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Bioaccessibility of plastic-related compounds from polymeric particles in marine settings: Are microplastics the principal vector of phthalate ester congeners and bisphenol A towards marine vertebrates?

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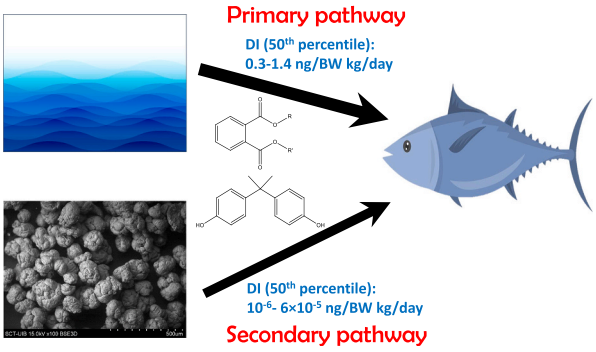
HIGHLIGHTS

- Evaluation of bioaccessibility tests mimicking fish gastrointestinal tract
- A dual compartment system is necessary for plastic-borne compounds.
- Out of 9 plastic-laden compounds, only DMP, DEP and BPA bear bioaccessibility>34 %.
- Role of microplastics as vectors against dissolved compounds in seawater
- Microplastics are not the main source of exposure of plasticizers to marine fish.

GRAPHICAL ABSTRACT



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ABSTRACT

Marine vertebrates are known to ingest significant amounts of microplastics (MPs). Once ingested, MPs might cause gastrointestinal injuries and serve as a path of harmful plastic components, such as phthalate esters (PAEs) and bisphenol A (BPA) in the food chain. However, there is a lack of standardized *in-vitro* methods capable of simulating fish uptake of chemicals from MPs in the environment as potential vectors of such contaminants. In this work, leaching and *in-vitro* oral bioaccessibility testing of PAEs and BPA from MPs were conducted batchwise using artificial seawater and gut fluids mimicking gastric, intestinal, and gastrointestinal compartments of marine vertebrates at physiological temperature. The environmental and physiologically relevant extraction tests were applied to medium-density polyethylene (PE) and polyvinyl chloride (PVC) certified reference materials containing eight PAEs of varying hydrophobicity, *namely*, dimethyl phthalate (DMP), diethyl phthalate (DEP), di-

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n-butyl phthalate, benzylbutyl phthalate, diethylhexyl phthalate, di-n-octyl phthalate, diisononyl phthalate and diisodecyl phthalate, and BPA (only in PE) as MP surrogates with realistic analyte concentrations of additives for primary MPs. The analysis of the leachates/gut fluid extracts was performed via dilute-and-shoot by ultra-high performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Only the most hydrophilic compounds, i.e. DMP, DEP and BPA, were found to get released significantly in saline waters, and exhibited the highest oral bioaccessibility rates (34–83 %). Based on our results, a dual-compartment physiologically relevant gastrointestinal test is recommended for appropriate estimation of fish bioaccessibility. The fish daily intakes of DMP, DEP and BPA from MPs, and seawater ingestion as well were estimated using several contamination scenarios (10th percentile as the low level, 50th percentile as the medium level and 90th percentile as the high level) based on probabilistic distributions and cumulative probability curves of measured environmental concentrations of (i) MPs in seawater throughout the world, (ii) DMP, DEP and BPA in beached MPs and those sampled in the open ocean (including both incurred and adsorbed contaminants), and (iii) DMP, DEP and BPA in seawater as reported in recent literature. Under a medium-level concentration scenario (50th percentile) in marine settings, and taking the gastrointestinal bioaccessibility factor into account, the daily intake of DMP, DEP and BPA from MPs accounted for a mere 0.02 % of the waterborne contribution. Hence, the ingestion of MPs should not be considered the primary route of fish exposure to BPA and the most polar PAEs in marine environments. However, more studies on the local and the global scales for mass concentrations of MPs and additives in marine settings are needed for further confirmation of our findings.

1. Introduction

Plastic materials bear several organic compounds added to modify their physicochemical properties, functionality and structural factors. Some examples of these compounds include additives such as plasticizers, flame retardants, light and thermal stabilizers, antioxidants, pigments, surfactants, lubricants, and residual monomers (Campanale et al., 2020; Kwon et al., 2017; Ramos et al., 2023). Plasticizers providing flexibility, softness and durability are the most frequently used plastic additives across the manufacturing process (Godwin, 2017; González-Mariño et al., 2019; Wadey, 2002). They encompass various types of chemicals, with phthalate esters (PAEs) as the most common organic components. Short-chain PAEs, such as dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DnBP) and benzylbutyl phthalate (BzBP), are frequently found in plastic films (Huang et al., 2018; Koo and Lee, 2004; Lim and Lee, 2020; Wang et al., 2016; Weuve et al., 2006). Long-chain PAEs, such as diethylhexyl phthalate (DEHP), di-n-octyl phthalate (DnOP), diisononyl phthalate (DiNP) or diisodecyl phthalate (DiDP), are commonly added to polyvinyl chloride (PVC), often comprising up to 50 % of its mass (Bouma and Schakel, 2002; Bu et al., 2021; Earls et al., 2003; Fasano et al., 2012; Xie et al., 2016). PAEs are deemed endocrine disruptors that primarily target the male reproductive system (Casals-Casas and Desvergne, 2011; Habert et al., 2009; Romani et al., 2014; Sedha et al., 2015). The European Parliament Directive 2005/84/EC banned DEHP, DnBP, and BzBP at concentration levels above 0.1 % by mass in toys and child-care articles (EC, 2014a). For higher-molecular mass PAEs, namely DiNP, DiDP, and DnOP, the Directive ban applies only to toys that can be introduced in children's mouth (EC, 2014b).

Another prevalent organic compound in plastic materials is bisphenol A (BPA). Its high solubility in water makes BPA prone to leaching into the aquatic environment or migrating out from various consumer products, including food packages, and even medical devices (Geens et al., 2012; Sajiki and Yonekubo, 2004). BPA is known to act as an oestrogen receptor agonist and androgen receptor antagonist, exerting a wide range of deleterious effects on the human reproductive system (Park et al., 2020; Wu et al., 2020). Numerous biomonitoring studies have confirmed that even low doses of BPA might cause harm in animal models (EFSA, 2023; Richter et al., 2007; Vandenberg et al., 2010), and its widespread use renders it a potentially hazardous substance for humans (Vandenberg et al., 2007; Sun et al., 2020). The European Union implemented regulations limiting BPA to 0.02 % (*w*/w) in thermal paper since January 2020 (EC, 2016) and had previously banned its use in polycarbonate drinking containers for infants and toddlers (EC, 2011).

