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Analytical methodology for unveiling human exposure to (micro) plastic additives

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ABSTRACT

This review describes a wide variety of analytical approaches for the assessment of human exposure to organic chemicals associated with plastic additives, focusing on works published in the last decade on plasticizers, bisphenols, flame retardants and antioxidants. Physiologically based extraction tests serve as preliminary in-vitro assays to determine the bioaccessibility of these compounds from micro/nanoplastics in body fluids of the gastrointestinal tract, skin, or lung. Whenever plastic-laden compounds become bioavailable, human metabolism is to be monitored through the assessment of phase I and II metabolites. In this regard, analytical methods based on chromatography and mass spectrometry for human biomonitoring of parent compounds and their metabolites in biological samples (mostly urine and plasma) are discussed in depth. This review also covers the role of wastewater-based epidemiology in determining the overall human exposure of a given population to plastic-related species.

1. Introduction

Under the holistic view framed by the One Health paradigm, the impact of plastics and nano/microplastics on health is a complex topic with endless discussions [1]. To show not only the complexity of the impact of nanoplastics and microplastics on health, but also how this impact resonates in scientific publications and mass-media, we can highlight two recent works. On the one hand, the Minderoo-Monaco Commission on plastics and human health, as thoroughly reported by Landrigan et al. [2], describes in detail the impact of plastics in human life and environment. On the other hand, the debate on whether the impact of microplastics and nanoplastics is overrated, or we simply overlook key information should be carefully considered, as recently opened by Backhaus and Wagner [3]. The complexity of the issue is directly related to the economic weight of plastic production (and producers' wealth) and its use, as well as to the overwhelming perception of plastic ware in our daily lives, especially that of waste and by-products. In fact, the impact of plastics on ecosystems and human daily life in terms of production, use and, above all, waste is staggering. Concern about health effects attributed to the exposure to plastic products are deeply rooted in developed countries. In this sense, the call to include plastics as persistent, bioaccumulative and toxic contaminants under the Stockholm convention [2,4], is in line with the latest research.

Global plastic material production ranged from 400 to 460 M tons in 2022 according to Plastics Europe [5] and OECD [6], and only 9% of the plastic waste was recycled. This means that approximately 350 M tons of plastic were wasted. Moreover, it is also estimated that 22% of the plastic waste is undermanaged, and up to 8 M tons are released into the oceans every year. Considering the susceptibility of marine organism to

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plastics and the wide variety of adverse effects on all the communities and ecosystems, new tools and procedures are also called for to address the assessment of environmental and human risk, as pointed out recently by Leistenschneider et al. [7].

Because plastics are polymers that contain a wide variety of additives, in this review we will name additives to all those compounds added to polymers to achieve or improve specific properties such as chemical and physical stability. Among them, we will find not only plasticizers but also antioxidants, flame-retardants, and colorants. A detailed description of these additives and plastic constituents is found in the papers of Godwin [8] and Al-Malaika et al. [9].

Because these additives can easily be released into the environment, (i) the monitoring of plastics and additives and (ii) the assessment of their human exposure and risks have been addressed in many articles and recent reviews. Regarding the fate and occurrence of additives, we can highlight the recent reviews by Hahladakis et al. [10] and Chen et al. [11], and among those covering the impact of plastic material on the environmental and human health, we could highlight the reviews by Yuan et al. [12], Borriello et al. [13] and Kannan and Vimalkumar [14].

In this review, we will focus on human exposure and biomonitoring of plastic additives and will cover the last decade. Furthermore, since additives comprise many chemical classes with numerous processing functions, we will limit the scope to those that are more relevant in terms of human exposure (see Table S1 in Supplementary Information, SI). Therefore, we will focus on both phthalate plasticizers (PAE) and alternative plasticizers (APs) including non-phthalate plasticizers or alternative plasticizers such as terephthalates and dicarboxylates, flame retardants, particularly halogenated phenolic chemicals and organophosphate ones (OPFRs), antioxidants, with emphasis on synthetic phenolic antioxidants (SPA), and bisphenols (e.g. bisphenol A, BPA). It is worth noting that bisphenols are not only used as additives, but as monomers in the synthesis of plastics (particularly in polycarbonate) and in other applications, such as e.g. thermal paper printing.

Since exposure is often chronic and at very low levels, the overall goal is to design robust observational studies and apply targeted and non-targeted analysis to monitor the fate of additives both in the external environment and in human biofluids. Following this rationale, in-vitro human bioaccessibility testing of additives is the first step considered in this review, as it shows the relationships between the external chemical exposure and the internal occurrence of those chemicals. Once additives become bioavailable, we will describe the current knowledge on their metabolism and excretion as a key step to understand human exposure to these xenobiotics. The second part of the review first examines human biomonitoring (HBM) procedures for the above-mentioned compound classes, pointing out the status of HBM strategies, as well as the key metabolites that are most frequently monitored. Then, the last section is devoted to wastewater-based epidemiology (WBE) as an indirect way to summarize the overall human exposome of a community in a time- and cost-effective way.

2. *In-vitro* human bioaccessibility tests

To provide a reliable assessment of the harmful effects that could be caused by plastic additives, it is important to stablish the link between the chemical exposure and their occurrence in human biofluids. In this sense, physiologically-based extraction tests (PBETs) of solid materials are well-established tools in human risk exposure as a substitute for the *in-vitro* assessment of the bioaccessibility of exogenous compounds [15–17]. Human bioaccessibility from solid matrices refers to the release of target species into body fluids as the first step towards their transfer into the systemic system as bioavailable species, with consequent potential triggering of harmful effects. In fact, bioaccessibility is the first step (i.e., liberation) of the so-called liberation, absorption, distribution, metabolism and excretion process. Bioaccessibility fractions serve as conservative estimates of human bioavailability under worst-case scenarios and could be considered as appropriate biomarkers of exposure to contaminated solid particles, including raw and weathered microplastics matrices, such as dust and foodstuffs. PBETs might be classified according to the route of exposure to the assessed pollutants: ingestion (oral), respiratory (lung) and dermal (skin). Fig. S1 summarizes the experimental conditions and biomimetic reagents used in the main in-vitro PBETs to study the bioaccessibility of compounds transported by plastics via different exposures. Although most studies of human bioaccessibility to organic plastic additives are oriented towards oral exposure, inhalation and dermal exposure across airborne particulate matter could be estimated by simulated lung fluids [18] or sweat [19], respectively, used as liquid extractant media (Table 1).

Concerning oral bioaccessibility, a large research effort was dedicated to extending from trace elements to a handful of legacy organic contaminants and to emerging contaminants [45]. Table 1 shows a comprehensive compilation of PBETs for plastic additives along with their most relevant characteristics and post-processing steps prior to the analysis of the bioaccessible fractions. Many PBETs are based on test of the different extraction conditions usually found in the gastrointestinal tract (GIT) (i.e., fasted and fed state, concentration and activity of enzymes, and distinct GIT compartments) but the biological relevance by experimental assessment against in-vivo bioavailability testing or (eco) toxicity testing is seldom reported [46]. PBETs for human bioaccesibility should consider the chemical complexity of gut fluids, as well as the variety of GIT compartments in a non-discrete digestion process. As far as we are concerned, the most suitable tests for oral bioaccessibility tests of plastic compounds are the Unified Bioaccessibility Method (UBM) [47] fasted state, and the relative in-vitro digestion model recommended by the Dutch Institute for Public Health and the Environment (RIVM) [48] in fed state and with greater amounts of enzymes (pepsin, pancreatin and lipase) and bile acids. In fact, both UBM and RIVM methods resemble three GIT compartments (mouth, stomach, and small intestine) with several inorganic and organic species and enzymes, used in additive sequential extraction mode (see Fig. S1 in SI). Table S2 comprehensively compiles bioaccessibility data (%) of PAEs, BPA and OPFRs as obtained from various PBETs. Several in-vitro PBET studies mimicking oral bioaccessibility reported a strong negative dependence of bioaccessibility % with log P (partition coefficient) for neutral organic contaminants [30,32,37]. A critical comparison of bioaccessibility values for PAEs in low-density polyethylene (LDPE) microplastics as obtained for RIVM against UBM in GI phase indicated that the fed-state model rendered increased leachability only for the most hydrophobic compounds, such as di(2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DiNP) and di-isodecyl phthalate (DiDP) from 18 to 32%, 17 to 22% and 19 to 27%, respectively [37]. However, the addition of food components, such as porridge and oil, has been reported to decrease the freely dissolved concentrations of OPFRs [32] because of potential binding of the hydrophobic targets to amino acids or fats.

According to the data compiled in Table 1, the so-called Ruby method [21] and its modifications, including extension to the colon compartment [49] have been frequently adopted for plastic-related compounds in fasted state, despite the absence of (i) saliva fluid, (ii) salt constituents, (iii) organic species, such as urea, and (iv) some enzymes, such as lipase, as compared to UBM or RIVM, making the accurate simulation of GIT extraction conditions questionable. After PBET, sample treatment procedures may be necessary for the analysis of bioaccessible fractions of MP additives in the supernatants of complex body fluids by column separation methods to enable the clean-up of salts and biomolecules [40].

Inherent in the concept of bioaccessibility for solid materials in the GIT tract under conservative conditions is that the rate-limiting step of the entire process is the release of the target compounds from the solid surfaces rather than the absorption of those leached through the intestinal epithelium. Based on those premises, dynamic leaching of compounds adsorbed to microplastics using multi-step extraction procedures in either batchwise or flow-based format or PBETs ensuring sink conditions [50] are considered to be better choices than the standard static

Table 1
Comprehensive compilation of *in-vitro* physiologically based extraction tests (PBET) for risk exposure of plastic additives from microparticles using surrogates of body fluids (*See Table S1 for the full names of compounds).*

Additive	Sample	PBET						Supernatant extraction	Sample extraction	Analytical technique	Bioavail. Test	Ref.
		Bioacc.	Test (method)	Food	Body fluids	Compart.	Exposure time					
Phthalates												
DnBP, BBzP, DEHP and DnOP	Micro-plastics	Oral (static)	Fasted (UBM)	No	S + G + I	Mouth + Stomach Small intestine	1h 4h	LLE (Hex, 3 ×)	No	GC-MS	No	[20]
DMP, DEP, DiBP, DnBP, BBzP, DEHP and DnOP	Indoor dust	Oral (static)	Fasted (modified Ruby et al. [21])	No	G + I	Stomach Small intestine	1h 4h	LLE (Hex:acetone, 3:1, 3 ×)	Soxhlet (acetone/CH_2Cl_2/Hex, 1:1:1)	GC-MS	No	[22]
DMP, DEP, DPrP, DiBP, DnBP, DMEP, DnHP, BBzP, DEHP, DCHP, DnOP, DiNP and DiDP	Indoor dust	Oral (static)	Fasted (modified Ruby et al. [21])	No	G + I	Stomach Small intestine	1 h 4h	LLE (Hex, 3 ×)	Soxhlet (acetone/CH_2Cl_2/Hex, 1:1:1)	GC-MS	No	[23]
DMP, DEP, DPrP, DiPrP, DiBP, DnBP, DMEP, DMPP, DEEP, DAP, DnPP, DiPP, BBzP, DnHP, DCHP, DDEP, DEHP, DnOP, DNP, DiNP and DiDP	Food samples (Grains, vegetables and fruits)	Oral (static)	Fasted (modified Ruby et al. [21])	No	G + I	Stomach Small intestine	1h 4h	USE (Hex:acetone, 1:1, 3 ×)	LLE (Hex/acetone, 1:1, 3 ×)	GC-MS	No	[24]
DMP, DEP, DiBP, DnBP, DEHP, DINCH, DEHTP, DPHP and DiNP	Indoor dust	Lung (static)	Gamble and ALF	No	Healthy and inflammatory lung	Lung	96h	LLE (Hex:MTBE, 3:1)	MAE (acetone: Hex, 1:1) and SPE clean-up (Hex)	GC-MS/MS	No	[25]
DMP, DEP, DiBP, DnBP, DMEP, BMPP, BBzP DnPP, DnHP, DCHP, DEHP, DEEP, DBEP, DPHP, DnOP and DiNP	Particulate matter	Lung (static)	Gamble and ALF	No	Healthy and inflammatory lung with A549 cell	Lung	96h	LLE (Hex, 3 ×)	ASE and Florisil column (Hex)	GC-MS	No	[26]
DEP, DnBP, DEHP, ATBC, DEHA and DEHTP	Indoor dust	Dermal (static)	SSSM	No	SSSM	Skin	1h	LLE and Florisil column (Hex, 3 ×)	ASE and Florisil column (Hex)	GC-MS	No	[27]
Bisphenols												
BPA	Seafood	Oral (static)	Fed (RIVM)	No	S + G	Mouth + Stomach Small intestine	2h 2h	LLE (ACN:C_2Cl_4:CH_3COOH anhydride, 2:1:2)	DLLME (C_2Cl_4:CH_3COOH anhydride, 1:2)	GC-MS	No	[28]
BPS	Soy drink	Oral (static)	Fasted and fed (INFOGEST)	No	S + G	Mouth Stomach Small intestine	2 min 2h 2h	Direct injection	USE (ACN)	LC-MS/MS	No	[29]
Flame retardants												
TClPP, TClEP, TPHP and TDClPP	Indoor dust	Oral (static)	Fasted (CE-modified Ruby et al. [21]) with Tenax	No	G + I + colon	Stomach Small intestine Colon	1.5h 4h 14h	LLE (Hex:EtOAc, 1:1, 3 ×)	No	LC-MS/MS	*In-vivo* test in rats	[30]
TClPP, TClEP, TnBP, TPHP, EHDPP and TDClPP	Indoor dust	Oral (static)	Fasted (modified Ruby et al. [21])	No	G + I	Stomach Small intestine	1h 4h	LLE (Hex, 3 ×)	USE (Hex, 3 ×)	GC-MS	No	[31]
TClEP, TClPP and TDClPP	Indoor dust	Oral (static)	Fasted (UBM) and fed (FOREhST)	Cereal, milk and oil	S + G + I	Mouth + Stomach Small intestine	2h 2h	Dilute and shoot (ACN)	MSPD (Hex and acetone)	LC-MS/MS	No	[32]

