency can be improved by combining it with other technologies like advanced oxidation processes, chlorination, and ozonation. The ultrafiltration-ozonation hybrid system employed by Si et al. [135] was able to remove up to 99% of all endocrine disruptors under study (17β-estradiol, estriol, 17α-ethynylestradiol, and bisphenol A), compared to 46% and 70% reached using only ultrafiltration and ozonation, respectively. For the same reasons, membrane bioreactor is usually combined with nanofiltration or reverse osmosis process, thus improving the removal rate of contaminants such as bisphenol A, alkylphenols and carbamazepine [136,137].

Biological processes (both aerobic and anaerobic), such as activated sludge treatment [138], anaerobic digester systems [139], and fungal bioreactors [140] are also frequently used in the removal of endocrine disruptors, especially in combination with other tertiary treatments to improve their efficiency [132,141,142]. Through different enzymatic mechanisms (e.g., adsorption, accumulation and so on) bacteria, microalgae, and fungi can efficiently degrade EDCs with better performances for mixed populations with respect to individual microorganisms [143,144]. In this context, marine microalgae species such as *P. globosa*, *N. oculata*, *D. salina*, and *P. subcordiformis* can remove nonylphenol (NP) from polluted aquatic ecosystems via biosorption, biodegradation, or biotransformation, with efficiencies ranging from 43% to 91% [145]. Extracellular ligninolytic enzymes secreted by white rot fungi, instead, can biodegrade EDCs such as bisphenol A and nonylphenol with removal efficiency from wastewater in the range of 60–100% for BPA and 65–90% for NP depending on the fungi species, incubation time, and initial concentration of pollutants [146]. Among microorganisms, fungi gave the best results in terms of their ability to biologically remove EDCs from water [147] thanks to their very active enzymatic systems [144,148].

Regarding advanced oxidation processes (AOPs), several studies are reported in the literature for ozonation, UV/peroxide [91], Fenton, and photocatalysis [149], usually in combination to obtain better results. As an example, the UV-ozone combined process [150] is more active in the removal from the water of EDCs such as bisphenol A, 17β-estradiol, and estriol than ozone alone, while chlorine oxidant produces several byproducts without a reduction of the estrogenic activity of EDCs [151]. The Fenton process coupled with biological treatment using up-flow anaerobic sludge blanket reactor showed an initial EE2 removal (1000 µg/L of these compounds were spiked in the samples daily) of 99%, also reducing toxicity from 73% to 30% [152].

The application of EDC treatments is based on the various concentrations and complexity of EDC compounds, and it requires accurate and appropriate sampling, determination, extraction, quantification, storage, and preservation procedures. The individuation of an appropriate removal treatment could consider the EDC characteristics, in some cases each EDC contaminant has different treatment procedures. In practice, the membrane filtration process is an efficient method for EDC removal without further treatments. Neverthe-

less, like other EDC treatment methods, the membrane filtrations are not able to remove emerging contaminants completely. At the same time, adsorption may be an effective process at low cost and wide spectrum of reliability, even if the process requires sorbent regeneration or disposal there are sustainable solutions using waste products. On the other hand, advanced oxidation processes such as Fenton were successfully utilized to remove E3, BPA, diethylstilbestrol (DES), E2, and EE2 with removal efficiencies of 84.9%, 99.5%, 99.1%, 97.8%, and 84.5%, respectively as reported by Sun et al. [153]. The photo-Fenton process also showed a removal efficiency for pharmaceutical compounds, many types of hormones, phenolic, pesticide, and PPCP compounds, ranging from 95% to 100% [154–156]. Nevertheless, the limitation of these processes was determined by the infeasible regeneration of iron ions and the final treatment of effluent to meet the discharge standards for iron concentrations. Thus, the overall factor of limitations and challenges in EDC treatment methods such as solubility, hydrophilicity, degradability, and polarity influenced the applicability of the treatment techniques from the degradation pathways and the byproducts produced. In Table 3 we report a comparison of the most common methodologies useful for EDC removal from water, with attention to water sources and EDC types, highlighting the effectiveness and drawbacks of each treatment, providing a potential outlook of EDC treatment strategies in water and wastewater treatment systems.

Table 3. Comparison of removal treatment strategies for endocrine-disrupting chemicals in water and wastewater systems.

