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Review article

Survey on endocrine-disrupting chemicals in seafood: Occurrence and distribution

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ABSTRACT

Currently, the presence of endocrine disrupting chemicals (EDCs) in the marine environment pose a potential risk to both wildlife and human health. The occurrence of EDCs in seafood depends of several factors such as source and amounts of EDCs that reach the aquatic environment, physicochemical features of EDCs, and its accumulation in trophic chain. This review highlights the occurrence and distribution of EDCs along the seafood in the last 6 years. The following EDCs were included in this review: brominated flame retardants (PBDEs, PBBs, HBCDDs, TBBPA, and novel flame retardants); pharmaceuticals (paracetamol, ibuprofen, diclofenac, carbamazepine), bisphenols, hormones, personal care products (Musk and UV Filters), and pesticides (organochlorides, organophosphates, and pyrethroids). Some of them were found above the threshold that may cause negative effects on human, animal, and environmental health. More control in some countries, as well as new legislation and inspection over the purchase, sale, use, and production of these compounds, are urgently needed. This review provides data to support risk assessment and raises critical gaps to stimulate and improve future research.

1. Introduction

Marine pollution has become a global environmental concern since the early decades of the 20th century. It arises from anthropogenic sources, including land- and sea-based activities that have substantial impacts in marine ecosystems, and impair human health. Damage to the marine environment is occurring already and increasing at a faster rate than the protection efforts. Improved knowledge about the pollutants and their effects on both the marine ecosystem and human health will be key to mitigate and anticipate their effects.

In the last decades, the presence of endocrine disruption chemicals (EDCs) has been reported in water environments all over the world, in marine sediments and aquatic species such as macroinvertebrates, mussels and fish. EDCs constitute a wide range of compounds, naturally-occurring or xenobiotic, that can alter function(s) of the endocrine system and consequently cause adverse health effects in organisms, its progeny or population stocks (Bergman et al., 2012). Some of these are non-regulated emerging EDCs, such as industrial chemicals/plastics (bisphenols, polybrominated diphenyl ethers-PBDEs), personal care products (UV-filters and musk fragrances, including benzophenone, galaxolide, and tonalide), pharmaceuticals (17α-ethynylestradiol EE2, paracetamol, ibuprofen, diclofenac, carbamazepine), and other regulated ones like organochlorinated pesticides (lindane, endosulfan, aldrin, dieldrin, methoxychlor, vinclozolin) organophosphate (chlorpyrifos, methamidophos, malathion, parathion and dichlorvos) and pyrethroids (deltamethrin, silafluofen, cypermethrin, permetrin, terallethrin, and bifenthrin) (Endocrine Disruptor List, 2021). The lack of regulation and monitoring of emerging EDCs in seafood makes their assessment urgent and imperative.

For that reason, several research programs have been settled at the European level such as the OSPAR Convention (The Convention for the Protection of the Marine Environment of the North-East Atlantic)

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(OSPAR, 1998) and the European Marine Strategy Framework directives (ED, 2008) to address this topic. Additionally, several research groups have been analyzing EDCs in seafood around the world as a way to assess their impact on human health. This review presents an update on the occurrence of different classes of EDCs such as brominated flame retardants, pharmaceuticals, bisphenols, hormones, personal care products (UV-filters, musk fragrances, and triclosan), and pesticide residues, in seafood. The use of monitoring data to characterize endocrine disruption contamination is crucial to understanding the extent of exposure and potential impact on the environment and human health. EDCs toxic effects and current legislation are also highlighted in the article. Moreover, the review identifies current knowledge gaps and potential future research needs in environmental analysis.

2. Literature searching

The search of published reports in the literature were performed using Google Scholar, Scopus®, Elsevier, Web of Science, Periódicos Capes and PubMed. Several keywords were included to identify published works on occurrence of endocrine-disrupting chemicals in fish and invertebrates. Two sets of terms were used to define the keywords for the literature survey in this study. The first set describes the seafood data: "seafood", "fish", "mussel", "crab", "algae", "shrimp", "mollusk/mollusc". The second set describes the type of pollutant compounds: "pesticide", "bisphenols" or "bisphenol A", "hormones", "musks", "UV-filters", "triclosan", "pharmaceuticals or pharmaceutically active compounds", "brominated flame retardants or BFRs", "polybrominated diphenyl ethers or PBDEs", "polybrominated biphenyl or PBBs", "hexabromocyclododecanes or HBCDDs/HBCDs", "tetrabromobisphenol". Survey included at least one entry from each of the two sets plus the term "occurrence" or "quantification". The terms have been searched across document titles, types, abstracts and keyword lists across all years from 2015 to 2020. Duplicates and review papers have been discarded. Only papers of the peer-reviewed journals written in English have been considered. Using this structure search strategy, the data of the papers have been included in the Tables in the Supplementary Information. In total, 258 papers have been considered for the present work (BFRs = 155 papers; pharmaceuticals = 23 papers; hormones = 5 papers; bisphenols = 16 papers; PCPs (musks and UV-filters) = 10 papers; pesticides = 49 papers). Other papers on legislation (European commission reports and Stockholm Convention), risk assessment, and toxicology were consulted for this review without any timeframe work.

2.1. Brominated flame retardants (BFRS)

Brominated flame retardants are a group of synthesized chemicals that tend to reduce the flammability of products containing them. Those compounds have been used significantly in the past decades, applied on many different materials, such as plastics, textiles and electronics to prevent fire by prolonging the time until the heated material catch fire (Wit, 2002).

The group of BFRs are composed by lipophilic compounds characterized by moderate to very high octanol-water coefficient partition (log Kow), with very few exceptions. Such chemicals comprise the following 5 major classes of flame retardants (FRs): brominated bisphenols, diphenyl ethers, cyclododecanes, phenols and phthalic acid derivatives (Bergman et al., 2012; EFSA, 2011a).

Once released in the environment, BFRs can reach soils, water bodies, sediments, and biota, raising concerns on the environmental and human health, especially because several BFRs, mainly the PBDEs, can act as endocrine disruptors (e.g., through the attachment to thyroid hormone receptors) (EFSA, 2012a; Ibhazehiebo et al., 2011).

BFRs could affect the male reproductive tract and semen quality in rodents (Chen et al., 2015), as well as decreased sperm quality in humans (Carignan et al., 2017). Some studies also reported estrogenic or anti-androgenic activities (Rosenmai et al., 2021). There is growing evidence that emerging BFRs have neurotoxic effects and may cross the blood-brain barrier to accumulate in brain tissue (Barón et al., 2015; Gan et al., 2016), leading to impaired cognitive and motor functions, exacerbating anxiety behavior, attention problems, and intellectual deficiencies (Bailey and Levin, 2015; Patisaul et al., 2013). BRFs also affect thyroid hormone (TH) levels (Johnson-Restrepo et al., 2015).

European Food Safety Authority (EFSA, 2011a, 2010) recommends monitoring of the following BFRs in foodstuffs: polybrominated diphenyl ethers (PBDEs – with emphasis in the congeners BDE28, 47, 99, 100, 153, 154, 183, and 209); hexabromocyclododecane (HBCDDs – including the α-, β-, and γ-congeners); polybrominated biphenyls (PBB – especially the congener PBB153); tetrabromobisphenol A (TBBPA) and other brominated phenols such as decabromodiphenyl ethane (DBDPE); hexabromobenzene (HBB); and bis(2,4,6-tribromophenoxy)ethane (BTBPE).

Considering the outcomes of the previous EFSA risk assessment on BFRs (EFSA, 2012a; 2012b; 2011a; 2011b; 2011c), the EU Commission recommended (2014/118/EU) that Member States should essentially monitor the presence of BFRs (EC, 2014) in wide range of foodstuffs, such as fish and other seafood. Monitoring activities should reflect consumption habits to give an accurate estimate of human exposure (Schrenk et al., 2020).