(*continued on next page*)

Table 1 (*continued*)

Additive	Sample	PBET						Supernatant extraction	Sample extraction	Analytical technique	Bioavail. Test	Ref.
		Bioacc.	Test (method)	Food	Body fluids	Compart.	Exposure time					
HBCD and TBBPA	Indoor dust	Oral (dynamic)	Fasted (CE-modified Ruby et al. [21])	No	G + I + colon	Stomach Small intestine Colon	1h 4 h 8h	SPE (CH_2Cl_2:Hex, 1:1)	No	LC-MS/MS	No	[33]
HBCD	Indoor dust	Oral (static)	Fasted (CE modified Ruby et al. [7])	No	G + I + colon	Stomach Small intestine Colon	1h 4h 16h	LLE (acetone:Hex, 1:1)	ASE and SPE clean-up (CH_2Cl_2: Hex, 1:1)	LC-MS/MS	No	[34]
TClEP, TClPP, TDClPP, TPHP, EHDPP, TEHP, TMPP and TnBP	Particulate matter	Oral (static)	Fasted (modified Ruby et al. [21])	No	G + I	Stomach Small intestine	2h 5h	LLE (acetone:Hex, 1:1)	SPE and Soxhlet (acetone:Hex, 1:1)	GC-MS	No	[35]
		Lung	Gamble		Healthy lung	Lung	4h					
HBCD and TBBPA	Indoor dust	Dermal	SSSM	–	SSSM	Skin	1h	QuEChERS (Hex: EtOAc, 1:1)	QuEChERS (Hex: EtOAc, 1:1)	LC-MS/MS	No	[19]
TClEP, TClPP and TDClPP								QuEChERS (Hex: EtOAc, 1:1) and SPE clean-up (Hex and EtOAc)	QuEChERS (Hex: EtOAc, 1:1) and SPE clean-up (Hex and EtOAc)	GC-MS		
Antioxidants												
BHT, BHT-quinol, BHT-Q and BHT-CHO	Food samples	Oral (static)	Fed (RIVM)	No	G + I with Caco-2 cells	Stomach + Small intestine	1h + 4h	Solvent exchange to MeOH:H_2O (1:1)	No	LC-MS	No	[36]
BHT-OH and BHT-COOH						Small intestine	2h	Direct injection		GC-MS		
Multiple additives												
DMP, DEP, DnBP, BzBP, DEHP, DnOP, DiNP, DiDP	Micro-plastics	Oral (static)	Fasted (UBM) and fed (RIVM)	No	S + G + I	Mouth + Stomach	Fasted (1h)/fed (2 h)	Dilute and shoot	USE (CH_2Cl_2)	LC-MS/MS	No	[37]
BPA						Small intestine	Fasted (4h)/fed (2h)	LLE (EtOAc)		GC-MS		
DMP, DEP, DnBP, BBzP, DEHP, DnOP, DiNP, DiDP and BPA	Micro-plastics	Oral (dynamic)	Fasted (UBM) and fed (RIVM)	No	S + G + I	Mouth + Stomach	Fasted (1h)/fed (2h)	SPE (ACN:MeOH, 90:10)	MAE (Hex/ acetone, 30:70)	LC-DAD	No	[38]
						Small intestine	Fasted (4h)/fed (2h)					
DnBP, DEHP, DnOP, DiDP and BPA	Plastic toys	Oral (static)	Artificial saliva	No	S	Mouth	20 min	LLE ($CHCl_3$)	USE ($CHCl_3$)	LC-DAD	No	[39]
DMP, DEP, DnBP, BBzP, DEHP, DnOP and BPA	Beach sand	Oral (static)	Fasted (UBM)	No	S + G + I	Mouth + Stomach	1h	DLLME (1-octanol)	MAE (Hex/ acetone, 30:70)	LC-MS	No	[40]
						Small intestine	4h					
DMP, DEP, DnBP, BBzP, DEHP, TClEP, TClPP, TPHP and TDClPP	Indoor dust	Oral (static)	Fasted (modified Ruby et al. [21])	No	G + I	Stomach Small intestine	1h 4h	USE (Hex, 3 ×)	USE (Hex, 3 ×)	GC-MS	No	[41]
DMP, DMEP, DEP, DiBP, DnBP, DiPP, DnPP, NPiPP, BBzP, DnHP, DEHP, DnOP, BPA, BPF, TnBP, TCP, TPHP, TPPO, TPrP, TBOEP, TClEP,	Particulate matter	Lung (static)	ALF and SBF	No	Lung and synthetic human plasma	Lung	27h	VALLE (EtOAc)	No	GC-MS/MS	SBF test	[42]

(*continued on next page*)

Table 1 (*continued*)

Additive	Sample	PBET						Supernatant extraction	Sample extraction	Analytical technique	Bioavail. Test	Ref.
		Bioacc.	Test (method)	Food	Body fluids	Compart.	Exposure time					
TClPP, TDClPP, TiBP and TEHP												
DnPP, DnHP, DEHP, DnOP, BPA, TClPP, TiBP and TPPO	Particulate matter	Lung (static)	ALF	No	Inflammatory lung	Lung	24h	LLE (EtOAc)	USE (Hex:acetone, 1:1, 3 ×)	GC-MS/MS	No	[43]
DMP, DEP, DnBP, BBzP, DEHP, DnOP, TnBP, TClPP, TDClPP, EHDPP, TBOEP, TEHP and TOP	Indoor dust	Lung (static)	SELF and ALF	No	Epithelial and inflamatory lung	Lung	SELF (48h) ALF (24h)	LLE (CH_2Cl_2:Hex, 3:1)	USE (CH_2Cl_2:Hex, 1:1, 3 ×) and SPE clean-up (CH_2Cl_2: Hex, 1:1)	GC-MS	No	[44]

Footnote: S: Saliva; G: Gastric; I: Intestinal; LLE: Liquid-liquid extraction; VALLE: Vortex-assisted liquid-liquid extraction; USE: Ultrasonic solvent extraction; DLLME: Dispersive liquid-liquid microextraction; SPE: Solid-phase extraction; DMSPE: Dispersive micro solid-phase extraction; MAE: Microwave assisted extraction; ASE: Accelerated solvent extraction; UBM: Unified Bioaccessibility Research Group of Europe (BARGE) method; RIVM: Relative in-vitro model; FOREhST: Fed organic estimation human simulation test; ALF: Artificial lysosomal fluid; SBF: Simulated body fluid; SELF: Simulated epithelial lung fluid; SSSM: Simulated artificial sweat and sebum mixture.

counterparts based on end-point detection (UBM, RIVM, Ruby methods) to ensure that the test conditions are representative to those occurring across the GIT. Taking a standard reference material of LDPE (CRM-PE002 from Spex CertiPrep) containing eight PAE congeners and BPA at the 3000 μg/g level (except for the heavier congeners), a comparative exploration of static versus dynamic flow-through leaching conditions might be obtained from the literature [37,38]. Experimental results show that dynamic and static protocols rendered comparable results for those readily leachable additives, such as dimethyl phthalate (DMP) with values > 80% for both fed and fasting states. On the contrary, an appreciable increase from 70 to 87% was found for moderate hydrophobic species (log P > 2), such as diethyl phthalate (DEP), under flow extraction conditions for both UBM and RIVM methods. However, greater differences should be still expected for less bioaccessible congener species with longer alkyl chains to overcome the solubility limited release in static extractions, although sensitive detection methods (i.e., mass spectrometry) and sample treatment procedures suitable for enrichment might be necessary to ensure reliable quantification of compounds with low bioaccessibility.

It is worth noting the relevance of indoor dust as a source of plastic additives through lung bioaccessibility despite the large variability on inhalation bioaccessibility of PAEs. Considering the so-called Gamble solution (GMB), which simulates the surfactant fluids released by alveolar cells and the artificial lysosomal fluid (ALF) counterpart, which mimics conditions inside lung cells associated to phagocytosis (inflammatory conditions), a thorough comparison of both methods has been carried out [26]. According to this work, the mean values of bioaccessibility for PAEs under inflammatory lung conditions (14.5–67.6% for ALF) were, in general terms, slightly higher than those of healthy individuals (8.9–62.8% for GMB), with the largest accessibility corresponding to DEHP. The differences observed between ALF and GMB methods are attributed to the more acidic intracellular environment in lung cells (pH 4.5 used in ALF) against the interstitial (i.e., extracellular) pH under healthy conditions (pH 7.4 used in GMB). It should be however considered that inhaled particles above 1-μm size are usually deposited in the pharyngeal and tracheal region, and then transported by the so-called mucociliary clearance system into the GIT [51]. Despite this fact, different research groups have resorted lung fluids rather than gut extractants for bioaccessibility testing of emerging contaminants in PM2.5 or dust particles <63 μm [25,26,42], yet this does not seem to be an entirely accurate estimate of human exposure to contaminated particles that are finally swallowed.

In-vitro dermal exposure via PBET has been rarely reported in the literature (see Table 1). In fact, most of the efforts devoted to assessing dermal bioaccessibility of PAEs in indoor air, cosmetics and clothing using human skin surface film liquid containing both synthetic sweat and sebum mixture (SSSM), as the latter plays a pivotal role on the leachability of organic species [19,27]. Experimental results indicated that plasticizers such as acetyl tributylcitrate (ATBC), di(2-ethylhexyl) adipate (DEHA) and di(2ethylhexyl) terephthalate (DEHTP) that were launched as alternates to conventional PAE counterparts exhibited dermal bioaccessibility values as high as 74–94% similar to those encountered for PAEs on the same indoor dust samples [27].

Finally, as the data compiled in Table 1 suggests, in-vivo validation of human PBETs for plastic-laden organic contaminants using animal models or the combination of PBETs with bioavailability testing using in-vitro cellular models is scarcely conducted. One exception is the HBM of urine to validate the parallel-layered skin compartmental model for dermal bioaccessibility [52]. Likewise, analytical validation of the PBETs results using quality assurance/quality control tools; i.e., based on mass balance validation (statistical comparison of the sum of the bioaccessible and the residual fractions against the total amount of a target compound in microplastics), is most often neglected, because of which the trueness of the reported bioaccessibility data might be debatable [53]. As a final note, although bioaccessible fractions of target species from solid materials are expected to be higher than those

bioavailable, because only a given fraction of leached species is usually able to cross epithelial tissues, this might not be the case for compounds associated to micro/nanoplastics <50 μm as these small particles have been detected in the systemic and lymphatic systems in which the plastic-laden compounds might become bioavailable [54,55].

3. Human metabolism and excretion

Once the plastic additives are leached from the solid particles (macroplastics and microplastics, dust, etc.) and some of the loaded components become bioavailable, they undergo different metabolic pathways. Human metabolism encompasses a diverse set of biotransformation processes that influence both foreign (xenobiotic) and internal (endobiotic) compounds, contributing to the efficient functioning and balance of the body. As a result, chemicals are removed from the bloodstream, undergo structural modifications (in most cases) and then, they are reintroduced into the circulation for eventual elimination through renal or biliary excretion.

Human metabolism is categorized into three phases: phase-I, phase-II, and the relatively newly proposed phase-III. However, phase-III is mainly involved in the binding of the metabolites to transport systems for the final elimination and, therefore, this study will focus on exploring the processes within phase-I (see Table S1) and phase-II for the plastic additives. In phase-I metabolism, lipophilic molecules are converted into more hydrophilic products by introducing polar functional moieties through enzymatic reactions, mediated by enzymes like Cytochrome P-450. Phase-II metabolism involves biosynthetic reactions in which a chemical moiety is transferred from a cofactor to a substrate that may be the parent contaminant or a phase-I by-product [56] (see examples in Fig. 1).

This section describes general aspects of human metabolism of plastic additives, with dedicated information on the main urinary excretion metabolites presented in Table S3. The data in Table S3 is compiled from metadata and curated studies, based on individual investigations, whenever possible. The excretion rates presented in Table S3 refer to the sum of phase-I and phase-II metabolites, since in many cases most HBM, after enzymatic deconjugation (see section 4.1), and WBE studies, due to natural deconjugation of glucuronides in sewage, only cope with phase-I metabolites.

The exploration of human metabolism consists of (i) the identification of the potential metabolic pathways and, subsequently, (ii) the development of toxicokinetic studies to estimate the molar excretion of these metabolites, through in-silico, in-vitro and/or in-vivo assays. It is crucial to note that both stages are significantly influenced by factors such as the route of exposure, age, ethnicity, or gender. Therefore, only in-vivo studies in humans accurately determine the metabolic pathways and molar excretion fractions. Moreover, selecting appropriate metabolites for each studied matrix is key to validating human exposure. For instance, phase-II glucuronide metabolites serve as major excretion products for many xenobiotic compounds but exhibit instability in certain matrices, such as wastewater [57].

3.1. Plasticizers

Although in recent years PAEs have been partially replaced by other chemicals, due to their endocrine disrupting potential and adverse effects [58], they still stand out as the most relevant class of plasticizers.

