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Trends in sensitive electrochemical sensors for endocrine disruptive compounds

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ABSTRACT

The endocrine system that provides communication and maintains homeostasis, is an important part of the body. Any defects or disruptions that affect the endocrine system may cause serious problems in the actions and functions of the body. Endocrine disruptive chemicals (EDCs) are exogenous chemicals or mixtures of chemicals that affects normal functions of the endocrine system by interfering with endogenous hormones and hormonal pathways and disrupting homeostasis. Numerous compounds are considered as endocrine disruptors such as bisphenols (BPs), phthalates, pesticides etc. and they are widely used for industrial purposes in many commercial products. Therefore, human exposure is almost inevitable. Besides that, EDCs may cause environmental pollution and are found in surface waters, wastewater, soil etc. To prevent exposure and hazardous effect, there are legislative regulations including restrictions and prohibitions of the use of EDCs. Due to these reasons; it is crucial to develop highly sensitive, low-cost, easy-to-use, and rapid sensors for the determination of EDCs in commercial and environmental samples. Although there are mostly chromatographic and spectrometric methods for the EDCs monitoring, electrochemistry surpasses them with advantageous properties such as easy application procedure, high sensitivity, very low limit of detection (LOD) values and low-cost.

In this review, major groups of EDCs will be explained with their recent and novel electrochemical sensor applications for their detection in commercial and environmental samples.

1. Introduction

The endocrine system, also known as hormone system, has a crucial role in providing communication between cells/tissues/organs by endocrine pathways and maintaining homeostasis of the body [1,2]. The endocrine system carries out its role through endocrine glands which are hypothalamus, pituitary gland, thyroid gland, parathyroid glands, adrenal glands, pancreas, and ovaries/testes [3]. Each of them is responsible for secretion of hormones that can bind specific receptor proteins of target cells. The endocrine system and endocrine glands are also interconnected and stimulation of one can result with a series of hormone secretions, stimulation of other glands and various cellular responses. Due to the sensitive balance and feedback process of the endocrine system, hormone secretion can be induced or reduced [1–3]. As an example of all the processes explained above; gonadotropin releasing hormone (GnRH) is produced by hypothalamus and GnRH stimulates the luteinizing hormone (LH) secretion by pituitary gland which targets ovaries in female body; as a result of this, estradiol that has significant roles in female reproductive system is produced and secreted by ovaries [2].

The fact that the endocrine system is involved in many important functions and actions in the body indicates that any defects and disruptions in this system may have critical consequences. Metabolic disorders such as Graves disease, diabetes, imbalances in acid-base or electrolyte concentrations in addition to these; other serious problems such as breast cancer and decrease in male reproductive capacity can be related with defects in the endocrine system [1].

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; APs, alkylphenols; Au-SPE, screen-printed gold electrode; BPA, bisphenol A; BPAF, bisphenol AF; BPAP, bisphenol AP; BPB, bisohenol B; BPE, bisphenol E; BPF, bisphenol F; BPS, bisphenol S; BPs, bisphenols; BPZ, bisphenol Z; CPE, carbon paste electrode; c-SWCNTs, carboxyl-functionalized single walled carbon nanotubes; CuO NFs, copper oxide nanoflowers; CV, cyclic voltammetry; DDT, dichloro-diphenyl-trichloroethane; DPV, differential pulse voltammetry; EC, European Commission; EDCs, endocrine disruptive chemicals; EIS, electrochemical impedance spectroscopy; EPA, Environmental Protection Agency; EU, European Union; GCE, glassy carbon electrode; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; LOD, limit of detection; MIP, molecularly imprinted polymer; MOFs, metal organic frameworks; MTCS, methyl-TCS; NP, 4-nonylphenol; OP, octylphenol; PCBs, polychlorinated biphenyls; PVC, polyvinyl chloride; RSD, relative standard deviation; SWV, square wave voltammetry; TBBPA, tetrabromo bisphenol A; TCS, triclosan.

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Endocrine disruption is described as the disruption of the hormonal and physiological balance of the body as a result of various natural or synthetic chemicals affecting the endocrine system, interfering with endocrine pathways [4]. Endocrine disruption may occur with either stimulation (hormone receptor agonist activity, decreased receptor degradation etc.) or inhibition (inhibition of hormone synthesis, hormone receptor antagonist activity etc.) of hormonal pathways [4].

Endocrine disruptive chemicals (EDCs) were firstly defined in 1996 by USA Environmental Protection Agency (EPA) as exogenous chemicals or mixtures of chemicals that affects normal functions of the endocrine system by interfering with endogenous hormones and hormonal pathways and disrupting homeostasis [5]. EDCs can be absorbed by different mechanisms such as oral or dermal and they can be effective in various times such as puberty and prenatal period [6]. EDCs cover a wide range of chemicals from pesticides to bisphenols (BPs) in the content of many plastic products and phthalates and parabens in personal care and cosmetic products [7] that we use frequently in our daily lives [8]. All significant groups of EDCs will be explained comprehensively in following sections.

The widespread use of EDCs for industrial and commercial purposes makes it almost impossible for humans to avoid exposure. Not only the daily products that we use and consume but also EDCs that cause environmental pollution by accumulating in water and soil can be a source of exposure. The amount and duration of exposure are also significant factors affecting the negative effects of EDCs; in addition to these, cumulative exposure can be quite dangerous [9].

Legislative regulations about the allowed maximum concentrations of EDCs in plastics, cosmetics, cleaning products and use of pesticides are made by European Commission (EC). Besides, there are no certain threshold values for adverse effects of EDCs and that makes it obligatory to have sensitive and strict regulations. The aim is reaching safe products that don't contain EDCs or contain a minimum amount of EDCs which have negative effects on not only humans and animals but also on natural life [10]. Therefore, it is important to have sensitive, rapid and low cost methods for the determination of EDCs in products and environmental matrices.

Determination of EDCs has always been a difficult task for researchers because those chemicals are generally found at very low concentrations in the sample media. Additionally; environmental samples or commercial products contain lots of compounds other than EDCs and create complex matrices.

In the literature; there are mostly chromatographic methods such as high performance liquid chromatography, liquid chromatography – mass spectrometry and gas chromatography – mass spectrometry for the detection of EDCs [5]. However, it is also known that these methods are expensive; require complex pre-treatment steps and too much solvent. Therefore; electrochemistry gains advantage over other analytical methods with being a low-cost, easy to use, highly sensitive and rapid technique. Besides, it allows miniaturization of sensors and modification of the electrode surface with various nanomaterials that enhance the sensitivity and selectivity. Today, sensor development studies focus on ease of use as well as high sensitivity and low LOD values. With the latest research, it is aimed to develop portable and even wearable sensor technologies. In this context, electrochemical sensors are superior to other analytical techniques thanks to their features such as flexibility, versatility and ease of application [11]. In addition to this, electrochemical applications are considered as clean techniques because they do not cause hazardous waste and allows making measurements with small volume of chemicals and samples [12].

In this review; most common groups of EDCs and most recent electrochemical applications for the determination of EDCs are discussed comprehensively.