The occurrence of MPs in the marine environment, and extended to human samples, has been an issue of increasing concern in recent years (Hassan et al., 2022; Saha et al., 2021; Malafaia and Barceló, 2023). It has been estimated that between 4.8 and 12.7 million tons of plastic are disposed of in the oceans, and this amount is continuously rising (Borrelle et al., 2020; Jambeck et al., 2015). MPs exhibit a wide range of distributions in size, shape, colour and polymer type (Brandon et al., 2016), and are known to be potentially ingested across all trophic levels in the marine environment, including marine invertebrates, bivalves, fish and marine mammals (Courtene-Jones et al., 2017; Dowarah et al., 2020; Fossi et al., 2016; Hernandez-Gonzalez et al., 2018; Ismail et al., 2019; Mistri et al., 2022; Panti et al., 2015). Once ingested, MPs might be responsible for deleterious physiological effects (Borrelle et al., 2020; Botterell et al., 2019; Pittura et al., 2018; Wright et al., 2013), but they might also transfer (ad)sorbed chemicals and plastic additives to biota (Borrelle et al., 2020; Bridson et al., 2021; Ding et al., 2024; Koelmans et al., 2014, 2023; Luo et al., 2019).

The digestive system of vertebrate species simulates a complex bioreactor in which various reactions under physiological conditions such as hydrolysis, take place. These reactions are affected by numerous abiotic and biotic factors, including enzyme activities, probiotics, and cellular membranes, among others, which collectively impact the fate of the (ad)sorbed contaminants onto MPs. It is important to note that the intake of contaminants does not always reflect their biological accessibility (also known as bioaccessibility) to an organism (Gilannejad et al., 2018; Solovyev et al., 2018). Oral bioaccessibility refers to the percentage of a total contaminant that can be extracted in the gastrointestinal tract (GIT), and is potentially available for intestinal absorption following ingestion, so-called bioavailability (Gonçalves et al., 2019; Saura-Calixto et al., 2007; Trujillo-Rodríguez et al., 2020).

Conducting *in-vivo* experiments to assess the bioaccessibility/bioavailability of a given target can be challenging and costly. An efficient alternative is to simplify the digestion process through *in-vitro* physiologically based assays as proxy of the gastrointestinal tract using laboratory equipment. *In-vitro* bioaccessibility tests for vertebrate aquatic biota have been traditionally focused on the nutritional evaluation of protein-rich feed ingredients as referred to amino acids and proteins (Moyano et al., 2015), yet recent efforts were expanded to ascertain the hydrolysis of feed carbohydrates under gut conditions (Gilannejad et al., 2019). Notwithstanding the fact that there is no harmonized test to serve as a standard biological mimic for organisms in natural and marine waters (Moyano et al., 2015), researchers have adopted some of the previous protocols to investigate the oral bioaccessible fractions of plastic additives and adsorbed contaminants onto plastic debris and secondary microplastics in aquatic species. To the best of our knowledge, however, all the reported protocols are based on overly simplistic gut conditions based on a single compartment (mostly gastric phase) (Chen et al., 2021; Coffin et al., 2019a, 2019b; Mohamed

Nor and Koelmans, 2019) or using unrealistic physiological conditions (e.g., taurocholate as bile salt at pH 4.0).

The aim of this work is to assess the actual impact of MPs on the exposure of marine vertebrates to plastic additives, such as PAEs and BPA. Firstly, the leaching process of PAEs and BPAs under marine conditions using saltwater as a leaching medium is investigated. Secondly, the fish bioaccessibility of PAEs and BPA from MPs using biorelevant physiologically-based extraction tests is explored using gastric and intestinal fluids in a single and two-compartment modes in a sequential (additive) extraction format. This is the first time that a dual-compartment test that closely mimics fish physiology is evaluated for the bioaccessibility of plastic-laded compounds. Additionally, the potential generation of degradation/transformation products under *in vitro* physiologically relevant digestion conditions is examined. To this end, two certified reference materials (CRM) containing PAEs and BPA with a wide range of polarities are selected: (i) medium-density polyethylene (PE) and (ii) polyvinyl chloride (PVC) both with average particle sizes down to 115 μm. Lastly, the fish daily intake of plastic additives through ingestion of MPs, for which oral bioaccessibility data is incorporated, is critically compared against that of seawater under varied environmental scenarios to elucidate whether MPs in the environment become the principal vector of those plastic-related materials towards marine vertebrates. To cope with the variability of available data on environmental concentrations of MPs and additives in recent literature, a probabilistic approach based on cumulative probability functions (CPF) is herein undertaken. It should be noted that, to the best of our knowledge, none of the previous probabilistic environmental risk assessment studies of MPs in marine settings include the effect of plastic-borne additives (Adam et al., 2021; Gu et al., 2024).

2. Materials and methods

2.1. Reagents and materials

LC-MS grade methanol (MeOH) and GC–MS grade ethyl acetate (AcOEt) were purchased from Fisher Scientific (Portsmouth, NH, USA). Pestinorm grade dichloromethane (DCM) was purchased from VWR (Radnor, PA, USA). Milli-Q (MQ) water was obtained through a Millipore water purification system (Burlington, MA, USA). Acetic acid was purchased from Scharlau (Sentmenat, Spain). Hydrochloric acid (37 % *w*/w), sodium hydroxide, tris(hydroxymethyl)aminomethane (Trizma-Base) and ammonium fluoride with purity ≥99 % were purchased from Merck KGaA (Darmstadt, Germany).

Analytical standards of BPA, DMP, DEP, DnBP, BzBP, DEHP, DnOP, DiNP, DiDP and deuterated plasticizers thereof used as internal standard (IS), namely, DMP-d4, DnBP-d4, BPA-d16, DEHP-d4, were purchased from Merck KGaA. Analytical standards of their main metabolites/hydrolytic products, namely, monomethyl phthalate (MMP), monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), mono-(2-ethylhexyl) phthalate (MEHHP), mono-(2-ethyl-5-carboxylpentyl) phthalate (MECPP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(hydroxyisononyl) phthalate (MHINP) were purchased from AccuStandard (New Haven, CT, USA). IS of metabolites/hydrolytic products, namely, MMP-d4, MBP-d4 and MEHHP-d4 were purchased from Toronto Research Chemicals (Toronto, ON, Canada). All standards were of a purity ≥97 %. Individual stock standard solutions of ca. 1,000 mg/L were prepared in AcOEt or MeOH. All standard solutions were stored at −20 °C pending use.

Two certified reference materials (CRM) of PE (CRM-PE002) and PVC (CRM-PVC001) MPs (Spex CertiPrep, Stanmore, UK), with average particle sizes (mean particle number) of 99 μm and 115 μm, respectively, and particle size distribution spanning from 28 to 550 μm, and 57 to 275 μm, respectively, as determined by laser diffraction analysis (Microtrac MRB-Sync, Microtrac Retsch, Haan, Germany), and with certified concentrations of DiDP and DiNP at ca. 30,000 μg/g, and DMP, DEP, DnBP, BzBP, BPA (only in PE), DEHP and DnOP at ca. 3000 μg/g were used in this study (see actual certified concentrations in Table S1). It should be noted that the concentration of plasticizers in raw plastics might exceed 10 % (*w*/w) (Hahladakis et al., 2018) as is the case with flexible PVC products.