2.1.1. Polybrominated diphenyl ethers (PBDEs)

PBDEs are lipophilic BFRs, formulated with three different bromination degrees (penta-BDE, octa-BDE, and deca-BDE mixtures). They are used in several commercial products and reach the environment and biota mainly by waste disposal (Wit, 2002). Due to their environmental occurrence and toxicity, the formulations penta- and octa-BDE were listed in 2009 as organic pollutants at the Stockholm Convention on Persistent Organic Pollutants (SC-POPs) and are no longer manufactured (UNEP, 2015). More recently, the 11th meeting of the SC-POPs Review Committee recommended deca-BDE formulation for listing in its Annex A (UNEP, 2017).

Although there are strict regulation for many PBDE mixtures and commercialized articles, there is still a lack of legislation regarding their presence in seafood products. According to EC (2019), a concentration of 1000 mg kg^{-1} for the sum of PBDEs in waste, including BDE-209, is the limit set as tolerable. However, considering the growth on accumulated scientific and technical progress, the Regulation (EU) 2019/1021 recommended reviewing that concentration limit and adopted a legislative proposal to reduce that value up to 500 mg kg, and recommended of acting not later than July 16, 2021 (EC, 2019). Despite existing regulations on the use and production of PBDE formulations, these compounds are still present in the environment, reaching relatively high levels in predators and possibly presenting differences according to the habitats and the distribution of organisms (Choo et al., 2018, 2019).

A reference dose established for four PBDE congeners consists in: 0.1 μg/kg body weight per day (μg/kg b. $w.^{-1}$ day^{-1}) for BDE-47; 0.1 μg/kg b. $w.^{-1}$ day^{-1} for BDE-99; 0.2 μg/kg b. $w.^{-1}$ day^{-1} for BDE-153; and 7 μg/kg b. $w.^{-1}$ day^{-1} for BDE-209 (EFSA, 2011a). Due to the limitations and uncertainties in the toxicological data on PBDEs, a tolerable daily intake (TDI) for PBDEs has not been established. Instead, the CONTAM Panel used the margin of exposure (MOE) approach in order to characterize the risk of those four PBDE congeners. The calculated MOEs are based on the ratio of the lower benchmark dose limit ($BMDL_{10}$) value and the estimated dietary exposure (EDI). Therefore, the higher the MOE for each compound, the lower the degree of concern. The MOE for PBDEs varies according to the frequency of consumption. However, a narrative should be considered in order to interpret those results. Although the MOEs for BDE-47, BDE-99, BDE-153, and BDE-209 have different MOE values, usually a MOE larger than 2.5 is enough to consider that there is unlikely to be a health concern (EFSA, 2011a).

Several papers regarding PBDE occurrence in wild, farmed, and processed seafood and seafood products have been published in recent

years (Table S1). The number of PBDE congeners analyzed varied from 3 to 40 (Ameur et al., 2020; Corsolini et al., 2016), and the main ones were the BDE-28, 47, 99, 100, 153, 154, 183, and 209. In general, BDE-47 is usually the most abundant congener reported in the biota samples (Cappelletti et al., 2015; Guo et al., 2017). A possible reason for BDE-47 predominance might be the assimilation efficiency of BDE-47 and BDE-99 congeners, which is reported as significantly higher than other congeners, such as BDE-28 and BDE-153 (Dietrich et al., 2015), and the effective debromination of BDE-99 to BDE-47 through biological removing the bromine atom from the meta-position in the molecule (Roberts et al., 2011), as well as when exposed to ultraviolet light (ATSDR, 2015), as example. Meanwhile, BDE-209 presented 97% of PBDEs contribution in seafood from Bohai Bay in China (Zheng et al., 2016). Such predominance can occur due to the use of decaBDE formulations in recent years (Abbasi et al., 2019).

Levels of the sum of PBDEs in seafood and seafood products recently published from around the world comprised the range of 10^{-3} to 10^{4} in the orders of magnitude, mainly in wet weight basis, which is an important basis to report concentrations of pollutants in parallel to human consumption. Those compounds (sum of 18 PBDE congeners – BDE 28, 47, 66, 85, 99, 100, 138, 153, 154, 183, 196, 197, 202, 203, 206, 207, 208, and 209) reached the concentration of 50,300 ng g^{-1} lipid weight (lw) in predatory fish tilapia, *Oreochromis* spp., from an e-waste site in Guangdong Chinese Province (Tao et al., 2019). In European environments, the highest PBDE levels were reported in wild fish *Abramis brama* from river Po (Italy) reached 912 ng g^{-1} dry weight (dw) of concentration, related to the high human population density in the monitored areas (Luigi et al., 2015). Considering the exposure of those organisms to the PBDEs in the environment, it is clearly observed that organisms inhabiting near dumpsites are more susceptible to achieve huge concentrations of those BFRs.

PBDEs are pointed out as endocrine disruptors (EFSA, 2011a). Most epidemiological studies suggest association between PBDEs and hyperthyroidism (clinical and subclinical) and disfunction of neurophysiological function (EFSA, 2011a). Due to the limited available epidemiological and toxicological data on PBDE congeners, access to their potential health risks continues as a challenge (El Megdiche et al., 2017). A recent study on BDE-47 congener in fish (40 days of parental exposure) demonstrated no evidence of effects on either reproduction or in the early life stage fish (González-Doncel et al., 2017). However, the synergism between BDE-47 and BDE-99 showed higher negative effects on thyroid hormone triiodothyronine (T3) reduction in exposed juvenile Chinook salmon (36.8 ng mixed PBDEs/g wet weight; ww), in comparison to treatment groups exposed separately to higher concentrations of BDE-47 or BDE-99 (Arkoosh et al., 2017). Exposure of parent zebrafish to BDE-209 can cause developmental toxicity in offspring and disruption of the thyroid endocrine system of offspring (Han et al., 2017). In fact, there is still no assurance about the effects of environmentally detected levels of PBDEs.

2.1.2. Polybrominated biphenyls (PBBs)

PBBs were commercially produced in three technical products - with hexaBBs, octaBBs, and decaBBs as main constituents - until the 1980s (except decaBB). Since 1983, PBBs formulations are under regulation in the European Union (EU) and may not be used in textile articles, which eventually will be in contact with the skin, and in 2006 another regulation defined that new electrical and electronic equipment available on markets shall not contain PBBs as FRs (EFSA, 2010). Although under regulation, there is a maximum tolerable percentage regarding the presence of PBBs in the homogeneous materials of 0.1% by mass (EFSA, 2010). The TDI established by World Health Organization consider 0.15 μg/kg b. w^{-1} day^{-1}. Furthermore, because non-*ortho* PBBs are dioxin-like in respect to their effects, the Committee of Toxicity recommends to use the toxicity equivalence factors (TEF) (chlorinated congeners) and to combine the toxicity equivalents (TEQ) of brominated contaminants, as well as the WHO-TEQ for chlorinated dioxins to provide an indication of the intake of chemicals with dioxin-like properties (EFSA, 2010).

Few studies on PBB occurrence in seafood were performed between 2015 and 2020 years, mainly in fish samples from Chinese reservoirs, Polish markets, Laurentian Great Lakes (USA), United Kingdom, European coastal North Atlantic, and markets from Taiwan (Table S1). The number of PBB congeners studied in the last years ranged from 2 to 22 including the congeners: PBB-1, 2, 3, 4, 7, 8, 9, 10, 15, 25, 26, 29, 30, 31, 38, 49, 53, 101, 103, 153, 155, 209 (Ding et al., 2019). Wild sea bass, herring, mullet, mackerel, and sardine from the United Kingdom, Norway in the North and the Algarve in the South, reached the maximum level of 1.0 ng g^{-1} ww (sum of PBB 49, 52, 80, 101, 153 and 209) (Zhihua et al., 2018). Another result to highlight is the study of Falandysz et al. (2020) in which edible cod liver oils and canned cod from Polish markets were analyzed and pointed out the maximum contribution of 1.4 ng g^{-1} lw in the sum of PBB-49, 52, 77, 80, 101, 126, 153, 169, 209.

