



Wastewater-based epidemiology to assess human exposure to personal care and household products – A review of biomarkers, analytical methods, and applications



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ABSTRACT

Humans are nowadays exposed to numerous chemicals in our day-to-day life, including parabens, UV filters, phosphorous flame retardants/plasticizers, bisphenols, phthalates and alternative plasticizers, which can have different adverse effects to human health. Estimating human's exposure to these potentially harmful substances is, therefore, of paramount importance. Human biomonitoring (HBM) is the existing approach to assess exposure to environmental contaminants, which relies on the analysis of specific human biomarkers (parent compounds and/or their metabolic products) in biological matrices from individuals. The main drawback is its implementation, which involves complex cohort studies. A novel approach, wastewater-based epidemiology (WBE), involves estimating exposure from the analysis of biomarkers in sewage (a pooled urine and feces sample of an entire population). One of the key challenges of WBE is the selection of biomarkers which are specific to human metabolism, excreted in sufficient amounts, and stable in sewage. So far, literature data on potential biomarkers for estimating exposure to these chemicals are scattered over numerous pharmacokinetic and HBM studies. Hence, this review provides a list of potential biomarkers of exposure to more than 30 widely used chemicals and report on their urinary excretion rates. Furthermore, the potential and challenges of WBE in this particular field is discussed through the review of pioneer WBE studies, which for the first time explored applicability of this novel approach to assess human exposure to environmental contaminants. In the future, WBE could be potentially applied as an "early warning system", which could promptly identify communities with the highest exposure to environmental contaminants.

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Abbreviations: 3-OH-EtP, ethyl protocatechuate; 3-OH-MeP, methyl protocatechuate; 5-OH-OC, 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate; ASE, accelerated solvent extraction; bbCID, broadband collision-induced dissociation; BBOEHP, bis(2-butoxyethyl) 2-hydroxyethyl phosphate; BBOEP, bis(2-butoxyethyl) phosphate; BP-3, 2,4-dihydroxybenzophenone (Benzophenone-3, Oxybenzone); BPA, bisphenol A; BPA-Glu, bisphenol A glucuronide; BPA-SO₄, bisphenol A sulfate; CPAA, 2-cyano-3,3-diphenylacrylic acid; DEHA, di-2-ethylhexyl adipate; DEHP, di(2-ethylhexyl) phthalate; DEHTP, di(2-ethylhexyl) terephthalate; DHB, 2,4-dihydroxybenzophenone (Benzophenone-1, BP-1); DHMB, 2,2'-dihydroxy-4-methoxybenzophenone (Benzophenone-8, BP-8); DINCH, di(isononyl)cyclohexane-1,2-dicarboxylate; DNBP, di-*n*-butyl phosphate; DPHP, di-(2-propylheptyl) phthalate; DPhP, diphenyl phosphate; EHDPhP, 2-ethylhexyldiphenyl phosphate; EHS, 2-ethylhexyl salicylate (Octisalate); EI, electron ionization; ESI, electrospray ionization; EtP, ethylparaben; GC-MS, gas chromatography-mass spectrometry; HBM, human biomonitoring; HPLC-MS/MS, high performance liquid chromatography-tandem mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MAE, microwave-assisted extraction; MEHA, mono-2-ethylhexyl adipate; MeP, methylparaben; MINCH, Monoisononyl-cyclohexane-1,2-dicarboxylate; MQL, method quantification limit; MRM, multiple reaction monitoring (MRM); MTBSTFA, *N*-tert-butyltrimethylsilyl-*N*-methyltrifluoroacetamide; OC, Octocrylene; OH-MINCH, Cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl) octyl ester; PE, primary effluent; PFRs, phosphorous flame retardants/plasticizers; PHBA, *p*-hydroxybenzoic acid; PHHA, *p*-hydroxyhippuric acid; PrP, propylparaben; QqQ, triple quadrupole; Q-ToF, quadrupole-time-of-flight; QTRAP, quadrupole-ion trap; RW, raw wastewater; SE, secondary (final) effluent; SIM, selected ion monitoring; SPE, solid-phase extraction; SPM, suspended particulate matter; TBOEP, tris(2-butoxyethyl) phosphate; TPhP, triphenyl phosphate; UAE, ultrasonic-assisted extraction; UHPLC-MS/MS, ultrahigh performance liquid chromatography-tandem mass spectrometry; WBE, wastewater-based epidemiology; WWTPs, wastewater treatment plants.

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1. Introduction

Human populations worldwide are exposed to an increasingly large number of environmental contaminants. In fact, pollution is nowadays considered to be the main environmental cause of disease and death, with approximately 9 million premature deaths in 2015, corresponding to 16 % of all deaths globally and more than 25 % of deaths in the most severely affected countries [1].

Beside contaminated air, dust, food and water, the main sources of potentially harmful chemical substances include numerous consumer products used in day-to-day life, such as cosmetics, pharmaceuticals, food packages, plastic materials, clothing, furniture, electronics, paints, lubricants, adhesives and many others. Parabens, UV filters, phosphorous flame retardants/plasticizers (PFRs), bisphenols, phthalates and alternative plasticizers are widely used chemicals in these products, which can have different adverse effects on human health [2–5]. Exposure to these substances can be assessed by human biomonitoring (HBM) studies [6,7], which involve the analysis of specific biomarkers (parent compounds and/or their metabolic products) in urine and other biological matrices from individuals. Although useful, this approach is hampered by several limitations, including high costs, selection bias (difficulties in selecting individuals representative of the entire population), ethical approval requirements and lack of temporal dimension (individuals are sampled only once or, at best, over a 24-h period) [8]. It is, therefore, difficult to extrapolate the results of HBM studies, typically performed only periodically and on the limited number of subjects, to the entire populations, as well as to monitor temporal trends in exposure to contaminants.

Wastewater-based epidemiology (WBE), sometimes referred to as sewage epidemiology [9] or sewage chemical-information mining [10], is a relatively novel concept for obtaining some relevant epidemiological information, including lifestyle and dietary habits, population health and exposure to contaminants. Similar as HBM, WBE is also based on the analysis of specific human biomarkers, often the same ones as in HBM studies. However, instead of biological matrices, WBE involves the analysis of municipal wastewater (sewage). This approach is based on the fact that biomarkers of almost everything we consume, or we are exposed to, enter the sewer network after being excreted from the human body. Therefore, raw sewage can be considered as a very diluted, pooled urine (and feces) sample of the entire population connected to a certain sewer network. In other words, WBE can be regarded as HBM study at the community scale. Nowadays it is a well-established approach for the assessment of illicit drugs consumption and, more recently, it has been applied to estimate the consumption of some legal substances as well [11–13]. Recent studies also investigated the applicability of the WBE approach to assess human exposure to food and/or environmental contaminants, including pesticides [14–17], mycotoxins [18], phthalates [19–22], PFRs [8,23,24] and bisphenol A (BPA) [25]. Although first insights are rather promising, the full potential of WBE in this field has yet to be explored. WBE can also be applied to monitor spread of infectious diseases and antimicrobial resistance [26]. Scientific interest in this field has markedly increased in recent months, mostly due to the COVID-19 outbreak [27]. As demonstrated in first exploratory studies [28,29], WBE could serve as an additional, complementary approach to estimate the prevalence of COVID-19 in communities.

One of the key challenges in WBE is the selection of appropriate biomarkers, which should be specific to human metabolism (or their exogenous sources should be minimal), excreted in sufficient amounts (preferably in urine), and stable in sewage (both during the transport in sewer and during sampling, storage and analysis). Some recent review papers addressed this issue by proposing or

evaluating biomarkers used in present and future WBE applications [11,12]. However, these papers did not focus exclusively on biomarkers of exposure to environmental contaminants and, therefore, did not systematically evaluate rather complex and scattered pharmacokinetic and HBM data to propose the most promising biomarker(s) for many potentially harmful environmental contaminants. Moreover, some pharmacokinetic [30–33] and WBE studies [19–25,34] relevant for this topic were published very recently.