Artificial seawater was prepared by dissolving the following salts in MQ water: 3 mg/L NaF, 2.4 mg/L $SrCl_2{\cdot}2H_2O$, 47.5 mg/L $Na_2B_4O_7$, 100 mg/L KBr, 700 mg/L KCl, 147 mg/L $CaCl_2{\cdot}2H_2O$, 4 g/L Na_2SO_4, 10.78 g/L, $MgCl_2{\cdot}6H_2O$, 23.5 g/L NaCl, and 200 mg/L $NaHCO_3$ (Kester et al., 1967). Various simulated gastric and intestinal fluids were prepared to evaluate the effect of distinct gut constituents and compartments on fish bioaccessibility (Carter et al., 1999; Coffin et al., 2019a, 2019b; Gilan-nejad et al., 2018; Hamdan et al., 2009). The gastric fluid contained 1 mg/L pepsin (Merck KGaA, ref: 1071850100, 0.7 FIP-U/mg protein) adjusted to pH to 2.0 ± 0.1 using HCl (37 %). For the intestinal fluid, a buffer solution containing 0.05 M Trizma-Base was first prepared and adjusted to pH 8.0 using 1 M NaOH. The intestinal enzyme solution (so-called Carter method) was composed of 3.2 g/L of pancreas trypsin (Merck KGaA, T7409, ≥ 1000 U/mg protein), 7.5 g/L pancreas alpha-chymotrypsin (Merck KGaA, C4129, ≥ 40 U/mg protein) and 2.8 g/L pancreas protease (Merck KGaA, P4630, ≥ 5 U/mg protein) in the Trizma buffer solution (pH 8) (Carter et al., 1999). To obtain the full intestinal fluid (enzymes + bile salts, so-called Hamdan method), 96 mg/L sodium taurocholate hydrate and 76 mg/L sodium chenodesoxycolate were added to the enzyme solution (Hamdan et al., 2009). All inorganic and organic constituents were purchased from Merck KGaA with a purity ≥97 %.

2.2. Desorption experiments

2.2.1. Leaching tests using aqueous extractants

The leaching procedure was performed by accurately weighing 0.1 g of PE or PVC MPs into glass test tubes by triplicate. Subsequently, 4 mL of MQ water or artificial seawater were added to each tube and the samples were incubated for 16 h at 25 ± 2 °C using an end-over-end shaker (Thermo Fisher Scientific, Bedford, MA, USA) at 37 rpm. Following the incubation, the samples were centrifuged for 30 min at 1500 rcf, and the supernatant was retrieved into a glass vial.

2.2.2. In-vitro fish bioaccessibility tests

Physiological extraction conditions of fish gut were mimicked by adjusting the pH and the chemical composition of the digestive fluids, and the typical residence times of the chyme in the gastric (viz., 4 h) and intestinal (viz., 12 h) compartments.

Bioaccessibility tests started by weighing 0.1 g of PE or PVC MPs into borosilicate glass test tubes in triplicate. Subsequently, 3 mL of the gastric fluid was added to the samples. The tubes were then placed on an end-over-end shaker set at 37 rpm for 4 h in a dark environment at 25 ± 2 °C. After the incubation period, the samples were centrifuged for 30 min at 1500 rcf, and the supernatant was collected for further analysis of the gastric (G) bioaccessibility.

Two types of intestinal fluids, namely, the enzyme solution (Carter's method) and the enzyme solution + bile acids (Hamdan's method), were used as single extractants added to 0.1 g of PE or PVC MPs. To this end, 4 mL of either intestinal fluid was added to the MPs (in triplicate) and subjected to end-over-end agitation at 37 rpm for 12 h at 25 ± 2 °C. The intestinal extracts were centrifuged alike the G phase and the supernatant retrieved for analysis of the intestinal bioaccessibility. For the two-compartment assay (gastrointestinal phase, GI), 4 mL of the intestinal fluid (Hamdan's method) was added to the G extract after incubation, followed by GI extraction for further 12 h at 25 ± 2 °C with agitation at 37 rpm (total extraction time of 16 h). The GI extracts were centrifuged at 1500 rcf for 30 min, and the supernatant retrieved for further analysis of the GI bioaccessibility.

2.3. Analysis of the G, the intestinal, the GI bioaccessible and the leachable fractions

The analysis of the leachable and the oral bioaccessible fractions was performed by dilute-and-shoot with a dilution of 1:125 (*v*/v) and 1:94 (v/v) of the gastric and (gastro)intestinal supernatants, respectively, for PAEs and BPA, and a dilution of 1:88 (v/v) and 1:66 (v/v) of the gastric and (gastro)intestinal supernatants, respectively, for metabolites/hydrolytic products in ultrapure water/MeOH (80:20, v/v). The selection of the amount of MeOH is aimed at preventing protein precipitation ($\leq$ 20 % organic solvent) to avoid losses of compounds bound to proteins while minimizing plasticizers sorption on the surface of the borosilicate glass and tubing of the analytical instrumentation. ISs were added to the final extract at a concentration level of 700 μg/L for PAEs and BPA, and 500 μg/L for metabolites/hydrolytic products. Aliquots of 1 mL of the extracts were filtered through hydrophilic polytetrafluoroethylene (PTFE) filters (Ø 13 mm, 0.22 μm) from Phenomenex (Torrance, CA, USA), followed by percolation of 250 μL of MeOH to prevent analyte losses. The extracts were analysed by liquid chromatography coupled to triple quadrupole mass spectrometric detection (LC-QqQ-MS).

2.4. QC/QA studies

PVC and PE MPs (CRM-PVCBLK and CRM-PEBLK, Spex Certiprep) without incurred analytes (blank CRM) were analysed in all the leaching tests and oral bioaccessibility methods for QC/QA purposes and the evaluation of contamination sources. In order to minimize the potential background contamination of PAEs, all glassware was baked at 300 °C for 12 h before use (González-Mariño et al., 2019).

Residual (non-leachable and non-bioaccessible) fractions of CRM-PE002 and CRM-PVC001 were also analysed as described in the next section for mass balance assessment.

2.5. Analysis of non-bioaccessible and non-leachable fractions

The MP residues after leaching or *in-vitro* G, intestinal or GI digestion tests were transferred onto a 3 × 3 cm steel mesh with a pore size of 20 μm (Filtra Vibración, Badalona, Spain), washed with 4 mL of ultrapure water, and then dried in an oven at 40 °C overnight. Subsequently, the MPs were transferred to a glass vial and extracted with 2 mL of DCM by ultrasonic solvent extraction (USE) during 30 min at room temperature in closed vials. 1 mL of supernatant was filtered through hydrophobic PTFE filters (Ø 13 mm, 0.22 μm).