2.1.3. Hexabromocyclododecanes (HBCDDs)

HBCDDs are brominated lipophilic organic compounds and were widely used as additive flame retardants, their stereoisomers are substituted with six bromines in the molecule, is formed through the addition of bromine atoms to 1,5,9-cyclododecatriene. The technical products of HBCDD are formed mainly by the stereoisomers α-, β-, and γ-HBCDD, although other congeners may also be present (δ- and ε-HBCDD). The occurrence of HBCDDs in the environment, food, and humans raised health concerns and the three main stereoisomers in technical products were selected by CONTAM Panel to be of primary interest (EFSA, 2011b).

Those compounds were listed in the 6th meeting of the SC-POPs due to their toxicity, stability, and long-range transport, being classified as persistent organic pollutants (POPs) (UNEP, 2017). HBCDDs were identified as priority hazardous substances under the Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy of the European Commission, and the Directive number 2013/39/EU of the European Parliament (EC, 2013a, 2013b). Recently, with the objective to protect human and environmental health by prohibiting, phasing out, or restricting HBCDDs manufacture and use, HBCDDs were listed in Annex I, Part A of the Council on POPs of European Parliament number 2019/1021 (EC, 2019). For HBCDDs, due to the same limitations and uncertainties as for PBDEs, usually a MOE larger than 8 is enough to consider that there is unlikely to be a human health concern (EFSA, 2011b).

In the last years, several studies evaluated the presence of HBCDDs in seafood (wild, farmed, and/or processed) focusing on the three main stereoisomers from technical products (Table S1, Supplementary material). HBCDDs reached levels ranging from below the limit of detection (<LOD) to 1020 ng g^{-1} lw (Table S1), with the higher levels being reported in wild fish from rivers and an e-waste recycling site in South China, with fish from that e-waste site (mud carp and snakehead) presenting the highest levels (640 and 518 ng g^{-1} lw, respectively) among the studied organisms (Sun et al., 2018b). HBCDD levels in European seafood ranged from <LOD to 45.6 ng g^{-1} ww, with the highest levels reported in wild fish from different lotic and lentic German ecosystems (Rüdel et al., 2020).

Recently, over 6000 analytical results for HBCDDs in food were used to estimate the exposure (dietary surveys and age groups) in the European population (Schrenk et al., 2020. Fish were the most expressive contributors to the chronic dietary lower-bound (LB) evaluation, revealing, based on the resulting MOE, that there is no case of health concern (although with an exception for breastfed infants with high milk consumption) in the current dietary exposure to those stereoisomers across European countries).

According to the uptake of the risk assessment of HBCDDs in food, their main targets for toxicity are the liver, reproductive and immune systems, neurodevelopment, and thyroid hormone homeostasis. Those

compounds are considered not genotoxic and the available evidence indicates that they are not carcinogenic (Schrenk et al., 2020).

2.1.4. Tetrabromobisphenol A (TBBPA) and other brominated phenols

TBBPA and its derivatives are widely used as FRs (EFSA, 2011c). Other brominated phenols, similarly to TBBPA, are also produced by binding 2, 3, or 5 bromine atoms in the phenol (EFSA, 2012b; 2011c). TBBPA is a lipophilic BFR that is covalently bound to several products, such as epoxy, vinyl esters, and polycarbonated resins, and its derivatives are present in polymer manufactures as an additive or reactive compounds (EFSA, 2011c; Lee et al., 2020). For TBBPA, due to the same limitations and uncertainties as for PBDEs and HBCDDs, usually a MOE larger than the default value 100 is enough to consider that there is unlikely to be a human health concern (EFSA, 2011c).

Numerous brominated phenols occur naturally in the environment, mainly di- and tribromophenols, and are commonly reported in biota tissues (Bidleman et al., 2019; Gribble, 2015). Brominated phenols identified as FRs comprise the 2,4-dibromophenol (2,4-DBP), 2,4,6-tribromophenol (2,4,6-TBP), pentabromophenol (PBP), and tetrabrominated bisphenol S (TBBPS) (EFSA, 2012b). In this way, some brominated phenols are considered as having both origins (naturally and anthropogenically produced). Due to the same limitations and uncertainties as for PBDEs, HBCDDs, and TBBPA, the establishment of a TDI for other brominated phenols (e.g. 2,4,6-TBP) was not appropriate, as well as a MOE (EFSA, 2012b).

Seventeen studies on TBBPA and other brominated phenols, including derivatives, were available worldwide between 2015 and 2020 on wild, farmed, and processed organisms, such as bivalves and fish (Table S1). TBBPA was the most reported compound in those studies (Table S1), with levels reaching 158 ng g^{-1} lw in farmed bivalve species from South Korea bays (Gu et al., 2017). In Europe, TBBPA was reported in seafood from markets, estuaries, freshwater, and from the Mediterranean Sea, with maximum values of 24.5 ng g^{-1} lw in seafood from European markets of six different countries (Aznar-Alemany et al., 2017).

Very limited studies on other brominated phenols were available in recent years, all of them in Europe. The congener 2,4,6-TBP was reported in mussels from European markets with a mean of 99 ng g^{-1} lw (Aznar-Alemany et al., 2017). In seafood products from Belgian markets, Poma et al. (2018) reported a mean of 2.07 ng g^{-1} ww of six brominated phenols and their derivatives (4-BP, 24-DBP, 26-DBP, 246-TBP, 246-TBA, TBBPS), with canned king crab and fresh gray shrimp presenting the highest levels (22.2 ng g^{-1} ww), and 2,4,6-TBP being the most detected congener (63%, ranging from 15 ± 52 pg g^{-1} ww to 358 ± 865 pg g^{-1} ww).

In the period 2015–2020 few studies were published evaluating the exposure of organisms to TBBPA. Ji et al. (2016) observed gender-specific alterations of metabolites and proteins in mussels from aquaculture farm from China, after exposure to TBBPA, as well as losses of frontal and lateral cilia and apoptosis in abfrontal cells in both female and male mussels. *In vivo* exposure with 2,4,6-TBP (0.4 mmol kg^{-1}) produced decreases in P-glycoprotein, which is an important transporter in the blood-brain barrier. Decreases in P-gp function at the BBB not only elevate the risk of increased deposition of toxic xenobiotic agents to the brain but also systemically may contribute to significant changes in absorption and elimination and altered pharmacokinetics of important metabolites throughout the body (Trexler et al., 2019).

2.1.5. Alternative (emerging and novel) brominated flame retardants

In the early 2000s, alternative halogenated flame retardants (such as the brominated ones - ABFRs) were applied as PBDEs and PBBs replacement products, in order to maintain the combustion delay in ordinary products (UNEP, 2008). Many of the ABFRs were removed from global markets once raised concern to environmental and human health (Bergman et al., 2012).

Although there is no legislation on the levels of ABFRs in foodstuffs, those FRs are reported in several environmental compartments, which, due to their occurrence, might lead to concern of human and environmental health (Guo et al., 2017; Li et al., 2015; Sühring et al., 2016). EFSA reports the existence of twenty-seven emerging/novel BFRs (EFSA, 2012a).

Emerging and novel BFRs were reported recently in seafood. The number of studied compounds in each paper ranged from 1 to 23 (Table S1). Levels of ABFRs reached 13,500 ng g^{-1} lw in wild tilapia, *Oreochromis* spp., from an e-waste dumpsite in China (sum of 5 compounds: DBDPE - decabromodiphenyl ethane; BTBPE - 1,2-bis(2,4,6-tribromophenoxy) ethane; HBB - hexabromobenzene; PBT - pentabromotoluene; and PBEB - pentabromoethylbenzene) (Tao et al., 2019). In Europe, several studies monitored different regions and countries (Greece, Italy, German, Spain, Norwegian, Slovenia, Croatia, Bosnia and Herzegovina and Serbia), analyzing samples collected in the environment (wild and farmed species) or bought in markets. Fish species presented higher ABFR frequency, with predominance of HBB (Giulivo et al., 2017; Sühring et al., 2016; Trabalón et al., 2017; Xu et al., 2017).

