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Review

The methods of identification, analysis, and removal of endocrine disrupting compounds (EDCs) in water

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ABSTRACT

The information regarding endocrine disrupting compounds (EDCs) was reviewed, including the definition and characteristics, the recent research trends concerning identification and analytical methods, and the applicable removal processes. EDCs include various types of natural and synthetic chemical compounds presenting the mimicking or inhibition of the reproductive action of the endocrine system in animals and humans. The ubiquitous presence with trace level concentrations and the wide diversity are the reported characteristics of EDCs. Biologically based assays seem to be a promising method for the identification of EDCs. On the other hand, mass-based analytical methods show excellent sensitivity and precision for their quantification. Several extraction techniques for the instrumental analysis have been developed since they are crucial in determining overall analytical performances. Conventional treatment techniques, including coagulation, precipitation, and activated sludge processes, may not be highly effective in removing EDCs, while the advanced treatment options, such as granular activated carbon (GAC), membrane, and advanced oxidation processes (AOPs), have shown satisfactory results. The oxidative degradation of some EDCs was associated with aromatic moieties in their structure. Further studies on EDCs need to be conducted, such as source reduction, limiting exposure to vulnerable populations, treatment or remediation of contaminated sites, and the detailed understanding of transport mechanisms in the environment.

Contents

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1. Introduction

Various adverse health effects of endocrine disrupting compounds (EDCs) have been reported in recent years [1–4]. Although numerous excellent studies have been implemented on the details of EDCs in various fields, concerns among the public keep rising and are being exaggerated through the mass media to some extent. Therefore, it is necessary to provide comprehensive knowledge of EDCs, including scientific results from previous research work and the summaries of recent EDCs research trends.

The first issue of EDCs reported was related to the incomplete removal of steroids in the wastewater treatment process [5]. Following the 1970s and 1980s, the presence of several human hormones and pharmaceuticals were primarily reported in the treatment process of wastewater and discharged aquatic environments [6–9]. In spite of several reported cases, EDCs did not draw much attention, because of the trace level concentration of detected EDCs and the lack of information on their significance in toxicity. Some researchers, however, considered the detected drugs and drug metabolites to be environmental contaminants [10].

The adverse effects of EDCs became an important issue and have received public attention, since the link between synthetic birth-control pharmaceuticals (e.g., ethynylestradiol) and their toxicological impact on fish had been reported [11–17]. The pseudo-estrogenic effect of certain chemicals has been known for decades [18–22]. However, the reported results showing that endogenous hormones and synthetic EDCs may have caused the sexual disruption of wild life, especially in the treated wastewater discharge area, brought about various further research studies on EDCs [12,23,24]. Currently, many types of EDCs were detected in a wide range of natural and engineered environments across the world, including surface water, ground water supplies, wastewater effluents, sea water, and sediment [2,25–28].

The U.S. EPA tried to establish the Endocrine Disruptor Screening Program (EDSP) to develop official screening methods and toxicity testing strategies for approximately 87,000 compounds. The European Organization for Economic Co-operation and Development (OECD) also has made an effort to develop a reliable method to confirm the significance of EDCs [29]. However, the proposed methods have not yet fully accepted within scientific communities [30]. Despite great efforts to prepare official guidelines of EDCs, their definition and terms are still quite ambiguous. Although many natural and synthetic chemicals have been widely considered as EDCs, numerous chemicals present in the environment still remain unidentified and are considered suspicious as potential EDCs. Moreover, many new chemicals are continually being produced, due to needs in various industrial sectors. In addition, evidence of endocrine disrupting activities of some identified EDCs is often controversial to some extent. Therefore, the definition and characteristics of EDCs were reviewed and summarized in this work. In particular, recent research results and trends were assessed regarding the adverse effects of EDCs, their identification methods, specific analyses, and removal processes. In summary, future research topics on EDCs were suggested.

2. Definition and characteristics of EDCs

EDCs are known as a class of chemicals which have xenobiotic and exogenous origins while mimicking or inhibiting the natural action of the endocrine system in animals and human, such as synthesis, secretion, transport, and binding. They maintain the homeostasis, reproduction, metabolism, development, and/or behavior of living species [31]. Various types of natural and synthetic chemical compounds have been identified as EDCs. However, the definition and range of chemicals showing the behaviors of EDCs vary significantly; thus, an issue has been raised as to whether certain chemicals should be considered as EDCs.

The primary effects of EDCs, as described earlier, are either the mimicking or inhibition of the behavior of natural hormones, such as estrogen, testosterone and/or thyroid. Depending on the endocrine endpoints, they can be estrogenic, androgenic, or thyroidal compounds [32–34]. Although the disruption of the androgen and thyroid functions might exerts greater or equal impacts on the environment, most research studies so far have focused on estrogenic EDCs [33]. Thus, EDCs are often referred to as estrogenic EDCs (e-EDCs) in the various studies [34].

The molecular structures of several EDCs, with accompanying varying functionalities, are summarized in Table 1. They are broadly classified into several categories, such as hormones (natural and synthetic estrogen or steroids), pharmaceuticals and personal care products (PPCPs), industrial chemicals, pesticides, combustion byproducts, and surfactants [34,35]. The EDCs shown in Table 1 have at least one aromatic structure in their molecular structures. Thus, it appears that the hydrophobic properties might comprise an important characteristic in studying and controlling EDCs in both natural and engineered environments.

