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Origin, dietary exposure, and toxicity of endocrine-disrupting food chemical contaminants: A comprehensive review

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) are a growing public health concern worldwide. Consumption of foodstuffs is currently thought to be one of the principal exposure routes to EDCs. However, alternative ways of human exposure are through inhalation of chemicals and dermal contact. These compounds in food products such as canned food, bottled water, dairy products, fish, meat, egg, and vegetables are a ubiquitous concern to the general population. Therefore, understanding EDCs' properties, such as origin, exposure, toxicological impact, and legal aspects are vital to control their release to the environment and food. The present paper provides an overview of the EDCs and their possible disrupting impact on the endocrine system and other organs.

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1. Introduction

During the last decades, the production of different kinds of chemicals has been considerably increasing worldwide, alongside the changes in peoples' lifestyles [1–3]. The endocrine system is a complicated network of internal body organs producing various hormones. The principal signaling molecules are carried through the circulatory system to the target. To preserve homeostasis in the human body, proper functioning of the endocrine system is an essential precondition. Endogenous and exogenous contributors may cause disorders of hormonal functions [4,5]. The causes of endocrine disruption have been the subject of intense debate within the scientific community. A growing body of literature has addressed the adverse effects of endocrine-disrupting chemical contaminants (EDCs). According to the definition of the World Health Organization (WHO), an endocrine-disrupting chemical is an exogenous substance or compound that changes the function(s) of the endocrine system and therefore leads to health side effects in a healthy organism, or its posterity, or (sub)populations [6]. In another definition announced by The United States Environmental Protection Agency (US EPA), an EDCs is introduced as an exogenous substance that may intervene in the synthesis, excretion, receptor binding, metabolism transport, or remove endogenous hormones, changing the endocrine homeostatic systems [7]. EDCs are contributed to altering reproductive function in males and females, elevated risk of cancer, including breast cancer [8], and the miRNAs transcription alteration [9], obesity, type 2 diabetes, neurodevelopmental delays in children, untypical growth patterns, and immune function abnormality. Human exposure to EDCs happens through inhalation, food and water ingestion, and direct dermal contact [1,10–12]. It is necessary to note that EDCs can be passed from mother to infant via breast milk and from pregnant women to the growing embryo through the placenta. Furthermore, children and pregnant mothers are considered the most sensitive individuals to EDCs [11]. International Agency for Research on Cancer (IARC) has published the carcinogenicity status of EDCs, presented in Table 1.

Up to now, many studies have intended to explain the disruptive role of EDCs on estrogen receptors (ERs), progesterone receptors (PRs), aryl hydrocarbon receptors (AHRs), thyroid hormone receptors (THRs), androgen receptors (ARs), mineralocorticoid receptors (MCRs), glucocorticoid receptors (GRs), and peroxisome proliferator-activated receptors (PPARs) [15–18]. For instance, the mechanism of AHR function after binding EDCs was schematically described in Fig. 1.

It is now well established that EDCs may cause the impairment of the normal function of hormones (principally by binding to the plasma proteins and hormone receptors) [19,20], impairment of the activity of endogenous hormones-metabolizing enzymes, interfering with the biosynthesis and biotransformation of natural hormones [15,19], dysregulation of the ion channel activity and transporting across the biological membranes [21], dysregulated DNA methylation, and modification of histones, as well as having an impact on noncoding RNA [7,22]. Globally, the annual cost of EDCs exposure is highly important, mostly related to neuroendocrine disorders. For instance, IQ decrease has also been related to prenatal or early postnatal exposure to polychlorinated biphenyls (PCBs) [23].

With reference to a population-based disease burden and cost analysis, the disease costs of EDCs in the Europe and USA have been reported 1.28% of GDP ($217 billion) and 2·33% of GDP ($340 billion). The difference was driven mainly by intelligence quotient (IQ) points loss and intellectual disability caused by exposure to polybrominated diphenyl ethers (873 000 IQ points lost and 3290 cases costing $12·6 billion in the European Union and 11 million IQ points lost and 43 000 cases costing $266 billion in the USA) [24].

The negative impact of exposure to EDCs may become apparent later in life. Additionally, exposure to EDCs makes the targeted organism more vulnerable due to the remodeling of tissues and organs during development and limited defense mechanisms [25,26]. EDCs may be present in many everyday products, including food, cans, cosmetics, plastic bottles, detergents, pesticides, toys, and flame retardants [11].

Due to the systematic lack of testing chemicals for EDC properties there is no good, authoritative overview of EDCs available. Regarding the worldwide occurrence of EDCs in foods and to specify the hazard of EDCs toxicity, the main goal of this review article is to examine existing knowledge in the case of agricultural and industrial endocrine-disrupting chemicals, mentioned by WHO, IARC and observed in high levels in foodstuff, which have been classified as dioxins, bisphenol A, polychlorinated biphenyl, polybrominated diphenyl ethers, phthalates, organochlorine pesticides, tributyltin, and heavy metals with particular reference to their origin, dietary exposure, toxicological impact on health, and legal restrictions.

2. Dioxins

Dioxins and dioxin-like substances that are structurally similar have exhibited environmentally and biologically stability, created a standard range of responses, and had a common mechanism of action. These chemicals include biphenyls, polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and similar substances. Before industrialization, dioxins were in low concentrations due to geological processes and natural combustion. Dioxins comprise two benzene rings bound by two oxygen atoms and include four to eight chlorines for up to 75 combinations or analogs [27]. Occupational, environmental, or accidental pollution can expose humans to dioxins. Nowadays, the burning of urban or homemade waste, medical waste, disposal area fires, and forest and agricultural fires are the largest sources of dioxins release [28]. Due to the high hydrophobicity, dioxins tend to store in fatty tissue. So, their level increases as they enter the food chain, where they finally enter the human body by eating polluted food [29]. According to US EPA, at least 90% of human exposures to dioxins in daily life come from contaminated animal food products, such as meat, animal fat, and dairy products, as the primary sources of intake [13,30,31]. The most influential factors on average dietary exposure for most European age groups are fish, meat, and cheese [32].

Dioxins are partly metabolized and removed from the human body, accumulating residue in fatty tissues. Dioxins are categorized as identified human carcinogens, resulting in noncancerous diseases such as diabetes, hypertension, and atherosclerosis. Prolonged exposure to dioxins leads to reproductive, immune, nervous, and endocrine system disorders. Short-term exposures to dioxin cause

Table 1
An updated classification of IARC [13], Origin and Dietary exposure for EDCs.

Chemical group	Origin	Main source of Dietary exposure	Agent	IARC group	year of report
Dioxins and dibenzofurans	byproduct in manufacturing and disposal processes (Organochloride Production, paper bleaching, incineration of chloride-containing substances	Milk and milk products, Bovine adipose tissue, eggs, fish	2,3,7,8-Tetrachlorodibenzo-para-dioxin	1	2012
	Volcanic eruptions, Forest fires, Incineration of hazardous, municipal and medical wastes, Cement plants, Chlorine bleaching of paper pulp or smelting, Traffic of motor vehicles	animal fats, dairy products, cereals, vegetables, meat, fish, shellfish	2,3,4,7,8-Pentachlorodibenzofuran	1	2012
Biphenyls	Production, utilization, and disposal of PCB treated products, Unintentional emission from combustion processes, Re-emission of PCBs from environmental reservoirs (e.g. soil, sediment, and water)	fish, meat, dairy products, fats	Polychlorinated biphenyls, dioxin-like (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)	1	2016
			Polybrominated biphenyls	2A	2016
Bisphenol	polycarbonate plastics, epoxy resins	canned food	Tetrabromobisphenol A	2A	2018
			Bisphenol A diglycidyl ether (Araldite)	3	1999
phthalate	pesticides, detergents and plasticizers	legumes, vegetables and cereals	Di (2-ethylhexyl) phthalate	2B	2013
Cd	volcanic activity, river transport, erosion, and weathering [14], or human activities, such as cigarette smoke, waste burning, metal ore combustion, fossil fuels, old Zn/Cd sealed water pipes or industrial pollution	agricultural products, fish, shellfish,	Cadmium and cadmium compounds	1	2012
As	occurring naturally in the soil, exceedingly unleashed via volcanic activity, erosion of rocks, human activity, and forest fires, soaps, paints, dyes, metals, drugs, semi-conductors, pesticides, and fertilizers	agricultural products, especially rice	Arsenic and inorganic arsenic compounds	1	2012
Pb	food cans, water pipes, contaminated drinking water, cosmetics, batteries, paint, traditional remedies, gasoline, Pb-crystal, Pb-glazed ceramics, cigarette smoke, jewelry, children's toys, vinyl lunch boxes	agricultural products, especially rice, root vegetables, cucurbits	Lead compounds, inorganic	2A	2006
Hg	natural phenomena (such as volcanic activity and weathering of rocks), human activities (coal-fired power plants, mining processes, metal refineries, electronic waste recycling factories, and municipal solid waste incinerators), pesticides	seafood, poultry	Methylmercury compounds	2B	1993
Organochlorine pesticides	disposal of polluted wastes into landfills, sewage discharge, industrial release, agricultural runoff, disposal of empty chemical containers, leaching of pesticides from surface soil to downstream water	vegetables and fruits, dairy products, meat, and fish	4,4′-dichlorodiphenyltrichloroethane (DDT)	2A	2018
			Dieldrin	2A	2019
			Methoxychlor	3	1987
			Dicofol	3	1987
			Hexachlorocyclohexane	2B	1987
			Heptachlor	2B	2001
			Endrin	3	1987
			Chlordane	2B	2001
			Chlordecones	2B	1987
			Toxaphene (Polychlorinated camphenes)	2B	2001

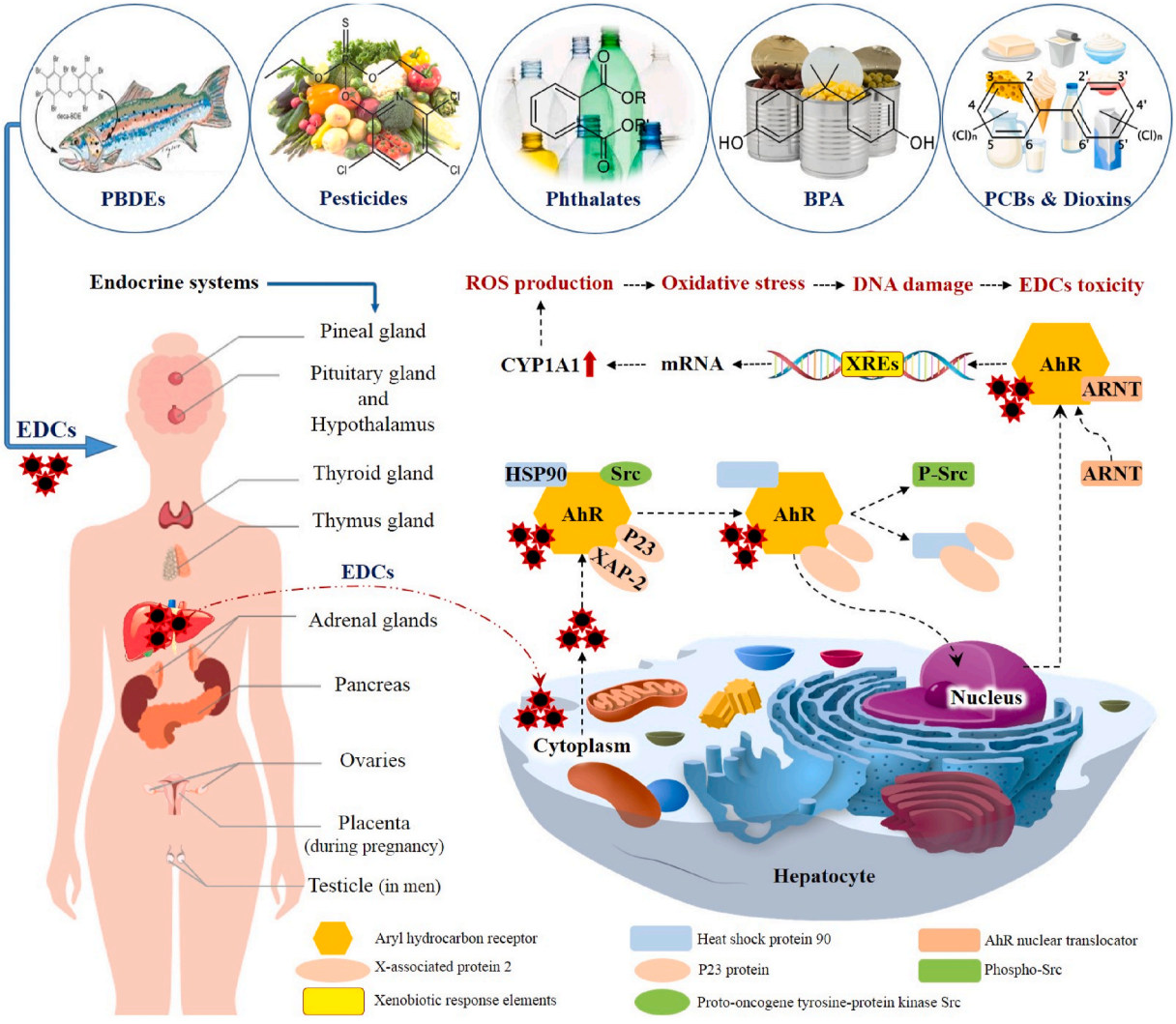


Fig. 1. EDCs-mediated activation of AHR and oxidative stress.

liver malfunction and Chloracne (a rare skin eruption of blackheads, cysts, and nodules). Infants and embryos are the most sensitive individuals to dioxin exposure. Scientific publications have reported multitudes of health effects, and they all categorize dioxins as one of the most toxic substances for the human body [28].

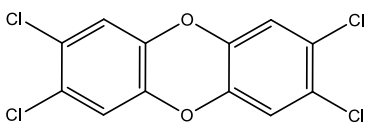
Aside from the toxicity of dioxins and their existence in the environment, many researchers have proved the chemical to be highly resistant to biodegradation, mainly because of very low solubility in water and high octanol-water partition coefficients (Kow). Toxic equivalent quantities (TEQs) are used for the toxicity of dioxins where the most toxic analog 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is evaluated as 1.0 and the less toxic analog as fractions of this. AHR is responsible for the toxicity of dioxins; a toxic equivalency factor (TEF) is used, presuming that the effects are accumulative and act through a common mechanism to cause toxicity [33].

2.1. PCDDs and PCDFs

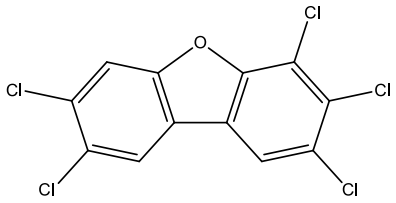
According to Stockholm Convention and US EPA, PCDDs and PCDFs, have been considered persistent organic pollutants (POPs), meaning they take a long time to decompose in the environment [34]. In western Japan in 1968, more than 2000 residents were intoxicated by the consumption of edible rice bran oil, which was polluted with high concentrations of PCDFs, PCDDs, and PCBs [35].

PCDDs and PCDFs are comprised of two benzene rings bound via oxygen atoms. In PCDDs, two rings are bonded by two oxygen bridges. However, a carbon bond and one oxygen bridge link PCDFs (Fig. 2) [28].