After human intake, these compounds undergo phase-I hydrolysis to produce the monoester metabolites. Additionally, long-branched plasticizers, characterized by lateral chains containing more than six carbons (e.g. DEHP), may undergo a secondary hydrolysis, resulting in the formation of oxidation products (alcohols, ketones, and acid moieties). Furthermore, all phase-I metabolic products have the potential to be conjugated to form phase-II glucuronide metabolites. The human metabolism and excretion rate of most phthalate esters is well-understood, except for some shorter-chain plasticizers, DMP and DEP,

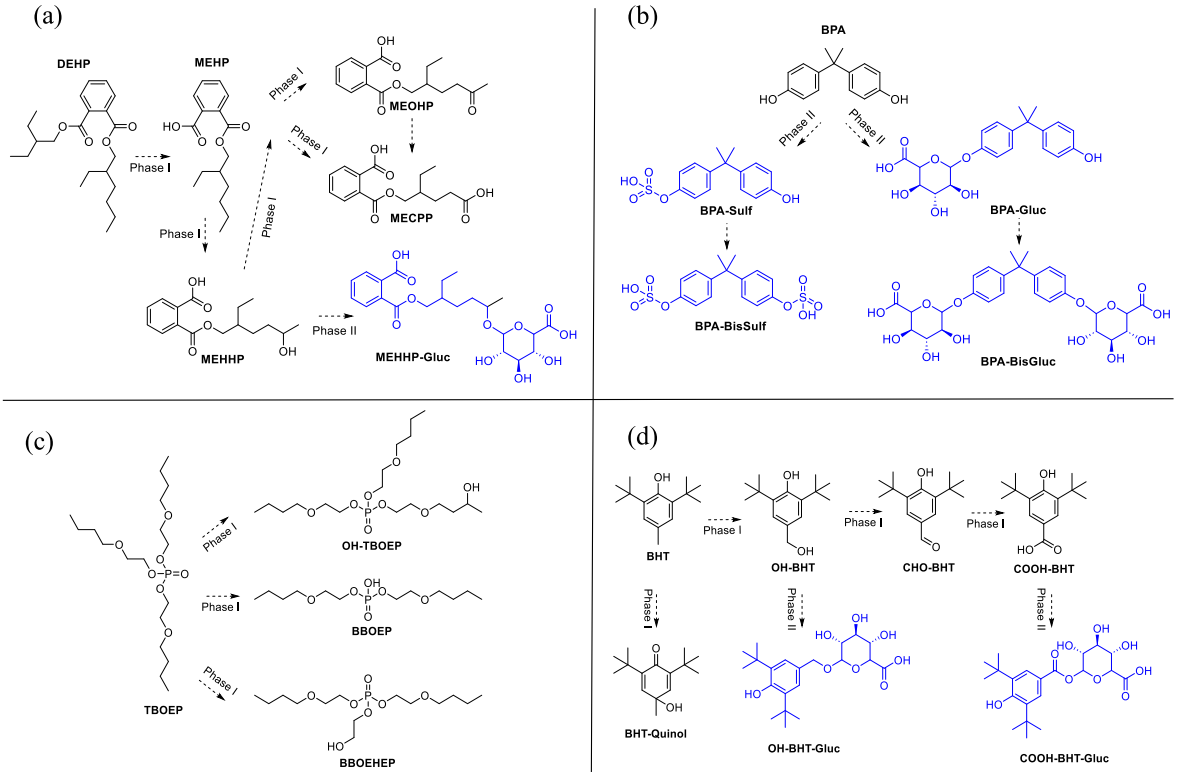

Fig. 1. Metabolic transformation pathways of: (a) di(2-ethylhexyl) phthalate (DEHP), (b) bisphenol A (BPA), (c) tri(2-butoxyethyl) phosphate (TBOEP), and (d) butylated hydroxytoluene (BHT). Phase-II metabolites are highlighted in blue. See Table S3 for further information. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(see Table S3). In addition, certain commercial formulations, like DiNP and DiDP, consist of technical blends that include several structural isomers, posing difficulties for their separation and identification [59].

Short-chain plasticizers are mainly excreted as monoester metabolites in urine with molar excretion rates higher than 50% and are, therefore, easily detected in biological matrices or wastewater [60]. On the other hand, long-chain plasticizers are mainly excreted in urine as phase-II glucuronides of the oxidized monoesters (see DEHP, Fig. 1a). However, as mentioned above, glucuronides are naturally deconjugated in wastewater [61] and, therefore, human exposure to these compounds is estimated in WBE studies through their corresponding oxidized phase-I metabolites or enzymatically deconjugated for urine analysis in HBM.

3.2. Bisphenols

Upon entering the human body, bisphenols undergo rapid absorption, conjugation, and subsequent excretion as phase-II metabolites, with marginal phase I metabolism. The primary conjugation involves glucuronidation at the hydroxyl group, yielding β-D-glucuronide, followed by a secondary conjugation to form bis-(β-D-glucuronide). Additionally, another biotransformation is observed through phase-II sulfation, leading to the production of monosulfate and bisulfate bisphenols (see BPA, Fig. 1b) [62]. The metabolic pathways are similar for all bisphenol congeners due to their analogous structures and are well-studied, with some exceptions (e.g. Bisphenol F (BPF) is postulated to be excreted mainly as sulfates instead of glucuronides [63]). Nevertheless, most toxicokinetic studies rely on in-vitro tools, resulting in a lack of studies to validate the actual molar excretion rate.

According to the available oral dosing studies in humans for BPA and bisphenol S (BPS), bisphenols are mainly metabolized as β-D-glucuronide in urine, with excretion rates higher than 50% (Table S3). Therefore, glucuronides serve as effective biomarkers of exposure in biological matrices but are not suitable for WBE, in which phase-II sulfate appears to be the exclusive option, in spite of their low excretion rates [64]. Deconjugation of biological samples (i.e., urine) would revert to the parent compound. Therefore, it is particularly relevant to minimize blank contamination in those cases.

3.3. Flame retardants

Available data from in-vivo metabolism studies indicate that halogenated phenols, such as tetrabromobisphenol A (TBBPA) and 2,4-dibromophenol (2,4-DBP), undergo a metabolism analogous to that of the bisphenol congeners. In contrast, the existence of hydrocarbon chains in OPFRs, e.g. tri(1,3-dichloro-2-propyl) phosphate (TDCIPP) or tri(2-butoxyethyl) phosphate (TBOEP, Fig. 1c), make them prone to phase-I biotransformations [65]. There is only one in-vivo toxicokinetic study that proposes excretion rates for TBOEP metabolites [66]. Therefore, data regarding the excretion of these class of compounds is still largely unknown (Table S3). Furthermore, certain OPFR metabolites are not exclusive from a single chemical (i.e., diphenyl phosphate, DPHP) [67]. Thus, data should be thoroughly evaluated to ensure the accurate source identification.

Despite these limitations, several metabolites have been widely used as biomarkers in HBM and WBE studies, such as di(1,3-dichloro-2-propyl) phosphate (BDCIPP), the major metabolite of TDCIPP [68]. However, the results of both approaches cannot be directly compared due to the lack of excretion fractions.

3.4. Antioxidants

Antioxidants' potential risk has only recently been recognized [69]. Consequently, human metabolism data is very limited. SPAs stand out as the only family for which in-vivo human metabolism studies have been conducted, while, for other antioxidants, potential biotransformation have been merely assessed through in-vivo studies in animals, and in-vitro or degradation assays. These qualitative studies pointed out that SPAs closely resemble long-chain phthalates' metabolic pathways, thus, leading to hydroxylation and consecutive oxidation and conjugation, as exemplarily shown for butylated hydroxytoluene (BHT) in Fig. 1d. In contrast, higher molecular weight alternatives (i.e., organophosphite antioxidants) tend to initially undergo dealkylation, followed by side-chain oxidation, akin their structurally analogous OPFRs [70]. Unfortunately, there is no data about excretion rates of these compounds.

Despite the scarcity of data, increasing toxicity reports have encouraged to carried out HBM studies on SPAs. Within these studies, metabolites of BHT (e.g., BHT-COOH) have been detected in higher concentrations than that of the precursor compound, pointing out the need for further development of exposure studies based on metabolic products [71].

4. Human biomonitoring (HBM)

Fig. 2a and b illustrate the number of works dealing with HBM of plastic additives in the last 10 years (source, Scopus, October 31, 2023) according to the biofluid (urine, blood/plasma/serum, or breast milk) and the type of compound (parent and/or metabolites) monitored, respectively. In the case of urine (see Fig. 2), while alkylated additives (i.e. PAEs, APs and OPFRs) are mainly found as phase I (see Table S1) and/or phase II metabolites, phenolic compounds are detected as the parent chemical and/or the corresponding phase II metabolite. In the case of plasma or breast milk, the parent or the corresponding phase I metabolites are detected as can be seen in the applications of HBM from 2019 to October 2023 listed in Table S4.

4.1. Determination of additives in human samples: analytical workflows

The type of biofluid and the physicochemical properties of the target analytes are the key features considered to develop analytical strategies. Concerning urine sampling, a wide variety of approaches is observed in the existing literature, primarily due to differences in scope, study design, and the donors involved. In most studies, spot urine samples are collected [72–74] preferably first-morning urine samples to minimize bias [75]. However, some studies collected 24-h urine samples [76,77], which may lower urine variability, although it may not be feasible in all cases due to donors' time availability or laboratory workload, among others. As a result, specific gravity [78,79] and creatinine [75,80,81] are useful parameters to normalize experimental concentrations and reduce the physiological variability of donors. Alternatively, analyte concentrations have been corrected with osmolarity [82], density [83], or volume values [84]. After sampling, urine samples are always stored between −20 °C and −80 °C before analysis, ensuring the cold chain from the sampling moment to the laboratory analysis [73,85].

The initial step for the determination of plastic additives in urine samples involves enzymatic hydrolysis to transform phase-II metabolites into phase-I (i.e., PAE, mPAEs, and OPFR, mOPFRs) or parent compounds (i.e., bisphenols), making them quantifiable with available analytical standards [86]. For this purpose, β-glucuronidase enzyme from Helix Pomatia has been primarily used [87], although β-glucuronidase/arylsulfatase have also been chosen to deconjugate either glucuronide- or sulfate-conjugates, respectively [76]. Besides, the hydrolysis of N- and O-glucuronides is enzyme dependent and, while genetically engineered β-glucuronidase has rendered good hydrolysis yields for N-glucuronides (i.e. triclocarban glucuronide), O-glucuronides are only fully hydrolyzed by using Helix Pomatia β-glucuronidase or Helix Pomatia β-glucuronidase/arylsulfatase [88]. Moreover, enzymatic hydrolysis is usually carried out at controlled pH (pH 5.0–6.5) and temperature (37 °C) usually overnight, although sometimes the reaction is stopped after a couple of hours. It might be also considered that some enzymes such as aryl sulfatase have lipase activity, being able to

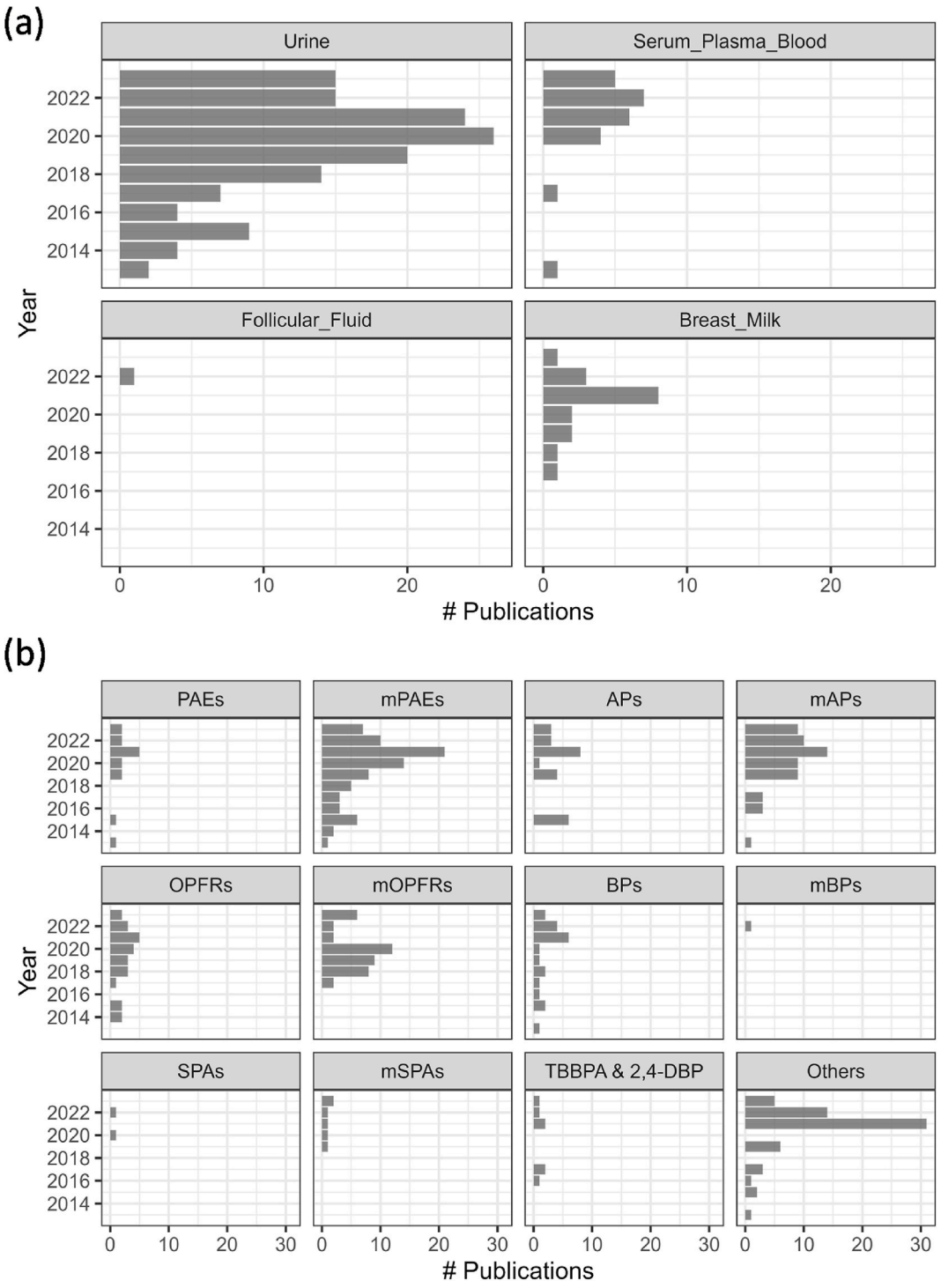

Fig. 2. Number of human biomonitoring researchers for plastic-related compounds over the last 10 years according to the biofluid (a) or family of compound (b) monitored. Source: Scopus October 31, 2023. BPs: bisphenols; APs: alternative plasticizers; mBPs: bisphenol metabolites; mAPs: metabolites of alternative plasticizers; mOPFRs: metabolites of organophosphate flame retardants; mPAEs: metabolites of phthalate esters; mSPAs: metabolites of synthetic phenolic acids, OPFRs: organophosphate flame retardants; PAEs: phthalate esters; SPAs: synthetic phenolic acids; Others: per- and polyfluoroalkyl substances, benzophenones, parabens, phenols, polyaromatic hydrocarbons and their metabolites, pesticides, hormones, phytoestrogens and mycoestrogens and their metabolites, biocides, volatile organic compounds, food additives, phytotoxins, quaternary ammonium compounds, metals, organic acids and industrial side-products.