PPCPs represent another group of EDCs which may have their toxicological potential on the natural environment. They are ubiquitous contaminants, especially in wastewater treatment plant (WWTP) effluents, and have been relatively well defined compared to other EDCs. The detected concentration in wastewater is of levels of nanograms per liter [36]. However, the known threshold concentration leading to potential estrogenic responses ranges from parts per billion to parts per trillion. Thus, it causes significant concern regarding the detectable presence of many EDCs in various water environments, including wastewater, surface water, sediments, groundwater, and drinking water [25,30,37,38].

The trace level concentration of EDCs creates a challenge for both the detection and removal processes. Fig. 1 shows the recently reported EDCs concentrations in various water sources in South Korea [2]. The results represent the relatively higher concentration of PPCPs in WWTP effluents and the omnipresence of EDCs in the natural systems. This study also reported on the incomplete elimination of EDCs, especially PPCPs, during conventional water and wastewater treatment processes, such as coagulation, sand filtration, or activated sludge [2]. This could be explained because most PPCPs are more polar than traditional contaminants, and the majority have acidic or basic functional groups. These properties create another obstacle for the research of PPCPs [39]. The biodegradability

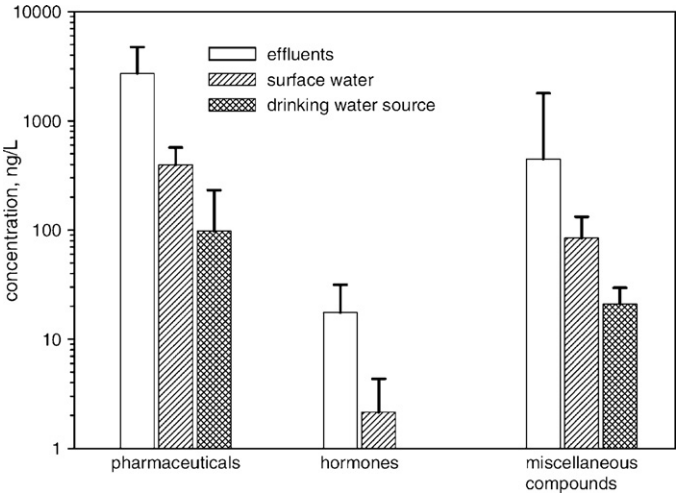


Fig. 1. Average and standard deviation of the concentrations of classified EDCs in wastewater effluent, surface water, and drinking water source in South Korea [2].

Table 1
Examples of various types of EDCs classified.

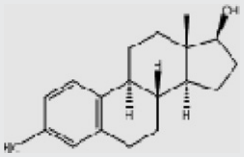
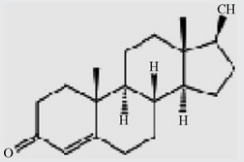
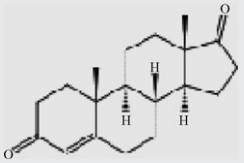
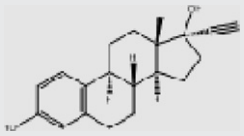
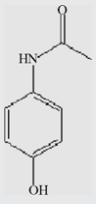
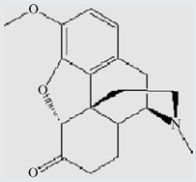
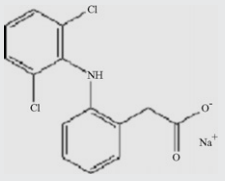
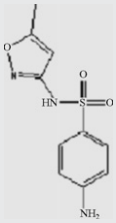
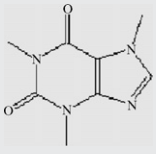
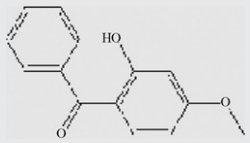
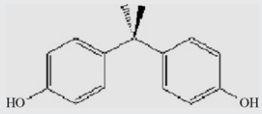
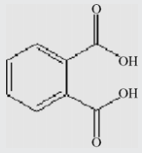
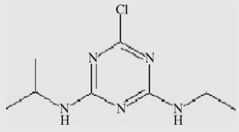
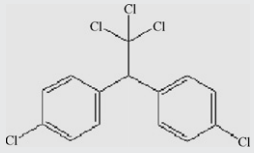
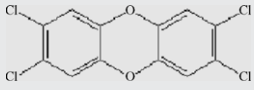
Class (use)	Compound	Structure
Steroid		
(Estrogen)	Estradiol	
(Androgen)	Testosterone	
	Androstenedione	
(Synthetic estrogen)	Ethynylestradiol	
Pharmaceutical		
(Analgesic)	Acetaminophen	
	Hydrocodone	
(Anti-arthritic)	Diclofenac	
(Antibiotic)	Sulfamethoxazole	
Personal care product		
(Stimulant)	Caffeine	

Table 1 (*Continued*)

Class (use)	Compound	Structure
(Sun screen)	Oxybenzone	
Industrial chemicals		
(Plastics)	Bisphenol A	
	Phthalate	
(Surfactant)	Nonylphenol	
Pesticides		
(Pesticide)	Atrazine	
	DDT	
Combustion by-product	Dioxin	

of individual PPCPs had varied, depending on their nature [40]. As a result, some PPCPs have often been detected in relatively considerable concentrations in the effluent of WWTP. The concentration of acidic pharmaceuticals, such as bezafibrate, naproxen, and ibuprofen, was as high as 4.6 μg/l in municipal WWTP [41]. In Lake Greifensee, located in Switzerland, carbamezapine was found to be one the most abundant pharmaceuticals which had been present in a discharged WWTP effluent [42]. The treatment efficiency of most PPCPs in the various WWTP processes was as low as 35%.