2. Endocrine Disrupting Chemicals

2.1. Alkylphenols/Phenols

Alkylphenols (APs) are formed by the combination of phenolic ring and alkyl chain as chemical structure. They are basically used in the production of phenolic resins as alkylphenol ethoxylates and have a wide use as industrial surfactants. Especially the leading compounds of this group 4-nonylphenol (NP) and octylphenol (OP) and other APs are found in the content of detergents, soaps, plastics, textile products, resins, and various containers and bottles [13]. 4-aminophenol and other phenolic compounds are also considered in this group of hazardous chemicals and utilized for same purposes in industry. Due to their widespread use in food contact materials such as plastic containers, APs pose a risk for human exposure [13]. Besides, they can be found in numerous matrices such as soil, water, sediments etc. because of the human related environmental pollution; additionally APs can be more dangerous in aquatic environments due to their lipophilic properties and ability to stay in water for a long time [14]. APs were identified as priority hazardous substances by EC because of their endocrine disrupting activities. For example; the mechanism of action of NP and its derivatives is binding estrogen receptors and displacing 17-β-estradiol. This results in decreased fertility in

Table 1
Most significant BPs in terms of industrial use and endocrine disrupting effects.

Bisphenol	Industrial Use	Endocrine Disrupting Effect	Reference
Bisphenol A (BPA)	Binding, plasticizing, strengthening, bonding and filling materials for food and beverage containers, medical equipments, sports equipments, baby bottles, water pipes, thermal papers etc.	Estrogenic activity, growth disorders in children, negative effects on immune system, certain types of cancers	[15,16]
Bisphenol B (BPB)	Manufacture of phenolic and polycarbonate resins	Highly estrogenic and anti-androgenic activity, negative effects on reproductive system and gonadal development	[16]
Bisphenol F (BPF)	In the composition of epoxy resins and coatings	Estrogenic and androgenic activity, negative effects on fetus	[16]
Bisphenol S (BPS)	As an alternative of BPA in polymers, raw material for the preparation of fire retardants	Estrogenic activity (lower), premature puberty, reproductive system disorders	[16]
Bisphenol AP (BPAP)	For the production of polymers as a start material	Androgen receptor down regulation	[16]
Bisphenol AF (BPAF)	In the composition of food-contact polymers as a cross-linking agent and monomer	Estrogen receptor antagonist	[16]
Tetrabromo Bisphenol A (TBBPA)	Flame retardant for the manufacturing of electronic devices	Disrupts the function of thyroid hormones	[17,18]

males and feminization; on the other hand OPs can cause reduced sperm production [13,14]. Allowed maximum concentrations of NP and OP are stated by guidelines of European Union. For inland surface waters allowed maximum concentrations are 0.3 μg/L and 0.1 μg/L for NP and OP. This value increases to 7 μg/L for NP in seawater [13,14]. Nevertheless these values can be as high as 30 μg/L in industrial areas due to higher pollution and this creates the higher risk for exposure and endocrine disrupting effects [14]. Therefore, their rapid and sensitive determination in various environmental media and commercial products is very important.

2.2. Bisphenols (BPs)

BPs are one of the largest and most significant group of EDCs due to their widespread use in commercial products that we use in our daily lives. There are numerous studies about their hazardous effects, contamination potential and determination in various media. Bisphenol analogues, the most important and most known member of which is bisphenol A (BPA), have industrial use in a wide scale ranging from plastic materials to paper products, from medical materials to sports equipment [15,16]. In the Table 1, industrial use and endocrine disrupting effects is summarized.

Under high temperature and acidic/alkaline conditions; BPA can migrate from polymer into the content of the polymer-based container. Migration potential of BPA can lead up to 1.6 μg/body mass daily exposure. High exposure potential, widespread use in commercial products and serious health concerns about BPA has led to legal restrictions and prohibitions by European Union (EU) [16]. EU stated that the specific migration limit must be 0.05 mg BPA/kg of food in order not to exceed tolerable daily intake of 4 μg/kg body weight [15]. These restrictions have started the use of alternatives of BPA such as BPB, BPS, BPF, BPAF etc. Nevertheless; all BP analogues not only have similar industrial use but also have similar structures and similar dangerous effects. For example; BPB can have even higher endocrine disrupting potential than BPA [16]. In the recent years, commercial products that are promoted as "BPA-free" and safe have started to gain popularity. Several studies showed that BPA-free products cannot be 100% safe because they may contain other BPs that have endocrine disrupting effects.

BPs are also the reason of serious environmental concerns due to their contamination potential for rivers, wastewater and surface water etc. Development of a simple, sensitive and rapid determination method for BPs in different matrices is a popular and difficult subject for researches because of the low concentrations of BPs in complex media [15].

2.3. Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are in the class of persistent organic pollutants and they are expressed with the chemical formula of $C_{12}H_{(10-n)}Cl_n$. Different amounts of chlorine atoms that PCBs have determine their persistence levels in the nature. Metabolization and elimination of low chlorinated PCBs are easier than highly chlorinated PCBs that can bioaccumulate for years [19]. PCBs had been used excessively from 1930's to 1970's when they were finally banned [20]. PCBs show endocrine disrupting effects by disrupting normal functions of thyroid hormones, steroid hormones and male/female reproductive system and they can cause several metabolic diseases such as type 2 diabetes [21]. In addition to these, PCBs have highly neurotoxic and immunotoxic effects. Their industrial use is primarily as flame retardants in different electrical devices and they are also used in sealants, plastics, paints and pesticides etc [19,20]. Although many years have passed since the prohibitions of PCBs, they are still found in environmental media such as water, air and soil in dangerous concentrations due to their bioaccumulative and long lasting properties. The pollutions caused by leaks or improper disposal during the time they were used intensively have remained permanent until today [21]. Hence, development of easy to use, rapid and highly sensitive sensors for their detection in environmental sources is very important.

2.4. Parabens

Parabens are the synthetic aryl and alkyl esters of para-hydroxybenzoic acid and they are most popular synthetic preservatives that are used in a wide area of products ranging from foods such as drinks, bakery products, olives etc. and pharmaceutical preparations to cosmetics and personal care products [22]. Preservative effect of parabens comes from their antimicrobial activity by prolonging shelf life. The longer the alkyl chain in the parabens, the more antimicrobial effect and hydrolysis resistance increases [22]. In addition to these preservative and stable properties; paraben and its derivatives (methylparaben, ethylparaben, propylparaben, buthylparaben etc.) are highly preferable alone or combined in lots of daily products as low cost options [23].

In the past years, parabens were considered safe and were used without any legal controls or regulations. Nevertheless their hazardous effects such as causing DNA damage and oxidative stress, endocrine disruptive effects (increasing the incidence of breast cancer and malignant melanoma) by binding estrogen receptors are proven [24]. They can also cause negative effects by transferring from mother to fetus [23]. Additionally; their wide use has led to environmental pollution and this is also an emerging concern. Most common way to exposure to parabens may be considered as dermal adsorption, after that ingestion and inhalation are regarded as other exposure ways [24]. Using various cosmetic products in our daily lives for almost a lifetime may cause a really long time exposure to parabens. A study shows that our total daily intake of parabens can be up to 80 mg due to pharmaceutical products (25 mg/day), cosmetic products (50 mg/day) we use and food (2.5 mg/day) we consume [24].