Therefore, the aim of this paper is to identify the potential biomarkers of human exposure to environmental contaminants, namely parabens, UV filters, PFRs, BPA, phthalates and alternative plasticizers, for a WBE-based assessment. The most suitable WBE biomarkers of the selected chemicals have been proposed after thorough review of pharmacokinetic, HBM and WBE literature. Moreover, the potential and challenges of WBE in the field of human exposure to environmental contaminants is discussed through the review of exploratory WBE studies.

2. Identification of potential WBE biomarkers of human exposure to personal care and household products

2.1. Parabens

2.1.1. Background

Parabens are a class of chemicals widely used as preservatives in food, cosmetics and pharmaceutical formulations. Chemically, they are esters of 4-hydroxybenzoic acid. They are frequently used combined, which increase their activity against microorganisms [35].

2.1.2. Potential health risk

For decades, parabens were considered to be safe. However, in the last 20 years, a concern has been raised regarding their endocrine disrupting potential, but also due to their possible role in breast cancer etiology [35,36]. Although the debate is ongoing, European Commission limited their maximum amount in cosmetic products sold in the EU market to 0.4 % for single compounds and 0.8 % for mixtures, with the additional restrictions for propylparaben (PrP) and *n*-butylparaben, while isopropylparaben, isobutylparaben, phenylparaben, benzylparaben and pentylparaben were banned from cosmetic products sold at the EU market [37].

2.1.3. Potential WBE biomarkers

In HBM studies, exposure to parabens is mainly assessed by the analysis of parent compounds in urine. As they are mostly excreted as glucuronide or sulfate conjugates [38], total concentrations (free + conjugated forms) are determined after enzymatic deconjugation [39]. Their common, but unspecific metabolites – *p*-hydroxybenzoic acid (PHBA) and *p*-hydroxyhippuric acid (PHHA; glycine conjugate of PHBA), are sometimes analyzed as well [40,41]. However, parent compounds and unspecific metabolites should be avoided as biomarkers in WBE, due to their possible additional sources in sewage, not necessarily reflecting the human exposure to specific compounds. Glucuronide conjugates, as rather unstable compounds, are generally not suitable WBE biomarkers due to their rapid hydrolysis by β -glucuronidase enzymes produced by fecal bacteria in sewage [19]. Although enzymatic deconjugation is a common, routine step in HBM studies, it can be recommended in WBE only in case of conjugated metabolites and not for conjugated parent compounds. Unlike glucuronides, sulfate conjugates, as more stable compounds, could be potentially used as WBE biomarkers. However, to the best of our knowledge, reference standards of sulfate conjugates of parabens are not commercially available. In HBM studies, their concentration is assessed indirectly, by analyzing parent parabens with and

without a deconjugation step, which is performed using sulfatase enzymes.

In a recent pharmacokinetic study, novel side-chain-oxidized metabolites were identified and proposed as additional, more specific biomarkers of exposure to butylparabens in HBM studies [41]. However, urinary excretion rate of ring-oxidized metabolite of methylparaben (MeP) was found to be much lower (0.1 %) [41]. Nevertheless, this compound, also known as methyl protocatechuate (3-OH-MeP), was used as a specific biomarker of exposure to MeP in HBM [42]. In fact, concentrations of 3-OH-MeP and ethyl protocatechuate (3-OH-EtP), analog ring-oxidized metabolite of ethylparaben (EtP), were found to be similar or even higher than the concentrations of parabens in urine samples, with a significant positive correlation between protocatechuates and their corresponding parent parabens. The discrepancy between the studies is difficult to explain, even if we take into account that protocatechuates can have natural origin, because this exposure is expected to be much lower than the exposure to parabens [42].

The human pharmacokinetic profile of PrP after oral administration has been recently studied. However, only parent PrP (mostly in conjugated form) and unspecific metabolites PHBA and PHHA have been determined [43]. The authors pointed out that the developed pharmacokinetic model has been evaluated only for oral route of exposure. However, dermal exposure could be even more relevant for parabens.

In Table 1, the main parabens are listed, along with their specific (oxidized) metabolites which could be used as biomarkers in WBE. Oxidized metabolites of PrP have not been identified yet, although they could be theoretically predicted [43]. Therefore, additional human pharmacokinetic studies, which would also include different routes of exposure (such as dermal) are needed for the correct interpretation of exposure to parabens in future studies.

2.2. UV filters

2.2.1. Background

UV filters represent a rather diverse group of chemicals with the common feature to protect skin against harmful UV—A and UV—B radiation. They are widely used in sunscreen lotions, but also in other cosmetics and a wide range of other products, including plastics, textile, food packages, adhesives, paints and rubbers. They can be divided into two main groups – inorganic, which mainly reflect and scatter UV radiation, and organic, which protect skin by absorbing harmful UV radiation. UV filters are often used in combination, to increase sun protection factor [44] or for stabilization purposes [45].

2.2.2. Potential health risk

Although UV filters are applied topically, they can enter the human body after being absorbed through the skin. Several organic UV filters and/or their metabolites can have adverse effects on human health, including endocrine disrupting properties [2] and some of them were banned from the sunscreen products available on the EU market. Current legislation allows around 30 compounds to be used as UV filters in cosmetic products in the EU, with the

additional restrictions regarding their maximum allowed concentrations [46].

2.2.3. Potential WBE biomarkers

In HBM, exposure to UV filters is mostly assessed by the analysis of parent compounds in urine (usually after enzymatic deconjugation) [47]. However, the number of HBM studies on UV filters seems to be comparatively lower than for some other groups of chemicals. Human pharmacokinetic studies are also relatively scarce and, in some cases, only data from metabolism studies with rats and/or *in vitro* studies are available. Among the most widely used UV filters, data are available for Benzophenone-3 (Oxybenzone), Octisalate, Enzacamene, Octocrylene, Avobenzone and Homosalate.

The metabolism of Benzophenone-3 (2-hydroxy-4-methoxybenzophenone; BP-3), probably the most widely used UV filter, was mainly investigated in rats [48,49]. Two major metabolites – 2,4-dihydroxybenzophenone (DHB) and 2,2'-dihydroxy-4-methoxybenzophenone (DHMB) were identified in urine in their free and conjugated forms and used as biomarkers of exposure to BP-3 in HBM. However, data from several *in vitro* and HBM studies with humans [50–52], suggest that excretion rate of DHMB might be very low. Therefore, DHB seems to be better biomarker of exposure to BP-3. It should be pointed out that these compounds, known as BP-1 and BP-8, respectively, are also used as UV filters themselves, however they are not allowed in cosmetic products sold at EU market [46]. A novel oxidative metabolite of BP-3 – 2,5-dihydroxy-4-methoxybenzophenone, was identified in a study with rat and human liver microsomes [50]. However, to the best of our knowledge, it has not been used in HBM so far. It is also noteworthy that metabolism of BP-3 seems to be rather different in different populations, depending both on age and ethnics [51].

Excretion rates of three most prominent oxidative metabolites of Octisalate (2-ethylhexyl salicylate; EHS) were determined after its oral administration [32]. Although the mean excretion rate of 2-ethyl-5-hydroxyhexyl 2-hydroxybenzoate (0.28 %) was slightly higher compared with 5-(((2-hydroxybenzoyl)oxy)methyl)heptanoic acid (0.24 %), the latter metabolite was detected with the highest frequency (88 %) in subsequent HBM study [53]. This discrepancy might be associated with the different pharmacokinetic profiles of EHS for different routes of exposure [54].

Two urinary metabolites were identified after dermal application of Enzacamene (3-(4-methylbenzylidene)camphor) – 3-(4-carboxybenzylidene)-6-hydroxycamphor (mostly in free form) and 3-(4-carboxybenzylidene)camphor (predominately in glucuronide form) [55]. Their excretion rates were lower than 0.5 %, which could be a result of dermal route of exposure.

In an oral dosing study, three metabolites of Octocrylene (2-ethylhexyl 2-cyano-3,3-diphenyl-2-acrylate; OC) were determined [31]. The major metabolite, 2-cyano-3,3-diphenylacrylic acid (CPAA), accounted for 45 % of the applied dose. However, this metabolite might not be specific to OC, because other structurally related compounds with CPAA moiety could also be metabolized to CPAA. The remaining two metabolites, 2-(carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate and 2-ethyl-5-hydroxyhexyl 2-cyano-

Table 1
Biomarkers proposed for WBE studies to assess human exposure to parabens.