Three of the alternative BFRs pointed out by EFSA for monitoring priority in food samples (EFSA, 2012b; 2012a; 2011a; 2011c), as well as their occurrence in seafood samples in the last six years are described herein.

HBB has been used as an additive to plastic, electronic devices, and paper in Japan; however, there are no reports of HBB production in Europe (EFSA, 2012a). The reported levels of HBB in seafood are generally low. HBB was presently reaching a mean of 1.0 ng g^{-1} lw in the Great Lakes (USA) fish - lake trout, *Salevinus namaycush*, and walleye, *Sander viteus* (Guo et al., 2017). In a recent study evaluating the presence of HBB in mussels from six European countries (Albania, Italy, Norway, Portugal, Spain and the United Kingdom), HBB was not detected (LOD of 0.20 ng g^{-1} lw) (Aznar-Alemany et al., 2018). In contrast, mollusk bivalves from the Chinese Bohai Sea showed a mean level of 2.5 ng g^{-1} lw in their tissues (Fu et al., 2019). Furthermore, seabream fish from Greek markets reached a level of 66 ng g^{-1} lw of HBB (Aznar-Alemany et al., 2017).

DBDPE has been used in almost the same applications as DecaBDE formulation. It was introduced more than thirty years ago in plastics, rubber products, electronic and electrical applications (EFSA, 2012a). DBDPE was not detected in seafood species available in European markets (Aznar-Alemany et al., 2017), as well as in wild freshwater fish species from three European rivers (Giulivo et al., 2017). In wild fish (lake trout and walleye) from the five Great Lakes (USA), DBDPE was rarely detected, with a concentration range of 0.02–0.91 ng g^{-1} lw (Guo et al., 2017). This low contribution is also reported in previous works (Vandermeersch et al., 2015). Different bivalve species from the Chinese Bohai Sea were reported with a DBDPE mean of 21.7 ng g^{-1} lw in their tissues (Fu et al., 2019).

BTBPE is produced since the mid-1970s as an additive FR. It was applied in polystyrene, resins and thermoplastics in substitution of OctaBDE formulations. In Europe, BTBPE was produced as a low-volume chemical (EFSA, 2012a). Few studies in the recent literature reported the presence of BTBPE in seafood. Among them, levels of BTBPE in fish from Laurentian Great lakes reached no more than 0.6 ng g^{-1} lw, being detected at a rate of 10.8–41.5% (Wu et al., 2019), and in lake trout and walleye also from the Great Lakes, BTBPE were rarely detected, with a range of 0.05–0.39 ng g^{-1} lw (Guo et al., 2017). The highest level reported for BTBPE in fish reached a mean of 1.12 ng g^{-1} lw in a sediment-associated fish species *Plecostomus* (*Hypostomus plecostomus*) from Chinese rivers (Sun et al., 2018a).

Overall, in the last year's most of the studies on BFRs were performed in European countries despite the large production of BFRs are mainly in other continents such as Asia and North America (Fig. 1). Among the BFRs, PBDEs were the most evaluated compounds in seafood, especially in wild fish (see Table S1)



Fig. 1. Occurrence of BFRs by continent and country.

2.2. Pharmaceuticals

Pharmaceutically active compounds (PhACs) are widely used for treatment of human and animal diseases and health promotion. Such drugs are high production volume chemicals including therapeutic groups, as antibiotics, lipid regulators, psychiatric and anti-inflammatory drugs, *etc.* (Kaplan, 2013). They are considered emerging contaminants and some of them can interact, at very low levels, with cell receptors, causing adverse effects on human health and wildlife balance (Fabbri and Franzellitti, 2016; Almeida et al., 2020; Kroon et al., 2020). PhACs are released in aquatic environments through urban sewage treatment plants discharges (Monteiro and Boxall, 2010; WHO-World Health Organization, 2011), or, on a smaller scale, animal production, aquaculture, and industry effluents (Sui et al., 2015; Wandermeersch et al., 2015). Some of these compounds bioaccumulate in aquatic wild animals and can contaminate consumers through seafood ingestion. Moreover, some PhACs can act as endocrine disruptors because they exhibit hormone-like effects or interfere with the hormonal signals of an organism.

In addition to synthetic steroid hormones, which are one of the most critical endocrine active pharmaceuticals (Christen et al., 2010), non-steroidal anti-inflammatory drugs (NSAIDs) have been shown as potential endocrine disruptors (Schmidt et al., 2011; Chen et al., 2019; Godoi et al., 2020). Paracetamol, diclofenac and its metabolite (4′-hydroxydiclofenac), ibuprofen, and naproxen showed different ways to interact with the endocrine system of aquatic organisms under acute or chronic exposure and presenting possible negative effects on their reproduction (Choi, 2018; Han et al., 2010; Kristensen et al., 2011; Gonzalez-Rey and Bebianno, 2012; Stepanova et al., 2013; Klopčič et al., 2018; Kwak et al., 2011). Carbamazepine did not cause lethal effects under acute exposure in crustaceans but showed significant effects on their molting and fecundity at low concentrations as 0.03 $\mu g.L^{-1}$ (Chen et al., 2019). In fishes, environmentally relevant concentrations (10 and 100 $\mu g.L^{-1}$) could form hermaphrodite gland in males and ovum maturation in females (Yan et al., 2018). The metabolite of the most known pesticide dichlorodiphenyltrichloroethane (DDT), *o,p′*-DDD, is used to treat adrenocortical carcinoma (ACC) and Cushing disease in Europe and the USA as the registered pharmaceutical Lysodren. Evidence of experiments with this compound suggests that it should be considered an adrenal EDC for humans and wildlife (UNEP et al., 2013). The selective serotonin reuptake inhibitor (SSRI) class of antidepressants is also known to interfere with the endocrine system in wildlife (UNEP et al., 2013). An example is fluoxetine which has shown the potential to affect sex hormones, reproductive function, behavior, feeding, and energy metabolism in fish and other aquatic vertebrates (Oakes et al., 2010; Peters and Granek, 2016). Furthermore, benzafibrate, flutamide, venlafaxine, fadrozole, finasteride, propylthiouracil, and other PhACs also seem to have potential (neuro) endocrine disruption (Kitahori et al., 1984; Fenske and Segner, 2004; Velasco--Santamaría et al., 2011; Best et al., 2014). Their chronic toxic effects in aquatic organisms have been observed in relatively lower concentrations. This increases the concern and importance not only of controlling the use of these medicines but also of knowing their synergistic effect in the presence of other compounds since substances are not isolated in the environment.

Although their endocrine disruption potential has been shown, none of the PhACs is yet recognized as EDCs or suggested as potential EDCs by existing guidelines (IPCP, 2016). Only the synthetic non-steroidal estrogen quadrosilan is inserted in the main list considered by UNEP (IPCP, 2016). Besides this hormone, no pharmaceuticals are among the 45 compounds included on the list of EDCs by the United Nations in 2018. Notwithstanding, several compounds used in medicines as additives (e.g., parabens, triclosan, octamethylcyclotetra-siloxane, tert-butylhydroxyanisole) are recognized as EDCs. Chemical intermediates to produce drugs, as resorcinol and 4-nitrophenol are also identified. On the other hand, some PhACs have been highlighted for screening purposes. Is the case of erythromycin, lindane, nitroglycerin, and quinoline, which were included in the Second List as candidates under the endocrine disruptor screening program due to their occurrence in sources of drinking water (EPA, 2014). Along with hormones, diclofenac was included in the European monitoring list of emerging aquatic pollutants for future regulation (EC, 2013a, 2013b). Equally important, dozens of

PhACs are listed by EPA in order to direct chemicals for potential endocrine disruptor screening and testing (EPA, 2012).

