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High production volume chemicals in seafood: A review of analytical methods, occurrence and population risk

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A B S T R A C T

The extended use of chemicals in both consumer and industrial products has led to a widespread ubiquity of compounds listed as high production volume chemicals (HPVs). Organophosphate esters, phthalate esters, benzothiazoles and benzotriazoles are part of this list, intended to prioritize their study to evaluate population's safety. Their fate throughout the environment reaches seafood, thus becoming accessible to the population via dietary intake. The reported negative effects led to the development of selective and sensitive methods capable of determining these compounds. The present review compiles the most used analytical methods for the determination of HPVs in seafood, mainly based on solid-liquid extraction, QuEChERS or pressurized liquid extraction, as extraction techniques, among others. The utility of efficient clean-up strategies is also discussed, aiming for reliable determinations while maintaining the instruments efficiency. Finally, an overview of the occurrence of these compounds in seafood and the exposure and risk associated to their ingestion is also discussed.
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1. Introduction

The continuous progress and adaptations to keep our current way of life have led society to become a major producer of many chemicals for both consumer and industrial products. This massive production of chemicals, whose impact on health is nowadays a concern, led the Organisation for Economic Co-operation and Development (OECD) to create a list of the chemicals with a production of over 1000 tones/year in at least one of the member countries [1]. In the same way, the US Environmental Protection Agency (EPA), also gathered the compounds produced in a minimum of 500 tonnes per year. The chemicals listed receive the name of High Production Volume Chemicals (HPV). The list is intended to prioritize chemicals in terms of the creation of data concerning

Abbreviations: 4TTR, 4-methyl-1-H-benzotriazole; 5TTR, 5-methyl-1-H-benzotriazole; ACN, Acetonitrile; APC, Aminopropyl silica; BBP, Benzyl butyl phthalate; BT, Benzothiazole; BTR, 1-H-benzotriazole; BTRs, Benzotriazole derivates; BTs, Benzothiazole derivates; ClBT, Chlorobenzothiazole; ClBTR, 5- chloro-1-H-benzotriazole; d.w., Dry weight; DBP, Dibutyl pththalate; DCM, Dichloromethane; DEHP, Di(2-ethylhexyl) phthalate; DnBP, Di-*n*-butyl pththalate; d-SPE, Dispersive solid-phase extraction; EDI, Estimated daily intake; EHDPP, 2-Ethylhexyl diphenyl phosphate; EI, Electron ionization; EPA, US Environmental Protection Agency; ESI, Electrospray ionization; EtAc, Ethyl acetate; EtOH, Ethanol; FPD, Flame photometric detector; GC, Gas chromatography; GCB, Graphitized carbon black; GC-MS, Gas chromatography-mass spectrometry; GM, Geometric mean; GPC, Gel permeation chromatography; H_2O, Water; Hex, Hexane; HPVs, High Production Volume Chemicals; HQ, Hazard quocient; HRMS, High resolution mass spectrometer; LC, Liquid chromatography; MeBT, 2-methylbenzothiazole; MeOH, Methanol; MeSBT, 2-(methylthio)benzothiazole; MSPD, Matrix solid-phase dispersion; NH_2BT, 2-aminobenzothiazole; NPD, Nitrogen-phosphorous detector; OECD, Organisation for Economic Co-operation and Development; OHBT, 2-hydroxibenzothiazole; OPEs, Organophosphate ester derivates; PAEs, Phthalate ester deterivates; PLE, Pressurized liquid extraction; PP, Polypropylene; QqQ, Triple quadrupole mass spectrometer; QTOF, Quadrupole- time of flight mass spectrometer; QTRAP, Quadrupole - ion trap mass spectrometer; QuEChERS, Quick, easy, cheap, effective, rugged and safe extraction; RfD, Reference dose; SCNMeSBT, 2-(thiocyanatomethylthio)benzothiazole; SIDS, Screening information datasets; SLE, Solid-liquid extraction; SPE, Solid-phase extraction; TBOEP, tris(2-butoxyethyl) phosphate; TCEP, tris(2-chloroethyl) phosphate; TCPP, tris(chloroisopropyl) phosphate; TnBP, tri-*n*-butyl-phosphate; TPP, triphenyl phosphate; TTR, Tolyltriazole; USE, Ultrasonic assisted extraction; UV, Ultraviolet detector; w.w., Wet weight; WWTP, Wastewater treatment plant; XTR, 5,6-dimethyl-1-H-benzotriazole.

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screening information datasets (SIDS) valuable to define risk assessments. It is, therefore, necessary to develop strategies and methods to control how these compounds are spreading worldwide and which are the implications of it. Organophosphate esters (OPEs), phthalate esters (PAEs), benzothiazoles (BTs), and benzotriazoles (BTRs) are only a few of the compound families which are included in this list, in which we can also find families such as benzotriazole UV light stabilizers (BUVS) [2,3] or synthetic phenolic antioxidants (SPAs) [4,5] Their characteristics enable the use of these compounds as fire ignition preventors (OPEs), plasticisers (PAEs and OPEs) and even corrosion inhibitors, ultraviolet light stabilizers, or antifungal agents (BTRs and BTs) (Fig. 1). The extended use of these compounds in everyday commodities has led to widespread contamination, with these being reported in many environmental fates such as air [6], dust [7], water [7,8] and even biota [9,10]. Their release through domestic and industrial discharges and the fact that these compounds cannot be totally removed at WWTP becomes an issue due to their path reaching aquatic environments. There, species inhabiting are directly exposed to these contaminants [11–13]. Amongst organisms susceptible to incorporate these contaminants into their organisms, seafood represents a major deal due to its ingestion by population via dietary intake [14–17]. The toxicity related to these group of compounds is nowadays a concern. Compounds such as DBP and DEHP are confirmed to have development and reproductive adverse effects in laboratory animals [18], whereas compounds like DnBP or BBP have been linked to steroid-hormone reduction [19]. OPEs exposure may lead to potential adverse effects with TCEP and TCPP being suspected as mutagenic, carcinogenic and even endocrine disruptors [20]. As regards BTs and BTRs, their toxicity has been reported by several studies [7,21–25], concluding that these compounds have shown respiratory irritant effects as well as dermal sensibilisation.

The ubiquitous presence of these compounds in seafood, along with the reported negative health effects, leads to an increasing urge of developing new analytical methods capable of providing useful data for the exposure and risk assessments associated with the consumption of those via dietary intake. This review is intended to comprise the most recently used analytical methodologies for the determination of these compounds in seafood samples, focusing on their extraction and clean-up strategies. Moreover, an overview of the occurrence of these compounds in different studies around the world will be presented, along with the exposure and risk assessment calculations performed by several studies regarding the effects that the consumption of those via fish intake can imply on human health.

2. Analytical methodologies

Data concerning the risk associated with the ingestion of these HPV chemicals via fish and seafood intake is the result of applying several toxicity models to the exposure levels calculated. At the same time, these exposure values are based on the experimental data found by the analysis of seafood samples. It is therefore necessary to develop sensitive and selective methods for their determination. To fulfil these requirements, efficient extractions, and clean-ups, as well as sensitive instrumental techniques to reach the required levels are usually needed. A summary of the extraction techniques used as well as clean-ups and determination techniques can be found in Table 1.

2.1. Extraction procedures

Seafood can be analysed both as the whole organism or divided into the different parts or organs that those are constituted of, e.g., muscle, liver, brain, plasma, etc. As the intention of the review is to cover the analytical methods susceptible to proving data necessary to perform exposure and risk assessment calculations of the ingestion of these compounds via dietary intake, only the common edible parts of the seafood will be considered. Thus, the analytical methods regarding fish muscle and other seafood which are usually served as the whole organism like shrimps or mussels will be discussed in this and the upcoming sections.

Before the sample extraction, a sample pre-treatment is usually performed to obtain a suitable part of the organism to be analysed. Therefore, fish muscle fillets are dissected from the organism. For other seafood species containing shells, these are usually removed and only the soft part is kept. Once the edible parts are extracted from the organism, these can be analysed wet [26–28] or lyophilised [29–31]. Dry weight analysis enables the interpretation of the data without considering the humidity percentage of the sample, whereas wet weight values are essential for the later exposure and toxicity assessment calculations. The process of lyophilising the sample can be performed in different ways: it can be dried using a freeze-drying system [32], or, as an alternative, water can be removed using dehydrating substances such as sodium sulfate (Na_2SO_4) [33]. Independently of the sample being treated wet or dry, a grinding and homogenization step is required before analysis.

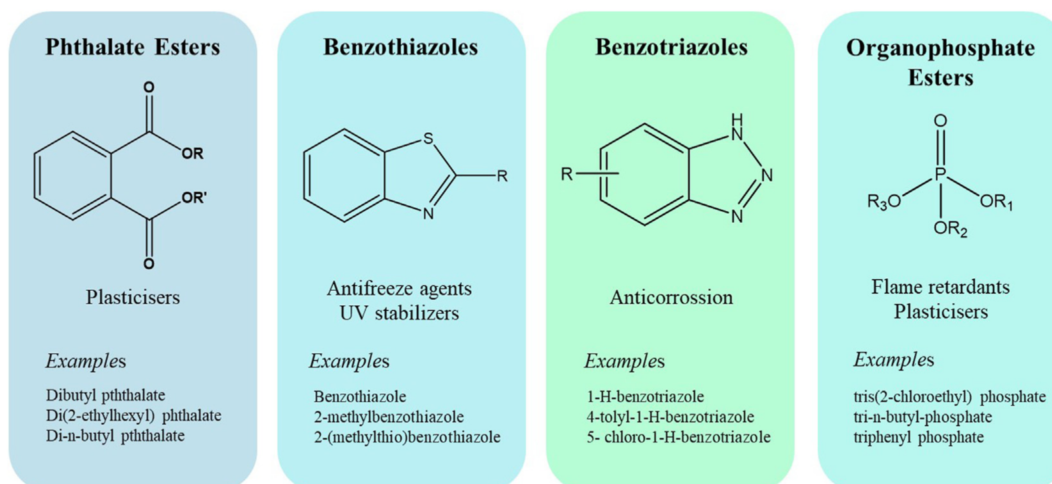

Fig. 1. Structure, principal applications, and examples of the considered high production volume chemicals families.