hydrolyze diester-PAEs to monoester-PAEs [88]. After enzymatic hydrolysis, additives are isolated from urine and subsequently cleaned-up by solid-phase extraction (SPE) in most of the works. While the reversed-phase mechanism has been the predominant SPE mode, using C18 or polymeric sorbents [89,90], mixed-mode SPE has also been selected to extract ionizable phase-I metabolites by combining reversed-phase sorbents with anion exchangers [91,92]. To a lesser extent, liquid-liquid extraction and salt-assisted liquid-liquid extraction have also been carried out using acetonitrile as the main extractant [93, 94]. Finally, urine centrifugation or dilution after centrifugation (i.e., 'dilute-and-shoot') has been proven to be a faster alternative with no potential losses, although no sample clean-up and preconcentration are

performed [95,96]. The extracts are often analyzed by liquid chromatography coupled with low-resolution tandem mass spectrometry (LC-MS/MS) [94,97,98], even though gas chromatography (GC) has also been employed [99]. These techniques allow the development of highly selective and sensitive analytical approaches to ensure a good identification and/or quantification of plastic additives. On the other hand, to get a holistic view of the impact of plastic additives on humans, biomonitoring programs should include a larger number of compound classes. In this sense, the use of liquid chromatography-high-resolution mass spectrometry (LC-HRMS) has facilitated the application of suspect and non-target screening approaches. These approaches imply some challenges for the analytical methodologies such as the use of less exhaustive and more generic sample treatments, including dilute-and-shoot [100,101], the improvement of the compound annotation workflows that minimize false positives and negatives due to the presence of endogenous metabolites that interfere in the identification [102] and the harmonization of quality assurance and quality control criteria [103,104], among others.

Besides urine, breast milk [105,106] and blood/plasma/serum [83,107], or even hair [108] or amniotic fluid [109] have been analyzed. A variety of analytical methods have been developed, not only because of the matrix type, but because parent compounds are also present in such matrices [110] or even together with phase-I metabolites [105,111]. Initially, spot samples are collected and stored at least at −20 °C before sample treatment. When phase-I metabolites are determined, enzymatic hydrolysis is performed similarly to urine samples [105,112]. However, this step is skipped in the determination of parent plastic-related compounds [113]. Given the higher protein content of some matrices, such as breast milk or blood/plasma/serum, protein precipitation is typically carried out by LLE or SALLE using acetonitrile [107,111]. Subsequently, the extracts are further cleaned-up by SPE using the same sorbents as mentioned above for urine [111], although normal-phase SPE has also been conducted for those additives extracted with non-polar organic solvents [105]. Finally, the extracts have been usually analyzed by LC-MS/MS [106,109], although GC-MS/MS has also been employed [105,112]. In contrast to urine, the final concentrations in those matrices are seldom corrected to minimize variability. Nevertheless, the lipid-content adjustment proposed for breast milk samples [113] could be a suitable correction method in future monitoring studies, considering the variability in lipid content depending on the pregnancy/-breastfeeding stage.

4.2. HBM of plastic additives

As can be seen in Fig. 2, the number of HBM papers increased until 2021, while a slight decrease was observed in 2022 (articles up to October 2023 were only considered). The latter decrease could be related to the lock-down due to COVID-19, which may have deterred biomonitoring programs.

According to Fig. 2b, mPAEs have been the most studied plastic-related chemicals over the last decade, while the number of human biomonitoring programs including mOPFRs and mAP gained increasing attention since 2016. The other families of compounds considered, bisphenols and antioxidants, are investigated in HBM studies in a lesser extent. The top monitored phase-I metabolites of plastic additives of PAEs, APs and OPFRs in the literature over last 10 years are shown in Fig. S2 and the complete names of the compounds are listed in Table S1 in SI.

Most of the works are limited to the analysis of a few compounds and only a few papers applying suspect and non-target screening approaches in human biofluids can be found in recent literature [114–119]. This fact clearly states the need to investigate and improve those workflows to obtain a more holistic view of the impact of plastic additives on humans, as commented above.

In the case of PAEs, concentrations up to thousands of nanograms per milliliter have been reported for several mPAEs in USA, Puerto Rico, Mexico, East Asia (China, Thailand, Indonesian and Japan) and several European Countries (see Table S4). On the contrary, a lack of biomonitoring data on phthalate exposures in Africa and South America regions is observed. Overall, metabolites of DEP, DEHP and monobutyl- (MnBP) di-*n*-butyl- (DnBP) and di-isobutyl- (DiBP) phthalates are those found in urine at the highest concentration levels. In the last years, due to the replacement of PAEs by APs, mAPs have been reported mainly in Europe, Asia and United States. Cyclohexane-1,2-dicarboxylic mono (hydroxyisononyl) ester (OH-MINCH), cyclohexane-1,2-dicarboxylic mono carboxyisononyl ester (cx-MINCH), and mono(2-ethyl-5-carboxypentyl) terephthalate (cx-MEPTP) are the most frequently detected metabolites at the highest concentration levels in urine (see Table S4).

As can be seen in Table S4, BPA has been globally monitored in humans, especially in Europe, but in North America and Asia as well. HBM programs identified a decrease in BPA levels found in urine, though there is an increasing trend of alternative bisphenols used as substitutes, especially BPF and BPS. Even so, similar BPA concentrations are still detected in comparison to their homologues, suggesting only a partial substitution of BPA in the market [91,96,99,107,120].

As can be seen in Table S4, OPFRs have been mainly monitored in urine at concentrations varying from low ng/mL levels up to hundreds of ng/mL. Among all OPFR metabolites, those detected at the highest concentration include DPHP [78,92,94], BDCIPP [73,79], di (1-chloro-2-propyl) phosphate (BClPP) [121], 2-ethylhexyl phenyl phosphate (EHPHP) [90], 4-hydroxyphenyl phenyl phosphate (4-OH-DPHP) [80], and dicresyl phosphates (DoCP and DpCP) [93]. Regarding SPAs, BHT-COOH is the major metabolite of BHT according to the literature (see Table S4), which is mainly excreted in urine [94].

Although to a lesser extent, other biological fluids such as plasma/blood, breast milk and amniotic fluid have been included in biomonitoring programs to assess the occurrence of plastic additives and metabolites in humans (Table S4). In contrast to urine analysis, where phase-I metabolites are mainly monitored, the determination of plasticizers in those matrices included both the parent compounds (PAEs and APs) and their metabolites (mPAEs and mAPs), whose presence, in particular APs (concentration range: 0.252–16.1 ng/mL), in breast milk was remarkable. Moreover, OPFRs are generally determined as metabolites while brominated flame retardants (i.e., HBCDD and TBBPA) are monitored as the parent compounds. Other compounds such as BPS have also been reported to be present in breast milk (concentration range: <0.008–0.05 ng/mL). Though most HBM studies have provided evidence of the presence of legacy contaminants in human milk, the occurrence of plasticizers and flame retardants has hardly been assessed, even though these compounds could accumulate in protein-rich biofluids, and this knowledge would allow the interpretation of potential health issues.

5. Wastewater-based epidemiology (WBE)

The WBE methodology relies on the fact that wastewater represents a diluted and composite sample of urine (and faeces) collected from the whole community linked to a specific sewage system. When individuals are exposed to a given compound, the body excretes the corresponding metabolites and/or parent compounds (see sections 3 and 4) and therefore, WBE can be considered as an overall average of public exposure. Moreover, some of those compounds often found in wastewater treatment plants (WWTPs) can be considered as exposure biomarkers if they remain stable in wastewater and have no other source than human urinary excretion. In fact, it is assumed that the amount excreted by a population during a specific time interval corresponds to the total load received by the WWTP. Consequently, by quantifying these biomarkers in the untreated sewage received at the WWTP (i.e. influent), a retrospective estimation of parent compounds exposure can be performed [122,123].

This methodology involves several pivotal steps, which are

exemplary outlined in Fig. 3 for DEHP, using the three main human metabolites in this case. First, a representative sample of wastewater must be collected for a chosen time interval. Typically, 24-h composite samples are collected using automatic samplers that ensure proportional sampling based on time, volume, or flow of wastewater entering the WWTP. The selection of biomarkers for their measurement in wastewater is a key issue. Usually, urinary HBM studies are taken as a reference for this selection because they provide information on the main metabolites generated and on the urinary excretion rates (see section 3).

A more detailed discussion on the potential of WBE to estimate the specific biomarkers used in the case of plastic related chemicals will be discussed afterwards (section 5.1). After this selection, the following step involves the analysis of wastewater composite-samples to determine their concentrations (Fig. 3). Given the complexity of wastewater matrices and the low concentrations of biomarkers (usually within the ng/L range), a preconcentration, and sometimes clean-up step, is necessary before chromatographic analysis, often achieved through SPE [123]. Similarly to HBM, chromatography and mass spectrometry methods are commonly used due to the need for high sensitivity and selectivity [123]. Afterwards, the measured concentrations are transformed to biomarker mass loads entering the WWTP, considering the flow of raw wastewater treated in the WWTP over the sampled 24-h period. Those mass loads are converted into intakes of parent compounds, using correction factors (CFs), which are calculated considering the molecular mass ratio between the parent compound and the metabolite, and the excretion rate obtained from metabolic studies. CFs used in the literature for the various biomarkers are shown in Table S5. The final step involves normalizing the experimental data. For this purpose, the estimated compound intake is divided by the number of inhabitants served by the WWTP and the results expressed as e.g. μg $inh^{-1}day^{-1}$ [125]. Also, these results can be transformed to daily intake, using the average population weight (in kg, considering the average weights by age group, and the population percentages provided in epidemiological studies for a given city, if available, or country) [64]. This standardization enables the comparison of results across different WWTPs and populations and also with reference values, such as the tolerable daily intake values set by the European Food Safety Authority (EFSA) or the reference doses (RfD) provided by the U.S. Environmental Protection Agency (US-EPA).

5.1. WBE biomarkers for plastic-related chemicals

In the case of plastic additives, the parent compounds are not good biomarkers of exposure due to their ubiquity, as they may be present in wastewater from several other sources rather than human excretion. Thus, phase-I or phase-II metabolites have been tested as biomarkers considering both excretion rates in urine and wastewater stability. In the case of phase-II metabolites, glucuronides have been usually discarded due to poor stability in wastewater derived from their rapid hydrolysis by β-glucuronidase enzymes produced by fecal bacteria in sewage [126], as already discussed in section 3.

In the case of PAEs, the use of the hydrolysis products (PAE monoesters) has been described for short-chain PAEs [1,124–129]. In contrast, oxidized products of those monoesters have been proposed for long-chain phthalates, such as mono-(oxo-isononyl) phthalate (oxo-MiNP) for the estimation of DiNP exposure [124], due to their higher excretion rates and longer half-lives. A similar choice often applies to APs, and terephthalates, for which both monoesters and other products of subsequent oxidations could be used, even considering that the excretion rates are low [124]. Given the mismatched results of WBE against HBM found for the Australian population [128], some authors have pointed out that PAE monoesters may also originate in the sewers from parental PAEs that are released into them, in addition to being excreted as urinary metabolites. To date, however, they constitute the only reported biomarkers to explore exposure trends by WBE.

In the case of OPFRs, the selection of appropriate metabolites for their use in WBE is highly dependent not only on excretion rates, but on their possible occurrence in industrial processes and products. This is the case of DPHP, which is a metabolite of TPHP, but is also used in industrial products. In this case, some hydroxylated metabolites, such as 3-hydroxyphenyl diphenyl phosphate (3-OH-TPHP), appear to be good alternatives [1,130,131]. In the case of chlorinated OPFRs, both the hydrolysis products and oxidation metabolites have been proposed as potential WBE biomarkers [131,132].

The very few WBE applications to measure BPA exposure have proposed the phase-II metabolite bisphenol A monosulfate (BPA-S) as the most suitable biomarker [1,64,127]. The metabolites selected in the literature whenever human exposure to a given substance is studied through WBE are shown in the supplementary material (Table S5). Other compounds discussed in this review have, so far, not been subject of WBE studies.