In the view of this information about dangerous effects of parabens; European Union made legal regulations for maximum allowed concentrations of parabens in commercial products: 0.4% w/w for each paraben and 0.8% w/w for total parabens [22]. Developing effective, sensitive and rapid methods for detection of parabens is challenging because the working media consists of lots of other chemicals along with parabens. For example personal care products include emollients, surfactants, microplastics etc. [23] Therefore it is important to use sensitive and interference-free methods.

2.5. Triclosan (TCS)

Triclosan (TCS) which is chemically designated as 5-chloro-[2,4-dichlorophenoxy] phenol is the popular antimicrobial ingredient of daily cleaning products such as detergents, soaps, disinfectants and personal hygiene products such as toothpaste due to its wide biocidal spectrum [25]. TCS also may be used as plastic additive in lots of different items ranging from toys to medical devices and pharmaceuticals. Even though TCS was banned in USA in 2016 it has been used exceedingly since it was first discovered 40 years ago [26]. Its lipophilic and persistent properties combined with over use has led to bioaccumulation especially in aquatic environments such as rivers, lakes and additionally in wastewater, sewage and irrigation water [25,27]. Before explaining endocrine disruptive effects on humans, it should be stated that TCS is highly toxic to aquatic organisms. TCS and its degradation products are frequently found in aquatic media and pose a danger to environment [28]. TCS is not considered toxic

to mammals and its use in commercial products is restricted but it is harmful to humans due to endocrine disrupting effects such as disrupting balance between hypothalamic, pituitary and thyroid processes, negative effects on the occurrence of breast cancer and ovarian cancer, disrupting neurodevelopment in children [25–27]. Chemical structure of TCS is similar to some EDCs like PCBs and BPA; this may explain the cause of endocrine disruptive effects [27]. TCS can biologically transform into methyl-TCS (MTCS) which is more persistent, more lipophilic and more bioaccumulative than TCS [28]. Human exposure ways to TCS and MTCS are mainly dermal contact (commercial products) and drinking water. TCS and MTCS can be found in nano- and micro-molar levels in fresh water [28], so it is important to use sensitive methods for determination, especially in aqueous environments.

2.6. Phthalates

Phthalates (also known as phthalic acid esters) are chemically dialkyl/aryl esters of 1,2 benzene dicarboxylic acid [29,30]. Their physicochemical properties can be variable since there are different types of phthalates depending on the number of carbon atoms in alkyl chain; for example phthalates with long alkyl chains (7-13 carbons) are classified as high molecular weight phthalates [31]. In general; phthalates are hydrophobic and viscous materials with high boiling and low melting points [30]. All different types of phthalates such as dimethyl phthalate, dibutyl phthalate, butyl benzyl phthalate and di n-octyl phthalate etc. are widely used in industrial and daily products [31]. They are mostly preferred as plasticizers in order to improve flexibility, durability and softness of plastic polymers like polyvinyl chloride (PVC) in toys, medical devices (such as administration sets and infusion solution bags), and food packages [29–33]. Cosmetics and personal care products are other sources using phthalates as solvents, suspension agents or lubricants for fragrances, nail polishes and hair products etc [29,30].

The data about adverse effects of phthalate exposure is mostly based on animal studies and can be summarized as endocrine disruptive effects such as dysregulations in male reproductive system, anti-androgenic effects, teratogenicity, demasculinizing effects etc [29,30]. Even though the effects of phthalates on human health are not proven yet, there are numerous studies that prove the risks especially on the reproductive system. Besides, with products containing phthalates are being parts of our lives, exceedingly, widespread exposure makes it necessary to take precautions. For example there are various regulations and prohibitions about phthalates for products used by children, especially in the USA, Canada and the European Union [29].

Temperature and pH variations induce the migration of phthalates from plastics to environment or food/water [31]. This is considered as the main way for exposure via ingestion or dermal contact [34]; on the other hand, although it depends on the phthalate concentration in the product, frequency and amount of use, exposure from cosmetics and personal care products are relatively less likely [30].

Phthalates and their metabolites can be found in environmental sources such as soil, fresh water and wastewater; in foodstuff and in biological fluids such as urine, saliva, blood serum, breast milk and amniotic fluid [31]. Therefore, it is important to develop sensitive, rapid and effective sensors for the determination of phthalates in complex media.

2.7. Pesticides

Pesticides are compounds that are used against harmful pests (weeds, insects, fungus etc.) to prevent, destroy or control them with toxic effects. They can be used both alone and as a combination of compounds. Since their discovery many years ago, pesticides have been widely used as a rapid and effective tool for protecting food resources [35]. Despite providing the aimed results; their excessive and uncontrolled use has caused long-term hazardous effects on the ecosystem. Pesticides can be toxic on useful microorganisms, alter the quality of soil and contaminate environmental sources such as groundwater [36]. Exposure to pesticides due to the foods consumed by people or contaminated natural resources has raised serious health concerns with proved endocrine disrupting effects of pesticides [37]. In Table 2 pesticides are summarized according to the target pest and endocrine disrupting effect.

Since revealing hazardous and endocrine disrupting effects of pesticides by numerous studies, their use is either banned or restricted by authorities. However, they can still be found in environmental sources because of their cumulative and non-

Table 2
Widely used pesticides with endocrine disrupting effects

Pesticide	Target	Mechanism of Action	Endocrine Disrupting Effect	Reference
Methoxychlor	Insects	Altering the function of the nervous system	Binding to estrogen receptors	[37]
Dichloro-diphenyl-trichloroethane (DDT)	Insects	Effecting the nervous system	Binding to androgen receptors, estrogen receptor agonist	[36]
Linuron	Herbs	Inhibition of photosynthetic electron transport	Binding to androgen receptors, thyroid receptor agonist	[36,38]
Kepone (Chlordecone)	Insects	Effecting the nervous system	Binding to steroid receptors	[36]
Lindane	Insects	Blocking GABA receptors	Binding to estrogen receptors	[39]
Dicarboximides (Vinclozolin, Procymidone, Iprodione)	Fungi	Inhibiting triglyceride biosynthesis	Antiandrogenic effects	[37,40]
Organophospates (Malathion, Parathion, Fenitrothion . . .)	Insects	Inhibiting acetylcholine cholinesterase	Antiandrogenic effects	[35,37]
Pyrethroids	Insects	Effecting the nervous system	Antiandrogenic effects	[37]
Ketoconazole	Fungi	Inhibition of the synthesis of ergosterol	Inhibition of steroid synthesis	[37]
Triazoles	Fungi	Not reported	Inhibition of aromatase activity	[37]
Thiram	Fungi	Not reported	Inhibition of norepinephrine synthesis and disrupting hypothalamic-pituitary-gonadal pathways	[37]
Atrazine	Herbs	Not reported	Increased incidence of mammary tumors	[37]
Amitraz	Insects	Mimicking the action of octopamine	Inhibiting α-adrenergic receptors	[37]
2,4-dichlorophenoxyacetic acid (2,4-D)	Herbs	Mimicking the action of the plant growth hormone auxin	Causing hypothyroid state and thyroid tumors	[37]

Table 3
Selected applications of electrochemical sensors for the determination of EDCs