Compound	Biomarker	Excretion rate (%) ^a	Ref.
Methylparaben (MeP)	Methyl 3,4-dihydroxybenzoate (Methyl protocatechuate; 3-OH-MeP)	0.1 (0.1–0.25)	[41] ^b
Ethylparaben (EtP)	Ethyl 3,4-dihydroxybenzoate (Ethyl protocatechuate; 3-OH-EtP)	NA	[42] ^c
<i>n</i> -Butylparaben (BuP)	3-Hydroxy- <i>n</i> -butylparaben (3-OH-BuP)	5.8 (4.5–7.1)	[41] ^b
<i>iso</i> -Butylparaben (iBuP)	2-Hydroxy- <i>iso</i> -butylparaben (2-OH-iBuP)	15.8 (9.9–21.5)	[41] ^b

^a Sum of free and conjugated forms; ^b Study on 3 subjects (two males and one female) after a single oral dose; ^c HBM study.

3,3-diphenyl acrylate (5-OH-OC), are highly specific for OC and have been successfully determined in urine samples [45]. However, although very consistent, their excretion rates are much lower, especially for 5-OH-OC (0.008 %), which could pose a substantial analytical challenge related to their determination in sewage.

Four metabolites of Avobenzone were recently identified [56]. However, their excretion rates are not available and, to the best of our knowledge, only parent compound has been determined in HBM studies so far [57].

Finally, it has been reported that Homosalate (3,3,5-trimethylcyclohexyl 2-hydroxybenzoate) is rapidly metabolized to two compounds – salicylic acid and trimethylcyclohexanol [58]. However, salicylic acid is used in medicine and in the production of some other pharmaceuticals, and it is also a major metabolite of acetylsalicylic acid, very popular over-the-counter drug. Therefore, lack of specificity and contribution from other sources will most probably prevent the use of salicylic acid as a biomarker of exposure to Homosalate.

Table 2 summarizes the potential biomarkers of the most popular UV filters which could be applied in future WBE studies. However, the accurate assessment of exposure to several popular UV filters is currently hindered by the lack of quantitative excretion data. Therefore, additional human pharmacokinetic studies, which would also include different routes of exposure, are needed.

2.3. Phthalates

2.3.1. Background

Phthalic acid diesters (phthalates) are plasticizers extensively used in the production of polyvinyl chloride (PVC) and other polymer materials for almost a century [59]. They can be found in numerous products, including building materials, furniture, car interiors, electric wires and cables, clothing, cosmetics, pharmaceuticals, food packages, pesticides, paints, lubricants, adhesives and medical devices [19,59–61]. As phthalates are used as additives (i.e. they are not chemically bound to polymers), they are easily released into the environment by direct release, migration, evaporation, leaching and abrasion [60].

2.3.2. Potential health risk

Due to their widespread use and continuous release from different products, humans are ubiquitously exposed to these compounds through ingestion, inhalation and dermal exposure

during their entire life, including intrauterine development, which raise a lot of concern, due to their numerous adverse effects on human health. Phthalates are well-known endocrine-disrupting chemicals, but they also disturb the reproductive system and sexual development of humans, especially males, and trigger several disorders in children [3]. Consequently, European Commission recently restricted maximal concentrations of four prominent phthalates to 0.1 % by weight, either individually or in any combination, in plasticized materials in the EU [62]. Some “traditional” phthalates were previously banned from toys and childcare articles. At the same time, di-(2-propylheptyl) phthalate (DPHP) has been increasingly used in the last decade as a less toxic alternative.

2.3.3. Potential WBE biomarkers

After entering the human body, phthalates are rapidly metabolized (hydrolyzed) to monoesters, which can be oxidized in a second step. Both monoesters and secondary metabolites can be conjugated with glucuronic acid before excretion [6]. The extent of oxidative modification depends on the chain length of the phthalate monoester, with approximately 70 % of the short-chain phthalates excreted as monoesters [63]. However, monoesters of the long-chain phthalates are further metabolized to much greater extent, yielding to formation of several oxidized metabolites [3,60,64]. Furthermore, commercially available formulations of diisononyl phthalate and diisodecyl phthalate are mixtures of several structural isomers, resulting in formation of numerous structurally similar metabolites, which are difficult to separate and identify [59]. Nevertheless, metabolism of the most common phthalates is generally well-studied [6] and many HBM studies were conducted in the last decades [61].

Parent compounds are not good biomarkers of exposure to phthalates even in HBM, due to their omnipresence, even in the cleanest analytical laboratories, posing a great analytical challenge for their accurate determination. For short-chain phthalates, monoesters are usually used, although contamination is also possible in this case [65], especially when using lipase-containing matrices [66]. Yet, monoesters are considered to be good biomarkers of exposure to short-chain phthalates when they are determined in urine, although some studies suggest that oxidized metabolites can be valuable additional biomarkers [65,66]. Due to their low excretion rates, monoesters of long-chain phthalates are rarely detected in HBM studies, which can lead to underestimation of the human exposure to these substances if monoesters are used

Table 2
Biomarkers proposed for WBE studies to assess human exposure to UV filters.

Compound	Biomarker	Excretion rate (%) ^a	Ref.
Benzophenone-3 (Oxybenzone; BP-3)	2,4-Dihydroxybenzophenone (DHB; BP-1)	NA	[52] ^b
	2,5-Dihydroxy-4-methoxybenzophenone (5-OH-BP-3)	NA	[50] ^b
Octisalate (2-ethylhexyl salicylate; EHS)	5-(((2-Hydroxybenzoyl)oxy)methyl)heptanoic acid (5-cx-EPS)	0.24 (0.14–0.41)	[32] ^c
	2-Ethyl-5-hydroxyhexyl 2-hydroxybenzoate (5-OH-EHS)	0.28 (0.13–0.54)	
	2-Ethyl-5-oxohexyl 2-hydroxybenzoate (5-oxo-EHS)	0.11 (0.06–0.20)	
Enzacamene (3-(4-methylbenzylidene)camphor; 4-MBC)	3-(4-Carboxybenzylidene)-6-hydroxycamphor	0.4 ± 0.15 ^d	[55] ^f
		0.3 ± 0.01 ^e	
	3-(4-Carboxybenzylidene)camphor	0.1 ± 0.02 ^d 0.07 ± 0.02 ^e	
Octocrylene (2-ethylhexyl 2-cyano-3,3-diphenyl-2-acrylate; OC)	2-Cyano-3,3-diphenylacrylic acid (CPAA)	45 (40–50)	[31] ^c
	2-(Carboxymethyl)butyl 2-cyano-3,3-diphenyl acrylate (DOCCA)	0.13 (0.11–0.16)	
	2-Ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5-OH-OC)	0.008 (0.005–0.011)	
Avobenzone (butyl methoxydibenzoylmethane)	Desmethylhydroxy avobenzone	NA	[56]
	Hydroxy avobenzone		
	Desmethylavobenzone carboxylic acid		
	Dehydrated dihydrohydroxy avobenzone		
Homosalate (3,3,5-trimethylcyclohexyl salicylate)	3,3,5-Trimethylcyclohexanol	NA	[58]

^a Sum of free and conjugated forms; ^b Study on human and rat liver microsomes; ^c Study on 3 male subjects after a single oral dose; ^d Male subjects; ^e Female subjects; ^f Study on 6 subjects (3 males and 3 females) after dermal application.

as biomarkers [60]. Thus, secondary (oxidized) metabolites are generally preferred for the long-chain phthalates, not only due to the higher excretion rates [63,64], but also due to their longer half-lives, better reflecting long-term exposure to these substances [67].

Biomarkers of the most prominent phthalates, including those already used in WBE studies [19–22], are given in Table 3. It is noteworthy that rather different excretion profiles of some compounds, such as DPHP, were reported [68,69] and, in these cases, additional pharmacokinetic studies are also recommended.

