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Review

Analytical methods for the assessment of endocrine disrupting chemical exposure during human fetal and lactation stages: A review

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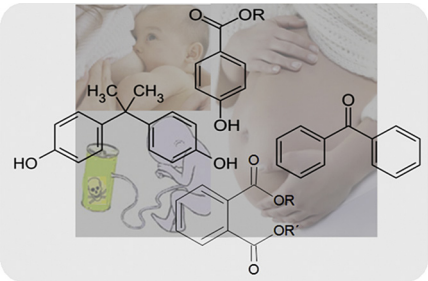
HIGHLIGHTS

- A review of analytical methods for the assessment of EDCs exposure during the first stages of the human life is developed.
- Placenta, cord blood, meconium, amniotic fluid, breast milk, blood and urine are the studied samples.
- The work is focused on four EDCs families: BPA, phthalates, UV-filters and parabens.
- The work mainly focused on sample preparation and the analytical techniques used.
- Assessment of exposure to EDCs during first stages of life will help to prevent future health issues.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present work, a review of the analytical methods developed in the last 15 years for the determination of endocrine disrupting chemicals (EDCs) in human samples related with children, including placenta, cord blood, amniotic fluid, maternal blood, maternal urine and breast milk, is proposed. Children are highly vulnerable to toxic chemicals in the environment. Among these environmental contaminants to which children are at risk of exposure are EDCs —substances able to alter the normal hormone function of wildlife and humans—. The work focuses mainly on sample preparation and instrumental techniques used for the detection and quantification of the analytes. The sample preparation techniques include, not only liquid–liquid extraction (LLE) and solid-phase extraction (SPE), but also modern microextraction techniques such as extraction with molecular imprinted polymers (MIPs), stir-bar sorptive extraction (SBSE), hollow-fiber liquid-phase microextraction (HF-LPME), dispersive liquid–liquid microextraction (DLLME), matrix solid phase dispersion (MSPD) or ultrasound-assisted extraction (UAE), which are becoming alternatives in the analysis of human samples. Most studies focus on minimizing the number of steps and using the lowest solvent amounts in the sample treatment. The usual instrumental techniques employed include liquid chromatography (LC), gas chromatography

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(GC) mainly coupled to tandem mass spectrometry. Multiresidue methods are being developed for the determination of several families of EDCs with one extraction step and limited sample preparation.

Contents

1. Introduction

Endocrine disrupting chemicals (EDCs) are a group of natural and synthetic chemicals that may interfere with the normal function of the endocrine system in animals and humans [1]. EDCs can act during fetal development, infancy, early childhood, puberty, adulthood and old age. In humans, the timing of EDC action often determines the strength of the impact. In adults the EDC has an effect when it is present, but when the EDC is withdrawn, the effect diminishes [2]. In contrast, exposure to EDCs during development (*in utero*, infancy and early childhood) can have permanent effects if the exposure occurs during the period when a specific tissue is developing. These effects may only become visible decades later. This is called “developmental programming” [3].

Hormones control the normal development of tissues from the fertilized sperm and egg to the fully developed fetus. Since some tissues continue developing after birth —like the brain and reproductive system— the sensitive period for these tissues is extended, sometimes for decades after birth. When a tissue is developing, it is more sensitive to the action of hormones and thus EDCs. Moreover, children's metabolic pathways, especially in the first months after birth, are immature. This means that children's ability to metabolize and excrete EDCs is lower than that of adults', making them more vulnerable to these chemicals [4].

The mechanisms through which EDC exposure during development can alter the development of specific tissues, leading to increased susceptibility to diseases later in life, are just beginning to be understood. It is clear that hormones play an important role in cell differentiation, which leads to the development of tissues and organs. Once tissues and organs are fully developed and active, then hormones have a different role: to control the integration of signals between tissues and organ systems and to maintain normal function. Early development (when hormones are controlling cell changes to form tissues and organs) is thus a very sensitive time frame for EDCs action. If an EDC is present during the developmental programming of a tissue, it could disrupt the normal hormone levels, leading to changes in tissue development-changes that would be stable across the lifetime and possibly confer sensitivity to disease later in life. These effects are not likely to be evident at birth, but may show up only later in life, from a few months to decades later [1]. The most prominent and well documented health concerns from exposure to endocrine disruptors are reproductive and developmental effects. Some of the disorders that have been seen in animal studies include oligospermia (low sperm count), testicular cancer, and prostate hyperplasia in adult males; vaginal adenocarcinoma, disorders of ovulation, breast cancer, and uterine fibroids in adult females. Disruption to thyroid functions, obesity, bone metabolism and diabetes are also linked to exposure endocrine disruptors [5–10].

In addition, children have greater exposure to EDCs for their body weight than adults. Children inhale four times more air, consume between six to eight times more calories and drink fourteen times more water per kilogram than an average adult. These differences result in children being exposed to greater burden of toxic chemicals from air, food and water [11].

Besides some naturally occurring compounds (lignans, coumestans, isoflavones, mycotoxins), numerous synthetic chemicals like bisphenol A (BPA) and its chlorinated derivatives, phthalates, organic UV-filters and parabens (PBs) have been implicated in endocrine disruption. The widespread use of these compounds and their potential risk to human health, have prompted interest in assessing human exposure [1,12–20], with special attention to children's exposure. Exposure may occur through inhalation, dermal contact or ingestion [1,11,12,18] and the metabolism may differ depending upon the exposure route and specific chemical structure characteristics [4,21,22]. Xenobiotics metabolism in humans is often divided into three phases: modification (phase I), conjugation (phase II), and further modification and excretion (phase III). These reactions act in concert to detoxify and remove these compounds from cells. In phase I, a variety of enzymes act to introduce reactive and polar groups into their substrates. Phase I reactions may occur by oxidation, reduction, hydrolysis, cyclization and decyclization, carried out by mixed function oxidases, often in the liver. If the metabolites of phase I reactions are sufficiently

polar, they may be readily excreted at this point. However, many products originated in phase I, are not eliminated rapidly and undergo a subsequent reaction in which an endogenous substrate combines with the newly incorporated functional group to form a highly polar conjugate. In subsequent phase II reactions, these activated xenobiotic metabolites are conjugated with charged species such as glutathione, sulfate, glycine or glucuronic acid. Sites on EDCs where conjugation reactions occur include carboxyl (−COOH), hydroxyl (−OH), amino ($-NH_2$), and sulfhydryl (−SH) groups. Products of conjugation reactions increase molecular weight and tend to be less active than their substrates, unlike phase I reactions, which often produce active metabolites. After phase II reactions, the conjugates may be further metabolized, and conjugates and their metabolites can be excreted from cells in phase III [4,21,22].

It has been postulated that free forms of EDCs can accumulate in certain human tissues due to their lipophilic nature producing harmful disrupting effects and passing to the offspring via placenta or breast milk [23–27]. In this context, it is particularly important to develop strategies for the study of this type of exposure and sensitive analytical methods that will allow the monitoring of EDCs in samples such as placenta, cord blood, breast milk, amniotic fluid, and urine and blood of pregnant women and their children. Due to the complexity of these matrices and the low concentration levels of EDCs, it is paramount to optimize new sample treatment procedures. Sample clean-up to remove the interference of matrix components in the analysis and stages for concentration of analytes are required to achieve a selective and sensitive determination of EDCs in human samples. The validation of single methods for multiresidue analysis of different families of those compounds is highly recommended, since this would reduce the overall analysis time, field sampling and total costs. Moreover, comprehensive information about multiple types of EDCs is required for risk assessment studies, as chemicals may interact to yield synergic toxicity effects on exposed organisms [4,11,12,18,28].

Some reviews have been published regarding analytical methods used for the determination of endocrine disrupting chemicals in the last years [29–33]. However, they tend to be focused in a specific family of compounds [29–31], do not focus in human matrix related with children [32] or do not study the wide range of compounds covered by this review [33]. In this context, the aim of the present review is to provide a comprehensive overview of the analytical methods developed in the last 15 years and applied in assessing EDCs exposure in children by means of the determination of BPA, PBs, organic UV-filters and phthalates in samples such as placenta, cord blood, amniotic fluid, breast milk and urine and blood of pregnant women and their children. The work particularly focuses on sample preparation and the instrumental techniques used for the determination of selected compounds.

2. Endocrine disrupting chemicals

The EDCs selected for review in the present work included bisphenol A and its chlorinated derivatives, phthalates, organic UV-filters and parabens. These compounds were chosen based on production/usage and potential hormonal activity.

2.1. Bisphenol A

BPA is the raw material used in the manufacturing of epoxy resins and polysulfones. It is also applied as antioxidant or stabilizer. However, the most important use of BPA is the production of polycarbonate plastics for a great variety of applications such as digital media (CDs, DVDs), electrical and electronic equipment, automobiles, sports safety equipment, reusable food and drink containers, infant feeding bottles, tableware, dummies, and medical devices among other uses [34]. Moreover, when BPA is present in treated waters, it may react with the residual chlorine originally used as disinfectant, and depending on the pH of the medium, produce chlorinated BPA derivatives [35]. Humans are exposed to BPA through the diet, inhalation of household dust, and dermal exposure [12,15].

Many studies on humans have shown that BPA exposure in adults may be associated with higher risk of sexual dysfunction, altered immune function, changes in levels of thyroid hormones, higher incidence of type-2 diabetes, cardiovascular disease, altered liver function and obesity [19]. Furthermore, exposure to BPA in early pregnancy may increase the risk of miscarriage, altered gestation length, low birth weight, increased male genital abnormalities and childhood obesity. Particularly relevant is the association between early BPA exposure and altered behavior and disrupted neurodevelopment in children (attention-deficit/hyperactivity disorder, depression, and anxiety) and the higher risk of wheeze and asthma [19].

2.2. Phthalates

The diesters of phthalic acid, known as phthalates, are industrial chemicals mainly used as plasticizers (substances added to plastics to increase their flexibility, transparency, durability, and longevity). In addition, they are used in a large variety of products, such as enteric of pharmaceutical pills, food packaging, adhesives and glues, medical devices, toys, personal care products or in medical applications such as catheters and blood transfusion devices. Phthalates are also found in lubricating oils, solvents, and detergents. The most common phthalates are diethylhexylphthalate (DEHP), diisononylphthalate (DINP), butylbenzylphthalate (BBP) and diethylphthalate (DEP). Exposure assessment to phthalates is difficult because of their extensive use and their ubiquitous presence in the environment.

Given that all phthalates are rapidly metabolized by cleavage of one or both of the two ester groups, metabolites like the primary monoesters are the obvious choice for analysis. However, even determination of those metabolites is susceptible to contamination, since they might be generated out of the parent diesters by various processes besides human metabolism, like chemical, enzymatic, microbiological, or photolytic hydrolysis. To definitely rule out contamination, some authors have focused on determining secondary metabolites generated in human metabolism by ω-1-oxidation of the monoester alkyl chain, such as mono(2-ethyl-5-hydroxyhexyl)phthalate (5-OH-MEHP) and mono(2-ethyl-5-oxohexyl)phthalate (5oxo-MEHP) [36,37].

Phthalate exposure is associated with adverse health effects, including respiratory effects, sexual dysfunctions or increased incidence of developmental abnormalities such as cleft palate and skeletal malformations. The most sensitive system is the immature male reproductive tract, with phthalate exposure resulting in increased incidence of cryptorquidism, decreased testes weight, decreased anogenital distance (distance between the anus and the base of the penis), and increased waist circumference and insulin resistance [24,36,38].

2.3. Organic UV-filters

Organic UV-filters are often used to protect skin against UV radiation damage. They are components of many daily used products such as cosmetics, skin creams, body lotions, hair sprays, hair dyes, shampoos and sunscreen, as well as in non-cosmetic products, such as carpets, furniture, clothing and washing powder. Here, the UV-filters are used to protect the

Table 1
Analytical methods for EDCs determination in urine in a perinatal stage.

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
BPA, BP-3, MPB, EPB, PPB, BPB, 11 phthalate metabolites, 3 chlorophenols	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS(APCI-)	0.2 −1.2 ng mL^{-1}	Total content (1.1−1280 ng mL^{-1}, 100%) Pregnant women and children	[40]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Column switching	LC-MS/MS(APCI-)	0.3 ng mL^{-1}	Free (<LOQ−0.7 ng mL^{-1}, 16%) and total content (0.3−50.5 ng mL^{-1}, 100%) Correlation between urinary concentrations mothers/children	[41]
MPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.1 −0.2 ng mL^{-1}	Total content, expressed as sum of PBs (LOD−23,200 ng mL^{-1}, 97%) Concentrations were lower during pregnancy than before pregnancy	[42]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Clean-up (multimode SPE cartridges)	LC-MS/MS (ESI	0.1 ng mL^{-1}	Total content (0.1−122.8 ng mL^{-1}, 99%) Negative correlation between urinary concentration and age of the pregnant women	[43]
BPA, MPB, EPB, PPB, BP-3, phthalates metabolites	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (C18)	LC-MS/MS (ESI-)	0.01 −1.14 ng mL^{-1}	Total content (LOD−822 ng mL^{-1}, 93%, BPA; LOD−955 ng mL^{-1}, 90%, PBs; LOD−2442 ng mL^{-1}, 98%, BP-3) Correlation between concentrations in mothers and children	[44]
MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.1 −0.2 ng mL^{-1}	Total content (LOD−475 ng mL^{-1}, 98%) Pregnant women exposure to PBs. Relationship with concentration in newborn infants	[45]
BPA, BP-3, MPB, PPB, BPB, triclosan, chlorophenols	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE(C18)	LC-MS/MS (APCI-)	0.1 −2.0 ng mL^{-1}	Total content (LOD−97.4 ng mL^{-1}, 97%, BPA; LOD−6040 ng mL^{-1}, 100%, PBs; 11.5−39700 ng mL^{-1}, 100%, BP-3) Pregnant women	[46]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE(C18)	LC-MS/MS (APCI-)	0.3 ng mL^{-1}	Total content (LOD−63.2 ng mL^{-1}, 82.1%) Pregnant women	[47]
MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (C18)	LC-MS/MS (ESI-)	0.5 −0.6 ng mL^{-1}	Total content (LOD−5380 ng mL^{-1}, 94%) Pregnant women	[48]
Phthalate metabolites	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (Oasis HLB)	LC-MS/MS (APCI-)	0.5 −3.0 ng mL^{-1}	Total content (LOD−761 ng mL^{-1}, 90%) Women after the delivery	[49]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APPI-)	0.4 ng mL^{-1}	Total content (LOQ−61 ng mL^{-1}, 100%) Newborns in a neonatal intensive care unit. Positive correlation between the use of medical devices and urinary concentration.	[50]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APPI-)	0.3 ng mL^{-1}	Free (LOD−1.5 ng mL^{-1}, 28%) and total content (LOD−50.9 ng mL^{-1}, 93%). 3−15 months infant population.	[51]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Protein precipitation (MeCN) - LLE (1-chlorobutane) - Derivatization (PFBBr)	GC-MS/MS (NICI)	0.3 ng mL^{-1}	Total content (LOD−9.4 ng mL^{-1}, 60%). 1 month infant population.	[52]

Abbreviations: $(OH)_3$-BP, trihydroxybenzophenone; 2-OH-BP, 2-hydroxybenzophenone; 3-OH-BP, 3-hydroxybenzophenone; 4-OH-BP, 4-hydroxybenzophenone; BP, benzophenone; BP-1, benzophenone 1; BP-10, benzophenone 10; BP-3, benzophenone 3; BP-8, benzophenone 8; BPA, bisphenol A; BPB, butylparaben; BP-OH, hydroxybenzophenone; BPP, benzylbutylphthalate; BPS, bisphenol S; BSTFA, N,O-bis(trimethylsilyl)trifluoroacetamide; BzPB, benzylparaben; CE-UV, capillary electrophoresis-ultraviolet detection; cLC-MS, capillary liquid chromatography-mass spectrometry; cLC-UV, capillary liquid chromatography-ultraviolet detection; Cl_x-BPA, bisphenol A chlorinated derivatives; DBP, dibutylphthalate; DEP, bis(2-ethyl hexyl)phthalate; DLLME, dispersive liquid−liquid microextraction; EI, electron impact; EPB, ethylparaben; ESI, electrospray ionization; GC-MS, gas chromatography-mass spectrometry; GC-NCI-MS, gas chromatography-negative chemical ionization-mass spectrometry; LC-ECD, liquid chromatography-electrochemical detection; LC-FLD, liquid chromatography-fluorescence detection; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-UV, liquid chromatography-ultraviolet detection; LLE, liquid−liquid extraction; MeCN, acetonitrile; MeOH, methanol; MEP, monoethylphthalate; MIP-SPME, molecularly imprinted polymer-solid phase microextraction; MMP, monomethylphthalate; MPB, methylparaben; PBs, parabens; PFBBr, pentafluorobenzylbromide; p-HB, para-hydroxybenzoic acid; p-NBCl, para-nitrobenzoyl chloride; PPB, propylparaben; SBSE, stir bar sorptive extraction; SPE, solid-phase extraction; SPME, solid-phase microextraction; TD-GC-MS, thermal desorption-gas chromatography-mass spectrometry; THF, tetrahydrofuran; TMSDM, trimethylsilyl diazomethane; UAEM-SFO, ultrasound assisted emulsification microextraction-solidification of floating organic droplet; UHPLC-MS/MS, ultra high performance liquid chromatography-mass spectrometry.

Table 2
Analytical methods for EDCs determination in urine.