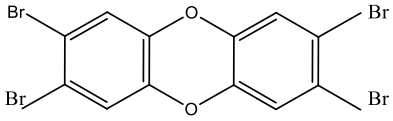
PCDDs and PCDFs are general terms used to explain 75 types of PCDDs and 135 types of PCDFs. Of these kinds, 17 isomers of 2,3,7,8-PCDDs/PCDFs are evaluated as harmful to human health [36]. These stable lipophilic chemicals can produce several toxic responses, including immunotoxicity, carcinogenicity, reproduction, and developmental disorders [37].



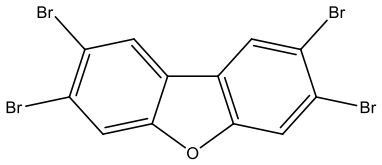
TCDD



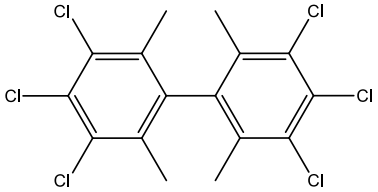
2,3,4,7,8-pentachlorodibenzofuran



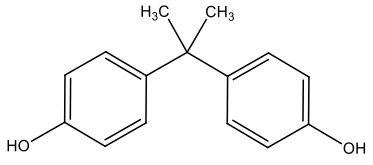
Tetrabromodibenzo-p-dioxin



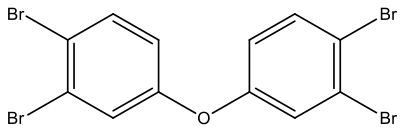
Tetrabromodibenzofuran



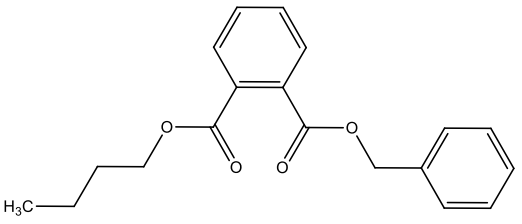
PCBs



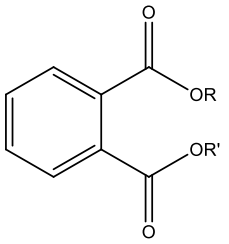
Bisphenol A



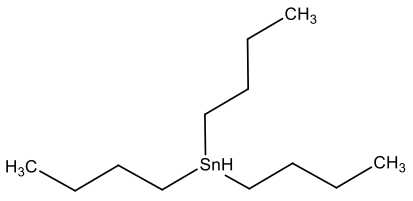
3,3',4,4'-Tetrabromodiphenyl ether (PBDE-77)



Butyl benzyl phthalate



General structure of Phthalates



Tributyltin

Fig. 2. Chemical structures of the main EDCs.

PCDDs/PCDFs may release in numerous natural processes, such as forest fires and volcanic eruptions. However, they are always undesirable byproducts, whose presence in the environment is primarily because of the release of manufacturing processes like burning dangerous, urban, and medical wastes, chlorine bleaching of paper pulp, cement plants, smelting, along with motor vehicles traffic [38]. Therefore, the emission levels of these chemicals from industrial processes have been reduced by elimination and control measures under national or international legislation and regulation. Due to the persistence of these compounds in the environment, they are carried by air and settled in the soil, water, and plants [3,39,40]. They are highly soluble in fat and low soluble in water [41]. The most significant exposure to PCDDs/PCDFs is mainly dairy products, followed by cereals, vegetables, meat, and fish [42]. They can bond to organic matters and sediment in the environment and are absorbed into the adipose tissues of humans and animals. Furthermore, they are not biodegradable and can store in the food chain [41].

In 2001, the Scientific Committee on Food of the European Commission estimated the risk of exposure to dioxins and dioxin-like PCBs (DL-PCBs) and established a tolerable weekly intake (TWI) at 14 pg TEQ per kg body weight. According to the new risk assessment by European Food Safety Authority (EFSA) CONTAM Panel in 2018, the EFSA has newly altered this amount to 2 pg TEQ per kg body weight [43].

2.2. TCDD

Among the PCDDs family, TCDD, a widely studied polychlorinated aromatic compound [44], is the most toxic chemical known as an almost ubiquitous environmental contaminant and a potent endocrine disruptor [45,46]. The toxicity of TCDD attributes to a high-level acute exposure which was especially exhibited after the Seveso industrial accident came about in July 1976, which exposed Italian residents to high levels of TCDD, resulting in high animal and plant mortality and many cases of Chloracne, mostly among children [46]. During Vietnam. War from 1961 to 1971, spreading the TCDD-contaminated Pesticides (Agent Orange) was linked to a high cancer mortality rate in 2005 [35].

However, in industrialized countries, TCDD is now omnipresent at low levels, mainly due to artificial activities [47]. Production and disposal operations such as organochloride manufacturing, paper decolorizing, and high-temperature burning chloride chemicals produce TCDD as a byproduct [48]. The released TCDD and its analogs are detected in the environment, including food, air, and soil [49]. The most influential factors in human exposure to TCDD and other dioxins are foodstuffs like milk and dairy products, bovine fatty tissue, hen's egg, and fish [50]. The main detrimental effects of exposure to TCDD are hepatotoxicity, digestive and breast cancer, embryo developmental problems, birth disorders such as the cleft palate and kidney deformity, immunotoxicity, cardiotoxicity, neurotoxicity, nausea; dyspnea, reproductive defects, asthma, and high blood pressure [51]. AHR motivation may mediate these alterations, which imparts cytochrome P450 enzymes involved in the oxidative metabolism of both artificial and natural substances, and by the uridine diphosphoglucuronosyl transferase, a Thyroid metabolizing enzyme, in the liver [52,53].

TCDD can pass through the placenta and influence thyroid functions, resulting in perinatal hypothyroidism, growth retardation, permanent brain damage, and persistent effects during childhood [53]. Maternal TCDD can decline growth hormone levels and glucocorticoid levels in newborns [54].

TCDD's half-life in humans is very extended; it has been approximately 7.1 and 11.3 years [55]. In December 1990, a tolerable daily intake (TDI) of 10 pg kg^{-1} body weight was set by a WHO meeting in Bilthoven, Netherlands [56].

2.3. Polybrominated dibenzo-p-dioxins and dibenzofurans (PBDDs/PBDFs)

Polybrominated dibenzo-p-dioxins and dibenzofurans (PBDD/PBDFs) include diaromatic molecules in which two benzene rings are joined together by a diether (dioxin) or furan bridge with different degrees of bromination (Fig. 2) [57]. They have been present in different matrices, including air, sediments, seafood, and human fat samples [58]. Regarding physiochemical and toxic characteristics, ominated dioxins and furans are comparable to their chlorinated ones, namely PCDDs/PCDFs. Compared with PCDDs/PCDFs, PBDD and PBDF are less resistant to photolytic reactions and, therefore, less durable in the environment [59]. Moreover, PBDD/PBDFs have a more considerable molecular weight, lower water solubility, lower vapor pressure, and higher melting point than PCDDs/PCDFs [60]. PBDD/PBDFs exhibited more susceptibility to degradation by ultraviolet light, and their capacity for bioaccumulation is considered to be higher than PCDD/PCDFs, owing to the lower energy of C–Br bonds (276 kJ/mol) than C–Cl bonds (328 kJ/mol) [60]. This probably affects the rate of occurrence in the environment and foodstuffs. The halogenation rate and the bromine atom's larger size may also have a biological effect. Nevertheless, these effects are comparable to the chlorinated congeners, including lethality, carcinogenicity, immunotoxicity, reproductive effects, thymus atrophy, teratogenesis, chloracne, and enzyme induction [61]. Hypothetically, there are 75 PBDDs and 135 PBDF compounds and 1550 Bromo/chloro dioxins mixtures, and 3050 Bromo/chloro furans mixtures. Like chlorinated dioxins, a binding to the positions 2, 3, 7, and 8 makes them the most toxic substances with a common mechanism of action with PCDD/PCDFs, the primary step of which includes attaching to the AHR [43].

PBDD/PBDFs have never had any industrial application and have never been deliberately produced [57]. Even though PBDD/PBDF congeners with lower bromine atoms can naturally be generated via biosynthetic and photochemical processes [62]. PBDD/PBDFs are usually produced under thermal conditions, such as burning brominated flame retardants (BFRs), disposal of electronic waste equipment, melting metal, and burning waste [63]. Like other constant lipophilic pollutants, chronic PBDD/PBDFs via diet are broadly considered the principal exposure [57]. Up to now, far too little attention has been paid to the presence of these compounds in food products [64]. In 2005, a total diet study (TDS) in the UK examining a full range of foods showed the occurrence of PBDD/Fs in all foodstuffs ranging from 0.003 in vegetables to 0.18 pg TEQ/g in oils and fats. Seafood and animal products, such as meat, dairy, offal, and fish, are mainly comprised of higher amounts. Amazingly, a full range of PBDF compounds has been detected in sugars and

preserves (chocolates, syrups, jams, and other confectionaries) [57].

2.4. Polychlorinated biphenyls

Polychlorinated Biphenyls (PCBs) are a group of industrial chemicals comprising a couple of phenyl rings, and one or multiple chlorines are introduced into the rings by a single bond [65]. They are organic, manufactured stable pollutants of chemical formula $C_{12}H_{10-x}Cl_x$ (Fig. 2). The different configurations of chlorine atoms produce 209 probable PCB congeners, some of which are more toxic than others [66]. Because of their physicochemical characteristics, degradation, bioaccumulation, and metabolism capabilities, congener composition in environmental media differ from relevant sources [67].

PCBs are usually chemically inactive, with excellent flame retardation, thermal conductivity, and electric insulation characteristics, resulting in various applications as dielectric fluids in transformers and capacitors, hydraulic fluids, heat transfer fluids, and additives in several closed and open usages [68]. Although PCBs in the United States and Europe have been prohibited since the 1970s, their stability, persistence in degradation, and hydrophobicity have caused considerable bioaccumulation in most parts of the ecosystem and human tissues [69]. The health effects associated with PCBs exposure include neurobehavioral changes, endocrine disorders (reducing serum thyroxine (T4)), and carcinogenicity. Background levels of PCBs from transplacental transfer are related to damaged neurological development in newborns and children; neuropsychological effects of PCBs have also been reported among the elderly [70,71].

Environmental emissions of PCBs have been related to three main processes (1) manufacturing, application, and disposal of PCBs-processed products; (2) accidental emission from burning operations; and (3) PCBs re-release from environmental reservoirs (e.g., soil, sediment, and water) [68]. However, nowadays, human exposure to PCBs has arisen mainly from the ingestion of food. The major routes of food contamination by PCBs are absorbed from the environment by livestock, birds, fish, and agricultural products through the food chain. Approximately 80% of total PCBs intake is associated with consuming fish, meat, fats, and dairy products. PCBs are observed at high levels in fatty foods of animal origin, mainly in fish [72,73]. In 2001, EU Scientific Committee on Food (SCF) set up a TWI of 14 pg TEQ/kg body weight per week, which complies with the provisional tolerable monthly intake (PTMI) of 70 pg TEQ per kg body weight established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2001. WHO obtained a TDI of 20 ng/kg body weight per day for (total) PCBs [67].

3. Bisphenol A

The substance 2,2-bis(4-hydroxyphenyl)propane (Fig. 2), usually known as Bisphenol A (BPA), is an EDCs that is used widely as a chemical compound in the production of plenty of polymeric materials, including polycarbonate plastics, the epoxy resins that are used in food containers [74–76].

Owing to the extensive uses of BPA, human exposure pathways are multifold. The primary exposure pathways to BPA are occupational (workers in the industry involved in the synthesis of BPA), environmental (contaminated aquatic environments, soil, and atmosphere), and food consumption (use of BPA-containing packages such as epoxy resins, Polycarbonate (PC) and Polyvinyl Chloride (PVC) plastic for food and beverages) [12,77], which is taking place through ingestion, inhalation, and dermal contact [78]. Besides, it should be mentioned that dermal exposure to BPA via thermal papers is remarkable. In some studies, BPA concentrations of thermal paper reported from 0.211 mg/g to 26.3 mg/g and its transfer rate has been ranged from 1072 to 21 522 ng/s in order to estimate BPA migration from thermal paper to skin [79,80]. However, one of the most important sources of human exposure to bisphenol is food and its packaging, which is the main focus of this article.

Human exposure to BPA arises mainly through food consumption. Overall, various studies have shown that the average concentration of total bisphenol in canned foodstuff is high, and among them, canned fish has shown the highest concentration. Thus canned food products are a dominant source of BPA [77,81]. For instance, Carwile et al. (2011) observed a significant increase (1200%) of urinary BPA content in the group that consumed 1 meal of canned soup for 5 days compared to the group that had consumed fresh food at the same time [82].

BPA can leak into the food through packaging, particularly containers made of epoxy resins. In Canada, the United States, and Europe, there have been numerous reports of high levels of BPA in the urine of people who consumed canned foods compared to the control group, which indicates a positive association between food intake of BPA and the release and migration of this compound from food packaging into food substance [83].

Determining the Migration Limits the maximum levels of substances permitted to migrate to food is known as a momentous approach to certifying the safety of plastic materials. Based on toxicity results, Specific Migration Limits (SML) have been set by EU regulation. For assurance of the overall quality of the plastic, the overall migration of all substances to a food may not be upper than 60 mg kg^{-1} of food or 10 mg dm^{-2} of the contact material, established as the Overall Migration Limit (OML) [84].

According to a former estimation by the Scientific Committee on Food, 0.6 mg of BPA per kg of food has been set as SML for plastic materials to assure that exposure to BPA stays under the TDI and does not threaten human health. Today, BPA use in polycarbonate infant feeding bottles is forbidden based on preventive principles [85].

BPA migration from food packages containing this compound is enhanced by heating, contact with alkaline and acidic substances, contact time, and microwave exposure, leading to BPA intake via food [12]. The content of microplastics in food enhances the release of BPA in human tissues [86,87]. The limit of migration of BPA from plastics in contact with food has been set according to the EFSA (0.6 mg kg^{-1}), which is reduced from 0.6 to 0.05 mg kg^{-1} in the 2018 revision [74,76].

Various national and international agencies have estimated the intake of BPA through diet in children and adults. WHO has

declared 0.2–1.9 μg kg^{-1} body weight per day for children > 3 years and 0.4–4.2 μg kg^{-1} body weight per day for adults. Also, the daily intake estimated by the Food and Drug Administration of the United States (US FDA) is 0.5–1.1 μg kg^{-1} BW per day for adults and 0.1–0.3 μg kg^{-1} body weight per day for children aged 12–24 months [77].

BPA possesses low to moderate hydrophobicity and therefore has a medium capacity in bioaccumulation. Also, because of rapid biodegradation at low doses, BPA bioaccumulation happens commonly at high concentrations [88].

After dietary exposure, BPA is absorbed by the gastrointestinal tract and transferred to the liver, where 90% of BPA is almost entirely metabolized by glucuronidation and to a lesser extent by sulfation (10%), which results in building up two passive forms of BPA, glucuronidated BPA and sulfated BPA, respectively [12,89].