Table 1

Matrix	Compounds	Extraction	Clean-up	Instrumental analysis/Column	R_{app} (%)	LODs	Ref.
Shrimp, Fish	**7 PAEs**	SLE (3–20 g d.w.sample) 3x Hex/Acetone (1:1)/mix 30 min	LLE Hex/ACN	GC-MS DB-5MS	56–101%	2–10 ng g^{-1} w.w. a	[34]
Fish	**8 PAEs**	SLE (5–20 g w.w.sample) 20 mL Hex/Acetone (1:1)/mix 30 min	GPC styrene - divinylbenzene	GC-MS DB-XLB	93–100%	0.25–80 μg kg^{-1} w.w. (5–100 μg kg^{-1} l.w.)	[35]
Fish, Crustaceans	**8 PAEs**	SLE (5–20 g w.w.sample) 20 mL Hex/Acetone (1:1)/mix 30 min	GPC styrene - divinylbenzene	GC-MS DB-XLB	88–104%	5–145 μg kg^{-1} l.w.	[36]
Fish, shrimp, oyster	**5 PAEs**	SLE (2 g w.w. sample) 10 mL EtOH/Water (8:2)/mix 1 min	d-SPE PSA	GC-MS DB-5MS	80–91%	2.53–9.61 μg L^{-1}	[38]
Fish	**10 PAEs**	SLE (5–20 g w.w.sample) 20 mL Hex/Acetone (1:1)/mix 30 min	GPC styrene - divinylbenzene	LC-APCI-QqQ BEH C18	89–100%	0.5–70 μg kg^{-1} w.w.	[86]
Fish	**3 PAEs**	SLE (w.w. sample) 2 × 3 mL DCM	–	LC-ESI-QqQ HSS C18	–	–	[100]
Shrimp	**5 PAEs**	SLE (0.5 g w.w. sample) 2 x (0.5 mL n-pentane + 3 mL n-pentane/MeOH (1:4))/mix 1 min	GPC	LC-ESI(+)-QqQ	98–100%	40 ng g^{-1} w.w.	[39]
Fish, shellfish	**5 OPEs**	SLE (0.5 g d.w. sample) 5 mL ACN/mix 1 min	d-SPE Z-sep SPE Florisil	GC-MS HT-8	53–71%	0.15–1 ng g^{-1} w.w.	[40]
Fish, mussel, oyster	**14 OPEs**	SLE (0.3 g d.w. sample) 5 mL ACN/mix 1 min	d-SPE PSA + C18 SPE Florisil SPE APC	GC-QqQ ZB-5	74–130%	0.001–0.33 ng g^{-1} w.w.	[83]
Fish	**8 OPEs**	USE (0.5 g w.w.sample) 2 × 5 mL Hex/Acetone (3:1) x 20 min	SPE Florisil	GC-MS HT-8	–	–	[33]
Fish	**16 OPEs**	USE (0.25 g d.w.sample) 2 × 15 mL Hex/Acetone (1:1) x 15 min	SPE Alumina + C18	LC-ESI(+)-QqQ Purosphere RP-18	45–115%	0.34–51.6 ng g^{-1} l.w.	[51]
Fish	**2 OPEs**	USE (1 g d.w.sample) 2 × 10 mL EtAc/Acetone (1:1) x 15 min	Acid attack Sulfuric Acid SPE Bond Elut ENV	LC-UV Hypersil GOLD	58–98%	0.04–0.17 μg g^{-1} w.w.	[52]
Fish, mussel, shrimp	**14 OPEs**	USE (0.1 g d.w.sample) 2 × 4 mL EtAc x 1 h	SPE NH_2	LC-ESI (+)-QqQ ACQUITY BEH-C18	48–80%	0.001–0.14 ng g^{-1} w.w.	[53]
Fish, oyster, shrimp	**9 OPEs**	USE (5 g d.w.sample) 5 mL ACN/Toluene (9:1) x 1 h	SPE FL-PR Florisil d-SPE Z-sep + DSC-18	LC-ESI (+/−)-QqQ Synergi Fusion-RP	60–96%	0.004–0.33 ng g^{-1} w.w.	[54]
Fish, shrimp, lobster	**15 OPEs**	USE (1 g w.w.sample) 5 mL ACN (5% Formic acid) x 2 h	d-SPE PSA + C18 SPE Oasis HLB	LC-ESI (+)-QqQ Betasil C18	63–121%	0.01–0.17 ng g^{-1} w.w.	[16]
Mussel	**7 OPEs**	USE (0.5 g d.w.sample) 2 × 15 mL Hex/Acetone (1:1) x 15 min	TurboFlow CycloneTM-P + C18-XL	LC-HESI-QqQ Purosphere RP-18	47–98%	0.19–19.3 ng g^{-1} l.w.	[55]
Fish	**14 OPEs**	USE (0.5 g d.w.sample) 2 × 15 mL Hex/Acetone (1:1) x 15 min	TurboFlow CycloneTM-P + C18-XL	LC-HESI-QqQ Purosphere RP-18	47–98%	0.19–19.3 ng g^{-1} l.w.	[41]
Fish	**9 OPEs**	USE (1 g w.w.sample) 3 × 10 mL MeOH x 15 min	SPE Strata X	LC-ESI (+)-QqQ Kinetex XB-C18	47–123%	0.02–0.30 ng g^{-1} w.w.	[42]
Fish, shrimp, mussel, bivalve	**7 OPEs**	USE (0.2 g d.w.sample) 3 × 10 mL ACN x 20 min	SPE GCB + NH_2	LC-ESI (+)-QqQ BEH-C18	95–115%	0.046–0.306 ng g^{-1} w.w.	[43]
Fish	**6 OPEs**	USE (0.5 g d.w.sample) 2 × 15 mL Hex/Acetone (1:1) x 15 min	TurboFlow CycloneTM-P + C18-XL	LC-ESI-QqQ Purosphere RP-18	48–102%	0.2–19.3 ng g^{-1} l.w.	[44]
Fish	**19 PAEs**	USE (1 g d.w.sample) 2 × 5 mL ACN x 20 min	d-SPE PSA + C18 + GCB	GC-QqQ DB-5MS	73–114%	0.23–0.96 ng g^{-1} d.w.	[45]
Fish	**14 PAEs**	USE (1 g d.w.sample) 2 × 20 mL MeOH/DCM (3:7, v/v) x 20 min	SPE Florisil + Silica	GC-MS DB-5	89–118%	0.17–0.53 ng g^{-1} d.w.	[46]
Fish	**4 PAEs**	USE (2 g w.w.sample) 10 mL DCM x 30 min	SPE Oasis HLB	GC-MS HP-5	88–117%	2.4–4.1 ng g^{-1} w.w.	[47]
Mussel	**4 PAEs**	USE (1 g d.w.sample) 1 × 10 mL DCM/Hex + 2 × 10 mL Hex/acetone x 20 min	SPE Florisil	GC-MS HP-5	78–101%	4–71 ng g^{-1} d.w.	[48]
Fish	**5 PAEs**	USE (2 g d.w.sample) 2 × 20 mL Hex/Acetone (8:2) x 20 min	SPE Florisil	GC-MS HP-5	56–101%	2–10 ng g^{-1} w.w.	[101]
Fish	**6 PAEs**	USE (5 g f.w.sample) 3 × 10 mL Hexane x 10 min	SPE Florisil	GC-MS HP-5	69–97%	0.003–0.018 ng g^{-1} w.w.	[49]
Fish	**7 PAEs**	USE (2 g d.w.sample) 2 × 20 mL Hex/Acetone (8:2) x 20 min	SPE Florisil	GC-MS ZB-5	57–87%	0.4–10 ng g^{-1} w.w.	[78]
Fish, squid, bivalve, shrimp	**6 PAEs**	USE (1 g d.w.sample) 5 mL Hexane + 1 mL $H_2$0 20%NaCl x 5 min		GC-MS ZB-5HT	53–94%	6.8–10 ng g^{-1} w.w.	[32]
Fish	**5 PAEs**	USE (2 g w.w.sample) 5 mL Acetone/Hexane (1:1,v/v) x 10 min		LC-ESI (+)-QqQ Accucore C18 aQ	70–120%	0.1–0.5 ng g-1 w.w.	[14]
Fish, shrimp, crab, shellfish	**15 PAEs**	USE (2 g f.w.sample) 2 × 10 mL Hex/DCM (1:1, v/v) x 30 min	SPE Cleanert PAE	GC-QqQ HP-35MS	70–117%	0.15–0.78 ng g^{-1} w.w.	[26]

(*continued on next page*)

Table 1 (*continued*)