The existing legislation for live animals and foodstuff of animal origin is focused on residues of veterinary medicinal products (Regulation (EU) No 37/2010) and hormones. Among them, antibiotics are the main PhACs legislated. Diclofenac has its maximum residual limits (MRLs) established only for bovine and porcine (ECR, 2010). Annual reports issued by EFSA summarize the monitoring data on these compounds in livestock, including aquaculture. About 1% of aquaculture total production is tested in European Union. The last report (2018) showed few non-compliant samples concerning NSAIDs and PhACs (EFSA, 2020). Thus, other drugs widely produced for human consumption are not yet regulated, which may threaten both the health of marine organisms and seafood consumers. Currently, environmental risk assessment (ERA) is performed by companies during the development of new medicines and assessed by European Medicine Agency (EMA) to approve their use protecting terrestrial and aquatic ecosystems (EMA, 2018).

Wastewater treatment plant effluents and river water have received major focus since the first detection of pharmaceuticals in the aquatic environment in the 70's decade (Tabak and Bunch, 1970; Madikizela et al., 2020). In contrast, their occurrence as an organic contaminant in seawater was discovered only in 2001 (Weigel et al., 2001). Since then, most studies have focused on seawater contamination, increasing the need for biota monitoring, which is relatively sparse. Knowledge about bioaccumulation of these compounds in seafood is fundamental for the population risk assessment and, consequently, it can be an effort for national and international legislation regarding MRLs. Table S2 shows recently published papers (from 2015 to the present) on the determination of PhACs that have demonstrated (for at least one study) endocrine disruption potential, in seafood. Highly consumed NSAIDs were the most abundant PhACs in seafood, although studies have not shown concentrations with endocrine-disrupting concern. Ibuprofen reaches up 1606 ng g^{-1} ww (mean 562 ng g^{-1}) in edible fish and bivalves farmed in Pearl River Delta, China (Xie et al., 2019; Table S2), while diclofenac concentrations ranged from 551.8 to 1812 ng g^{-1} dw in wild fishes (panga, hottentot and snoek) from Kalk Bay harbor in South Africa (Ojemaye and Petrik, 2019). This exemplifies the human exposure to potential EDCs through both wild and farmed seafood species. Furthermore, studies have also shown bioaccumulation of PhACs in all fish parts (Álvarez-Muñoz et al., 2015; Kim et al., 2017, Ojemaye and Petrik, 2019; Ismail et al., 2021). In South Africa, diclofenac present in the fillet showed a very high chronic and acute risk for human consumption (Ojemaye and Petrik, 2019). However, human health risks assessed via seafood consumption in most studies seem to be negligible in relation to pharmaceuticals (Xie et al., 2019; Xao et al., 2021; Ismail et al., 2021). Dexamethasone, which has acceptable daily ingestion of 2 μg kg^{-1} bw, had higher concentrations in fish liver (43.56 ng g^{-1} dw), although it has also been found in reproductive organs and muscle (Ismail et al., 2021). Paracetamol presented levels up to 33.26 ng g^{-1} dw in the liver, gills, and intestine of panga (*Pterogymnus liniarius*) from Kalk Bay harbor, South Africa (Ojemaye and Petrik, 2019). In Europe, PhAC levels in seafood were lower than those observed in Asia and Africa, being the Mediterranean mussel (*M. galloprovincialis*) the most contaminated species (Rocha et al., 2018; Álvarez-Muñoz et al., 2019; Miossec et al., 2020). Venlafaxine (36.1 ± 4.0 ng g^{-1} dw) and citalopram (20.6 ± 0.2 ppb dw) prevailed in the edible content of mussels from Italy (Álvarez-Muñoz et al., 2015). In Spain, diclofenac (28.3–30.3 ng mL^{-1}) was the most abundant compound in hemolymph of this species (Álvarez-Ruiz et al., 2021). Carbamazepine, in turn, showed levels below the limit of quantification in almost all studies (Table S2). In South America, only two studies monitored these compounds in seafood. Maximum levels ranged from 0.19 μg kg^{-1} ww of diazepam to 1.9 μg kg^{-1} ww of propanolol in freshwater fish muscle (sabago, boga and dorado) from Uruguay River (Rojo et al., 2019). Finally, to the best of our knowledge, the only study in marine biota described the occurrence of PhACs in two coastal areas in Brazil (Parnaiba River Delta and Sepetiba Bay) (Mello et al., 2022). Although most compounds had concentrations below LOQ, an antibiotic prohibited in animal foods in Europe (chloramphenicol) were detected in fishes and mussels.

Overall, venlafaxine, carbamazepine, and diclofenac were the PhAC most studied in the last 6 years in seafood (Fig. 2 and Table S2). Similar to those verified in BFRs, wild species were the most evaluated followed by farming. However, there is also a lack of studies pointing to the evaluation of food processing conditions on PhACs in seafood, aiming for potential human exposure assessment. In fact, the impact of cooking as a mitigation strategy to reduce exposure levels to these contaminants shall not be disregarded (Salaramoli et al., 2016; Alves et al., 2017; Sobral et al., 2020).

2.2.1. Hormones

Human reproductive and fertility functions are highly regulated by endogenous hormones. Endogenously produced estrogens (e.g. estrone, 17β-estradiol) and progesterone are key for a well-regulated female reproductive health, exerting very important influence in the regulation of the menstrual cycle and in the early maintenance of a healthy pregnancy. On the other hand, testosterone plays a major role in male reproductive health (Amenyogbe et al., 2020; Azizi-Lalabadi, M. and Pirsaheb, M., 2021).

Despite the importance of this hormones to endocrine function to the animals, their extensive excretion, extensive human use and inadequate sewage removal, results in a widespread occurrence in aquatic ecosystems. Besides natural occurring hormones, attention should also be drawn to synthetic estrogens as contraceptive estrogens (e.g. 17α-ethynilestradiol), as well as and diethylstilbestrol (DES) which, as although its human use has been banned, it is still used to enhance the growth of livestock (Celia et al, 2018; Weber et al., 2019; Moore et al., 2020; Azizi-Lalabadi, M. and Pirsaheb, M., 2021). This can lead to their bioaccumulation in aquatic animals and consequently generate nefarious effects, namely the feminization of male fish, altered endocrine systems, inhibit the development of sexual organs, having even the potential of causing hormone-related cancers in humans, as are prostate and breast cancers (Celia et al, 2018; Weber et al., 2019; Moore et al., 2020; Azizi-Lalabadi, M. and Pirsaheb, M., 2021). The potentially dangerous effects that these compounds may pose to human health have led regulatory authorities to impose limits on their human consumption. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an acceptable daily intake (ADI) of 0–0.05 μg kg^{-1} bw for 17β-estradiol, 0–30 μg/kg bw for progesterone, and 0–2 μg/kg bw for testosterone (JECFA, 2000). Also, currently, 17β-estradiol and 17α-ethynilestradiol are on the European Commission's watch list for possible future inclusion in the priority substance list of the European Water Framework Directive (Directive, 2013/39/EU).

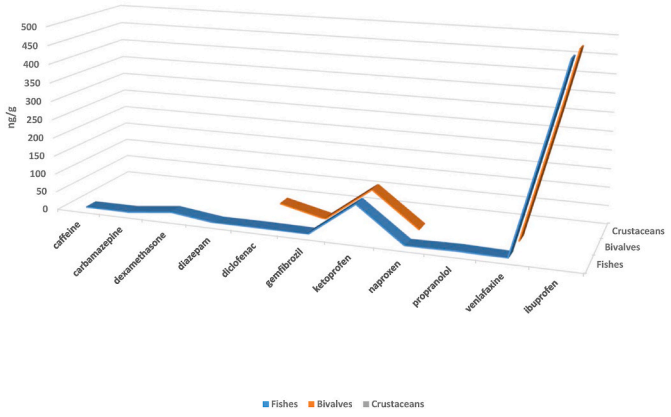


Fig. 2. Higher average of pharmaceutical in wild seafood reported from 2015 to 2020 (see more details in Table S2).