Compound	Sensor	Technique	Linear Range	LOD/LOQ	Buffer or Media	Sensitivity (μA/μmol L^{-1})	Real Sample	Recovery %	References
BPA	Bentonite/CPE	SWV	0.68-15 μM	0.0211 μM	0.2 M pH 7.4 Phosphate buffer	1.137 μA/μmol L^{-1}	Tap water Blood serum Urine samples	97.83-101.78 97.83-98.46 97.83-101.54	[46]
BPA	(Ru^0/PANI/g-C_3N_4) /GCE	DPV	0.01-1.1 μM	0.18 nM	pH 7.0	1.6025 μA/μmol L^{-1}	Urine samples	80.4-101.4	[47]
BPA	ssDNA-MB/ Aptamer/Au/ PET electrode	LSV	4.4 pM-440 nM	1.75 pM	0.05 M pH 7.0 Phosphate buffer solution	−2.78 μA/μg L^{-1}	Tap water PC drinking bottle	98.2-125.0 89.6-98.2	[48]
BPA	NiNPs/NCN/CS/GCE	DPV	0.1-2.5 μM 2.5-15.0 μM	45 nM	0.1 M pH 5.0 Phosphate buffer solution	0.13 μA/μmol L^{-1}	Milk samples	96.0-105.0	[49]
BPA BPS	CTpPa-2/GCE	DPV	0.1-50 μM 0.1-50 μM	0.02 μM 0.09 μM	0.1 M pH 7.0 Phosphate buffer solution	−0.1263-(-0.0501) μA/μmol L^{-1} -0.0923-(-0.0451) μA/μmol L^{-1}	Bottle samples	87.0-91.0 89.6-92.2	[50]
BPAF	MWCNTs-COOH/GCE	DPV	0.02-8.0 μM	7.70 nM	0.2 M pH 6.0 Phosphate buffer solution	−0.00411 μA/μmol L^{-1}	Water samples Rubber gloves	95.0-108.4 99.45-108.6	[51]
BPAF BPF	MWCNT-COOH/GCE	DPV	0.6-1.6 mM 0.6-1.6 mM	0.1742 mM 0.1243 mM	0.2 M pH 6.0 Phosphate buffer solution	−0.2561 μA/μmol L^{-1} -0.3194 μA/μmol L^{-1}	Rubber glowes Wastewater	97.50-103.75 98.75-102.50	[52]
BPB	PB/MWCNTs-COOH/GCE	CV	0.05 μM-0.175 mM	0.5 nM	0.1 M pH 5.0 Phosphate buffer solution	−0.0226 μA/μmol L^{-1}	Real samples	98.0-102.5	[53]
BPE BPF BPB BPZ	Cu-MOF-Tyr-Chit/GCE	CV AMP	0.05-3.0 μM 0.05-3.0 μM 0.125-8.0 μM 0.25-5.0 μM	15 nM 16 nM 56 nM 33 nM	50 mM pH 7.0 Phosphate buffer solution	5.51 μA/μmol L^{-1} 4.66 μA/μmol L^{-1} 1.34 μA/μmol L^{-1} 1.13 μA/μmol L^{-1}	Wastewater	Not reported	[54]
BPF	MWCNT-COOH/GCE	DPV	0.12-6.01 μg mL^{-1}	0.11 μg mL^{-1}	0.2 M pH 6.0 Phosphate buffer solution	−0.279 μA/μmol L^{-1}	Water bottle Milk packing Juice packing	102.3-105.3 93.8-103.0 97.4-101.1	[55]
BPS	hNiNS/GQDs/ MIPs/GCE	DPV	0.1-50 μM	0.03 μM	0.1 M pH 4.0 Citric acid buffer solution	0.5914-0.2175 μA/μmol L^{-1}	Plastic samples	94.4-99.6	[56]
BPS	MIP-B, N, F-CQDs/AgNPs/ GCE	DPV	0.01-50 μM	0.0112 μM	0.1 M pH 5.0 Citric acid buffer solution	0.16295 μA/μmol L^{-1}	Actual samples	99.3-106.5	[57]
TBBPA	MIP-GR-NBD/CE	DPV	0.50-4.50 nM	0.23 nM	0.1 M pH 7.0 Phosphate buffer solution	0.010 μA/μmol L^{-1}	Water samples	100.2-100.3	[58]
TBBPA	MIPPy-GR-CNTs/GCE	DPV	0.01-10 nM	0.0037 nM	pH 7.5 Phosphate buffer solution	0.105 μA/μmol L^{-1}	Fish samples	93.3-107.7	[59]
TBBPS	MIP(DiM)@ AuNPs/CPE	DPV	0.1-10 nM	0.029 nM	0.2 M pH 6.0 Phosphate buffer solution	3.86 μA/μmol L^{-1}	Water samples	98.7-107.3	[60]
Triclosan	PVC-COOH/ MIP/Au-SPE	DPV	0.1-1000 pg mL^{-1}	0.23 pg mL^{-1}	pH 7.4 Phosphate buffer solution	0.6 μA/pg mL^{-1}	Wastewater sample	100	[61]
Triclosan	MIP/AuNPs/ POM/rGO/ GCE	DPV	0.5–50.0 nM	0.15 nM	pH 7.0 Phosphate buffer solution	Not reported	Wastewater Lake water	98.9-99.8 99.8-100.1	[62]
p-nonylphenol	MWCNTs@ rGONRs/GCE	CSDPV	1.0 nM-10.0 fM	4.8 fM	0.1 M pH 7.0 Phosphate buffer solution	2.554 μA/fmol L^{-1}	Tap water Fşish Sewage water	110.0 111.0-120.0 109.2-112.0	[63]
Octylphenol	MIPEDOT-Au/GNRs/ GCE	LSV	0.02-8.0 μM	1.0 nM	0.05 M H_2SO_4	7.28 μA/μmol L^{-1}	River water Bottled water Urine	105.0-106.0 97.0-101.0 107.0-111.0	[64]
Fenitrothion	ZrO2-NPs/RGO/ MoS2-Au/AuE	SWV	5.0-600 ng mL^{-1}	2.2 ng mL^{-1}	0.2 M pH 5.0 Acetate buffer solution	0.01 μA/ng mL^{-1}	Tap water Cropland water Canal water	78.0-90.0 80.0-95.5 80.0-90.0	[65]
Chlorpyrifos	CuO NFs- cSWCNTs/ Nafion/GCE	DPV	0.1-150 ng mL^{-1}	70 pg mL^{-1}	15 mM pH 7.4 Phosphate buffered saline	4.028 μA/ng mL^{-1}	Apple Celery cabbage	97.08-106.72 95.98-103.05	[66]

Table 3 (*Continued*)