2.4. Alternative plasticizers

2.4.1. Background

Due to their adverse effects on human health, many “traditional” phthalates have been gradually replaced by several alternative plasticizers, including DPHP, di-2-ethylhexyl adipate (DEHA), di(2-ethylhexyl) terephthalate (DEHTP) and di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH). DEHA and DEHTP are mostly used as

substitutes for di(2-ethylhexyl) phthalate (DEHP), while DINCH is an alternative to high-molecular weight phthalates.

2.4.2. Potential health risks

Alternative plasticizers are considered to be less toxic than traditional phthalates, although the comprehensive data on their toxicity and possible adverse effects are still missing [75].

2.4.3. Potential WBE biomarkers

In the human body, DEHA is hydrolyzed to mono-2-ethylhexyl adipate (MEHA). MEHA can be further transformed into non-specific metabolites, mostly adipic acid. Two additional oxidative metabolites were identified in *in vitro* studies and proposed, in addition to MEHA, as specific human biomarkers of exposure to DEHA. However, their excretion rates seem to be low and the preliminary results suggested that their application may be limited to the highly exposed populations [76]. Indeed, a very recent pharmacokinetic study reported mean urinary excretion rates of three oxidized metabolites in humans between 0.05 % and 0.20 %

Table 3
Biomarkers used/proposed for WBE studies to assess human exposure to phthalates.

Compound	Biomarker	Excretion rate (%) ^a	Ref.
Dimethyl phthalate (DMP)	<i>Monomethyl phthalate (MMP)</i>	NA	[61]
Diethyl phthalate (DEP)	<i>Monoethyl phthalate (MEP)</i>	NA	[61]
Di- <i>n</i> -butylphthalate (DnBP)	<i>Mono-<i>n</i>-butyl phthalate (MnBP)</i>	69	[63] ^b
		84.2	[65] ^c
	3-Hydroxy-mono- <i>n</i> -butyl phthalate (3OH-MnBP)	6.9	[65] ^c
Di- <i>iso</i> -butylphthalate (DiBP)	<i>Mono-<i>iso</i>-butyl phthalate (MiBP)</i>	70.7	[65] ^c
	2-Hydroxy-mono- <i>iso</i> -butyl phthalate (2OH-MiBP)	19.5	[65] ^c
Benzyl butyl phthalate (BzBP)	<i>Monobenzyl phthalate (MBzP)</i>	73	[63] ^b
	<i>Mono-<i>n</i>-butyl phthalate (MBP)</i>	6	
Di(2-ethylhexyl) phthalate (DEHP)	<i>Mono-2-ethylhexyl phthalate (MEHP)^d</i>	6.3 ± 2.0	[70] ^f
		7.3	[71] ^c
		5.9	[67] ^e
	<i>Mono-(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP; MEHHP)</i>	15.6 ± 3.2	[70] ^f
		24.7	[71] ^c
		23.3	[67] ^e
	<i>Mono-(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP; MEOHP)</i>	11.3 ± 2.7	[70] ^f
		14.9	[71] ^c
		15.0	[67] ^e
	<i>Mono-(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP; MECCP)^g</i>	13.9 ± 3.5	[70] ^f
		21.9	[67] ^c
		18.5	[67] ^e
	<i>Mono-[2-(carboxymethyl)hexyl] phthalate (2cx-MMHP)</i>	5.4 ^h	[67] ^c
		4.2 ^h	[67] ^e
Dicyclohexyl phthalate	<i>Monocyclohexyl phthalate (MCHP)</i>	NA	[21] ⁱ
Di- <i>n</i> -octyl phthalate (DnOP)	<i>Monooctyl phthalate (MnOP)</i>	13	[63] ^b
	<i>Mono(3-carboxypropyl) phthalate (MCPP)</i>	NA	[21] ⁱ
Di- <i>iso</i> -nonyl phthalate (DiNP) (mixture of isomers)	<i>Mono-<i>iso</i>-nonyl phthalate (MiNP)</i>	3.1 ± 1.0	[70] ^f
		2.2	[72] ^c
	<i>Mono-(4-methyl-7-hydroxy-octyl) phthalate (7OH-MMeOP)</i>	12.3 ± 3.2	[70] ^f
		20.2	[73] ^c
	<i>Mono-(4-methyl-7-oxo-octyl) phthalate (7oxo-MMeOP)</i>	6.6 ± 1.8	[70] ^f
		10.6	[73] ^c
	<i>Mono-(4-methyl-7-carboxyheptyl) phthalate (7cx-MMEHP)</i>	10.9 ± 3.1	[70] ^f
		10.7	[73] ^c
Di- <i>iso</i> -decyl phthalate (DiDP) (mixture of isomers)	<i>Mono-<i>iso</i>-decyl phthalate (MiDP)</i>	NA	[74] ^j
	<i>Monocarboxyisononyl phthalate (MCiNP)</i>	NA	
	<i>Monooxoisodecyl phthalate (MOiDP)</i>	NA	
	<i>Monohydroxyisodecyl phthalate (MHIDP)</i>	NA	
Di(2-propylheptyl) phthalate (DPHP)	<i>Mono-2-(propyl-6-hydroxy-heptyl) phthalate (OH-MPHP)</i>	10.7 ± 3.6	[68] ^k
		2.3 ± 1.3	[69] ^l
	<i>Mono-2-(propyl-6-oxoheptyl) phthalate (oxo-MPHP)</i>	13.5 ± 4.0	[68] ^k
		3.6 ± 2.0	[69] ^l
	<i>Mono-2-(propyl-6-carboxy-hexyl) phthalate (cx-MPHxP)</i>	0.48 ± 0.13	[68] ^k
		0.12 ± 0.07	[69] ^l

Note: biomarkers already used in WBE studies are written in italic.

^a Sum of free and conjugated forms; ^b Study on 8 subjects after a single oral dose (high or low); ^c Study on 1 male subject after a single oral dose; ^d Excluded from the WBE study by González-Mariño et al. [19] due to the unsatisfying instrumental performance; ^e Study on 1 male subject after a single oral dose (high, medium and low) (24 h); ^f Study on 20 subjects (10 male and 10 female) after a single oral dose (high or low); ^g Excluded from the WBE study by González-Mariño et al. [22] due to the repeated detection in instrumental blanks; ^h Semi-quantitative estimation; ⁱ HBM and WBE study; ^j HBM study; ^k Study on 5 male subjects after a single oral dose; ^l Study on 6 male subjects after a single oral dose.

[33]. Among them, mono-5-carboxy-2-ethylpentyl adipate seems to be the most suitable biomarker of exposure to DEHA in HBM, which was confirmed by the pilot HBM study [77]. Another recent study reported high detection frequency of mono-(2-ethyl-5-oxohexyl) adipate [78]. However, concentrations of all oxidized metabolites were low already in urine, which could hamper their use in WBE due to the sensitivity limitations.

In a recent pharmacokinetic study, 1-mono-(2-ethyl-5-carboxyl-pentyl) terephthalate was found to be the most prominent biomarker of exposure to DEHTP, with the excretion rate of 13 % [79]. This was confirmed by its detection frequency of 100 % in a subsequent HBM study [80]. Other DEHTP metabolites are also analogous to metabolites of DEHP, but their excretion rates seem to be much lower, although in a recent HBM study, concentrations of mono-(2-ethyl-5-hydroxyhexyl) terephthalate up to 266 $\mu\text{g L}^{-1}$ were determined [78]. It remains to be seen if the levels of these biomarkers in sewage would be high enough to allow their use in WBE studies as well.