5.2. WBE-based human exposure

PAEs are undoubtedly the most studied plastic-related chemicals exploiting WBE, with DEP and DnBP as the compounds presenting the highest levels of exposure, with estimated values, in some cases, >1 mg inh^{-1} day^{-1} [116,121]. Exposure levels derived from WBE have not been yet reported for APs, such as DINCH, due to low levels of metabolites in wastewater, although the WBE approach has been proposed as a viable alternative [64,124]. As for BPA, there are several articles reporting human exposure derived from the determination of BPA-S [1,64,127]. However, the results obtained are highly dependent on the CF selected, derived from different metabolic studies, with a range of reported CFs for BPA varying from 0.16 [64] up to 24.7 [1].

In the case of flame retardants, TPHP, TBOEP and 2-ethylhexyldiphenyl phosphate (EHDPHP) were those metabolites presenting the highest mass loads (>10 μg inh^{-1} day^{-1}) in all WBE studies [1,130,131]. Yet in some studies, only mass loads of metabolites were considered, and no CF was applied. In the case of TBOEP, using a CF of 13.9 for urinary

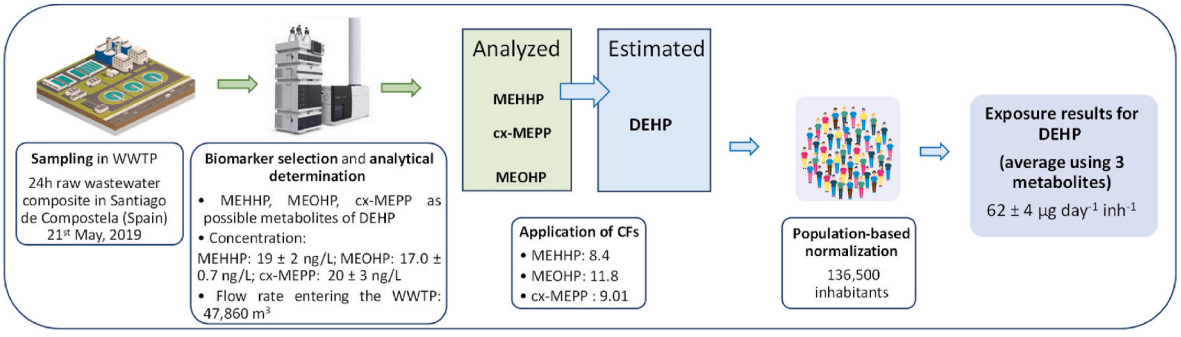

Fig. 3. Step-by-step workflow for the estimation of DEHP exposure through WBE as applied to a WWTP in Santiago de Compostela as a model example [124]. For abbreviations see Table S1. Note: Images created by Freepik.es® and the authors.

excretion of di(2-butoxyethyl) 2-hydroxyethyl phosphate (BBOEHEP), the values obtained in some cities (i.e., 1783 ± 830 μg inh^{-1} day^{-1} estimated in Antwerp (Belgium) in 2021) are higher by far from those stablished as RfD [1].

WBE is considered a promising indirect biomonitoring tool; however, it is important to note the uncertainty of the data, primarily influenced by numerous factors, such as (i) the stability of the metabolites in wastewater or in-sewer (i.e., the possible in-sewer transformation of phthalate diesters to phthalate monoesters, which calls into question the selection of these biomarkers), (ii) sorption processes [127,133], (iii) variations in CF depending on sources of excretion rate data, or (iv) the different methodologies used to estimate the size of the analyzed population (demographic data, connections to the waste network, biological or chemical oxygen demand, etc.). Particularly, proving the biomarkers as being exclusively originated from human urinary excretion, and further curated CFs values are required. Furthermore, so far, the number of WBE applications is still limited to a few chemicals and needs to be expanded to demonstrate the opportunities offered by WBE.

6. Conclusions and outlook

This review gives insights into the recent achievements and advances in the evaluation of human exposure to plastic additives using a selection of representative papers. Nowadays, challenging issues, such as HBM and the analysis of human exposure to organic contaminants, have become feasible for many compounds as a consequence of advances in (bio)analytical tools and methods.

However, we also want to address some weaknesses and opportunities that need to be taken into account to fill many of the existing gaps. One clear gap is the lack of more standardized in-vitro models and adequate in-vivo validation of bioaccesibility models for many plastic additives. However, efforts are currently geared towards in-vitro bioavailability testing using cell models, or advanced biochemical assays in animal models using endogenous biomarkers of effect.

The metabolism and the HBM of contaminants are closely related, as the main challenge is to identify and select the main metabolic transformation products. Currently, many of the known metabolites have been described based on in-vitro and/or in-silico models involving common (or known) transformation pathways. Though both approaches are generally satisfactory, many compounds are ignored and therefore key information regarding adverse outcome pathways may be overlooked. The implementation of up-to-date non-targeted analytical approaches in ongoing HBM studies may in the next future complement the current knowledge and remarkably overcome this gap.

WBE is still a growing field that can complement HBM studies and be useful for monitoring not only the exposure to chemicals but life-style habits, the spread of infectious diseases, or consumption of drugs. However, the inherent difficulties in the analysis of such samples and the need to implement robust links between the exposure and adequate biomarkers of exposure require further research. In this sense, the mentioned non-targeted analysis in HBM can be very helpful for the identification of excretion by-products or the transformations occurring in WWTPs.

Finally, it is worth mentioning that we already have at hand a plethora of data of frequently monitored contaminants but still a large part of the chemicals will remain unknown. Furthermore, if we shift the focus from human health to the uprising challenges in environmental health, the need to fill the gaps is even greater.

CRediT authorship contribution statement

Andrea Estévez-Danta: Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Juan F. Ayala-Cabrera:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Javier López-Vázquez:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Mikel Musatadi:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Rosa Montes:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Nestor Etxebarria:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **José Benito Quintana:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Maitane Olivares:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Ailette Prieto:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Rosario Rodil:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Manuel Miró:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Olatz Zuloaga:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Funding acquisition, Data curation, 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

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trac.2024.117653.

References

[1] I. Senta, S. Rodríguez-Mozaz, L. Corominas, A. Covaci, M. Petrovic, Applicability of an on-line solid-phase extraction liquid chromatography – tandem mass spectrometry for the wastewater-based assessment of human exposure to chemicals from personal care and household products, Sci. Total Environ. 845 (2022) 157309, https://doi.org/10.1016/j.scitotenv.2022.157309.

[2] P.J. Landrigan, H. Raps, M. Cropper, C. Bald, M. Brunner, E.M. Canonizado, D. Charles, T.C. Chiles, M.J. Donohue, J. Enck, P. Fenichel, L.E. Fleming, C. Ferrier-Pages, R. Fordham, A. Gozt, C. Griffin, M.E. Hahn, B. Haryanto, R. Hixson, H. Ianelli, B.D. James, P. Kumar, A. Laborde, K.L. Law, K. Martin, J. Mu, Y. Mulders, A. Mustapha, J. Niu, S. Pahl, Y. Park, M.-L. Pedrotti, J.A. Pitt, M. Ruchirawat, B.J. Seewoo, M. Spring, J.J. Stegeman, W. Suk, C. Symeonides, H. Takada, R.C. Thompson, A. Vicini, Z. Wang, E. Whitman, D. Wirth, M. Wolff, A.K. Yousuf, S. Dunlop, The Minderoo-Monaco Commission on plastics and