The non-bioaccessible G, intestinal and GI fractions were diluted 1:214 (*v*/v) in all cases, with MeOH. IS were added to a concentration of 700 μg/L and analysed by LC-QqQ-MS.

2.6. LC-MS/MS analysis

The bioaccessible and non-bioaccessible fractions of the eight PAEs and BPA and metabolites/hydrolytic products was conducted by LC-QqQ-MS that consisted of a Waters Acquity UPLC H class system (Milford, MA, USA) coupled to a triple quadrupole mass spectrometer Xevo TQD (Waters). Multiple reaction monitoring (MRM) of selected transitions, together with their corresponding collision energies (CE) and cone voltage (CV) values, retention times (RT) and labelled compounds used as IS are listed in Tables S2 and S3.

Separation of PAEs and BPA was carried out using a Synergi 4u Fusion-RP 80 Å C_{18} column (100 mm × 2.0 mm × 4.0 μm) from Phenomenex with a dual eluent system consisting of (A) 1 mM NH_4F in MQ water and (B) 1 mM NH_4F in MeOH at a flow rate of 0.4 mL/min. The gradient elution started with 5 % B, increasing to 95 % B in 10 min, and held at 95% B for 3 min. Return to initial conditions (5 % B) was performed in 0.1 min and held at 5 % B for 3 min further for reconditioning. The injection volume was set to 1 μL.

Separation of phthalate metabolites/hydrolytic products was carried out using a Raptor Biphenyl 90 Å C_{18} column (150 mm × 2.1 mm × 1.8 μm) from Restek (Bellefonte, PA, USA) as described elsewhere (Estévez-Danta et al., 2021). Briefly, a dual eluent system consisting of (A) 0.1 % of acetic acid in MQ water and (B) 0.1 % of acetic acid in MeOH at a flow rate of 0.3 mL/min was used. The gradient elution started with 50 % B, increasing to 100 % B in 17 min, and held at 100% B for 5 min. and finally returning to initial conditions (50 % B) in 0.05 min and held at 50 % B for 5 min further for reconditioning. The injection volume was set to 2 μL.

The software MassLynx v4.1 and TargetLynx v4.1 (Waters) were used for the control and the data treatment, respectively.

2.7. Statistical analysis and probability functions

Statistical treatment of environmental and fish bioaccessibility data was performed using the Statgraphics Centurion XVIII software (Statpoint Technologies, Warrenton, VA, USA). Analysis of variance (ANOVA) was conducted to compare the aqueous leaching against fish G, intestinal and GI bioaccessible fractions of PAEs and BPA. The statistical significance boundary was set to $\alpha = 0.05$ in all cases.

The R programming language (R version 4.2.3) was employed to generate lognormal distributions for the density of MPs in marine waters using μ and σ parameters, alongside minimum and maximum values extracted from Beiras and Schönemann (2020). A script was developed to accurately model the distribution based on these parameters, and subsequently validated against the reported values in Beiras and Schönemann (2020) to ensure fidelity. Furthermore, comprehensive datasets for the worldwide distribution of MPs were compiled, merging data from various geographical areas and fitting them to lognormal distributions. Additionally, concentrations of PAEs and BPA in beached and open-ocean MPs were extracted from Fred-Ahmadu et al. (2020) and Hirai et al. (2011), respectively. These datasets were subjected to fitting procedures involving lognormal, gamma, or exponential distributions to determine the best fit, and evaluated them using the Akaike information criterion. Notably, the lognormal distribution consistently provided the best fit in all cases. Mean and standard deviation calculations were conducted for the product of global MP concentrations and the concentration of each contaminant in MPs using the parameters defining lognormal distribution, thereby facilitating the generation of the respective datasets. Subsequently, CPFs were computed and plotted for the product. Percentiles were selected to estimate values for low-level, medium-level, and high-level scenarios, such as the 10th, 50th (median), and 90th percentiles, respectively.

Datasets for PAEs in seawater were assembled from Paluselli and Kim (2020), Zhang et al. (2020), Paluselli et al. (2018), Cao et al. (2022), and Dhavamani et al. (2022). For BPA in seawater, data from Staples et al. (2018) were selected based on minimum, median, 95th percentile, and maximum values, and lognormal distributions were generated and validated against the same article's reported values. Finally, CPFs were generated using the PAEs and BPA concentrations in seawater datasets. Percentiles were calculated as indicated above to provide insights into three distinct scenarios based on the distribution plots.

3. Results and discussion

3.1. Analytical performance of the chromatographic and extraction methods

The LC methods based on external calibration using isotopologues as IS were assessed in terms of linearity, precision and limits of quantification (LOQs) for the target compounds and hydrolytic products thereof (see Tables S2 and S3). For precursors in Table S2, the dynamic linear range extended from 10 μg/L to 5 mg/L, except for DEP, DnBP and DEHP, which ranged from 2 μg/L to 5 mg/L, and BPA that spanned from 0.05 to 5 mg/L. In all cases, the determination coefficients, calculated using least squares regression, were consistently > 0.9990. Repeatability

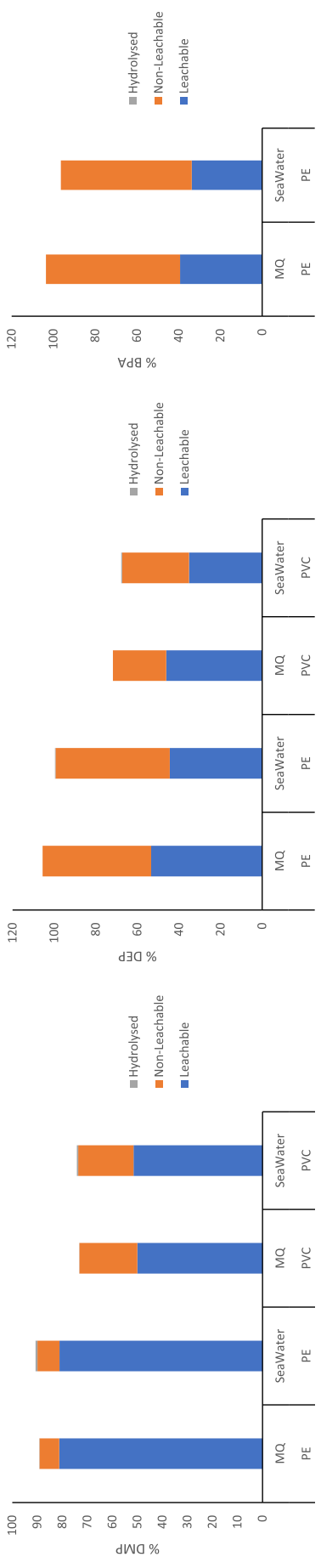

Fig. 1. Leaching of plastic-borne compounds in ultrapure water and seawater from PE and PVC MPs. Note that only those compounds detectable in the water extractant phases are herein illustrated (full data is available in Table S5).

evaluation at the 100 μg/L level for 5 replicates yielded relative standard deviations (RSD) ranging from 6 to 18 % for both parents and hydrolytic products. The LOQs, calculated for a signal-to-noise ratio of 10, ranged from 0.90 and 10 μg/L, thus entailing a significant improvement for BPA and DnOP compared to our previous study (López-Vázquez et al., 2022).