Human metabolism of DINCH is very extensive and complex. Cyclohexane-1,2-dicarboxylic acid is a major, but non-specific metabolite, while only 2 % or less is excreted as a simple monoester (monoisononyl-cyclohexane-1,2-dicarboxylate; MINCH). Other metabolites, formed by oxidation, are more promising as DINCH biomarkers, especially cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl) octyl ester (OH-MINCH), with the average excretion rate of 10.7 % and 14.5 %, depending on the study, followed by cyclohexane-1,2-dicarboxylic mono oxoisononyl ester and cyclohexane-1,2-dicarboxylic mono carboxyisononyl ester [81,82]. These metabolites were detected in the urine samples [82,83], however their distribution did not fully reflect the human excretion profiles. The authors of one of the studies pointed out that back-calculation from individual spot urine samples is likely unreliable to determine individual exposure, but could be used on a population scale [82]. In another study, the detection frequency of OH-MINCH was much lower (8 %), even below the detection frequency of MINCH (17 %) [78]. Nine additional DINCH metabolites were recently identified after its oral administration [84]. Some of the side chain breakdown products, with the excretion rates up to 2.7 %, might be suitable additional biomarkers of exposure to DINCH in HBM, and possibly also in WBE studies.

The most promising candidates for WBE biomarkers of human exposure to DEHA, DEHTP and DINCH, identified in the pharmacokinetic and HBM studies, are listed in Table 4.

2.5. Phosphorous flame retardants/plasticizers

2.5.1. Background

Flame retardants are chemicals added to polymers both to prevent combustion and to delay the spread of fire after ignition [4]. They have been used for more than 50 years in different products, including furniture, textiles, floor polish, resins, paints, electronics, PVC plastics, food packaging, lubricants and hydraulic fluids [8]. Chemically, flame retardants belong to different groups, some of which, such as polybrominated compounds, were either banned or their use has been greatly restricted due to their persistency, bioaccumulation and/or toxicity. Many of these harmful substances have been gradually replaced by PFRs, which are very diverse chemicals, with different physico-chemical properties [4]. They can be both organic and inorganic. Moreover, although some of them can be chemically bounded to the polymers, they are mainly mixed into the polymer as additives, which facilitate their release into the environment [8]. Halogenated PFRs are used as flame retardants, while nonhalogenated PFRs are mostly used as plasticizers.

2.5.2. Potential health risks

Although introduced as less persistent and toxic alternative to other groups of flame retardants, some PFRs are also suspected to have several adverse effects on human health, including carcinogenicity and reproductive system alterations [4].

2.5.3. Potential WBE biomarkers

in vitro studies with human liver microsomes showed that the major PFRs metabolites are formed by oxidative dealkylation/dearylation and hydroxylation [85–90]. These qualitative studies identified metabolites of the most prominent PFRs, however their urinary excretion rates are still largely unknown, with the exception of tris(2-butoxyethyl) phosphate (TBOEP), which excretion profile was determined after its oral administration [30]. Nevertheless, PFRs metabolites have been successfully used as biomarkers in HBM. After monitoring major metabolites of 6 PFRs, Dodson et al. proposed the most suitable biomarkers for future HBM studies [91].

Regarding metabolism of specific PFRs, some points should be highlighted. For instance, diphenyl phosphate (DPhP) is a metabolite of both triphenyl phosphate (TPhP) and 2-ethylhexyldiphenyl phosphate (EHDPHP), but its formation rate in

Table 4
Biomarkers proposed for WBE studies to assess human exposure to some alternative plasticizers.

Compound	Biomarker	Excretion rate (%) ^a	Ref.
Di-2-ethylhexyl adipate (DEHA)	Mono-2-ethylhexyl adipate (MEHA)	NA	[76] ^b
	Mono-5-carboxy-2-ethylpentyl adipate (5cx-MEPA)	0.20 (0.17–0.24)	[33] ^c
	Mono-2-ethylhydroxyhexyl adipate (5OH-MEHA)	0.07 (0.03–0.10)	
	Mono-(2-ethyl-5-oxohexyl) adipate (5oxo-MEHA)	0.05 (0.01–0.06)	
Di(2-ethylhexyl) terephthalate (DEHTP)	1-Mono-(2-ethyl-5-carboxyl-pentyl) terephthalate (5cx-MEPTP)	13.0 (7.0–20.4)	[79] ^d
	1-Mono-(2-ethyl-5-hydroxy-hexyl) terephthalate (5OH-MEHTP)	1.8 (1.3–2.4)	
	1-Mono-(2-ethyl-5-oxo-hexyl) terephthalate (5oxo-MEHTP)	1.0 (0.57–1.6)	
	1-Mono-(2-carboxyl-methyl-hexyl) terephthalate (2cx-MEHTP)	0.28 (0.17–0.42)	
	Cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl) octyl ester (OH-MINCH)	10.7 (7.7–12.9)	[81] ^d
Di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH)	Cyclohexane-1,2-dicarboxylic mono oxoisononyl ester (oxo-MINCH)	14.5 (9.2–17.6)	[82] ^e
	Cyclohexane-1,2-dicarboxylic mono oxoisononyl ester (oxo-MINCH)	2.0 (1.5–2.6)	[81] ^d
	Cyclohexane-1,2-dicarboxylic mono oxoisononyl ester (oxo-MINCH)	4.8 (2.9–7.5)	[82] ^e
	Cyclohexane-1,2-dicarboxylic mono oxoisononyl ester (cx-MINCH)	2.0 (1.8–2.3)	[81] ^d
	Cyclohexane-1,2-dicarboxylic mono oxoisononyl ester (cx-MINCH)	4.0 (2.8–5.0)	[82] ^e
	Monoisononyl-cyclohexane-1,2-dicarboxylate (MINCH)	0.72 (0.31–1.3)	[81] ^d
	Monoisononyl-cyclohexane-1,2-dicarboxylate (MINCH)	2.0 (0.8–3.2)	[82] ^e
	Cyclohexane-1,2-dicarboxylic acid mono carboxyhexyl ester (MCHxCH)	2.71 ± 0.34	[84] ^d
	Cyclohexane-1,2-dicarboxylic acid mono carboxybutylester (MCBCH)	1.07 ± 0.16	[84] ^d
	Cyclohexanol-1,2-dicarboxylic acid mono carboxyoctyl ester (MCHeCH)	0.96 ± 0.26	[84] ^d

^a Sum of free and conjugated forms; ^b HBM study; ^c Study on 4 subjects (2 males and 2 females) after a single oral dose; ^d Study on 3 male subjects after a single oral dose; ^e Study on 6 subjects (3 males and 3 females) after a single oral dose.

serum is substantially higher for TPhP compared with EHDPHP [92]. However, DPhP can also be formed from other aryl PFRs, such as resorcinol bis-diphenylphosphate [90], and, therefore, it should be used as a biomarker of exposure to all aryl PFRs rather than to TPhP alone, while hydroxylated metabolites can be used as specific biomarkers of exposure to TPhP [93]. However, due to their higher detection limits, hydroxylated metabolites could not be detected in a pilot HBM study conducted by Bastiansen et al. [93]. Consequently, despite the limitations discussed above, DPhP is usually included in HBM studies as a biomarker of exposure to TPhP [91,94]. Similarly, di-*n*-butyl phosphate (DNBP) is not specific metabolite of tri-*n*-butyl phosphate [91]. Furthermore, besides being metabolites of PFRs, both DNBP and DPhP are also used in some industrial processes and products [95,96].

Bis(2-butoxyethyl) 2-hydroxyethyl phosphate (BBOEHEP) seems to be more promising biomarker of exposure to TBOEP than bis(2-butoxyethyl) phosphate (BBOEP), not only due to the much higher excretion rate of BBOEHEP, but also due to the long half time of BBOEP, which might also explain rather high discrepancy between excretion rates and concentrations of these two metabolites determined within the same study [30]. In fact, in some HBM studies, concentrations of all three TBOEP metabolites were found to be similar [94], although their excretion rates are very different [30].

Beside bis(2-chloroethyl) phosphate, parent compound is also recommended to be used for tris(2-chloroethyl) phosphate biomonitoring, due to its low clearance from the human body [85,91]. Biomarkers of the most prominent PFRs for WBE applications are listed in Table 5. Most of them have been already used in three WBE studies conducted so far [8,23,24].

2.6. Bisphenols

2.6.1. Background

Bisphenols are a large group of compounds containing phenol rings joined together by a bridging atom, mostly carbon [97]. They are used in the production of polycarbonate plastic and epoxy resins, which are then used in a variety of industrial and consumer products, such as food and beverage containers, drinking bottles, thermal papers and dental sealant and composites [98,99]. Among different bisphenols, BPA has been the most widely used for decades.