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
BP-3, BP-1, BP-8	- SPME (C18), direct fiber immersion	GC-MS (EI)	5–10 ng mL^{-1}	Free content (<LOQ) BP-3 and BP-1 were found after a topical application of a sunscreen	[53]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18) - Derivatization (PFBBr)	GC-NCI-MS	0.1 ng mL^{-1}	Free (<LOD) and total content (0.11–0.50 ng mL^{-1}, 100%)	[54]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - LLE (diethyl eter)	LC-ECD	0.2 ng mL^{-1}	Free (<LOD) and total content (0.2–19.1 ng mL^{-1}, 100%)	[55]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Column switching extraction system - Direct sample injection	LC-MS (ESI)	0.1 ng mL^{-1}	Total content (0.26–0.38 ng mL^{-1}, 50%)	[56]
BPA, 6 alkylphenols	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE/derivatization in situ (PFBBr)	GC-NCI-MS	0.1 ng mL^{-1} (BPA) 0.1–0.7 ng mL^{-1} (alkylphenols)	Total content (0.4–21.1 ng mL^{-1}, 96%, BPA)	[57]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18) - Derivatization (PFBBr) - Clean-up (Florisil)	GC-NCI-MS	0.1 ng mL^{-1}	Total content (0.2–3.8 ng mL^{-1}, 100%)	[58]
BPA, nonylphenol, estrogenic hormones	- Acid hydrolysis (HCl) - SPE (ENVI-C18) - Derivatization (p-NBCl)	LC-FLD	2.7–8.3 ng mL^{-1}	Total content (<LOD–3.95 ng mL^{-1}, 80%, BPA)	[59]
16 Phthalate metabolites	- Automated sample preparation - Enzymatic hydrolysis (β-glucuronidase) - On-line SPE	LC-MS/MS (ESI-)	0.15–4.30 ng mL^{-1}	Total content (<LOD–1730 ng mL^{-1}) 8 of the analytes were quantified in 100% of the samples	[60]
BPA, alkylphenols, chlorophenols	- Enzymatic hydrolysis (β-glucuronidase) - Protein precipitation (MeCN) - SBSE/derivatization (acetic acid anhydride)	TD-GC-MS (EI)	0.01–0.05 ng mL^{-1}	Total content (0.93–5.41 ng mL^{-1}, 80%, BPA)	[61]
BPA, 3 phytoestrogens	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18)	LC-ECD	0.2–0.5 ng mL^{-1}	Total content (LOD–2.24 ng mL^{-1}, 52%, BPA)	[62]
BPA, BP-3, triclosan, 6 chlorophenols	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.1–2.0 ng mL^{-1}	Total content (LOD–11.5 ng mL^{-1}, 87%, BPA; 6.8–2120 ng mL^{-1}, 100%, BP-3)	[63]
MPB, EPB, PPB, BPB, BzPB	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.1–0.2 ng mL^{-1}	Free (LOD–10.9 ng mL^{-1}, 64%) and total content (0.3–726 ng mL^{-1}, 100%) BzPB was not detected	[64]
BPA	- Enzymatic hydrolysis onto sol–gel column - Inmunoaffinity extraction columns	LC-FLD	0.2 ng mL^{-1}	Free (0.2–1.2 ng mL^{-1}, 80%) and total content (0.2–5.6 ng mL^{-1}, 100%)	[65]
BP-3	- Single Drop Microextraction with ionic liquid	LC-UV	1.3 ng mL^{-1}	Free content Quantification of BP-3 after topical application of a sunscreen cream	[66]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Coacervative microextraction: decanoic acid + THF - Directly injected of extract	LC-FLD	7.5 ng mL^{-1}	Total content (4.0–49 ng mL^{-1}, 100%)	[67]
DEP, DBP, MEP, MMP, BPP	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (Strata XL)	LC-MS/MS (ESI-)	0.1–0.5 ng mL^{-1}	Total content (0.1–13.8 ng mL^{-1}) Elevated occurrence of MEP and MMP after topical application	[68]
BP, BP-OH, 2-OH-BP, BP-3, BP-10	- Enzymatic hydrolysis (β-glucuronidase) - Dilution with water - SBSE	TD-GC-MS (EI)	0.05–0.1 ng mL^{-1}	Total content Low concentrations for all the analytes	[69]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - HF-LPME (toluene)	GC-MS (EI)	0.02 ng mL^{-1}	Total content (0.1–0.4 ng mL^{-1}, 100%) Only three analyzed samples	[70]

(*continued on next page*)

Table 2 (*continued*)

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
	- Derivatization (acetic acid anhydride)				
BPA, triclosan	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18) - Derivatization (PFBCl) - Clean-up (acid silica)	GC-ECNI-MS (EI)	0.2 ng mL^{-1} 0.05 ng mL^{-1}	Total content (0.58–5.20 ng mL^{-1}, 100%, BPA)	[71]
BP, BP-OH, 2-OH-BP, 3-OH-BP, 4-OH-BP, BP-1, BP-3, BP-10	- Enzymatic hydrolysis (β-glucuronidase) - Derivatization (acetic acid anhydride) - HF-LPME (toluene)	GC-MS (EI)	0.01–0.05 ng mL^{-1}	Total content (0.36–4.91 ng mL^{-1},100%, BP-3; 0.27–10.0 ng mL^{-1}, 100%, BP-OH)	[72]
BPA	- MIP-SPME - Chemical desorption (MeOH, 5% acetic acid)	LC-UV	7.6 ng mL^{-1}	Free content Application of the procedure in spiked pool urine	[73]
MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.1–0.2 ng mL^{-1}	Total content (0.3–1110 ng mL^{-1}, 100%) Study by sex, age and race/ethnicity	[74]
BPA, bisphenol B	- Enzymatic hydrolysis (β-glucuronidase) - DLLME (MeCN–Cl_4C) - Derivatization (acetic acid anhydride)	GC-MS (EI)	0.03 ng mL^{-1}	Free (0.47–1.64 ng mL^{-1}, 45%) and total content (0.39–4.99 ng mL^{-1}, 85%) Bisphenol B was rarely detected	[75]
BP-1, BP-2, BP-3, BP-8, 4-OH-BP	- Enzymatic hydrolysis (β-glucuronidase) - LLE (ethyl acetate)	LC-MS/MS (ESI-)	0.05–0.15 ng mL^{-1}	Total content (0.33–330.0 ng mL^{-1}, 100%) Users of sunscreen products have very high levels of BP-3 and BP-1	[76]
BP-3, BP-4	- On-line SPE (amino)	LC-UV	30 ng mL^{-1}	Free content Excretion study from topical application throughout 48 h	[77]
BP-1, BP-3, BP-8, $(OH)_3$-BP	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18)	LC-MS/MS (ESI+)	0.03–0.10 ng mL^{-1}	Free and total content Occurrence study after BP-3 topical application on one volunteer	[78]
MPB, PPB, BPB, BP-3, BPA, phthalate metabolites, phytoestrogens	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.1–0.5 ng mL^{-1}	Total content (1.8–320.0 ng mL^{-1}, 100%) Correlations between urinary concentrations and earlier pubertal stages in girls	[79]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.3 ng mL^{-1}	Total content (0.4–211 ng mL^{-1}, 95%) Correlations between dietary intake of BPA and urinary excretion in children	[80]
MPB, EPB, PPB, BPB, BzPB	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (C18) system	LC-MS/MS(ESI-)	0.02–0.36 ng mL^{-1}	Total content (LOD–2002 ng mL^{-1}, 98%) Correlations between seminal contents and urine concentrations	[81]
BPA	- Dilution (water) - MIP-SPE	CE-UV	84 ng mL^{-1}	Free content	[82]
BPA, nonylphenol, octylphenol	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18)	UHPLC-MS/MS(ESI-)	0.10–0.15 ng mL^{-1}	Total content (0.43–5.41 ng mL^{-1}, 15%, BPA)	[83]
BPA, 5 phthalate metabolites	- Enzymatic hydrolysis (β-glucuronidase) - SPE (C18)	LC-MS/MS(ESI-)	0.1–1.0 ng mL^{-1}	Total content (>LOD–11.2 ng mL^{-1}, 100%, BPA) MEP (median: 43.7 ng mL^{-1}) MPB (median: 10.2 ng mL^{-1})	[84]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (C18)	LC-MS/MS(APCI-)	0.2 ng mL^{-1}	Total content (0.2–42 ng mL^{-1}, 70%)	[85]
BPA, Cl_x-BPA	- LLE (ethyl acetate) (BPA and Cl_x-BPA free) - SPE (amino) (conjugates)	LC-MS/MS (ESI-)	0.01–0.05 ng mL^{-1}	Free (LOD–0.2 ng mL^{-1}, 15%) and total content (0.3–50.5 ng mL^{-1}, 100%) of BPA. Free content of Cl_x-BPA (LOD–0.6 ng mL^{-1}, 20%).	[86]
BPA, triclosan, chlorophenols	- Dilution with water - UAEM-SFO (dodecanol)	CE-UV	1.0–2.0 ng mL^{-1}	Free content (<LOD, 100%, BPA)	[87]
BPA, BP-3, triclosan, chlorophenols	- Enzymatic hydrolysis (β-glucuronidase) - Column switching	LC-MS/MS (APCI-)	0.06–0.13 ng mL^{-1}	Total content (LOD–24.3 ng mL^{-1}, 82.9%, BPA; LOD–162.0 ng mL^{-1}, 98.4%, BP-3) Higher BPA exposure in infants (6–11 years old) than teenagers (11–16) and adults (17–21)	[88]
MPB, EPB, PPB, BPB, BzPB	- Enzymatic hydrolysis (β-glucuronidase) - SPE (Elut-Nexus)	LC-MS/MS (APCI-)	0.01–0.02 ng mL^{-1}	Total content (0.35–608 ng mL^{-1}, 100%) Remarkable exposure for young women	[89]
MMP, MBP, MEP, MEHP, MBzP	- Enzymatic hydrolysis (β-glucuronidase) - Magnetic SPE	GC-MS (EI)	0.02–0.05 ng mL^{-1}	Total content (LOD–40.3 ng mL^{-1}, 91.6%)	[90]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - LLE (ethyl acetate)	LC-MS/MS (ESI-)	0.10 ng mL^{-1}	Total content (LOD–8.70 ng mL^{-1}, 96%) Higher concentrations in adults	[91]
BPA, 11 phthalate metabolites, endogenous steroid compounds	- Enzymatic hydrolysis (β-glucuronidase) - SPE (Oasis MAX)	UHPLC-MS/MS (ESI+)	0.10–1.87 ng mL^{-1}	Total content (median: 0.64 ng mL^{-1}, 96.7%, BPA; medians: 0.89–81.8 ng mL^{-1}, 100%, phthalates)	[92]

Table 2 (*continued*)

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
	- Derivatization (Dansylation)				
MPB, EPB, PPB, BPB, BzPB, p-HB	- Enzymatic hydrolysis (β-glucuronidase) - LLE (ethyl acetate)	LC-MS/MS (ESI-)	0.03–0.20 ng mL^{-1}	Free (LOD–10.6 ng mL^{-1}, 83%) and total content (3.79–4870 ng mL^{-1}, 100%), expressed as sum of PBs Remarkable occurrence of PPB and MPB in adults and children	[93]
DPHP and metabolites	- Enzymatic hydrolysis (β-glucuronidase) - LLE (tert-butylmethylether)	LC-MS/MS (ESI-)	0.2–0.5 ng mL^{-1}	Total content Excretion study after oral dosage of bis(2-propylheptyl)phthalate	[94]
BPA, Cl_x-BPA, BPS, MPB, EPB, PPB, BPB, BP-1, BP-2, BP-3, BP-6, BP-8, 4-OH-BP	- Enzymatic hydrolysis (β-glucuronidase) - DLLME (acetone/Cl_3CH)	UHPLC-MS/MS(ESI+/-)	0.03–0.20 ng mL^{-1}	Free and total content (1.5–39.0 ng mL^{-1}, 30%, BPA; 0.9–346.0 ng mL^{-1}, 100%, PBs; 0.6–44.0 ng mL^{-1}, 95%, BPs) Gender differences of exposure to PBs	[95]
BPA, BPS, MPB, EPB, PPB, BPB, IsPPB, IsBPB, BP-1, BP-2, BP-3, BP-6, BP-8, 4-OH-BP	- Enzymatic hydrolysis (β-glucuronidase) - DLLME (acetone/Cl_3CH) - Derivatization (BSTFA)	GC-MS/MS (EI)	0.04–0.20 ng mL^{-1}	Free and total content (0.5–46.0 ng mL^{-1}, 45%, BPA; 1.0–1171 ng mL^{-1}, 100%, PBs; 0.3–99.0 ng mL^{-1}, 90%, BPs)	[96]
BPA, Cl_x-BPA	- LLE (MeCN)	UHPLC-MS/MS (ESI-)		Free content (LOD–1.4 ng mL^{-1}, 50%, BPA; LOD–1.5 ng mL^{-1}, 30%, Cl_x-BPA).	[97]
9 Phthalate metabolites	- Enzymatic hydrolysis (β-glucuronidase) - LLE (hexane)/ derivatization (TMSDM)/clean-up (Florisil) before GC analysis - SPE (C18) before LC analysis	GC-MS (EI) UHPLC-MS/MS (ESI-)	0.03–4.15 ng mL^{-1} 0.08–0.49 ng mL^{-1}	Total content (LOD–605 ng mL^{-1}, 100%)	[98]
MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - DLLME (acetone/Cl_3CH)	cLC-UV cLC-MS	7.0–9.0 ng mL^{-1} 11.0–22.0 ng mL^{-1}	Total content (68.0–867.0 ng mL^{-1}; 100%). No occurrence of BPB	[99]

Abbreviations: $(OH)_3$-BP, trihydroxybenzophenone; 2-OH-BP, 2-hydroxybenzophenone; 3-OH-BP, 3-hydroxybenzophenone; 4-OH-BP, 4-hydroxybenzophenone; BP, benzophenone; BP-1, benzophenone 1; BP-10, benzophenone 10; BP-3, benzophenone 3; BP-8, benzophenone 8; BPA, bisphenol A; BPB, butylparaben; BP-OH, hydroxybenzophenone; BPP, benzylbutylphthalate; BPS, bisphenol S; BSTFA, N,O-bis(trimethylsilyl)trifluoroacetamide; BzPB, benzylparaben; CE-UV, capillary electrophoresis-ultraviolet detection; cLC-MS, capillary liquid chromatography-mass spectrometry; cLC-UV, capillary liquid chromatography-ultraviolet detection; Cl_x-BPA, bisphenol A chlorinated derivatives; DBP, dibutylphthalate; DEP, bis(2-ethylhexyl)phthalate; DLLME, dispersive liquid–liquid microextraction; EI, electron impact; EPB, ethylparaben; ESI, electrospray ionization; GC-MS, gas chromatography-mass spectrometry; GC-NCI-MS, gas chromatography-negative chemical ionization-mass spectrometry; LC-ECD, liquid chromatography-electrochemical detection; LC-FLD, liquid chromatography-fluorescence detection; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-UV, liquid chromatography-ultraviolet detection; LLE, liquid–liquid extraction; MeCN, acetonitrile; MeOH, methanol; MEP, monoethylphthalate; MIP-SPME, molecularly imprinted polymer-solid phase microextraction; MMP, monomethylphthalate; MPB, methylparaben; PBs, parabens; PFBBr, pentafluorobenzylbromide; p-HB, para-hydroxybenzoic acid; p-NBCl, para-nitrobenzoyl chloride; PPB, propylparaben; SBSE, stir bar sorptive extraction; SPE, solid-phase extraction; SPME, solid-phase microextraction; TD-GC-MS, thermal desorption-gas chromatography-mass spectrometry; THF, tetrahydrofuran; TMSDM, trimethylsilyl diazomethane; UAEM-SFO, ultrasound assisted emulsification microextraction-solidification of floating organic droplet; UHPLC-MS/MS, ultra high performance liquid chromatography-mass spectrometry.

Table 3
Analytical methods for EDCs determination in serum in a perinatal stage.

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
BPA	- SPE (C18)	ELISA	0.2 ng mL^{-1}	Total content (0.60–14.36 ng mL^{-1}, 100%) Maternal serum and amniotic fluid	[100]
BPA	- Acid hydrolysis (HCl) - Column switching system	LC-FLD	0.04 ng mL^{-1}	Total content (0.21–0.76 ng mL^{-1}, 100%) Serum level and ascetic fluid	[101]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - LLE (Cl_2CH_2) - SPE (Florisil-C18) - Derivatization (MSTFA)	GC-MS/MS	0.03 ng mL^{-1}	Total content (LOD–10.4 ng mL^{-1}, 67%) Pregnancy women	[102]
5 Phthalates and their metabolites	- LLE (pentane/acetone) - LLE (hexane/MTBE) - Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (Oasis HLB)	GC-MS	0.13–1.4 ng mL^{-1}	Total content (0.05–129 ng mL^{-1}, 70%) Women after delivery	[49]

Abbreviations: 4-OH-BP, 4-hydroxybenzophenone; BP, benzophenone; BP-1, benzophenone 1; BP-10, benzophenone 10; BP-2, benzophenone 2; BP-3, benzophenone 3; BP-6, benzophenone 6; BP-8, benzophenone 8; BPA, bisphenol A; BPB, butylparaben; BPP, benzylbutylphthalate; BzPB, benzylparaben; cLC-MS, capillary liquid chromatography-mass spectrometry; cLC-UV, capillary liquid chromatography-ultraviolet detection; DBP, dibutylphthalate; DEP, bis(2-ethylhexyl)phthalate; DLLME, dispersive liquid–liquid microextraction; EI, electron impact; EPB, ethylparaben; ESI, electrospray ionization; GC-MS, gas chromatography-mass spectrometry; GC-NCI-MS, gas chromatography-negative chemical ionization-mass spectrometry; LC-ECD, liquid chromatography-electrochemical detection; LC-FLD, liquid chromatography-fluorescence detection; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-UV, liquid chromatography-ultraviolet detection; LLE, liquid–liquid extraction; MeCN, acetonitrile; MeOH, methanol; MEP, monoethylphthalate; MMP, monomethylphthalate; MPB, methylparaben; MSTFA, N-Methyl-N-(trimethylsilyl) trifluoroacetamide; PBs, parabens; PFBBr, pentafluorobenzylbromide; PFPA, pentafluoropropionic anhydride; PPB, propylparaben; SPE, solid-phase extraction; SPME, solid-phase microextraction.