3. The toxicity, detection, and removal of EDCs

The presence and resulting adverse effects of EDCs are currently accepted in both the academic and public sectors. The necessity of further EDCs research is also fully supported. Various examinations regarding EDCs are being conducted across the world. The on-going EDCs research trends can be classified into three major categories, such as the identification and determination of the effects of EDCs, the development and improvement of analytical methods, and the application and modification of water treatment options for the removal of EDCs. In the following sections, details of each area will be discussed.

3.1. Toxicological effects and determination of EDCs

The adverse effects of EDCs regarding reproductive health in humans and wildlife have become a major concern among the pub-

lic [43]. The correlation between exposure to EDCs and the health of human and wildlife, including any unknown long-term impacts, is a very complicated and controversial issue which is difficult to confirm. The actual effects of exposure to EDCs, based on toxicological tests, have been reported [34,44,45]. Diethylstilbestrol is one of several EDCs which had been prescribed as an orally active synthetic nonsteroidal estrogen. It was reported that the compound may cause a decrease of sperm counts in human males [46]. However, these results were slightly suspicious because they have not been confirmed by further studies [47,48]. On the other hand, similar effects caused by other EDCs had been encountered in different regions. The trend of reanalyzed data for male sperm counts showed a decline in sperm density in the Unites States and Europe [49]. It was also found that there was a correlation between lower sperm counts and high concentrations of polychlorinated biphenyl (PCB) in blood serum studies conducted in the Netherlands [50]. Many parts of human tissues show estrogen receptor expressions, including the brain, immune system, cardiovascular system, lungs, mammary glands, liver, kidneys, reproductive tract (ovaries, testes, uterus, prostrate), adipose tissue, and bones [51]. The transport of EDCs to offspring has also been reported through a study of rat tissue [52]. Additional detailed discussions on a variety of aspects of human heath, affected by the exposure to EDCs, may have been determined by other studies [53].

Due to the improvement of the sensitivity of analytical instruments, more synthetic compounds have been identified as potential EDCs. Table 2 introduces several case examples [54,55]. They include alkylphenol ethoxylate nonionic surfactants and their degradation byproducts, food additives, fragrances, antioxidants, flame retardants, plasticizers, industrial solvents, disinfectants, fecal sterols, polycyclicaromatic hydrocarbons, and high-use domestic pesticides. Most compounds are not regulated yet. However, they may be the most probable target compounds for EDCs regulation with the collection of sufficient data to prove their toxic effects on human health [17,56,57].

Table 2
Classes of selected emerging suspicious EDCs [54,55].

Compound class	Examples
Pharmaceuticals	
Veterinary and human antibiotics	Trimethoprim, erythromycin
Analgesics and anti-inflammatory drugs	Codein, ibuprofen, acetaminophen, acetylsalicylic acid, diclofenac, fenoprofen
Psychiatric drugs	Diazepam
Lipid regulators	Bezafibrate, clofibric acid, fenofibric acid
β-Blockers	Metoprolol, propranolol, timolol, betaxolol, sotalol, atenolol, metoprolol
β_2-Sympathominetics	Terbutalin, salbutamol
X-ray contrast media	Iopromide, iopamidol, diatrizoate
Steroids and hormones	Estradiol, estrone, estriol, diethylstilbestrol
Personal care products	
Fragrances	Nitro, polycyclic and macrocyclic musks
Sunscreen agent	Benzophenone, methylbenzylidene camphor
Insect repellents	N,N-Dimethyltoluamide (DEET)
Antiseptics	Triclosan, chlorophene
Flame retardants	Polybrominated diphenyl ethers (PBDEs), tetrabromobisphenol A, tris(2-chloroethyl)phosphate (TCEP)
Miscellaneous products	
Surfactants and surfactant metabolites	Alkylphenol ethoxylates (APEO), alkylphenols, alkylphenol carboxylates, pentafluorooctane sulfonate (PFOS)
Industrial additives and agents	Chelating agents (EDTA), aromatic sulfonates
Gasoline additives	Dialkyl ethers, methyl 4-butyl ether (MTBE)
Disinfection by-products	Iodo-THMs, bromoacids, bromoacetonitriles, bromoaldehydes, cyanoformaldehyde, bromate, NDMA
Algal and cyanobacterial toxins	Saxitoxin, anatoxin-a, mycrocystin, nodularin, cyclindrospermopsin

Nowadays, regulatory efforts in setting guidelines about EDCs have been put into place. The U.S. EPA has set an Ambient Water Quality Criteria for nonylphenol of 28 μg/l for acute exposure (maximum 1 h concentration) and 6.6 μg/l for chronic exposure (4 day exposure period, occurring more than once over 3 yrs) in freshwater environments [58]. In saline waters, the acute criterion is approximately 7.0 μg/l and the chronic criterion is 1.7 μg/l. Ambient Water Quality Criteria are not regulatory guidelines, but have been suggested for water quality control to protect aquatic life.

One of the effective methods to determine EDCs is in regards to biologically based assays. It usually provides either qualitative or quantitative responses. Although the mass-based analytical methods provide excellent sensitivity and precision to quantify EDCs, they are limited in describing the overall estrogenic effects, such as the synergistic or anti-estrogenic influences in the presence of multiple EDCs [59]. In addition, the noted biological methods are intended to measure the level of individual EDCs, based on the assumption that the target compound has been identified as an EDC and much is known about its chemical properties. Therefore, biological assays are useful methods in studying the effects of EDCs as well as the identification of suspicious compounds posing as EDCs. However, traditional toxicity tests may not be always suitable for certain water samples [60].