2.6.2. Potential health risks

Many concerns have been raised in recent years due to estrogenic properties of BPA, which may cause different adverse effect in humans, especially children [5]. Consequently, BPA was banned from numerous consumer products and in many cases gradually replaced with analog bisphenols [97]. However, recent studies show that these analog compounds, structurally similar to BPA, can have similar or even higher toxicity compared with BPA [99].

2.6.3. Potential WBE biomarkers

In humans, BPA is rapidly conjugated and excreted, mostly as glucuronide (BPA-Glu). In fact, BPA-Glu was the only metabolite identified in an oral dosing study with 6 volunteers [100]. In a similar, more recent study with 14 subjects, both BPA-Glu and BPA-sulfate (BPA-SO₄) were determined, with the urinary excretion rates of 87 % and 3 %, respectively [101], which is in accordance with some HBM data [102]. However, percentages of BPA excretion products determined in other HBM studies were quite different. For instance, Liao and Kannan [103] reported the average percentage of BPA-Glu of only 57 %, while percentage of BPA-SO₄ in a study by Ye et al. was as high as 21 % [98]. However, as already pointed out (Subsection 2.1.), glucuronides are not suitable biomarkers in WBE studies and, thus, BPA-SO₄ seems to be the only promising WBE biomarker of exposure to BPA [25].

Human metabolism data for other bisphenols are very scarce and, if exist, they mostly involve *in vitro* studies. However, glucuronidation seems to be the main metabolic pathway as well [97].

3. WBE studies for the assessment of human exposure to environmental contaminants

So far, quantitative WBE studies for the assessment of human exposure to environmental contaminants included in this paper have been conducted only for phthalates [19–22], PFRs [8,23,24] and BPA [25]. All these studies used metabolites of the selected compounds as biomarkers of exposure, and most of them also investigated their stability in sewage, which is a key feature of potential WBE biomarkers. Recently, a qualitative WBE study on biomarkers of selected UV filters was conducted as well [34]. In addition, some other studies also reported per capita

Table 5
Biomarkers used/proposed for WBE studies to assess human exposure to PFRs.

Compound	Biomarker	Excretion rate (%)	Reference
Triphenyl phosphate (TPhP)	<i>Diphenyl phosphate (DPhP)^a</i> <i>4-Hydroxyphenyl phenyl phosphate (HO-DPhP)</i> <i>4-Hydroxyphenyl diphenyl phosphate (4-HO-TPhP)^b</i> <i>3-Hydroxyphenyl diphenyl phosphate (3-HO-TPhP)</i>	NA	[8,23] ^c [91,93] ^d
2-Ethylhexyldiphenyl phosphate (EHDPHP)	<i>2-Ethylhexyl phenyl phosphate (EHPPH)</i> <i>2-Ethyl-5-hydroxyhexyl diphenyl phosphate (5-HO-EHDPHP)</i> <i>Diphenyl phosphate (DPhP)^a</i>	NA	[8,23] ^c [91,93] ^d
Tris(2-butoxyethyl) phosphate (TBOEP)	<i>Bis(2-butoxyethyl) 2-hydroxyethyl phosphate (BBOEHEP)</i> <i>Bis(2-butoxyethyl) phosphate (BBOEP)</i> <i>Bis(2-butoxyethyl) 3'-hydroxy-2-butoxyethyl phosphate (3-HO-TBOEP)</i>	8.4 (2.1–21.5) 0.78 (0.62–1.01) 0.02 (0–0.03)	[30] ^e [8,23] ^c
Tri- <i>n</i> -butyl phosphate (TNBP)	<i>Di-<i>n</i>-butyl phosphate (DNBP)^a</i>	NA	[91,93] ^d
Tris(2-chloroethyl) phosphate (TCEP)	<i>Tris(2-chloroethyl) phosphate (TCEP)</i> <i>Bis(2-chloroethyl) phosphate (BCEP)^a</i>	NA	[8,23,24] ^c [91,93] ^d
Tris(2-chloroisopropyl) phosphate (TCIPP)	<i>1-Hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP)</i> <i>Bis(1-chloro-2-propyl) phosphate (BCIPP)^f</i>	NA	[8,23,24] ^c [91,93] ^d
Tris(1,3-dichloro-2-propyl) phosphate (TDCIPP)	<i>Bis(1,3-dichloro-2-propyl) phosphate (BDCIPP)</i>	NA	[23,24] ^c [91,93] ^d

Note: biomarkers already used in WBE studies are written in italic.

^a Non-specific metabolite; ^b Excluded from the WBE study by Been et al. [8] due to the unsatisfying instrumental performance; ^c WBE studies; ^d HBM studies; ^e Study with 6 subjects (3 male and 3 females) after a single oral dose; ^f Excluded from the exploratory WBE study by Been et al. [8], but used in the subsequent WBE study [23].

Table 6
Overview of the analytical methods used for the determination of human biomarkers of parabens, UV filters, phthalates, PFRs and BPA in WBE and similar studies.

Compounds	Sample type	Sample extraction	Recovery/trueness	MQL	Method	Separation (LC/GC column and LC eluents)	MS detection (spectrometer type, ionization, operating mode)	Ref.
Parabens and their metabolites	RW, PE and SE	SPE: Oasis MCX	70–105 %	0.1–100 ng/L	HPLC-MS/MS (quantitative)	Pinnacle DBAQ C18 (50 mm × 2.1 mm; 1.9 μm)	QTRAP ESI-MRM	[104]
	SPM and sludge	Solid-liquid extraction + SPE	52–109 %	0.1–100 ng/g				
Parabens and their metabolites	RW and SE	SPE: Oasis MCX	74–102 %	0.1–50 μg/L	HPLC-MS/MS (quantitative)	Zorbax SB-Aq (150 mm × 2.1 mm; 3.5 μm)	QqQ ESI-MRM	[105]
	SPM and sludge	Solid-liquid extraction + SPE	64–104 %					
Parabens (+ other personal care products)	RW, SE and river water	SPE: Oasis HLB	River water: 70–91 % (parabens)	0.38–0.84 ng/L (parabens)	UHPLC-MS/MS (quantitative)	Xbridge BEH-C18 XP (100 mm × 2.1 mm; 2.5 μm)	ESI-MRM	[106]
UV filters (including BP-1)	RW	–	67–130 %	0.13–0.55 μg/L	HPLC-MS/MS (quantitative)	Kinetex biphenyl (50 mm × 2.1 mm; 2.6 μm)	QTRAP ESI+MRM	[109]
Benzophenons and their derivatives + bisphenols	RW, SE, SPM and sludge	SPE: Oasis MCX	60–88 % (benzophenons)	0.1–0.8 μg/L (benzophenons)	HPLC-MS/MS (quantitative)	Betasil C18 (100 mm × 2.1 mm; 5 μm)	QqQ ESI-, ESI+MRM	[108]
			52–85 % (bisphenols)	0.2–1.8 μg/L (bisphenols)				
Benzophenons and their derivatives	RW, PE and SE	SPE: Oasis MCX	81–122 %	0.25–0.5 ng/L	HPLC-MS/MS (quantitative)	Betasil C18 (100 mm × 2.1 mm; 5 μm)	QTRAP ESI-MRM	[107]
			SPM and sludge	SPM: 99–108 % Sludge: 84–105 %				
UV filters and their metabolites	RW, urine	SPE: Oasis MCX and MAX	86–107 % (UV filters)	0.009–0.95 ng/L (UV filters)	HPLC-MS/MS (qualitative/quantitative)	Acquity BEH C18 (50 mm × 2.1 mm; 1.7 μm)	Q-ToF ESI+, ESI-bbCID	[34]
Metabolites of phthalates	RW, SE	SPE: Oasis HLB	RW: 76–100 %	RW: 0.5–32 ng/L SE: 0.5–31 ng/L	HPLC-MS/MS (quantitative)	Luna Phenyl-Hexyl (150 mm × 2 mm; 3 μm)	QqQ ESI-MRM	[19,22]
Metabolites of phthalates	RW, SE	SPE: Oasis HLB	Ultrapure water: 98–111 %	1–10 ng/L	UHPLC-MS/MS (quantitative)	Gemini C18 (100 mm × 2 mm; 3 μm)	QqQ ESI-MRM	[20]
Metabolites of phthalates	RW, urine	SPE: Supelco-Select HLB	64–98 % (RW)	0.0032–1.9 μg/L (RW)	UHPLC-MS/MS (quantitative)	Kinetex F5	QTRAP ESI-MRM	[21]
Metabolites of PFRs	RW	SPE: Bond-Elut C18	31–100 %	0.8–65 ng/L	HPLC-MS/MS (quantitative)	Eluent A: 99 % H ₂ O, 1 % MeOH, 0.1 % acetic acid Eluent B: MeOH	QqQ ESI+, ESI-MRM	[8,23]
Metabolites of chlorinated PFRs	RW	SPE: Oasis WAX	90–100 %	4–15 ng/L	GC-MS (quantitative;	Kinetex Biphenyl (100 mm × 2.1 mm; 2.6 μm) Eluent A: H ₂ O + 2 % MeOH + 5 mM CH ₃ COONH ₄ Eluent B: MeOH + 2 % H ₂ O + 5 mM CH ₃ COONH ₄		[24]