Matrix	Compounds	Extraction	Clean-up	Instrumental analysis/Column	R_{app} (%)	LODs	Ref.
Mollusc	**4 BTRs** 4 **BTs**	USE (0.1 g d.w.sample) 2 × 5 mL Hex/DCM (1:1) x 20 min	SPE Oasis HLB	GC-QqQ (BTs) TG-5MS LC-ESI(+)-QqQ (BTRs) CSH Phenyl Hexyl	51–120%	0.607–5.12 ng g^{-1} d.w.	[50]
Fish	**13 OPE**	MSPD (0.5 g d.w. sample) sample +1.2 g activated silica +3 g deactivated florisil/E: 10 mL ACN	–	GC-NPD DB-5	65–104%	0.2–3.1 ng g^{-1} w.w.	[71]
Mussel	**13 OPEs**	MSPD (0.5 g f.w. sample) sample +1 g anhydrous Na_2SO_4 + 2 g florisil +1 g alumina/ W:5 mL Hex/DCM (1:1)/E: 10 mL Hex/Acetone (6:4)		LC-ESI(+)-QqQ Purospher STAR Luna C18	69–122%	0.06–5 ng g^{-1} d.w.	[28]
Fish	**6 PAEs**	MSPD (2 g d.w. sample) sample alone/W: 6 mL EtAc/E: 6 mL EtAc	–	GC-MS DB-5MS	79–109%	6–11 ng g^{-1} d.w.	[72]
Fish, shrimp, oyster, scallop	**4 PAEs**	MSPD (1 g f.w. sample) sample +2 g florisil +0.1 g GCB +2 g anhydrous Na_2SO_4/E: 20 mL EtAc	–	LC-UV VP-ODS	85–106%	0.682–1.892 ng	[73]
Bivalve	**1 PAE**	MSPD (0.1 g d.w. sample) sample +0.4 g C18 + 0.1 g Florisil/E: 1.2 mL ACN +2.6 mL H_2O	In-tube SPME GC TRB-5	GC-MS DB-5MS	–	10 μg L^{-1} (measured concentration)	[74]
Fish, shellfish	**6 PAEs**	MSPD (0.1 g d.w. sample) sample + C18 + florisil/E: 5.75 mL MeOH/DCM		GC-MS DB-5MS	59–96%	20–50 ng g^{-1} w.w.	[75]
Mussel	**3 PAEs**	MSPD (0.1 g w.w. sample) sample +0.5 g Florisil +0.5 g Na2SO4 + 0.2g sea sand/E:9 mL MeOH/ACN (3:7)		LC-DAD ACE 5C18-PFP	89.1–104%	0.42–1.65 ng g^{-1} w.w.	[76]
Fish	**2 BTs** **5 BTRs**	USE-MSPD (0.5 g d.w. sample) sample +1 g florisil +10 mL H2O + USE x 10 min		LC-ESI(+)-QTOF Poroshell 120 EC-C18	BTS: 73–91% BTRs: 70–93%	BTs: 0.05–0.1 ng g^{-1} BTRs: 0.05–0.5 ng g^{-1}	[77]
Fish	**7 PAEs**	PLE (0.5 g d.w. sample) 3 cycles (5 min, 100 °C) Hex/DCM (1:1) + Hex/Acetone (1:1)	SPE Florisil	GC-QqQ ZB-SemiVolatiles	89–170%	1.29–11.5 ng g^{-1} d.w.	[61]
Fish, mussel	**10 OPEs**	PLE (3–6 g d.w. sample) 2 cycles (100 °C) EtAc/ Cyclohexane (5:2) + 1 cycle (100 °C) Cyclohexane/Diethyl Ether (9:1)	GPC Biobeads	GC-HRMS DB-5	64–132%	0.05–23 ng g^{-1} l.w.	[59]
Fish	**8 OPEs**	PLE + SPME (1 g w.w. sample) 1 cycle (150 °C, 5 min) H_2O (10% ACN) 10 mL extract in SPME vial + 3 g NaCl + immersion SPME (PDMS/DVB) x 40 min	In-cell Acidified silica	GC-FPD HP-5		0.01–0.208 ng g^{-1} w.w.	[56]
Fish	**11 OPEs**	PLE (0.5–2 g w.w. sample) 1 cycle DCM/Hex (1:1)	SPE Aminopropyl silica	LC-ESI(+)-QqQ Waters symmetry C18	–	0.02–0.16 ng g^{-1} w.w.	[79]
Fish	**10 OPEs**	PLE (whole organism d.w.) 3 cycles (70 °C) DCM/Acetone (1:1)	SPE NH2	LC-ESI-QqQ Luna C18	43–134%	0.2–29 ng g^{-1} w.w.	[80]
Fish	**10 OPEs**	PLE (d.w. sample equivalent to 0.25 mg lipid) 1 cycle DCM/Acetone (1:1)	GPC Silica gel SPE HybridSPE	LC-ESI-QqQ Luna C18	–	–	[57]
Fish	**3 OPEs**	PLE (1 g d.w. sample) 1 cycle (100 °C, 5min) EtAc	In-cell Hex/DCM GPC Alumina + Silica + Florisil + PSA	GC-MS DB-5 MS	58–107%	0.06–1.35 ng g^{-1} w.w.	[58]
Fish, shrimp	**17 OPEs**	PLE (1 g d.w. sample) 1 cycle (100 °C, 5min) EtAc	In-cell Hex/DCM GPC Alumina + Silica + Florisil + PSA	GC-MS DB-5 MS	77–97%	0.06–1.29 ng g^{-1} w.w.	[31]
Fish	**5 BTs**	PLE (1 g d.w. sample) 1 cycle H_2O (80 °C, 5min, 1500 psi) SPME 10 mL extract PDMS/DVB, immersion 40 min, 80 °C	In-cell Hexane	GC-IonTrap ZB-5	86–135%	0.5–10 ng g^{-1} d.w.	[17]
Fish	**3 BTRs**	PLE (1 g d.w. sample) 2 cycles EtAc/DCM (1:1) (100 °C, 5 min)	In-cell Florisil SPE C18	LC-ESI(+)-QqQ Purospher STAR HR R-18	–	0.33–5.91 ng g^{-1} d.w.	[60]
Fish	**10 OPEs**	QuEChERS (1g f.w. sample) 4 mL ACN (5% F.A.)/ 400 mg NaCl + 400 mg MgSO4	d-SPE PSA + C18 + Alumina	LC-ESI(+)-QqQ Waters BEH C18	73–106%	0.05–0.42 ng g^{-1} w.w.	[9]
Fish	**13 OPEs**	QuEChERS (4 g f.w. sample) 4 mL ACN/2 g $MgSO_4$/NaCl (4:1)	Online SPE PSA, C18, Carbon X	GC-QqQ DB-5MS LC-ESI-QTRAP/Q-Orbitrap Nano Acquity UPLC + BEH C18	69–122%	0.5–1 ng g^{-1} w.w.	[66]
Fish	**9 OPEs**	QuEChERS (0.5 g d.w. sample) 10 mL H_2O + 10 mL ACN/+ 4 g MgSO4 + 1 g NaCl +1 g	LipiFiltr	GC-QqQ HP-5MS	67–116%	0.05–2 ng g^{-1} d.w.	[10]

		sodiumcitrate +0.5 g disodium citrate sesquihydrate					
Fish	**13 PAEs**	QuEChERS (5 g f.w. sample) 5 mL ACN (1% F.A.)/ 2 g NaCl	d-SPE PSA	GC-QqQ HP-5MS	71–116%	0.01–10 ng g^{-1} w.w.	[64]
Fish, shrimp, mussel	**5 PAEs**	QuEChERS (2 g f.w.sample) 2 mL H_2O + 10 mL ACN/1 g NaCl	SPE PSA	GC-QqQ HP-5MS	53–120%	0.019–2.2 ng g^{-1} w.w.	[27]
Fish, mussel, shrimp	**5 PAEs**	QuEChERS (2 g f.w.sample) 2 mL H_2O + 10 mL ACN/1 g NaCl	SPE PSA	GC-QqQ HP-5MS	60–120%	0.034–2.2 ng g^{-1} w.w.	[67]
Fish, mussel	**7 PAEs** **9 OPEs**	QuEChERS (0.5 g d.w. sample) 10 mL DCM/EtAc (1:1) + vortex 1 min + sonicated 10 min	d-SPE PSA + C18 d-SPE Florisil + Alumina	GC-MS HP-5MS	52–91%	0.001–0.06 ng g^{-1} d.w.	[29]
Fish	**6 PAEs** **6 mPAEs**	QuEChERS (1 g d.w. sample) 10 mL H_2O pH 2 + 10 mL ACN/+ 4 g MgSO4 + 1 g NaCl +1 g sodiumcitrate +0.5 g disodium citrate sesquihydrate	PAEs: d-SPE LipiFliltr mPAEs: d-SPE C18	LC-(ESI +/−)-HRMS (Orbitrap) Ascentis Express C18	PAEs: 14–66% mPAEs: 13–77%	PAEs: 2.5 –75 ng g^{-1} d.w. mPAEs: 1–25 ng g^{-1} d.w.	[69]
Fish	**2 BTRs** **3 OPEs**	QuEChERS (0.5 g d.w. sample) H_2O + ACN (V_{ACN}/V_{H2O} = 2:1)/4 g MgSO4 + 1 g NaCl	d-SPE PSA + C18	LC-ESI(+)-QTRAP ACQUITY BEH-C18	34–101%	0.02–0.50 ng g^{-1} d.w.	[68]
Mussel, razor shell. Oyster, cockle	**1 BTR**	QuEChERS (1 g d.w. sample) 5 mL H_2O + 15 mL ACN/4 g $MgSO_4$ + 1 g NaCl +1 g sodiumcitrate +0.5 g disodium citrate sesquihydrate	d-SPE PSA + C18 SPE Ostro™ Phospholipid removal	LC-ESI(+)-HRMS STAR RP-18	62–148%	0.10 ng g^{-1} d.w.	[30]
Shellfish	**1 BTR**	QuEChERS (1 g d.w. sample) 5 mL H_2O + 10 mL ACN/4 g $MgSO_4$ + 1 g NaCl +1 g sodiumcitrate +0.5 g disodium citrate sesquihydrate	d-SPE PSA + C18 SPE Ostro™ Phospholipid removal	LC-ESI(+)-HRMS STAR RP-18	78–98%	0.10–0.50 ng g^{-1} d.w.	[84]
Fish	**4 BTRs**	QuEChERS (2 g f.w. sample) 5 mL H_2O + 10 mL ACN (1% Acetic acid)/6 g $MgSO_4$ + 1.5 g sodium acetate	d-SPE PSA + C18	LC-ESI(+)-QqQ Zorbax SB-C18	51–120%	0.02–0.11 ng g^{-1} w.w.	[82]
Fish	**9 PAEs**	Soxhlet (2–3g d.w. sample) 120 mL Acetone/ DCM/Hex (1:1:1) x 18 h	SPE Activated copper + florisil	GC-MS HP-5MS	73–116%	5 ng g^{-1} d.w.	[94]
Fish	**3 PAEs**	Soxhlet (5 g d.w. sample) 120 mL DCM x 6–8 h	SPE Alumina + Na_2SO_4	LC-UV (254 nm) C18	–		[102]
Fish	**6 PAEs**	ASE (2g d.w. sample) 6 mL EtAc at 9 mL/min x 10 min +2 mL/min x 50 min		GC-MS DP-5MS	102%		[103]
Fish	**11 OPEs**	Soxhlet (10 g d.w. sample) 80 mL Hex/Acetone (1:1) x 1 h	GPC SPE Florisil	GC-MS DB-5 MS	58–103%	0.005–0.641 ng g-1 w.w.	[87]
Fish	**11 OPEs**	Soxhlet (1 g d.w. sample) Hex/Acetone (1:1) x 24 h	SPE Florisil	LC-ESI(+)-QTOF ACQUITY BEH-C18	73–109%	0.16–2 ng g^{-1} w.w.	[92]
Shrimp, crab, oyster	**11 OPEs**	Soxhlet (1 g d.w. sample) 150 mL Hex/Acetone (1:1) x 48 h	SPE Envi - Florisil	GC-QqQ HP-5 MS	75–110%	0.016 –0.484 ng g^{-1} d.w.	[104]
Fish	**14 OPEs**	MAE (1 g d.w. sample) 0 mL Hex/Acetone (1:1)/ 30 min/130 °C	GPC Biobeads SPE Deactivated Silica	GC-MS DB-5MS	39–105%	0.006–0.021 ng g^{-1} l.w.	[105]
Fish	**8 OPEs**	UVAE (2.5 g d.w. sample) 5 mL ACN/Toluene (9:1)/USE 1h/MSPD with 1 g $MgSO_4$	SPE Florisil d.SPE Z-SEP + C18 SPE Aminopropyl Silica	GC-MS HT-8 ()	67–111%	1.4–3.7 ng g^{-1} d.w.	[106]
Fish	**5 PAEs**	DI-SPME Fiber preconditioning with phosphate buffer with agitation during 3 h + introduction of the fiber in the fish fillet for 25 min + removal of the fiber + wash in a vial with 1 mL H2O + desorption with 80 µL MeOH/H2O (80; 20)		LC-ESI (+)-QqQ Accucore C18 aQ		0.2–0.3 ng g^{-1} d.w.	[14]