Several mechanisms are involved in the biological assays to determine EDCs, such as cell proliferation, ligand binding, luciferase induction, vitellogenin induction, or antigen–antibody interactions. Cell proliferation utilizes the estimation for cell growth and reproduction in different samples, while ligand binding quantifies the number of specific estrogen binding sites [61,62]. Luciferase induction measures the amount of luciferase induced from estrogen receptors and response elements with luminescence after cell lysing and the addition of luciferin [63,64]. Vitellogenin induction quantifies the amount of vitellogenin in the plasma of female fish liver after extraction, which is secreted as a response to estrogens. In addition, the production of vitellogenin in male fish can be seen as an indication of endocrine disruption [65,66]. Antigen–antibody interactions use the principle of immunoassays based upon the non-covalent binding of antigen to antibodies [67,68].

Biologically based assays may be applied with whole organisms, cellular, or non-cellular materials, such as antibodies or estrogen receptors. The details of three assays, based on testing materials, will be further described in subsequent sections.

3.1.1. *Whole organism assays*

Whole organism assays utilize the endocrine disruption process in amphibians, fish, birds, and insects in order to monitor the EDCs in aquatic environments. The responses in the organisms are determined by deformities, reproductive deficiencies, egg and offspring development, and serum protein production, such as vitellogenin. The populations of wild leopard frogs (*Rana pipiens*) have been known to be particularly sensitive to the exposure of EDCs, based on a study of their gonadal abnormalities [69,70]. Many assays for estrogens, using fish, have been developed, such as those for rainbow trout (*Oncorhynchus mykiss*), fathead minnow (*Pimephales promelas*), sheephead minnow (*Cyprinodon variegates*), and zebrafish (*Brachydanio rerio*) [63,71–75]. Some genetically engineered species that respond to EDCs, such as transgenic zebrafish (*Brachydanio rerio*) that have been bioengineered with luciferase expression coordinated to vitellogenin production [63] and medaka fish (*Oryzias latipes*) or shubunkins (*Carassius auratus*) designed to

express a green fluorescence protein in response to vitellogenin production, have also been ultilized [33,76].

The most advantageous aspect of whole organism assays is that the method may quantify the actual effects of EDCs on a target species as well as the usage of the species as a representative biological indicator in their habitats, which are particularly sensitive to EDCs exposure. In addition, the method may provide a cumulative estrogenic effect caused by exposure to a mixture of EDCs in a given environment. The major disadvantage of this method is associated with the deficiency of a specific organism response to certain EDCs. Although a biological indicator species responds to EDCs, either the specific cause or the exact location of the source may be ambiguous. Therefore, additional studies should be conducted.

3.1.2. Cellular bioassays

Cellular bioassays are one of the analytical methods comparable to mass-based analytical techniques in terms of sensitivity. This method shows a rapid response process without additional equipment requirements, such as a mass spectrometer or a tandem mass spectrometer. However, cellular bioassays may not provide a consistent response for a quantitative analysis of specific EDCs, especially in environmentally complex samples containing multiple EDCs or other toxic constituents.

Cellular assays basically use a protein expression system, representing the estrogen response formed or stimulated by a dimer which is produced from the binding between the estrogen and the estrogen receptors. Luciferase and β-galactosidase are some examples of these types of response proteins. The former can be quantified with a luminometer after cell lysis, and the latter can be measured with a spectrophotometer, using a back-calculation from the amount of colored products after the enzyme-catalyzed reaction process has been completed. The details of cellular assays are comprehensively covered in other reports [34,77].

3.1.3. Non-cellular assays

The bioassays introduced in previous sections have certain limitations caused by the usage of whole cells, such as membrane permeability, cell function, organism life stages, and toxicity responses to a given sample. However, non-cellular assays can circumvent these potential problems with reasonable detection limits for the analysis of EDCs. In addition, some assays, such as enzyme-linked immunosorbent assays (ELISA) and enzyme-linked receptor assays (ELRA), provide a quantitative measurement of EDCs although they require the use of laboratory systems [78–80]. Currently, ELISA kits are commercially available for many of the known and suspected EDCs [67].

Non-cellular assays have the potential to be applied to a portable biosensor for EDCs. Endotect™ and the RIver ANAlyser (RIANA) systems are commercially available examples. The Endotect™ biosensor receptor-binding assay employs a human estrogen receptor (hER) connected to a fluorescent molecule, in such a way that any generated fluorescence from the binding process with the EDCs can be measured by using an evanescence-type detector [81]. The RIANA consists of a multi-analyte immunosensor that uses total internal reflection fluorescence in order to determine the levels of three target analytes (e.g., atrazine, isoproturon, estrone) [82]. The immunosensor uses antibodies instead of hormone receptors. The chemical-specific region of the antibody contains a fluorescence tag, which shows the fluorescence process as it binds with EDCs which act as an antigen. The test results of RIANA constituted an accepted level in terms of the determination of the three target analytes with low variability and the measurement of the analytes in various water sources [82].