BPA is a relatively unstable substance with a half-life of about 5.3 h [90]. It is quickly removed primarily by glucuronidation from the blood through the kidneys and warded off in urine. Due to a sufficient amount of glucuronidated BPA (more than 90% after 6 h of intake) excreted in the urine as the major metabolite of BPA, estimating the exposure rate is preferable through urinary measurements of BPA [91]. In addition to urine, different biological samples, including blood, amniotic fluid, breast milk, hair, and other tissues, can be used for BPA bioassay [92–94].

Several studies and scientific data on the accumulation and measurement of BPA in tissue have been published. In research, the concentration of BPA in the liver, brain, and adipose tissue of adults, the amount of BPA was observed in the range of 0.9–2.77 ng/g for the liver, up to 2.36 ng/g in the brain, and 1.12–12.28 ng/g for the adipose tissue [95].

Canada was the first to categorize BPA as a toxic chemical contaminant and has prohibited its use in baby bottles since 2008 [89]. After that, The European Commission (EC) and US FDA forbade the use of BPA in manufacturing plastic baby bottles in January 2011 and July 2012, respectively [74,96]. In addition to these restrictions, the US FDA has declared 5 mg kg^{-1} body weight per day as the No Observed Adverse Effects Limit (NOAEL) [76]. US EPA and EFSA have regulated a maximum acceptable intake of 50 μg kg^{-1} body weight per day for BPA as a reference point, but EFSA decided to reduce the TDI from 50 to 4 μg kg^{-1} body weight per day in 2015 [74,89,96].

The main effect on the endocrine glands due to exposure to BPA is the estrogenic function of this compound. The estrogenic activity of BPA was discovered in 1936, following injection into female rats and observation of stimulation of vaginal epithelium layers [97]. Due to having hydroxyphenyl groups, it was proven that BPA could function as a faint estrogen mimic [98]. BPA acts like natural estrogen (17-β-estradiol) [99]. It has been shown to have several disruptive effects on the endocrine glands via interacting with different physiological receptors, including ERs (α and β), G protein-coupled receptor (GPR30), ARs, estrogen-related receptor gamma (ERRγ), thyroid hormone receptors (THR α and β), aryl hydrocarbon receptor, and glucocorticoid receptor [78,89,100–102].

Estrogens are involved in various physiological processes, including growth, development of breast tissue and sexual organs, reproduction, and homeostasis of several tissues, via the binding and the activation of classical ERs (α and β) [103].

Although BPA has a much lower affinity (1000–2000 fold less) compared to the natural hormone 17-β-estradiol as the most active estrogen, it can bind to both hormone receptors ERα and ERβ and act as an Endocrine disruptor by mimicking or interfering with the actions of estrogen [104].

GPR30 is a non-classical ER that mediates estrogen-dependent transmembrane rapid signaling. GPR30 mRNA is expressed in various tissues, including the prostate, ovary, epithelium, and placenta. Activation of this molecule in different cells causes consequences such as regulating cell growth, migration, and apoptotic cell death, especially in tumor cells. BPA can bind to and activate GPR30 even at low doses. Studies have also shown that low doses of BPA increase GPR30 and the production of specific inflammatory proteins such as IL8, IL6, and MCP1, and also the BPA-GPR30 complex promotes the proliferation of testicular seminoma cells *in vitro* [105,106].

BPA is an antagonist for another nuclear receptor named androgen receptor (AR) through interfering with AR binding and the constitution of a BPA-AR complex, which makes endogenous androgens unable to regulate androgen-dependent gene transcription [12]. A study has demonstrated that the BPA antagonist effect on androgen receptors causes reducing AR translocation and prevents of formation of functional complexes that are the prerequisite of transcription [102].

Also, Xin Huang et al. (2019) reported new evidence to accurately understand the androgen antagonistic activity mechanism of BPA on AR. These results showed that BPA could compete with 5α-dihydrotestosterone (DHT) for binding to androgen receptors (ARs) [107].

ERRγ is a subset of the nuclear estrogen-related receptor (ERRs include α, β, and γ) family that does not bind directly to estradiol. Some studies have shown that EERγ has a strong affinity for BPA, and BPA can interact with this receptor. Although EER is active and has a ligand-independent transcriptional activity, the results of one study showed that even low doses of BPA may increase the risk of breast cancer through the expression of the EER MMP2-mediated pathway [105].

Several studies have also demonstrated how thyroid hormones (T3 and T4) are targets for the endocrine-disrupting activity of BPA. BPA can bind thyroid hormone receptors due to its resemblance of structure to TR, especially TRβ, and acts as an antagonist. BPA has been found to prevent TR-mediated transcription of T3-response genes and directly affect thyroid function by enhancing the expression of several genes involved in thyroid cell proliferation and activity. Besides, BPA can interfere with thyroid hormone synthesis, transport, and metabolism [108,109].

This compound also has been diagnosed as a risk factor for type 2 diabetes in rodents by changing the function of pancreatic β-cells [21].

Innumerable studies have investigated the reproductive toxicity of BPA in animals that have received low doses of BPA [78,110]. For instance, Machtinger et al. (2013) performed an *in vitro* study on a dose-response association of BPA exposure with human oocyte maturation. By increasing the dose of BPA, the percentage of oocytes reaching the metaphase II stage decreases, and the percentage of oocytes degenerated increases [111]. Another investigation by Tang et al. (2012) studied the adverse effect of BPA on the prostate and

concluded that BPA is toxic to this gland due to the changes in the morphology of the prostate [112].

The adverse effects of BPA on various systems and organs have been shown in both *in vitro* and *in vivo* animal experiments, including neural disorders, immunosuppression, metabolic malfunction, renal failure [89], endocrine toxicity, mutagenicity, and carcinogenicity. Also, BPA may raise the risk of obesity, coronary heart diseases, and diabetes [99].

In recent years, there have been ample findings and evidence about the neural impact of BPA, so concerns are growing about prenatal BPA exposure and its possible effects on the offspring's brain development, behavior, and emotions [98]. Some animal research has demonstrated that rodent fetuses' exposure to BPA causes changes in their adulthood behavior [17], likely due to changes in the neurotransmitters [113].

Since BPA can penetrate the placental blood-brain barrier, it can be a critical threat to the developing nervous system of the fetus and infant, mainly including memory impairment, cognitive impairment, and sexual differentiation disorders also embryotoxicity by inducing oxidative stress, which has been shown in neonates of laboratory animals studied [114]. Many mother-child cohort studies have indicated the relationship between prenatal urinary BPA concentration and children's behavior [115]. As a result, based on human and animal studies in recent years, this fact has been accepted that prenatal exposure to BPA can affect the embryo's nervous system and behavior in different ways.

On the other hand, BPA has complex suppressive or stimulatory effects on the immune system, such as the negative impact on immune cells, especially T cells, the capability to bind to AHR, stimulate oxidative stress, inflammation, mitochondrial damage, and cell death, [12,89].

Finally, given the toxic effects of BPA on human health proven in multiple studies, the guidelines and regulations established by US FDA, CODEX, and EFSA must be followed, and the occurrence of BPA in daily human life should be monitored. In addition, further studies on the toxicity and dietary risk assessment of BPA are necessary to perform.

4. Polybrominated diphenyl ethers (PBDEs)

PBDEs (Fig. 2) are usually used as flame retardants in many products, such as home electronics (TVs, computers, and copiers), textiles, wire insulation, carpets, and products consisting of polyurethane foam (mattresses and upholstered furniture). These chemicals can leak into water and soil during manufacture or after breaking down and finding a way to the rivers [116]. PBDEs contain 209 compounds with the chemical formula of $C_{12}H_{(10-x)}$ $Br_{(x)}O$ ($x = 1$ to 10). PBDEs show low water solubility (<1 μg/L) and high log Kow values (>5). Lower brominated PBDEs have shown higher vapor pressures than higher brominated PBDEs. Technically, Penta-, Octa- and Deca-BDE are commercially produced PBDE mixtures [117].

The main pathways of exposure to PBDEs are inhalation, skin contact, and dietary intake, depending on age, sex, PBDEs analogs, and geographical area [118]. However, it has been shown that dietary intake is one of the most important ways of human exposure to PBDEs [119].

PBDEs can accumulate via the food chain and pose a serious human risk. It is believed that widespread use of a broad range of PBDE-containing products is not the main point [117]. Extensive industrial production and usage of PBDEs in various products from the 1970s (until the prohibition) and repeated recycling of old products led to broad and continuous washing of PBDEs in the environment, leading to continuous human exposure. Given the lipophilic nature and extensive existence of PBDEs in fishes, fish consumption has long been considered a vital source of exposure to PBDEs in humans [18]. PBDEs content elevates with the fat content of the fish, which can influence the bioavailability of PBDEs. Aside from fish consumption, human exposure to PBDEs through other food categories, including meat, eggs, dairy products, and vegetables, has also been reported [117]. The approximated average daily intake of PBDEs (mainly BDE-47, -99, and −153) by adults via diet is 0.6 and 4.0 ng/kg body weight per day in the United States and Europe, respectively [120]. Numerous toxic characteristics of PBDEs have been proved. Their important targets are the thyroid hormones, liver, nervous, and reproductive systems. Furthermore, PBDEs can impair DNA by inducing reactive oxygen species (ROS), and their existence in the blood can result in atherosclerosis and other adverse cardiovascular problems [121]. Estimating intelligence quotient (IQ) points loss, and intellectual disability reflects PBDEs exposure [122].

5. Phthalates

Phthalates (Fig. 2) are synthetic compounds that can contaminate food and cause health problems. They are made by reacting phthalic anhydride with a variety of alcohols. This category comprises many chemicals referred to as phthalic acid esters (PAEs), commonly used in various industries. Common phthalates are Diethyl phthalate (DEP), Di-(2-Ethylhexyl) phthalate (DEHP), Di-isononyl phthalate (DINP), Di-isodecyl phthalate (DIDP), Benzyl Butylphthalate (BBP), and Di-*n*-butyl phthalate (DBP), commonly applied in food packaging and the manufacture of food-contact plastics. The easy release of these compounds from plastics to food, water, soil, and air makes them environmental pollutants globally that can accumulate along the food production chain. Recent studies reported high phthalates in soft drinks, wine, mineral water, oil, and ready-to-eat meals. Then, the human may be exposed through ingestion, inhalation, dermal, or iatrogenic pathway [123]. Phthalates have different physical and chemical properties, then their impacts on humans and the environment are not the same, and their relation to many human diseases is still under discussion [124].

Humans are continuously exposed to phthalates because they are found in the environment (e.g., children's toys, personal care products, detergents, polyvinyl chloride flooring) and in the diet through food production processes and packaging. Recently in America, the detection of phthalates has been reported in the pooled breast milk of women and infant formula [125].

During production and transportation, phthalates can quickly move from various food contact substances into foods and beverages via using PVC gloves to handle foods or PVC piping in the olive oil industry or for milking, storing (from printing inks or glues on food

packaging, or coatings on contaminated cooking utensils), and preparation as well as releasing phthalates into the atmosphere in the production course up to the removal path of goods made from plastics. Generally, they are probably biomagnified to the top of the food chain [126].

Due to relocation and leakage, food packaging materials may be a significant origin of PAEs in retailing foods. Plastic-made PVC products, including a cover gasket for a glassy container, food packing film paper, board packing (manufactured from reprocessed materials), and aluminum foil-paper laminates, are examples of phthalate-containing packaging [126].

Because food is the most common source of phthalate toxicity in humans, it is critical to determine the toxic amounts of phthalates in foodstuff. PAEs are lipophilic then and usually present in fatty foods [127]. In the following parts, the most recent research literature on the presence of phthalates in a broad range of foods and beverages (dairy products, edible oils and fats, edible plants, meat and poultry, soft drinks, alcoholic beverages, and water) was discussed.

Because of their high ethanol content, alcoholic drinks are highly susceptible to PAE contamination. Indeed, ethanol can promote PAE migration by its action as a solvent to extract PAE [128]. The inner layer of wine storing and fermenting tanks, consisting of epoxy resins or polyester and fiberglass, was the primary cause of DBP and DIBP contamination in wines and spirits [129].

Bottled mineral water contamination by PAEs can be caused by the following factors: the staple properties and technological means applied in producing bottles, the substances used during production, pollution of water resources with the waste of plastics decomposed from landfills, the use of recycled PET, and cross-pollution in the bottle-making workshop because of the widespread environmental presence of PAEs' and the pollution with cap fastening resins. The PAE concentration of PET bottled mineral water can be influenced by storage time, pH, temperature (30–60 °C), and sunlight exposure [124]. Nonetheless, Bono-Blay et al. (2012) believe that protected groundwater intended for bottling does not significantly contaminate with PAEs [116].

The movement of PAE from PET to the soft drink was 5–40 folds greater than that of mineral water. Since mineral water has low acidity (pH = 5.8), phthalate level in preservative-free mineral water is low (20.22 g L^{-1}). Soft drinks' high acidity (pH < 3) increased PAE migration [130].

Even though phthalates are fat-soluble compounds, the elevated infusing temperature for preparing tea will partly compensate for the poor water solubility. Plastics used in packaging seem to be the possible origin of phthalates in industrial tea and coffee derivatives. Plastics or a plastic coating are usually used in making teabags [131].

In a Swiss industry study (2005), PAEs were found in high concentrations in oily packaged food because plasticizers migrated from PVC gaskets of caps for glass jars into the foodstuff [132]. The report of Marega et al. (2009) on phthalate contamination in the olive oil production chain suggests that pollution can occur during harvesting time and transporting olives to the factory. In addition, high levels of PAE were found alongside the olive oil generation chain, most likely due to interaction between the olives, paste, and oil with pipes and plastic substances. Nevertheless, pollution concentrations were generally less than the Commission Directive 2007/19/CE recommended restrictions in most cases [133].

According to previous studies, oil contamination by phthalate can decrease during refining, so the oil extracted by pressure usually has more phthalate contents. Chemical processing caused phthalates to be eliminated differently based on their molecular weight, though physical refining was used to exclude all phthalates [134]. Studies showed that edible oils could have severe estrogenic impacts on humans 45–396 folds more than bottles of water [135].

Milk and dairy products have a high risk of phthalate contamination because they are high-fat foods. Many ways cause contamination in the whole milk production chain from farm to forks, such as raw milk contamination by polluted feed, milking process by PVC tubing, transportation of milk by cooling tank, and packaging materials. Creams had the largest concentrations of phthalates, while light milk had the lowest [136].

In the Taiwanese population, an investigation of meat products showed that they could be contaminated by leaching from materials during the production process or packaging. However, scientists reported that the toxicity of phthalates resulting from eating meat products does not threaten human health [137]. Meat consumption could be higher in different populations leading to higher exposure levels. Exposure levels deriving from meat consumption are below the established TDI, but all the contributions should be considered from the diet to be sure that phthalate exposure does not threaten human health.

Because soils' PAEs can be picked up and accumulated by plants, daily consumption of vegetables can bring risks to human health. Plastics, particularly film covering, are among the most significant resources of PAEs in soil; sewage irrigation, use of fertilizers, and sewer slush can increase PAE concentration in the soil. Studies on the absorption and translocation of PAEs by whole plants of certain edible vegetables revealed that the total levels of PAEs in various plants vary, depending on the differences in lipid content. Since roots have a higher lipid content, they can accumulate hydrophobic compounds preferentially [138].