Removal Techniques	Water Source/ EDC Type	Advantages	Limitations
Adsorption	<ul style="list-style-type: none"> – Drinking water and wastewater – Pesticides, triclosan, naproxen, ibuprofen, ketoprofen, trimethoprim, acebutolol, diazepam, diltiazem 	<ul style="list-style-type: none"> – Great efficiency – Low operative and maintenance costs – No byproducts – Easy to apply – Low energy consumption 	<ul style="list-style-type: none"> – Sorbent regeneration or disposal – Use of non-conventional adsorbents enhances the – Adequate contact time and dosage affect the performance – Low removal of carbamazepine and propranolol
Membrane filtration	<ul style="list-style-type: none"> – Wastewater – Emerging compounds, such as PPCPs, pesticides, BPA, E1, E2, EE2, 17β-estradiol-17-acetate, NP, triclosan 	<ul style="list-style-type: none"> – Wide spectrum of activity – Ultrafiltration methodology able to remove a high level of all endocrine disruptors 	<ul style="list-style-type: none"> – High cost – Toxic waste byproduct – Concentrates (brine) are primarily discharged to the surface water – The challenges of treatment and discharge of the contaminants accumulated during the process – Post treatments
Biological process	<ul style="list-style-type: none"> – Water and wastewater – Rstrogenic compounds EE2, E2, 17α-acetate, pentachlorophenol, 4tert-octylphenol, triclosan – no toxic substances 	<ul style="list-style-type: none"> – High biodegradation level to 90% – No byproducts – Low costs 	<ul style="list-style-type: none"> – Efficacy related to different enzymatic mechanisms – Incubation time – Pretreatment of sample as initial concentration of pollutant
Advanced oxidation processes	<ul style="list-style-type: none"> – Water and wastewater – E3, BPA, diethylstilbestrol (DES), E2, and EE2, carbamazepine, hormones, phenolic, pesticide, PPCPs, and pharmaceutical compounds, antibiotics (such as ciprofloxacin, amoxicillin, sulfathiazole, and sulfamethazine), nonylphenol deca-ethoxylate 	<ul style="list-style-type: none"> – Wide spectrum of efficiency – Removal up to 80% of EDC compounds – High degree of sensitivity 	<ul style="list-style-type: none"> – High costs – Regeneration of active substance – Post-treatment water – Byproducts

A comparison of advanced oxidation processes for EDC removal was reported in the literature on the basis of multiple factors (such as process engineering, environmental, economic, and social parameters) and numerically scored (from 1 to 5 corresponding to descriptive variable of “very low” to “very high”) to describe the different performances. The results of this study highlighted that H_2O_2/O_3 (perozonation) received the highest average ranking (3.45), and other processes showed comparable performance thanks to advantages related to an established technology, regulation, and public acceptance [157]. However, the Photo-Fenton process could be considered the best treatment for endocrine-disrupting compounds thanks to its technical characteristics and higher efficient removal of many different compounds such as hormones, phenolic compounds and pesticides.

In conclusion, since many EDCs are not degraded enough by the available microorganisms, biodegradation must be associated with other methods such as membrane filtrations and advanced oxidation processes to improve removal percentages. As a consequence, combined techniques are recommended for better utilization of the current treatment technologies in order to minimize the concentration of EDCs in water.

3.5. EDC Accumulation in Dynamic Systems

In this section, it has been shown that EDCs are persistent contaminants and are being detected throughout the water cycle (surface water, both freshwater and seawater, groundwater, rainwater runoff, wastewater, and drinking water) at different concentration levels. Accumulation of such pollutants in dynamic systems is difficult to assess, due to water transport across the water cycles. Despite the fact that natural attenuation can remove contaminants from the cycles, strong evidence of the persistence of EDCs in groundwater have been reported. For example, EDCs as sulfamethoxazole, 4-nonylphenol, 17β -estradiol, and pharmaceutical residues, have been detected in the same groundwater for decades, causing a long-term and probably sustained contamination of this water [158]. Moreover, sorption of these contaminants to sediments, which in some cases provides natural purification of surface water and groundwater, can result in a long-term source. Several examples are reported in the literature regarding EDC accumulation in the river and marine sediments [159–161]. Nonylphenol at a concentration of 22–645 $\mu\text{g}/\text{kg}$ was detected in sediments of a Spanish river (the Llobregat River) [160] that receive waters from a sewage treatment plants, while in China 7.55–20.8 $\mu\text{g}/\text{kg}$ of NP and 2.31–13.16 $\mu\text{g}/\text{kg}$ of BPA were observed at the Pearl River Estuary [161] and 77–199 $\mu\text{g}/\text{kg}$ of BPA in the Bahe River [162]. Furthermore, phtalates were detected at a concentration of 12–610 $\mu\text{g}/\text{kg}$ in sediments of the Mediterranean Sea [159]. Due to the low biodegradability of the majority of EDCs, their persistence may affect soil biota and they can also be resuspended in water to be again in the water cycle.