Table 4
Analytical methods for EDCs determination in serum.

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
BPA	- Acid hydrolysis - Protein removal (MeOH) - SPE (C18)	LC-ECD	0.01 ng mL^{-1}	Total content Methodological study	[103]
BPA	- Protein removal (formic acid) - SPE (C18) - Derivatization (PFBBr)	GC-NCI-MS	0.005 ng mL^{-1}	Free Content (0.39–0.80 ng mL^{-1}, 100%)	[104]
DEHP, MEHP	- Column switching system	LC-MS (ESI+/-)	1.0 –5.0 ng mL^{-1}	Free content None of them were detected	[105]
Phthalate metabolites	- Protein denaturation (fosforic acid) - Enzymatic hydrolysis (β-glucuronidase) - SPE (Elut-Nexus)	LC-MS/MS (ESI-)	0.6 –1.3 ng mL^{-1}	Total content Methodological study	[106]
DMP, DEP, DBP, BBP, DEHP, DOP	- Protein removal (MeCN) - SPME (direct immersion)	GC-MS (EI)	0.015 ng mL^{-1}	Total content Methodological study	[107]
DEHP, MEHP	- Protein denaturation - LLE (acetone)	LC-MS/MS (ESI–/+)	4.2 ng mL^{-1} 1.5 ng mL^{-1}	Total content (5.7 ng mL^{-1}) Only MEHP in one of five samples	[108]
14 Phthalate metabolites	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (C18)	LC-MS/MS (ESI-)	0.32 –1.33 ng mL^{-1}	Total content Methodological study	[109]
BPA, triclosan, Br_4-BPA	- Protein removal/acid hydrolysis (formic acid) - SPE (C18-Florisil) - Derivatization (PFPA)	GC-NCI-MS	0.05 –0.3 ng mL^{-1}	Total content (0.20–1.77 ng mL^{-1}, 70%, BPA)	[110]
BPA, BP-3, MPB, EPB, PPB, BPB, BzPB, chlorophenols	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APPI-)	0.1 –1.1 ng mL^{-1}	Total content (LOD–301 ng mL^{-1}, 100%, PBs; BPA and BP-3 were quantified in one of fifteen samples)	[111]
BPA, bisphenol B	- Acid hydrolysis ($HClO_4$) - LLE (MeCN)	LC-MS/MS (ESI-)	0.50 ng mL^{-1}	Total content (0.79–7.12 ng mL^{-1}, 25.9%, BPA; 0.88–11.94 ng mL^{-1}, 17.2%, bisphenol B) Relationship BPA level/endometriosis	[112]
DMP, DEP, DBP, DEHP	- SPE (Oasis MAX)	GC-MS (EI)	0.7 –4.5 ng mL^{-1}	Total content (<LOD–342 ng mL^{-1}) High occurrence of DBP and DEHP	[113]
MPB, EPB, PPB	- Enzymatic hydrolysis (β-glucuronidase) - Protein removal (formic acid) - Automated SPE (C18)	LC-MS/MS (APCI-)	0.2 –0.7 ng mL^{-1}	Total content (1.0–142.7 ng mL^{-1}, 30–63%, PBs) Relationship MPB level and use of PCPs	[114]
BPA and conjugates forms	- LLE (ethyl acetate) (BPA) - SPE (amino) (conjugates)	LC-MS/MS (ESI-)	0.01 –0.05 ng mL^{-1}	Free (0.020–0.100 ng mL^{-1}, 100%) and total content (0.036 –0.121 ng mL^{-1}, 100%) of BPA	[115]
MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - Protein removal (acetone) - DLLME (acetone/Cl_3CH)	LC-MS/MS (ESI-)	0.1 –0.2 ng mL^{-1}	Free (LOD–2.7 ng mL^{-1}, 25%) and total content (0.9–29.9, 90%, MPB; 0.8–5.4 ng mL^{-1}, 50%, PPB)	[42]
4-OH-BP, BP-1, BP-2, BP-3, BP-6, BP-8	- Enzymatic hydrolysis (β-glucuronidase) - Protein removal (acetone) - DLLME (acetone/Cl_3CH)	LC-MS/MS (ESI-)	0.1 –0.3 ng mL^{-1}	Free (only detected) and total content (<LOQ–0.7 ng mL^{-1}, 90%, BP-1; 0.9–1.2 ng mL^{-1}, 40%, BP-3)	[116]
MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - DLLME (acetone/Cl_3CH)	cLC-UV cLC-MS	7.0 –9.0 ng mL^{-1} 11.0 –22.0 ng mL^{-1}	Total content (68.0–867.0 ng mL^{-1}; 100%). No occurrence of BPB	[99]

Abbreviations: 4-OH-BP, 4-hydroxybenzophenone; BP, benzophenone; BP-1, benzophenone 1; BP-10, benzophenone 10; BP-2, benzophenone 2; BP-3, benzophenone 3; BP-6, benzophenone 6; BP-8, benzophenone 8; BPA, bisphenol A; BPB, butylparaben; BPP, benzylbutylphthalate; BzPB, benzylparaben; cLC-MS, capillary liquid chromatography-mass spectrometry; cLC-UV, capillary liquid chromatography-ultraviolet detection; DBP, dibutylphthalate; DEP, bis(2-ethylhexyl)phthalate; DLLME, dispersive liquid–liquid microextraction; EI, electron impact; EPB, ethylparaben; ESI, electrospray ionization; GC-MS, gas chromatography-mass spectrometry; GC-NCI-MS, gas chromatography-negative chemical ionization-mass spectrometry; LC-ECD, liquid chromatography-electrochemical detection; LC-FLD, liquid chromatography-fluorescence detection; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-UV, liquid chromatography-ultraviolet detection; LLE, liquid–liquid extraction; MeCN, acetonitrile; MeOH, methanol; MEP, monoethylphthalate; MMP, monomethylphthalate; MPB, methylparaben; MSTFA, N-Methyl-N-(trimethylsilyl) trifluoroacetamide; PBs, parabens; PFBBr, pentafluorobenzylbromide; PFPA, pentafluoropropionic anhydride; PPB, propylparaben; SPE, solid-phase extraction; SPME, solid-phase microextraction.

products from the effects of UV-radiation. The family of benzophenones (BPs) is one of the most frequently used groups of UV-filters. BPs consists of 12 main compounds, called from benzophenone-1 (BP-1) to benzophenone-12 (BP-12), as well as, other less known as 2-hydroxybenzophenone (2-OH-BP), 3-hydroxybenzophenone (3-OH-BP) and 4-hydroxybenzophenone (4-OH-BP). Other important families of UV-filters widely used are camphor derivatives such as 3-(4-methylbenzylidene) camphor (4-MBC) and 3-benzylidene camphor (3-BC) and salicylates such as benzyl salicylate (BS), phenyl salicylate (PhS), octyl salicylate (OS) and homosalate (HS). Despite their widespread use, there is an increased concern about some of these compounds because of their possible estrogenic activity. Evidence from animal studies indicates that these substances can cause

Table 5
Analytical method for EDCs determination in placenta and related matrices.

Analytes/Sample	Sample treatment	Analytical technique	LOD	Comments	Ref.
BPA(Cord blood, maternal blood, ovarian follicular fluid, amniotic fluid)	- Separate serum from blood	ELISA	0.5 ng mL^{-1}	Free content (~1–2 ng mL^{-1}, follicular fluid, foetal serum and full-term amniotic fluid; ~5 fold higher, amniotic fluid 15–18 weeks gestation) No significant correlation between maternal and foetal BPA serum concentrations	[117]
BPA(Maternal serum, amniotic fluid)	- SPE (HLB)	ELISA	0.2 ng mL^{-1}	Free content (0.63–14.36 ng mL^{-1}, maternal serum; 0.20–5.62 ng mL^{-1}, amniotic fluid)	[100]
BPA(Placenta, cord blood, maternal blood)	- Placenta: Add water - Blood: Obtain plasma - LLE (ethyl acetate) - Derivatization (BSTFA)	GC-MS (EI)	0.01 ng mL^{-1} (serum) Not given in placenta	Free content (0.3–18.9 ng mL^{-1}, maternal plasma; 0.2–9.2 ng mL^{-1}, foetal plasma; 1.0–104.9 ng g^{-1}, placental tissue) BPA plasma concentrations higher in male than in female foetuses	[118]
BPA, 7 alkyl phenols, 7 organ chlorine pesticides (Cord blood)	- Separate plasma from blood - SPE (C18) - Derivatization (BSTFA)	GC-MS (EI)	0.05 ng mL^{-1} (BPA)	Free content (<LOD–15.17 ng mL^{-1}, 88%, BPA)	[119]
10 Phthalate metabolites (Amniotic fluid)	- Enzymatic hydrolysis (β-glucuronidase) - Dilution (MeCN, H_2O, NH_4OH) - SPE (Nexus)	LC-MS/MS (APCI-)	0.50–1.6 ng mL^{-1}	Total content (<LOD–263.9 ng mL^{-1}) Only MEP, MBP and MEHP were found in the analyzed samples	[120]
14 Phthalate metabolites (Meconium)	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (HLB)	LC-MS/MS (ESI-)	0.2–0.7 ng g^{-1}	Total content (0.4–74.8 ng g^{-1}, 40–100%) Only MCPP, MECPP, MEOHP and MEHHP were found in the analyzed samples	[121]
8 Phthalate metabolites (Placenta, cord blood)	Placenta: - LLE (ethyl acetate: cyclohexane) - SPE (Oasis HLB) Cord blood: - Separate plasma from blood - Dilution and acidification - SPE (Oasis HLB)	LC-MS/MS (ESI-)	0.05–0.5 ng g^{-1} (placenta)	Free content (0.099–49.67 ng g^{-1}, placental tissue; 0.065–9.68 ng mL^{-1}, cord plasma) A human placental perfusion model is used for the estimation of foetal exposure to phthalates	[122]
BPA(Cord blood, maternal blood)	- Obtain serum - Enzymatic hydrolysis (β-glucuronidase) - LLE (MTBE)	LC-FLD	0.6 ng mL^{-1}	Total content (<LOD–66.48 ng mL^{-1}, 84%, maternal serum; <LOD–8.86 ng mL^{-1}, 40%, cord serum) Positive correlation between maternal and foetal BPA concentrations	[123]
5 Phthalate metabolites (Amniotic fluid, maternal urine)	- Enzymatic hydrolysis (β-glucuronidase) - SPE (Nexus)	LC-MS/MS (ESI-)	0.9–1.4 ng mL^{-1}	Total content (28.4–233.0 ng mL^{-1}, amniotic fluid; 3.6–1420.0 ng mL^{-1}, maternal urine) Significant positive correlation between MBP concentrations in urine and amniotic fluid	[124]
11 Phthalate metabolites (Amniotic fluid, maternal urine)	- Enzymatic hydrolysis (β-glucuronidase) - Add phosphoric acid (Amniotic fluid) - Centrifugation	LC-MS/MS (ESI-)	0.15–0.50 ng mL^{-1} (amniotic fluid)	Total content (<LOD–35.7 ng mL^{-1}) No significant correlations between levels in urine and amniotic fluid	[125]
DEP, DBP, DEHP, MBP, MEHP(Cord blood, maternal blood, meconium)	Blood: - Separate serum from blood - Enzymatic hydrolysis (β-glucuronidase) - SPE (Nexus) Meconium: - Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (HLB)	LC-MS/MS (ESI-)	0.2–1.0 ng mL^{-1} (serum) 1.0 ng g^{-1} (meconium)	Phthalate and phthalate metabolites levels lower in cord blood than in maternal blood >70% of the samples had quantifiable levels of the analyzed compounds	[126]
BPA, 8 hydroxylated polybrominated biphenyl ethers (Cord blood, maternal blood)	- Separate serum from blood - Dilution (water, HCl, 2-propanol) - LLE (hexane/MTBE) - Derivatization (dansyl chloride) - Addition of water/hexane - Clean-up (silica gel column)	LC-MS/MS (ESI+)	0.6 ng mL^{-1} (BPA)	Free content (<LOD–0.7 ng mL^{-1}, 8%, cord serum, BPA; <LOD–5.4 ng mL^{-1}, 27%, maternal serum, BPA) BPA levels higher in maternal serum than in cord serum	[127]
BPA, Cl_x-BPA(Placenta)	- Homogenization (water) - LLE (ethyl acetate)	LC-MS/MS (APCI-)	0.2–0.6 ng g^{-1}	Free content (0.7–58.8 ng g^{-1}, 20–51%) Cl_4-BPA was not found in any of the samples	[128]

(*continued on next page*)

Table 5 (*continued*)

Analytes/Sample	Sample treatment	Analytical technique	LOD	Comments	Ref.
BPA(Placenta, foetal liver)	- Homogenization (acetate buffer solution) - Enzymatic hydrolysis (β-glucuronidase) - LLE (MeCN) - Dilution and SPE (C18) - Derivatization (acetic anhydride)	GC-MS (EI)	LOQs: 0.77 ng g^{-1} (placenta) 1.2 ng g^{-1} (liver)	Free (0.60–64 ng g^{-1}, 86%, placental tissue; 1.3–27 ng g^{-1}, 57%, liver tissue) and total content (1.43–280 ng g^{-1}, 94%, placental tissue; 3.67–124 ng g^{-1}, 88%, liver tissue)	[129]
BPA(Cord blood, maternal blood)	- Separate plasma - Add ammonium acetate buffer - LLE (hexane/diethyl ether) - Acidify with perchloric acid	LC-UV	0.13 ng mL^{-1}	Free content (0.3–29.4 ng mL^{-1}, maternal plasma; <1 ng mL^{-1} most cord plasma samples)	[130]
11 Phthalate metabolites (Cord blood, breast milk, urine)	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE	LC-MS/MS (ESI-)	Not given	Total content (<LOD–39.7 ng mL^{-1}, cord blood) Lower concentration of phthalate metabolites in breast milk and cord blood than in urine	[131]
BP-1, BP-2, BP-3, BP-6, BP-8, 4-OH-BP(Placenta)	- Homogenization (water) - LLE (ethyl acetate)	UHPLC-MS/MS (APCI+)	0.07–0.3 ng g^{-1}	Free content (0.6–9.8 ng g^{-1}, 6–88%) Neither BP-3 nor BP-8 were found in the analyzed samples	[132]
MPB, EPB, PPB, BPB(Placenta)	- Homogenization (water) - LLE (ethyl acetate)	UHPLC-MS/MS (APCI-)	0.03–0.06 ng g^{-1}	Free content (0.2–10.0 ng g^{-1}, 40–96%) All the analyzed samples had at least one of the selected PBs	[133]
BP-1, BP-3, BP-6, BP-8, 4-OH-BP, MPB, EPB, PPB, BPB, BPA, Cl_x-BPA(Placenta)	- Homogenization (water) - LLE (ethyl acetate)	UHPLC-MS/MS (APCI-)	0.03–0.6 ng g^{-1}	Free content (1.2–15.4 ng g^{-1}, BPA; 0.1–8.7 ng g^{-1}, PBs; 0.2–1.0 ng g^{-1}, BPs) Neither Cl_x-BPA nor BP-1, BP-2, BP-3 and BP-8 were detected in the analyzed samples	[25]
BPA(Amniotic fluid)	- Enzymatic hydrolysis (β-glucuronidase) - Add formic acid - SPE (C18)	LC-MS (ESI-)	0.1 ng mL^{-1}	Free (0.31–0.43 ng mL^{-1}, 45%) and total content (0.36–0.75 ng mL^{-1}, 80%)	[134,135]
BPA(Placenta, foetal liver)	- Homogenization (acetate buffer) - Enzymatic hydrolysis (β-glucuronidase) - LLE (MeCN) - SPE (C18) - Derivatization (acetic anhydride)	GC-MS (EI)	LOQs: 0.99 ng g^{-1} (Placenta) 1.4 ng g^{-1} (Foetal liver)	Free (0.55–165 ng g^{-1}, 88%, placental tissue; 1.02–37.7 ng g^{-1}, 71%, liver tissue) and total content (1.43–280 ng g^{-1}, 93%, placental tissue; 3.67–124 ng g^{-1}, 88%, liver tissue)	[136]
6 Phthalates metabolites, perfluorooctane sulfonic acid, cotinine (Amniotic fluid, maternal serum)	- Enzymatic hydrolysis (β-glucuronidase) - Precipitation proteins (MeCN)	LC-MS/MS (ESI-)	0.01–0.10 ng mL^{-1}	Total content (96–99%) Only 5cx-MEPP and 7cx-MMeHP were found in the analyzed samples	[137]
MEHP, 2 alkylphenols (Cord blood, maternal blood, meconium)	Blood: - Separate serum and denature proteins - Enzymatic hydrolysis (β-glucuronidase) - Acidify and SPE (Nexus) Meconium: - Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (HLB)	LC-MS/MS (ESI-)	1 ng g^{-1} (meconium) 0.2–1 ng mL^{-1} (serum)	Total content (1.7–6.74 μg mL^{-1}, 66%, MEHP, maternal serum; 0.01–4.92 μg mL^{-1}, 76%, MEHP, cord serum) Significant correlation between the concentrations of MEHP in maternal and cord blood	[138]
BS, PhS, OS, HS, 4-MBC, 3-BC(Placenta)	- Homogenization (water) - LLE (ethyl acetate)	LC-MS/MS (APCI+/-)	0.4–0.6 ng g^{-1}	Free content None of the target UV-filters were found in the analyzed samples	[139]
BP-1, BP-2, BP-3, BP-8, 4-OH-BP(Maternal blood, Cord blood, children urine)	Blood: - Enzymatic hydrolysis (β-glucuronidase) - IPA-LLE (MTBE/ammonium acetate/tetrabutyl ammonium hydrogen sulfate) Urine: - Enzymatic hydrolysis (β-glucuronidase) - LLE (MTBE/ethyl acetate)	LC-MS/MS (ESI-)	LOQs: 0.06–0.67 ng mL^{-1}	Total content (0.26–2.55 ng mL^{-1}, cord blood; 0.32–2.30 ng mL^{-1}, maternal blood) BP-2 and BP-8 were not detected in any of the analyzed samples	[140]
BPA(Cord blood, maternal blood)	- Enzymatic hydrolysis (β-glucuronidase)	LC-MS/MS (ESI-)	LOQ 0.10 ng mL^{-1}	Total content (<LOD–0.79 ng mL^{-1}, 27%, cord blood; <LOD–29.0 ng mL^{-1}, 67%, maternal blood)	[91]