It was discovered that vegetables grown in greenhouses had more DBP and DEHP than in open fields. Furthermore, PAEs accumulated more in vegetable leaves than in soils. In the greenhouses, the air-borne levels of DEHP, DBP, and DIBP were seriously greater than in outdoor ones. The findings indicate that vegetable plants can absorb PAEs from the air via their leaves. The overall PAEs in leaves of vegetables from hothouses and those retailed on markets revealed that DEHP concentration was positively associated with the greenhouse cultivation period, implying that DEHP can be extracted from plastic films whereas DBP from fertilizers and insecticides [139]. According to the studies, the transfer of these compounds from packages into foods is affected by the kind of the packaging material (PVC, polyethylene terephthalate (PET), gaskets of lids for glass jars and cartons), fat and ethanol content of foods, pH, the level of lipophilicity, and biodegradation processes. Notably, the level of the mentioned compounds appears to rise alongside the food chain, from animal or plant origins to processed foodstuff, such as dairies (milk, cheese, and butter), wines, and oils. Remarkably, edible plants can show a combined danger for animal and human usage [140].

Recently, diets, including PAEs-polluted food and water, have been the primary means of exposing humans, responsible for over 67% of cases. According to published guidance, contact with DBP, DEHP, and BBP from water bottles is far below the maximum

contaminant levels (MCL) reported by WHO [141].

Data show that phthalates from fast food containers do not add enormously to total customer exposure [142]. The research was conducted to identify potential phthalate pollution routes in food products purchased on the Belgian market. High phthalate concentrations were detected in bread that was often consumed, and it was contaminated due to the use of polluted ingredients and migration from phthalate-containing food containers used during processing. The analysis of the phthalate concentration profiles of bread, apple, cheese, and salami has shown that manufacturing – not packaging – plays a crucial role in phthalate concentration in foods [143].

The physical-chemical properties of PAEs have a significant effect on their aquatic toxicity (Fig. 3). The Kow affects their environmental toxicity, bioaccumulation, and biodegradation. The Kow, an indicator of lipophilic property, rises as the number of carbon atoms on the side chain increases, making longer-chain PAEs have further bioaccumulation in organisms. On the other hand, compounds with strong hydrophobicity (log Kow $>$ 6) do not demonstrate a similar pattern. According to acute and chronic toxicity data, the higher phthalates ($\geq$C6) are less toxic than, the lower phthalates ($<$C6) to marine organisms, even at levels close to the limit of solubility. To summarize, phthalate bioaccumulation factors (BAFs) are demonstrated by low-molecular-weight (LMW) phthalates that are greater than expected by a lipid–water partitioning model, and species-specific variations exist in metabolic transition ability among marine organisms.

In PAEs of median molecular weight (i.e., DBP and BBP), bioaccumulating trends are compatible with the general lipid–water partitioning model, while BAFs are lower in high-molecular-weight (HMW) phthalates, including DEHP, due to tropic dilution in marine organisms. Chemicals are less absorbed by marine organisms at greater log Kow and, thus, log Koc (adsorption coefficient); thus, BAFs are decreased as a result of both less penetrability and higher biodegradability or metabolic rates. As a result, HMW PAEs have lower ecotoxicity than LMW PAEs, and their effectual content in the body reduces as the alkyl chain length increases [124]. Bioaccumulation and bioconcentration factors (BAFs and BCFs) illustrate the tendency of chemicals to accumulate in specific organisms and high accumulation potential attributes to values of more than 1000 [144].

The existence of PAE in foods, drinks, and their packing has recently been clarified more obviously. Based on European REACH Regulation, phthalate esters are placed in the Candidate List of "substances of very serious concern" (SVHC) for Authorization. After a while, certain phthalates in plastics that contact food and beverages are banned entirely. WHO and US EPA set an MCL for DEHP at 6/8 μg/L. In the EU Water Framework Directive, DEHP is categorized as a "priority hazardous substance" and "toxic to reproduction" under the EU regulation. Directive 2006/141/EC and Directive 2006/125/EC have announced that DINP, DIDP, and BBP can merely be utilized as plasticizers infrequently used substances and plasticizers in disposable substances that contact non-fatty foods, excluding baby formulations and follow-on ones and for packaged cereal-based diets and baby foods [124].

As announced by REACH, DEHP has been substituted with DINP and DIDP, which are not dangerous to reducing environmental and health problems. HMW PAEs, including DINP and DIDP, are covered in REACH but have no harm to the healthiness of humans [145].

Based on liver effects, EFSA set individual TDIs of 0.15 mg/kg bw per day For DINP and DIDP, 0.5 mg/kg bw per day for BBP, 0.05 mg/kg bw per day for DEHP, and 0.01 mg/kg bw per day for DBP [146].

Although DIBP is not permitted in food packaging, the European Union (EU) has defined Specific Migration Limits (SMLs) in plasticized containers, foods, and beverages for five phthalates (DBP: 0.3 mg/kg, DEHP: 1.5 mg/kg, and BBP: 30 mg/kg, DIDP and DINP: 9 mg/kg, others: 60 mg/kg in food substance) are based on the directive No. 10/2011 EC of 14 January 2011. The SMLs are the Maximum Accepted Concentration (MAC) of a specific material released into food and food simulants from a substance [147].

Widespread exposure to PAEs raises severe concerns about their effects on human health. Recently, data has accumulated that these molecules will behave as presumed EDCs via interaction with various endocrine molecular routes when transformed into primary and secondary metabolites.

After being ingested, PAEs are transformed chemically through esterase or lipase hydrolysis into their relevant monoesters or phthalic acid, followed by sulphonation or glucuronidation in a second step before excretion. Endocrine and hormonal dysregulation, breast and skin cancer, endometriosis, early puberty, sex abnormalities, infertility, altered fetal growth, obesity, type II diabetes, attention-deficit hyperactivity disorder, autism spectrum disorders, hepatotoxicity, cardiotoxicity, allergy, nephrotoxicity, and asthma have also been linked to PAE exposure [124]. It was discovered that there is strong support for a relationship between anogenital distance in males and lower semen quality, neurodevelopment, and the risk of childhood asthma. It was showed weak to moderate support for phthalates/metabolites correlation with the onset of many diseases such as low birthweight, endometriosis, low testosterone, ADHD, Type 2 diabetes, and breast/uterine cancer [148].

Mínguez-Alarcón et al. (2018) found decreases of 37% and 42% in sperm concentration and count, respectively, by investigating their relationship with exposure to PAEs and in a sample of American males over a particular period time (2000–2017). Many experiments have shown that PAEs play a role in reproductive toxicity [149].

PAEs are endocrine disruptors because they can adversely modulate hormone activities and mechanisms, interacting with ERs, PRs, and THRs. As a result, they compete with endogenous steroid hormones.

PAEs in males will cause the "testicular dysgenesis syndrome," known as "phthalate syndrome," which accounts for cryptorchidism hypospadias, decreased anogenital distance, infertility-changed seminal and testicular cancer. The capacity of the mentioned substances in interaction with the hypothalamic-pituitary-gonadal axis and participation in signaling routes responsible for steroid homeostasis and biosynthesis may be referred to as the molecular mode of action behind the "phthalate syndrome" [150]. The syndrome above may also be caused by Sertoli dysfunction, resulting in Leydig cell inhibited meiosis, spermiogenesis, and testosterone synthesis, regulated by oxidative stress and suppression of insulin-like growth factor 3 (Igf-3) [151]. After DBP treatment in male rats, a significant rise in malondialdehyde formation in the testis, as the indicator of oxidative stress and lipid peroxidation, is known as the main factor in the functional impairment of sperm [152].

Remarkably, ROS are believed to disturb plasma membranes of sperms replete with polyunsaturated fatty acids, lower testosterone levels, and induce apoptosis and mitochondrial membrane destruction in spermatogenic cells, lowering sperm production. In addition, they discovered a phenotypic testicular modification caused by DEHP *in vivo* [153]. PAEs-mediated decreases in serum testosterone and other main controllers of sperm development, such as follicle-stimulating hormone (FSH) and lactate dehydrogenase (LDH), are likely to cause testicular dysfunction. According to a new study, a positive relationship exists between Mono-2-Ethylhexyl phthalate (MEHP) and FSH/LH [154].

An unusual hypomethylation of the H19 gene with paternal imprint and hypermethylation of the LIT1 gene with maternal imprint is another epigenetic process by which PAEs could cause endothelial dysfunction [155]. A possible explanation may be that PAEs-mediated oxidative stress prevents methyl CpG-binding proteins from binding to CpGs, resulting in DNA demethylation [156].

Decrease fetal gestational age, follicular atresia, endometriosis, infertility, puberty, increased pregnancy loss, and decreased oocyte yield are effects of exposure to phthalates in women. DEHP was found in breast milk, exposing newborns to these toxins through breastfeeding. The impact of phthalates on the female reproductive tract is most probably associated with MEHP. PAEs can imitate hormone production by coupling to various human receptors, causing estrogenic or anti-estrogenic effects [124].

PAE is also a possible risk factor for thyroid endocrine system dysfunction. Furthermore, since the thyroid system is so closely

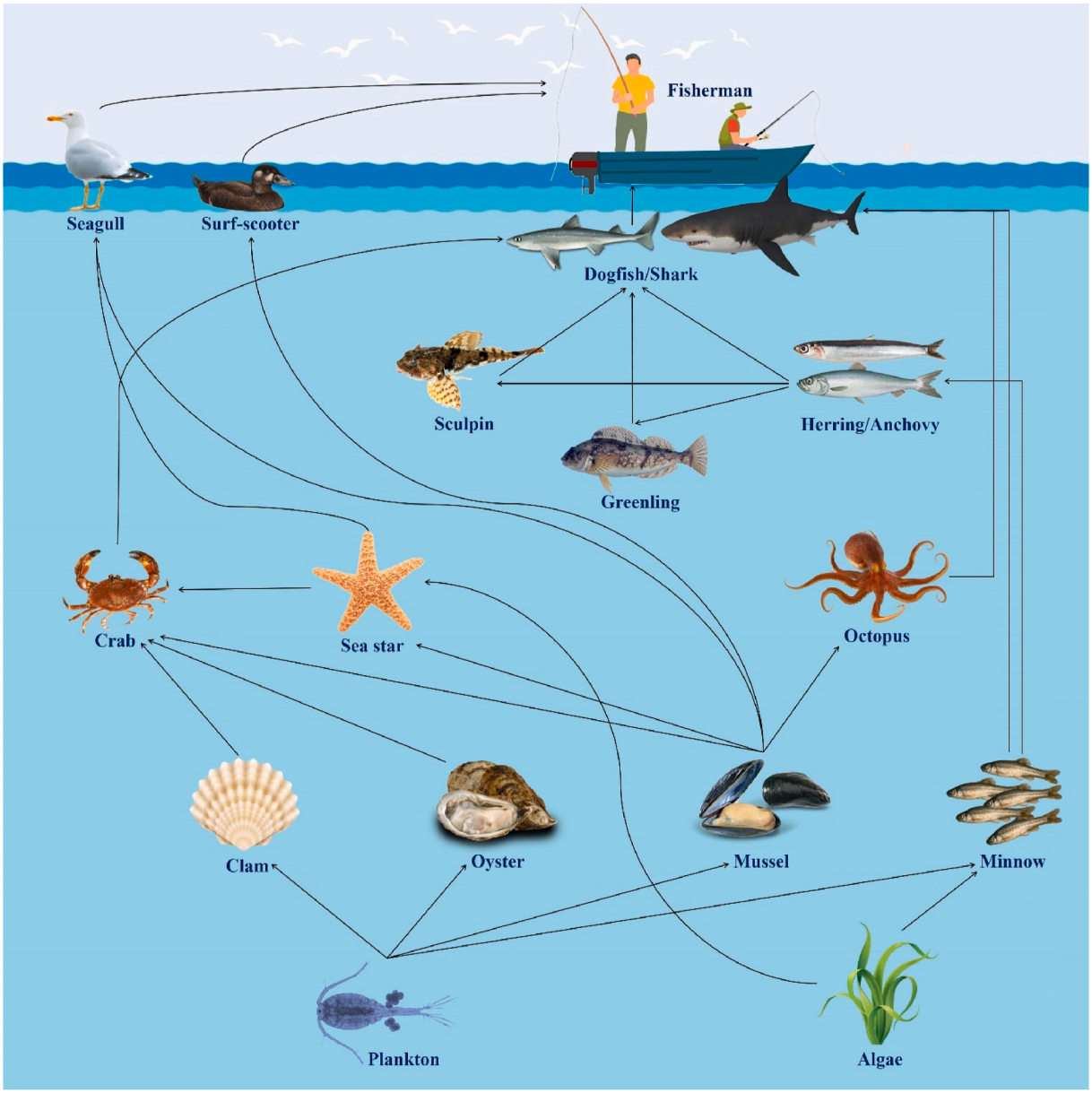


Fig. 3. A Food web bioaccumulation of phthalates through marine system [].

linked to the reproductive system, a cross-sectional analysis examined the relationship between urinary PAE concentrations and thyroid hormones. According to the study by Meeker and Ferguson (2011), higher doses of MEHP were associated with less serum free thyroxine (FT4) or serum thyroid-stimulating hormone (TSH). Higher doses of DEHP were found to cause thyroid gland hyperplasia and hypertrophy [157]. Total thyroxine (T4), free T4, and total triiodothyronine (T3) are all negatively correlated with urinary DEHP, while TSH is positively associated [158]. On the other hand, DEHP metabolites were found to be linked to T3 levels in adolescents. The decrease in serum thyroid hormones is probably the result of a DEHP-mediated regulation of thyroid hormone metabolism, biotransformation, biotransport, biosynthesis, and TSH receptor numbers [85].

It is worth noting that specific endocrine-disrupting agents, including PAEs and BPA, will function synergistically in the human body to cause additive effects [159].

In conclusion, despite the need to minimize the distribution of PAEs, it is tough to replace them as plasticizers due to their excellent properties. As a result, it is critical to recognize innovative manufacturing technology capable of improving the efficiency of food packing to reduce chemical relocation and degradation of foods, beverages, oils, and other consumer goods. The most challenging task continues to be the difficulties of harmonizing multiple regulations in various countries and the standardization of test requirements and procedures of biological monitoring in humans [124].

6. Organochlorine pesticides (OCPs)

The world economy has been rapidly industrializing over the last century. Therefore, we observe a remarkable release of xenobiotic compounds into the ecosystem. OCPs are a critical menace to the global environment and threaten human health owing to their propensity for dispersion, long-distance transportation, and bioaccumulation in the food chain [160,161]. Because of their severe environmental and adverse health effects, the existence of OCPs residues in foodstuffs, sediment, water, soil, air, and blood serum has led to worldwide concern. OCPs are described as permanent and bioaccumulating chemicals susceptible to long-term transportation [162,163]. OCPs are non-polar, fat-soluble, hydrophobic, toxic, and bioaccumulative environmental chemical pollutants composed of carbon, hydrogen, and chlorine [164,165]. These are divided into six main groups [166–168]: 1. Dichlorodiphenyltrichloroethane (DDT) and its analogs (e.g., methoxychlor, dicofol); 2. Hexachlorobenzene; 3. Hexachlorocyclohexane (HCH) and its isomers (α-HCH, β-HCH, γ-HCH, and δ-HCH); 4. Cyclodienes (e.g. endrin, aldrin, endosulfan, dieldrin, heptachlor, chlordane, isobenzan); 5. Chlordecone, Kelevan, and Mirex; 6. Toxaphene. Some physical traits and chemical structures of the main OCPs are presented in Table 2.