human health, Annals of Global Health 89 (2023) 23, https://doi.org/10.5334/aogh.4056.
[3] T. Backhaus, M. Wagner, Microplastics in the environment: much ado about nothing? A Debate, Glob. Chall. 4 (2020) 1900022, https://doi.org/10.1002/gch2.201900022.
[4] J.J. Alava, A. Jahnke, M. Bergmann, G.V. Aguirre-Martínez, L. Bendell, P. Calle, G.A. Domínguez, E.M. Faustman, J. Falman, T.N. Kazmiruk, N. Klasios, M. T. Maldonado, K. McMullen, M. Moreno-Báez, G. Öberg, Y. Ota, D. Price, W. J. Shim, A. Tirapé, J.M. Vandenberg, Z. Zoveidadianpour, J. Weis, A call to include plastics in the global environment in the class of Persistent, Bioaccumulative, and Toxic (PBT) Pollutants, Environ. Sci. Technol. 57 (2023) 8185–8188, https://doi.org/10.1021/acs.est.3c02476.
[5] Plastics Europe: Plastics – the Fast Facts, 2023. https://plasticseurope.org/wp-content/uploads/2023/10/Plasticsthefastfacts2023-1.pdf. (Accessed 10 November 2023).
[6] OECD, global plastics outlook, Economic Drivers, Environmental Impacts and Policy Options, organisation for economic co-operation and development, Paris, 2022. https://www.oecd-ilibrary.org/environment/global-plastics-outlook_de747aef-en. (Accessed 10 November 2023).
[7] D. Leistenschneider, A. Wolinski, J. Cheng, A. ter Halle, G. Duflos, A. Huvet, I. Paul-Pont, F. Lartaud, F. Galgani, É. Lavergne, A.-L. Meistertzheim, J.-F. Ghiglione, A critical review on the evaluation of toxicity and ecological risk assessment of plastics in the marine environment, Sci. Total Environ. 896 (2023) 164955, https://doi.org/10.1016/j.scitotenv.2023.164955.
[8] A.D. Godwin, 24 - plasticizers, in: M. Kutz (Ed.), Appl. Plast. Eng. Handb, second ed., William Andrew Publishing, 2017, pp. 533–553, https://doi.org/10.1016/B978-0-323-39040-8.00025-0.
[9] S. Al-Malaika, F. Axtell, R. Rothon, M. Gilbert, in: M. Gilbert (Ed.), Chapter 7 - Additives for Plastics, Brydsons Plast. Mater. Eighth Ed., Butterworth-Heinemann, 2017, pp. 127–168, https://doi.org/10.1016/B978-0-323-35824-8.00007-4.
[10] J.N. Hahladakis, C.A. Velis, R. Weber, E. Iacovidou, P. Purnell, An overview of chemical additives present in plastics: migration, release, fate and environmental impact during their use, disposal and recycling, J. Hazard Mater. 344 (2018) 179–199, https://doi.org/10.1016/j.jhazmat.2017.10.014.
[11] Y. Chen, Q. Chen, Q. Zhang, C. Zuo, H. Shi, An overview of chemical additives on (micro)plastic fibers: occurrence, release, and health risks, Rev. Environ. Contam. Toxicol. 260 (2022) 22, https://doi.org/10.1007/s44169-022-00023-9.
[12] Z. Yuan, R. Nag, E. Cummins, Human health concerns regarding microplastics in the aquatic environment - from marine to food systems, Sci. Total Environ. 823 (2022) 153730, https://doi.org/10.1016/j.scitotenv.2022.153730.
[13] L. Borriello, M. Scivicco, N.A. Cacciola, F. Esposito, L. Severino, T. Cirillo, Microplastics, a global issue: human exposure through environmental and dietary sources, Foods 12 (2023) 3396, https://doi.org/10.3390/foods12183396.
[14] K. Kannan, K. Vimalkumar, A review of human exposure to microplastics and insights into microplastics as obesogens, Front. Endocrinol. 12 (2021). https://www.frontiersin.org/articles/10.3389/fendo.2021.724989. (Accessed 10 November 2023).
[15] ISO 17402:2008, ISO 17402:2008, ISO (n.d.). https://www.iso.org/standard/38349.html (accessed November 14, 2023).
[16] ISO 17924:2018, ISO 17924:2018, ISO (n.d.). https://www.iso.org/standard/64938.html (accessed November 14, 2023).
[17] C.L.S. Wiseman, Analytical methods for assessing metal bioaccessibility in airborne particulate matter: a scoping review, Anal. Chim. Acta 877 (2015), https://doi.org/10.1016/j.aca.2015.01.024.
[18] A. Mukhtar, A. Limbeck, Recent developments in assessment of bio-accessible trace metal fractions in airborne particulate matter: a review, Anal. Chim. Acta 774 (2013) 11–25, https://doi.org/10.1016/j.aca.2013.02.008.
[19] G. Pawar, M.A.-E. Abdallah, E.V. de Sáa, S. Harrad, Dermal bioaccessibility of flame retardants from indoor dust and the influence of topically applied cosmetics, J. Expo. Sci. Environ. Epidemiol. 27 (2017) 100–105, https://doi.org/10.1038/jes.2015.84.
[20] D.F.M.S. Mohamed, D.Y. Kim, J. An, M. Kim, S.-H. Chun, J.-H. Kwon, Simplified unified BARGE method to assess migration of phthalate esters in ingested PVC consumer products, Int. J. Environ. Res. Public. Health 20 (2023) 1907, https://doi.org/10.3390/ijerph20031907.
[21] M.V. Ruby, K.A. Fehling, D.J. Paustenbach, B.D. Landenberger, M.P. Holsapple, Oral bioaccessibility of dioxins/furans at low concentrations (50−350 ppt toxicity equivalent) in Soil, Environ. Sci. Technol. 36 (2002) 4905–4911, https://doi.org/10.1021/es020636l.
[22] Y. Kang, Y.B. Man, K.C. Cheung, M.H. Wong, Risk assessment of human exposure to bioaccessible phthalate esters via indoor dust around the Pearl River Delta, Env, Sci. Technol. 46 (2012) 8422–8430, https://doi.org/10.1021/es300379v.
[23] W. Wang, F.-Y. Wu, M.-J. Huang, Y. Kang, K.C. Cheung, M.H. Wong, Size fraction effect on phthalate esters accumulation, bioaccessibility and in vitro cytotoxicity of indoor/outdoor dust, and risk assessment of human exposure, J. Hazard Mater. 261 (2013) 753–762, https://doi.org/10.1016/j.jhazmat.2013.04.039.
[24] T. Zhang, B. Ma, L. Wang, Phthalic acid esters in grains, vegetables, and fruits: concentration, distribution, composition, bio-accessibility, and dietary exposure, Environ. Sci. Pollut. Res. Int. 30 (2023) 2787–2799, https://doi.org/10.1007/s11356-022-22415-z.
[25] K. Kademoglou, G. Giovanoulis, A. Palm-Cousins, J.A. Padilla-Sanchez, J. Magnér, C.A. de Wit, C.D. Collins, In Vitro inhalation bioaccessibility of phthalate esters and alternative plasticizers present in indoor dust using artificial lung fluids, Environ. Sci. Technol. Lett. 5 (2018) 329–334, https://doi.org/10.1021/acs.estlett.8b00113.
[26] M. Huang, Y. Zeng, K. Luo, B. Lan, J. Luo, L. Zeng, Y. Kang, Inhalation bioacessibility and lung cell penetration of indoor PM2.5-bound PAEs and its implication in risk assessment, Environ. Pollut. 322 (2023) 121216, https://doi.org/10.1016/j.envpol.2023.121216.
[27] D. Zeng, Y. Kang, J. Chen, A. Li, W. Chen, Z. Li, L. He, Q. Zhang, J. Luo, L. Zeng, Dermal bioaccessibility of plasticizers in indoor dust and clothing, Sci. Total Environ. 672 (2019) 798–805, https://doi.org/10.1016/j.scitotenv.2019.04.028.
[28] S.C. Cunha, R.N. Alves, J.O. Fernandes, S. Casal, A. Marques, First approach to assess the bioaccessibility of bisphenol A in canned seafood, Food Chem. 232 (2017) 501–507, https://doi.org/10.1016/j.foodchem.2017.04.006.
[29] A. Lestido-Cardama, B.M. Sánchez, R. Sendón, A. Rodríguez-Bernaldo de Quirós, L. Barbosa-Pereira, Study on the chemical behaviour of Bisphenol S during the in vitro gastrointestinal digestion and its bioaccessibility, Food Chem. 367 (2022) 130758, https://doi.org/10.1016/j.foodchem.2021.130758.
[30] M. Fang, H.M. Stapleton, Evaluating the bioaccessibility of flame retardants in house dust using an in vitro tenax bead-assisted sorptive physiologically based method, Environ. Sci. Technol. 48 (2014) 13323–13330, https://doi.org/10.1021/es503918m.
[31] R.-W. He, Y.-Z. Li, P. Xiang, C. Li, X.-Y. Cui, L.Q. Ma, Impact of particle size on distribution and human exposure of flame retardants in indoor dust, Environ. Res. 162 (2018) 166–172, https://doi.org/10.1016/j.envres.2017.12.014.
[32] J.B. Quintana, M. Rosende, R. Montes, T. Rodríguez-Álvarez, R. Rodil, R. Cela, M. Miró, In-vitro estimation of bioaccessibility of chlorinated organophosphate flame retardants in indoor dust by fasting and fed physiologically relevant extraction tests, Sci. Total Environ. 580 (2017) 540–549, https://doi.org/10.1016/j.scitotenv.2016.11.210.
[33] M.A.-E. Abdallah, E. Tilston, S. Harrad, C. Collins, In vitro assessment of the bioaccessibility of brominated flame retardants in indoor dust using a colon extended model of the human gastrointestinal tract, J. Environ. Monit. 14 (2012) 3276–3283, https://doi.org/10.1039/C2EM30690E.
[34] S. García-Alcega, C. Rauert, S. Harrad, C.D. Collins, Does the source migration pathway of HBCDs to household dust influence their bio-accessibility? Sci. Total Environ. 569–570 (2016) 244–251, https://doi.org/10.1016/j.scitotenv.2016.04.178.
[35] Y. Zeng, S. Chen, Y. Fan, Q. Li, Y. Guan, B. Mai, Effects of carbonaceous materials and particle size on oral and inhalation bioaccessibility of PAHs and OPEs in airborne particles, Environ. Sci. Pollut. Res. 28 (2021) 62133–62141, https://doi.org/10.1007/s11356-021-14848-9.
[36] R. Zhang, Q. Zhang, L.Q. Ma, X. Cui, Effects of food constituents on absorption and bioaccessibility of dietary synthetic phenolic antioxidant by caco-2 cells, J. Agric. Food Chem. 68 (2020) 4670–4677, https://doi.org/10.1021/acs.jafc.9b07315.
[37] J. López-Vázquez, R. Rodil, M.J. Trujillo-Rodríguez, J.B. Quintana, R. Cela, M. Miró, Mimicking human ingestion of microplastics: oral bioaccessibility tests of bisphenol A and phthalate esters under fed and fasted states, Sci. Total Environ. 826 (2022) 154027, https://doi.org/10.1016/j.scitotenv.2022.154027.
[38] A. Sixto, B. El-Morabit, M.J. Trujillo-Rodríguez, E.J. Carrasco-Correa, M. Miró, An automatic flow-through system for exploration of the human bioaccessibility of endocrine disrupting compounds from microplastics, Analyst 146 (2021) 3858–3870, https://doi.org/10.1039/D1AN00446H.
[39] G.A. de Lima, J.M. Santos, A.P.S. Paim, A.F. Lavorante, Bioaccessibility study and simultaneous quantification of endocrine disruptors (bisphenol A and phthalates) in utensils and toys for infants using HPLC–UV, Chem. Pap. 76 (2022) 189–202, https://doi.org/10.1007/s11696-021-01847-w.
[40] M.J. Trujillo-Rodríguez, R.M. Gomila, G. Martorell, M. Miró, Microscale extraction versus conventional approaches for handling gastrointestinal extracts in oral bioaccessibility assays of endocrine disrupting compounds from microplastic contaminated beach sand, Environ. Pollut. 272 (2021) 115992, https://doi.org/10.1016/j.envpol.2020.115992.
[41] R. He, Y. Li, P. Xiang, C. Li, C. Zhou, S. Zhang, X. Cui, L.Q. Ma, Organophosphorus flame retardants and phthalate esters in indoor dust from different microenvironments: bioaccessibility and risk assessment, Chemosphere 150 (2016) 528–535, https://doi.org/10.1016/j.chemosphere.2015.10.087.
[42] J. Sánchez-Piñero, N. Novo-Quiza, J. Moreda-Piñeiro, S. Muniategui-Lorenzo, P. López-Mahía, A multi-residue method for the analysis of organic pollutants released from atmospheric PM2.5 in simulated biological fluids: inhalation bioaccessibility and bioavailability estimation, Anal. Chim. Acta 1280 (2023) 341862, https://doi.org/10.1016/j.aca.2023.341862.
[43] J. Sánchez-Piñero, N. Novo-Quiza, C. Pernas-Castaño, J. Moreda-Piñeiro, S. Muniategui-Lorenzo, P. López-Mahía, Inhalation bioaccessibility of multi-class organic pollutants associated to atmospheric PM2.5: correlation with PM2.5 properties and health risk assessment, Environ. Pollut. 307 (2022) 119577, https://doi.org/10.1016/j.envpol.2022.119577.
[44] X. Liu, X. Wang, Q. Xue, Y. Tian, Y. Feng, Inhalation bioaccessibility and risk assessment for PM-bound organic components: Co-effects of component physicochemical properties, PM properties, and sources, J. Hazard Mater. 459 (2023) 132291, https://doi.org/10.1016/j.jhazmat.2023.132291.
[45] O.M. Rodriguez-Narvaez, J.M. Peralta-Hernandez, A. Goonetilleke, E.R. Bandala, Treatment technologies for emerging contaminants in water: a review, Chem. Eng. J. 323 (2017) 361–380, https://doi.org/10.1016/j.cej.2017.04.106.
[46] M.J. Trujillo-Rodríguez, M. Rosende, M. Miró, Combining in vitro oral bioaccessibility methods with biological assays for human exposome studies of contaminants of emerging concern in solid samples, TrAC Trends Anal. Chem. 132 (2020) 116040, https://doi.org/10.1016/j.trac.2020.116040.
[47] S. Denys, J. Caboche, K. Tack, G. Rychen, J. Wragg, M. Cave, C. Jondreville, C. Feidt, In vivo validation of the unified barge method to assess the