There has been an improvement in fluorescent indicators, electrochemical sensors, and microarray relative binding assays. A recently discovered fluorescent indicator, known as the single cell coactivator recruitment (SCCoR), distinguishes between estrogen agonists and antagonists through a specialized ligand binding domain approach. A coactivator recruitment surface generated from this approach screens natural and synthetic estrogens in living cells by using a fluorescence resonance energy-transfer technique [83]. SCCoR could be applied to living cells to determine estrogenic activities with the dose-dependent fluorescent response mechanism, and it has the potential to transform target cells of many different species into biosensors. A piezoelectric sandwich-type assay is one example of an electrochemical sensor. It uses an immobilized estrogen response element (ERE) in the biosensor, which binds to the complex between 17β-estradiol and an estrogen receptor, and responds to concentration levels as low as 2.2 μg/l [84].

3.2. Analysis and quantification of EDCs

The authentic characteristics of EDCs, such as their occurrence of EDCs at trace concentration levels and with extremely diverse groups, make the detection and analysis procedures quite challenging. To overcome difficulties in the analysis, various methods have been developed. Currently, the most prevailing methodological approach designed to analyze EDCs incorporates a mass-based analysis process. Generally speaking, the mass-based methods employing mass spectrometry (MS) show relatively low detection limits as compared to other methods. The detection limits of several analytical methods are summarized in Table 3 [34,85,86].

These mass-based analytical methods have been widely used as some of the effective analytical tools to determine various kinds of trace level organic compounds in many different water sources. Depending on the target compounds, various combinations of instruments and detectors can be applied to obtain improved analytical results, such as GC/MS, HPLC/MS, LC/UV, and GC/tandam mass spectrometer, etc. These sophisticated instruments usually require significant capital investment and personnel training, but the analytical results provide excellent quantitative information.

The mass-based analytical method generally consists of a pretreatment or extraction step followed by an instrumental analysis comprised of specific settings for each target compound based on its chemical properties. In many cases, the pretreatment or extraction step plays an important role in determining the overall level of analytical performances in practice. In spite of the significance of the extraction methods, they have not received much attention. Thus, in this section, various extraction methods have introduced and compared with each other for the analysis of EDCs.

Several extraction methods have been already developed and applied with respect to proper alterations to improve performance. Common extraction methods that can be applied in practice are as

Table 3
Reported detection and quantification limits of different analytical methods for various EDCs in water samples.

Method	Detection limit (ng/l)	Ref.
E-Screen	0.27	[34]
ER-CALUX[a]	0.14	[34]
YES[b]	0.3–30	[34]
ELISA[c]	20–40	[34]
LC–MS/MS	0.08–33	[85]
SPE–GC/MS	12–32	[85]
GC–MS/MS	0.05–2.4	[34]
SPME–HPLC[d]	0.064–1.2	[34]
SPE–HPLC/ESI-MS/MS[e]	3.5–44	[86]

[a] Estrogen responsive chemically activated luciferase expression.
[b] Yeast estrogen screen.
[c] Enzyme-linked immunosorbent assay.
[d] Solid-phase microextraction–high performance liquid chromatography.
[e] Solid-phase extraction–high performance liquid chromatography with positive electrospray ionization and tandem mass spectrometry.

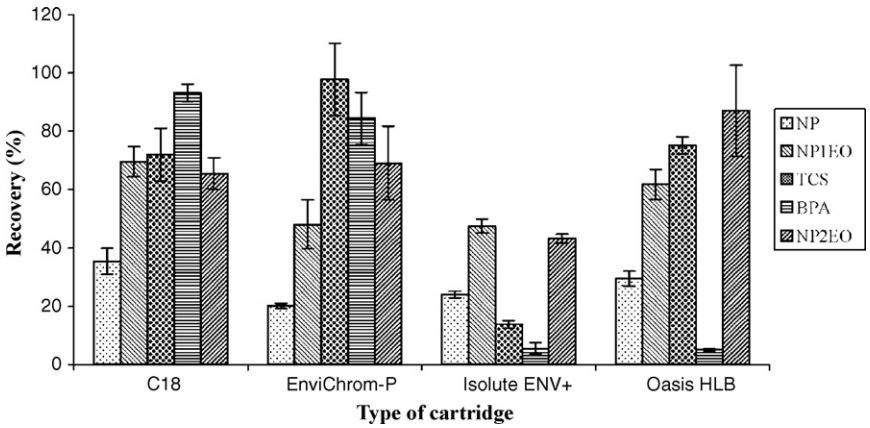


Fig. 2. Mean recoveries (%) of the target compounds in wastewater using different types of SPE cartridges, such as nonylphenol (NP), nonylphenol monoethoxylate (NPIEO), triclosan (TCS), bisphenol A (BPA), and nonylphenol diethoxylate (NP2EO) [93].

follows: solid phase extraction (SPE), solid phase microextraction (SPME), and liquid phase microextraction (LPME). The details of the advanced instrumentation techniques will not be reviewed in this article at this time, but the principles of the techniques are well explained in other studies [87].

3.2.1. Solid phase extraction method

SPE or liquid–solid extraction uses a solid phase as a selective sorbent to separate a particular analyte onto the surface through adsorption, while in contacting with liquid or gaseous samples. The solid phase sorbent, containing insolated analyte, is then purified with a washing solution to remove unwanted constituents retained with the target analyte, which is eventually desorbed from the solid phase through elution with the specific organic solvent [88]. The solid phase sorbent is usually packed into small tubes or cartridges, such as a small liquid chromatographic column. It is also available in the shape of discs with a filtration apparatus. Both types are commercially available from many manufacturers with a specific housing for suction or pressurization to pass the sample solutions through. The U.S. Geological Survey (USGS) National Water Quality Laboratory (NWQL) recommended that a SPE method be followed by GC/MS to analyze 67 compounds, including EDCs and suspected EDCs in domestic and industrial wastewater [89]. However, HPLC is also commonly used after SPE [90]. They suggested the use of disposable solid-phase cartridges containing polystyrene–divinylbenzene resins and a 4:1 mixture of dichlromethane and diethyl ether as an eluent. The recovery rate at 4 μg/l was 74 ± 7%, and the detection limit was 0.15 μg/l.