Table 5 (*continued*)

Analytes/Sample	Sample treatment	Analytical technique	LOD	Comments	Ref.
	- LLE (MTBE/ethyl acetate)				
BPA, BP-3, MPB, EPB, PPB, BPB, triclosan, 2 dichlorophenols (Maternal urine, amniotic fluid)	- Enzymatic hydrolysis (β-glucuronidase) - Addition of formic acid - On-line SPE (C18)	LC-MS/MS (APCI-)	Not given	Total content (<LOD–0.4 ng mL^{-1}, 3%, BPA, amniotic fluid; 61%, BP-3, amniotic fluid; 6–42%, PBs, amniotic fluid) EPB was not found in the analyzed amniotic fluid samples	[141]
MPB, EPB, PPB, BPB, *p*-HB(Placenta)	- LLE (ethanol)	LC-UV	Not given	A human placental perfusion model is used for the estimation of foetal exposure to PBs	[142]
15 Phthalates (Cord blood)	- Dilution (water) - LLE (hexane/MTBE)/ LLE (hexane) - Clean-up (aminopropylene column)	GC-MS (EI)	0.04 –0.31 ng mL^{-1}	Free content (18–100%) DBP, DiBP and DEHP were found in all the analyzed samples	[143]
BPA, pesticides (Brain foetal tissue, liver foetal tissues)	- SPE (hexane) - SPE (C18)	GC-MS (EI) GC-TOF-MS	0.2 ng g^{-1}	Free content BPA was not found in any of the analyzed samples	[144]
BPA(Maternal blood, cord blood)	- Obtain serum from blood - LLE (ethyl acetate) - Derivatization (MTBSTFA)	GC-MS (EI)	0.01 ng mL^{-1}	Free content (<LOD–4.46 ng mL^{-1}, 97%, maternal serum; <LOD–4.60 ng mL^{-1}, 95%, cord serum) Positive correlation between maternal serum and foetal serum BPA concentrations	[145]
MPB, EPB, PPB, BPB, BP-1, BP-2, BP-3, BP-6, BP-8, 4-OH-BP(Placenta)	- Lyophilization - MSPD (C18, ethyl acetate)	LC-MS/MS (ESI+/-)	0.1 ng g^{-1}	Free content (<LOD–16.1 ng g^{-1}, 10–90%, PBs; <LOD–4.9 ng g^{-1}, 30–60%, BPs) BP-2, BP-6, 4-OH-BP and BP-8 were not detected in any of the analyzed samples	[146]
BPA, Cl_x-BPA, MPB, EPB, PPB, BPB, BP-3(Placenta)	- Lyophilization - MSPD (silica/PSA, MeOH)	LC-MS/MS (ESI+/-)	0.1 ng g^{-1}	Free content (<LOD–16.8 ng g^{-1}, 10–100%, PBs; <LOD–14.5 ng g^{-1}, 60%, BPA; <LOD–5.3 ng g^{-1}, 60%, BP-3)	[147]

Abbreviations: 3-BC, 3-benzylidene camphor; 4-MBC, 4-methylbenzylidene camphor; 4-OH-BP, 4-hidroxybenzophenone; 5cx-MEPP, mono(2-ethyl-5-carboxypentyl) phthalate; 7-cx-MMeHP, mono(4-methyl-7-carboxyheptyl)phthalate; APCI, atmospheric pressure chemical ionization, BPs, benzophenones; BP-1, benzophenone 1; BP-2, benzophenone 2; BP-3, benzophenone 3; BP-6, benzophenone 6; BP-8, benzophenone 8; BPA, bisphenol A; BPB, butylparaben; BS, benzyl salicylate; BSTFA, N,O-bis(trimethylsilyl)trifluoroacetamide; Clx-BPA, bisphenol A chlorinated derivatives; DBP, dibutylphthalate; DEHP, diethylhexylphthalate; DEP, diethylphthalate; DiBP; diisobutylphthalate; EI, electron impact; EPB, ethylparaben; ESI, electrospray ionization; EPB, ethylparaben; GC-MS, gas chromatography-mass spectrometry; IPA-LLE, ion-pair assisted liquid–liquid extraction; LC-FLD, liquid chromatography-fluorescence detection; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-UV, liquid chromatography-ultraviolet detection; LLE, liquid–liquid extraction; MBP, monobutylphthalate; MCPP, mono(3-carboxypropyl)phthalate; MeCN, acetonitrile; MECPP, mono(2-ethyl-5-carboxypentyl)phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl)phthalate; MEHP, mono(2-ethylhexyl)phthalate; MeOH, methanol; MEOHP, mono(2-ethyl-5-oxohexyl)phthalate; MEP, monoethylphthalate; MPB, methylparaben; MSPD, matrix solid phase dispersion; MTBE, methyl tert-butyl ether; MTBSTFA, N-tert-butyldimethylsilyl-N-methyltrifluoroacetamide; OS, octylsalicylate; PBs, parabens; p-HB, para-hydroxybenzoic acid; PhS, phenylsalicylate; PPB, propylparaben; PSA, primary secondary amine; SPE, solid-phase extraction; UHPLC-MS/MS, ultra high performance liquid chromatography-mass spectrometry.

reproductive and developmental toxicity, and may also affect the hypothalamic-pituitary-thyroid axis (HPT) which controls the release of thyroid hormones in the body. Some of these compounds have been related to female sexual behavior and increased uterine weight of treated mice and rats [17,24].

2.4. Parabens

Parabens, the alkyl esters of *p*-hydroxybenzoic acid (*p*-HB), are widely used as antimicrobial preservatives, especially against mold and yeast, in cosmetic products and pharmaceuticals, and in food and beverage processing. Methylparaben (MPB), ethylparaben (EPB), propylparaben (PPB) and butylparaben (BPB) are the most commonly used compounds, either individually or in combination. The widespread use of parabens arises from their low toxicity, broad inertness, worldwide regulatory acceptance and low cost. The exposure level is reflected by the frequent detection of the compounds in urine. At least one of the PBs was found in nearly 100% of tested urine samples. However, there is an increasing tendency to avoid the use of parabens because of the growing evidence about their possible adverse effects. In this respect, some *in vivo* studies suggest that exposure to these compounds increases uterine weight in immature mice, decreases testosterone secretion and produces reproductive tract alterations in male rodents [13,39].

3. Analytical methods for EDCs determination in human fluids and tissues

Tables 1–6 show the research works dealing with the determination of EDCs in human samples classified according to the studied matrix. The matrices selected for this review have been urine (Tables 1 and 2); serum and plasma (Tables 3 and 4); amniotic fluid, placental tissue, meconium and cord blood (Table 5); and breast milk (Table 6). Tables include the sample treatment, instrumental techniques, and since LODs or limits of quantification (LOQs) are strongly influenced by these techniques, it has been also included together with some information about frequency of detection of analytes, when data were available.

Tables 1, 3, 5 and 6 summarize methods for the determination of the selected analytes in the samples under study related to child exposition. Tables 2 and 4 show the overall exposure of the population but where the techniques used for extraction and analysis could be of interest for biomonitoring studies and determination of exposure in childhood.

3.1. Sample preparation

3.1.1. Sample collection

An important aspect to take into consideration for the analysis of the selected compounds is the necessity of taking precautions to

Table 6
Analytical method for EDCs determination in human breast milk.

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
BPA	- Alkaline digestion (ethanolic KOH) - LLE (diethyl ether) - SPE (amino) - Derivatization (BSTFA)	GC-MS(EI)	0.09 ng g^{-1}	Total content (<0.09–0.70 ng g^{-1}, 66.6%)	[148]
BPA	- LLE (hexane) - LLE (Cl_3CH) - SPE (C18) - Derivatization (DIB-Cl)	LC-FLD	0.11 ng mL^{-1}	Free content (0.28–0.97 ng mL^{-1}, 100%)	[149]
13 Phthalates metabolites	- Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (Oasis HLB)	LC-MS/MS (APCI-)	0.2 –1.9 ng mL^{-1}	Total content (1.3–15.9 ng mL^{-1}, 100%) We detected mEHP and mNP in all of the samples	[150]
6 Phthalates metabolites	- Enzymatic hydrolysis (β-glucuronidase) - LLE (ethyl acetate/cyclohexane) - SPE (Oasis HLB)	LC-MS/MS (ESI-)	0.01 –0.5 ng mL^{-1}	Total content (<0.01–10900 ng mL^{-1}, 100%)	[151]
BPA, BP-3	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-)	0.28 –0.51 ng g^{-1}	Free (<LOD–6.3 ng mL^{-1}, 60%, BPA; <LOD–1.5 ng mL^{-1}, 15%, BP-3) and total content (<LOD–7.3 ng mL^{-1}, 90%, BPA; <LOD–3.2 ng mL^{-1}, 60%, BP-3)	[152]
BPA(Human colostrums)	- Fat and protein precipitation (MeCN) - SPE (Oasis HLB)	ELISA	0.3 ng mL^{-1}	Total content (1–7 ng mL^{-1}, 100%)	[153]
BPA, MPB, EPB, PPB, BPB, BzPB, BP-3	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APPI-)	<1 ng mL^{-1}	Free (0.41–1.54 ng mL^{-1}, 100%, BPA; 0.32–3.04 ng mL^{-1}, 50%, PBs; 1.24 ng mL^{-1}, 25%, BP-3) and total content (0.73–1.62 ng mL^{-1}, 100%, BPA; 0.70–3.00 ng mL^{-1}, 100%, PBs; 1.28 ng mL^{-1}, 25%, BP-3)	[154]
BP-2, BP-3, 3-BC, 4-MBC, EHMC, HMS	- Sodium sulfate - LLE (n-hexane/acetone) - LLE (Cl_2CH_2/acetone)	LC-MS (ESI+) GC-MS (EI)	1.0–2.0 ng g^{-1}	Free content (2.1–121.4 ng g^{-1} lipid, 0–64.7%) Only BP-2 was determined by LC	[155]
5 Phthalates and their metabolites	- LLE (pentane/acetone) - LLE (hexane/MTBE) - Enzymatic hydrolysis (β-glucuronidase) - Automated SPE (Oasis HLB)	GC-MS LC-MS/MS (APCI-)	0.47 –3.0 ng mL^{-1}	Phthalates (0.22–305 ng mL^{-1}, 19–97.6%, GC-MS)) Metabolites (0.49–6.5 ng mL^{-1}, 2.4–38%, LC-MS/MS)	[49]
BPA	- LLE (2-propanol)	LC-FLD LC-MS/MS (ESI-)	0.6 ng mL^{-1} 0.39 ng mL^{-1}	Free (0.65–29.9 ng mL^{-1}, 100%) and total content (0.65–42.6 ng mL^{-1}, 90%)	[156]
BP-2, BP-3, others UV-filters	- LLE (hexane)	GC-MS (EI) LC-MS (ESI+)	1.0–2.0 ng g^{-1}	Free content (22.12–52.23 ng g^{-1}, 78%, UV-filters) BP-2 was analyzed by LC-MS	[24]
MPB, EPB, PPB, BPB, 11 phthalate metabolites	- Enzymatic hydrolysis (β-glucuronidase) - LLE (MeCN)	LC-MS/MS (ESI-)	0.5 –1.0 ng mL^{-1}	Total content (1.12–34.05 ng mL^{-1}, 26%, PBs; 37%, phthalate metabolites)	[24]
BPA, Cl_x-BPA	- On-line SPE (C8)	LC-MS/MS (ESI-)	0.01 –0.09 ng mL^{-1}	Free content (0.8–3.29 ng mL^{-1}, 100%) Detected chlorinated BPA derivatives	[157]
BPA, Cl_x-BPA(Human colostrums)	- On-line SPE (C8)	LC-MS/MS (ESI-)	0.01 –0.09 ng mL^{-1}	Free (0.54–6.12 ng mL^{-1}, 90%) Detected chlorinated BPA derivatives	[158]
MPB, EPB, PPB	- Protein precipitation (MeCN) - MIP-SPE	LC-UV	LOQ: 10–20 ng mL^{-1}	Free content	[159]
BPA(Human colostrums)	- Enzymatic hydrolysis (β-glucuronidase) - LLE (2-propanol)	LC-MS/MS (ESI-)	NO DATA	Free (<LOD–54.2 ng mL^{-1}, 39.8%) and total content (<LOD–57.3 ng mL^{-1}, 70.6%)	[160]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APPI-)	0.3 ng mL^{-1}	Free (<LOD, 30%) and total content (1.3 ng mL^{-1}) Breast milk and formula samples did not differ in total BPA concentration	[50]
BPA	- Fat and protein precipitation (MeCN/hexane) - SPE (Oasis HLB) - Derivatization (pyridine-3-sulfonyl)	LC-MS/MS (ESI+)	0.22 ng mL^{-1}	Free content (≤0.22–10.8 ng mL^{-1}, 100%)	[161]
BPA, Cl_x-BPA, MPB, EPB, PPB, BPB, BP-1, BP-3, BP-6, BP-8, 4-OH-BP	- Fat and protein precipitation (MeCN/aqueous precipitation solution) - SBSE - Derivatization (BSTFA)	LC-MS/MS (ESI+/-) GC-MS/MS (EI)	0.1 –0.3 ng mL^{-1} 0.1 –1.5 ng mL^{-1}	Free content (3.2–10.8 ng mL^{-1}, 90%, BPA; 0.8–38.7 ng mL^{-1}, 80%, PBs; 0.8 –9.9 ng mL^{-1}, 90%, BPs)	[26]

Table 6 (*continued*)

Analytes	Sample treatment	Analytical technique	LOD	Comments	Ref
BPA, Cl_x-BPA, MPB, EPB, PPB, BPB, BP-1, BP-2, BP-3, BP-6, BP-8, 4-OH-BP	- Fat and protein precipitation (MeCN/ Aqueous precipitation solution) - Clean-up (C18, $MgSO_4$)	LC-MS/MS (ESI±)	0.02 –0.05 ng mL^{-1}	Free content (0.6–13.8 ng mL^{-1}, 60%, BPA; 0.2–0.4 ng mL^{-1}, 20%, Cl_2-BPA 0.1–7.5 ng mL^{-1}, 90%, PBs; 0.2–17.4 ng mL^{-1}, 90%, BPs)	[162]
MPB, EPB, PPB, BPB	- Lyophilization - SM-SLLME (hexane/ dichloromethane)	LC-MS/MS (ESI-)	0.1 –0.2 ng mL^{-1}	Free content (0.5–27.2 ng mL^{-1}, 90%)	[51]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Fat and protein precipitation (MeCN) - SPE (C18)	GC-MS (EI)	0.21 ng g^{-1}	Free (0.036–2.3 ng g^{-1}, 16.5%) and total content (0.036–2.5 ng g^{-1}, 25.9%)	[163]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APPI-)	0.3 ng mL^{-1}	Free (LOD–0.5 ng mL^{-1}, 20%) and total content (0.5–1.3 ng mL^{-1}, 75%)	[164]
BPA	- MSPD (LiChrolut-MeOH/MeCN)	LC-UV	5.3 ng g^{-1}	Application to commercial cow milk samples	[165]
BP-1, BP-3, BP-6, BP-8, 4-OH-BP	- Lyophilization - UAE (MeCN) - Clean-up (C18, PSA, $MgSO_4$)	LC-MS/MS (ESI+)	0.1 –0.2 ng mL^{-1}	Free content (0.31–15.7 ng mL^{-1}, 90%)	[166]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Protein precipitation (MeCN) - LLE (1-chlorobutane) - Derivatization (PFBBr)	GC-MS/MS (NICI)	0.3 ng mL^{-1}	Free (<LOD–1.6 ng mL^{-1}, 4%) and total content (<LOD–1.9 ng mL^{-1}, 5%) The correlations observed between maternal breast milk and infant urine concentrations	[52]
BPA, BP-3, MPB, EPB, PPB, BPB	- Enzymatic hydrolysis (β-glucuronidase) - On-line SPE (C18)	LC-MS/MS (APCI-; APPI-)	0.1 –0.51 ng mL^{-1}	Total content (0.3–1.1 ng mL^{-1}, 50%, BPA; 0.1–2.3 ng mL^{-1}, 100%, PBs; 0.5 –10.4 ng mL^{-1}, 50%, BP-3)	[167]
BPA	- Enzymatic hydrolysis (β-glucuronidase) - Protein precipitation (acetone) - SPE (HR-X) - SPE (MIP) - Derivatization (MSTFA)	GC-MS/ MS(EI)	0.003 ng g^{-1}	Total content (0.03–1.16 ng g^{-1}, 100%)	[168]