4. Effects of Exposure to EDCs and Health Implications

4.1. EDCs' Mode of Action

The effect of EDCs could be described in three different actions: endocrine activity [18]; deleterious and/or pathologic endocrine mediated activity [24]; the cause-effect relationship between substance and endocrine activity in exposed subjects [163–165]. The European Safety Authority (EFSA) proposes that EDCs disrupt the endocrine system by binding hormonal receptors and/or regulating genomic expression. Moreover, mechanisms involved in endocrine disruption seem to be related to epigenetic alterations, like histone modifications and methylation and/or acetylation of DNA [166,167]. Nuclear hormone receptors (NHRs) are the main receptors that are targeted by EDCs [168]. Thus, endocrine disruptors may mimic the natural hormone's function, acting as agonists or antagonists of them [169–171]. NHRs are activated by steroid hormones and can induce long-term effects in their target cells. As an example, the estrogen receptor, androgen receptor, progesterone receptor, pregnane X receptor, constitutive androstane receptor, thyroid hormone receptor, retinoid X receptor, glucocorticoid receptor, and mineralocorticoid receptor belong to the NHRs family [172]. Ultimately, EDCs can bind to or interact with

or activate hormone receptors; antagonize hormone receptors; alter hormone synthesis, receptor expression, transport across cell membranes, distribution levels and metabolism of hormones and signal transduction in hormone-responsive cells; induce epigenetic modifications in hormone-producing or hormone-responsive cells [173,174]. Figure 4 shows the schematic representation of the main EDC modes of action.

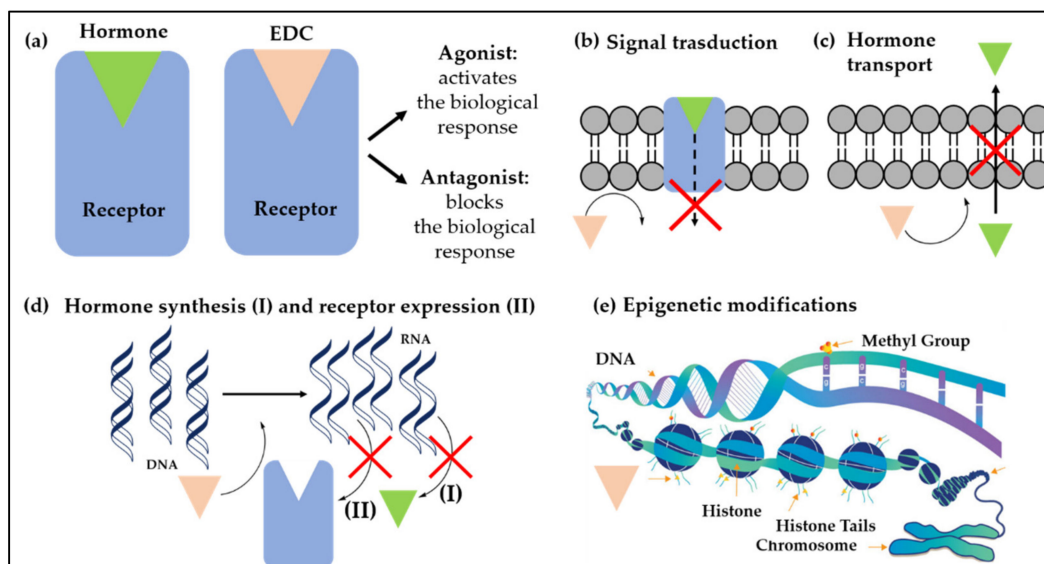


Figure 4. Schematic representation of the main EDC modes of action: (a) bind to hormone receptors acting as agonist or antagonist; (b) alter signal transduction; (c) block hormone transport across cell membranes; (d) alter hormone synthesis or receptor expression; (e) induce epigenetic modifications.