One of the most important parameters in the application of a SPE method is the selection of an appropriate solid sorbent to the target analyte as well as the use of solvents for washing and elution. The choice of derivatization is also important [91]. Depending on the use of a solid sorbent, analytical results of the target compound showed noticeable differences [92]. Fig. 2 shows examples of the analytical differences of target materials, by using various types of SPE cartridges [93]. Depending on the type of cartridges, the recovery rates of an identical anlayte varied from 10 to 90% [93]. Several types of solid phase materials and solvents, employed to analyze specific EDCs in previous research studies, are summarized in Table 4 [93–95].

The adsorption parameters of selected solid sorbents are also additional factors to be considered for the SPE method, such as adsorption capacity and contact time. To prevent 'adsorption breakthrough', the number of available sites on the sorbent should exceed the number of analyte molecules to be sorbed. Thus, the capacity of SPE cartridges or discs should be confirmed before their intended application. The flow rate of a sample through the solid sorbent phase should be calibrated to allow minimal contact time between the analyte and the sorbent. The typical flow rates for a SPE cartridge are 3–10 ml/min, and rates of 10–100 ml/min are common for disc types [88].

The SPE, followed by the GC/MS method, as previously mentioned, is recommended by the USGS NWQL as an official method for the analysis of known and suspected EDCs [89]. The selection of target compounds is based on their endocrine disrupting potential or toxicity. Previously, the traditional analytical method for organic contaminants in water samples was comprised of continuous liquid–liquid extraction (CLLE) with an organic solvent [96]. The recommended SPE method is faster and more efficient than CLLE. In addition, SPE requires less solvent while producing smaller amounts of toxic wastes.

3.2.2. Solid phase microextraction method

The SPME method primarily uses the adsorption of an analyte onto the surface of a coated silica fiber. The adsorbed analyte is then desorbed at the injection port of a suitable instrument, such as the GC. Various types of fibers and their holders with specific coating layers for a proper analyte are commercially available in addition to newly modified methods [97]. This detailed information is can be obtained elsewhere [88].

The partitioning of an analyte between an aqueous sample and a stationary phase on a fiber is the main principle of the SPME method. According to other researchers, the amount of an analyte adsorbed onto the silica-coated fiber at equilibrium is directly related to its concentration in the sample [98]. The sensitivity of the SPME method can be assured, since the polymeric stationary phases used for SPME have a high affinity for organic molecules. The complete extraction of analytes from the sample is debatable. Therefore, SPME operates at an equilibrium mode with proper calibration to provide reliable, quantitative data. It was also reported that in the case where the sample volume was much larger than the stationary-phase volume, the amount of analytes adsorbed by the stationary phase was not related to the sample volume [98]. This feature can be especially advantageous in field sampling. For example, analytes present in natural waters with low concentrations can be effectively sampled for SPME, then transported to the laboratory for subsequent analyses. The dynamics of SPME are controlled by mass transport through the diffusion of the analytes from the aqueous stage to the stationary phase of the coated fiber, and can be improved by stirring the aqueous sample [98].

The application of SPME can vary in practice. Firstly, direct and headspace SPME can be differentiated, depending on where the coated fiber is placed for the extraction. Occasionally, a derivatization reagent is added to enhance the performance of instruments,

Table 4
Summary of solid phase materials and solvents among several reported SPE applications for the analysis of EDCs.

GC column	Detection limit (ng/l)	Applied solid phase material and solvents	Ref.
DB-5 MS	0.03–410	SPE cartridge: C-18 Sep-Pac® Oasis HLB cartridge® Envi-Chrom P® Isolute ENV+® Conditioning: methanol, Milli-Q water Washing: Milli-Q water Final elution: Dichloromethane–hexane (4:1).	[93]
HP-5 MS	26.5	SPE cartridge: Oasis HLB cartridge® Conditioning: Ethyl acetate, methanol, Milli-Q water Washing: methanol–water (5:95) Final elution: Ethyl acetate	[94]
HP-1	0.80 (w/o derivatization) 0.004 (w/derivatization)	SPE cartridge: Envi-Chrom P® Conditioning: unknown Washing: distilled water Final elution: acetone	[95]

especially for the analysis of EDCs. Not only the selection of derivatization reagents, but also the place where the derivatization reaction was intended to occur makes significant differences for the analysis of EDCs. For example, a study analyzing alkylphenols and bisphenol A (BPA) in water samples employed a direct extraction method using a polymer-coated hollow fiber with N,o-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) as a derivatization reagent at the injection port of the GC/MS [99,100]. The method detection limit had ranged from 0.07 to 2.34 ng/l, and the linear calibration range was from 0.01 to 15 μg/l. In addition, an in-sample derivatization technique, with the headspace SPME/GC–MS method, was reportedly used for the simultaneous analysis of nonylphenol, nonylphenol mono and diethoxylates, and their acidic metabolites [101,102]. To confirm this method, the researchers compared the experimental results to several other scenarios, including derivatization after direct SPME and in-sample derivatization with various agents, followed by headspace SPME, using fibers coated with different materials.