Compound	Sensor	Technique	Linear Range	LOD/LOQ	Buffer or Media	Sensitivity (μA/μmol L^{-1})	Real Sample	Recovery %	References
Methyl parathion	CuO-TiO2/GCE	DPV	0-2000 ppb	1.21 ppb	0.1 M pH 6.0 Phosphate buffer solution	0.0412 μA/ppb	Ground water samples	98.80-106.72	[67]
PCB77	MoS2-rGO/Thi/ AuNP/GCE	DPV	0.3 fg mL^{-1}-0.1 ng mL^{-1}	80 ag mL^{-1}	0.1 M pH 7.4 Phosphate buffer solution	6.075 μA/μmol L^{-1}	River water Tap water Agricultural soil	96.5-108.5 95.5-105.6 97.6-106.6	[68]
Compound	Sensor	Technique	Linear Range	LOD/LOQ	Buffer or Media	Sensitivity	Real Sample	Recovery %	References
Tebuconazole	MIP/Au-PB/ SH-G/AuNPs / GCE	DPV	0.05 μM-0.4 mM	12.5 nM	0.1 mol L^{-1} KNO3	5.72 μA/mmol L^{-1}	Cucumber Green vegetable Strawberry	80.0-85.8 95.0-119.0 85.0-97.8	[69]
Dibutyl phthalate	MCGO@ AuNs-MIPs/ GCE	EIS	02.5 nM-5.0 μM	80 nM	2.0 mM K_3[Fe(CN)6] solution.	1.06 μA/ μmol L^{-1}	Drink samples	97.0-104.0	[70]
Di(2-ethylhexyl) phthalate	Fc-AED/GO/ GCE	EIS	0.6-160 μM 160-1000 μM	0.06 μM 0.9 μM	0.2 M pH 7.0 Phosphate buffer solution	0.015 mA/mmol L^{-1} 0.052 mA/mmol L^{-1}	Liquor samples	Not reported	[71]
Ethylparaben	C60NRs-NH-Ph/GCE	SWV	0.01-0.52 μM	3.8 nM	pH 7.0 Phosphate buffer solution	39.915 μA/μmol L^{-1}	Commercial cosmetic product	96.87-100.3	[72]
Methylparaben Ethylparaben Propylparaben Butylparaben	MIP/GCE	SWV	20-100 μM 5-100 μM 5-80 μM 5-80 μM	0.40 μM 0.20 μM 0.20 μM 0.20 μM	Not reported	Not reported	Cosmetic	97.2-103.1	[5]
17-β-estradiol	Poly(3,6 diamino-9 ethylcarbazol)/ MIP/GCE	EIS	1 aM-10 μM	0.36 aM	pH 9.0 Phosphate buffer solution	Not reported	Human serum samples	96.6-104.6	[73]
Estrone 3-sulfate sodium salt	MIP/CPE	CV	0.004-6 nM	1.18 μM	5 mM $[Fe(CN)_6]^{3-/4-}$ 0.1 M KNO_3	6.9663 μA/nmol L^{-1}	Pregnant mare urine	96.7-101.9	[74]
Sulfamethoxazole Trimethoprim	GR-ZnO nanorods/GCE	DPV	1-40 μM 40-220 μM 1-10 μM 1-180 μM	0.4 μM 0.3 μM	0.1 M pH 7.0 Phosphate buffer solution	0.0987 μA/μmol L^{-1} 0.0269 μA/μmol L^{-1} 0.4123 μA/μmol L^{-1} 0.0746 μA/μmol L^{-1}	Tap water Lake water Urine Serum	95.3-103.0 93.5-105.0 94.0-104.0 94.6-105.0	[75]
Fluoxetine Citalopram Sertraline	PVC/PEDOT-C14-PLE	ITSV	100-1000 nM	35 nM 45 nM 25 nM	Aqueous solution	−0.6761 μA/nmol L^{-1} -0.6765 μA/nmol L^{-1} -0.6353 μA/nmol L^{-1}	Tap water River water	Not reported	[76]
Diclofenac	Crystal Violet -Fe (β- CD)	Potentiometry	0.1 μM-10 mM	0.11 μM	pH 7.0 Phosphate buffer solution	Not reported	Wastewater Pharmaceutical preparations	Not reported 98.38-101.0	[77]

GCE: Glassy carbon electrode, **CPE:** Carbon paste electrode, **CE:** Carbon electrode, **CV:** Cyclic voltammetry, **DPV:** Differential pulse voltammetry, **SWV:** Square wave voltammetry, **LSV:** Linear sweep voltammetry, **EIS:** Electrochemical impedance spectroscopy, **AMP:** Amperometry, **CNPs:** Carbon nanoparticles, **MWCNTs:** Multi-walled carbon nanotubes, **AuNPs:** Gold nanoparticles, **AgNPs:** Silver nanoparticles, **MIPs:** Molecularly imprinted polymers, **TiO_2NPs:** titanium dioxide nanoparticles, **AuPdNPs/GNs:** AuPd nanoparticles-Loaded graphene nanosheets, **Chit (CS):** Chitosan, **CTAB:** Cetyltrimethylammonium bromide, **g-C_3N_4:** Graphitic carbon nitride, **PANI:** Polyaniline, **ssDNA:** single-stranded DNA, **MB:** methylene blue, **GNPs:** Graphene nanoplatelets, **Ionic liquid (IL):** 1-butyl-2, 3-dimethylimidazolium tetrafluoroborate, **PtPd NPs:** PtPd bimetallic nanoparticles, **G-IL:** Graphene- Ionic liquid, **np-Au:** Nanoporous gold, **GA-CS:** Glutaraldehyde cross-linked chitosan, **CTpPa-2:** Crystalline covalent organic framework, **NiNP/NCN:** Nickel nanoparticle/nitrogen-doped carbon nanosheet/chitosan, **NBD:** Amine-terminated benzenediazonium, **GR:** Graphene, **DiM:** Difunctional monomer, **PB:** Prussian blue, **MOFs:** Metal-organic frameworks, **Tyr:** Tyrosinase, **hNiNS:** Hollow nickel nanospheres, **GQDs:** Graphene quantum dots, **B, N, F-CQDs:** Three-doped carbon quantum dots. **GCE:** Glassy carbon electrode, **CPE:** Carbon paste electrode, **SPE:** Screen-printed electrode, **AuE:** Gold electrode, **CV:** Cyclic voltammetry, **PLE:** Pencil lead electrode, **DPV:** Differential pulse voltammetry, **SWV:** Square wave voltammetry, **LSV:** Linear sweep voltammetry, **CSDPV:** Cathodic stripping different pulse voltammetry, **ITSV:** Ion transfer stripping voltammetry, **MIP:** Molecularly imprinted polymer, **PVC-COOH:** Carboxylic polyvinyl chloride, **GO:** Graphene oxide, **rGO:** Reduced graphene oxide, **AuNPs:** Gold nanoparticles, **POM:** Polyoxometalate, **MWCNTs:** Multi-walled carbon nanotubes, **EDOT:** 3,4-ethylenedioxythiophene, **PEDOT:** Poly(3,4-ethylenedioxythiophene), **GNR:** Graphene nanoribbon, **MoS2:** molybdenum sulfide, **ZrO2-NPs:** Zirconia nanoparticles, **cSWCNTs:** Carboxyl-functionalized single walled carbon nanotubes, **CuO NFs:** Copper oxide nanoflowers, **NiMnO@pr-GO:** Nickel manganous oxide nanoparticles decorated partially reduced graphene oxide, **PB:** Prussian blue, **SH-G:** Thiol graphene, **MGO@AuNPs-MIPs:** Magnetic graphene oxide @ gold nanoparticles-molecular imprinted polymers, **Fc-AED:** Ferrocene-terminated poly(amine) ester dendrimer, **C60NRs-NH-Ph:** Functionalized fullerene nanorod, **β- CD:** β-cyclodextrin.

biodegradable characteristics. Thus, it is highly important to sensitively detect pesticides in as environmental samples, plants or biological fluids.