2.1.1. Solid-liquid extraction

The use of simple solid-liquid extraction has been successfully applied for the determination of HPVs in seafood. A good partitioning of the compounds between the sample and the extraction solvent can be achieved with mechanical shaking either using a shaking table [34–37] or vortex [38–40]. However, most of the methods incorporate sonication for better penetration of the solvent into the seafood sample, thus using ultrasonic-assisted extraction (USE) [14,16,26,32,33,41–55]. Parameters such as extraction solvent, solvent volume, and sonication time are considered key factors for a successful extraction. Regarding extraction solvent, mixtures of Hex/Acetone (1:1) are mostly used for the extraction of PAEs and OPEs from seafood, yielding recoveries between 45 and 123%. As for BTs and BTRs, more apolar solvent mixtures such as Hex/DCM are used, with recoveries comprised between 51 and 120% [50]. Greener approaches have also been described using mixtures of EtOH/H_2O (8:2) for the extraction of PAEs from fish, oyster, and shrimp samples with recoveries of 80–91%. Concerning the extraction solvent, Lorenzo et al. [42] denoted the higher ability of solvent mixtures of extracting non-polar compounds, thus leading to higher matrix effects and more critical clean-up steps, and suggested the use of MeOH on its own instead of mixtures when extracting seafood samples. With respect to the solvent volume used for the extraction, total volumes of 5–40 mL are used for sample weights between 0.1 and 5 g. Assuring quantitative extractions also involves the amount of time the sonication is performed, for HPVs and seafood samples, this time varies between 5 min and 2 h being the longest time for the extraction of OPEs from fish, oyster, shrimps and lobsters [16,54].

Albeit using larger extraction solvent volumes, SLE can be considered a great option for the extraction of HPVs from seafood samples given its simplicity, effectivity, and relatively low cost. Considering time demand, sonication can be pointed out as the bottleneck, enlarging the time needed to perform the extraction, especially given the fact that most of the samples need to be reextracted at least once to achieve satisfactory recoveries. Moreover, centrifugation is usually necessary to properly separate the extract, thus incorporating another analytical step. It should be pointed out that a tendency for the reduction of sample weight is seen throughout the years, thus leading to a reduction of the volume of solvent used and hence a greener approach.

2.1.2. Pressurized liquid extraction

The lower solvent consumption, as well as its fast and semi-automated procedure, has turned PLE into a highly attractive option. Its presence in the extraction of HPVs from seafood is usually found in literature, with methods involving all the families comprised in this review. For the number of cycles, temperature, and static time, common values are found for most of the methods described to date, then being 1 cycle [17,31,56–58], 100 °C [31,58–60] and 5 min [17,31,58–61], yielding recoveries within 43–135% for sample weights between 0.5 and 6 g (d.w.). Several extraction solvents have been used for this purpose, mainly being DCM mixtures with hexane or acetone (DCM/Hex or DCM/Acetone), ethyl acetate on its own, or even water. Most of the solvents prior listed can be used for successful extraction of PAEs and OPEs whereas compounds such as BTRs have been proved to be successfully extracted from fish muscle samples using a mixture of EtAc/DCM (1:1) and 2 cycles (100 °C, 5 min) [60]. Even though methods involving water for the extraction of OPEs and BTs are described in the literature, authors such as Hidalgo-Serrano et al. [62] have described the apparition of foam in the collection vessel which interrupted the process and they have linked this problem with the use of water and the high lipid content present in some fish species.

Methods involving PLE have been proven to be useful for the determination a wide range of HPVs in seafood, which emphasizes the elevated grade of extraction potential that this technique offers but also the loss of selectivity during the extraction process [58,60,63]. Even though being a low selectivity extraction technique could lead to the development of multi-residue methods capable of determining a wide range of analytes from different families at the same time, it also represents a problem when extracting samples from a complex matrix. In the case of seafood, using PLE as the extraction method leads to a higher percentage of matrix interferents such as lipids being extracted along with the target analytes, thus hindering the determination and making clean-up steps more critical [31,56]. Different alternatives for the obtention of a cleaner extract directly from PLE have been studied and will be discussed later on in the clean-up strategies section.

2.1.3. QuEChERS

Far from its initial purpose, the use of QuEChERS has expanded to the determination of other compound families, in which HPVs are also included. The composition of the extraction salts or the solvent volumes and ratios are parameters usually modified to adapt for each of the compound families and studied commodities. Regarding the solvent, ACN remains the most used extraction solvent with volumes ranging from 4 to 15 mL for sample weights between 0.5 and 2 g (d.w.)/1–5 g (w.w.) with recoveries within 51–148%. The addition of water is also a common procedure, especially when working with lyophilised samples. It is usually added in a 1:1 (v/v) ratio for OPEs, whereas compounds such as PAEs and BTRs tend to make use of higher ACN ratios for their extraction (from 1:2 to 1:5). The addition of pH modifiers into ACN such as 1–5% formic acid [9,64] or 1% acetic acid [65] have also been proven to provide satisfactory results in the determination of these compounds, mainly increasing their recovery (71–116% for OPEs and PAEs). Concerning the extraction salts used to increase the partitioning of the compounds between water and ACN, most of the methods described for HPVs determination in seafood make use of the original (OR) [9,27,64,66–68] or the EN 15662 (EN) [10,69,70] methods, which usually contains mixtures of NaCl and $MgSO_4$ for the first or NaCl, $MgSO_4$ and a citrate buffer (sodium citrate + disodium citrate sesquihydrate) for the later. Even though methods determining BTRs in different seafood species using the same salts are found in the literature, a study conducted by Yao et al. [65] demonstrated the higher efficiency of the AOAC method for the determination of BTR, 5TTR, ClBTR, and XTR from fish muscle samples. The authors did point out the negative effect that acidic pH of the extraction solvent had on the recoveries of BTRs, concluding that acidic phases led to increased hydrolysis of BTRs, thus diminishing their recovery.

The use of QuEChERS in the determination of HPV chemicals is growing on account of the good results obtained as well as their easy implementation given the lack of expensive materials or instruments. A problem currently found when using QuEChERS is its low enrichment factor. This could be solved by either increasing the sample weight or reducing the final extract volume. However, both options lead to higher co-extracted matrix concentrations, thus leading to more critical clean-up steps. Nonetheless, the wide range of compounds that can be extracted using this technique leads to the development of multi-residue methods, as well as when using pressurized liquid extraction, but with the advantage of extracting less interferences. Moreover, the described methods include the following clean-up which can be performed directly with the obtained extract (d-SPE), enabling an easy and effective procedure.

2.1.4. Matrix solid-phase dispersion

The possibility of performing both the extraction and the clean-

up in a single step has led matrix solid-phase dispersion (MSPD) to become a useful methodology for the extraction of HPVs compounds from seafood samples. Sample weights between 0.1 and 2 g are usually packed into an SPE cartridge mixed with a dispersant and a co-sorbent. Sorbents such as florisil [28,71–76] and activated silica [28] have been successfully used as dispersants mixed with the sample. Among them, florisil stands out as the most used sorbent for the determination of OPEs and PAEs in seafood. Even though florisil can behave both as dispersant and co-sorbent due to its capacity of retaining lipids and other interferences, additional co-sorbents such as alumina [71], GCB [73] or C18 [74,75] have been used for further clean-up of the extracts. Regarding elution, solvents such as ACN [28,74], Hex/Acetone [71], EtAc [72,73], MeOH/DCM [75] and MeOH/ACN [76] have been used with satisfactory results (recoveries comprised between 59 and 122%). The mixture of MeOH/ACN along with the use of florisil as dispersant yielded the highest recoveries (89–104%) for the determination of PAEs from bivalves. Campone et al. [71] also denoted the importance of the solvent election and its role in the washing step, indicating that a mixture of Hex/DCM (1:1) could lead to an efficient lipid removal while avoiding a substantial analyte loss.

Even though not extensively used due to its laborious procedure, MSPD can be seen as an alternative with clear advantages such as reduced sample size, fast procedure, reduced solvent volume, and lack of required equipment. However, attention must be paid to the fact that MSPD uses the sample matrix as the extraction core itself, it becoming an issue in terms of reproducibility, not only since every sample is different but also because of the differences produced in the confection of the MSPD itself every time.