Abbreviations: 4-OH-BP, 4-hydroxybenzophenone; APCI, atmospheric-pressure chemical ionization; APPI, atmospheric pressure photoionization; BP-1, benzophenone 1; BP-2, benzophenone 2; BP-3, benzophenone 3; BP-6, benzophenone 6; BP-8, benzophenone 8; BPA, bisphenol A; BPB, butylparaben; BSTFA, N,O-bis(trimethylsilyl) trifluoroacetamide; Cl_x-BPA, chlorinated derivatives; EI, electron impact; ELISA, enzyme-linked immunosorbent assay; EPB, ethylparaben; ESI, electrospray ionization; GC-MS, Gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; LC-MS, liquid chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-UV, liquid chromatography-ultraviolet detection; LLE, Liquid–liquid extraction; MeCN, acetonitrile; MeOH, methanol; MIP, Molecularly imprinted polymer; MISPE molecularly imprinted solid-phase extraction; MPB, methylparaben; MSTFA, N-Methyl-N-(trimethylsilyl)-trifluoroacetamide; MTBE, methyl tert-butyl ether; NICI-MS, negative-ion chemical ionization-mass spectrometry; PBs, parabens; PFBBr, pentafluorobenzylbromide; PPB, propylparaben; PSA, primary secondary amine; SM-SLLME, stir-membrane solid-liquid-liquid microextraction; SPE, solid-phase extraction; UAE, ultrasound-assisted extraction.

avoid contamination in collection and storage. In this way, for urine and blood samples, authors only recommend the use glassware material accurately clean with solvents [43,44,47,85,90,91,98,101,102,106–108,112–114]. For the analysis of BPA, some authors also recommend the use of BPA-free deionized water [43,56,57,70,75,104,105]. Many authors remark the importance of checking the blanks [44–46,54,71,74,79,80,86,88,89,93,99,102,107–114]. In the case of placental tissue samples, the authors do not describe many precautions. In general, the sample is accurately weighed, and a triangular portion, that included maternal and fetal sides as well as central and peripheral parts, is taken. Each portion is fragmented, beaten and placed into a container. Then, the samples are homogenized, frozen at −86 °C until the analysis in the laboratory [25,27,128,132,133,139,146,147]. Finally, breast milk has been the matrix in which more considerations have been taken. These include cleaning breast and nipples thoroughly before sampling with tap water [24,155,167] or with deionized water [159,164]; asking mothers not to use any creams or cleansers on the breast before sampling [24,52]; avoiding the use of breast pumps, expressing the milk sample directly into the glass bottle [150,153,157,158]; using fuoroelastomer pumps previously rinsed with ethanol [49]; rinsing the milk pump with hot tap water [155] or using BPA-free manual breast pump [24]. Regardless the nature of the sample, the most frequently precaution taken for the analysis of BPA and phthalates is to exclude plastic ware throughout the analytical procedure and replace with glass ware [119,122,123,126,130,131,138,143,145,151,153,156–161]. In addition, some authors use previously washed glass ware with acid [161], with methanol, acetonitrile (MeCN) and acetone [124], or with water followed by methanol and conditioning in an oven overnight at 200 °C [129].

3.1.2. Sample pre-treatment

For blood analysis, a previous step to isolate serum or plasma is usually applied. While plasma is obtained by centrifugation of fresh blood with an anticoagulant, serum is obtained by centrifugation of blood samples without anticoagulant. In these matrices, it is also common to precipitate proteins to reduce matrix interferences.

Typically, this procedure is achieved mixing the sample with organic solvents followed by a separation of proteins by centrifugation.

For other human samples such as placenta or liver, a homogenization step is typically required, usually mechanical homogenization in a buffer solution [129,136]. In the case of placenta samples, homogenization has also been performed using an ultrasound probe that allows the tissue to separate, followed by shaking with deionized water [25,128,132,133,139], or simply with a mechanical homogenizer [118,122]. Meconium is homogenized adding H_3PO_4 and shaking [121,126].

Owing to the high fat and protein content of human milk, isolation of the target analytes becomes critical for the development of any analytical method. The selection of an adequate sample pre-treatment and treatment is crucial to reduce matrix effects. A previous step is commonly required for fat and protein precipitation. MeCN has been widely used for this purpose [52,153,159,162,163]. The mixture of MeCN and a solution containing zinc acetate dihydrate, hydrated phosphotungstic acid, glacial acid and deionized water, has been also successfully used [26]. Apart from MeCN, another solvent such as 2-propanol was used, obtaining a clear supernatant with no lipid layer [152]. Additionally, in order to facilitate sample manipulation, some authors have carried out a previous lyophilization of the sample. Milk is previously frozen at −80 °C and then introduced into the lyophilizator. Once lyophilized, samples are kept in a desiccator until the analysis [51,166].

In biological matrices, the compounds usually appear as free and conjugated forms; therefore an acid or enzymatic hydrolysis step is usually required to determine the total content (free + conjugated). Without the hydrolysis step, the free content can be determined, and the difference between free and total contents would be the conjugated amount. Hydrolysis with concentrated HCl [59,103,101,110,112] is used because it is simpler and less time consuming than enzymatic hydrolysis. However, since it is a mild process, more selective and generates less by-products, enzymatic hydrolysis is preferred instead of acid hydrolysis at present. Thus, enzymatic hydrolysis by incubation of sample under specific conditions with β-glucuronidase or with β-glucuronidase/sulfatase (*Helix pomatia or Escherichia coli*) is the most common technique for total content EDC determination [24,41–50,52,60–65,67–72,74–76,78–81,83–85,88–100,103,104,106,109,120,123–126,131,134,135,137,138,140,141,150,151,153,154,160,163,164,167]. After enzymatic hydrolysis, the enzyme is sometimes precipitated with cold MeCN [71,75,90]; organic acids such as formic and acetic acid [44,46,48,72,73,77,78,84,88,91,93,98,99,101,103,104,106,125,128,135,150]; inorganic acids [46,80,99,106,110,114] and bases [42,81]; or with the reactives used in the own extraction procedure [41,45,47,72,81,82,86,87,89,96,100,102,106,107,111,112,123,129–131]; and then separated by centrifugation. Finally, the supernatant undergoes the following sample preparation step.

Blount et al. [37] indicate that, in the case of phthalate monoesters analysis, *H. pomatia* β-glucuronidase/sulfatase should be avoided because of its enzymatic activity that hydrolyzes phthalate diesters to generate phthalate monoesters. *E. coli* β-glucuronidase (K12; Roche Biomedical, Indianapolis, IN) can be used instead is these cases [24,44,49,60,64,84,94,98,106,109,120,121,124,126,131,137,138,150,151].

3.1.3. Sample treatment

Due the complexity of biological samples, an extraction technique is usually required to purify and isolate the target compounds from the matrix. Moreover, because of EDC levels in human samples are very low, these extraction techniques must be able to concentrate the analytes and therefore to improve the sensitivity of the analytical method. Tables 1–6 summarize the extraction techniques used in the methods published in the literature. Liquid–liquid extraction (LLE) and solid-phase extraction (SPE) have been traditionally used. However, in order to reduce the solvent amounts and to increase concentration factors, microextraction techniques such as extraction with molecular imprinted polymers (MIPs) [169], solid-phase microextraction (SPME) [53], stir-bar sorptive extraction (SBSE) [170], ultrasound assisted emulsification microextraction with solidification of floating organic droplet (UAEM-SFO) [41] or hollow-fiber liquid-phase microextraction (HF-LPME) [171], dispersive liquid–liquid microextraction (DLLME) [172], stir-membrane solid-liquid-liquid microextraction (SM-SLLME) [51], matrix solid phase dispersion (MSPD) [174] or ultrasound-assisted extraction (UAE) [175] have also been proposed.

A. Liquid–liquid extraction. LLE is a time-consuming technique that often requires large volumes of organic solvents and is difficult to automate. Urine, serum, cord serum, maternal serum, placenta and human breast milk has been analyzed using this extraction technique.

Urine is the biological sample more commonly extracted using LLE due to its simple composition in comparison with other types of biological samples. BPA [55,86,91], benzophenones derivatives [76], parabens [93] and phthalate metabolites [94,98] has been analyzed in this matrix. In the case of serum samples, the use of LLE for sample treatment is not been very common. Nevertheless, some analytical procedures have been developed (DEHP and MEHP [108] or BPA [102,112,115]). It is important to remark that the application of LLE to serum samples has two effects, sample extraction and protein denaturalization. Therefore, in these cases LLE also implies a sample clean-up. Regarding cord serum and maternal serum, LLE with ethyl acetate [118,147], methyl *tert*-butylether (MTBE) [123], hexane/MTBE (1:1, v/v) [127] and hexane/diethylether (DEE) (70:30, v/v) [130] was used to extract BPA. A limit of detection (LOD) up to 62.5 times lower was obtained using LLE with ethyl acetate and gas chromatography-mass spectrometry (GC–MS) analysis with a previous derivatization step than the obtained using LLE with MTBE and liquid chromatography-fluorescence detection (LC-FLD) analysis (0.01 ng g^{-1} *vs*. 0.625 ng g^{-1}). In other work, two LLE steps were carried out initially with a mixture hexane/MTBE (1:1, v/v) followed by hexane, and analyzed by GC–MS [125] for the extraction of 15 phthalates from cord blood.

Placenta tissue has also been studied. Because this matrix is homogenized (pre-treatment) before extraction with water or buffer solution, the result is a rather liquid sample, a sort of mousse or foam. Therefore, the extraction of this homogenized sample could be considered an LLE process. Then, a liquid extraction is carried out after homogenization. Ethyl acetate has been the most used solvent for BPA [25,118,128], parabens [25,133] and UV-filters [25,132,139]. LODs for parabens were up to 10 times lower than the obtained for BPA and its chlorinated derivatives (0.03–0.06 ng g^{-1} *vs*. 0.2–0.6 ng g^{-1}). Ethanol has been also used for the extraction of 4 parabens and *p*-hydroxybenzoic acid from placental tissue [142]. In this case, the aim of the work was the use of a human placental perfusion model for the estimation of fetal exposure to parabens. Finally, an extraction with ethyl acetate/cyclohexane (95:5, v/v) was carried out for the extraction of eight phthalate monoesters from placenta samples and quantification by LC–MS/MS [122].

BPA, PBs, phthalates and BPs has been extracted from breast milk samples with MeCN [24,163,166]. The LODs obtained ranged from 0.1 to 0.5 ng mL^{-1}. In addition, a multi-residue method based on a simplified sample treatment involving a step of fat and protein precipitation using MeCN and a solution containing zinc acetate dihydrate, hydrated phosphotungstic acid, glacial acid and deionized water, is also proposed. Very good sensitivity was obtained for BPA and chlorinated derivatives, PBs and BPs from 0.02 ng mL^{-1} to

0.05 ng mL^{-1} [162]. Also, different solvents such as 2-propanol, chloroform, chlorobutane, diethyl ether and hexane has been also used for the extraction of BPA [52,148,149,156,160] from human milk samples. A mixture of ethyl acetate/cyclohexane (95:5, v/v) was used for the extraction of six phthalates using LC-MS/MS as detection technique [151]. Very low LODs (0.01–0.5 ng mL^{-1}) were obtained. LLE also has been used for the analysis of UV-filters in human breast milk samples. The samples were centrifuged and the analytes extracted together with lipids using sodium sulfate and *n*-hexane/acetone (1:1, v/v) followed by dichloromethane/acetone (1:1 v/v) [155].

LLE can be modified using ion-pair (IP) assisted liquid–liquid extraction (IPA-LLE). It is usually performed by adding an ion pair reagent to the sample solution containing ions of the target analytes, to form IP complexes with higher partition coefficients than the target analytes thus enhancing their transfer into the extractant (organic) phase. This technique has been recently used for the extraction of BPA [91] and five benzophenones UV-filters [140] from cord blood and maternal blood. Both studies used tetrabutylammonium hydrogen sulphate as ion-pair reagent. Similar LOQs were obtained for BPA, BP-1 and 4-OH-PB (0.1, 0.09 and 0.06 ng mL^{-1}, respectively) whereas for BP-8, BP-3 and BP-2 LOQs were between 4.1 and 6.7 times higher than for BPA (0.41, 0.47 and 0.67 ng mL^{-1}, respectively).

B. Solid-phase extraction. SPE has been widely used for the analysis of EDCs. SPE is well adapted to multi-residue analysis, including compounds with a wide range of polarities and physicochemical properties. SPE can be used off-line, on continuous, or coupled on-line to a chromatographic technique. It should be noted that automated and on-line SPE systems have been widely used in biomonitorization studies due to their high reproducibility and continuous-working mode. Urine and serum samples have been usually treated with SPE in both off-line and on-line modes. BPA, alkylphenols, PBs, BPs, phthalates and other EDCs have been determined in urine and serum using these procedures.

Octadecyl silica sorbents (C18) have been widely used for the analysis of BPA, using SPE in the off-line mode, in urine [54,58,59,62,71,83,84], serum [100,103,104,109], human breast milk [163], amniotic fluid [134,135], cord blood [119] and tissues, previously homogenized, such as placenta [129,136], fetal liver [129,136,144], and fetal brain [144]. The LOD obtained for BPA in cord plasma was half of that obtained for amniotic fluid (0.05 ng mL^{-1} *vs.* 0.1 ng mL^{-1}). Regarding placenta and liver tissues [129,136], SPE with C18 sorbent was used as a clean-up step after LLE with MeCN. C18 sorbents have been used for the extraction of BPs [78], phthalates [83] and phthalate metabolites from urine [98]. SPE with C18 sorbents was used as clean-up step after LLE with diethyl ether, hexane or chloroform for BPA [149,162], BPs [162,166] and PBs [162] determination.

SPE with Nexus® sorbent (methacrylate-divinylbenzene copolymer) also has been used to analyze EDCs. Nexus® presents some advantages since no pre-conditioning is required and its large particle size makes it adequate for extractions from highly viscous samples. This sorbent was successfully used for the extraction of PBs from urine [89] and several phthalates and phthalate metabolites from serum [106], amniotic fluid [120,124], maternal urine [124], and cord serum and maternal serum [126,138]. LC–MS/MS was used as analytical technique in all cases obtaining similar LODs for urine, amniotic fluid and serum.

Although less commonly, another sorbent used for the analysis of BPA, is Oasis® HLB (divinylbenzene/*N*-vinylpyrrolidone copolymer). This sorbent was used successfully applied for the extraction of BPA from maternal serum and amniotic fluid [100] using enzyme-linked immunosorbent assay (ELISA). Good sensitivity was achieved with a LOD of 0.2 ng mL^{-1}. Oasis® HLB sorbents were used for the extraction of BPA from human milk [161] or colostrum samples [153]. It was also used for the determination of eight phthalate monoesters in placenta and cord serum [122]. In this study, a human perfusion model was used to estimate fetal exposure to phthalates, and in the case of placenta samples, LLE was applied before the SPE clean-up step. The LODs obtained for placenta tissue were markedly better than the ones for cord serum (up to 10 times, 0.05 ng g^{-1} *vs.* 0.5 ng mL^{-1} for mono (2-ethyl-5-hydroxyhexyl)phthalate (mEHHP)) using the same instrumental technique. Oasis® HLB sorbent was also successfully used to extract several phthalates and phthalate metabolites from meconium [121,126]. Moderate sensitivity was achieved with LODs ranging from 0.2 to 1 ng g^{-1}.

The sorbent Oasis® MAX (mix-mode anion exchanger) was used successfully for the extraction BPA and eleven phthalate metabolites in urine [90], and extraction of four phthalates in serum [113].

In addition, and due to some of its advantages such us it is automatable and reduces manual preparation steps, on-line SPE coupled to LC–MS/MS is becoming very popular for the analysis of EDCs in human samples. This technique has been widely used to determine BPA, BPs, PBs, phthalates and phthalate metabolites in human urine [40,42,44–48,57,60,63,64,68,74,77,79–81,85], and BPA and PBs in serum [109,111,114]. These methods have provided vast amounts of data for evaluating human exposure to EDCs. Furthermore, on-line SPE has been used to analyze eleven phthalate metabolites in cord blood, breast milk and maternal urine [131]; several phthalates and phthalate monoesters in meconium [121,126,138]; and BPA, BP-3 and four PBs plus other EDCs in amniotic fluid and maternal urine [141]. On-line SPE coupled to LC–MS/MS is the most used technique for the analysis of EDCs (BPA, Cl_x-BPA, PBs, BP-3 or phthalate metabolites) in human breast milk samples or colostrum [49,50,150,154,157,158,164,165]. The LODs obtained were from 0.1 to 0.5 ng mL^{-1} in all cases.

C. Other extraction techniques. In addition to classical LLE and SPE, a large amount of techniques has been applied for the determination of EDCs in the selected matrices.