2.8. Natural/Synthetic Sex Hormones

Natural and synthetic sex hormones include different types of estrogens (estriol, estradiol, diethylstilbestrol etc.) and progestogens (progesterone, levonorgestrel, norethindrone etc.) and their derivatives that are widely used for medical purposes as well as in industrial applications [41]. Sex hormones are the most significant group of endocrine disruptors due to their highly potent estrogenic activity even at very low concentrations. Adverse effects of estrogens and progestogens are focused on the reproductive system and can be summarized as feminization, decrease fertility and hermaphroditism. Birth control, hormone replacement therapy, treatment of breast and prostatic cancers, treatment of menstrual, menopausal and post-menopausal disorders are major indications of estrogens. Androgens are mostly preferred for increasing muscle mass and physical strength as supplements [42]. Progestogens can be used either alone or with estrogens for the management of disorders such as endometriosis, infertility and menstrual disorders and some types of cancers such as endometrial and breast. While daily exposure due to such uses ranges between 20 – 50 μg for estrogens, this amount can be up to 2 mg for progestogens. Chronic exposure for humans, contamination of aquatic environments and hazardous effects for wildlife are the reasons that make their determination very important in the context of exposure and risk assessment [41].

2.9. Pharmaceutical Compounds

Pharmaceutical compounds are important and indispensable chemicals that always cover a large part of our lives. Environmental contamination caused by drug waste and residues has been a significant problem for years. However, the increased variety and use of drugs in recent years has brought this issue to the serious levels globally [43]. Drug waste generated by pharmaceutical manufacturing industry, hospitals and households are major sources of environmental contamination [44]. Although the drug active compounds have different mechanisms of action, they are similar in terms of basic features such as being effective at the lowest possible dose and stability to reach requested target in the body. These properties cause them not only stay in the environment without degradation for a long time but also difficult to determine in environmental matrices because of the very low concentrations. Contamination of fresh water sources with various pharmaceuticals such as antibiotics (tetracyclines, quinolones), analgesics (diclofenac, ibuprofen), antidiabetics (metformin), antifungals (ketoconazole, clotrimazole) and psychiatric drugs (fluoxetine, sertraline, citalopram) causes serious impact on not only humans but also aquatic organisms due to long term exposure. These effects include increased risk of cancer, genotoxicity, neurotoxicity and cytotoxicity etc. in humans but endocrine disrupting effects are more apparent in aquatic organisms such as fish, frogs and invertebrates [45].

3. Recent Studies on the Electrochemical Determination of EDCs

Due to the advantageous properties of electrochemistry such as offering highly sensitive and rapid analysis, studies focusing on the electrochemical determination of EDCs are increasing, recently. In the Table 3, we summarize the most recent and novel applications of electrochemical sensors for the determination of EDCs in various media.

Alves et al. reported the electrochemical determination of BPA at bentonite modified carbon paste electrode (CPE). Cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS) and square wave voltammetry (SWV) were applied to determine the characteristics of the proposed electrode. To demonstrate the suitability and potential of the developed method for sample analysis, the Bentonite/CPE sensor was used to detect BPA in water, blood serum and urine samples [46].

In another study, Ponnaiah et al. investigated ruthenium nanoparticles, polyaniline and graphitic carbon nitride (Ru0/

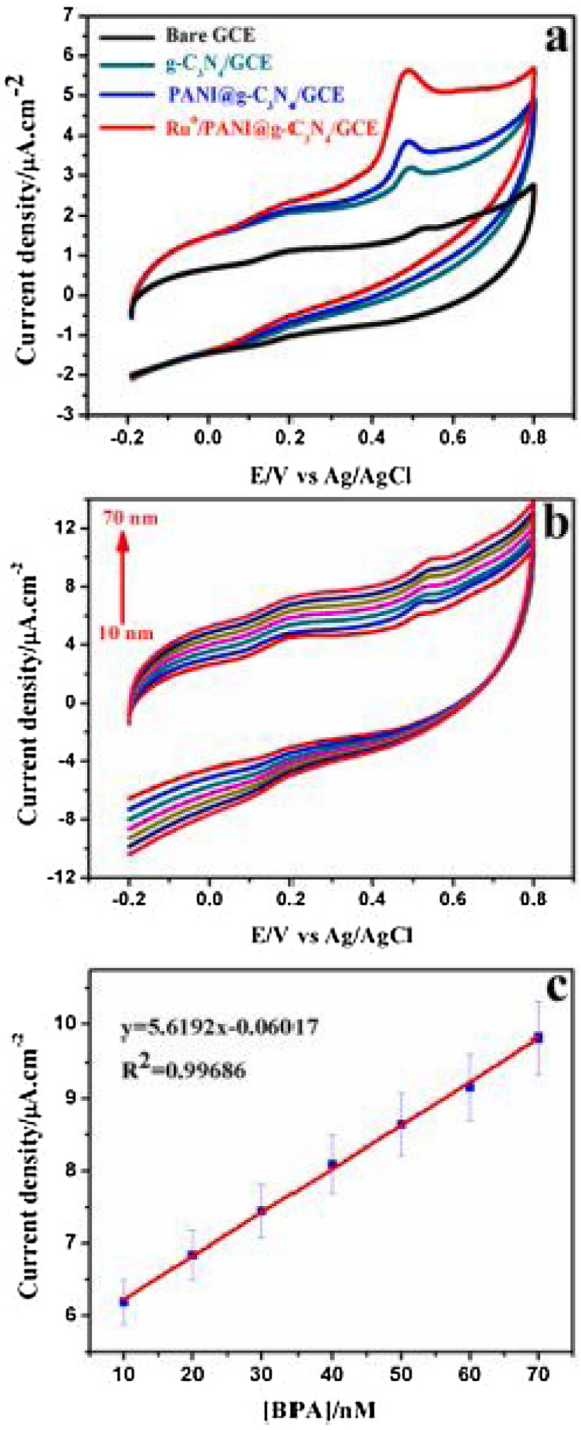

Fig. 1. Cyclic voltammetry curves for (a) bare GCE and different modified electrodes with BPA (10 nM), (b) the addition of different concentrations of BPA (10–70 nM) at pH 7.0, and (c) the linear dependence calibration plot of BPA concentation vs oxidation peak current density. Reprinted with permission from reference [40]. Copyright (2019) Elsevier®.