Apart from chemical factors in SPME applications, several operational factors are also crucial in an analysis, such as sample stirring speeds as well as the extraction time and temperature required to reach the equilibrium between the aqueous and stationary phases on the SPME fiber [103]. The effects of ionic strength and the matrix of the sample as well as the operation factors were examined to optimize the method [101]. Natural organic matter and colloids present in water and wastewater samples can affect the recovery of EDCs in SPME [104]. If all operational parameters are fixed, the analysis process can be automated with the reduced usage of solvents, as compared to other methods [105]. In addition, the fiber can be reused and recycled with proper care. The SPME can be utilized as an excellent alternative for the analysis of EDCs.

3.2.3. Liquid phase microextraction method

Liquid extraction or liquid–liquid extraction (LLE) is, as mentioned before, a typical method for the analysis of organic solutes in water samples. This method requires a relatively large amount of organic solvents, as well as an additional concentration step, so it produces larger amounts of toxic wastes. Liquid phase microextraction, solvent microextraction (SME), or single drop microextraction (SDME) methods have been developed to solve these problems while reducing the analysis time [106,107]. In order to analyze BPA in river water samples, LPME was applied [108]. A droplet of solvent was exposed directly in a stirring water sample using a microsyringe. Then, the solvent droplet withdrawn was injected into the GC/MS with derivatization, at the injection port. Several operation parameters were explored to confirm the appropriateness of the analytical procedure, including solvent selection, exposure time, and mixing speed, by comparing the peak area under various conditions. According to an LPME method using toluene as a solvent, the detection and quantification limits of BPA were 2 and 10 ng/l, respectively.

One of the greatest challenges of the LPME method involves the retention of a droplet of solvent in a sample container, which is being agitated during the exposure period. In some cases, the size of the droplet is reduced with the exposure time, which could be caused by either the shear force of the sample stirring or the dispersion of the solvent into a water sample. An improved suggestion is the use of hollow fibers to protect solvent droplets in LPME [109]. In the improved LPME procedure, a porous polypropylene hollow fiber, filled with an organic solvent, was directly exposed to the extraction of several EDCs from water samples. The exposed solvent and BSTFA were then injected into the GC/MS port simultaneously for derivatization. The analyzed results were compared with those using headspace SPME and LLE. The detection and quantification limits of this method were in the range of 0.005–0.015 and 0.012–0.026 μg/l, respectively. The suggested hollow fiber LPME method was found to be a rapid, simple alternative, as an extraction method for EDCs.

In summary, the mass-based analytical techniques provide excellent quantitative results, but usually require significant equipment capital investments, such as a tandem mass spectrometer [110]. On the other hand, biologically based assays require less expensive microplate luminometers or spectrophotometers, and provide enhanced qualitative estrogenic responses [34]. To achieve both quantitatively and qualitatively successful analysis results for EDCs, a combined approach incorporating two types of analyses was proposed, known as a bioassay-directed chemical analysis (BDCA) method [85]. In regards to this type of analysis, sample screening was performed by using a yeast estrogen screen (YES) assay for total estrogenic activity; then, the analysis for specific chemical species was conducted by using LC–MS/MS [85,111]. Another application method was bioassay-directed fractionation, which consists of a cell bioassay (E-SCREEN), in conjunction with acid-base partitioning (F1 and F2) and the silica gel column fractionation of neutral fractions (F3–F7) [112]. In addition, the recombinant yeast assay (RYA), combined with chemical identification by LC–MS, was used [113].

3.3. Applicable treatment options to remove EDCs

Various separation or oxidation techniques have been considered as a potential treatment option for the effective removal of EDCs from water. Unfortunately, the chosen treatment option did not consistently conform to the desired removal efficiency level. One possible reason might be due to sub-micro level concentration

and varying chemical properties of EDCs. The removal efficiencies of individual EDCs had varied depending on unit operations and processes commonly used in WWTP [55]. The results suggest that the proper removal process for an individual target compound needs to be carefully selected in accordance with the characteristic property of each EDC.

3.3.1. Separation processes

Conventional separation techniques, such as coagulation, flocculation and precipitation processes, are not effective in removing EDCs, especially for low molecular weight compounds ranging from 100 to 500 Da [114–116]. Advanced separation processes, such as adsorption, membrane filtration, and ion exchange, normally show superior removal efficiencies (up to 95%), depending on the compounds tested [55]. Membrane separation, employing dense reverse osmosis (RO) and nanofiltration (NF) membranes, is reported to be efficient in removing micro-contaminants, such as EDCs and PPCPs [2,117–120], but the rejection was incomplete with some fluctuations in the range of 10–95%. Membrane properties, such as hydrophobicity and surface charges, played a significant role in the retention of such compounds, because they exist at extremely low levels, with different functional groups [120–122]. The water matrix also affected the performance of membranes such as NOM [123–125]. A modified NF membrane, in which the surface charge was virtually neutral at pH 6.5, gave a greater rejection rate for BPA (>95%) in comparison to the original membrane. However, the rejection efficiency for ibuprofen and salicylic acids had decreased due to the loss of membrane charges [122].

The removal of micro-contaminants by means of low-pressure membrane processes, such as microfiltration (MF), ultrafiltration (UF), and loose NF/RO, is limited due to their bigger pore sizes [116], but might become more selective with their combination with adsorption [126], biodegradation [127,128], and catalysis [129,130] while achieving EDCs removals as significant as tight NF or RO. This type of selectivity can be useful for the design of proper treatment sequences related to the primary, secondary, and tertiary treatment options for specific EDCs [2].