bioaccessibility of arsenic, antimony, cadmium, and lead in soils, Environ. Sci. Technol. 46 (2012) 6252–6260, https://doi.org/10.1021/es3006942.
[48] C.H.M. Versantvoort, A.G. Oomen, E. Van de Kamp, C.J.M. Rompelberg, A.J.A. M. Sips, Applicability of an in vitro digestion model in assessing the bioaccessibility of mycotoxins from food, Food Chem. Toxicol. 43 (2005) 31–40, https://doi.org/10.1016/j.fct.2004.08.007.
[49] E.L. Tilston, G.R. Gibson, C.D. Collins, Colon extended physiologically based extraction test (CE-PBET) increases bioaccessibility of soil-bound PAH, Environ. Sci. Technol. 45 (2011) 5301–5308, https://doi.org/10.1021/es2004705.
[50] J.H. Bridson, E.C. Gaugler, D.A. Smith, G.L. Northcott, S. Gaw, Leaching and extraction of additives from plastic pollution to inform environmental risk: a multidisciplinary review of analytical approaches, J. Hazard Mater. 414 (2021) 125571, https://doi.org/10.1016/j.jhazmat.2021.125571.
[51] S.L. Wright, F.J. Kelly, Plastic and human health: a micro issue? Environ. Sci. Technol. 51 (2017) 6634–6647, https://doi.org/10.1021/acs.est.7b00423.
[52] M. Hu, Z. Zhang, Y. Zhang, M. Zhan, W. Qu, G. He, Y. Zhou, Development of human dermal PBPK models for the bisphenols BPA, BPS, BPF, and BPAF with parallel-layered skin compartment: basing on dermal administration studies in humans, Sci. Total Environ. 868 (2023) 161639, https://doi.org/10.1016/j.scitotenv.2023.161639.
[53] C. Rodríguez-Navas, M. Rosende, M. Miró, In-vitro physiologically based extraction of solid materials: do we have reliable analytical methods for bioaccessibility studies of emerging organic contaminants? TrAC Trends Anal. Chem. 91 (2017) 42–52, https://doi.org/10.1016/j.trac.2017.03.005.
[54] G. Malafaia, D. Barceló, Microplastics in human samples: recent advances, hot-spots, and analytical challenges, TrAC Trends Anal. Chem. 161 (2023) 117016, https://doi.org/10.1016/j.trac.2023.117016.
[55] H.A. Leslie, M.J.M. van Velzen, S.H. Brandsma, A.D. Vethaak, J.J. Garcia-Vallejo, M.H. Lamoree, Discovery and quantification of plastic particle pollution in human blood, Environ. Int. 163 (2022) 107199, https://doi.org/10.1016/j.envint.2022.107199.
[56] M.D. Coleman, Front matter, in: Hum. Drug Metab., John Wiley & Sons, Ltd, 2020, pp. i–xvii, https://doi.org/10.1002/9781119658016.fmatter.
[57] L. Lopardo, A. Cummins, A. Rydevik, B. Kasprzyk-Hordern, New analytical framework for verification of biomarkers of exposure to chemicals combining human biomonitoring and water fingerprinting, Anal. Chem. 89 (2017) 7232–7239, https://doi.org/10.1021/acs.analchem.7b01527.
[58] M. Roggeman, C. Gys, A. Klimowska, M. Bastiaensen, B. Wielgomas, Y. Ait Bamai, A. Covaci, Reviewing the variability in urinary concentrations of non-persistent organic chemicals: evaluation across classes, sampling strategies and dilution corrections, Environ. Res. 215 (2022) 114332, https://doi.org/10.1016/j.envres.2022.114332.
[59] H. Frederiksen, N.E. Skakkebaek, A.-M. Andersson, Metabolism of phthalates in humans, Mol. Nutr. Food Res. 51 (2007) 899–911, https://doi.org/10.1002/mnfr.200600243.
[60] W.A.C. Anderson, L. Castle, M.J. Scotter, R.C. Massey, C. Springall, A biomarker approach to measuring human dietary exposure to certain phthalate diesters, Food Addit. Contam. 18 (2001) 1068–1074, https://doi.org/10.1080/02652030110050113.
[61] G. D'Ascenzo, A. Di Corcia, A. Gentili, R. Mancini, R. Mastropasqua, M. Nazzari, R. Samperi, Fate of natural estrogen conjugates in municipal sewage transport and treatment facilities, Sci. Total Environ. 302 (2003) 199–209, https://doi.org/10.1016/S0048-9697(02)00342-X.
[62] D. Gramec Skledar, L. Peterlin Mašič, Bisphenol A and its analogs: do their metabolites have endocrine activity? Environ. Toxicol. Pharmacol. 47 (2016) 182–199, https://doi.org/10.1016/j.etap.2016.09.014.
[63] C. Dumont, E. Perdu, G. de Sousa, L. Debrauwer, R. Rahmani, J.-P. Cravedi, M.-C. Chagnon, Bis(hydroxyphenyl)methane—bisphenol F—metabolism by the HepG2 human hepatoma cell line and cryopreserved human hepatocytes, Drug Chem. Toxicol. 34 (2011) 445–453, https://doi.org/10.3109/01480545.2011.585651.
[64] L. Lopardo, B. Petrie, K. Proctor, J. Youdan, R. Barden, B. Kasprzyk-Hordern, Estimation of community-wide exposure to bisphenol A via water fingerprinting, Environ. Int. 125 (2019) 1–8, https://doi.org/10.1016/j.envint.2018.12.048.
[65] A. Liu, Z. Zhao, G. Qu, Z. Shen, J. Shi, G. Jiang, Transformation/degradation of tetrabromobisphenol A and its derivatives: a review of the metabolism and metabolites, Environ. Pollut. 243 (2018) 1141–1153, https://doi.org/10.1016/j.envpol.2018.09.068.
[66] W. Völkel, V. Fuchs, M. Wöckner, H. Fromme, Toxicokinetic of tris(2-butoxyethyl) phosphate (TBOEP) in humans following single oral administration, Arch. Toxicol. 92 (2018) 651–660, https://doi.org/10.1007/s00204-017-2078-7.
[67] A. Ballesteros-Gómez, N. Van den Eede, A. Covaci, In vitro human metabolism of the flame retardant resorcinol bis(diphenylphosphate) (RDP), Environ. Sci. Technol. 49 (2015) 3897–3904, https://doi.org/10.1021/es505857e.
[68] R.E. Dodson, N. Van den Eede, A. Covaci, L.J. Perovich, J.G. Brody, R.A. Rudel, Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies, Environ. Sci. Technol. 48 (2014) 13625–13633, https://doi.org/10.1021/es503445c.
[69] W. Wang, P. Xiong, H. Zhang, Q. Zhu, C. Liao, G. Jiang, Analysis, occurrence, toxicity and environmental health risks of synthetic phenolic antioxidants: a review, Environ. Res. 201 (2021) 111531, https://doi.org/10.1016/j.envres.2021.111531.
[70] R. Liu, S.A. Mabury, Rat metabolism study suggests 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid as a potential urinary biomarker of human exposure to representative 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate antioxidants, Environ. Sci. Technol. 55 (2021) 14051–14058, https://doi.org/10.1021/acs.est.1c03493.
[71] R. Liu, S.A. Mabury, Unexpectedly high concentrations of 2,4-di-tert-butylphenol in human urine, Environ. Pollut. 252 (2019) 1423–1428, https://doi.org/10.1016/j.envpol.2019.06.077.
[72] H. Frederiksen, E.N. Upners, M.L. Ljubicic, M.B. Fischer, A.S. Busch, C.P. Hagen, A. Juul, A.-M. Andersson, Exposure to 15 phthalates and two substitutes (DEHTP and DINCH) assessed in trios of infants and their parents as well as longitudinally in infants exclusively breastfed and after the introduction of a mixed diet, Environ. Int. 161 (2022) 107107, https://doi.org/10.1016/j.envint.2022.107107.
[73] M.E. Ingle, D. Watkins, Z. Rosario, C.M. VélezVega, A.M. Calafat, M. Ospina, K. K. Ferguson, J.F. Cordero, A. Alshawabkeh, J.D. Meeker, An exploratory analysis of urinary organophosphate ester metabolites and oxidative stress among pregnant women in Puerto Rico, Sci. Total Environ. 703 (2020) 134798, https://doi.org/10.1016/j.scitotenv.2019.134798.
[74] G. Lee, S. Kim, Y. Kho, S. Kim, S. Lee, G. Choi, J. Park, S. Worakhunpiset, H.-B. Moon, K. Okanurak, M. Geounuppakul, J. Tangtitawong, K. Wetsutthanon, D. Trisurat, K. Choi, Urinary levels of phthalates and DINCH metabolites in Korean and Thai pregnant women across three trimesters, Sci. Total Environ. 711 (2020) 134822, https://doi.org/10.1016/j.scitotenv.2019.134822.
[75] J.P. Buckley, J.R. Kuiper, D.H. Bennett, E.S. Barrett, T. Bastain, C.V. Breton, S. Chinthakindi, A.L. Dunlop, S.F. Farzan, J.B. Herbstman, M.R. Karagas, C. J. Marsit, J.D. Meeker, R. Morello-Frosch, T.G. O'Connor, M.E. Romano, S. Schantz, R.J. Schmidt, D.J. Watkins, H. Zhu, E.D. Pellizzari, K. Kannan, T. J. Woodruff, Exposure to contemporary and emerging chemicals in commerce among pregnant women in the United States: the environmental influences on Child Health Outcome (ECHO) program, Environ. Sci. Technol. 56 (2022) 6560–6573, https://doi.org/10.1021/acs.est.1c08942.
[76] M. Kasper-Sonnenberg, H.M. Koch, P. Apel, M. Rüther, C. Pälmke, T. Brüning, M. Kolossa-Gehring, Time trend of exposure to the phthalate plasticizer substitute DINCH in Germany from 1999 to 2017: biomonitoring data on young adults from the Environmental Specimen Bank (ESB), Int. J. Hyg Environ. Health 222 (2019) 1084–1092, https://doi.org/10.1016/j.ijheh.2019.07.011.
[77] D.C. Pacyga, D.K. Haggerty, M. Nicol, M. Henning, A.M. Calafat, J.M. Braun, S. L. Schantz, R.S. Strakovsky, Identification of profiles and determinants of maternal pregnancy urinary biomarkers of phthalates and replacements in the Illinois Kids Development Study, Environ. Int. 162 (2022) 107150, https://doi.org/10.1016/j.envint.2022.107150.
[78] P.A. Bommarito, A. Friedman, B.M. Welch, D.E. Cantonwine, M. Ospina, A. M. Calafat, J.D. Meeker, T.F. McElrath, K.K. Ferguson, Temporal trends and predictors of gestational exposure to organophosphate ester flame retardants and plasticizers, Environ. Int. 180 (2023) 108194, https://doi.org/10.1016/j.envint.2023.108194.
[79] S.C. Hammel, S. Zhang, A.M. Lorenzo, B. Eichner, H.M. Stapleton, K. Hoffman, Young infants' exposure to organophosphate esters: breast milk as a potential source of exposure, Environ. Int. 143 (2020) 106009, https://doi.org/10.1016/j.envint.2020.106009.
[80] M. Li, Y. Yao, Y. Wang, M. Bastiaensen, A. Covaci, H. Sun, Organophosphate ester flame retardants and plasticizers in a Chinese population: significance of hydroxylated metabolites and implication for human exposure, Environ. Pollut. Barking Essex 257 (2020) (1987) 113633, https://doi.org/10.1016/j.envpol.2019.113633.
[81] Z. Lyu, K.H. Harada, S. Kim, T. Fujitani, Y. Cao, T. Hitomi, Y. Fujii, Y. Kho, K. Choi, Exposure to phthalate esters in Japanese females in Kyoto, Japan from 1993 to 2016: temporal trends and associated health risks, Environ. Int. 165 (2022) 107288, https://doi.org/10.1016/j.envint.2022.107288.
[82] H. Frederiksen, O. Nielsen, H.M. Koch, N.E. Skakkebaek, A. Juul, N. Jørgensen, A.-M. Andersson, Changes in urinary excretion of phthalates, phthalate substitutes, bisphenols and other polychlorinated and phenolic substances in young Danish men; 2009-2017, Int. J. Hyg Environ. Health 223 (2020) 93–105, https://doi.org/10.1016/j.ijheh.2019.10.002.
[83] P. S, L. S, G. I, L. E, B. Jp, L. T, L. C, K. H, G. A, Exposure of Swedish adolescents to elements, persistent organic pollutants (POPs), and rapidly excreted substances - the Riksmaten adolescents 2016-17 national survey, Int. J. Hyg Environ. Health 251 (2023), https://doi.org/10.1016/j.ijheh.2023.114196.
[84] G. Schwedler, E. Rucic, R. Lange, A. Conrad, H.M. Koch, C. Pälmke, T. Brüning, C. Schulz, M.I.H. Schmied-Tobies, A. Daniels, M. Kolossa-Gehring, Phthalate metabolites in urine of children and adolescents in Germany. Human biomonitoring results of the German Environmental Survey GerES V, 2014–2017, Int. J. Hyg Environ. Health 225 (2020) 113444, https://doi.org/10.1016/j.ijheh.2019.113444.
[85] X. Zhang, S. Tang, T. Qiu, X. Hu, Y. Lu, P. Du, L. Xie, Y. Yang, F. Zhao, Y. Zhu, J. P. Giesy, Investigation of phthalate metabolites in urine and daily phthalate intakes among three age groups in Beijing, China, Environ. Pollut. Barking Essex 260 (2020) (1987) 114005, https://doi.org/10.1016/j.envpol.2020.114005.
[86] A. Gkrillas, H. Dirven, E. Papadopoulou, M. Andreassen, H. Hjertholm, T. Husøy, Exposure estimates of phthalates and DINCH from foods and personal care products in comparison with biomonitoring data in 24-hour urine from the Norwegian EuroMix biomonitoring study, Environ. Int. 155 (2021) 106598, https://doi.org/10.1016/j.envint.2021.106598.
[87] N.K. Jayatilaka, P. Restrepo, Z. Davis, M. Vidal, A.M. Calafat, M. Ospina, Quantification of 16 urinary biomarkers of exposure to flame retardants, plasticizers, and organophosphate insecticides for biomonitoring studies, Chemosphere 235 (2019) 481–491, https://doi.org/10.1016/j.chemosphere.2019.06.181.