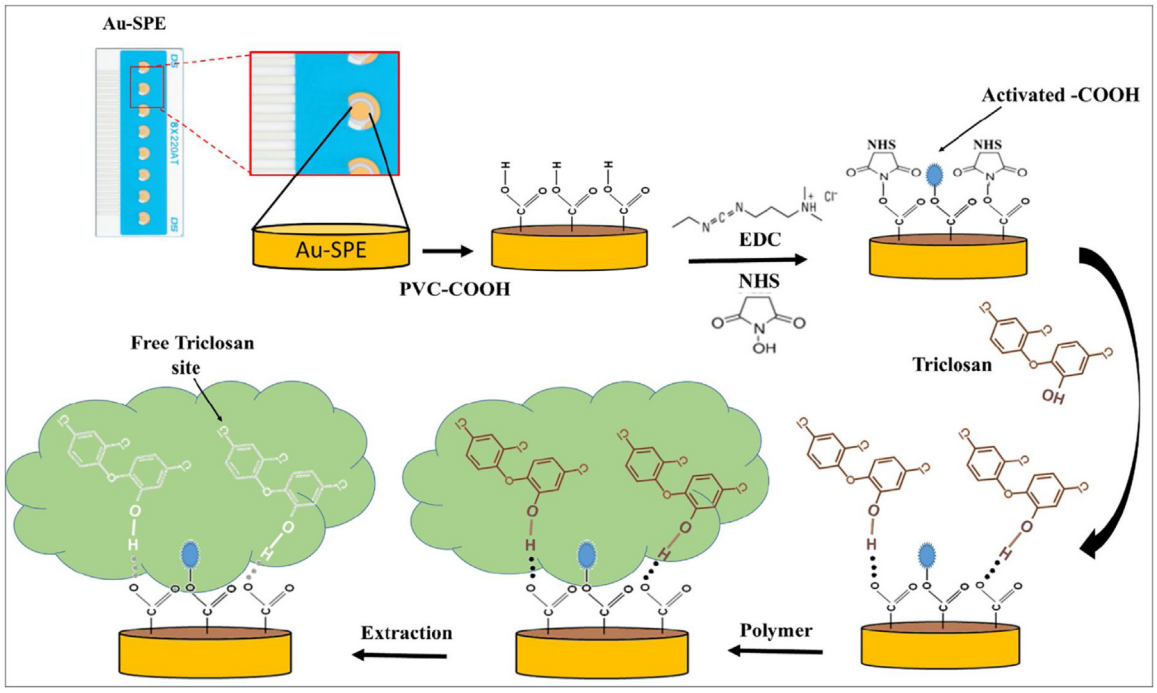

Fig. 2. Schematic representation of the Au-SPE/PVC-COOH/MIP procedure. Reprinted with permission from reference [54]. Copyright (2019) Elsevier®.

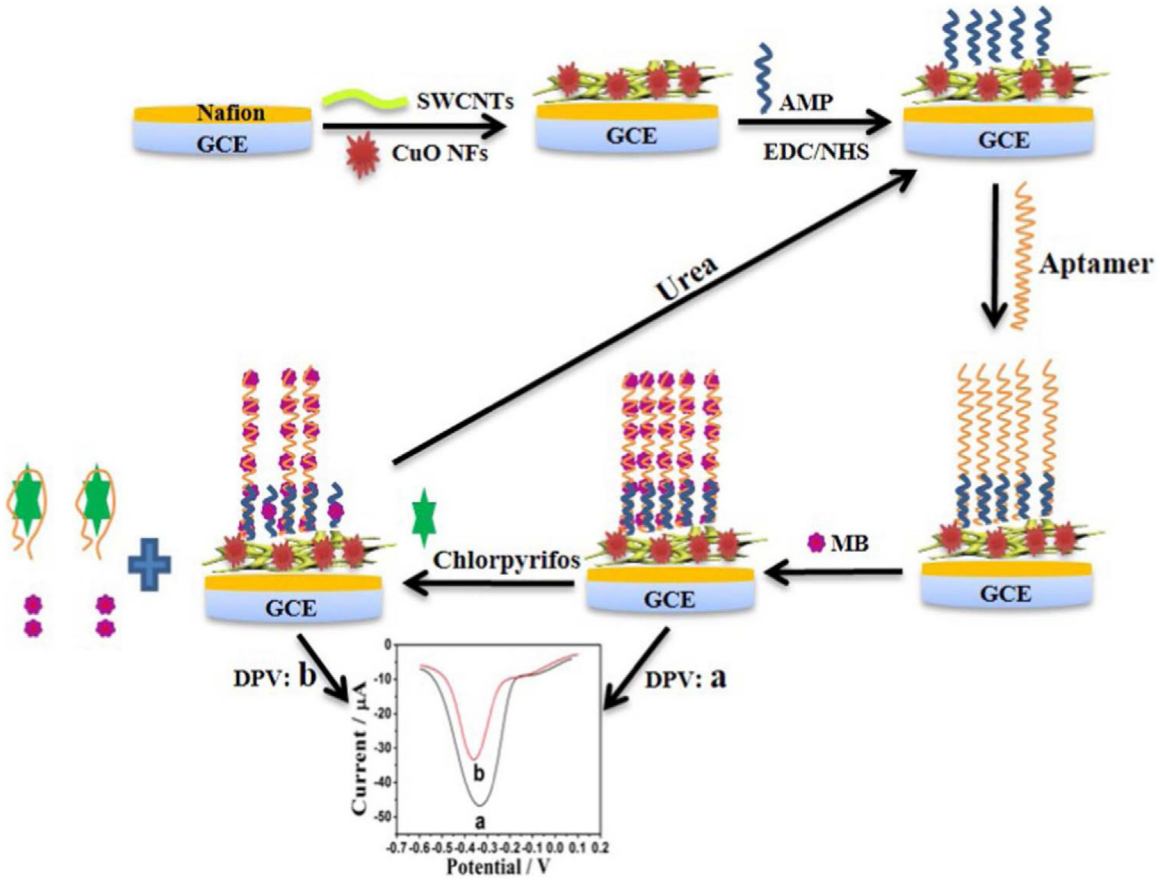

Fig. 3. Schematic illustration of the regenerative electrochemical aptasensor for selective detection of chlorpyrifos. Reprinted with permission from reference [59]. Copyright (2018) Elsevier®.

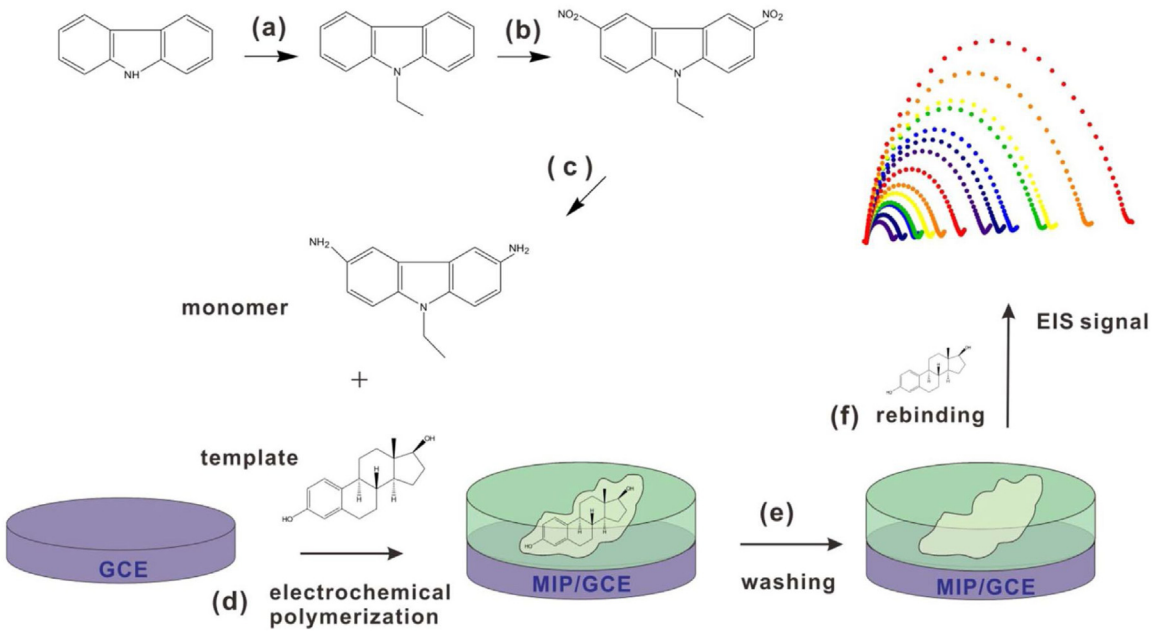

Fig. 4. Synthetic route for 3,6-diamino-9-ethylcarbazole and preparation process of the MIP sensor. Reprinted with permission from reference [66]. Copyright (2018) Elsevier®.