The trueness of the determination of bioaccessible PAEs and BPA in the G and GI (Hamdan's method) phases spiked at a concentration of 400 μg/L ranged from 75 to 118 % and 71 to 110 %, respectively, with RSDs ≤18 % in all cases (see Table S4). The LOQs ranged from 113 to 400 μg/L for the G fluid and from 85 to 301 μg/L for the GI fluid. Therefore, the bioaccessible fractions of the plastic-laden compounds for the studied MPs can be quantified above 0.02 % (*w*/w) for those at the highest concentration (DiNP and DiDP) and from 0.1 to 1.1 % (w/w) for the remaining compounds.

The method trueness of the total determination of PAEs and BPA in the PE and PVC reference materials by USE yielded recoveries ranging from 57 to 90 %, and 77 to 117 %, respectively, with RSD < 20 % (López-Vázquez et al., 2022), and LOQs spanning from 0.45 to 12 μg/g. Consequently, the non-bioaccessible fraction can be quantified above 0.01 % (w/w) for DiNP and DiDP and from 0.06 to 0.6 % (w/w) for the remainder of the compounds in the MPs analysed.

3.2. Leaching of PAEs and BPA in seawater

Leaching tests with single extractants were conducted to investigate the leaching of PAEs and BPA from PE and PVC MPs in MQ water and seawater following the analytical procedures described in Section 2.2.1.

The experimental results demonstrated that only the most hydrophilic compounds, i.e. DMP, DEP and BPA, were released to a significant extent from both types of MPs in either aqueous media with leaching rates ranging from 34 to 81 % (w/w) (Table S5 & Fig. 1). For the remainder of PAEs, leachable fractions were negligible. These findings align well with previous studies that (i) employed a dynamic on-line leaching test with simulated seawater for PAEs and BPA for the same CRM MPs (Fikarová et al., 2019) and (ii) determined leachable short-chain PAEs from PE bags and PVC cables (Paluselli et al., 2019). However, it should be noted that the leaching rates might be influenced by additional factors, such as MP weathering, particle size, temperature, and biofilm formation (Binda et al., 2024; Li et al., 2024; Wang et al., 2024; Zhao et al., 2022). The conversion yields of DMP and DEP into the hydrolytic products (MMP and MEP) were down to 0.8 % (w/w) in the leachable fractions of both freshwater and marine water simulating extractants.

The effects of the polymer composition and the aqueous extractant onto the leachable fractions of BPA, DMP and DEP were investigated using multifactor ANOVA (Table S6). Regarding BPA, the effect of MP chemical composition could not be evaluated because BPA is only certified in PE MPs. The ANOVA test revealed that the type of polymer significantly influences the leaching of both DMP and DEP (p-value ≤ 0.0001), with statistically higher desorption from PE MPs for both water extractants, most likely due to the rubbery-like nature of PE that is characterized by increased surface hydrophobicity (less prone to retain the most polar additives) compared to glassy PVC (X. Liu et al., 2020; P. Liu et al., 2020). The type of aqueous medium did not exhibit a significant effect on DMP and BPA (p-value = 0.7074 and 0.1027, respectively) indicating a similar leaching behaviour in MQ and seawater, as opposed to DEP (p-value < 0.0001). As to the latter, leaching was reduced with the addition of salts, attributed to a salting-out like effect in seawater, thereby suggesting longer residence times of DEP adsorbed to MPs in marine settings. Two-factor parameter interactions were not statistically significant for neither DMP and DEP.

The mass balance obtained by the sum of the leachable plus the residual and the hydrolytic fractions for DMP, DEP and BPA rendered absolute recoveries for PE and PVC MPs ranging from 89 to 118 % and 68 to 98 %, respectively, for both MQ and seawater.

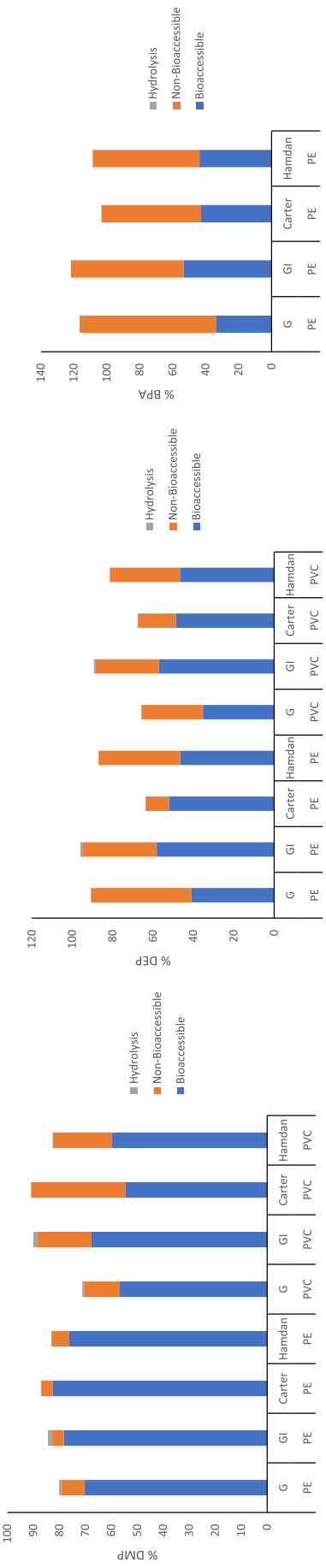

Fig. 2. Comparative assessment of bioaccessible fractions of plastic-borne compounds from PE and PVC MPs using a variety of fish gut fluids. Note that bioaccessibility data are only shown for the three most leachable compounds (full data is available in Table S7).

Table 1
Multifactor ANOVA p-values.

Factor	DMP	DEP	BPA
A: MP composition	**<0.0001**	0.1957	–
B: Physiologically based extraction test (PBET)	**0.0059**	**<0.0001**	**0.0040**
MP composition-PBET interaction	**0.0063**	0.6990	–

Statistically significant values ($\alpha = 0.05$) are given in bold.
Acronyms: MP: microplastic; DMP: dimethyl phthalate; DEP: diethyl phthalate; BPA: bisphenol A.