[88] P. Dwivedi, X. Zhou, T.G. Powell, A.M. Calafat, X. Ye, Impact of enzymatic hydrolysis on the quantification of total urinary concentrations of chemical biomarkers, Chemosphere 199 (2018) 256–262, https://doi.org/10.1016/j.chemosphere.2018.01.177.
[89] P. Stuchlík Fišerová, L. Melymuk, K. Komprdová, E. Domínguez-Romero, M. Scheringer, J. Kohoutek, P. Přibylová, L. Andrýsková, P. Piler, H.M. Koch, M. Zvonař, M. Esteban-López, A. Castaño, J. Klánová, Personal care product use and lifestyle affect phthalate and DINCH metabolite levels in teenagers and young adults, Environ. Res. 213 (2022) 113675, https://doi.org/10.1016/j.envres.2022.113675.
[90] M. Bastiaensen, C. Gys, A. Colles, V. Verheyen, G. Koppen, E. Govarts, L. Bruckers, B. Morrens, I. Loots, A. De Decker, V. Nelen, T. Nawrot, S. De Henauw, N. Van Larebeke, G. Schoeters, A. Covaci, Exposure levels, determinants and risk assessment of organophosphate flame retardants and plasticizers in adolescents (14–15 years) from the Flemish Environment and Health Study, Environ. Int. 147 (2021) 106368, https://doi.org/10.1016/j.envint.2020.106368.
[91] S. Lu, D. Yang, X. Ge, L. Li, Y. Zhao, C. Li, S. Ma, Y. Yu, The internal exposure of phthalate metabolites and bisphenols in waste incineration plant workers and the associated health risks, Environ. Int. 145 (2020) 106101, https://doi.org/10.1016/j.envint.2020.106101.
[92] Z. Percy, A.M. Vuong, M. Ospina, A.M. Calafat, M.J. La Guardia, Y. Xu, R.C. Hale, K.N. Dietrich, C. Xie, B.P. Lanphear, J.M. Braun, K.M. Cecil, K. Yolton, A. Chen, Organophosphate esters in a cohort of pregnant women: variability and predictors of exposure, Environ. Res. 184 (2020) 109255, https://doi.org/10.1016/j.envres.2020.109255.
[93] D. Luo, W. Liu, Y. Tao, L. Wang, M. Yu, L. Hu, A. Zhou, A. Covaci, W. Xia, Y. Li, S. Xu, S. Mei, Prenatal exposure to organophosphate flame retardants and the risk of low birth weight: a nested case-control study in China, Environ. Sci. Technol. 54 (2020) 3375–3385, https://doi.org/10.1021/acs.est.9b06026.
[94] W. Wang, K. Kannan, Quantitative identification of and exposure to synthetic phenolic antioxidants, including butylated hydroxytoluene, in urine, Environ. Int. 128 (2019) 24–29, https://doi.org/10.1016/j.envint.2019.04.028.
[95] K. Urbancova, R.J. Sram, J. Hajslova, J. Pulkrabova, Concentrations of phthalate and DINCH Metabolites in urine samples from Czech mothers and newborns, Expo, Health 14 (2022) 17–27, https://doi.org/10.1007/s12403-021-00415-7.
[96] T. Husøy, M. Andreassen, H. Hjertholm, M.H. Carlsen, N. Norberg, C. Sprong, E. Papadopoulou, A.K. Sakhi, A. Sabaredzovic, H.a. a.M. Dirven, The Norwegian biomonitoring study from the EU project EuroMix: levels of phenols and phthalates in 24-hour urine samples and exposure sources from food and personal care products, Environ. Int. 132 (2019) 105103, https://doi.org/10.1016/j.envint.2019.105103.
[97] N.C. Mohanto, Y. Ito, S. Kato, T. Ebara, K. Kaneko, T. Tsuchiyama, M. Sugiura-Ogasawara, S. Saitoh, M. Kamijima, Quantitative measurement of phthalate exposure biomarker levels in diaper-extracted urine of Japanese toddlers and cumulative risk assessment: an adjunct study of JECS Birth Cohort, Environ. Sci. Technol. 57 (2023) 395–404, https://doi.org/10.1021/acs.est.2c04816.
[98] Y. Sjöström, K. Hagström, C. Lindh, I.-L. Bryngelsson, M. Larsson, J. Hagberg, Exposure to phthalates and DiNCH among preschool children in Sweden: urinary metabolite concentrations and predictors of exposure, Int. J. Hyg Environ. Health 250 (2023) 114161, https://doi.org/10.1016/j.ijheh.2023.114161.
[99] C. Pirard, C. Charlier, Urinary levels of parabens, phthalate metabolites, bisphenol A and plasticizer alternatives in a Belgian population: time trend or impact of an awareness campaign? Environ. Res. 214 (2022) 113852 https://doi.org/10.1016/j.envres.2022.113852.
[100] M. Musatadi, A. Andrés-Maguregi, F. De Angelis, A. Prieto, E. Anakabe, M. Olivares, N. Etxebarria, O. Zuloaga, The role of sample preparation in suspect and non-target screening for exposome analysis using human urine, Chemosphere 339 (2023) 139690, https://doi.org/10.1016/j.chemosphere.2023.139690.
[101] Y. Gu, J.T. Peach, B. Warth, Sample preparation strategies for mass spectrometry analysis in human exposome research: current status and future perspectives, TrAC Trends Anal. Chem. 166 (2023) 117151, https://doi.org/10.1016/j.trac.2023.117151.
[102] M. Musatadi, I. Baciero-Hernández, A. Prieto, M. Olivares, N. Etxebarria, O. Zuloaga, Development and evaluation of a comprehensive workflow for suspect screening of exposome-related xenobiotics and phase II metabolites in diverse human biofluids, Chemosphere 351 (2024) 141221, https://doi.org/10.1016/j.chemosphere.2024.141221.
[103] N. Caballero-Casero, L. Belova, P. Vervliet, J.-P. Antignac, A. Castaño, L. Debrauwer, M.E. López, C. Huber, J. Klanova, M. Krauss, A. Lommen, H.G. J. Mol, H. Oberacher, O. Pardo, E.J. Price, V. Reinstadler, C.M. Vitale, A.L.N. van Nuijs, A. Covaci, Towards harmonised criteria in quality assurance and quality control of suspect and non-target LC-HRMS analytical workflows for screening of emerging contaminants in human biomonitoring, TrAC Trends Anal. Chem. 136 (2021) 116201, https://doi.org/10.1016/j.trac.2021.116201.
[104] M. Pourchet, L. Debrauwer, J. Klanova, E.J. Price, A. Covaci, N. Caballero-Casero, H. Oberacher, M. Lamoree, A. Damont, F. Fenaille, J. Vlaanderen, J. Meijer, M. Krauss, D. Sarigiannis, R. Barouki, B. Le Bizec, J.-P. Antignac, Suspect and non-targeted screening of chemicals of emerging concern for human biomonitoring, environmental health studies and support to risk assessment: from promises to challenges and harmonisation issues, Environ. Int. 139 (2020) 105545, https://doi.org/10.1016/j.envint.2020.105545.
[105] M. Deng, X. Liang, B. Du, D. Luo, H. Chen, C. Zhu, L. Zeng, Beyond classic phthalates: occurrence of multiple emerging phthalate alternatives and their metabolites in human milk and implications for combined exposure in infants, Environ. Sci. Technol. Lett. 8 (2021) 705–712, https://doi.org/10.1021/acs.estlett.1c00476.
[106] J. Ma, H. Zhu, K. Kannan, Organophosphorus flame retardants and plasticizers in breast milk from the United States, Environ. Sci. Technol. Lett. 6 (2019) 525–531, https://doi.org/10.1021/acs.estlett.9b00394.
[107] T. Jamnik, M. Flasch, D. Braun, Y. Fareed, D. Wasinger, D. Seki, D. Berry, A. Berger, L. Wisgrill, B. Warth, Next-generation biomonitoring of the early-life chemical exposome in neonatal and infant development, Nat. Commun. 13 (2022) 2653, https://doi.org/10.1038/s41467-022-30204-y.
[108] M. Barghi, E.-S. Shin, S.-D. Choi, R. Dahmardeh Behrooz, Y.-S. Chang, HBCD and TBBPA in human scalp hair: evidence of internal exposure, Chemosphere 207 (2018) 70–77, https://doi.org/10.1016/j.chemosphere.2018.05.032.
[109] I. Katsikantami, M.N. Tzatzarakis, A.K. Alegakis, V. Karzi, E. Hatzidaki, A. Stavroulaki, E. Vakonaki, P. Xezonaki, S. Sifakis, A.K. Rizos, A.M. Tsatsakis, Phthalate metabolites concentrations in amniotic fluid and maternal urine: cumulative exposure and risk assessment, Toxicol Rep 7 (2020) 529–538, https://doi.org/10.1016/j.toxrep.2020.04.008.
[110] W. Huang, X.-F. Pan, S. Tang, F. Sun, P. Wu, J. Yuan, W. Sun, A. Pan, D. Chen, Target exposome for characterizing early gestational exposure to contaminants of emerging concern and association with gestational diabetes mellitus, Environ. Sci. Technol. 57 (2023) 13408–13418, https://doi.org/10.1021/acs.est.3c04492.
[111] G. Zheng, E. Schreder, J.C. Dempsey, N. Uding, V. Chu, G. Andres, S. Sathyanarayana, A. Salamova, Organophosphate esters and their metabolites in breast milk from the United States: breastfeeding is an important exposure pathway for infants, Environ. Sci. Technol. Lett. 8 (2021) 224–230, https://doi.org/10.1021/acs.estlett.0c00916.
[112] J. Rovira, M.Á. Martínez, M. Mari, S.C. Cunha, J.O. Fernandes, I. Marmelo, A. Marques, L.S. Haug, C. Thomsen, M. Nadal, J.L. Domingo, M. Schuhmacher, Mixture of environmental pollutants in breast milk from a Spanish cohort of nursing mothers, Environ. Int. 166 (2022) 107375, https://doi.org/10.1016/j.envint.2022.107375.
[113] M. Huang, J. Li, Z. Xiao, Z. Shi, Tetrabromobisphenol A and hexabromocyclododecane isomers in breast milk from the general population in Beijing, China: contamination levels, temporal trends, nursing infant's daily intake, and risk assessment, Chemosphere 244 (2020) 125524, https://doi.org/10.1016/j.chemosphere.2019.125524.
[114] N. Caballero-Casero, G. Castro, M. Bastiaensen, C. Gys, N. van Larebeke, G. Schoeters, A. Covaci, Identification of chemicals of emerging concern in urine of Flemish adolescents using a new suspect screening workflow for LC-QTOF-MS, Chemosphere 280 (2021) 130683, https://doi.org/10.1016/j.chemosphere.2021.130683.
[115] C. Christia, K.M. da Silva, G. Poma, A. Covaci, Identification and semi-quantification of metabolites of new plasticizers in urine collected from flemish adults and children, Chemosphere 307 (2022) 135781, https://doi.org/10.1016/j.chemosphere.2022.135781.
[116] D.E. Goin, D. Abrahamsson, M. Wang, T. Jiang, J.-S. Park, M. Sirota, R. Morello-Frosch, E. DeMicco, M.G. Zlatnik, T.J. Woodruff, Disparities in chemical exposures among pregnant women and neonates by socioeconomic and demographic characteristics: a nontargeted approach, Environ. Res. 215 (2022) 114158, https://doi.org/10.1016/j.envres.2022.114158.
[117] M. Musatadi, B. González-Gaya, M. Irazola, A. Prieto, N. Etxebarria, M. Olivares, O. Zuloaga, Multi-target analysis and suspect screening of xenobiotics in milk by UHPLC-HRMS/MS, Separations 8 (2021) 14, https://doi.org/10.3390/separations8020014.
[118] S. Thomas, J.M. Gauglitz, A. Tripathi, F. Vargas, K. Bertrand, J.H. Kim, C. Chambers, P.C. Dorrestein, S.M. Tsunoda, An untargeted metabolomics analysis of exogenous chemicals in human milk and transfer to the infant, Clin. Transl. Sci. 15 (2022) 2576–2582, https://doi.org/10.1111/cts.13393.
[119] A. Wang, D.P. Abrahamsson, T. Jiang, M. Wang, R. Morello-Frosch, J.-S. Park, M. Sirota, T.J. Woodruff, Suspect screening, prioritization, and confirmation of environmental chemicals in maternal-newborn pairs from San Francisco, Environ. Sci. Technol. 55 (2021) 5037–5049, https://doi.org/10.1021/acs.est.0c05984.
[120] H. Frederiksen, O. Nielsen, H.M. Koch, N.E. Skakkebaek, A. Juul, N. Jørgensen, A.-M. Andersson, Changes in urinary excretion of phthalates, phthalate substitutes, bisphenols and other polychlorinated and phenolic substances in young Danish men; 2009–2017, Int. J. Hyg Environ. Health 223 (2020) 93–105, https://doi.org/10.1016/j.ijheh.2019.10.002.
[121] X. Wu, D. Zhang, Y. Chen, J. Shen, X. Li, Q. Zheng, J. Ma, J. Xu, M. Rao, X. Liu, S. Lu, Organophosphate ester exposure among Chinese waste incinerator workers: urinary levels, risk assessment and associations with oxidative stress, Sci. Total Environ. 854 (2023) 158808, https://doi.org/10.1016/j.scitotenv.2022.158808.
[122] B. Kasprzyk-Hordern, F. Béen, L. Bijlsma, W. Brack, S. Castiglioni, A. Covaci, B. S. Martincigh, J.F. Mueller, A.L.N. van Nuijs, T. Oluseyi, K.V. Thomas, Wastewater-based epidemiology for the assessment of population exposure to chemicals: the need for integration with human biomonitoring for global One Health actions, J. Hazard Mater. 450 (2023) 131009, https://doi.org/10.1016/j.jhazmat.2023.131009.
[123] I. Senta, S. Rodríguez-Mozaz, L. Corominas, M. Petrovic, Wastewater-based epidemiology to assess human exposure to personal care and household products – a review of biomarkers, analytical methods, and applications, Trends Environ. Anal. Chem. 28 (2020) e00103, https://doi.org/10.1016/j.teac.2020.e00103.
[124] A. Estévez-Danta, R. Rodil, B. Pérez-Castaño, R. Cela, J.B. Quintana, I. González-Mariño, Comprehensive determination of phthalate, terephthalate and di-iso-nonyl cyclohexane-1,2-dicarboxylate metabolites in wastewater by solid-phase extraction and ultra(high)-performance liquid chromatography-tandem mass

spectrometry, Talanta 224 (2021) 121912, https://doi.org/10.1016/j.talanta.2020.121912.
[125] I. González-Mariño, L. Ares, R. Montes, R. Rodil, R. Cela, E. López-García, C. Postigo, M. López de Alda, E. Pocurull, R.M. Marcé, L. Bijlsma, F. Hernández, Y. Picó, V. Andreu, A. Rico, Y. Valcárcel, M. Miró, N. Etxebarria, J.B. Quintana, Assessing population exposure to phthalate plasticizers in thirteen Spanish cities through the analysis of wastewater, J. Hazard Mater. 401 (2021) 123272, https://doi.org/10.1016/j.jhazmat.2020.123272.
[126] I. González-Mariño, R. Rodil, I. Barrio, R. Cela, J.B. Quintana, Wastewater-based epidemiology as a new tool for estimating population exposure to phthalate plasticizers, Environ. Sci. Technol. 51 (2017) 3902–3910, https://doi.org/10.1021/acs.est.6b05612.
[127] R. Kumar, S. Adhikari, E. Driver, J. Zevitz, R.U. Halden, Application of wastewater-based epidemiology for estimating population-wide human exposure to phthalate esters, bisphenols, and terephthalic acid, Sci. Total Environ. 847 (2022) 157616, https://doi.org/10.1016/j.scitotenv.2022.157616.
[128] S. Tang, C. He, P. Thai, S. Vijayasarathy, R. Mackie, L.-M.L. Toms, K. Thompson, P. Hobson, B. Tscharke, J.W. O'Brien, J.F. Mueller, Concentrations of phthalate metabolites in Australian urine samples and their contribution to the per capita loads in wastewater, Environ. Int. 137 (2020) 105534, https://doi.org/10.1016/j.envint.2020.105534.
[129] P. Du, Z. Zhou, H. Huang, S. Han, Z. Xu, Y. Bai, X. Li, Estimating population exposure to phthalate esters in major Chinese cities through wastewater-based epidemiology, Sci. Total Environ. 643 (2018) 1602–1609, https://doi.org/10.1016/j.scitotenv.2018.06.325.
[130] F. Been, M. Bastiaensen, F.Y. Lai, A.L.N. van Nuijs, A. Covaci, Liquid chromatography–tandem mass spectrometry analysis of biomarkers of exposure to phosphorus flame retardants in wastewater to monitor community-wide exposure, Anal. Chem. 89 (2017) 10045–10053, https://doi.org/10.1021/acs.analchem.7b02705.
[131] F. Been, M. Bastiaensen, F.Y. Lai, K. Libousi, N.S. Thomaidis, L. Benaglia, P. Esseiva, O. Delémont, A.L.N. van Nuijs, A. Covaci, Mining the chemical information on urban wastewater: monitoring human exposure to phosphorus flame retardants and plasticizers, Environ. Sci. Technol. 52 (2018) 6996–7005, https://doi.org/10.1021/acs.est.8b01279.
[132] V. Castro, R. Montes, J.B. Quintana, R. Rodil, R. Cela, Determination of 18 organophosphorus flame retardants/plasticizers in mussel samples by matrix solid-phase dispersion combined to liquid chromatography-tandem mass spectrometry, Talanta 208 (2020) 120470, https://doi.org/10.1016/j.talanta.2019.120470.
[133] P.M. Choi, J. Li, J. Gao, J.W. O'Brien, K.V. Thomas, P.K. Thai, G. Jiang, J. F. Mueller, Considerations for assessing stability of wastewater-based epidemiology biomarkers using biofilm-free and sewer reactor tests, Sci. Total Environ. 709 (2020) 136228, https://doi.org/10.1016/j.scitotenv.2019.136228.