These compounds have high stability, and their half-life varies from months to years and sometimes decades. Their durability is mainly owing to the carbon-chlorine (C–Cl) bond, which is resistant to hydrolysis and increases with the increasing number of chlorine atoms [169,170]. Therefore, chemicals with more halogen are more resistant to degradation than compounds with less halogen substitution [165].

Many OCPs make the nuclear receptors involved and elicit similar toxicity results. For instance, methoxychlor and p, p'-DDE have been known as weak anti-androgens and estrogens [171]. There is evidence of their accumulation in the adipose tissue in non-target organisms and are related to several illnesses, especially breast cancer [172]. As a result, OCPs are known as some of the most critical toxic chemicals declared by the Agency for Toxic Substances and Disease Registry (ATSDR) within the United States Department of Health and Human Services [173]. Over the last several decades, OCPs have been employed to eliminate diseases and pests' carriers in the agriculture, housing, and public health division, resulting in better crop yields, elimination of pest infections, reduced waste, and improved public health via the eradication of native disease carriers. However, OCPs are severe environmental threats due to their mode of action and direct impact on target and non-target organisms. They have been hydrophobic, ubiquitous, stable, and resistant to degradation [162,174,175]. The lipophilic ability of OCPs causes them to bind to fatty tissue in animals and humans. This feature also stabilizes them in the environment via water, sediment plants, and soil accumulation. As a global health concern, accumulating OCPs in animal tissues can be highly threatening [163]. OCPs are resistant to physical, chemical, photochemical, and microbiological degradation, and long-term transportation has turned them into local, regional, and global pollutants [176]. Investigations have documented their existence through long transportation in the arctic region. Such long-range motion was related to characteristics, including semi-volatility and chemical stability [177,178]. For example, the existence of OCPs in the higher geographical regions of the Northern Hemisphere has been reviewed in the literature [179]. Much research has proved the temperature-dependent reaction of OCPs in high-altitude regions [180]. In the southern hemisphere, however, little information was accessible on the temperature-dependent transfer of these materials to the region. However, OCPs have been reported to be present even in the very cold region of Antarctica [177,178]. OCPs are released from domestic, industrial, and agricultural sources into the environment. They are significant threats to human health and ecosystems due to their potential for bioaccumulation and toxicities in organisms [181]. Health problems related to OCPs include endocrine disorders, neurological damage, immune system suppression, cancer, and death [163, 182]. Annually, at least 220 000 people die worldwide from pesticide poisoning [183]. Despite the ban on the production and usage of OCPs in numerous countries, they are still broadly applied in several developing countries [184,185]. Research has indicated the existence of OCPs in environmental samples with more concentrations than organophosphate pesticides (OPPs) in regions where OCPs are consistently used to control pests [186,187]. New investigations have revealed OCPs in sediment, water, soil, plants, fish, and animal samples [176,187,188]. Many OCPs were also found in body fluids, such as serum, urine, and breast milk [176,189]. Most studies on OCPs have been based primarily on levels and distribution in environmental samples [190–194].

The input pathways of OCPs to the environment (air, soil, and water) are industrial discharge from the factory and releasing polluted wastes into landfills [195]. OCPs may be transported far by the wind before settling in water and soil [196]. Therefore, they can travel long distances from their application points [197]. OCPs in marine environments may result from sewage discharge, direct use, atmospheric deposition, wastewater release, agricultural runoff, and disposal of empty chemical containers [198]. However, the

Table 2
Physical and chemical characteristics of OCPs.

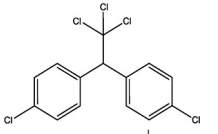
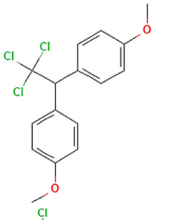
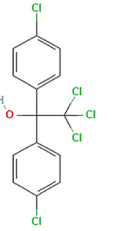
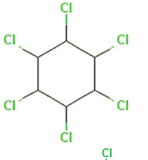
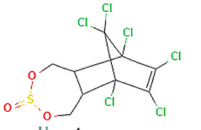
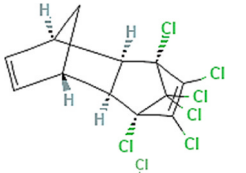
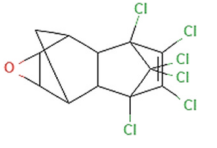
Pesticide	Synonym	CAS number	Molecular formula	Molecular weight	Melting point (°C)	boiling point (°C)	Chemical structure
Dichloro-diphenyltrichloroethane	p,p'-DDT	50-29-3	C14H9Cl5	354.5	108.5	260	
Methoxychlor	Dimethoxy-DDT	72-43-5	C16H15Cl3O2	345.6	87	346	
dicofol	Kelthane	115-32-2	C14H9Cl5O	370.5	77.5	180 (at 0.1 mm Hg)	
Hexachlorocyclohexane	alpha-HCH beta-HCH gamma-HCH	319-84-6	C6H6Cl6	290.85	112.5	311	
Endosulfan	Benzoepin	33213-65-9	C9H6Cl6O3S	406.9	106	106 (at 0.7 mm Hg)	
Aldrin	Aldrite	309-00-2	C12H8Cl6	364.9	104 °C	145 (at 2 mm Hg)	
Endrin	dieldrin	72-20-8	C12H8Cl6O	380.9	175.5	245	

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Table 2 (*continued*)

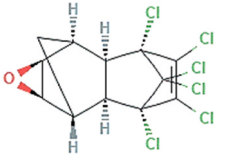
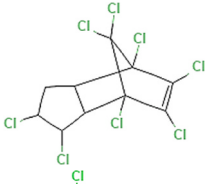
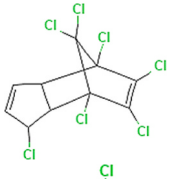
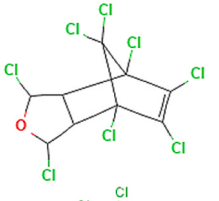
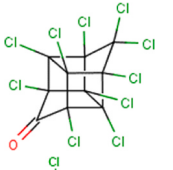
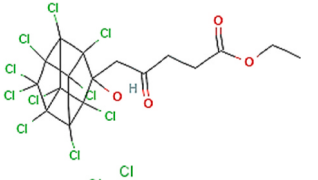
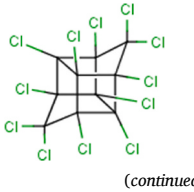
Pesticide	Synonym	CAS number	Molecular formula	Molecular weight	Melting point (°C)	boiling point (°C)	Chemical structure
Dieldrin	HEOD	60-57-1	C12H8Cl6O	380.9	175.5	330	
chlordane	Octachlor	57-74-9	C10H6Cl8	409.8	106.0 °C	175 (at 1 mm Hg)	
heptachlor	Heptachlorane	76-44-8	C10H5Cl7	373.3	95.5	145 (at 1.5 mm Hg)	
isobenzan	Telodrin	297-78-9	C9H4Cl8O	411.7	121	–	
Chlordecone	Kepone	143-50-0	C10Cl10O	490.6	350	350	
Kelevan	Despirol	4234-79-1	C17H12Cl10O4	634.8	91	–	
Mirex	Dechlorane	2385-85-5	C10Cl12	545.5	485	485	

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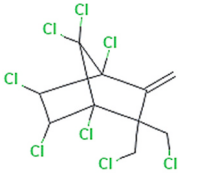
Table 2 (*continued*)

Pesticide	Synonym	CAS number	Molecular formula	Molecular weight	Melting point (°C)	boiling point (°C)	Chemical structure
Toxaphene	Camphechlor	8001-35-2	C10H8Cl8	411.8	65–90	–	

cause of the unexpected contamination of pesticides in water is the leaching of pesticides from agricultural lands and surface soil to downstream water, adversely affecting benthic organisms [199]. Due to their lipophilicity, these pesticides accumulate and are biomagnified [200]. Several OCPs are volatile. However, some may adhere to airborne or soil particles [201]. Dieldrin and DDT metabolites may settle in the soil for years, where they finally penetrate the food chain via absorption. Animals and humans are then affected by OCPs by consuming contaminated food. OCPs are removed from the soil and suspended in the air throughout the use, where they are replaced [202].

Moreover, they can be absorbed by plants or penetrate the soil and contaminate groundwater. In aquatic conditions the pesticide can absorb or excrete suspended solids and accumulate more in the base sediments where such substance is bioaccumulated in aquatic organisms like fish [201]. OCPs can be concentrated directly in fish tissue from surrounding water and diets, where contaminants can be transmitted through the food chain [203,204].

Humans are primarily exposed to pesticides through food consumption, respiration, and dermal contact [175]. Diet is the primary source of daily exposure to OCPs, which are lipophilic (fat-soluble), abundantly existing in oily products [205]. Therefore, they can be transmitted primarily by consuming fatty foods, including fish, meat, and dairy products. Eating polluted fruits and vegetables may also lead to dietary exposure to OCPs. Research has shown that more than 90% of OCPs come from food, mainly fish [205]. Fish is broadly consumed by many people worldwide [206]. The Cancer Risk data of OCPs in fish samples show values higher than the acceptable standard of 10^{-4}, showing the potential exposure to cancer via fish consumption [167]. Kolani et al. (2016) studied twenty OCPs in 150 vegetable samples (lettuce, tomatoes, and cabbage) gathered from Togo farms [207]. All vegetable samples studied were polluted with at least one pesticide residue, 17% of which showed values above the highest residual range of the European Union [208]. Anwar et al. (2011) stated worryingly high concentrations of endosulfan (774 μg/kg) in apple fruits bought from Pakistan [209]. Such stable organic contaminants may also be accumulated by breeding animals from polluted water and feed through the use of pesticides in animal production regions (treatment of sheepfolds, cowsheds, pigsties, warrens, and/or treatment of animals themselves) [210]. As a result, both these contamination pathways can cause the bioaccumulation of stable pesticides in food products of animal sources, including milk, meat, fish, fats, and eggs [211]. In Ghana, OCPs residues were determined in dairy products (cheese, milk, and yogurt) from selected farms [212]. The most recent studies on EDCs concentrations in various food products have been collected in Table 3.

Infants are often exposed to OCPs via breast milk, while fetuses can be exposed in the uterus through the placenta. Furthermore, humans may be exposed to OCPs via polluted drinking water and air. Professionally, people can be exposed to pesticides while producing, formulating, or using pesticides [237]. People who work directly with pesticides can be exposed to toxins by dermal contact and inhalation. In addition, children might be exposed to pharmaceutical products polluted with pesticides [238]. Appropriate regulatory agencies such as the US FDA, US EPA, WHO, and the Occupational Safety and Health Agency (OSHA) have established standards for some OCPs in the food, environment, and workplace. The primary goal of allowable restrictions is to protect people from the adverse outcomes of OCPs [239].

The majority of pesticides are planned to damage or destroy pests. However, since the biological system of pests and humans are similar, human health can be endangered by affecting various human systems and organs. According to the reports, pesticides may threaten close bystanders, consumers, and laborers throughout production and transportation [240–243]. Some pesticides cause external damage and irritation and internal poisoning diseases. It should be noted that although the application of OCPs is forbidden in several countries, their occurrence in human tissues and the environment remains a significant concern [244,245]. Higher stability, lipophilicity, and slow excretion from the body make OCPs durable in the environment and food chain. The accumulation of pesticides in human fatty tissue is done by consuming contaminated food, particularly animal and fish fats, resulting in toxic effects and accumulation of OCs chemicals [246]. The health risks of OCs are referred to as the type of pesticide and the amount and length of exposure [240,241]. As a result, there are four principal input pathways for pesticides: dermal contact, ocular, respiratory, and diet [241]. The side effects of OCPs on body health range from acute to chronic.

When there are multiple routes of exposure, finding a particular health issue for an OCP is challenging. OCPs are seen in human body tissues (breast milk, blood, and adipose tissue), where they gradually break down, accumulate in adipose tissues, and stay in human bodies for an extended period [247]. Epidemiological reports have shown a relationship between Parkinson's disease and exposure to OCPs [168]. The permissible remaining limits for individual and overall OCPs concentration in drinking water are 0.1 and 0.50 μg/L, respectively [167,248]. Based on US EPA classifications, aldrin and dieldrin have been categorized as potential human carcinogens according to animal investigations [249].

Furthermore, the IARC has distinguished them as probably carcinogenic to humans (Group 2A) [13]. Ingestion of a high dose of dieldrin and aldrin led to kidney damage and convulsions or other nervous system impacts [167]. However, prolonged exposure to medium concentrations of dieldrin or aldrin has been shown to result in chronic convulsion, dizziness, headaches, vomiting, irritability, and out-of-control muscle movements [250].

As a potential human carcinogen, Heptachlor assigned as Class 2B has been proven to cause liver tumors in rats and mice. Side effects on the nervous system and immune disorders were evident in animals affected by heptachlor epoxide during gestation and infancy. Reduced body weight before death was revealed in the newborn animals exposed to high levels of heptachlor. Chlordan is associated with the effects of reproductive disorders and immunosuppression in wildlife. The health effects of chlordane chemicals are anxiety, depression, migraines, respiratory infections, and diabetes [167,251]. Endosulfan is a problematic agrochemical due to its acute toxicity, bioaccumulation potential, and impact as an endocrine disruptor [252]. On the other hand, it has been reported that DDE can bind to ARs in animals [185].

Few studies have stated a relationship between breast cancer and OCPs exposure [253]. Utilizing animal models, Korrick and Sagiv (2008) reported that exposure to DDT/DDE in early life was related to reduced mental or behavioral functions in further development

Table 3
The concentrations of EDCs in various food products based on the most recent studies.