Table 6 (Continued)

Compounds	Sample type	Sample extraction	Recovery/trueness	MQL	Method	Separation (LC/GC column and LC eluents)	MS detection (spectrometer type, ionization, operating mode)	Ref.
PFRs	RW	SPE: Oasis MCX	50–112 %	0.03–3 µg/L	derivatization with MTBSTFA) GC-MS (quantitative)	HP-5MS (30 m × 0.25 mm; 0.25 µm) BXP5 (25 m × 0.22 mm; 0.25 µm)	Q-ToF EI single MS EI SIM	[111]
PFRs	RW, PE and SE SPM Sludge and ash	SPE: Oasis HLB ASE UAE	86–110 % 84–109 % Sludge: 83–97 % Ash: 86–101 %	1–1000 ng/L 0.05–10 ng/g 0.05–10 ng/g	HPLC-MS/MS (quantitative)	Luna C ₁₈ (150 mm × 4.6 mm; 3 µm) Eluent A: MeOH/H ₂ O (1/9) + 0.15 % formic acid Eluent B: MeOH + 0.2 % formic acid	QqQ ESI+, ESI- MRM	[110]
BPA-SO ₄	RW	SPE: Oasis HLB	64 %	5.5 ng/L	UHPLC-MS/MS (quantitative)	BEH C ₁₈ (50 mm × 2.1 mm, 1.7 µm) Eluent A: 1 mM NH ₄ F Eluent B: MeOH	Q-ToF ESI+, ESI- Full scan + bbCID	[25]

environmental emission of specific environmental contaminants, such as parabens [104–106], UV filters [107–109], PFRs [110,111] and bisphenols [112], and, in few cases, some metabolites were also included. However, many of these studies were more focused on their occurrence and behavior during wastewater treatment, rather than on application of the WBE concept. Furthermore, none of them investigated stability of biomarkers in sewage. Nevertheless, these studies provide information that might be relevant for future WBE applications, including analytical methods performance, concentrations levels and partitioning behavior of potential biomarkers in wastewater and, therefore, are also briefly discussed in the following subsections.

3.1. Analytical methods

An overview of the analytical methodologies used in WBE or similar studies which reported environmental emission of selected compounds is presented in Table 6. Except for two GC–MS methods for PFRs [24,111], all other methods were based on LC–MS/MS, which is nowadays the most common technique for the analysis of polar environmental contaminants. In most of these methods, electrospray ionization (ESI) and multiple reaction monitoring (MRM) mode on triple quadrupole (QqQ) or quadrupole-ion trap (QTRAP) mass spectrometers were employed for the detection and quantification of the target compounds. Parabens and their metabolites [104–106], as well as phthalate monoesters [19–22], were analyzed exclusively in negative ionization polarity, while compounds belonging to other groups were analyzed both in positive and negative polarity, depending on their characteristics. In two studies, quadrupole-time-of-flight (Q-ToF) mass spectrometers, applying data independent broadband collision-induced dissociation (bbCID) mode, were also used [25,34]. Q-ToF was also employed in a GC–MS method for determination of chlorinated PFRs after derivatization with silylating reagent [24]. In this method, electron ionization (EI) and single MS mode were used, while selected ion monitoring (SIM) mode was applied in another GC–MS method for PFRs determination [111].

Except for one method on UV filters, which employed direct injection [109], all other methods included sample treatment step using solid-phase extraction (SPE), which is nowadays the most

frequently used technique for the extraction of polar organic contaminants from water samples. Polymeric reversed-phase and mixed-mode strong cation-exchange sorbents (Oasis HLB and MCX, respectively) were used in most methods, however other types of sorbents, including mixed-mode strong and weak anion-exchange sorbents (Oasis MAX [34] and WAX [24], respectively), as well as hydrophobic, endcapped silica phase (Bond-Elut C18) [8,23], were also employed.

WBE methods were generally focused only on the dissolved fraction of wastewater. However, some related studies on parabens and benzophenones also included the analysis of suspended particulate matter (SPM) and sludge, which were extracted by solid-liquid extraction followed by SPE [104,105,107]. Parent PFRs were also analyzed in SPM and sludge [110], but, in these cases, other extraction techniques were employed (Table 6).

The most important method performance parameters, such as recovery/trueness and method quantification limits (MQLs) are reported in Table 6. In general, MQLs were rather different – from low ng/L up to low µg/L level.

3.2. Main findings

3.2.1. Parabens

The first WBE study on parabens is yet to be conducted. Although human exposure to parabens by wastewater analysis was recently assessed in China [106], this study is less relevant for the WBE approach, because parent parabens were used as biomarkers. Two other studies determined environmental emission of parabens and their metabolites from wastewater treatment plants (WWTPs) in the United States and India [104,105]. Both studies included 3–OH–MeP and 3–OH–EtP, potential WBE biomarkers of exposure to MeP and EtP, respectively (Table 1), and their concentrations were up to several hundred ng/L in raw wastewater (RW) [104,105]. In fact, taking into account that urine constitutes approximately 1 % of the total wastewater volume [113], median concentrations of both biomarkers in RW of two WWTPs in Albany (United States) [104] (128 and 66 ng/L for 3–OH–MeP and 78 and 32 ng/L for 3–OH–EtP, respectively) were in a good agreement with their median concentrations determined in HBM study in the same area (11.8 and 2.9 µg/L for 3–OH–MeP and 3–OH–EtP, respectively) [42],

indicating their potential in the WBE approach. Similar as in a HBM study [42], their mass loads in RW were comparable or even higher than the mass loads of parent parabens. These studies also highlighted the possible importance of analytes incorporated into the SPM. For instance, although average fractions of 3-OH-MeP and 3-OH-EtP adsorbed to SPM were rather low (1–2 % of their total amounts in RW), in some individual samples this fraction reached 15 % and 14 % for 3-OH-MeP and 3-OH-EtP, respectively [89]. Therefore, possible contribution of analytes incorporated into the SPM should be considered in future WBE studies on parabens.

3.2.2. UV filters

With the exception of one exploratory study [34], the WBE approach has not been applied to assess human exposure to UV filters so far, although some recent studies reported their per capita loads in RW. For instance, 7 UV filters were determined in influent of 36 Australian WWTPs [109]. Mass loadings of some benzophenones were also determined in WWTPs in India [108] and the United States [107]. Although these studies were focused on parent UV filters, they included BP-1 (DHB) and BP-8 (DHMB), which are also metabolites of BP-3. Concentrations of BP-1, potential WBE biomarker of BP-3 (Table 2), were rather similar in India and the United States (up to approximately 120 ng/L), while higher levels were determined in Australian influents (up to 600 ng/L). In their study, Wang and Kannan [107] highlighted the importance of SPM for the overall mass loads of some compounds in wastewater. However, average fraction of the total loads of BP-1 adsorbed to influent SPM was very low (<1 %).