In recent literature, there is a heated debate concerning the presence or otherwise of phenomena such as the non-monotonic dose-response relationships (NMDRC) and low-dose effects of endocrine disruptors. The existence of these phenomena is very important because it has a significant impact on the way risk assessments are conducted for these chemicals. Concerning low-dose effects, low doses are considered those below the doses used for traditional toxicological studies or tested in traditional toxicology assessments or occurring in the range of human exposures [175]. The NMDRC is defined as a nonlinear relationship between dose and effect, occurring where the slope of the dose–response curve changes sign somewhere within the range of doses examined [175]. Traditional approaches in regulatory toxicology assume that the dose–response curve is always monotonic. Under this assumption, high-dose testing can be used as the standard for assessing chemical safety. However, if an NMDRC is present, there is no certainty that the lack of adverse effects at high doses also confirms safety at low doses and consequently possible effects at low doses cannot be predicted by those occurred at higher doses. For example, in the case of hormones, even moderate changes in concentration in the low-dose range can produce substantial changes in receptor occupancy and therefore generate significant changes in biological effects. Due to the non-monotonic behavior, concepts such as potency and threshold are difficult to assess for EDCs. In fact, under the hypothesis of a monotonic relationship, risks associated with hazards can be greatly reduced by decreasing exposure. Whereas, it might be necessary to eliminate the hazard entirely to ensure safety when an NMDR is observed because the reduction of exposure may have uncertain effects on risk [176]. Moreover, it makes it very difficult to predict a safe level of exposure and it cannot be assumed that there are thresholds below which EDC exposures are safe. This is the position of The Endocrine Society, supported by decades of endocrine science [177]. However, there is no consensus in the scientific community on the existence of these phenomena and their relevance in toxicology. In contrast to The Endocrine Society’s position, in fact, other authors assert that toxicology and biology predict that the threshold of adversity

(defined as a position that separates dose levels at which the effect can occur from dose levels at which it will not occur) also exists at all endpoints for endocrine disruptors, even if it cannot be measured due to experimental science limits in determining the shape of the dose response at very low doses [23]. For these purposes, experimental values used in conventional toxicity testing for regulatory risk assessment are the NOAEL (no observed adverse effect level) defined as the highest dose at which there was not an observed adverse effect and the LOAEL (lowest observed adverse effect level) i.e., the lowest dose at which there was an observed adverse effect. The reference dose for toxicological studies strongly depends on the EDC type considered. Several epidemiology studies on EDCs indicate that harm is occurring in animals and humans that are exposed at or below the “safe” dose suggesting that the methods nowadays employed in regulatory toxicology must be improved to correctly predict EDCs contribution to human diseases or to identify the doses that can cause harm [178].

The dangerous effect of EDCs moves over a wide range of concentrations taking into account the heterogeneity in chemical structures of this class of compounds. The potency of a chemical to activate specific hormone receptors is determined by its affinity and efficacy. A compound with low affinity must have a good efficacy to bind the receptor site; thus a sufficient concentration is necessary to produce a cellular response [179]. Typically endogenous hormones have both higher affinity and higher efficacy than exogenous chemicals that make them very potent. For example, bisphenol A is reported to be 6 orders of magnitude less potent than 17β -estradiol [180]. As a consequence, considerably higher concentrations of synthetic EDCs with respect to natural hormones are required to attain sufficient receptor occupancy or to displace endogenous ligands, and so show observable adverse effects. For this reason, some authors assert that human exposure to synthetic EDCs is generally negligible as compared to natural ones that have higher endocrine activity [181]. However, in the case of phenolic compounds, such as alkylphenols and bisphenol A, concentrations (up to mg/L) detected in wastewater [182] were higher than the natural steroidal estrogen 17β -estradiol and the synthetic contraceptive 17α -ethinylestradiol that have higher estrogenic activity (ng/L) [183].

4.2. Transport of EDCs to Humans

Several papers considered the presence of EDCs effects in marine organisms: it is well known that fish, such as zebrafish, medaka and fathead minnow, food fish like carps (*Cirrhinus mrigala*, *Catla*, and *Labeo rohita*), followed by murrels (*Channa marulius*, *C. punctatus* and *C. striatus*), and catfish (*Clarias gariepinus*, *C. batrachus* and *Heteropneustes fossilis*) could be used as bioindicators to understand toxicity related to ingestion, sorption, bioaccumulation, and translocation, identifying the presence of EDCs [45,184,185].

EDCs bioaccumulate in the organisms via uptake of the chemicals directly from the environment (deconcentration) or by ingestion of other organisms containing the pollutants. Once they have entered a food chain, their concentrations tend to increase with trophic status (biomagnification), leading to the highest concentrations in the top predator. Moreover, biomagnification may also be due to increased body size and lipid contents, and higher metabolic activities.