Molecular imprinted polymers. Several research groups, in order to get high extraction selectivity, have developed procedures based in molecular imprinted polymers (MIPs). These solid phases are able to retain a specific analyte or reduced group of analytes from the rest of the matrix. MIPs can be used in a variety of physical forms including fibres, covering of SBSE devices or sorbents included in SPE cartridges (MISPE) [169].

Tan et al. [73] have developed a MIP-fiber device for determining BPA in urine samples, applying chemical desorption with methanol (5% acetic acid) for removing the analyte from the MIP. MISPE variant coupled with capillary electrophoresis has been used by Mei et al. [82] for the determination of BPA in urine samples. MISPE has also been used for the determination of parabens in human breast milk samples [159] using LC–UV. The LOQs obtained ranged between 10 and 20 ng mL^{-1}. Nevertheless, MIP systems have not been much exploited so far because despite their advantages such as specificity, reproducibility, and their economic efficiency compared to conventional SPE sorbents, MIPs cannot be used in multiclass or multiresidue analyses.

Solid-phase microextraction. The first SPME procedure appeared in 1998 [53], when several benzophenones in urine were determined by direct immersion of a C18 fiber in the sample. Nevertheless, this type of SPME has been rarely used, and other SPME devices have gained in importance in the last years.

Stir-bar sorptive extraction. SBSE, introduced in 1999 by Baltussen et al. [170], has been used for the extraction of non-polar and medium-polarity compounds from liquid samples or liquid extracts. After sorption, the compounds are chemically or thermally desorbed [176]. SBSE has been used by Kawaguchi et al. for the

determinations of BPA, alkylphenols and chlorophenols [61], and BPs [69] in urine. These two research studies use a thermal desorption device for introducing the analytes in the GC system.

In addition, a study on the determination of BPA, Cl_x-BPA, PBs and BPs in human milk using stir-bar sorptive extraction has been also proposed. In this case, a previous step is proposed for fat and protein precipitation using the mixture of MeCN and a solution containing zinc acetate dihydrate, hydrated phosphotungstic acid, glacial acid and deionized water [26]. Good sensitivity was obtained with LODs ranging from 0.1 to 0.3 ng mL^{-1} with ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) analysis and from 0.1 to 1.5 ng mL^{-1} with GC–MS/MS analysis.

Liquid-phase microextraction. Regarding to hollow-fiber liquid-phase micro-extraction (HP-LPME) [150], the works of Kawaguchi et al. should be remarked [70,72]. This analytical team determined BPA [70] and several BPs [72] in urine. In both procedures, toluene was used as extraction solvent, and an "in situ" derivatization with acetic acid anhydride was performed. Although this technique has been widely applied in environmental and food matrices, EDC determination in biological samples has seldom been used.

Ultrasound-assisted emulsification microextraction and solidification of floating organic droplet. UAEM-SFO is another LPME technique that has not been exploited yet for EDCs determination. Nevertheless, Wang et al. [87] developed a UAEM-SFO procedure for determining BPA, triclosan and chlorophenols in urine. The extraction power of this technique is clear and although the instrumental system was capillary electrophoresis with UV detection (CE-UV), the LODs found were lower than 0.02 μg mL^{-1}.

Dispersive liquid–liquid microextraction. DLLME, introduced in 2010 by Rezaee et al. [172], has been exploited by Vela-Soria et al. for the determination of several EDC groups in urine [95,96,99] and serum [42,99,116]. Good sensitivity was obtained with LODs from 0.03 to 0.20 ng mL^{-1} with UHPLC-MS/MS analysis and from 0.04 to 0.20 ng mL^{-1} with GC-MS/MS analysis in urine. In serum, LODs ranged from 0.1 to 0.30 ng mL^{-1} with UHPLC-MS/MS analysis. This technique has demonstrated to be very useful in EDCs determination, providing low extraction times and very high extraction efficiencies.

Stir-membrane solid-liquid-liquid microextraction. Stir membrane extraction (SME) uses a polymeric membrane as extracting phase [173]. The use of liquid extracting phases has allowed the development of stir-membrane liquid–liquid microextraction (SM-LLME). A study has developed a simultaneous solid-liquid-liquid microextraction with a stir-membrane system (SM-SLLME) for the determination of four parabens in lyophilized human breast milk samples [51]. Obtained LODs ranged from 0.1 to 0.2 ng mL^{-1}.

Matrix solid phase dispersion. MSPD was introduced by Barker in 1989 [174] to solve the troubles inherent to processing solid and semi-solid matrices. This technique has been used for first time for the determination of BPA in milk with LODs of 5.3 ng g^{-1} [165].

Recently, MSPD coupled with LC–MS/MS has been used for the determination of PBs and BPs with C18 sorbent [146], and BPA, Cl_x-BPA, PBs and BP-3 with silica/PSA sorbents [147] in placental tissue samples previously lyophilized.

Ultrasound-assisted extraction. UAE is a very common extraction technique. Ultrasonic energy causes an effect known as "cavitation", which generates numerous tiny bubbles in liquid media and mechanical erosion of solids and particle rupture. The most available and cheapest source of ultrasound irradiation is the ultrasonic bath but a more efficient system is now used, a cylindrical powerful probe for the sonication of samples [175]. Only one study has been published on the use of UAE for the determination of benzophenone-UV filters in human breast milk samples previously lyophilized [166].

3.2. Instrumental techniques

An appropriate analytical separation technique must be selected in order to enhance the determination of the target compounds. Tables 1–6 show the most commonly employed instrumental techniques for the detection and quantification of BPA, PBs, organic UV-filters and phthalates and its metabolites in selected human samples.

Gas chromatography and liquid chromatography coupled to mass spectrometry (MS or MS^2) are the most usual choices. The selection of GC or LC is usually based on the physico-chemical properties of the analytes. LC is selected for the determination of more polar and less volatile compounds, while GC is used to quantify volatile or volatizable compounds. Although BPA has been determined in brain and liver fetal tissue using GC without a previous derivatization step [144], it is usually derived by using silylating or acylation reagents. The inclusion of a derivatization step has advantages such as the improvement of the chromatographic behavior of analytes as well as sensitivity and selectivity in MS detection. However, it has also disadvantages such as the increase of complexity, chances of error and total analysis time. N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and pentafluorobenzyl bromide (PFBBr) have been widely used for the determination of BPA in human samples. Thus, BSTFA has been employed for the analysis of BPA in urine [96], placenta and fetal liver [118,119] and breast milk [49,148] and PFBBr in urine [54,57,58,166], serum [104], and breast milk and meconium [52]. Other derivatization agents have also been used (Tables 1–6). BPs has been analyzed using GC–MS in urine and breast milk directly [27,69,155] or after derivatization with BSTFA [49,96] or acetic acid anhydride [62]. PBs has been analyzed using GC–MS in urine after derivatization with BSTFA [49,96]. Although phthalates and their metabolites have been analyzed preferably by LC in human samples, we have found a few studies in which GC–MS is successfully used for the determination of phthalates and phthalate metabolites in urine [98], serum [113], cord blood [143], and breast milk [49]. MS with electron impact ionization (EI) is the most commonly ionization mode used in GC–MS [24,26,53,61,69–72,75,90,96,107,113,118,119,129,136,143–145,148,163,168]. Two important advantages of EI ionization are the small influence of molecular structure on response and the large number of characteristic fragment.

The best choice for EDC analysis is usually LC. As shown in Tables 1–6, LC has been selected in several studies to determine BPA and PBs with different detectors coupled to the LC. For example, UV–Vis detection has been used for the determination of PBs in urine and serum [99], and in placenta samples [142]; and for the determination of BPs in urine [66,77] and breast milk [159]. This detection system has also been used for the determination of BPA in urine [73], cord blood and maternal blood samples [130], and breast milk [165]. LC-FLD has not been very used for the determination of EDCs because most EDCs do not exhibit native fluorescence. However, LC-FLD was successfully used for the determination of BPA in urine [59,65,67], serum [101], cord blood and maternal blood [123], and in breast milk [149,156]. GC–MS or LC–MS were used for confirmation.

The recent advances in analytical instrumentation have allowed the unequivocal identification and confirmation of the presence of any compound at very low levels using LC–MS/MS. The triple quadrupole (QqQ) is the most common, useful and sensitive tool for EDCs analysis. The multiple reactions monitoring (MRM) mode allows monitoring two transitions between precursor and product ions; it is possible to quantify and confirm the presence of EDCs in human matrices at very low concentration levels. Regarding multistage mass spectrometry ($LC–MS^n$) interfaces, electrospray

ionization (ESI) is the most frequently used ionization mode for the analysis of EDCs in urine [44,48,56,60,68,76,78,81,83,84,86,91–95,98,99], serum [103,105,106,108,110,112,115,116], placenta and related matrices [121,122,124–127,131,134–136,138,140,146,147], and breast milk [24,26,51,151,155–158,160–162,166]. ESI is a soft ionization technique, suitable for polar and moderately non-polar compounds. However, a critical aspect when using ESI for quantitative analysis is the influence of ion suppression or enhancement in complex samples. Atmospheric pressure chemical ionization (APCI) has also been used as interface in the LC–MS^n analysis of EDCs in urine [40–42,45–47,63,64,74,79,80,85], serum [114], placenta and related matrices [120,128,132–135,139,141], and breast milk [49,150,152,167]. APCI provides more ionization options for low polarity substances. Although to a lesser extent than in ESI, matrix effect can also appear. Many authors use appropriate isotopically labeled compounds as surrogate or internal standards (i.e., $^{13}C_{12}$-labeled BPA, $^{13}C_{12}$-BPA; $^{13}C_{12}$-labeled BP-3, $^{13}C_{12}$-BP-3; $^{13}C_{12}$-labeled monomethylphthalate, $^{13}C_{12}$-mMP; $^{13}C_{12}$-labeled monoethylhexylphthalate, $^{13}C_{12}$-mEHP; deuterated monoethylhexylphthalate, mEHP-d_4; deuterated ethylparaben EPB-d_{10}, deuterated BPA; BPA-d_{14}) to compensate matrix effects for the analogous native analytes (BPA, BP-3, monomethylphthalate, mMP and monoethylhexylphthalate, mEHP).

Capillary electrophoresis has been rarely used for the determination of EDCs in human samples. Only two methods have been published regarding the determination of BPA in urine [82,87].

4. Discussion

Most of the literature related with the determination of EDCs in human samples has been referred to BPA, but other EDCs such as phthalates, parabens and organic UV-filters have been also analyzed.

The classic LLE and SPE techniques have been the most used. These techniques imply some desirable advantages for any sample processing (simplicity and no necessity of advanced technical equipments). However, their well-known deficiencies (time-consumption, large volumes of organic solvents, and no selective extraction in the case of LLE) have led to the emergence of new sample treatment techniques, focusing particularly into microextraction techniques. In this sense, recently DLLME, SBSE, MSPD or SM-SLLME, between others, have became alternatives to the above mentioned classic techniques.

With respect to EDCs determination in human urine and serum samples, is important to highlight that the number of published papers focused on the perinatal stage is scarce. LLE and SPE have been until now the more used techniques for treating urine and serum samples (see Tables 1–4). SPE provides good results in EDCs exposure assessment. The remarkable versatility of SPE has been exploited for many researching groups in the development and application of multi-residue procedures. Nevertheless, in our opinion, SPE implies an expensive cost of treatment, perhaps no acceptable for some laboratories. HF-LPME, coacertive microextraction and DLLME has been some of the proposed alternatives (see Tables 1–4). Although these extraction techniques provide good extraction recoveries, high preconcentration factors and less volume of organic solvents, the lack of automation of these procedures means a trouble for adopting them in routine analysis laboratories.

To process semi-solid matrices like placenta is known to be a difficult task. However, recently the MSPD technique is becoming an attractive alternative approach because it uses small sample size (previously lyophilized), minimizes solvent use and it is amenable to automation (see Table 5).

Up to now, amniotic fluid samples have been analyzed by means of SPE. Despite its advantages such as great selectivity, high recoveries and good reproducibility, it has disadvantages such as there are many steps involved and its cost (see Table 5). Regarding cord blood, only the classic LLE and SPE techniques have been used (see Table 5).

In the case of EDCs determination in breast milk, LLE and SPE techniques have been recently replaced or displaced by new techniques like MIPs (used only for the determination of three parabens), SBSE, MSPD, SM-SLLME or UAE (see Table 6).

5. Conclusions and perspectives

The assessment of EDCs human exposure implies multiresidue methods with capacity of determining larger number of EDC compounds, taking into account that the endocrine disrupting phenomena is a synergic effect of disrupting compounds mixtures. In the last few years, an increasing number of analytical methods have been developed to determine EDCs in a great variety of human samples. The majority of the studies have demonstrated the presence of a large amount of EDCs in these types of samples.

In this context, major advances have been made recently in sample treatment methods and instrumental techniques for the detection (identification and quantification) of these compounds.

With regard to the extraction techniques, most studies has been focused on minimizing the number of steps and in the use of low solvent amounts. In addition, microextraction techniques are becoming alternatives in the analysis of human samples.

Also, multiresidue methods are being developed for the determination of several families of EDCs with one extraction step and limited sample preparation.

GC–MS/MS and LC–MS/MS are the most powerful instrumental techniques for quantifying and confirming the presence of EDCs in human samples. Although GC–MS and GC–MS/MS are widely used, the methods based on these techniques are typically more tedious and complex due, for example, to the necessity of introduce derivatization steps for certain compounds. However, LC–MS/MS working with QqQ in MRM mode offers the required sensitivity without the need of these stages. Because of advantages like reduced analysis time and cost, less experimental variability and less contact with the samples, on-line-SPE-LC–MS/MS has become one of the most popular techniques.

On the other hand, recent advances in LC–MS using time of flight (ToF) or orbitrap analyzers would provide a very suitable alternative to QqQ instruments. The high resolution power (>25,000–100,000 *full width at half maximum*, *FWHM*) *and* mass accuracy (<5 ppm) of these instruments, allow the screening of targeted as well as untargeted analytes. Moreover, the capacity to maximize the information from a sample (full scan) allows retrospective analysis.

In order to determine human exposure to EDCs, the identification and quantification of these compounds in different human samples will continue to be a relevant research topic over the next decade. Assessment of exposure to EDCs during gestation and lactation will help prevent health issues arising in the future.

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References

[1] E. Diamanti-Kandarakis, J.P. Bourguignon, L.C. Giudice, R. Hauser, G.S. Prins, A.M. Soto, R.T. Zoeller, A.C. Gore, Endocrine-Disrupting Chemicals: An endocrine society scientific statement, Endocr. Rev. 30 (2009) 293–342.

[2] Endocrine Disrupting Chemicals, in: Åke Bergman, Jerrold J. Heindel, Susan Jobling, Karen A. Kidd, R. Thomas Zoeller (Eds.), Summary for Decision-makers, 2012. Available at: http://apps.who.int/iris/bitstream/10665/78102/1/WHO_HSE_PHE_IHE_2013.1_eng.pdf.

[3] S.C. Langley-Evans, Developmental programming of health and disease, Proc. Nutr. Soc. 65 (2006) 97–105.

[4] WHO, State of the Science of Endocrine Disrupting Chemicals, World Health Organization, 2012. Available at: http://www.who.int/ceh/publications/endocrine/en/.

[5] G. Ormond, M.J. Nieuwenhuijsen, P. Nelson, M.B. Toledano, N. Iszatt, S. Geneletti, P. Elliott, Endocrine Disruptors in the Workplace, Hair Spray, Folate Supplementation, and Risk of Hypospadias: Case-Control Study. Environ, Health Perspect. 117 (2009) 303–307.

[6] S. Villeneuve, D. Cyr, E. Lynge, L. Orsi, S. Sabroe, F. Merletti, G. Gorini, M. Morales-Suárez-Varela, W. Ahrens, C. Baumgardt-Elms, L. Kaerlev, M. Eriksson, L. Hardell, J. Févotte, P. Guénel, Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe, Occup. Environ. Med. 67 (2010) 837–844.

[7] D. Li, Z. Zhou, D. Qing, Y. He, T. Wu, M. Miao, J. Wang, X. Weng, J.R. Ferber, L.J. Herrinton, Q. Zhu, E. Gao, H. Checkoway, W. Yuan, Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction, Hum. Reprod. 25 (2010) 519–527.

[8] I. Iavicoli, L. Fontana, A. Bergamaschi, The effects of metals as endocrine disruptors, J. Toxicol. Environ. Health Sci. 2 (2009) 206–223.

[9] W. Mnif, A.I.H. Hassine, A. Bouaziz, A. Bartegi, O. Thomas, B. Roig, Effect of endocrine disruptor pesticides: A Review, Int. J. Environ. Res. Public Health 8 (2011) 2265–2303.

[10] J.T. Brophy, M.M. Keith, A. Watterson, R. Park, M. Gilbertson, E. Maticka-Tyndale, M. Beck, H. Abu-Zahra, K. Schneider, A. Reinhartz, R. DeMatteo, I. Luginaah, Breast cancer risk in relation to occupations with exposure to carcinogens and endocrine disruptors: a Canadian case-control study, Environ. Health 11 (2012) 87.

[11] P.J. Landrigan, A. Garg, D.B.J. Droller, Assessing the effects of endocrine disruptors in the National Children's Study, Environ. Health Perspect. 111 (2003) 1678–1682.

[12] L. Vandenberg, R. Hauser, M. Marcus, N. Olea, W.V. Welshons, Human exposure to bisphenol A (BPA), Reprod. Toxicol. 24 (2007) 139–177.

[13] P.D. Darbre, P.W. Harvey, Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks, J. Appl. Toxicol. 28 (2008) 561–578.