Most recent studies in seafood have been conducted in China (Table S3). Natural occurring hormones, as well as 17α-ethynilestradiol, have been detected in a myriad of fish and mussel species, with concentrations reaching levels as high as 315.6 ± 6.5 ng g^{-1} dw in native mussels collected in Shenzen, China (Chiu et al., 2018). DES, known as a cancer-causing synthetic estrogen (IARC Group 1) has been detected in wild fish species purchased from fishermen in southern China (Zhou et al., 2018), an alarming sign that humans may still be exposed to this hazardous chemical.

2.3. Bisphenols

Bisphenols are a group of contaminants to which humans are ubiquitously exposed. The main route of human exposure to these compounds is through the diet, although it also occurs through dust inhalation and skin contact. Bisphenols are mostly present in epoxy resins that form the inner coating of metal cans, thus preventing their corrosion and leakage of harmful heavy metals. The most commercialized bisphenol is bisphenol A (BPA), which is a known endocrine-disrupting compound (EDC). BPA has been shown to have estrogenic activity and thus been linked with harmful health events, such as altered fertility, low birth weight, metabolic diseases (e.g. type 2 diabetes and obesity), and even hormonal-related cancers such as breast and prostate cancer (Wazir and Mokbel, 2019; Rochester, 2013). These alarming scientific findings led regulatory agencies and governments worldwide to face BPA with caution, establishing severe limits on its consumption – EFSA set a temporary-TDI of 4 μg kg^{-1} bw/day in 2015 (EFSA, 2015a, 2015b) - and even banning it from some particular objects of daily use as baby bottles for example (Government of Canada, 2010; FDA, 2012, EFSA, 2015a, 2015b). Nowadays, EFSA are committed to re-evaluate BPA toxicity; after completed the development of the BPA hazard assessment protocol in 2017 and tested the study appraisal methodology in 2019, EFSA plans to finalise BPA assessment in 2022.

In response to the ban and extreme regulation of BPA, industries have thus shifted towards the replacement of BPA by structural analogs. To this date, 16 BPA analogs have been reported. The trouble with BPA analogs is that very limited evidence exists regarding their effects on human health. In fact, studies have shown that these alternative compounds may not be as innocuous as initially expected, having for example BPS, BPF, BPB, and BPAF been shown to have effects similar to or even greater than the ones presented by BPA (Chen et al., 2016; Martínez et al., 2020).

By far, BPA has been the most studied bisphenol in general and in seafood in particular (Table S4). Although, there is still very limited evidence when it comes to the study of BPA analogs and as these compounds are the result of very slight alterations in the chemical structure, it is imperative that more research is produced analyzing the presence of BPA analogs in seafood. Recent studies have shown that BPA contamination is ubiquitous among various seafood matrices, with levels reaching concentrations as high as 4277.40 ng g^{-1} dw in cockles for example (Álvarez-Muñoz et al., 2019). As regards BPA analogs, few studies are available, although levels can range from < LOD to 408.0 ng g^{-1} dw in seafood matrices (Tian et al. 2020), which highlights the importance of close monitoring of these increasingly common environmental contaminants.

Overall, most of the studies have been performed in processed seafood, so there is a lack of evaluation on bioaccumulation and biomagnification of bisphenols in the seafood chain. Preferential distribution of a bisphenol into a trophic level may cause localised effects, and so single compartment measurements may fail to characterize the potential risk to all chain. Monitoring studies in analogs of BPA are recommended due to the replacement made by the plastic industry in the recent years.

2.4. Personal care products (musk and UV filters)

Personal care products (PCPs) are a unique group of emerging environmental contaminants, due to their inherent ability to induce physiological effects in humans at low doses. An increasing number of studies have confirmed the presence of various PCPs in different environmental compartments, which raises concerns about the potential adverse effects to humans and wildlife (Ebele et al., 2017). The PCPs are divided into four groups: 1. Disinfectants, 2. Conservation agents, 3. Fragrances and 4. UV filters. Taking in consideration their tendency to bioaccumulate in aquatic biota and their EDCs properties, the main focus herein will be UV-filters (benzophenones, camphor derivatives, cinnamate derivatives) musk fragrances and disinfectants (triclosan).

UV-filters are compounds used in sunscreen and personal care products as well as in some plastics, paints, and textiles. Due their frequent use particular as personal care products, they are regularly released into the environment. For this reason, the marine toxicity of UV filters has recently received special attention. They have been found to be bioaccumulative in marine organisms and biomagnified through the marine food chain (e.g. corals, crabs, shrimps, prawns, squids, fish, dolphins, and seabirds) (Gago-Ferreiro et al., 2013; ; Castro et al. 2018; Tsui et al., 2017), as well as, demonstrated to cause different biological and toxicological responses (e.g. survival, behavior, growth, development, and reproduction, among many others) (Araújo et al., 2018; Corinaldesi et al. 2018). Although, toxic effects in humans after such a prolonged low dose exposure to UV-filters and musks have hardly been investigated. Kunz and Fent (2006) demonstrated that UV-filters show anti-estrogenic, androgenic, and/or anti-androgenic activity through human estrogen and androgen receptor assays.

UV-filters authorized for use in the EU are regulated (Regulation (EC) No. 1223/2009) and have to comply with a series of safety standards; however no legislative limit has been established for the aquatic environment. Exception for ethylhexyl methoxycinnamate (EHMC) which was included in the Watch List as a priority pollutant in surface waters according to the Environmental Quality Standards Directive (2008/105/EC, 2013a, 2013b).

Musk frangances are found in a wide diversity of products like household chemicals, soaps, and detergents, with high concentrations in personal care products. Since nitro musks [musk moskene (MK) musk xylene (MX) and musk ketone (MK)] have been withdrawn from the European market, polycyclic musks, in particular galaxolide (HHCB) and tonalide (AHTN) have been widely used. Due to their high lipophilicity, they tend to bioaccumulate, affecting the biota at low trophic levels. Despite no legal limits have been established in seafood, the European Chemical Agency (ECHA) provided human risk assessment reports for HHCB, AHTN, MX and MK, with Oral Non-Observed Adverse Effect Levels (NOAEL) of 150, 5, 7.5, and 2.5 mg kg^{-1}bw day^{-1}, respectively (ECHA 209). Regarding other musks such as cashmeran, celestolide, phantolide, traseolide, or HHCB-Lactone due to the lack of toxicological information threshold values for risk characterization have not been established yet.

In the last 6 years, several scientific studies have confirmed the presence of both UV-filters and musk in fish, crustaceans, and mussels of different origins and localization as reported in Table S5. The majority of the samples were originated or commercialized in European countries, the highest degree of UV-filter contamination was observed in monkfish (153 μg kg^{-1}; total of 11 compounds) while mackerel was the most contaminated species with musk (156 μg kg^{-1}; a total of 7 polycyclic musks and) (Cunha et al., 2018). In several surveys studies in seafood (Cunha et al. 2015, 2018; Gadelha et al., 2019; Rocha et al. 2018) the maximum value of UV-filters was found for octocrylene (OC) (to 103.3 μg kg^{-1}) while HHCB (to 414.40 μg kg^{-1}) was the most prevalent and abundant musk (Table S5). The ratio of positive samples for both OC and HHCB was usually high (around 30%) in comparison to other analytes in study (Cunha et al. 2018; Gadelha et al. 2019). No differences between wild and farmed fish were observed in the survey of Cunha et al. (2018).

In addition, the data of the same survey indicated that industrial fish experiences a similar situation with respect to exposure to UV filters, then both wild and farmed fish, while for musks lower levels were obtained in industrial samples than from other origins (Cunha et al., 2018).

Regarding to the factors that influence bioaccumulation/biomagnification, no correlation between UV-filters and lipids content in fish samples were perceived (Tang and ChengNieHanHan, 2019; Gago-Ferrero et al., 2015), but species-specific differences were observed (Cunha et al. 2018).