2.1.5. Extraction methods comparison

Given the literature to date previously discussed, HPVs can be extracted from seafood in many different ways. Comparing different extraction methods can be quite tedious as many parameters can be involved. Regarding the recoveries, most of the methods comprise their recoveries in a wide range, mainly going from the low 30–40% (usually related to the most volatile compounds) to the surroundings of 120%. As the methods described make use of different determination techniques as well as different analysers, the reported recoveries, which usually are difficult to differentiate between relative or apparent, may also include the effects caused by the matrix. Thus, given this and the fact that there are no remarkable differences, using recoveries as a parameter to select the best extraction technique may not be the best option. Similarities are found when talking about method limits of detection. It is obvious that the methods involving triple quadrupole mass spectrometers or HRMS may reach lower values (reaching 0.001 ng g^{-1} (w.w.) for some of the compounds). However, methods such as standard SLE or USE require higher sample weights to reach those levels (up to 5 g of sample), whereas other techniques such as PLE or QuEChERS use smaller amounts, which later translates to fewer matrix coextractants. Regarding their extraction capacity and selectivity, the different properties of the studied compounds demand the use of methods with low selectivity such as QuEChERS (partially limited to low-midpolar compounds) and PLE. Despite the lack of selectivity being an advantage, the highly exhaustive extraction of PLE may lead to the over-extraction of many matrix endogenous compounds such as lipids. These compounds could act as interferences, especially those from species with higher lipidic content, hindering the determination of the target compounds and making the clean-up more difficult. Another topic that usually becomes a concern when determining PAEs and OPEs is the contamination of the samples throughout the process due to the use of plastic material that may contain some of the compounds. Authors such as Muñoz-Ortuño et al. [74] tested the use of glass instead of polypropylene cartridges for the extraction of DEHP from bivalves using MSPD, concluding that similar signals were observed. On its part, Jimenez et al. [29] performed experiments to evaluate the presence of PAEs in PP tubes used for QuEChERS extraction, finding concentrations of DEHP 2 to 36 times higher than when using glass ones. Avoiding this issue can be easy for extraction techniques not directly linked to the use of plastic such as USE and can be addressed for extraction methods where plastic can be easily substituted by glass homologs as in QuEChERS (glass tubes instead of PP tubes) or MSPD (glass cartridges instead of plastic). Concerning this, authors such as Chen et al. [77] have developed alternative strategies to MSPD combining vortex mixing and sonication avoiding the use of mortar and SPE cartridges, thus preventing the possibility of PAE contamination. Keeping the eyes on the progress towards greener analytical chemistry, parameters such as organic solvent, energy and time consumption, generated laboratory waste, reusability, and automatization are key. Methods such as USE do not align with these principles due to their high usage of organic solvent, whereas this issue is minimized for methodologies such as PLE or QuEChERS. However, the demand of energy counterparts for PLE, while the laboratory waste generated by QuEChERS may be an important issue. The use of glass tubes as well as their miniaturization (reduction of the sample weight and solvent consumption) could help minimizing this issue, as well as make QuEChERS partially reusable. With microextraction being one of the greenest options, methods such as the developed by Panio et al. [14] for the determination of PAEs in fish fillets using direct immersion SPME are excellent references for future method development. Despite being an excellent alternative, the fiber must be cleansed once the extraction is performed, in this case, the authors reported no loses when ultrapure water was used. However, due to higher polarity of some of the HPVs such as benzothiazoles and benzotriazoles, further investigation should be considered to evaluate possible loses on this step. All in all, QuEChERS extraction seems to align with most of the important parameters such as good recoveries, easy procedure, and minimal sample weight. Moreover, it can be considered a relatively green approach if used with reusable material and in a miniaturized way. Its applicability manages to extract a wide range of compounds while the amount of matrix coextractants is generally lower than when using other techniques such as PLE, thus leading to multitarget analysis as well as reducing the necessity of incorporating exhaustive clean-ups. A sum-up of the most used conditions of each of the techniques along with some of the advantages and disadvantages of each of them can be found in Fig. 2.

2.2. Clean-up strategies

Seafood samples are considered high complexity matrix samples due to the huge amount of co-extractive substances that are usually found when these are analysed. From matrix endogenous highly polar compounds to ionic species and lipids, it represents an analytical challenge to selectively determine certain compounds without getting rid of these other substances that may act as interferents and cause signal enhancement or suppression. Clean-ups are intended to eliminate or at least diminish the presence of these interferences in the obtained extracts, thus leading to a more efficient determination but also preventing the instrument from losing efficiency. The following sections will discuss the different approaches followed by the methods described in the literature concerning this topic. Table 1 compiles the clean-up methodologies used for each of the listed methods.

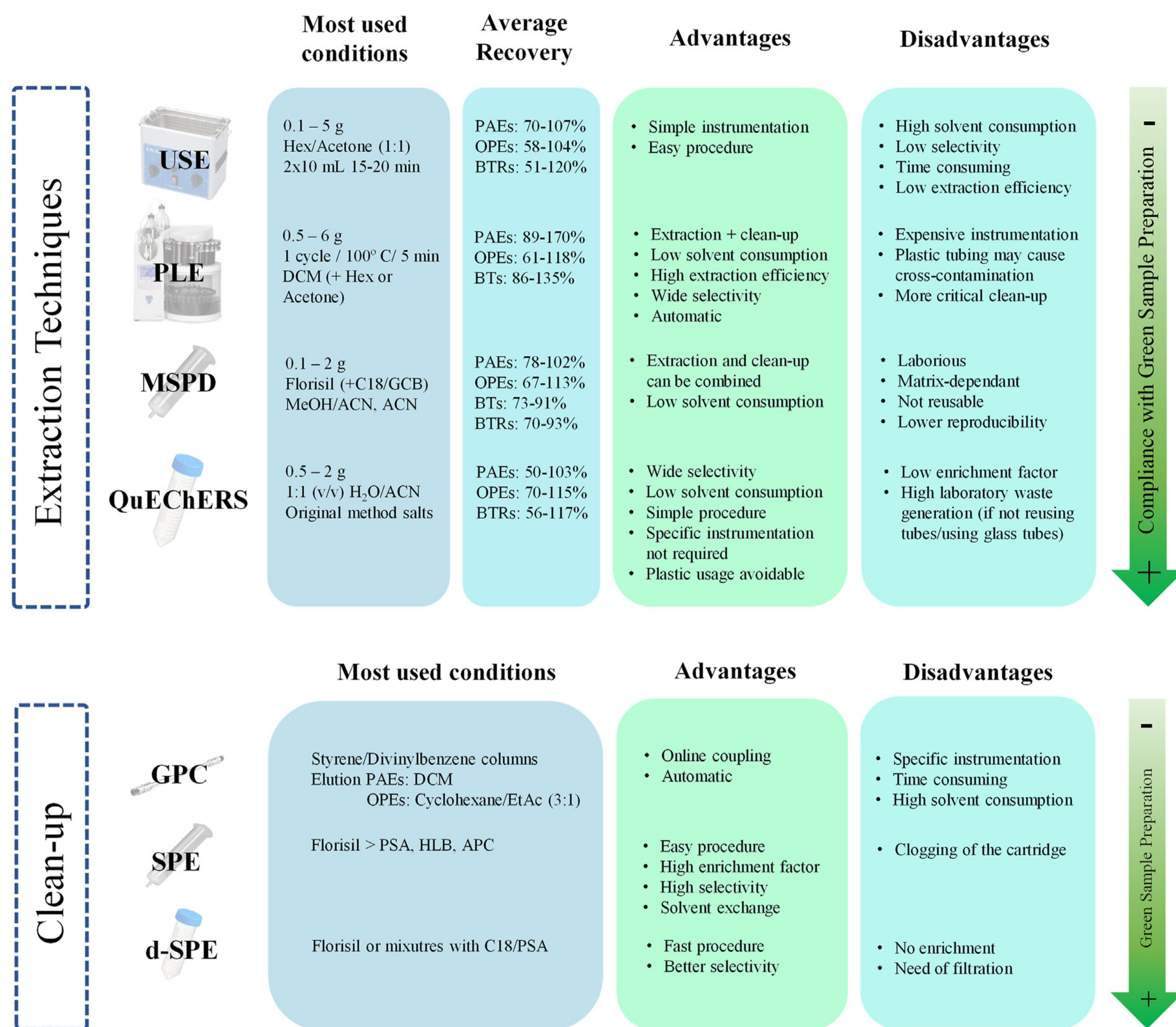

Fig. 2. Comparison of the most used extraction and clean-up techniques for the determination of HPVs in seafood samples.

2.2.1. Solid-phase extraction (SPE)

Solid-phase extraction is the most used clean-up technique when working with seafood samples. Both the sample and the properties of the compounds must be taken into account when selecting the most convenient sorbent. Sorbents such as florisil, PSA, HLB, or aminopropyl-silica (APC) are described in the literature as efficient clean-up sorbents for HPVs in seafood extracts. Among these, florisil appears as the most used by authors for the determination of PAEs [27,48,49,61,78], whereas OPEs seem to be better extracted when using APC cartridges [53,79,80]. Regarding the elution solvent, most of the methods described make use of DCM even though other solvents like acetone, diethyl ether or ACN can be also successfully applied. Authors such as Gu et al. [81] pointed out the importance of the election of the elution solvent. In their study, prawn, fish, and mollusc extracts clean-ups were tested, comparing the elution solvent between hexane and ACN. Even though hexane yielded higher recoveries, authors chose ACN as fewer interferences were observed in the chromatograms. Regarding BTRs and BTs, Oasis HLB cartridges have been used for the clean-up of molluscs extracts performing a washing step using H_2O with a 10% MeOH and finally eluting with pure MeOH [50]. The use of a single SPE procedure is sometimes not enough for an efficient clean-up, thus leading to the incorporation of subsequent SPE procedures to enhance its results. Authors like Santín et al. [51] studied the efficiency of florisil, alumina, and silica SPE cartridges as a clean-up for USE extracts of barbels, carps, and trouts in search of 16 OPEs and denoted that its standalone applicability resulted in high matrix effects and low recoveries. They observed that the problem could be solved if cartridges of C18 were paired along with the previously stated. Thus, the combination of basic alumina + C18 and elution using ACN resulted in recoveries yielding between 48 and 113% and RSD values below 10%.