Type of chemical	Number of samples	Type of Food product	Results	country	References
BPA	52	Barreled drinking water	61/5% of samples were found to contain BPA, maximum concentration of 898.7 ng/L	China	[213]
	30	Canned meat (sausages, pâtés, and whole meals)	found in all samples, Range: 4.4–202.3 μg/kg	Portugal	[214]
	93	Fruit juice	BPA was identified in ~83% of the juice samples, Range: 0.14–28.97 μg/L	Saudi Arabia	[215]
	23	Canned legumes	found in 91% of the samples, Range: 1.51–21.22 ng/mL	Italy	[80]
	79	Canned convenience foods, Canned vegetable oils, olives, and soft drinks	detected in 45 of 79 samples. Fish products had the highest level of BPA with 0.102 mg/kg	Turkey	[216]
phthalates	54	paper-based food packaging	all measured lower than 10 μg/g and in fact, most had concentrations less than 1 μg/g	United States	[142]
	1016	edible vegetable oil sources edible oil blend (n = 400), soybean oil (n = 155), peanut oil (n = 121) and rapeseed oil (n = 340)	Detection rate: DEHP = 1.94–7.78% DBP = 5.16–13.48	China	[217]
	9	edible oils	Total Mean: 0.72–6.01 mg/kg, DiNP, DEHP, DiDP, DBP, DiBP, DEP, and BBP, with 0.90, 0.81, 0.79, 0.71, 0.22, 0.17, and 0.10 mg/kg, respectively. The seven-phthalates-derived average estrogen equivalence values in edible oils are 45–396 times those in bottled water.	global	[135]
	60	livestock and poultry meat (30 unpackaged pork and 30 unpackaged chicken)	pork: 0.62–0.80 mg/kg, chicken: 0.42–0.45 mg/kg	Taiwan	[137]
	32	commercial tea infusions	Black tea = 593.8 μg/L Green Tea = 578.7 μg/L	Italy	[131]
	98	vegetable greenhouse agriculture	0.95–8.09 mg/kg	China	[140]
	64	fast foods	DEHT:2510 μg/kg	United States	[218]
PCBs	84	Vegetables	Mean: 2.30–97.00 ng/g dw	Pakistan	[219]
		Beans	Mean:2.71–151.67 ng/g		
		Grains	Mean: 2.71–151.67 ng/g		
	60	Butter	Mean: 21.701 9.02 ng/g fat	Iran	[220]
	120	Dairy products (Yogurt, Doogh, Kashk)	Mean: 15.17 ± 3.44 ng/g fat (EU limit, 40 ng/g fat)	Iran	[221]
PBDDs	126	Egg	TEQ range: 0.05–0.57 pg/g	Poland	[43]
	160	Fish (n = 19)	Range: 0.025–0.093 pg TEQ/g	Italy	[61]
		Mussels (n = 8)	Range: 0.022–0.036 pg TEQ/g		
		Beef (n = 6)	Range: 0.020–0.045 pg TEQ/g		
		Poultry meat (n = 5)	Range: 0.013–0.019 pg TEQ/g		
		Hens eggs (n = 6)	Range: 0.024–0.048 pg TEQ/g		
		Pork (n = 6)	Range: 0.016–0.026 pg TEQ/g		
		Cow milk (n = 6)	Range: 0.012–0.023 pg TEQ/g		
		Ship milk (n = 4)	Range: 0.011–0.020 pg TEQ/g		
	182 (marine fish)	Sardines (n = 12)	Min: <0.001–0.012 ng/kg w.w. Max: 0.021–0.042 ng/kg w.w. Mean: 0.006–0.022 ng/kg w.w.	UK	[222]
		Mackerel (n = 14)	Min: <0.001–0.010 ng/kg w.w. Max: 0.012–0.031 ng/kg w.w. Mean: 0.004–0.015 ng/kg w.w.		
		Herring (n = 6)	Min: <0.001–0.014 ng/kg w.w. Max: 0.013–0.034 ng/kg w.w. Mean: 0.005–0.019 ng/kg w.w.		
		Grey Mullet (n = 9)	Min: <0.001–0.008 ng/kg w.w. Max: 0.017 0.021 ng/kg w.w. Mean: 0.005–0.013 ng/kg w.w.		
		Sprat (n = 15)	Min: <0.001–0.007 ng/kg w.w. Max: 0.012–0.026 ng/kg w.w. Mean: 0.004–0.016 ng/kg w.w.		
		Sea Bass (n = 13)	Min: <0.001–0.010 ng/kg w.w. Max: 0.010 0.022 ng/kg w.w. Mean: 0.003–0.014 ng/kg w.w.		
		Turbot (n = 6)	Min: 0.008 0.013 ng/kg w.w. Max: 0.008 0.013 ng/kg w.w. Mean: 0.002–0.008 ng/kg w.w.		
PCDD/FS	35	Fish	Concentration: 0.50 pg WHO-TEQ/g w.w.	Italy	[223]
		Seafood	Concentration: 0.16 pg WHO-TEQ/g w.w.		
		Meat	Concentration: 1.70 pg WHOTEQ/g lipid weight		

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Table 3 (*continued*)

Type of chemical	Number of samples	Type of Food product	Results	country	References
		Meat based products	Concentration: 1.03 pg WHO-TEQ/g lipid weight		
		Milk and dairy products	Concentration: 0.78 pg WHO-TEQ/g lipid weight		
		Hen eggs	Concentration: 0.71 pg WHO-TEQ/g lipid weight		
		Fats	Concentration: 0.27 pg WHO-TEQ/g lipid weight		
		Olive oil	Concentration: 0.09 pg WHO-TEQ/g lipid weight		
	99	Raw, non-processed Liver samples:	Mean: 0.018 pg WHO-TEQ g-1 w.w.	Poland	[224]
		Chicken (n = 21)	Range: 0.010–0.0350.018 pg WHO-TEQ g-1 w.w.		
		Pig (n = 14)	Mean: 0.071 WHO-TEQ g-1 w.w.		
			Range: 0.013–0.545 WHO-TEQ g-1 w.w.		
		Cattle (n = 20)	Mean: 0.067 WHO-TEQ g-1 w.w.		
			Range: 0.012–0.340 WHO-TEQ g-1 w.w.		
		Sheep (n = 44)	Mean: 0.597 WHO-TEQ g-1 w.w.		
			Range: 0.013–1.83 WHO-TEQ g-1 w.w.		
	115	Farmed fish:	Mean: 0.22–0.88 pg g-1 w.w.	Greece	[225]
		Farmed sea bream (n = 42)			
		Farmed sea bass (n = 34)	Mean: 0.13–0.68 pg g-1 w.w.		
		Farmed trout (n = 7)	Mean: 0.10–0.43 pg g-1 w.w.		
		Wild fish (n = 32)	Mean: 0.49–0.13 pg g-1 w.w		
	445	Meat Beef (50 steak and 83 hamburger)	Range: 0.79–2.41 pg TEQ/g fat	Italy	[226]
		Pork (50 loin and 122 sausage)			
		Chicken (70 breast sample)			
		Turkey (70 breast sample)			
TCCD	_	Fish	Range: 3.5 to 12.7 pgTEQ WHO 2005 g −1	Tanzania	[227]
			Mean: 8.1 pg/g		
OCPs	One gram	Beans	Heptachlor, Mean: ND	Nigeria	[228]
			Aldrin, Mean: 1.25 ± 1.94 (mg/kg)		
			γ-BHC, Mean: ND		
			p,p′-DDE, Mean: 0.22 ± 0.35 (mg/kg)		
			Dieldrin, Mean: 4.46 ± 5.07 (mg/kg)		
			Endrin, Mean: 0.33 ± 0.52 (mg/kg)		
			p,p′-DDD, Mean: 0.21 ± 0.34 (mg/kg)		
			Endosulfan II, Mean: 1.08 ± 0.25 (mg/kg)		
			p,p′-DDT, Mean: 0.24 ± 0.37 (mg/kg)		
			Endrin CHO, Mean: 3.54 ± 2.47 (mg/kg)		
			Endosulfan I, Mean: 1.76 ± 2.72 (mg/kg)		
	One gram	Cowpea	Mean concentration:	Nigeria	[228]
			Heptachlor: 0.64 ± 0.69 (mg/kg)		
			Mean concentration:		
			Aldrin: 4.28 ± 2.89 (mg/kg)		
			Mean concentration:		
			γ-BHC: 0.80 ± 0.13 (mg/kg)		
			Mean concentration: p,p′-DDE: 0.57 ± 0.56 (mg/kg)		
			Mean concentration:		
			Dieldrin: 10.44 ± 8.02 (mg/kg)		
			Mean concentration:		
			Endrin: 0.83 ± 0.83 (mg/kg)		
			Mean concentration: p,p′-DDD: 1.15 ± 0.54 (mg/kg)		
			Mean concentration:		
			Endosulfan II: 8.80 ± 7.6 (mg/kg)		
			Mean concentration: p,p′-DDT: 0.96 ± 0.81 (mg/kg)		
			Mean concentration:		
			Endrin CHO: 7.04 ± 4.50 (mg/kg)		
			Mean concentration:		
			Endosulfan I: 5.83 ± 6.25 (mg/kg)		
	5	Leafy vegetable (Amaranthus Spinosus)	Cyclohexanes, Mean: 1.122 ± 0.444 (μg/kg)	Nigeria	[229]
			DDT, Mean: 1.412 ± 0.361 (μg/kg)		
			DDD, Mean: 1.280 ± 0.317 (μg/kg)		
			Dicofol, Mean: 0.386 ± 0.135 (μg/kg)		
			Perthane, Mean: 1.226 ± 0.333 (μg/kg)		
			Methoxychlor, Mean: 1.450 ± 0.394 (μg/kg)		
			Aldrin, Mean: 0.960 ± 0.283 (μg/kg)		
			Dieldrin, Mean ± Std: 0.694 ± 0.232 (μg/kg)		
	5	Leafy vegetable (Amaranthus Spinosus)	Heptachlor, Mean ± Std: 0.782 ± 0.274 (μg/kg)	Nigeria	[229]
			Chlordane, Mean ± Std: 1.086 ± 0.307 (μg/kg)		
			Endosulfan, Mean ± Std: 0.538 ± 0.160 (μg/kg)		
			Hexachlorobenzene, Mean ± Std: 0.362 ± 0.098 (μg/kg)		

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Table 3 (*continued*)

Type of chemical	Number of samples	Type of Food product	Results	country	References
			Pentachlorobenzene, Mean ± Std: 0.360 ± 0.063 (μg/kg) Mirex, Mean ± Std: 1.102 ± 0.288 (μg/kg) Toxaphene, Mean ± Std: 1.130 ± 0.306 (μg/kg) Alpha HCH, Mean ± Std: 1.596 ± 0.427 (μg/kg) Beta HCH, Mean ± Std: 1.432 ± 0.388 (μg/kg) Gamma HCH, Mean ± Std: 1.866 ± 0.483 (μg/kg)		
	100	Brinjal- Radish Tomato- Bitter gourd Cabbage-Brinjal Cucumber- Brinjal Chilli- Bitter Cauliflower- Cabbage Chilli- Cabbage	Aldrin, Range: 1.13 ± 0.65–5.42 ± 1.32 μg/kg p,p'-DDE, Range: 1.43 ± 0.15–5.65 ± 1.09 μg/kg CisChlordane Range: 0.85 ± 0.15–3.67 ± 1.01 μg/kg p,p'-DDT, Range: 1.04 ± 0.45–5.90 ± 1.87 μg/kg Endrin, Range: 2.29 ± 0.28–4.32 ± 1.21 μg/kg α-Endosulfan, Range: 0.77 ± 0.34–7.74 ± 2.45 μg/kg Lindane-I, Range: 1.08 ± 0.39–2.93 ± 0.98 μg/kg	Bangladesh	[230]
	100	Grape fruit-Water melon Guava- Water melon Banana- Water melon Lemon- Banana Papaya- Banana	Aldrin, Range: 0.93 ± 0.47–3.67 ± 1.98 μg/kg p,p'-DDE, Range: 0.38 ± 0.21–2.25 ± 1.07 μg/kg p,p'-DDT, Range: 0.328 ± 0.18–0.61 ± 0.29 μg/kg β-Endosulfan, Range: 0.23 ± 0.03–0.89 ± 0.39 μg/kg Lindane-I, Range: 0.53 ± 0.32–1.03 ± 0.79 μg/kg	Bangladesh	
Heavy metals	1 gr	Vegetables (Carrot, Onion, Cabbage, Garlic, Ginger)	Pb Concentration: 10.1–14.3 mg/kg The concentration of Pb in all vegetables was higher than the safe limits. Cr Concentration: ND Cd Concentration: ND	Nigeria	[231]
	99	Muscles of fish E. Lucius (n = 10)	Cd Range: 0.003–0.005 mg/kg of wet weight Pb Range: 0.034–0.074 mg/kg of wet weigh Hg Range: 0.071–0.287 mg/kg of wet weigh	Morocco	[232]
		S. lucioperca (n = 9)	Cd Range: 0.003–0.004 mg/kg of wet weigh Pb Range: 0.045–0.087 mg/kg of wet weigh Hg Range: 0.071–0.254 mg/kg of wet weigh		
		M. salmoides (n = 23)	Cd Range: 0.002–0.004 mg/kg of wet weigh Hg Range: 0.056–0.161 mg/kg of wet weigh		
		L. macrochirus (n = 35)	Cd Range: 0.001–0.003 mg/kg of wet weigh Pb Range: 0.051–0.115 mg/kg of wet weigh Hg Range: 0.078–0.140 mg/kg of wet weigh	Mechraa-Hammadi Dam	[232]
		S. erythrophthalmus (n = 22)	Cd Range: 0.003–0.004 mg/kg of wet weigh Pb Range: 0.049–0.106 mg/kg of wet weigh Hg Range: 0.043–0.081 mg/kg of wet weigh		
	93	Rice (n = 57)	Cr Mean: 10.78 ± 8.48 mg/kg dw Range: 0.45–32.49 mg/kg dw As, Mean: 1.87 ± 1.1 mg/kg dw Range: 0.72–6.05 mg/kg dw Cd, Mean: 0.081 ± 0.086 mg/kg dw Range: 0.001–0.37 mg/kg dw Pb, Mean: 4.34 ± 4.35 mg/kg dw Range: 0.21–18.04 mg/kg dw	Bangladesh	[233]
		Bitter gourd (Momordica charantia) (n = 9)	Cr, Mean: 28.72 ± 9.99 mg/kg dw Range: 14.35–47.67 mg/kg dw As, Mean: 1.52 ± 0.39 mg/kg dw Range: 1.01–2.03 mg/kg dw Cd, Mean: 3.15 ± 2.13 mg/kg dw Range: 0.81–6.70 mg/kg dw Pb, Mean: 5.96 ± 1.76 mg/kg dw Range: 3.34–8.53 mg/kg dw	Bangladesh	
		Papaya (Carica papaya) (n = 6)	Cr, Mean: 21.23 ± 11.35 mg/kg dw Range: 8.69–26.30 mg/kg dw As, Mean: 1.91 ± 0.79 mg/kg dw Range: 0.79–2.99 mg/kg dw Cd, Mean: 1.26 ± 0.30 mg/kg dw Range: 0.84–1.69 mg/kg dw Pb, Mean: 6.65 ± 2.52 mg/kg dw Range: 3.92–10.20 mg/kg dw	Bangladesh	
		Okra (Abelmusch us esculentus) (n = 6)	Cr, Mean: 23.42 ± 5.79 mg/kg dw Range: 15.22–28.51 mg/kg dw As, Mean: 2.55 ± 0.70 mg/kg dw Range: 1.53–3.64 mg/kg dw Cd, Mean: 2.86 ± 1.39 mg/kg dw Range: 1.35–4.84 mg/kg dw	Bangladesh	

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Table 3 (*continued*)