Diet also plays an important role in the exposure to EDC through beverages. In China, in fact, several EDCs such as phthalates (14,400 ng/L), parabens, bisphenol analogs, benzophenone-type UV filters (20 ng/L), and triclosan (10 ng/mL) were discovered in 116 popular beverage samples. The results suggested that phthalates were the predominant EDCs in all beverages with daily intakes lower than their respective maximum acceptable doses suggested by various agencies, indicating a low potential health risk [186].

Based on the data reported above concerning drinking water contamination with EDCs, a possible route for human exposure is represented by drinking water. The World Health Organization (WHO) has proposed the following three representative EDCs for drinking water contamination and benchmark values: 0.01 $\mu\text{g/L}$ for bisphenol A, 0.001 $\mu\text{g/L}$ for 17β -estradiol, and 0.3 $\mu\text{g/L}$ for nonylphenol. As indicated by the WHO,

currently there is no evidence of risks to health from drinking water but these parameters have been included in the Directive on the basis of the precautionary principle since aquatic life is much more sensitive to the effects of estrogenic EDCs than humans [187]. In the last years in the US, the levels in drinking water have been reported to be at or below these numbers [188]. The US EPA (United States Environmental Protection Agency) did not propose restrictions for EDCs in the United States. Endocrine disruptors will be subjected by EPA to a comprehensive risk assessment by taking into account the differences between the levels of exposure that can produce adverse effects, and the typical exposure levels experienced by humans and wildlife in order to determine if this safety standard is appropriate to protect public health and the environment [189]. Although in 2018 the European Commission adopted a proposal for a revised drinking water directive that would add limit values for endocrine-disrupting chemicals to the list of criteria for monitoring water quality, it must be taken into account that humans and other organisms are often exposed to mixtures of chemical substances, the composition of which is not known and that the assessment scheme based on a single substance is not adequate.

4.3. Effect of EDCs: Animals, Humans, and Mixture Effect

The main concern related to endocrine disruptors is represented by the disorder they can activate in humans or wildlife by modifying the level of hormones in the body [190–192], given their mechanism of accumulation in tissues and the environment. In this subsection we report several studies on the effects observed in animals and humans due to exposure to EDCs.

4.3.1. Effect on Animals

In wildlife, EDCs are suspected in the decline of certain species (e.g., possible increased sterility in the American alligator), change of sex in fish and shellfish, and other problems [193–196]. In fact, some pesticides (thiocarbamates, chlororganics, imidazoles, triazoles, triazines) determine an antiandrogenic action, highlighted by the changes in macroscopic sexual findings in aquatic animals (particularly for exposure to herbicides and fungicides) such as the demasculinization in rats and fish [197], the production of estrogens and hermaphroditism in frogs [198], and other developmental disorders of the male gonad in alligators [199]. For example, a study on *Daphnia Magna* has shown that endosulfan sulfate disrupts the ecdysteroidal system (regulating processes such as molting and embryonic development) and juvenile hormone activity (regulating the sex ratio) of crustaceans [200,201]. Many studies have highlighted that EDCs can cause adverse effects in animals, including gene suppression and gene activation, even at very low concentrations (parts per billion and parts per trillion) [202–204]. Bosveld et al. reported some reproductive outcomes, hormone metabolism, and circulating steroid levels of fish-eating birds caused by effects of organohalogenes [205]. Even in teleosts, seals, whales, and other mammals, several studies described the EDC-induced reproductive failure and thyroidal anomalies due to PCB and polybrominated diphenyl ether (PBDE) contamination [49,206,207]. Some experiments in zebra fish brain indicated that in the presence of diethylhexyl phthalate in the environment, particularly with very low doses, such as 0.02 mg/L, the organism could have a negative modulation of appetite stimulus, also confirmed by the real-time quantitative reverse transcription PCR analysis performed on key molecules involved in appetite control [208]. Moreover, pesticides such as dichlorodiphenyltrichloroethane (DDT) can block the receptors, inhibiting their function and the activity of hormones, thus altering hormonal feedback [209,210]. In many cases, the interaction of pesticides with the hormonal (endocrine) system of wildlife has led to impaired reproduction and gradual population decline of certain species [211]. It has several consequences on the endocrine system such as demasculinization and feminization of gonads [194] of male vertebrates, control of ovarian growth exerted by the neurohormones secreted at the eyestalk of the crab *Neohelice granulata* [212], and long-term histofunctional changes in the thyroid gland on the crocodilian specie of *C. latirostris* during embryonic development [213]. The endocrine-disrupting

activity of these pesticides and their metabolites (e.g., dialkyl phosphates) has been observed in different animals. In particular, it was observed a homeostasis imbalance of hormones associated with the hypothalamus-pituitary-gonad axis [214] and hypothalamus-pituitary-adrenal axis [215] in rats, and with the hypothalamus-pituitary-thyroid axis in zebrafish [216].