All in all, the extended use of SPE is sustained by the good results observed for this clean-up strategy. It also allows easier solvent exchange as well as higher preconcentration of the extract avoiding evaporation if eluted with low solvent volumes. However, some drawbacks should be assessed for SPE. The use of highly lipidic extracts in this technique could lead to the clogging of the cartridges, thus diminishing the extraction efficiency and leading to unreliable results. Moreover, SPE cartridges are usually made of plastic, which could be an interference source when analysing PAEs as previously stated for MSPD.

2.2.2. Dispersive solid-phase extraction (d-SPE)

Clean-ups are usually found tedious due to the incorporation of another analytical step into the procedure. Strategies such as SPE

need some preconditioning of the cartridge, and subsequent sample loading, cleaning, and elution steps, which can be found quite laborious as well as extend the overall method time demand. Dispersive solid-phase extraction (d-SPE) has been an extremely useful tool due to its high efficiency as well as simplicity. Usually used after QuEChERS extraction, d-SPE uses sorbents dispersed in the obtained extracts to adsorb the interferences. Methods involving the use of d-SPE for extracts of seafood samples mainly concur on the use of sorbents like primary-secondary amine (PSA), C18, and their mixtures. Xu et al. [64] evaluated the use of d-SPE for the determination of PAEs from QuEChERS extracts of fish samples from Shanghai markets. PSA, C18, PSA + C18, and neutral alumina were evaluated in terms of apparent recovery, being PSA the sorbent that yielded higher recoveries. Jakismka et al. [68] also tested the efficiency of d-SPE using PSA along with other alternatives such as PSA + C18, PSA + C18 + GCB, and C18 + GCB. In this case, BTR, TTR, TBOEP, and TCPP achieved higher recoveries when C18 was incorporated along with PSA in the d-SPE. The results of these studies match with PSA [38,64] and PSA + C18 [68,82] being the most used sorbents to perform d-SPE for the determination of PAEs, BTRs, and OPEs in seafood samples. This can be explained due to the ability of PSA binding nonpolar lipids via hydrogen bonds and C18 retaining long-chain fatty compounds. Even though d-SPE achieves great recoveries while diminishing the matrix effect of fish and seafood samples, sometimes compounds such as OPEs and BTRs seem to be more affected by matrix co-extractants, thus leading to more intensive clean-up procedures. In this sense, additional steps are incorporated into the method, them being either an additional d-SPE or an SPE clean-up. Examples of that can be found in the methods described by Castro-Jiménez et al. [29] or Poma et al. [83] where an additional d-SPE with Florisil + alumina and two SPE using Florisil and Aminopropyl silica (APC) were used respectively. For BTRs in bivalves and fish, Álvarez-Muñoz et al. [30,84] incorporated an additional clean-up after the PSA + C18 d-SPE focused on the phospholipid removal using an Ostro SPE plate.

The fast, inexpensive, and easy-to-use procedure that is d-SPE leads to this technique being one of the most extended clean-ups nowadays. Nonetheless, attention must be paid to the fact that a filtration or centrifugation step needs to be performed afterward. Moreover, higher sample amounts, as well as species with higher lipid contents, may need further clean-up once a single d-SPE is performed.

2.2.3. Chromatographic related techniques

The use of chromatography fundamentals can achieve a successful role in cleaning the extracts obtained from seafood samples. Techniques such as gel permeation chromatography (GPC) enable a more efficient determination due to the obtention of cleaner extracts. It is therefore widely used in the clean-up of extracts where target analytes need to be separated from high molecular weight compounds such as pigments, resins, or lipids [85]. Studies such as the ones conducted by Fierens et al. [35,36], Sakhi et al. [86], or Sundkvist et al. [59] used GPC with styrene/divinylbenzene columns for the removal of lipids from the extracts for the determination of PAEs and OPEs. The elution of the compounds was carried out with DCM for PAEs while OPEs were eluted using a mixture of cyclohexane/EtAc (3:1). Even though GPC can be used as a stand-alone clean-up strategy, some authors have coupled this technique with others to achieve better results. Thus, combinations of GPC with SPE clean-ups [57,87,88] have been described in the literature. Aznar-Alemany et al. [89] and Giulivo et al. [41] both also described the use of online clean-up coupled with LC for the determination of OPEs in mussel and fish samples, respectively. A combination of two columns was selected for this purpose, Cyclone™-P followed by C18-XL yielding recoveries between 47 and 98%.

Using GPC as a clean-up strategy can be useful when working with samples with a high lipidic content such as seafood. Nevertheless, GPC can be tedious due to the long waiting times as well as the higher solvent consumption. On the other hand, online coupling with clean-up columns greatly improves the method's overall time demand, as the elevated automatization of the process leads to its reduction. However, specific instruments are needed to fulfill this purpose, thus increasing the cost.

2.2.4. Clean-up comparison

Clean-up procedures are usually mandatory when working with seafood samples due to their high complexity. Thus, special attention must be paid when selecting the most appropriate clean-up. Regarding the efficiency of the clean-up procedures, it needs to be pointed out that most of the methods described in the literature do not show matrix effects values or compare how the clean-up step reduces its presence. This could be linked to the use of surrogate standards before sample extraction, usually neglecting the importance of a convenient clean-up. Even though this strategy is faster and easier to implement, a minimal clean-up should be performed specially for seafood samples to lengthen the instrument's efficiency. Strategies such as SPE and d-SPE are the most extended due to their easy application and good results. As observed, florisil appears as a great sorbent when using both of them. Its combination with other sorbents such as C18 or PSA could even enhance its effectiveness. The combination of these sorbents can be easier to achieve when working with d-SPE, as bulk sorbents can be mixed in a single tube. Despite strategies such as GPC having good results, its large solvent consumption, the long extraction times as well as the need for additional instrumentation, may not be an affordable and ecological alternative for most laboratories. As regards the use of novel devices such as Cleanert PAE or LipiFiltr, the application of selective cartridges like Cleanert PAE restricts the range of compounds to determine. On the contrary, selective sorption of lipids as the one given by LipiFiltr provides good results in a non-restrictive way, however, due to its novelty, the price of these cartridges may lead to an overall method price rising, especially taking into account the single use of these.

All in all, its easy applicability after QuEChERS extraction, the possibility of incorporating more than one sorbent at a time, and the good results observed in the literature, takes d-SPE one of the most competitive strategies to perform as a clean-up for the determination of HPVs in seafood.

2.3. Determination techniques

Once the extraction is performed, HPVs should be analysed to determine their presence in the extracts. The preferred techniques for this purpose are gas and liquid chromatography, mainly coupled to mass spectrometry, either simple or in tandem. As per the preference for gas or liquid chromatography, PAEs are mostly determined using GC due to their low polarity and high volatility. For OPEs, these can be determined either by gas or liquid chromatography. Finally, the higher polarity inherent in BTs and BTRs turn these compound families more suitable to be determined using LC. The use of GC instead of LC allows easier separations of some of the isomeric compounds derived from benzotriazole such as tolyltriazole isomers (4 and 5-tolyltriazole, 4/5TTR). The selection of the chromatographic technic can also be influenced by the sample. For seafood, as high complexity samples, the matrix effect can be something to take into consideration. Mechanisms involved in the signal enhancement or suppression in hyphenated chromatographic systems are quite different when presented for gas and liquid chromatography. As per liquid chromatography and its soft ionization (mainly when using ESI), a competition between the

analyte and the interferences for the proton transfer could lead to a modified signal, whereas the higher ionization energy (EI) used in GC-MS systems is supposed to overcome this problem. Nonetheless, adsorption of matrix compounds in free active sites present in the column or injector of the GC systems could cause some disparity when comparing the signals of neat and matrix-containing standards [90]. Those mechanisms could be used in favor of the determination of HPVs in seafood samples, as the use of GC could reduce the matrix effect, thus leading to the development of easier and more reliable methods. However, this can only be applied to the determination of compounds with GC amenable properties. Most of the presented compound families, as seen in Table 1, can be analysed via GC or LC, however, analytes such as benzotriazoles yield low sensitivities when using GC systems due to their higher polarity. Strategies like higher enrichment factors or injection volumes as well as derivatization could overcome this problem. Still, further investigation is needed in this field as, to date, literature dealing with the use of GC for the determination of benzotriazoles in samples such as seafood is scarce.

Regarding the columns used for GC analysis, most of the methods use capillary columns with low polarity properties, being 5% phenyl 95% dimethylpolysiloxane (e.g. ZB-5, HP-5, DB-5) the most common. For column length, inner diameter, and film thickness, the standard 30 m × 0.25 μm x 0.25 mm is presented as the best option. LC systems mainly use columns based on C18 stationary phases (e.g. Poroshell C18, Purosphere C18, Acquity BEH C18) with lengths ranging between 50 and 150 mm. Concerning the analyser, mass spectrometry is currently the most used technique either single or in tandem. Due to the higher instrumental signal of PAEs, low limits of detection can be achieved using single quadrupole systems combined with GC [46,47,72]. Some methods take advantage of QqQ for the determination of these compounds in seafood, especially when using LC [39,86]. For OPEs, QqQ is the preferred option [43,45,51,53,66,83], even though literature contains studies using other mass spectrometry systems such as QTRAP [66], HRMS [91] or QTOF [92], and even other detectors like nitrogen-phosphorous detector (NPD) [71], flame photometric detector (FPD) [56] or UV [52]. Methods involving the determination of benzothiazoles and benzotriazoles in fish mainly use tandem mass spectrometry or high-resolution mass spectrometry [30,50,63,77]. While electron ionization (EI) is the main used source for GC-MS, electrospray ionization (ESI) in positive mode is extensively used for the determination of these compound families when working with LC-MS(/MS).