[14] C.A. Frye, E. Bo, G. Calamandrei, L. Calzá, F. Dessì-Fulgheri, M. Fernández, L. Fusani, O. Kah, M. Kajta, Y. Le Page, H.B. Patisaul, A. Venerosi, A.K. Wojtowicz, G.C. Panzica, Endocrine Disrupters: A review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems, J. Neuroendocrinol. 24 (2011) 144–159.

[15] J. Muncke, Endocrine disrupting chemicals and other substances of concern in food contact materials: An updated review of exposure, effect and risk assessment, J. Steroid Biochem. Mol. Biol. 127 (2011) 118–127.

[16] S. Flint, T. Markle, S. Thompson, E. Wallace, Bisphenol A exposure, effects, and policy: A wildlife perspective, J. Environ. Manag. 104 (2012) 19–34.

[17] M. Krause, A. Klit, M.B. Jensen, T. Søeborg, H. Frederiksen, M. Schlumpf, W. Lichtensteiger, N.E. Skakkebaek, K.T. Drzewiecki, Sunscreens are they beneficial for health? An overview of endocrine disrupting properties of UV-filters, Int. J. Androl. 35 (2012) 424–436.

[18] European Commission, State of the Art Assessment of Endocrine Disrupters, Final report. Project contract number 070307/2009/550687/SER/D3, 2012. Available at: http://ec.europa.eu/environment/chemicals/endocrine/pdf/sota_edc_final_report.pdf.

[19] J.R. Rochester, Bisphenol A and human health: A review of the literature, Reprod. Toxicol. 42 (2013) 132–155.

[20] A.G. Asimakopoulos, I.N. Pasias, K. Kannan, N.S. Thomaidis, Human exposure to chemicals in personal care products and health implications, in: The Handbook of Environmental Chemistry, 2014, Springer International Publishing, Switzerland, 2014.

[21] L.H. Pottenger, J.Y. Domoradzki, D.A. Markham, S.C. Hansen, S.Z. Cagen, J.M. Waechter Jr., The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration, Toxicol. Sci. 54 (2000) 3–18.

[22] M.G. Soni, I.G. Carabin, G.A. Burdock, Safety assessment of esters of p-hydroxybenzoic acid (parabens), Food Chem. Toxicol. 43 (2005) 985–1015.

[23] M. Stefanidou, C. Maravelias, C. Spiliopoulou, Human exposure to endocrine disruptors and breast milk, Endocr. Metab. Immune Disord. Drug Targets 3 (2009) 269–276.

[24] M. Schlumpf, K. Kypke, M. Wittassek, J. Angerer, H. Mascher, D. Mascher, C. Vökt, M. Birchler, W. Lichtensteiger, Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: correlation of UV filters with use of cosmetics, Chemosphere 81 (2010) 1171–1183.

[25] F. Vela-Soria, I. Jiménez-Díaz, R. Rodríguez-Gómez, A. Zafra-Gómez, O. Ballesteros, M.F. Fernández, N. Olea, A. Navalón, A multiclass method for endocrine disrupting chemical residue analysis in human placental tissue samples by UHPLC-MS/MS, Anal. Methods 3 (2011) 2073–2081.

[26] R. Rodríguez-Gómez, A. Zafra-Gómez, F.J. Camino-Sánchez, O. Ballesteros, A. Navalón, Gas chromatography and ultra high performance liquid chromatography tandem mass spectrometry methods for the determination of selected endocrine disrupting chemicals in human breast milk after stir-bar sorptive extraction, J. Chromatogr. A 1349 (2014) 69–79.

[27] F. Vela-Soria, I. Rodríguez, O. Ballesteros, A. Zafra-Gómez, L. Ballesteros, R. Cela, A. Navalón, Simplified matrix solid phase dispersion procedure for the determination of parabens and benzophenone-ultraviolet filters in human placental tissue samples, J. Chromatogr. A 1371 (2014) 39–47.

[28] C.G. Daughton, T.L. Jones-Lepp, Pharmaceuticals and personal care products in the environment, in: ACS Symposium Series 791, Oxford University Press, Washington, USA, 2001.

[29] C. Piao, L. Chen, Y. Wang, A review of the extraction and chromatographic determination methods for the analysis of parabens, J. Chromatogr. B 969 (2014) 139–148.

[30] A. Chisvert, Z. León-González, I. Tarazona, A. Salvador, D. Giokas, An overview of the analytical methods for the determination of organic ultraviolet filters in biological fluids and tissues, Anal. Chim. Acta 752 (2012) 11–29.

[31] S. Kim, K. Choi, Occurrences, toxicities, and ecological risks of benzophenone-3, a common component of organic sunscreen products: a mini-review, Environ. Int. 70 (2014) 143–157.

[32] V. Yusa, X. Ye, A.M. Calafat, Methods for the determination of biomarkers of exposure to emerging pollutants in human specimens, TRAC-Trends Anal. Chem. 38 (2012) 130–142.

[33] I. Jiménez-Díaz, A. Zafra-Gómez, O. Ballesteros, A. Navalón, Analytical methods for the determination of personal care products in human samples: an overview, Talanta 129 (2014) 448–458.

[34] Bisphenol A website. Available at: http://www.bisphenol–a.org.

[35] T. Yamamoto, A. Yasuhara, Chlorination of bisphenol A in aqueous media: formation of chlorinated bisphenol A congeners and degradation to chlorinated phenolic compounds, Chemosphere 46 (2002) 1215–1223.

[36] H.M. Koch, B. Rossabach, H. Drexler, J. Agerer, Internal exposure of the general population to DEHP and other phthalates–determination of secondary and primary phthalate monoester metabolites in urine, Environ. Res. 93 (2003) 177–185.

[37] B.C. Blount, K.E. Milgram, M.J. Silva, N.A. Malek, J.A. Reidy, L.L. Needham, J.W. Brock, Quantitative detection of eight phthalate metabolites in human urine using HPLC-APCI-MS/MS, Anal. Chem. 72 (2000) 4127–4134.

[38] Phthalates, TEACH Chemical Summary. U.S. EPA, Toxicity and Exposure Assessment for Children's Health. Available at: http://www.epa.gov/teach/chem_summ/phthalates_summary.pdf.

[39] D. Błędzka, J. Gromadzińska, W. Wąsowicz, Parabens. From environmental studies to human health, Environ. Int. 67 (2014) 27–42.

[40] L. Casas, M.F. Fernández, S. Llop, M. Guxens, F. Ballester, N. Olea, M.B. Irurzun, L.S. Rodríguez, I. Riaño, A. Tardón, M. Vrijheid, A.M. Calafat, J. Sunyer, Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children, Environ. Int. 37 (2011) 858–866.

[41] M. Kasper-Sonnenberg, J. Wittsiepe, H.M. Koch, H. Fromme, M. Wilhelm, Determination of bisphenol A in urine from mother-child pairs-results from the Duisburg birth cohort study, Germany, J. Toxicol. Environ. Health, Part A 75 (2012) 429–437.

[42] K.W. Smith, J.M. Braun, P.L. Williams, S. Ehrlich, K.F. Correia, A.M. Calafat, X. Ye, J. Ford, M. Keller, J.D. Meeker, R. Hauser, Predictors and variability of urinary paraben concentrations in men and women, including before and during pregnancy, Environ. Health Perspect. 120 (2012) 1538–1543.

[43] M. Casas, D. Valvi, N. Luque, A. Ballesteros-Gómez, A.E. Carsin, M.F. Fernández, H.M. Koch, M.A. Méndez, J. Sunyer, S. Rubio, M. Vrijheid, Dietary and sociodemographic determinants of bisphenol A urine concentrations in pregnant women and children, Environ. Int. 56 (2013) 10–18.

[44] H. Frederiksen, J.K.S. Nielsen, T.A. Moerck, P.W. Hansen, J.F. Jensen, O. Nielsen, A.M. Andersson, L.E. Knudsen, Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs, Int. J. Hyg. Environ. Health 216 (2013) 772–783.

[45] S. Kang, S. Kim, J. Park, H.J. Kim, J. Lee, G. Choi, S. Choi, S. Kim, S.Y. Kim, H.B. Moon, S. Kim, Y.L. Kho, K. Choi, Urinary paraben concentrations among pregnant women and their matching newborn infants of Korea, and the association with oxidative stress biomarkers, Sci. Total Environ. 461–462 (2013) 214–221.

[46] J.D. Meeker, D.E. Cantonwine, L.O. Rivera-González, K.K. Ferguson, B. Mukherjee, A.M. Calafat, X. Ye, L.V.A. Del Toro, N. Crespo-Hernández, B. Jiménez-Vélez, A.N. Alshawabkeh, J.F. Cordero, Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico, Environ. Sci. Technol. 47 (2013) 3439–3447.

[47] L. Quirós-Alcalá, B. Eskenazi, A. Bradman, X. Ye, A.M. Calafat, K. Harley, Determinants of urinary bisphenol A concentrations in Mexican/Mexican-American pregnant women, Environ. Int. 59 (2013) 152–160.

[48] S. Shirai, Y. Suzuki, J. Yoshinaga, H. Shiraishi, Y. Mizumoto, Urinary excretion of parabens in pregnant Japanese women, Reprod. Toxicol. 35 (2013) 96–101.

[49] J. Högberg, A. Hanberg, M. Berglund, S. Skerfving, M. Remberger, A. Calafat, A.F. Filipsson, B. Jansson, N. Johansson, M. Appelgren, H. Håkansson, Phthalate diesters and their metabolites in human breast milk, blood or serum and

urine as biomarkers of exposure in vulnerable populations, Environ. Health Perspect. 116 (2008) 334–339.
[50] S.M. Duty, K. Mendonca, R. Hauser, A.M. Calafat, X. Ye, J.D. Meeker, R. Ackerman, J. Cullinane, J. Faller, S. Ringer, Potential sources of bisphenol A in the neonatal intensive care unit, Pediatrics 113 (2013) 483–489.
[51] R. Rodríguez-Gómez, M. Roldán-Pijuán, R. Lucena, S. Cárdenas, A. Zafra-Gómez, O. Ballesteros, A. Navalón, M. Valcárcel, Stir-membrane solid-liquid-liquid microextraction for the determination of parabens in human breast milk samples by ultra high performance liquid chromatography-tandem mass spectrometry, J. Chromatogr. A 1354 (2014) 26–33.
[52] T.E. Arbuckle, L. Weiss, M. Fisher, R. Hauser, P. Dumas, R. Bérubé, A. Neisa, A. LeBlanc, C. Lang, P. Ayotte, M. Walker, M. Feeley, D. Koniecki, G. Tawagi, Maternal and infant exposure to environmental phenols as measured in multiple biological matrices, Sci. Total Environ. 508 (2015) 575–584.
[53] T. Felix, B.J. Hall, J.S. Brodbelt, Determination of benzophenone-3 and metabolites in water and human urine by solid-phase microextraction and quadrupole ion trap GC–MS, Anal. Chim. Acta 371 (1998) 195–203.
[54] J.W. Brock, Y. Yoshimura, J.R. Barr, V.L. Maggio, S.R. Graiser, H. Nakazawa, L.L. Needham, Measurement of bisphenol A levels in human urine, J. Expo. Anal. Environ. Epidemiol. 11 (2001) 323–328.
[55] K. Ouchi, S. Watanabe, Measurement of bisphenol A in human urine using liquid chromatography with multi-channel coulometric electrochemical detection, J. Chromatogr. B 780 (2002) 365–370.
[56] K. Inoue, M. Kawaguchi, Y. Funakoshi, H. Nakazawa, Size-exclusion flow extraction of bisphenol A in human urine for liquid chromatography-mass spectrometry, J. Chromatogr. B 798 (2003) 17–23.
[57] Z. Kuklenyik, J. Ekong, C.D. Cutchins, L.L. Needham, A.M. Calafat, Simultaneous measurement of urinary bisphenol A and alkylphenols by automated solid-phase extractive derivatization gas chromatography/mass spectrometry, Anal. Chem. 75 (2003) 6820–6825.
[58] T. Tsukioka, J. Brock, S. Graiser, J. Nguyen, H. Nakazawa, T. Makino, Determination of trace amounts of bisphenol A in urine by negative-ion chemical-ionization-gas chromatography/mass spectrometry, Anal. Sci. 19 (2003) 151–153.
[59] L. Mao, C. Sun, H. Zhang, Y. Li, D. Wu, Determination of environmental estrogens in human urine by high performance liquid chromatography after fluorescent derivatization with p-nitrobenzoyl chloride, Anal. Chim. Acta 522 (2004) 241–246.
[60] K. Kato, M.J. Silva, L.L. Needham, A.M. Calafat, Determination of 16 phthalate metabolites in urine using automated sample preparation and on-line preconcentration/high-performance liquid chromatography/tandem mass spectrometry, Anal. Chem. 77 (2005) 2985–2991.
[61] M. Kawaguchi, N. Sakui, N. Okanouchi, R. Ito, K. Saito, S.I. Izumi, T. Makino, H. Nakazawa, Stir bar sorptive extraction with in situ derivatization and thermal desorption-gas chromatography-mass spectrometry for measurement of phenolic xenoestrogens in human urine samples, J. Chromatogr. B 820 (2005) 49–57.
[62] Z. Liu, M.S. Wolff, J. Moline, Analysis of environmental biomarkers in urine using an electrochemical detector, J. Chromatogr. B 819 (2005) 155–159.
[63] X. Ye, Z. Kuklenyik, L.L. Needham, A.M. Calafat, Automated on-line column-switching HPLC–MS/MS method with peak focusing for the determination of nine environmental phenols in urine, Anal. Chem. 77 (2005) 5407–5413.
[64] X. Ye, Z. Kuklenyik, A.M. Bishop, L.L. Needham, A.M. Calafat, Quantification of the urinary concentrations of parabens in humans by on-line solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry, J. Chromatogr. B 844 (2006) 53–59.
[65] K. Schoeringhumer, M. Cichna-Markl, Sample clean-up with sol-gel enzyme and immunoaffinity columns for the determination of bisphenol A in human urine, J. Chromatogr. B 850 (2007) 361–369.
[66] L. Vidal, A. Chisvert, A. Canals, A. Salvador, Sensitive determination of free benzophenone-3 in human urine samples based on an ionic liquid as extractant phase in single-drop microextraction prior to liquid chromatography analysis, J. Chromatogr. A 1174 (2007) 95–103.
[67] A. García-Prieto, M.L. Lunar, S. Rubio, D. Pérez-Bendito, Determination of urinary bisphenol A by coacervative microextraction and liquid chromatography-fluorescence detection, Anal. Chim. Acta 630 (2008) 19–27.
[68] N.R. Janjua, H. Frederiksen, N.E. Skakkebaek, H.C. Wulf, A.M. Andersson, Urinary excretion of phthalates and paraben after repeated whole-body topical application in humans, Int. J. Androl. 31 (2008) 118–130.
[69] M. Kawaguchi, R. Ito, H. Honda, N. Endo, N. Okanouchi, K. Saito, Y. Seto, H. Nakazawa, Measurement of benzophenones in human urine samples by stir bar sorptive extraction and thermal desorption-gas chromatography-mass spectrometry, Anal. Sci. 24 (2008) 1509–1512.
[70] M. Kawaguchi, R. Ito, N. Okanouchi, K. Saito, H. Nakazawa, Miniaturized hollow fiber assisted liquid-phase microextraction with in situ derivatization and gas chromatography-mass spectrometry for analysis of bisphenol A in human urine sample, J. Chromatogr. B 870 (2008) 98–102.
[71] T. Geens, H. Neels, A. Covaci, Sensitive and selective method for the determination of bisphenol-A and triclosan in serum and urine as pentafluorobenzoate-derivatives using GC–ECNI/MS, J. Chromatogr. B 877 (2009) 4042–4046.
[72] R. Ito, M. Kawaguchi, Y. Koganei, H. Honda, N. Okanouchi, N. Sakui, K. Saito, H. Nakazawa, Development of miniaturized hollow-fiber assisted liquid-phase microextraction with in situ acyl derivatization followed by GC–MS for the determination of benzophenones in human urine samples, Anal. Sci. 25 (2009) 1033–1037.
[73] F. Tan, H. Zhao, X. Li, X. Quan, J. Chen, X. Xiang, X. Zhang, Preparation and evaluation of molecularly imprinted solid-phase microextraction fibers for selective extraction of bisphenol A in complex samples, J. Chromatogr. A 1216 (2009) 5647–5654.
[74] A.M. Calafat, X. Ye, L.Y. Wong, A.M. Bishop, L.L. Needham, Urinary concentrations of four parabens in the U.S. population: NHANES 2005-2006, Environ. Health Perspect. 118 (2010) 679–685.
[75] S.C. Cunha, J.O. Fernandes, Quantification of free and total bisphenol A and bisphenol B in human urine by dispersive liquid-liquid microextraction (DLLME) and heart-cutting multidimensional gas chromatography-mass spectrometry (MD-GC/MS), Talanta 83 (2010) 117–125.
[76] T. Kunisue, Q. Wu, S. Tanabe, K.M. Aldous, K. Kannan, Analysis of five benzophenone-type UV filters in human urine by liquid chromatography-tandem mass spectrometry, Anal. Methods 2 (2010) 707–713.
[77] Z. León, A. Chisvert, A. Balaguer, A. Salvador, Development of a fully automated sequential injection solid-phase extraction procedure coupled to liquid chromatography to determine free 2-hydroxy-4-methoxybenzophenone and 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid in human urine, Anal. Chim. Acta 664 (2010) 178–184.
[78] Z. León, A. Chisvert, I. Tarazona, A. Salvador, Solid-phase extraction liquid chromatography-tandem mass spectrometry analytical method for the determination of 2-hydroxy-4-methoxybenzophenone and its metabolites in both human urine and semen, Anal. Bioanal. Chem. 398 (2010) 831–843.
[79] M.S. Wolff, S.L. Teitelbaum, S.M. Pinney, G. Windham, L. Liao, F. Biro, L.H. Kushi, C. Erdmann, R.A. Hiatt, M.E. Rybak, A.M. Calafat, Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls, Environ. Health Perspect. 118 (2010) 1039–1046.
[80] M.K. Morgan, P.A. Jones, A.M. Calafat, X. Ye, C.W. Croghan, J.C. Chuang, N.K. Wilson, M.S. Clifton, Z. Figueroa, L.S. Sheldon, Assessing the quantitative relationships between preschool children's exposures to bisphenol A by route and urinary biomonitoring, Environ. Sci. Technol. 45 (2011) 5309–5316.
[81] H. Frederiksen, N. Jorgensen, A.M. Andersson, Parabens in urine, serum and seminal plasma from healthy Danish men determined by liquid chromatography-tandem mass spectrometry (LC–MS/MS), J. Expo. Sci. Environ. Epidemiol. 21 (2011) 262–271.
[82] S. Mei, D. Wu, M. Jiang, B. Lu, J.M. Lim, Y.K. Zhou, Y.I. Lee, Determination of trace bisphenol A in complex samples using selective molecularly imprinted solid-phase extraction coupled with capillary electrophoresis, Microchem. J. 98 (2011) 150–155.
[83] J. Xiao, B. Shao, X.Y. Wu, X.J. Sun, Y.N. Wu, A study on bisphenol A, nonylphenol, and octylphenol in human urine samples detected by SPE-UPLC-MS, Biomed. Environ. Sci. 24 (2011) 40–46.
[84] M. Chen, L. Tao, E.M. Collins, C. Austin, C. Lu, Simultaneous determination of multiple phthalate metabolites and bisphenol-A in human urine by liquid chromatography-tandem mass spectrometry, J. Chromatogr. B 904 (2012) 73–80.
[85] S.J. Genuis, S. Beesoon, D. Birkholz, R.A. Lobo, Human excretion of bisphenol A: blood, urine, and sweat (BUS) study, J. Environ. Public Health (2012) 10, 185731.
[86] C. Liao, K. Kannan, Determination of free and conjugated forms of bisphenol A in human urine and serum by liquid chromatography-tandem mass spectrometry, Environ. Sci. Technol. 46 (2012) 5003–5009.
[87] H. Wang, H. Yan, C. Wang, F. Chen, M. Ma, W. Wang, X. Wang, Analysis of phenolic pollutants in human samples by high performance capillary electrophoresis based on pretreatment of ultrasound-assisted emulsification microextraction and solidification of floating organic droplet, J. Chromatogr. A 1253 (2012) 16–21.
[88] H. Frederiksen, L. Aksglaede, K. Sorensen, O. Nielsen, M. Main Katharina, E. Skakkebaek Niels, A. Juul, A.M. Andersson, Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MS/MS, Int. J. Hyg. Environ. Health 216 (2013) 710–720.
[89] W.L. Ma, L. Wang, Y. Guo, L.Y. Liu, H. Qi, N.Z. Zhu, C.J. Gao, Y.F. Li, K. Kannan, Urinary concentrations of parabens in chinese young adults: Implications for human exposure, Arch. Environ. Contam. Toxicol. 65 (2013) 611–618.
[90] N. Rastkari, R. Ahmadkhaniha, Magnetic solid-phase extraction based on magnetic multi-walled carbon nanotubes for the determination of phthalate monoesters in urine samples, J. Chromatogr. A 1286 (2013) 22–28.
[91] W. Zhang, H. Sun, K. Kannan, Blood and urinary bisphenol A concentrations in children, adults, and pregnant women from China: Partitioning between blood and urine and maternal and fetal cord blood, Environ. Sci. Technol. 47 (2013) 4686–4694.
[92] H.X. Wang, B. Wang, Y. Zhou, Q.W. Jiang, Rapid and sensitive analysis of phthalate metabolites, bisphenol A, and endogenous steroid hormones in human urine by mixed-mode solid-phase extraction, dansylation, and ultra-performance liquid chromatography coupled with triple quadrupole mass spectrometry, Anal. Bioanal. Chem. 405 (2013) 4313–4319.
[93] L. Wang, Y. Wu, W. Zhang, K. Kannan, Characteristic profiles of urinary p-hydroxybenzoic acid and its esters (parabens) in children and adults from the United States and China, Environ. Sci. Technol. 47 (2013) 2069–2076.
[94] G. Leng, H.M. Koch, W. Gries, A. Schuetze, A. Langsch, T. Bruening, R. Otter, Urinary metabolite excretion after oral dosage of bis(2-propylheptyl) phthalate (DPHP) to five male volunteers – characterization of suitable