3.3. *In-vitro fish bioaccessibility tests*

The release extent of additives from MPs across the fish GIT was determined by measuring the leachable compounds in biorelevant gut fluids, including the G phase, the enzyme solution (Carter's method), the intestinal fluid (enzymes + bile salts, Hamdan's method) and the GI phase. It is important to note that the bioaccessible fraction represents the maximum amount of compound that can potentially be bioavailable and thus reach the blood stream. The percentage of bioaccessibility under the action of the distinct digestive fluids is presented in Table S7 and Fig. 2. Analysis of blank PE and PVC MPs rendered negligible concentrations of the target compounds, excepting DEP, DBP, DEHP and DINP in the bioaccessible and the residual fractions, and thus they were subtracted from the measured concentrations. For the most hydrophilic compounds, i.e., DMP, DEP and BPA, fish bioaccessibility values ranged between 34 % and 83 %, while oral bioaccessibility was always below 8 % regardless of the body fluid and the MP chemical composition for the remaining compounds. Once again, these results indicate that only the most hydrophilic PAEs or BPA are substantially bioaccessible (López-Vázquez et al., 2022; Mohamed et al., 2023; Sixto et al., 2021) or leachable (Section 3.2). The hydrolysis of PAEs in the time course of the oral bioaccessibility tests was also evaluated. MMP, MEP and phthalic acid were the only degradation products identified across the varied GIT fluids, with transformation rates in all cases down to 1.6 %. Mass balance assessment rendered absolute recoveries spanning from 64 to 117 % for all plastic-borne compounds in the various body fluids regardless of the chemical composition of the polymer.

The fundamental principles underlying the leachability of plastic-related compounds in biotic environments (Li et al., 2024) and the mechanistic models accounting for the leaching phenomena of plastic additives in marine environments (Do et al., 2022) have been recently discussed. In this work, the dependence of the magnitude of the oral bioaccessibility values upon both the MP chemical composition and the *in-vitro* simulated digestion method was investigated using multifactor ANOVA. As shown in Table 1, the ANOVA test indicated that the digestion method is statistically significant (p-values < 0.05) for the three most bioaccessible compounds (i.e. DMP, DEP and BPA). The G fraction exhibited the lowest bioaccessible fraction, which might be attributed to the shorter contact time and the absence of surface-active biomolecules, while the two-step GI digestion incorporating bile acids featured the highest bioaccessibility. It should be noted that fish bioaccessibility of plastic-laden compounds, and thus their risk assessment/exposure, is usually underestimated in the literature because a mere single body fluid extractant is considered in the majority of the publications (Coffin et al., 2019a, 2019b; Mohamed Nor and Koelmans, 2019). For DMP, the polymer matrix and the interaction between the two parameters, viz., the extraction method and the MP chemical composition, were also statistically significant. Akin to water leaching, the bioaccessibility of DMP was higher from PE against PVC MPs, and this effect was more severe for the Carter's method with enzymes only, again indicating the desorption irreversibility of PVC-borne compounds regardless of the complexity of the body fluid. When comparing the oral bioaccessibility results with those of aqueous leaching, only the GI bioaccessible fraction was significantly superior to that of leaching in MQ water (Fig. 3) thereby evincing that multiple-step (additive),

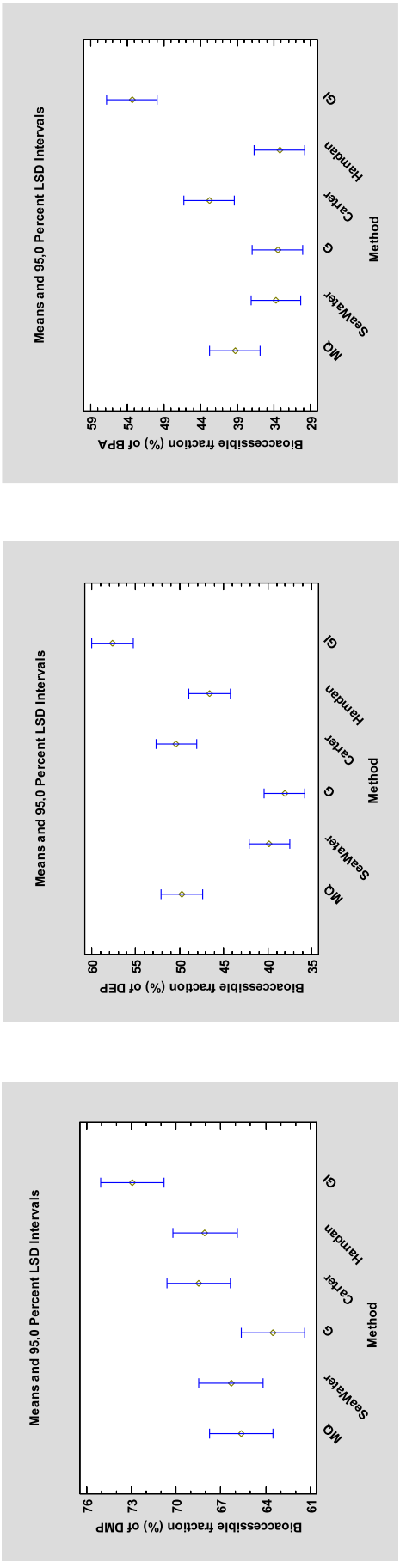

Fig. 3. Comparative assessment of environmental leaching against fish bioaccessibility for DMP, DEP and BPA in PE MPs.

sequential or dynamic extraction procedures should be called for to enable reliable risk assessment/exposure studies of plastic-borne additives on marine vertebrates.

3.4. MP contribution to PAEs and BPA exposure to aquatic marine organisms

The PAEs and BPA exposure to aquatic organisms might occur through the ingestion of water, MPs, non-polymeric particulate matter and feeding. However, this work is aimed at comparing the contribution of MPs as potential vectors against dissolved concentrations in seawater as the primary source. Incorporating alternative sources of exposure to the study would lead to more realistic estimates, yet the *worst-case scenario*, that is, the maximum contribution of MPs to the overall exposure, is herein contemplated.

The daily intake (*DI*, ng/kg/day) (X. Liu et al., 2020; P. Liu et al., 2020) of MP-associated pollutants was calculated using Eq. (1), in which $Q_{pollutant}$ (ng/g) stands for the concentration of PAEs or BPA in MPs, *F* denotes the bioaccessibility (expressed as ratio, instead of %) in the GI fluid (*worst-case* scenario) for PVC or PE MPs, C_{MP} (g/m^3) is the mass concentration of MPs in the marine environment, *V* (m^3/day) stands for the uptake rate of water and *W* (kg) is the body (fish) weight.

$$DI_{MP} = \frac{Q_{pollutant} \times F \times C_{MP} \times V}{W} \quad (1)$$

The concentrations of PAEs and BPA in MPs ($Q_{pollutant}$) vary significantly depending on the source, pursued (micro)plastic application, weathering conditions and polymer chemical nature. It might range from low ng/g in MPs collected from seawater to mg/g in raw plastic materials. We have herein focused on experimentally measured BPA and PAEs in MPs from open ocean and remote and urban beaches, including both incurred additives and those adsorbed in the environment (Fred-Ahmadu et al., 2020; Hirai et al., 2011). To account for the variability of measured concentrations of plastic-laden compounds, data sets with available concentrations in the literature (viz., about 40 experimental data for each contaminant in the two publications above) were represented via CPFs (see Fig. 4A).