3. Occurrence, human exposure, and risk assessment

3.1. Phthalate esters

The occurrence of phthalate esters has been widely studied and several articles describe their widespread presence in many environmental fates, including seafood. A recap study published in 2014 by Serrano et al. [93] placed seafood as a varied phthalate concentration food group, denoting concentrations between 13 μg kg^{-1} and 928.6 μg kg^{-1} (w.w.) in samples throughout the world. In the same way, the authors denoted the minimal contribution of seafood ingestion (0.1–0.6%) to the total dietary intake of DEHP for the population of the US, being young infants (1–2 years) the most affected group with daily intakes of 0.05 μg kg^{-1} day^{-1}. Opposite to this study, He et al. [15] constated that seafood had the highest PAEs concentrations out of all the analysed food groups for the population of Yanjji (China), with concentrations between 658 and 1610 ng g^{-1} w.w. (DEHP and DBP being the highest contributors), and EDIs up to 2530 ng kg^{-1} bw day^{-1} for DEHP, still representing low exposure. The presence of PAEs in different seafood samples was also denoted by Gu et al. [67], expressing concentrations (Σ_5PAEs) between 5 and 46.3 ng g^{-1} w.w. in fish, 3.3–219.3 ng g^{-1} w.w. in mollusc and 5.0–57.3 ng g^{-1} w.w. in prawn. Hu et al. [27] analysed fish samples from the Yangtze River Delta, China. DEHP and DBP were the compounds with higher detection frequency with mean concentrations of 1941 ng g^{-1} w.w. and 78.7 ng g^{-1} w.w. respectively. A study conducted by Cheng et al. [94] on the bioaccessibility of phthalate esters present in the twenty most consumed species from Hong Kong concluded that percentages between 2.44 and 45.5% of the raw PAEs concentrations were bioavailable. Given the bioavailable concentrations (0.20–1.23 μg g^{-1} w.w.) and after performing risk calculations, fish consumption was considered safe by the authors. Most of the studies conclude that DEHP is the compound with the highest concentrations as well as highest detection frequency in seafood samples. Due to its elevated concentrations and its negative health effects, experiments focused on the determination and behavior of this compound are usually found in the literature. Guerranti et al. [95] evaluated the exposure and risk of the Italian population to the intake of DEHP when ingesting Atlantic bluefin tuna fillets, concluding that the estimated ingestion was very far from being any risk for the Italian population. Regarding the sources from which these compounds reach the seafood, Sakhi et al. [86] proposed plastic food packaging as one of the possible sources of phthalate contamination, while Cheng et al. [94] stated that fish can accumulate DEHP from water and ingestion of contaminated sediments and food.

3.2. Organophosphate esters

The occurrence of OPEs in fish has been recently put in the spotlight due to their presence in most of the analysed samples. Sundkvist et al. [59] started reporting their appearance back in 2010 when comparing fish samples collected in sites with potential sources of OPEs with background locations. OPEs profiles from background locations (Swedish lakes) showed similarities, being TCPP and TPP the most abundant, which led to the belief of OPEs diffusive sources. Nonetheless, TBOEP and TDCPP appeared in samples collected after a WWTP while higher concentrations of TBP, which is usually a component of aircraft hydraulic fluids, were found in specimens collected from an effluent receiving water from a nearby airport. High concentrations were found in samples of catfish (*C. fuscus*) and grass carp (*C. idellus*) from Pearl River, China [88]. There, TnBP, TCEP, TCPP, and TBOEP were found in all the analysed samples at concentrations ranging from 43.9 to 2946 ng g^{-1} l.w. for TnBP, 11.7–281 ng g^{-1} l.w. for TCEP, 62.7–883 ng g^{-1} l.w. for TCPP and 164–8842 ng g^{-1} l.w. for TBOEP. The presence of chlorinated OPEs is heavily sustained in the literature, Gao et al. [96] analysed samples of different fish species (grass carp, croaker, crucian and perk) from a Nanjing supermarket (China), being TCEP and TDCPP the only two OPEs present in all the samples. These compounds were also found in estuarine food webs of the Western Scheldt, Netherlands, where Brandsma et al. [80] determined those in both benthic and pelagic species. The studies conducted by Malarvannan et al. [33] on the levels and profiles of OPEs in European eels (*Anguilla Anguilla*) from a highly industrialised Flanders region showed differences from the previous studies in terms of compounds proportion in samples, being the following for the Belgian samples: TDCPP (64%) > TPP (17%) > EHDPP (12%) > TBOEP (5%) > TCEP (1%) > TDCPP (1%). The differences in the concentrations of OPEs found between the river and marine fish species were stated by Giulivo et al. [41] stating that river fish species had higher concentrations (55.5–646 ng g^{-1} l.w., Σ_{14}OPEs) than the marine ones (14.6–15.8 ng g^{-1} l.w.), with TBP as the most abundant. This effect could be explained due to the discharges from industries, WWTPs,

and other local sources in rivers. Reports of these compounds being present in fish led to the apparition of studies focused on their presence in consumer foodstuffs. Studies on the Swedish population intake of OPEs through food performed by Poma et al. [40] revealed that fish in the market baskets of the population had mean concentrations of TCEP, TPP, EHDPP, TDCPP, and TCPP of 0.10, 0.46, 2.46, 0.29 and 0.08 ng g^{-1} w.w., respectively. Data concerning the distribution of the compounds in the different food categories considered fish the group with percentages between 2 and 8% of the total OPEs. Later on, Poma et al. [83] continued the study on food groups, this time for Belgian foodstuffs, reinforcing the low contribution of fish and seafood to the total OPEs distribution (6%). Even though the previous studies placed fish and seafood as a minor contributor to the total OPEs intake in market baskets, a study conducted in Southeast Queensland, Australia placed fish and seafood behind plant-based foods (vegetable, cereal, and fruit), but on top of the animal products with median concentrations of 1.8 ng g^{-1} w.w. (Σ_9OPEs) over dairy products (1.4 ng g^{-1} w.w.), meat (1.0 ng g^{-1} w.w.) and eggs (1.0 ng g^{-1} w.w.) [54]. The higher presence of OPEs in seafood instead of meat has been reported by other studies conducted in the USA [16,66] where median concentrations of seafood were 7.1 and 8.7 ng g^{-1} w.w. versus 6.7 and 6.2 ng g^{-1} w.w. in meat, respectively. It is also observed that, like most of the commented studies, chlorinated OPEs appear on top in detection frequency. Some studies have also conducted exposure and risk assessment calculations based on the concentrations found in the different analysed species. A previously commented study by Sundkvist et al. [91] stated that everyday consumption of eelpout would result in a total exposure of 180 ng g^{-1} day^{-1} (Σ_8OPES), which is far below the 40 μg g^{-1} day^{-1} suggested by the guideline. Other studies such as the ones conducted by Kim et al. [97] regarding fish species from Manila Bay (Philippines) estimated a dietary intake of 5.9 μg g^{-1} day^{-1} (Σ_9OPES), while dietary intakes associated with the consumption of eels by local fishermen from a region of Flanders ranged between 0.18 (TBOEP) − 1.0 (TCPP) ng kg^{-1} day^{-1}. These studies, together with the ones by Poma et al. [40,83] at Sweeden and Belgium regarding consumer baskets, all conclude that the risk associated with the ingestion via seafood intake is minor, with values even being up to several orders of magnitude below the reference doses (RfD).

3.3. Benzotriazoles

The presence of benzotriazoles in fish was first studied by Cancilla et al. [98] when proving the environmental impact of anti-icing fluids for aircrafts present in an effluent receiving those compounds from an airport runoff. Fathead minnow specimens accumulated 4TTR and 5TTR after their exposure to a stream located after the outfalls of the airport. Jakimska et al. [68] also reported the presence of 4/5TTR in fish samples present in rivers in Spain. Particularly, the appearance of triazoles was noted in fish samples of two locations heavily influenced by external factors such as a city with an important industrial input (Llobregat river, 10.18 ng g^{-1} d.w.) and the outfalls of a WWTP (Ebro River, 1.25 ng $^{-1}$ d.w.). Following the line of the effects of WWTP Yao et al. [82] remarked the high detection frequency (100%) of BTR, 4/5TTR, and ClBTR (concentrations from <0.25 ng g^{-1} w.w. for ClBTR to 3.88 ng g^{-1} w.w. for BTR) in fish samples from the Dondjing River, which receives domestic wastewater discharges from the nearest city. Later on, Yao et al. [99] further confirmed the presence of BTR and 5TTR in fish samples from Pearl River and Yangtze River in China with concentrations ranging between 0.27 − 0.90 and 0.30−0.40 ng g^{-1} w.w. for each river, respectively. Greek Evrotas River endemic chub specimens were analysed by Díaz-Cruz et al. [60], confirming the presence of 5TTR in concentrations comprised between 3.5 and 6.2 ng g^{-1} d.w. The study also reported the strong tendency that this compound has to bioaccumulate in fish tissues. Specimens of tilapia (*Tilapia aurea*), striped bass (*Morone saxatilis*), grouper (*Epinephelinae*), and billfish (*Makaira nigricans*) were collected from local fish stores at Chung-Li City, Thailand, and analysed in search of triazoles [77]. Results found in those samples agreed with the previous studies in terms of the congeners found in the samples as well as their distribution. Thus, BTR appeared in concentrations from 42.5 to 71.3 ng g^{-1} d.w. followed by ClBTR (3.7−4.2 ng g^{-1} d.w.) and 4/5TTR (0.4−0.9 ng g^{-1} d.w.). Jia et al. [50] found a shift in that tendency when analysing molluscs from the Bohai Sea, China. In contrast to the other studies, XTR appeared at concentrations twice what was found for BTR in molluscs (GM of 14.4 ng g^{-1} d.w. for XTR vs. GM of 6.47 ng g^{-1} d.w. for BTR) and a 100% detection frequency. Related to these results, estimated daily intakes (EDI) were calculated for BTR ingestion via mollusc consumption, with values comprised between 5.34 and 8.71 ng kg^{-1} bw day^{-1} were estimated for Σ5BTRs, assessing that children and teenagers were more exposed to triazoles. Previously commented studies such as the one conducted by Yao et al. [99] also calculated the risk associated with the ingestion of BTR through fish consumption resulting in a maximum hazard quotient (HQ) values ranging between 1.19E-07 and 7.87E-06, which were far below 1, meaning that the health risk was minimum.