Type of chemical	Number of samples	Type of Food product	Results	country	References
			Pb, Mean: 21.12 ± 11.34 mg/kg dw Range: 8.32–35.87 mg/kg dw		
		Bean (Phaseolus vulgaris) (n = 3)	Cr, Mean: 18.16 ± 4.88 mg/kg dw Range: 12.52–21.10 mg/kg dw As, Mean: 1.67 ± 0.42 mg/kg dw Range: 1.26–2.11 mg/kg dw Cd, Mean: 1.58 ± 0.64 mg/kg dw Range: 0.94–2.25 mg/kg dw Pb, Mean: 7.10 ± 2.11 mg/kg dw Range: 4.71–8.74 mg/kg dw	Bangladesh	
		Brinjal (Solanum melongena) (n = 5)	Cr, Mean: 21.78 ± 11.07 mg/kg dw Range: 10.40–33.40 mg/kg dw As, Mean: 2.12 ± 0.54 mg/kg dw Range: 1.57–2.88 mg/kg dw Cd, Mean: 0.87 ± 0.23 mg/kg dw Range: 0.64–1.26 mg/kg dw Pb, Mean: 7.01 ± 2.11 mg/kg dw Range: 3.77–9.49 mg/kg dw	Bangladesh	
		Chilli (n = 4)	Cr, Mean: 16.41 ± 6.22 mg/kg dw Range: 8.12–21.57 mg/kg dw As, Mean: 2.15 ± 0.59 mg/kg dw Range: 1.48–2.91 mg/kg dw Cd, Mean: 1.12 ± 0.31 mg/kg dw Range: 0.81–1.43 mg/kg dw Pb, Mean: 13.48 ± 9.86 mg/kg dw Range: 7.32–28.18 mg/kg dw	Bangladesh	
	497	Sausages	Mean: Cr (6.040 μg/kg) > Pb (1.524 μg/kg) > Ni (0.525 μg/kg) > Cd (0.115 μg/kg) > As (0.066 μg/kg)	Iran	[234]
	1 kg	Tomato	As: 1.93 ± 0.50 mg/kg dw Pb: 3.63 ± 0.11 mg/kg dw Cd: 0.56 ± 0.05 mg/kg dw Cr: 1.49 ± 0.01 mg/kg dw Hg: 3.43 ± 0.05 mg/kg dw	Ethiopia	[235]
	1 kg	Cabbage	As: 5.73 ± 0.37 mg/kg dw Pb: 7.56 ± 0.23 mg/kg dw Cd: 1.56 ± 0.05 mg/kg dw Cr: 1.49 ± 0.01 mg/kg dw Hg: 4.23 ± 0.28 mg/kg dw	Ethiopia	
	92	Canned tuna	Cd Mean: 0.02 ± 0.019 mg/kg Pb Mean: 0.18 ± 0.2 mg/kg Hg Mean: 0/22 mg/kg None of the tested samples exceeded the CAC limit	Iran	[236]

[254]. Potentials for reproductive dysfunction and neurotoxicity of DDT were shown in both vertebrates and invertebrates' varieties. The strong estrogenic action of DDT has been proven in mammals. In a study on diabetes in Mexican Americans, an increased prevalence of the disease was related to DDE and DDT serum glucose concentrations [255]. Chlorinated benzene in humans can lead to ulceration, liver disorder, hair loss, skin lesions, and thyroid damage [256]. Hematologic disorders, including leukopenia, thrombocytopenia, anemia, granulocytosis, eosinophilia, and monocytosis, are associated with chronic human exposure to γ-HCH. Exposure to γ-HCH indoors and at work causes aplastic anemia in humans [167]. The nervous system can be damaged by exposure to high levels of Lindane, causing various symptoms from dizziness and headaches to convulsions, ataxia, altered menstruation, seizures, and eventual death [257,258]. Exposure to β-HCH during pregnancy is associated with changes in thyroid hormone levels, influencing brain development. Research has proven that all hexachlorocyclohexane isomers can practically be predicted to cause human cancer [255]. Another study has shown that OCPs lead to estrogenic impacts in females and anti-androgenic impacts in males [245].

OCPs are stable environmental pollutants acting as endocrine toxicants and disruptors in organs. They are among the most important chemicals threatening human health [100]. OCPs can function as teratogens, disrupting the neuroendocrine and endocrine glands, suppressing the immune and reproduction system, and dysregulating metabolism [259].

Endocrine-related routes were distinguished in a modified Toxicogenomics Database susceptible to this compound class using a computational approach, and these included reproduction (steroid biosynthesis, gonadotropins, oxytocin, estradiol, androgens), thyroid hormone, and insulin [260]. Studies show that these agrochemicals activate ERs, ARs, and retinoic acid receptors with a comparatively large affinity, despite the variations in their effectiveness. Chlorine pesticides, because of their stability and high toxicity to marine and earthy wild animals in addition to humans, stay significant and worrying agrochemicals [260–262]. It has been proven that OCPs act as endocrine disruptors, preventing essential hormonal signaling functions in invertebrates and vertebrates. Studies show that various OCPs act as weak estrogens or anti-androgens and may interfere with other hormonal systems, such as those generated by the Thyroid [263–266]. They also act as neuroendocrine disruptors. For instance, there is a relationship between intake

of dieldrin and Parkinson's disorder. Furthermore, such chemicals inhibit natural metabolism, mitochondrial oxidative respiration, and immune function. Therefore, OCPs may directly or indirectly influence endocrine systems by disrupting metabolism, ATP creation, and hormone synthesis [267–269]. The endocrine system is formed early in growth, and exposure to toxins may disorder the growth pathway of endocrine tissues. Several teratogenic influences have been shown in fish farming with OCPs exposure [260,270].

Ton et al. (2006) introduced a teratogenicity indicator as the dose ratio leading to 50% death (LC50) over the dose leading to 50% developmental abnormalities (EC50), i.e., the ratio of LC50/EC50. A scoring indicator >1 as teratogenic was evaluated. There was a relative teratogenic indicator of 3.5 for DDT at 96 host fertilization in the mentioned research, while the dieldrin value was 0.1 [271]. These values were compared with TCDD with high teratogenic potential with a rate of 15.3. DDT and dieldrin have also been found to reduce heart rate, cause tremors in the early stages of the fetus, and destroy dopaminergic and cholinergic neurons. This is because hormone-secreting factors can be stimulated or inhibited by dopamine and acetylcholine in the central nervous system [268].

Neurodevelopment and the ontogeny of the dopaminergic system can be influenced by early exposure to OCPs. A potential for deformity and malformations have been reported in response to the toxaphene toxins [272]. Increased dieldrin concentration, skeletal deformity, and cardiac hemorrhaging have been observed [268,271]. Toxaphene is a complicated mix of substances formed by the reaction of chlorine gas with camphene. Exposure to 15–20 mg of toxaphene per liter can cause deformity, including lack of pigmentation, the toxicity of spinal deformity, and yolk sack edema. Toxaphene can block blood flow to the heart, even though there is a heartbeat [273]. However, OCPs are complex molecules that can act as endocrine disruptors. Evaluation of fetal toxicity to various chlorinated organic pesticides showed that, even in the early stages of embryonic formation, OCPs might alter the egg yolk precursor protein called vitellogenin (vtg) [274]. An increase was observed in vtg1 expression in fetuses by heptachlor, endosulfan, and methoxychlor. Some OCPs show estrogenic chemicals when vertebrates, including humans, undergo sensitive sex determination stages [260]. In fact, following a single pulse of the chemical into the egg, there was a complete change of male to female sex for ten weeks [275].

In summary, OCPs are teratogens and change the growth process of vertebrates and cause abnormality, mainly due to the functioning of estrogen or anti-androgens, leading to the change in neuroendocrine that alter the brain form [260].

From the viewpoint of neurotoxic effects, numerous studies on OCPs have previously concentrated on a possible relationship between neuropsychological impairment and prenatal exposure to OCPs [276]. According to research, OCs, like DDT, are excreted in breast milk and pass the placenta, resulting in postnatal poisoning in infants, especially neurodevelopmental malfunctions. The risk of developing autism spectrum malfunctions with maternal exposure to OCPs throughout pregnancy has been demonstrated in previous studies [277,278]. Many documentations have shown a positive correlation between neurodevelopmental malfunctions and pre-and postnatal OCs exposure, such as autism, memory loss, impaired psychomotor and cognitive development, Parkinson's disease, and anxiety [167,278].

7. Tributyltin (TBT)

TBT (Fig. 2) is a poisonous substance in the group of organotin chemicals applied for different industrial targets such as slime monitoring in paper mills, sanitizing of circulating industrial cooling waters, textiles (mainly sportswear), antifouling agents, and the preservation of wood, giving direct skin contact to TBT. Because of its broad application as an anti-interference agent in boat paints, TBT is a usual pollutant of marine and freshwater ecosystems exceeding acute and chronic poisoning concentrations [279].

This indicates that TBT is more concentrated in marine habitats, potentially bioaccumulating aquatic organisms. Organotin chemicals can also enter the food chain and, finally human body upon human consumption of oysters, farmed salmon, mussels, and clams [280]. Fundamentally, there are several effects of TBT which are well recognized in organotin substances, which produce different effects when aquatic life is exposed to these compounds. These effects include; larva death, growth retardation, developmental and reproductive effects, immune toxicity, and carcinogenicity [281].

Consumption of polluted drinking water, beverages, and especially marine food is significant for human exposure to TBT [282]. However, despite the proof that these origins expose humans to organotin chemicals, little data on butyltin accumulation in humans are available. Biotic degradation is the leading way to delete TBT pollution in the water and sediment [279]. The procedure takes place through debutylation and makes the less poisonous metabolites dibutyltin (DBT), monobutyltin (MBT), and inorganic tin [283]. Mammalians are susceptible to the toxic effects of TBT. Humans exposed unintentionally or professionally to organotins experience seizures, periods of severe pain, and mental disorders [284]. According to immune function studies, a TDI value for TBT of 0.25 μg/kg body weight per day was established [279].

TBT exposure can interfere with the development and normal function of the female reproductive organs in the HPG axis, such as the anterior pituitary, ovary, and hypothalamus, thereby reducing fertility [285,286]. In addition, TBT exposure caused an increase in serum testosterone levels and cystic follicles and a reduction in total healthy ovarian follicles and inflammation, followed by the increased presence of macrophage and mast cells [287].

Biological effects of TBT on the male reproductive system indicate retarded sexual development, prohibition of sex steroid metabolism, epididymis, decrease in size of the testis, decreased sperm count, sperm viability, morphology, and density, as well as coagulating gland abnormal testicular histology [288]. TBT impairs the testicular cholesterol homeostasis and steroidogenesis by disrupting the cholesterol transporter apolipoprotein E (APOE), nuclear receptor, and steroidogenic enzymes [289].

Several studies on adipose tissue have indicated that EDCs are increasingly implicated in the pathogenesis of obesity, and TBT has been introduced as the leading environmental obesogen [290].

TBT acts as an agonist for PPARG and RXRA, nuclear hormone receptors (NRs), using alterations in gene expression and stimulating adipogenesis by inducing their differentiation from mesenchymal stem cells and/or from pre-adipocytes [291].

In adults, TBT induces not only weight gain but also metabolic disruption (i.e., hepatic steatosis, hyperinsulinemia, hyperleptinemia), and adipocyte formation in bone [292].

Furthermore, there is a frame of facts indicating that TBT can also be considered a thyroid disruptor, thereby eventually triggering the development of obesity and metabolic disorder [293].

From the viewpoint of neurological disorders, the administration of TBT elicited eccentric behavior, decreases in synaptogenesis in rats, and a reduction in brain weight within the cerebellum, suggesting that a primary target of TBT is the central nervous system [294]. Evidence also suggests that TBT induces neuronal damage by barricading an important cellular antioxidant mechanism, glutathione s-transferase, and ultimately generating ROS [295].

Recently reported that TBT induces cell death in cultured rat cortical neurons, demonstrating an increment of extracellular glutamate content, overactivation of glutamate receptors, phosphorylation of extracellular-regulated kinase, and production of ROS. The mechanism of TBT-induced glutamate release remains equivocal, but TBT was reported to disrupt mitochondrial activity by suppressing ATP synthase, resulting in a reduction of ATP levels [296].

8. Heavy metals

Heavy metals, as natural constituents of the earth's crust, are well-known as persistent non-degradable environmental contaminants; bioaccumulating over a while in human and animal bodies through food and water intake, as well as inhalation [297–300].

Generally, the term "heavy metals," highly toxic to living organisms, refers to metals and metalloids with relatively high densities (more than 5 g/cm^3). Some researchers insist on replacing the controversial term "heavy metals" with "potentially toxic elements" [301], chiefly including Arsenic, cadmium, chromium, lead, and mercury, which enter the human body through ingestion, inhalation and dermal contact [299,302–305].

8.1. Arsenic (As)

Arsenic, as a metalloid, is the 20th most copious element on earth. Arsenate and arsenite compounds, the inorganic forms of As, are lethal to humans and other organisms in the environment [306,307]. Arsenic is a pure crystal in many minerals or in conjunction with Sulphur and other metals. It can exist in various allotropes, although only the grey form has important use in industry [308].

Aside from occurring naturally in the environment, arsenic can be exceedingly unleashed via volcanic activity, erosion of rocks, human activity, and forest fires [309]. Also. Some As-containing products include soaps, paints, dyes, metals, drugs, semi-conductors, pesticides, and fertilizers. In some cases, animal feeding operations release arsenic into the environment in larger quantities [310].

Intake of food and drinking water are significant sources of general population exposure to arsenic [311]. Entering the body arsenic by food consumption is mainly attributed to fish and seafood. The inorganic forms of As in food appears to be much more toxic than the organic form [312]. In 2001, US EPA lowered the allowable limit of arsenic in drinking water from 50 μg/kg to 10 ppb [313,314].

In 1989, JECFA defined the PTWI as 15 μg/kg bw per week, which was withdrawn in 2010. The EFSA has set BMDL01 As at 0.3–8 μg/kg bw per day, based on findings in the field of human cancer. Regarding the most conservative limit, a result is a 70-kg person with a daily intake limit of 21 μg/day of inorganic As [315].

Higher levels of Exposure to As can possibly cause death. Ingestion of a lower amount may appear as nausea and vomiting, abnormal heartbeat, decrease in the number of white and red blood cells, a sensation of "pins and needles" in hands and feet, and blood vessels impairment [309]. Long-term exposure can lead to cardiovascular disease, diabetes, skin lesions, and cancers of the skin, kidney, and bladder [316].

The substantial target organ of arsenic toxicity is a neural system, which can pass through the blood-brain barrier and attenuate concentration and learning [317]. As-induced neurotoxicity seems to follow several mechanisms, including oxidative stress, decreased acetylcholinesterase activity, and thiamine deficiency [318]. Chronic neurological symptoms of As exposure are encephalopathy, peripheral neuropathy, and delirium [319].

Several epidemiological studies have observed a significant association between arsenic exposure and adverse infant outcomes, indicating spontaneous abortion, low birth weight, and infant mortality [320]. As intake may induce gonad dysfunction in males via suppressing testosterone synthesis, necrosis, and apoptosis, significantly causing infertility, low sperm quality, and erectile failure [321]. As can accumulate in testes and accessory sex organs, such as the prostate gland, epididymis, and seminal vesicle [322].

In females, the reproductive cycle is influenced by As, such as lessening the plasma levels of estradiol and progesterone, inhibiting ovarian steroidogenesis, declining ovarian uterine and follicular cells, and prolonged diestrus [323].

Research has shown that arsenic has a direct and indirect role in developing Thyroid disorder [324]. Arsenic trioxide (As_2O_3) and sodium arsenite ($NaAsO_2$), called Arsenicals, play a pivotal role in thyroid malfunction by accumulating in thyroid tissue, altering the activity of thyroid hormone nuclear receptors [325], inhibiting TPO activity *in vitro*, inducing an increase of total and free T3 levels, a decrease of hepatic 5′ deiodinase activity in rats, and inducing goiter in human [326].

Accumulating As in the kidney leads to dysfunction of the proximal tubules and glomerulus, which makes the association between As exposure and renal damage clear [327]. As toxicity to the kidney may be mediated by ROS, which enhances lipid peroxidation and cellular damages, including apoptosis. Long-term exposure to As is believed to cause tubular interstitial damage, glomerular collapse, and glomerular sclerosis [328]. Acute tubular necrosis, increased creatinine and blood urea nitrogen levels characterize acute kidney disease due to As exposure [327,328].