As for the concentrations of MPs in the marine environment (C_{MP}), large variabilities are encountered across the distinct seas and oceans. Log-normal probability distributions of C_{MP} in the Mediterranean Sea, North Atlantic Ocean, North Pacific Ocean and Indian Ocean/South Pacific Ocean were represented in a cumulative order using the data reviewed by Beiras and Schönemann (2020) (see Fig. 4B), on the basis of which a wide-ranging worldwide distribution with a data set of >300 experimental points was calculated (see Fig. 4B). The latter distribution ($C_{MPworldwide}$) was selected for estimating *DI*, the product of which with $Q_{pollutant}$ CPF for DMP, DEP and BPA is shown in Fig. 4C. Three distinct scenarios (see Table 2) for $Q_{pollutant} \times C_{MPworlwide}$ (given as ng pollutant/m^3 carried by MPs) were considered to calculate the *DI* of PAEs and BPA, using the 10th percentile (low level concentration), 50th percentile (medium level concentration) and 90th percentile (high level concentration). The *F* used in *DI* estimation was the GI bioaccessibility data reported in Table S6, which encompassed the sum of GI bioaccessible and hydrolytic fractions in either PE or PVC MPs.

The uptake rate of water (*V*) differs significantly among fish species and freshwater/marine environments. Perrott et al. (1992) conducted a study estimating the drinking rate in 12 fish species, ranging from 1.0 to 7.76 × 10^{-6} m^3/kg/h for seawater species. As for the Japanese medaka (*Oryzias latipes*), Tipsmark et al. (2020) estimated a drinking rate of 5 × 10^{-6} m^3/kg/h in freshwater, which doubled in seawater. Consequently, the uptake rate per body weight (*V*/*W*) for seawater fish ranges from approximately 24 to 240 × 10^{-6} m^3/BW kg/day. Therefore, three uptake rates were herein considered: 24, 100 and 240 × 10^{-6} m^3/BW kg/day.

DI associated to MPs (DI_{MP}) varies greatly depending on the scenario considered. In the worst-case scenario (90th percentile along with the

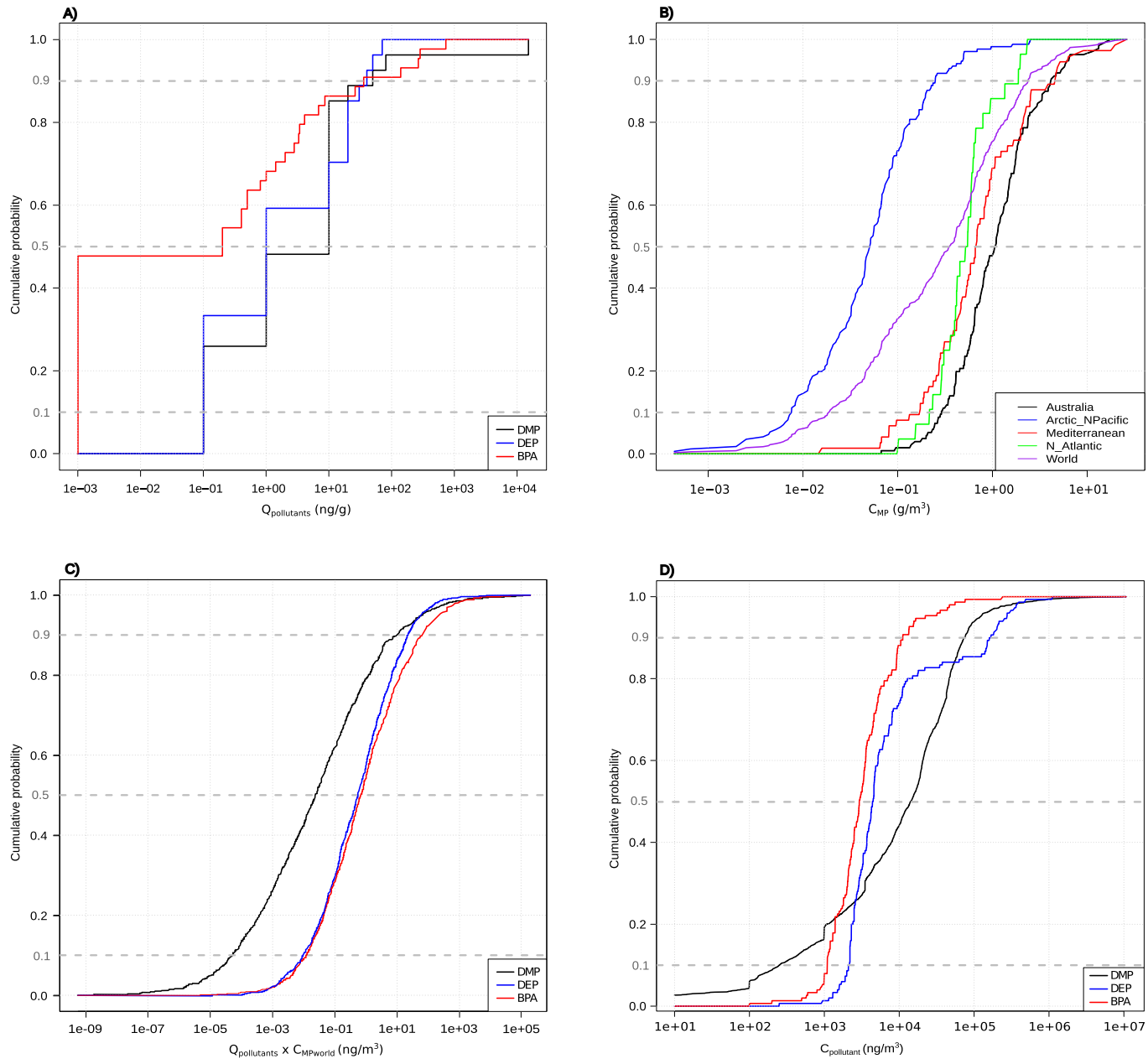

Fig. 4. Cumulative probability functions of A) additive concentrations in MPs ($Q_{pollutant}$); B) MP concentrations in seawater (C_{MP}) across the Pacific, Atlantic and Indian Ocean, Mediterranean Sea and throughout the world; C) $Q_{pollutant} \times C_{MPworld}$; and D) additive concentrations dissolved in seawater ($C_{pollutant}$).