3.4. Benzothiazoles

Data concerning the occurrence of benzothiazoles in fish samples is highly scarce in the literature. To date, few articles have proven the presence of these compounds in fish and seafood. Trabalón et al. [17]studied the presence of BT, ClBT, MeSBT, NH_2BT, and OHBT in samples of the ten most consumed seafood species from Tarragona, Spain. Results showed that BT was present in most of the analysed samples with the highest concentrations in a range between 13 and 82 ng g^{-1} d.w. followed by NH_2BT (11−70 ng g^{-1} d.w.), ClBT (6−38 ng g^{-1} d.w.) and MeSBT (11−24 ng g^{-1} d.w.). Squid was the species with the highest concentration of a single compound (BT at 82 ng g^{-1} d.w.) whereas mussel appeared as the species with the most present benzothiazoles. As with benzotriazoles, Jia et al. [50] also described the presence of BT, MeSBT, OHBT, NH_2BT, SCNMeSBT, MeBT in molluscs from nine industrial coastal cities. BT, SCNMeSBT, MeBT, and MeSBT were detected in all the analysed samples (n = 166), being BT the compound with the highest concentration in a range between 132 and 13400 ng g^{-1} d.w. (GM: 595 ng g^{-1} d.w.), followed by SCNMeSBT (GM: 67.1 ng g^{-1} d.w.), MeBT (GM: 24.2 ng g^{-1} d.w.), OHBT (GM: 20.1 ng g^{-1} d.w.), MeSBT (GM: 14.2 ng g^{-1} d.w.) and finally NH_2BT (GM: 0.165 ng g^{-1} d.w.). In contrast with the previously stated by Trabalón et al. [17], OHBT was more present in molluscs despite it not being found in any of the fish species from Tarragona. On the other hand, NH_2BT, which was found in fish samples, was present at much lower concentrations in molluscs. BT concentrations appear at way higher rates in mollusc compared with the fish samples from Tarragona which may indicate higher bioaccumulation. The presence of OHBT in fish samples was also denoted by Chen et al. [77], whose study found concentrations ranging from 15.4 to 26.1 ng g^{-1} d.w. in samples of striped bass, billfish, tilapia, and grouper from Chung-li city (Taiwan) local markets. Regarding exposure and risk assessment, both Trabalón et al. [17] and Jia et al. [50] conducted calculations for the exposure and risk associated with the ingestion of benzothiazoles via dietary intake. In both cases, BT appeared as one of the major congeners with EDI values between 22 and 94.9 ng kg^{-1} bw day^{-1}. The existence of repeated dose oral expose values such as NOAEL for benzothiazoles is only available for benzothiazole (BT). Thus, calculations related to toxicity can only be performed for this

Table 2
Estimated Daily Intakes (EDI, ng/kg body weight/day) of different HPVs present in seafood.

Compounds	Population	Species	EDI	Most affected group	Top contributors	Ref.
Σ_{11}OPEs	China	Shrimp, oyster, crab	24	Young males (6–18 years)	TCEP, TCPP	[107]
Σ_1PAE	Taiwan	Shrimp	0.07	Adult males	DEHP	[39]
Σ_6BTs	China	Mollusc	95	Children and teenager males	BT	[50]
Σ_5BTRs	China	Mollusc	8.7	Children and teenager females	BTR, XTR	[50]
Σ_5BTs	Spain	Fish, mussel, squid	48	Adult women, Senior women	BT	[17]
Σ_1PAE	US	Fish	0.6	Females of reproductive age	DEHP	[93]
Σ_6PAEs	China	Fish	1500	General population	DEHP	[15]
Σ_6PAEs	China	Fish	85	General population	DEHP	[34]
Σ_{11}OPEs	US	Fish	1.8	Toddlers (1 to <6 years)	TBOEP, TnBP, TCPP	[16]
Σ_9OPEs	Philippines	Fish	5.9	General population	TEHP, TEP, TnBP	[97]
Σ_5OPEs	Sweden	Fish	20	Adults	TCPP, TBOEP, EHDPP	[59]
Σ_7OPEs	Belgium	Fish	300	Adults	EHDPP, TPhP, TCPP	[83]

compound. In this sense, and with a reference value (RfD) of 5000 ng kg^{-1} bw day^{-1}, both studies concluded that minor risk was associated with the ingestion of BT via dietary intake, with levels reaching up to 2–3 orders of magnitude lower than reference BT RfD value for molluscs.

3.5. Overall HPVs occurrence and toxicity

The presence of PAEs in seafood is the most notable in terms of higher concentrations and detection frequency, especially for DEHP, with variable concentrations reaching the high μg g^{-1} w.w. Being the most known compound family, data on their occurrence as well as investigation on their potential bioaccessibility are easily found in the literature. The occurrence of OPEs in seafood is, as observed, an emerging topic gaining more attraction every day. Believed to be widespread by diffusive sources, their presence in fish from locations all over the world has been widely proven. Their study can lead to an onsite interpretation of OPEs contamination, as local sources represent a highly important indicator of the different OPEs used by a certain location, as well as the impact of surrounding industries or the appearance of unwanted leakages. As regards levels and distribution, concentrations surrounding the low ng g^{-1} w.w. are mostly found, whereas chlorinated OPEs, represent the most frequently detected congeners. Most of the data found in the literature constrain the concentrations of benzotriazoles and benzothiazoles found in seafood at low ng g^{-1}, with slightly higher levels for the latter. As per their concentration distribution on the different fish species, no significant differences are noticeable given the available data. It is however highly proven that industrialisation and domestic discharges are the main sources of the widespread occurrence of these contaminants in seafood. Nevertheless, data concerning the concentration of these compounds in commercially available fish and seafood species is scarce.

The exposure and risk associated with the presence of HPVs in seafood seem to be far from being a problem, with most of the studies placing its dietary intake far below the reference dose (RfD) This chronic risk (long-term) is usually obtained as the result of the comparison between the estimated daily intake (EDI) and a reference dose value. These RfD values are established upon the NOAEL values (non-observed-adverse-effect-level), which are found experimentally by means of assays involving rodents' dose-response effects upon the repeated administration of known concentrations of the studied compound. Organisations like the Environmental Protection Agency (EPA) or the European Food Safety Authority (EFSA) provide reference dose values for some of the compounds, especially for the most well-known like phthalates and some organophosphates. However, data regarding the reference doses for benzothiazoles and benzotriazoles are still uncertain. Table 2 compiles some of the results involving the estimated daily intakes (EDIs) of OPEs, PAEs, BTs and BTRs present in seafood along with the population group with the highest impact and the compounds with the highest contribution. As observed in the table, PAEs EDI values are greater when compared to the other families, a fact directly linked with the presence of DEHP, which always appear as the highest contributor. Regarding OPEs, EDIs values are comprised in a wide range between 1.8 and 300 ng/kg body weight/day, which can associate with the different concentrations found in the samples along with the number of congeners included in the total sum. For BTRs and BTs, slightly higher results are found for the latter, also agreeing with the concentration levels typically found in the samples. As for the most affected groups, differences are found between the studies, mainly based on the seafood intake, which can be linked with the geographic and cultural differences of the populations where the studies were conducted.

It is also important to mention that none of the previously described studies reported EDI values higher than the reference doses (RfD) for any of the studied compounds nor a hazard quotient (HQ) which indicated a risk to the population when consuming seafood. Nonetheless, synergic effects and alternative and complementary exposure pathways such as inhalation, dermal exposition, or ingestion of particulate matter or other foodstuffs are not included in the previous values, thus only giving a partial view of how the presence of HPVs could lead to a real menace towards population health.

4. Conclusions

High production volume chemicals presence in seafood is nowadays attracting more attention. Its ability to give information on both the environmental status and the exposure and risk associated due to the ingestion of contaminated seafood turns its study into a fundamental strategy. The progress towards the development of effective, sensitive, and greener methods has led to the use of QuEChERS as an excellent alternative to determine these compounds. Its easy procedure, along with the wide selectivity and proven good results suggest that this technique should be extended to even more HPVs family's determination in seafood. Regarding one of the most critical steps, the clean-up, strategies such as dispersive solid phase extraction using sorbents like florisil, C18, and PSA yield good results in terms of apparent recovery as well as reduction of matrix effect. Focus should be pointed towards florisil application as clean-up sorbent, as most of the methods involving its use convey on its effectiveness. Other alternative clean-up strategies such as LipiFiltr are quite promising. Even though methods for most of the compounds are found in the literature, families such as benzothiazoles and benzotriazoles are yet to be further investigated, both in terms of development of alternative determination methodologies as well as monitorization of their

occurrence in seafood samples. Further progress is expected in this field in terms of miniaturization, greener approaches, and novel methodologies capable of overcoming challenging and crucial steps of the determination of HPVs in seafood. Future research should also focus on the determination of the possible metabolites and degradation products that may be present in the samples as a result of both their incorporation from external sources and their metabolic degradation once ingested. The ubiquitous presence of most of these compounds in several seafood samples should lead to the development of replacement compounds with lesser or ideally no negative effects on the population, thus reducing their presence in seafood or any other fate susceptible of being accessible to the population. Regarding population's exposure and toxicity risk via dietary intake, values of estimated daily intake (EDI) were found under the reference dose (RfD) for those compounds with an available value, suggesting chronic toxicity due repeated dose intake through fish consumption is minor. Albeit toxicity values being low, no studies regarding the synergic and metabolic effects, or even the bioaccessibility of some of the compounds have been portrayed, thus diminishing the certainty of these risk values being correct. Future research on this topic is needed so as to enhance the data to portray more accurate calculations and provide better risk assessment reports.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Authors report financial support was provided by Spain Ministry of Science and Innovation.

Data availability

No data was used for the research described in the article.

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