PANI/g-C3N4) modified glassy carbon electrode (GCE) for the determination of BPA. The synthesized Ru0/PANI/g-C3N4 demonstrated high electrocatalytic activity towards the electrochemical oxidation of BPA. CV is used for showing the modification effect for oxidation of BPA. (Fig.1) Differential pulse voltammetry (DPV) was used for the determination of BPA, and the fabricated electrochemical sensor exhibited a linear response to BPA in the range of 0.01-1.1 μM with the limit of detection (LOD) of 0.18 nM. In addition to that, the developed (Ru0/PANI/g-C3N4)/GCE sensor was applied to detect the BPA in drinking water, and adequate results were obtained [47].

In another work, Lu et al. reported the electrochemical tyrosinase nanosensor based on metal-organic frameworks (MOFs) and chitosan for the determination of BPA at GCE by CV and amperometry. A typical current response curve was observed during successive addition of various concentrations of BPs in 50 mM pH 7.0 phosphate buffer solution. The linear range values of Bisphenol E (BPE), BPF, BPB, Bisphenol Z (BPZ) were estimated as 0.05-3.0 μM, 0.05-3.0 μM, 0.125-8.0 μM, 0.25-5.0 μM with the LOD values of 15 nM, 16 nM, 56 nM, 33 nM, respectively. Meanwhile, the Cu-MOF-Tyr-Chit/GCE sensor was successfully applied to detect the level of BPA in wastewater. Additionally, it has been found to be a selective sensor for the detection of high concentrations of heavy metals [54].

Motia et al. have reported the fabrication of a highly sensitive electrochemical sensor for the simultaneous determination of TCS and BPA based on molecularly imprinted polymer (MIP), assembled on screen-printed gold electrode (Au-SPE) (Fig. 2). Under the optimized conditions, DPV was used to investigate the detection performance of PVC-COOH/ MIP/Au-SPE toward BPA in pH 7.4 phosphate buffer solution with different concentrations of TCS. LOD was estimated to be 0.23 pg mL^{-1} (S/N = 3). The sensor was successfully applied to detect TCS in wastewater sample. The developed electrochemical sensor exhibited good recovery, close to 100 %. The relative standard deviation (%RSD) was about 2.8, which demonstrated that PVC-COOH/ MIP/Au-SPE is acceptably reproducible. For the detection of TCS traces in water sources, the results have shown that it is a simple, useful, sensitive, stable and low-cost alternative [61].

For organophosphoros pesticide chlorpyrifos, which threatens human health and is widely used in agriculture, a direct electrochemical detection system was developed by Xu et al. with the nanocomposite consisting of copper oxide nanoflowers (CuO NFs) and carboxyl-functionalized single walled carbon nanotubes (c-SWCNTs). Firstly, Nafion solution (0.05 wt%) was dropped onto GCE and then mixed with an appropriate volume ratio of CuO NFs suspension and c-SWCNTs suspension was added on the Nafion/ GCE. CuO NFs-SWCNTs-modified GCE was fabricated for the determination of chlorpyrifos (Fig. 3). Under the optimal experimental conditions, the sensor has LOD of 70 pg mL^{-1} and linearity from 0.1 ng mL^{-1} to 150 ng mL^{-1}. Results revealed that the constructed electrochemical sensor has great sensitivity. In addition, a sensitivity value of 4.028 μA $ngmL^{-1}$ was obtained from the linear regressive equation. This electrochemical aptasensor was also successfully applied to determination of chlopyrifos in apples and celery cabbages [66].

In a recent study, Liu and coworkers studied electrochemical behavior of the primary female sex hormone (17-β-estradiol) on a GCE. Poly(3,6-diamino-9-ethylcarbazole) based molecularly imprinted polymer sensor was decorated onto the surface of GCE for the electrochemical detection of 17-β-estradiol by EIS (Fig. 4). LOD value of 0.36 aM and linear range of 0.1 aM to 10.0 μM were found by EIS technique. The resulting fit of the calibration plot shows a good correlation with R^2 of 0.9849 and the buffer is phosphate-buffer solution (PBS, pH = 7.0). The developed poly(3,6 diamino-9 ethyl carbazol)/MIP/GCE was successfully applied for detection of 17-β-estradiol in human serum samples. This study showed recoveries from 96.6% to 104.6% and a RSD value less than 6.96%. The proposed method was successfully applied for the 17-β-estradiol quantification in the real samples with acceptable recoveries [73].

4. Current Challenges

Due to the latest developments in technology, new perspectives are also needed in the field of sensor development. Determining compounds in complex matrices is one of the most challenging tasks for the analysis of EDCs. Additionally, most samples contain

more than one endocrine disruptive compound and due to this, determination of multiple compounds simultaneously may be necessary. In addition to aimed compounds, lots of samples such as environmental, commercial or biological contain other compounds that are considered as interferences. Therefore, it is important to develop a sensor that can make measurements without negative effects of interferences. Consequently; more sensitive and selective sensors should be developed for the real sample analysis of EDCs. It is also a difficult process to extract required compounds for sample preparation. Researchers currently work on new integrated systems that will facilitate easy sample preparation and measurements. Electrochemical sensors are low-cost and eco-friendly and they can be easily miniaturized. Those advantages create opportunities to develop portable and disposable sensors for easier applications in the future. Especially in the analysis of environmental samples, it is important to develop portable and reusable devices that can be used in the field. Considering all of these, novel approaches and technological developments will be determinative factors for the future of the analysis of EDCs.

5. Conclusion

During recent years, growing number of studies on proving the endocrine disrupting effects of various chemicals have raised serious health concerns. With increased awareness about safety of products that are used daily, people have started to pay more and more attention to the content of the products and the packaging. Besides, legislative regulations and prohibitions are stricter nowadays. Because of all these reasons, it is really important to determine EDCs sensitively in various samples such as environmental samples, food and drinks, personal care products etc. In this context, electrochemistry is a sensitive, rapid, easy to use and economical method for the determination of EDCs. Its versatility and ability to enhance performance of the sensors by modification with nanomaterials provide the development of advantageous sensors.

In this review, the most significant EDCs and their sensitive determination were examined from the perspective of nanomaterial based electrochemical sensors. Most recent and novel studies were summarized in a table.

Declaration of Competing Interest

The authors report no declarations of interest.

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