Geographic distributions of PCP may give an indication of the characteristics and sources of pollution, even if fish sometimes tend to change localities. In Cunha et al. (2018) survey was observed higher levels of both UV-filters and musk in seafood from the North-East Atlantic Ocean when compared with Asia, Atlantic southwest, Mediterranean, and the North Sea. High levels of EDs have been detected on the coast of China, in mussels, when compared to levels of these contaminants in these same organisms and other seafood from other regions. Castro et al. (2018) assessed the level of contamination of mussels from all over the Portuguese coast, observed that the highest levels of UV filters and musks were found in places with the highest population density and the highest level of industrialization. In this study it was also observed a temporal distribution of UV filters, with the higher levels in mussels being found after the summer, as expected due to the increase of recreational activities in these places during this season.

Concerning health risk from exposure to UV-filters and musk in seafood, the survey of Cunha et al. (2018) showed that the levels found in samples commercialized in Europe did not present a risk, since the values of daily consumption of this seafood are below the levels considered dangerous. Rocha et al. (2018) report also no danger to consumers of *Paracentrotus lividus,* notwithstanding the UV-filters found in these samples. In contrast, in the highly urbanized Guanabara Bay (Rio de Janeiro, Brazil), dietary muscle consumption represents from 0.3 to 15.2 ng UVFs.kg^{-1} bw. day^{-1}, and is higher than those reported for POPs (Molins-Delgado et al., 2018).

Triclosan (TCS) is also PCPs that have been the focus of scientific studies in the last years, due to their disruption endocrine actions and extensive exposure. Moreover, environmental transformation may turn it into chlorinated dibenzo-p-dioxins or methyl-triclosan (MTCS) which are either more toxic and more stable than TCS (Weatherly and Gosse, 2017). The Scientific Committee on Consumer Safety (European Commission, 2011) considered the NOAEL of triclosan of 12 mg/kg body weight/day. Triclosan act as antimicrobial agents and are widely used in ordinary products such as toothpaste, textiles, cosmetics, and other household products. A number of studies have demonstrated its presence and toxicity, particularly in fish, crustaceans, and microalgae (Zhang et al. 2016; Lu et al., 2019).

Yu and Wu (2015) determined EDCs in fish populations, where seven of 13 compounds were detected in blood, with total concentrations up to 39 ng. mL^{-1} (BPA, diclofenac, estrone, genfibrozil, ibuprofen, naproxen, triclosan). Seven chemical substances were detected in fish (bile, blood, and muscle). This discovery suggests the need for further studies in order to assess the presence of these compounds, their routes, and their destination in the environment.

Overall, metabolites of personal care products such as UV-filters, musk, and triclosan need to be considered in further research as well as the evaluation of their effects on the seafood.

2.5. Pesticides

Pesticides are defined as any compound applied to crops with the goal to prevent, destroy, or control harmful organisms, as well as to protect plant products during production, storage, and transport. These compounds include chlorinated pesticides such as DDT, hexachlorobenzene (HCB), mirex, endrin, lindane; pyrethroids such as cypermethrin and deltamethrin, as antiparasitic agents, and organophosphates such as azamethiphos as delousing farmed fish, as well as flubenzurons and emamectin benzoate as avermectins. The European Union makes available a database containing the authorized pesticides, as well as the maximum residue limits for each compound to wild, farmed, and/or processed seafood in that continent (Tornero e Hanke, 2016; FoodEx2 maintenance, 2019; EC 2020). Regarding limits of exposure, DDT is classified by IARC in the group 2 B; however for estimating the risk a ADI of 20 μg/kg bw is considered while for HCB, also classified in thee group 2 B by IARC, a ADI of 1 μg/L is considered, corresponding to an excess of lifetime cancer risk of 10^{-5} (FAO/WHO, 2022). For Aldrin/dieldrin an ADI of 1 μg/kg bw is given from the effect to central nervous system and liver toxicity in humans (FAO/WHO, 2022). For Endrin a ADI of 0.2 μg/kg bw is given from the effect to central nervous system (FAO/WHO, 2022). For Permethrin an ADI of 50 μg/kg bw is given from evidence of liver toxicity while for deltamethrin the ADI is 50 μg/kg bw (FAO/WHO, 2022), for Lindane a TDI of 5 μg/kg bw is given for evidence of liver and kidney toxicity (FAO/WHO, 2022), and for Azamethiphos an ADI of 25 μg/kg bw is considered (FAO/WHO, 2022).

Determination of pesticides in seafood is related by several authors around the world (Miranda and Yogui, 2016; Campillo et al., 2017; Kaczyński et al., 2017; Baqar et al., 2018; Riaz et al., 2018; Rocha et al., 2018; Kilercioglu et al., 2018; Gadelha et al., 2019; Lopes et al., 2020; Ferreira et al., 2020). Table S6 shows the published papers on pesticide contamination in seafood, from 2015 until the present.

2.5.1. Chlorinated pesticides

Chlorinated pesticides (OCPs) included endocrine-disrupting chemicals such as DDT, HCB, mirex, endrin, lindane, heptachlor, chlordane, endosulfan, methoxychlor, aldrin, and their metabolites. These agrochemicals can bioaccumulate in the human body and have an affinity for lipid-rich tissue. Some studies suggested that the contamination can be a contributor to the development of 2 diabetes mellitus (T2D), due to the interference in glucose uptake and adipocyte function, resulting in proinflammatory responses and disrupt energy metabolism (Burns et al. 2014; Maisano et al. 2016). The contamination is also related to neurodegenerative diseases and cancers (Govett et al., 2011). The most common way of OCPs exposure is through ingestion, but also can to expose by inhalation of dust and vapors, and by cutaneous absorption. These substances can follow the transplacental via, as well as be transferred by lactational transference, according to the physicochemical and structural characteristics of each one, such as octanol-water partition coefficient, molecular weight, polarity and degree of chlorination (Zhang et al., 2018a, 2018b). Individuals can be exposed to these compounds since before birth and early childhood (Lam et al., 2013; Burns et al. 2014). Despite the ban of certain OCPs in some parts of the world in the early 1970s, these compounds still contaminate the environment due to their persistence, and their half-life which is approximately of eight months to p,p'-DDT and about seven years to their metabolite p,p'-DDE, and about three years for α-HCH (Govett et al., 2011; Burns et al. 2014; Maisano et al. 2016; Bettinetti et al., 2016; Ferreira et al., 2020, Lee et al., 2020b).

Mussels, as an environmental sentinel, are broadly used as a biological indicator for monitoring coastal water pollution particularly OC pesticides (Ulusoy et al., 2016, Milun et al., 2016; Beyer et al., 2017; Campillo et al., 2017; Viñas et al., 2018, Milun et al., 2020) (Table S6). Among the OCPs evaluated, DDE, a DDT metabolite, is commonly found around Europe in fish mullet muscle samples (Kljaković-Gašpić et al. 2015) but also in zooplankton (Bettinetti et al. 2016) usually in levels below the limit maximum of residues. However, one sample of *Thunnus thynnus* from Straits of Messina, investigated by Saija et al. (2016), presented a DDT metabolite (until 122 ± 6.02 ng g^{-1} in 4,4′DDE) at higher levels than Italian legal limits (0.01 ng g^{-1}). Additionally, 4, 4′-DDE metabolite was the major contributor of total OCPs on Yellowfin tuna (*Thunnus albacares*) harvested from across the world's oceans (Nicklisch et al. 2017). Wild Bluefin tuna (*Thunnus thynnus*) was the most contaminated fish by OCPs in the FAO zone (Chiesa et al.2016).

Klinčića. et al. (2020a al., 2020b) investigated the levels and distribution of OCPs in samples of wild and farmed bluefin tuna from the Adriatic Sea, results indicated moderate pollution of OCPs in farmed tuna with levels decreased in the order: liver > muscle > branchiae, with concentrations of ΣDDTs between 347 and 778 ng.g-1 lw in wild, tuna. Munschy et al. (2020) reported generalized contamination of the southern oceans by POPs, although at low levels, with the higher levels being of DDT metabolites found in liver samples of swordfish (*Xiphias gladius*) of Seychelles.