The liver is a major target organ of human arsenic carcinogenesis [329]. The liver is vulnerable to prolonged exposure to small amounts of arsenic; however, the precise degree of human sensitivity to arsenic cannot be predicted [330]. Findings have

demonstrated an association between chronic As exposure and abnormal liver function, hepatoportal sclerosis, hepatomegaly, liver fibrosis, and cirrhosis [331]. The As toxicity is diagnosed by demonstrating a high As level in urine, nails, and hairs [332].

8.2. Mercury (Hg)

Mercury (Hg), as a potentially toxic element, has aroused global public health concern [333]. Hg occurs in the metallic form (Hg^0), organic form (commonly methyl or ethyl mercury), and inorganic form (Hg^+, Hg^{2+}), which exists in water, air, and soil. Metallic mercury is liquid at room temperature and can be readily evaporated, absorbed from the lungs (80%), and distributed throughout the body [334].

Inhalation of the high amount of Hg vapor may result in central nervous system disorders, interstitial pneumonitis, and acute bronchitis [335].

The most noxious form of Hg is attributed to the organic Hg, mainly detected as methyl/ethyl Hg. The primary sources of Hg exposure include seafood, poultry, pesticides, vaccines, medical devices [336], dental amalgams, skin-lightning creams, button cell batteries, broken thermometers, and compact fluorescent light bulbs [337]. Organic Hg causes neurological disturbances and skin manifestations. Hg-related kidney failure is chiefly related to a nephrotic syndrome with membranous nephropathy pattern and tubular malfunction with enhanced urinary excretion of albumin, retinol-binding protein, transferrin, and β-galactosidase [338]. After acute exposure to Hg, acute tubular necrosis appears, usually accompanied by oligo-anuria [339].

Hg could be released into the environment via natural phenomena (such as volcanic activity and weathering of rocks), human activities (coal-fired power plants, mining processes, metal refineries, electronic waste recycling factories, and municipal solid waste incinerators) [340]. The provisional tolerable weekly intake (PTWI) for Hg is 4 μg/kg body weight per week set by JECFA [341].

Hg ingesting via the gastrointestinal tract and carrying to all tissues takes about 30 h while inhaling Hg vapor last for less than 24 h [342]. Hg prefers to accumulate in the liver, kidney, brain, spleen, lymph nodes, skeleton, and muscles, exerting neurotoxic, mutagenic, teratogenic, and endocrine disrupting impact [343].

Hg exposure has been associated with female reproductive problems, such as polycystic ovary syndrome, dysmenorrhea, amenorrhoea, early menopause, endometriosis, benign breast disorders, galactorrhoea, and infertility [344].

The mechanisms of Hg toxicity in males are not completely clear, but a strong association between Hg and reproductive disorders has been proved via preclinical studies [345]. Hg can interfere in spermatogenesis and affects epididymis [346].

Hg could play a role in the pathogenesis of thyroid cancers, autoimmune thyroiditis, and hypothyroidism, but its prevalence [347]. Thyroid dysfunction seems associated with preventing the five deiodinases, with diminished free T3 and increased reverse T3 [348].

Alteration of hepatic structure and function could be emerged after Hg accumulation in the liver [349], followed by elevated serum ALT, bilirubin and ornithine carbamoyltransferase levels, hepatomegaly, centrilobular hepatic steatosis, detracting hepatic coagulation factors synthesis [350], metabolic enzymes disturbance, hepatic mitochondrial dysfunction, lipid peroxidation products unbalance, and proliferation of the endoplasmic reticulum [351].

8.3. Cadmium (Cd)

Cadmium (Cd) belongs to group XII of the periodic table of chemical elements [352]. Thus it is physically and chemically similar to mercury and zinc. ATSDR has announced Cd as the seventh most toxic heavy metal [319], and the IARC has put Cd and its compounds in Group 1 (carcinogenic to humans) [13]. Cd can be released to the environment through natural activities, such as volcanic activity (both on land and in the deep sea), river transport, erosion, and weathering [14], or human activities, such as cigarette smoke, waste burning, metal ore combustion, fossil fuels [353]. Contaminated food (fish, shellfish, organ meats, grains, root vegetables, and green vegetables) and water (old Zn/Cd sealed water pipes or industrial pollution) are the significant dietary exposure to Cd for non-smokers and those with no occupational exposure [354–356].

The value of PTWI has been defined for Cd as 0.007 mg/kg bw, recommended by JECFA. The WHO and EPA have assigned the acceptable limit of 0.003 and 0.005 mg L^{-1} for Cd in drinking water, respectively [312].

Cd exposure has been commonly connected with various illnesses, including chronic kidney disease, diabetes, hypertension, and cancer of various organs [357].

Acute and chronic cadmium toxicity impacts the liver and kidney as the primary target organs [358]. Cadmium is highly toxic to the kidney and accumulates in the proximal tubular cells in higher concentrations. Thus, cadmium exposure can cause renal dysfunction and kidney disease. Also, cadmium exposure can cause hypercalciuria, calcium metabolism disturbances, and renal stone formation [306]. The biological half-life of cadmium is 3–4 months in blood and 7–26 years in the kidney. It is noteworthy that Cd accumulates within human tissues because of its low rate of excretion from the body [359].

Cd toxicity is severely reflected in reproductive organs (testes and ovaries in adults) and developing embryos, which are very susceptible to Cd-induced toxicity [360].

Although the mechanisms by which Cd causes infertility are not fully understood, in several animal species, Cd accumulation has been observed in male reproductive organs, which leads to male reproductive problems [361], such as atypical morphology of testes and spermatozoa, decrement of sperm output and viability, and even complete infertility [362].

In females, Cd toxicity can occur as declined steroidogenesis, hindering the function of the ovary and development of oocytes, ovarian hemorrhage, and necrosis, resulting in an increased rate of spontaneous abortion, decreased rate of live births, and prolonged time of pregnancy [353].

Due to its complex histological structure and functions, the thyroid gland is often the target of most EDCs, including Cd [363,364].

Mitochondria are supposed to be the main intracellular targets for Cd. The adverse effects of chronic toxicity include colloid cystic goiter, parafollicular cell diffuse and nodular hyperplasia and hypertrophy, adenomatoid follicular hyperplasia with low-grade dysplasia, and thyroglobulin hypo- and secretion [363].

Cd causes brain damage. Subjective symptoms of occupational exposure to Cd are supposed to be predicted and prevalent, such as sleep disturbances, Insomnia, fatigue, headache, and anorexia, as well as motor and sensory malfunctions [365].

The liver is the primary organ susceptible to damage on being exposed to Cd^{2+}. The occurrence of an inflammatory state and direct action on liver cells has been considered a mode of action for Cd^{2+}-induced hepatotoxicity [366]. Histopathological findings indicate that Acute Cd exposure may lead to liver-related mortality, mainly due to severe fibroplasias, hepatic necroinflammation, elevated levels of serum hepatic enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), non-alcoholic steatohepatitis (NASH), and non-alcoholic fatty liver disease (NAFLD) [350], hyperplasia, apoptosis, enlarged liver sinus, and hilum, as well as neutrophil infiltration and chemotaxis to the lesion [367]. Cd does not act as a redox reactive metal; induction of oxidative stress mediates its toxicity. The primary modes of action in Cd-induced hepatotoxicity are (1) oxidative stress by direct merging with sulfhydryl groups on proteins and glutathione; and (2) a subsequent inflammatory injury [368].

8.4. Lead (Pb)

Lead (Pb), a low melting point, highly malleable metal, has been applied to many diverse uses from ancient to the present [369]. Pb-containing sources include food cans, water pipes, contaminated drinking water, cosmetics, batteries, paint, traditional remedies, gasoline, Pb-crystal, Pb-glazed ceramics, cigarette smoke, jewelry, children's toys, vinyl lunch boxes, and even contaminated candy [370]. Pb toxicity is a great public health concern, specifically in children, owing to more hand-to-mouth activity and high potential to absorb an elevated amount of water-soluble Pb [371].

Primary routes for Pb absorption comprise ingestion, inhalation, percutaneous, and transdermal [372]. Common symptoms of acute exposure could appear as fatigue, headache, abdominal pain, loss of appetite, hallucinations, hypertension, sleep disorders, arthritis, vertigo, and renal dysfunction [306]. When the Pb levels in the blood reach about 40–60 μg/dL, chronic toxicity is characterized by lethargy, persistent vomiting, encephalopathy, convulsions, delirium, and coma [373]. Pb-induced oxidative stress through the generation of ROS has been identified as a primary contributory factor in the pathogenesis of adverse health effects [374].

Pb exposure affects pregnancy in females mainly by attenuating fertility potential, menstruation disorders, miscarriage, pregnancy hypertension, postponed conception time, impairing hormonal production and circulation, preeclampsia, preterm birth, and early membrane rupture [375]. Revealed impacts of Pb in men incorporate decreased charisma, consequences for spermatogenesis (diminished motility and numbers, expanded irregular morphology), chromosomal harm, barrenness, anomalous prostatic capacity, and changes in serum testosterone [376].

For a decade, Pb's impact on thyroid activity has been known. Some investigators suggested that Pb negatively influences both peripheral thyroid hormone and TSH concentrations [377], as well as Selenium metabolism, a critical element for the synthesis of thyroid hormones [378].

Environmental exposure to low levels of Pb is associated with chronic renal insufficiency [379]. Acute Pb toxicity causes impairment of the proximal tubular architecture and histological changes, such as eosinophilic intranuclear inclusions in tubular cells consisting of Pb-protein complexes and mitochondrial swelling [338]. Long-term exposure to Pb may cause consequent glomerulosclerosis, vasoconstriction, increased urate secretion, interstitial fibrosis, hypertension [380], alterations in the hepatocytes, sinusoids, and the portal triads. The changes in the hepatocytes were mainly necrosis, cytoplasmic swelling, anisokaryosis, binucleation, nuclear vesiculation, glycogen reduction, and hydropic degeneration [381].

In vitro models have revealed the action mechanisms for acute Pb poisoning, involving a decrease in hepatic CYP450 content [382], impairs the integrity of the heme biosynthetic pathway [383], lipid peroxidation, ROS generation, apoptosis, and oxidative DNA damage [350]. The values of Pb half-life were determined as 20–30 years in bones, 40 days in soft tissue, and 35 days in the blood [384]. The JECFA has established a PTWI for Pb as 0.025 mg/kg body weight [385] and also recommended a dose of 10 μg/L and 0.5 $\mu g/m^3$ for Pb in drinking water and air, respectively, in order to identify the magnitude of effects originated from Pb exposure. A value of 50 μg/L in blood has been considered a threshold dose for the adverse effects on intelligence quotient [337,386].

9. Conclusions

Based on the conclusion of previous assessments and relevant literature, it is becoming challenging to ignore the existence of health-influencing chemical pollutants in the food chain. The past forty years have seen a significant increase in various endocrine-associated diseases with consequences to different hormonal functions, including endocrine cancers (mainly prostate, ovarian, and breast), infertility, premature puberty, attention deficit hyperactivity disorder, obesity, and diabetes. Considering the increasingly rapid advances in production and consumption of products containing EDCs and enhanced exposure to these compounds, which interfere with the normal function of the endocrine system, a considerable investigation has grown around the detrimental role of EDCs on public health. Newborns and children are the most susceptible individuals to the damaging endocrine impact of EDCs, particularly developmental disorders and abnormal physiology. To decline the exposures to EDCs, urgent preventive strategies are required. A better understanding of the vital link between EDCs and health problems will help reduce the formation and release of the EDCs, which would be achieved by minimization of these chemicals as contaminants in products, the use of less hazardous substances, lessening the generation of medical and municipal waste, implementation of low-waste technology, the promotion of the recovery and recycling of waste generated, regular monitoring of EDCs amounts in foodstuff and environment, training courses in hospitals and schools to

improve general understanding of EDCs and the consequences of exposure to such pollutants, especially in early life. On the other hand, other control measures beyond individual capacity should be developed and implemented by national and local regulations.

10. Limitations

Challenges in determining the carcinogenicity of certain compounds: The assessment of carcinogenicity for specific compounds presents inherent challenges. Long-term exposure assessments and extensive epidemiological evidence are necessary to establish a credible association between compound exposure and cancer development. Further research is needed to comprehensively investigate the complex nature of these compounds and establish their potential carcinogenicity.

Limited human studies on the toxicity effects of endocrine-disrupting compounds: The scarcity of prospective or retrospective studies conducted on human populations regarding the toxic effects of endocrine-disrupting compounds represents a notable limitation. A comprehensive understanding of the impact of these compounds on human health necessitates well-designed human studies that encompass exposure levels, health outcomes, and potential confounding factors. More research is required to address this knowledge gap and enhance our understanding of the effects of endocrine-disrupting compounds on human populations.

Insufficient studies on exposure level to endocrine-disrupting compounds through food, particularly across different countries: The dearth of research investigating the daily exposure to endocrine-disrupting compounds through food, especially in diverse geographical regions, constitutes a significant limitation. Accurately determining the specific levels and patterns of exposure to these compounds through food is critical for evaluating the potential health risks they pose to various populations. Additionally, disparities in food safety laws and regulations between regions can exert a substantial influence on exposure levels and the prevalence of endocrine-disrupting compounds in food. These disparities may arise from variations in pesticide usage, agricultural practices, food processing methods, and regulatory frameworks. Therefore, it is imperative to consider the regional context and specific food safety regulations when assessing the exposure and potential health effects of endocrine-disrupting compounds.

Author contribution statement

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Declaration of competing interest

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Abbreviations

AHR	Aryl hydrocarbon receptor
APOE	apolipoprotein E
ARs	Androgen receptors
ATSDR	Agency for Toxic Substances and Disease Registry
BAFs	bioaccumulation factors
BCFs	bioconcentration factors
DBP	Di-*n*-butyl phthalate
DEP	Diethyl phthalate
DEHP	Di-(2-ethylhexyl) phthalate
DINP	Di-isononyl phthalate
DIDP	Di-isodecyl phthalate
DL-PCBs	dioxin-like PCBs
DMSA	dimercaptosuccinic acid
EC	European Commission
EDCs	endocrine-disrupting chemicals
EFSA	European Food Safety Authority
ERRγ	Estrogen-related receptor gamma
ERs	Estrogen receptors
FSH	follicle-stimulating hormone
GPR30	G protein-coupled receptor
HMW	high-molecular-weight
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LDH	lactate dehydrogenase
LMW	low-molecular-weight

MCL	maximum contaminant levels
MDA	malondialdehyde
NOAEL	No Observed Adverse Effects Limit
OCPs	Organochlorine pesticides
OSHA	Occupational Safety and Health Agency
PAE	phthalic acid esters
PBDEs	Polybrominated Diphenyl Ethers
PCBs	Polychlorinated biphenyl
PCDDs	polychlorinated dibenzodioxins
PRs	Progesterone receptors
PTMI	provisional tolerable monthly intake
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
SCF	EU Scientific Committee on Food
TDI	tolerable daily intake
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalency Quantity
TWI	tolerable weekly intake
TSH	thyroid-stimulating hormone
US FDA	Food and Drug Administration of the United States
US EPA	The United States Environmental Protection Agency
WHO	World Health Organization

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