The above reported effects are observed in species that are likely to be exposed to EDCs or that are used as a mammalian model for humans (e.g., rats). Most of them are related to sexual disorders that could have negative consequences in the preservation of animal species.

4.3.2. Effect on Humans

Several human organs and related glands are targeted by endocrine disruptors such as the brain (hypothalamus, pineal and pituitary glands), thyroid and parathyroid, adrenal gland, thymus, pancreas and gonads (testes and ovaries) as shown in Figure 5.

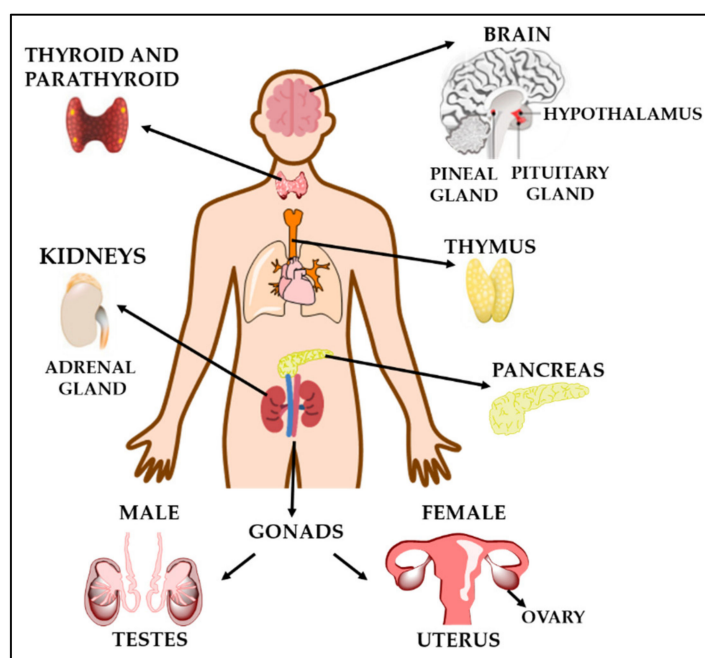


Figure 5. Representation of main endocrine glands targeted by EDCs.

EDCs cause antiandrogenic effects even in humans. Moreover they mimic the estrogenic action, as confirmed by both experiments *in vivo* and *in vitro* [217–222]. This great attention to the reproductive system underlines how it can represent a sentinel organ for environmental stresses. In fact, epidemiological data and the most recent studies report human semen as an important source of early biomarkers in comparison with blood for assessing the environmental impact on human health, confirming its high sensitivity [223–225].

Pesticides were tested for antagonism to a human androgen receptor (hAR) by highly sensitive transactivation assays using Chinese hamster ovary cells. Results have shown that 66 of 200 pesticides under study exhibited antiandrogenic activity [29]. Supporting evidence of the dangerous effects of EDCs on the endocrine system and their complicated regulation mechanisms have been widely reported in the literature [226]. Organochlorine pesticides, used worldwide for several decades, are characterized by bioaccumulation in the environment, especially in the food chain, through which they reach the human body, and are largely detected in population screenings often correlated with various diseases [227]. In fact, cross-sectional association between use of OCPs and risk of hypothyroidism and hyperthyroidism among female spouses ($n = 16,529$) in Iowa and North Carolina (USA) was reported in the Agricultural Health Study in 1993–1997. In Taiwan [228] cow milk