In a recent exploratory study, a novel analytical framework (“wastewater fingerprinting assay”), based on suspect screening by high resolution MS, was applied for the identification of human biomarkers of several UV filters in urine and wastewater in the UK. With this approach, metabolites of BP-3, EHS and Homosalate were identified in wastewater. However, in the case of Homosalate, unspecific metabolite, salicylic acid, was determined [34].

3.2.3. Phthalates and alternative plasticizers

So far, WBE has not been applied to investigate human exposure to alternative plasticizers, while four WBE studies investigated exposure to traditional phthalates – two in Spain [19], one in China [20] and one in Australia [21]. In all these studies, exposure to short-chain phthalates were calculated from the loads of phthalate monoesters, which were regularly detected (>99 %) in RW, up to low $\mu\text{g/L}$ level. Secondary (oxidized) metabolites were mostly used to assess the exposure to DEHP, but their concentrations and mass loads were generally lower [19–22]. Stability experiments, performed in the exploratory study by Gonzalez-Mariño et al., confirmed that most of the investigated biomarkers are fairly stable in RW at pH 2 and room temperature for at least 48 h [19]. However, recent study by Tang et al., which also included the parallel analysis of phthalate biomarkers in urine samples from individuals, showed that the human excretion might not be their major source in wastewater. In fact, the contribution of human excretion was lower than 25 % for biomarkers of short-chained phthalates and only 0.33 % for monomethyl phthalate (MMP), biomarker of dimethyl phthalate [21]. Similar findings for MMP, but not for other phthalate biomarkers, were obtained in another recent study, which assessed exposure to phthalates in 13 Spanish cities [22]. Therefore, further validation of WBE approach is advised [19,21,22], including identification of the additional sources of phthalate biomarkers and stability studies in real sewers. This would be important to verify the findings of WBE studies, which suggested that exposure to several phthalates might be higher than the safe reference values, especially for toddlers and children [19,20,22].

3.2.4. Phosphorous flame retardants/plasticizers

A first exploratory WBE study on PFRs was conducted in Belgium, using the same biomarkers which were previously used in HBM studies. With the exception of few compounds for which instrumental performance was not satisfying, the preliminary results suggested that PFRs metabolites are good WBE biomarkers of exposure to PFRs – they are fairly stable and not extensively formed from the parent PFRs in wastewater [8]. During the method development, possible contribution of conjugates was investigated by enzymatic deconjugation experiments, however it was concluded that this step can be omitted. Overall, almost all selected compounds could be determined in RW samples from 4 cities, with the concentrations ranging from few ng/L to 1 $\mu\text{g/L}$. The promising results were also obtained in a follow-up study in 5 European cities, which included few additional biomarkers. However, the WBE-based assessment of exposure to PFRs in this study seem to be comparatively higher than expected from HBM, which might be related to different factors, including other excretion routes (especially feces), additional sources in wastewater and/or degradation of parent compounds in real sewage systems [23].

A novel analytical method was recently developed for the determination of biomarkers of three chlorinated PFRs in wastewater applying the WBE approach. Stability tests confirmed suitability of the investigated biomarkers for WBE studies [24], however only biomarker of exposure to tris(chloropropyl) phosphate could be detected in real RW samples, with concentrations around 60 ng/L.

Some other studies also investigated environmental emission of PFRs by wastewater analysis, however mostly parent PFRs were included [110,111]. Yet, 2 PFRs metabolites, namely DPhP and bis (1,3-dichloro-2-propyl) phosphate, were included in one of the studies, which indicated the possible importance of PFRs biomarkers incorporated into the SPM. For instance, 18 % of the total DPhP mass loads in RW was adsorbed to SPM [110].

3.2.5. Bisphenols

In a very recent exploratory WBE study, BPA-SO₄ was successfully used as a biomarker of exposure to BPA [25]. The authors used two different excretion factors (8.4 and 3 %) to estimate human exposure to BPA, highlighting the conflicting results of the previous studies. Total concentrations of BPA-SO₄ in RW were rather high, ranging from 0.7–121 $\mu\text{g/L}$, with only minor fraction (<7 %) adsorbed onto SPM. Stability tests confirmed that BPA-SO₄ is a suitable biomarker of exposure to BPA, however the authors pointed out that additional studies are needed to obtain a more robust correction factor for BPA intake calculation.

3.3. Discussion and outlook

Pioneer quantitative studies exploring the applicability of the WBE approach for the assessment of human exposure to environmental contaminants selected in this review focused on phthalates, PFRs and BPA. However, applicability of the WBE approach to assess human exposure to parabens and alternative plasticizers is yet to be explored, while only one qualitative study was conducted for some UV filters.

In general, the first insights are rather promising – most selected biomarkers seem to be fairly stable in RW and their concentrations are mostly high enough to allow their reliable quantitative determination. However, there are still several limitations and challenges which hamper obtaining accurate and reliable results in this particular WBE field.

The first limitation, which does not refer only to WBE, but also to some HBM studies, is the lack of the reliable, quantitative excretion data for several compounds, including some representatives of parabens, UV filters and PFRs. Although their major

metabolites are, in most cases, identified, excretion rates are still unknown for some substances. Even for the compounds which metabolism is generally well-studied, numerous uncertainties and, in some cases, conflicting results still exist. This is not surprising taking into account that most pharmacokinetic studies conducted so far involved very limited number of participants (sometimes only one), often not representative for the entire population, and only one route of exposure (mostly oral). Therefore, for the correct interpretation of the results obtained by the WBE approach, including intake calculation and risk assessment, additional pharmacokinetic studies, which would include larger number of subjects, representative for the entire population, and/or different scenarios of exposure (including dermal) would be very beneficial. In some cases, urinary excretion might not be the only source of some target compounds (e.g. biomarkers of phthalates and PFRs) in wastewater, which also require further investigation.

Additional contribution from analytical chemists is essential for the further development of the WBE filed. All methods published so far were focused exclusively on one group of chemical substances. To facilitate comprehensive assessment of human exposure to environmental contaminants, it would be highly desirable to develop analytical methods which would include biomarkers of larger number of substances belonging to different groups. Moreover, only one WBE method published so far investigated possible importance of enzymatic deconjugation [8]. Although this step probably can be omitted for many glucuronides, due to their complete deconjugation in sewage, this should be verified during the method development. In that sense, it is noteworthy that in many human pharmacokinetic studies, only total urinary excretion factors, which include both free and conjugated forms of biomarkers, are reported. Another analytical challenge is related to relatively low concentrations of some biomarkers already in urine, which might prevent their determination in sewage, due to the sensitivity limitations. Furthermore, only one WBE study published so far investigated the possible importance of biomarkers incorporated into the suspended solids [25], although some recent reports indicate that fraction adsorbed to SPM might be relevant for the overall mass loads of some compounds in RW [104,110].

Although the stability of biomarkers in wastewater is usually investigated during the method development, only in-sample stability experiments were performed. However, more complex in-sewer stability experiments, mimicking real conditions in sewage, are still missing and should be performed in the future, as acknowledged by the authors of the existing WBE studies [8,19].

4. Conclusions

- 78 potential biomarkers of human exposure to parabens, UV filters, PFRs, BPA, phthalates and alternative plasticizers were identified.
- One of the main limitations in the applicability of the proposed biomarkers is the lack of pharmacokinetic studies which provide robust excretion factors, especially to quantify the exposure to parabens, UV filters, PFRs and BPA. Another limitation is the lack of the studies addressing in-sewer stability of the potential biomarkers and, in some cases, their possible contribution from other sources.
- A few subsets of the proposed biomarkers have been already used in the exploratory WBE studies to assess human exposure to phthalates, PFRs and BPA.
- While LC—MS/MS methods have been applied to assess human exposure to phthalates and BPA, both LC—MS/MS and GC—MS methods have been applied to analyze PFRs. So far, there is no

method which includes multiple chemical substances from different groups or the analysis of suspended solids.

- This review highlights the potential of WBE to be applied as a monitoring approach to assess trends of exposure to environmental contaminants at a fine spatio-temporal resolution.

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Declaration of Competing Interest

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

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