3.3.2. Adsorptive removal

Adsorption, using granular activated carbon (GAC), generally removes most organic contaminants, including EDCs [2,131]. However, to ensure the stability of the process, adsorption parameters and operational factors require strict control, such as kinetic and equilibrium constants, contact time, solubility, carbon type, competition with natural organic matter, etc [114,132–135]. Great attention has been focused on the selective adsorption of individual EDCs using various adsorbents. Any modification of such adsorbents is also another important field of research regarding EDCs [136,137]. The efficient removal of EDCs, using a macroporous adsorption medium, was reported with a combination of moving-bed reactors. The medium consisted of a macroporous poly(vinyl alcohol) cryogel with molecularly imprinted polymer (MIP) particles [138]. A modified mesoporous silica, prepared by the grafting of alkylsilanes with intermediate chain lengths, removed nonylphenol in aqueous samples efficiently in the presence of phenol [136]. In addition, several types of surface modified mesoporous silica were synthesized and compared with activated carbon for the selective removal efficiency of BPA [137]. Although the actual amount of removed BPA was less than that of the activated carbon, the surface modified mesoporous silica achieved better recycle efficiencies. In addition, a modified adsorbent (iron-tetrasulfophthalocyanine (FeTsPc)-immobilized Amberlite), combined with H_2O_2 oxidation, resulted in an effective removal of BPA, cefaclor, diclofenac, and ibuprofen [139]. A similar combined process of adsorption and oxidation was also reported, with zeolite and UV photolysis, for estrogen removal purposes [105].

3.3.3. Biological and chemical conversion

Conventional biological processes, such as activated sludge, biofiltration, and soil aquifer treatment, have shown limited EDCs removals, which were mostly derived from biodegradable and/or other compounds readily attached to particles [140,141]. Some research studies showed the metabolic characteristics of nitrifiers to achieve the removal of EDCs [142]. Chemical and advanced oxidative processes (AOPs), such as chlorination and ozonation, are effective in reducing the concentrations of several classes of EDCs and PPCPs. The removal efficiency is generally proportional to the oxidation power, and is a function of the contaminant structure and oxidant dose [39,115,143–145]. Particularly, the chemical structure of target compounds affects the oxidation rate of EDCs. The compounds, which were lacking in aromatic moieties, such as atrazine, meprobamate, and tri(2-chloroethyl)phosphate (TCEP), presented oxidative removal efficiencies of less than 60% by ozonation, and, subsequently, less than 5% of TCEP was removed [115]. The applicability of other AOP processes, such as photo-oxidation with UV light, ultrasonic cavitation, Fenton oxidation, and ozonation with hydrogen peroxide generation, had been also examined by using BPA as an EDC [115,146–148]. The overall BPA oxidation rate was quite high in most AOP applications, and the pH value was found to be an important factor in controlling the removal efficiency. A proposed breakdown mechanism was as follows: the generation of hydroxyl radicals and the destruction of the aromatic structure of BPA under their attack. The application of UV radiation-hydrogen peroxide (H_2O_2/UV-C) process for the removal of dimethyl phthalate (DMP) had achieved a high degree of DMP mineralization in aqueous solutions [148].

In addition to the processes mentioned above, some emerging treatment technologies are available for the degradation and/or separation of EDCs and toxic chemicals, such as supercritical fluid extraction [149], photodecomposition with specially designed media [150–152], and electrical oxidation with corona discharge [153].

4. Summary and future research on EDCs

Various types of natural and synthetic chemical compounds representing the mimicking or inhibition of the natural action of endocrine system in animals and humans, especially in regards to the reproduction, have been defined as EDCs. The trace levels concerning the concentration of EDCs and their diversity in various aquatic environments have been recognized. Such characteristics are the main obstacles for the measurement and removal of EDCs.

One of the on-going research trends of EDCs involves the identification and determination of their effects on both the environment and humans. Biological assays appear to be the most desirable method to study the qualitative aspects of EDCs. The assays can provide overall estrogenic effects, such as synergistic or anti-estrogenic influence, due to the existence of multiple EDCs as well as suspect compounds. The application of the assays can be categorized into several classes, such as whole organism assays, cellular bioassays, and non-cellular assays, on the basis of the applied medium. For the quantitative analysis, mass-based analytical methods disclose the excellent sensitivity and precision for individual EDCs. These methods generally consist of an extraction step, followed by a specific instrumental analysis procedure. The extraction step plays a key role in determining the overall level of analytical performances in practice, and several techniques have been developed, such as LLE, SPE, SPME, and LPME.

Several treatment options are available for the removal of EDCs. Various separation or oxidation techniques have been considered and examined as proper treatment methods for various EDCs. Conventional treatment techniques, such as coagulation, flocculation,

precipitation, and activated sludge process, are not highly effective for the removal of EDCs, while advanced treatment processes (e.g., GAC, membrane separation, and ozonation) have shown satisfying results. The oxidation of EDCs, having aromatic moieties, may be initiated based on these types of chemical structures.

Although there have been numerous research studies on various aspects of EDCs, several barriers are still present in the public and academic communities. Besides the on-going studies on EDCs, more efforts are required, such as source reduction, limiting the exposure of vulnerable populations, and the treatment or remediation of contaminated sites. In addition, the establishment of large-scale monitoring networks designed to enable a better understanding of fate and transport mechanisms in the environment, including soil, water, and air, is necessary.

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