and beef consumption as well as menstruation characteristics were significantly associated with several OCPs (in particular hexachlorocyclohexanes) residues in breast milk. Furthermore, a correlation between β - and γ -hexachlorocyclohexanes and the infertility diseases of Taiwanese women was observed, so dietary habits might affect the exposure to these EDCs. The use of the OCPs chlordane, the fungicides benomyl and maneb/mancozeb, and the herbicide paraquat was significantly associated with thyroid dysfunctions such as hypothyroidism and hyperthyroidism (both solely for maneb/mancozeb). These results suggest a synergic role of organochlorines with fungicides in the development of thyroid diseases among women [229]. Different epidemiological studies have been conducted on the possible association between glyphosate (widely employed herbicides) exposure and the high risk of adverse reproductive outcomes and birth defects in the progeny, showing that women exposed to glyphosate increase the risk of late miscarriages and a decrease in fecundability. Moreover, this exposure during pregnancy is associated with an increase of anogenital distance in both males and females, increased testosterone levels in the female and several disturbances of developmental and reproductive parameters in progeny, such as retardation of the fetal skeleton [230]. Other EDCs such as phthalates were characterized by reproductive toxicity in humans and animals, many of them were antiandrogenic and they can cause infertility and reproductive problems in males [231]. They are more toxic to young children, who are much more susceptible to exposure, including fetal life [232]. A statistically significant and negative association between exposure to phthalates (such as monoethyl phthalate, monobutyl phthalate, and monobenzyl phthalate) and anogenital distance (AGD), penis length and width was observed in Mexican male newborns [233]. Concerning bisphenol A, it has several harmful effects on human health, especially for women. Thanks to its estrogenic activity, bisphenol A can bind to α - and β -estrogen receptors and act as a reproductive toxicant and affect fertility even at very low concentrations [234,235]. In fact, in a recent study, bisphenol A was detected in all infertile women with polycystic ovary syndrome [236]. Current research reveals that endocrine disruptors also interfere with energy metabolic homeostasis. Indeed, these compounds may decrease basal metabolic rate, modificate the regulation of appetite and satiety, impair adipose tissue by enhancing the number and size of adipose cells and varying their endocrine regulation and adipocytokine production [237]. An exposure to these chemicals (called obesogens) during early development increases such adverse health consequences, in addition to a predisposition to weight gain despite a correct balance of diet and physical activity [190,238]. Another target of endocrine-disrupting compounds is represented by the diencephalic system. In fact, besides their interaction with endocrine receptors, EDCs may mimic neurotransmitter actions, thus altering the proper function of the central nervous system [239]. Moreover, several EDCs, including bisphenol A, phthalates, polychlorinated biphenyls, and organochlorine pesticides, influence diabetes pathogenesis, and differential exposure to them might also contribute to racial/ethnic and economic inequality [240]. A correlation between exposure to endocrine disruptors and attention-deficit hyperactivity disorder, autism spectrum disorder, intellectual disability, global developmental delay, communication disorders, and neurodevelopmental disorders are reported by several studies. In particular, some EDCs, such as polybrominated diphenyl ethers, hexachlorobenzene, and bisphenol A, are reported to be a serious risk factor for the onset of neurodevelopmental disorders [241]. Furthermore, maternal exposure to plastic-derived endocrine-disrupting compounds (e.g., bisphenols, bis (2-ethylhexyl) phthalate and dibutyl phthalate) during the early development stages may affect pregnancy outcomes by altering embryo and placental development [242]. In fact, EDCs can produce more deleterious effects if exposure occurs during early development, referred as the time frame in which hormones are controlling cell changes to form tissues and organs. Exposure to EDCs during the developmental programming of a tissue, at lower doses than are required for effects in adults, could lead to changes in tissue development with effects that, although not apparent at birth, may appear later in life. However, these harmful consequences on the fetus development and postnatal health need to be further investigated by long-term studies. Typically the concentrations of

EDCs found in the aquatic environment are lower than those at which these chemicals are considered harmful by regulatory toxicology. Nevertheless, for these particular chemicals, low doses could also have dangerous effects. Based on these considerations, research on effects of long-term exposures to low doses of EDCs should be performed in order to better evaluate the implications for human health.

4.3.3. Additive or Synergistic Effects of EDC Blends: Mixture Effects

In 2017 Barouki et al. [243] reported the additive or synergistic effects of EDCs; although a single compound could be innocuous, the combination of several endocrine disruptors might have dangerous consequences (i.e., the cocktail effect). The issue of blends has to be taken into consideration in the study of EDCs. The risk assessment, in fact, in the traditional scheme considers the effects of individual substances and does not take into account the possible effects of the mixtures present in the environment. In addition, due to the presence of mixtures, there is an awareness, at a scientific and regulatory level, that the risk deriving from these chemicals is underestimated. More attention and insights concerning the effects of chemical multi-exposure are hoped for by the authorities of the European Union. For this reason, particular caution is required even towards the lowest concentration levels. On the one hand, this is intended to be a critical reflection for the benefit of the experts because of the necessity of scientific insights, and on the other, for the legislators and administrators that can achieve increasingly sustainable management of the environment. However, the risk correlated to EDC mixtures is hard to assess due to the complexity of overall toxicity, their interaction, and the attendance of a sensitive period [181,244,245]. To improve the assessment of human exposure to chemical mixtures, researchers can apply *in vitro* assays to analyze the human health effects of these mixtures in biological samples. Moreover, the combination of *in vitro* assays with advanced high-resolution analytical tools can be advantageous to assess exposure and effect in humans due to mixtures of chemicals of concern and consequently identify chemicals that should be considered by regulatory authorities [246,247]. Definitely, the hypothesized causal relationship between EDC exposure and endocrine diseases needs to be further verified by long-term studies carried out on a wider number of subjects.