2.5.2. Pyrethroids

Pyrethroids are the most used pesticides in household or post-harvest, due to their high efficiency against a large range of insect pests, with relatively low toxicity for mammalians species. Pyrethroids insecticides included compounds such as deltamethrin, silafluofen, cypermethrin, permetrin, terallethrin, bifenthrin, prallethin, and others (Schechter et al., 1949; Matsuo, 2019). Despite their low human toxicity, there have been several reports of poisoning related to both occupational exposure and deliberate ingestion of pyrethroids (Ramchandra et al., 2019). Pyrethroids act in several channels as sodium and chloride, and in proteins. Therefore, they can interfere with the excitatory neurons, inducing cholinergic syndrome (CS) as acute toxic signs, characterized by hyperexcitability, choreoathetosis, and profuse salivation; or Tsyndrome mainly characterized by tremors (Matsuo, 2019; Ramchandra et al., 2019).

Rocha et al. (2018) identified some pyrethroids insecticides, transfluthrin, cyhalothrin, permethrin, cyfluthrin, cypermethrin, fenvalerate, bifenthrin, phenothrin, fluvalinate, deltamethrin, and flumethrin, in roe or gonads of sea urchin (*Paracentrotus lividus*) from North West (NW) Portuguese coast, however at low levels, indicating a safe human consumption of this seafood (see Table S6 for more details). Gadelha et al. (2019) reported five pyrethroid (tetramethrin, bifenthrin, cyhalathrin, fenvalerate and permethrin) insecticides in farmed oysters from Aveiro (Portugal North Cost) with quantified levels of bifenthrin (0.03 ng.g-1 lw) and cyhalothrin (0.07 ng.g-1 lw).

2.5.3. Organophosphorus pesticides

Organophosphorus pesticides (OPs) as chlorpyrifos, methamidophos, malathion, parathion, dichlorvos (and others) were the most widely used insecticides in Europe. These substances can cause acute neurotoxicity mainly related to the inhibition of acetylcholinesterase (AChE) activity, but there is evidence that some of the developmental neurotoxicity (DNT) effects may be caused independently of AChE inhibition. The exposure while in the womb or at a young age can induce to DNT, which is toxic to the developing nervous system of the fetus or child. Children exposed to OPs can suffer neurodevelopmental effects as attention deficit disorders (ADHD) and autism. The current authorization for chlorpyrifos on the European market was expired on January 31, 2019 (Lim and Bolstad, 2019). Regarding seafood contamination, some studies have shown that feeds used in aquaculture might contain trace amounts of OPs (Jeon et al., 2016; Ismail et al., 2018). Moreover, wild fishes as Atlantic cod (*Gadus morhua*) that usually feed on leftover pellets near fish farms overtime may be vulnerable to OPs (Olsvik et al., 2019). Several studies about the determination of OPs in seafood have been published around the world (Table S6) (Riaz et. Al, 2018; Zhang et al., 2018a, 2018b; Azzouz et al., 2019; Mijangos et al., 2019; Lopes et al., 2020; Martins et al., 2020).

Overall, pesticide residues in seafood are still a huge issue nowadays. For example, despite some OCPs compounds have been restricted and banned, isomers of DDT are frequently detected in top predators, due to bioaccumulation and biomagnification along with the food web. Pyrethroids and OPs are also frequently detected in seafood as a result mainly of their increased use in agriculture. Fig. 3 show the maximum levels of OCPs, pyrethroids and OPs reported for relevant wild seafood based taking into account the data of Table S6, the major levels have been in detected in OCPs.

3. Conclusions

Over the past 6 years, extensive research showed a widespread presence of several endocrine disruptors in seafood with particular emphasis on emerging EDCs such as brominated flame retardants,

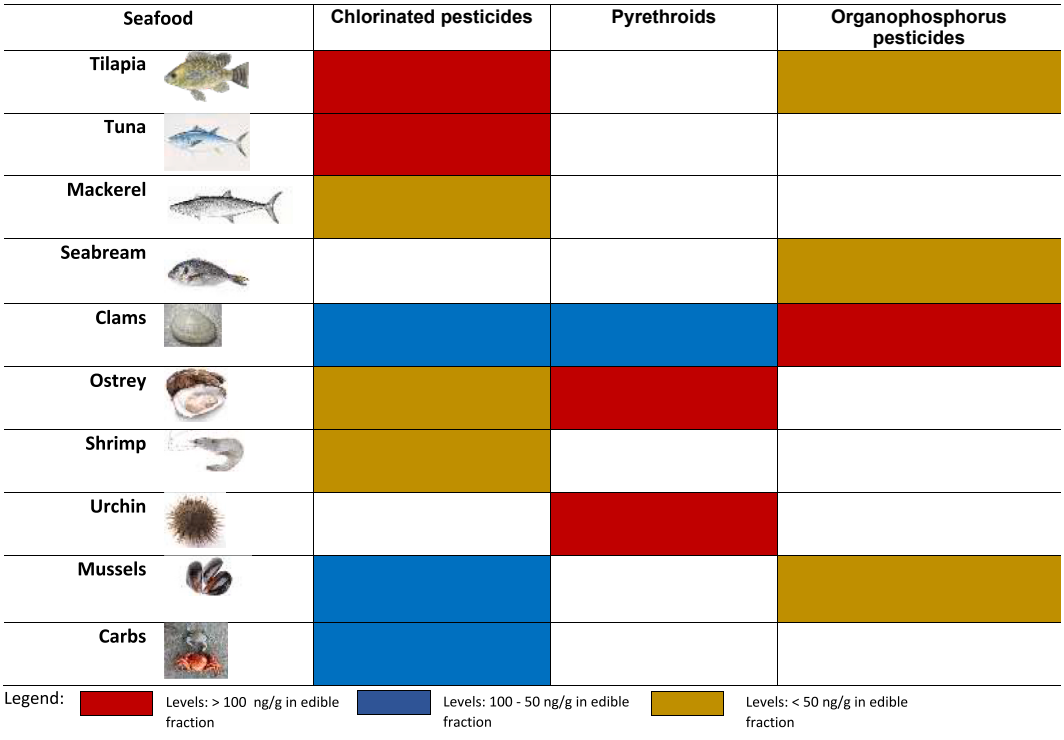


Fig. 3. Maximum pesticides residues levels in wild seafood reported from 2015 to 2020 (see more details in Table S6).

bisphenols, and personal care products. In addition, many regulated pollutants as pesticides have been shown to be regularly present in higher trophic levels. The occurrence of EDCs in seafood is a global problem, although it has been particularly studied in Europe and Asia. Notwithstanding the great amount of work already done, there are still considerable gaps in the identification and quantification of EDCs along the seafood chain including biotransformation products, because only a limited range of target analytes in each class of EDCs have been studied. Additionally, the number of studies targeting several classes of EDCs simultaneously is still scarce. More research in this area will be important for estimating the risk of human exposure to EDCs after ingestion of contaminated seafood. Although there is already some legislation on this subject, this review intends to highlight the need of more strict guidelines on the presence of EDCs in seafood, due to the health problems that can arise from it. Furthermore, the continuous environmental monitoring of the presence of those EDCs in seafood is needed to help public decisions in food and environmental safety, as well as in order to mapping hotspots of the presence of such toxicants.

Contribuitions authors

Sara C. Cunha: Conceptualization; Writing - Original Draft, **Writing – review & editing**, Supervision and Funding. D. Menezes-Sousa, F. V. Mello and J. Miranda: Writing - Original Draft, **Writing – review & editing.**Fabiola H. S. Fogaca, Mariana B. Alonso and João Paulo M. Torres - **review & editing.**José O. Fernandes: Conceptualization; **Writing – review & editing**, Funding.

Compliance with ethical standards

The authors declare no conflict of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112886.

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