Table 2
Estimated DI_{MP} (ng/BW kg/day) of PAEs and BPA from PE and PVC MPs at three concentration levels based on the 10th, 50th and 90th percentiles from the cumulative probability function of $Q_{pollutant} \times C_{MPworld}$ (see Fig. 4c) and the varied fish uptake rates of seawater.

V/W (m^3/BW kg/day)	Scenario	DMP			DEP			BPA	
		$Q_{pollutant} \times C_{MPworld}$ (ng/m^3)	DI_{MP} (ng/BW kg/day)		$Q_{pollutant} \times C_{MPworld}$ (ng/m^3)	DI_{MP} (ng/BW kg/day)		$Q_{pollutant} \times C_{MPworld}$ (ng/m^3)	DI_{MP} (ng/BW
			PE	PVC		PE	PVC		PE
2.4E−05	Low level (10th percentile)	0.011	2.10E−07	1.85E−07	8.74E−03	1.24E−07	1.22E−07	3.87E−05	4.92E−10
1E−04	Medium level (50th percentile)	0.73	5.81E−05	5.11E−05	0.42	2.47E−05	2.43E−05	0.02	1.06E−06
2.4E−04	High level (90th percentile)	51.0	9.74E−03	8.57E−03	21.5	3.04E−03	2.99E−03	10.5	1.34E−03

Acronyms: DI: daily intake; PAEs: phthalate esters; DMP: dimethyl phthalate; DEP: diethyl phthalate; BPA: bisphenol A; PE: polyethylene; PVC: polyvinyl chloride; MPs: microplastics.

Table 3
Estimated DI_{water} (ng/BW kg/day) of PAEs and BPA from seawater ingestion at three concentration levels based on the 10th, 50th and 90th percentiles from the cumulative probability function (see Fig. 4d) and the varied fish uptake rates of seawater.

V/W (m^3/BW kg/day)	Scenario	DMP		DEP		BPA	
		$C_{pollutant}$ (ng/m^3)	DI_{water} (ng/BW kg/day)	$C_{pollutant}$ (ng/m^3)	DI_{water} (ng/BW kg/day)	$C_{pollutant}$ (ng/m^3)	DI_{water} (ng/BW kg/day)
2.4E−5	Low level (10th percentile)	1.10E+03	2.64E−02	2.17E+03	5.21E−02	2.52E+02	6.05E−03
1E−4	Medium level (50th percentile)	2.94E+03	0.29	4.45E+03	0.44	1.43E+04	1.43
2.4E−4	High level (90th percentile)	1.12E+04	2.7	1.61E+05	38.6	7.44E+04	17.9

Acronyms: DI: daily intake; PAEs: phthalate esters; DMP: dimethyl phthalate; DEP: diethyl phthalate; BPA: bisphenol A.

highest level of V), DI_{MP} ranged from 1.3 pg/BW kg/day for BPA to 9.7 pg/BW kg/day for DMP. However, under the best-case scenario, DI_{MP} was ca. 7 orders of magnitude lower for BPA, amounting to a mere ranging between 0.5 ag/BW kg/day (Table 2).

The contribution of the water ingestion pathway to the fish exposure of DMP, DEP and BPA was estimated according to Eq. (2), for which $C_{pollutant}$ (ng/m^3) stands for the concentration of PAEs or BPA dissolved in seawater. The variability of experimental data reported by distinct authors was addressed by plotting normal probabilistic distributions and their associated CPFs of BPA concentrations sampled in North American and European seawaters (Staples et al., 2018) and PAEs from the Mediterranean Sea (Paluselli et al., 2018), Red Sea (Dhavamani et al., 2022), East China Sea (Cao et al., 2022; Zhang et al., 2020) and Korean South Sea (Paluselli and Kim, 2020) as depicted in Fig. 4D. Again, three distinct concentration scenarios were considered for every contaminant in seawater, i.e., low level (10th percentile), medium level (50th percentile) and high level (90th percentile) concentrations as obtained from their respective CPFs (see Table 3).

$$DI_{water} = \frac{C_{pollutant} \times V}{W} \quad (2)$$

DI of DMP, DEP and BPA due to seawater ingestion (DI_{water}) across the different scenarios showed again a large span, ranging from 6 pg/BW kg/day to 39 ng/BW kg/day (see Table 3), with a worst-case scenario (90th percentile) >3 decades higher than that of DI_{MP}.

Considering the intermediate scenario (50th percentile concentrations) for both MP and seawater intake, and accounting for the variability and uncertainty of experimental data using the CPFs, the DI_{MP} of DMP, DEP and BPA are, in all cases, < 0.02 % of DI_{water}. Thus, our results signalled that the MPs contribution to the DMP, DEP and BPA exposure to marine fish can be considered negligible as compared to the waterborne dissolved fraction. This is in line with previous findings exploiting theoretical models, in which physiological conditions are accounted for, indicating that MP ingestion by marine vertebrates is not likely the main factor increasing the exposure and risk of organic contaminants, including plasticizers, to fish species (Bakir et al., 2016; Koelmans et al., 2016). In fact, Diepens and Koelmans (2018) reported that the effects of microplastics on the accumulation of hydrophobic organic species in fish generally are low whenever MP made up <3 % of the fish diet.

4. Conclusions

Our findings demonstrated that, because of the moderate to high hydrophobicity of most plastic additives, only the most hydrophilic compounds, *namely*, DMP, DEP and BPA are those that, once ingested, bear the highest fish bioaccessibility regardless of the composition of the gut fluids and number of GI compartments. However, a multiple-step (additive) extraction using gastric plus intestinal fluids is proven necessary for proper estimation of oral bioaccessibility rates of the most polar PAEs and BPA under "*worst-case*" scenarios. These same compounds are those that leach rapidly and at a large extent from plastic materials into the environment, both in fresh and salt water, and can therefore be found in the aquatic environment at relevant concentrations in zones that are prone to accumulate plastic debris. Our results of the daily fish intake estimation of PAEs and BPA from both water and MP (PE and PVC) ingestion, using CPFs, suggested that MP ingestion does not seem to be the main source of exposure, and thus the "Trojan horse" effect of MPs for those compounds seems to be negligible. However, plastic litter might be, in fact, regarded as one of the main source apportionment of such organic chemicals to marine waters. It should be added that there is a scarcity of available data in the literature on the actual concentrations of plasticizers and BPA onto MPs sampled in marine settings and thus more research is needed both at the local and global scales. Further research is also underway in our lab to implement the dual-compartment gastric plus gastrointestinal extraction in an automatic flow-through mode for better mimicking marine vertebrate physiology.

CRediT authorship contribution statement

Javier López-Vázquez: Writing – original draft, Visualization, Validation, Investigation, Formal analysis. **Manuel Miró:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **José Benito Quintana:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Formal analysis. **Rafael Cela:** Resources, Methodology. **Pere Ferriol:** Visualization, Formal analysis, Data curation. **Rosario Rodil:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.scitotenv.2024.176308.

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