4.4. Strategies for the Reduction of EDC Pollution

Considering the above reported effect of EDC pollution, some strategies for the reduction of their sources and paths into the environment could be employed. Drinking water supplies must be protected from EDC contamination through tighter controls on sources and efficient treatment technologies. The discharge of chemicals into the sewer system must be banned and monitored in order to identify individual sources of contaminants. The same approach should be adopted for controlling the improper disposal of pharmaceutical and hospital waste and leaching of chemicals used in industrial and household items. Inclusion of limits for emerging contaminants such as EDCs in industrial wastewater discharges could lead to the reduction of the amount of harmful chemicals released to municipal wastewater by companies [248]. Moreover, several compounds with higher endocrine-disrupting potency should be replaced by environmentally friendly alternatives. This is especially relevant for pharmaceuticals and personal care products, plastic-derived compounds (phthalates and bisphenols), and pesticides. The use of some pesticides or antibiotics in animal husbandry has to be strongly restricted in all countries. Higher removal efficiencies must be reached for EDC removal in particular for heavily polluted wastewater and drinking water. Great attention must be paid to minimize the formation of treatment byproducts, notably in the case of chlorination processes due to the fact that chlorinated EDCs are often more potent than their parent compounds, e.g., in the case of BPA [94]. In conclusion, more appropriate limits for EDC concentration in water have to be proposed to ensure human safety, based on future studies on human health effects of long-term low-dose exposure to those EDCs that reach the human body through the consumption of water.

5. Conclusions

Endocrine disruptors have accumulated in the aquatic environment with consequent potential adverse exposure effects on humans such as homeostasis of the endocrine axis that leads to neurological, developmental, immunological, and reproductive disorders. Some chemicals that fall into this category are sex-steroid hormone mimics, pesticides, and fertilizers, derived from the waste of industries, agriculture, pharmaceuticals, and sewage treatment plants. In this review, we analyzed the most recent literature related to EDCs in the environment, particularly in water, analytical methods, removal techniques and their potential human exposure routes and health implications. The key learning points of this review are contamination of water (freshwater, seawater, wastewater and drinking water); strengths and limitations of current analytical methods employed in endocrine disruptors detection; advantages and disadvantages of treatment technologies useful for EDC removal from water; biological effects on animals and humans. Some EDCs as hormones (E1, E2, E3, EE2), carbendazim, chlorpyrifos, dimethoate, iprodione, methomyl, tebuconazole, alkyl phenols, phthalates, and bisphenol A are almost ubiquitous in significant quantities in all the matrices, suggesting that they can easily enter our body. Most of the studies showed evidence of toxic effects in animals, which are part of the human diet. The analytical limits must, in particular, be adjusted to allow comparison with the EQS, which are often significantly lower, taking into account the provisions of the European Directives, which sets minimum efficiency criteria for the methods used to monitor the status of waters, sediments, and biota. EDC contamination is a complex phenomenon that is difficult to predict, both due to the large number of substances used and the multiplicity of paths they can follow in the environment. It must, therefore, be taken into account that humans and other organisms are often exposed to mixtures of chemical substances, the composition of which is not known a priori and that the assessment scheme based on a single substance is not adequate. It is necessary to take note of this evidence, confirmed worldwide, with a more cautious approach in the authorization phase. In order to better evaluate the implications for human health and confirm the hypothesized causal relationship between EDC exposure and endocrine diseases, studies on a wider number of subjects also exposed to low doses of EDCs for longer times should be performed.

Author Contributions: Conceptualization, L.M., O.M. and P.M.B.; methodology, C.P. and M.R.; validation, M.R., A.P. and L.M.; formal analysis, C.P. and M.R.; resources, O.M. and A.P.; writing—original draft preparation, M.R. and C.P.; writing—review and editing, C.P., M.R., P.M.B., L.M. and O.M.; visualization, C.P., M.R., A.P., P.M.B., L.M. and O.M.; supervision, L.M. and O.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: This research has been funded by the University of Salerno (FARB 2017). The authors gratefully acknowledge Ylenia Miele for English language revision and Antonio Faggiano for graphical support.

Conflicts of Interest: The authors declare no conflict of interest.

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