biomarkers for human biomonitoring, Toxicol. Lett. 231 (2014) 282–288.
[95] F. Vela-Soria, O. Ballesteros, A. Zafra-Gómez, L. Ballesteros, A. Navalón, UHPLC-MS/MS method for the determination of bisphenol A and its chlorinated derivatives, bisphenol S, parabens, and benzophenones in human urine samples, Anal. Bioanal. Chem. 406 (2014) 3773–3785.
[96] F. Vela-Soria, O. Ballesteros, A. Zafra-Gómez, L. Ballesteros, A. Navalón, A multiclass method for the analysis of endocrine disrupting chemicals in human urine samples. Sample treatment by dispersive liquid-liquid microextraction, Talanta 129 (2014) 209–218.
[97] F. Venisse, C. Grignon, B. Brunet, S. Thévenot, A. Bacle, V. Migeot, A. Dupuis, Reliable quantification of bisphenol A and its chlorinated derivatives in human urine using UPLC–MS/MS method, Talanta 125 (2014) 284–292.
[98] L. Herrero, S. Calvarro, M.A. Fernández, J.E. Quintanilla-López, M.J. González, B. Gomara, Feasibility of ultra-high performance liquid and gas chromatography coupled to mass spectrometry for accurate determination of primary and secondary phthalate metabolites in urine samples, Anal. Chim. Acta 853 (2015) 625–636.
[99] E.J. Carrasco-Correa, F. Vela-Soria, O. Ballesteros, G. Ramis-Ramos, J.M. Herrero-Martínez, Sensitive determination of parabens in human urine and serum using methacrylate monoliths and reversed-phase capillary liquid chromatography–mass spectrometry, J. Chromatogr. A 1379 (2015) 65–73.
[100] H. Yamada, I. Furuta, E.H. Kato, S. Kataoka, Y. Usuki, G. Kobashi, F. Sata, R. Kishi, S. Fujimoto, Maternal serum and amniotic fluid bisphenol A concentrations in the early second trimester, Reprod. Toxicol. 16 (2002) 735–739.
[101] N. Kuroda, Y. Kinoshita, Y. Sun, M. Wada, N. Kishikawa, K. Nakashima, T. Makino, H. Nakazawa, Measurement of bisphenol A levels in human blood serum and ascetic fluid by HPLC using a fluorescent labeling reagent, J. Pharm. Biomed. Anal. 30 (2003) 1743–1749.
[102] I. Kosarac, C. Kubwabo, K. Lalonde, W. Foster, A novel method for the quantitative determination of free and conjugated bisphenol A in human maternal and umbilical cord blood serum using a two-step solid phase extraction and gas chromatography/tandem mass spectrometry, J. Chromatogr. B 898 (2012) 90–94.
[103] K. Inoue, K. Kato, Y. Yoshimura, T. Makino, H. Nakazawa, Determination of bisphenol A in human serum by high-performance liquid chromatography with multi-electrode electrochemical detection, J. Chromatogr. B 749 (2000) 17–23.
[104] Y. Yoshimura, J.W. Brock, T. Makino, H. Nakazawa, Measurement of bisphenol A in human serum by gas chromatography/mass spectrometry, Anal. Chim. Acta 458 (2002) 331–336.
[105] K. Inoue, M. Kawaguchi, F. Okada, Y. Yoshimura, H. Nakazawa, Column-switching high-performance liquid chromatography electrospray mass spectrometry coupled with on-line of extraction for the determination of mono- and di-(2-ethylhexyl) phthalate in blood samples, Anal. Bioanal. Chem. 375 (2003) 527–533.
[106] K. Kato, M.J. Silva, J.W. Brock, J.A. Reidy, N.A. Malek, C.C. Hodge, H. Nakazawa, L.L. Needham, D.B. Barr, Quantitative detection of nine phthalate metabolites in human serum using reversed-phase high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry, J. Anal. Toxicol. 27 (2003) 284–289.
[107] I. Colon, J.M.D. Dimandja, High-throughput analysis of phthalate esters in human serum by direct immersion SPME followed by isotope dilution-fast GC/MS, Anal. Bioanal. Chem. 380 (2004) 275–283.
[108] S. Takatori, Y. Kitagawa, M. Kitagawa, H. Nakazawa, S. Hori, Determination of di(2-ethylhexyl)phthalate and mono(2-ethylhexyl)phthalate in human serum using liquid chromatography-tandem mass spectrometry, J. Chromatogr. B 804 (2004) 397–401.
[109] M.J. Silva, E. Samandar, J.L. Preau Jr., J.A. Reidy, L.L. Needham, A.M. Calafat, Automated solid-phase extraction and quantitative analysis of 14 phthalate metabolites in human serum using isotope dilution-high-performance liquid chromatography-tandem mass spectrometry, J. Anal. Toxicol. 29 (2005) 819–824.
[110] A.C. Dirtu, L. Roosens, T. Geens, A. Gheorghe, H. Neels, R. Blust, A. Covaci, Determination of bisphenol-A, triclosan and tetrabromobisphenol-A in human serum using SPE and GC/ECNI-MS, Organohalogen Compd. 69 (2007), 347/1–347/4.
[111] X. Ye, L.J. Tao, L.L. Needham, A.M. Calafat, Automated on-line column-switching HPLC-MS/MS method for measuring environmental phenols and parabens in serum, Talanta 76 (2008) 865–871.
[112] L. Cobellis, N. Colacurci, E. Trabucco, C. Carpentiero, L. Grumetto, Measurement of bisphenol A and bisphenol B levels in human blood sera from healthy and endometriotic women, Biomed. Chromatogr. 23 (2009) 1186–1190.
[113] Z.Y. Guo, P.P. Gai, J. Duan, J.X. Zhai, S.S. Zhao, S. Wang, D.Y. Wei, Simultaneous determination of phthalates and adipates in human serum using gas chromatography-mass spectrometry with solid-phase extraction, Biomed. Chromatogr. 24 (2010) 1094–1099.
[114] T.M. Sandanger, S. Huber, M.K. Moe, T. Braathen, H. Leknes, E. Lund, Plasma concentrations of parabens in postmenopausal women and self-reported use of personal care products: the NOWAC postgenome study, J. Expo. Sci. Environ. Epidemiol. 21 (2011) 595–600.
[115] F. Vela-Soria, O. Ballesteros, I. Rodríguez, A. Zafra-Gómez, L. Ballesteros, R. Cela, A. Navalón, A new treatment by dispersive liquid-liquid microextraction for the determination of parabens in human serum samples, Anal. Bioanal. Chem. 405 (2013) 7259–7267.
[116] F. Vela-Soria, O. Ballesteros, A. Zafra-Gómez, L. Ballesteros, A. Navalón, A new method for the determination of benzophenone-UV filters in human serum samples by dispersive liquid-liquid microextraction with liquid chromatography-tandem mass spectrometry, Talanta 121 (2014) 97–104.
[117] Y. Ikezuki, O. Tsutsumi, Y. Takai, Y. Kamei, Y. Taketani, Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure, Hum. Reprod. 17 (2002) 2839–2841.
[118] G. Schonfelder, W. Wittfoht, H. Hopp, C.E. Talness, M. Paul, I. Chahoud, Parent bisphenol A accumulation in the human maternal-foetal-placental unit, Environ. Health Perspect. 110 (2002) 703–707.
[119] B.L.L. Tan, M.A. Mohd, Analysis of selected pesticides and alkylphenols in human cord blood by gas chromatograph-mass spectrometer, Talanta 61 (2003) 385–391.
[120] M.J. Silva, J.A. Reidy, A.R. Herbert, J.L. Preau, L.L. Needham, A.M. Calafat, Detection of phthalate metabolites in human amniotic fluid, Bull. Environ. Contam. Toxicol. 72 (2004) 1226–1231.
[121] K. Kato, M.J. Silva, L.L. Needham, A.M. Calafat, Quantifying phthalate metabolites in human meconium and semen using automated off-line solid-phase extraction coupled with on-line SPE and isotope-dilution high-performance liquid chromatography-tandem mass spectrometry, Anal. Chem. 78 (2006) 6651–6655.
[122] T. Mose, G.K. Mortensen, M. Hedegaard, L.E. Knudsen, Phthalate monoesters in perfusate from a dual placenta perfusion system, the placenta tissue and umbilical cord blood, Reprod. Toxicol. 23 (2007) 83–91.
[123] Y.J. Lee, H. Ryu, H. Kim, C.S. Min, J.H. Lee, E. Kim, B.H. Nam, J.H. Park, J.Y. Jung, D.D. Jang, E.Y. Park, K. Lee, J. Ma, H. Won, M. Im, J. Leem, Y. Hong, H. Yoon, Maternal and foetal exposure to bisphenol A in Korea, Reprod. Toxicol. 25 (2008) 413–419.
[124] P.C. Huang, P.L. Kuo, Y.Y. Chou, S.J. Lin, C.C. Lee, Association between prenatal exposure to phthalates and the health of newborns, Environ. Int. 35 (2009) 14–20.
[125] M. Wittassek, J. Angerer, M. Kolossa-Gehring, S.D. Schäfer, W. Klockenbusch, L. Dobler, A.K. Günsel, A. Müller, G.A. Wiesmuller, Foetal exposure to phthalates -a pilot study, Int. J. Hyg. Environ. Health 212 (2009) 492–498.
[126] Y. Zhang, L. Lin, Y. Cao, B. Chen, L. Zheng, R.S Ge, Phthalate levels and low birth weight: a nested case-control study of Chinese newborns, J. Pediatr. 155 (2009) 500–504.
[127] Y. Wan, K. Choi, S. Kim, K. Ji, P. Chang, S. Wiseman, P.D. Jones, J.S. Khim, S. Park, J. Park, M.H.W. Lam, J.P. Giesy, Hydroxylated polybrominated diphenyl ethers and bisphenol A in pregnant women and their matching foetuses: placental transfer and potential risks, Environ. Sci. Technol. 44 (2010) 5233–5239.
[128] I. Jiménez-Díaz, A. Zafra-Gómez, O. Ballesteros, N. Navea, A. Navalón, M.F. Fernández, N. Olea, J.L. Vílchez, Determination of bisphenol A and its chlorinated derivatives in placental tissue samples by liquid chromatography-tandem mass spectrometry, J. Chromatogr. B 878 (2010) 3363–3369.
[129] J. Zhang, G.M. Cooke, I.H.A. Curran, C.G. Goodyer, X.L. Cao, GC–MS analysis of bisphenol A in human placental and foetal liver samples, J. Chromatogr. B 879 (2011) 209–214.
[130] W.C. Chou, J.L. Chen, C.F. Lin, Y.C. Chen, F.C. Shih, C.Y. Chuang, A concentrations in maternal and umbilical cord blood in regard to birth outcomes and adipokine expression: a birth cohort study in Taiwan, Environ. Health 10 (94) (2011) 1–10.
[131] S. Lin, H.Y. Ku, P.H. Su, J.W. Chen, P.C. Huang, J. Angerer, S.L. Wang, Phthalate exposure in pregnant women and their children in central Taiwan, Chemosphere 82 (2011) 947–955.
[132] F. Vela-Soria, I. Jiménez-Díaz, R. Rodríguez-Gómez, A. Zafra-Gómez, O. Ballesteros, A. Navalón, J.L. Vílchez, M.F. Fernández, N. Olea, Determination of benzophenones in human placental tissue samples by liquid chromatography-tandem mass spectrometry, Talanta 85 (2011) 1848–1855.
[133] I. Jiménez-Díaz, F. Vela-Soria, A. Zafra-Gómez, A. Navalón, O. Ballesteros, N. Navea, M.F. Fernández, N. Olea, J.L. Vílchez, A new liquid chromatography-tandem mass spectrometry method for the determination of parabens in human placental tissue samples, Talanta 84 (2011) 702–709.
[134] A.G. Edlow, M. Chen, N.A. Smith, C. Lu, T.F. McElrath, Foetal bisphenol A exposure: concentration of conjugated and free bisphenol A in amniotic fluid in the second and third trimesters, Reprod. Toxicol. 34 (2012) 1–7.
[135] M. Chen, A.G. Edlow, T. Lin, N.A. Smith, T.F. McElrath, C. Lu, Determination of bisphenol-A levels in human amniotic fluid samples by liquid chromatography coupled with mass spectrometry, J. Sep. Sci. 34 (2011) 1648–1655.
[136] X.L. Cao, J. Zhang, C.G. Goodyer, S. Hayward, G.M. Cooke, I.H.A. Curran, Bisphenol A in human placental and foetal liver tissues collected from Greater Montreal area (Quebec) during 1998–2008, Chemosphere 89 (2012) 505–511.
[137] M.S. Jensen, B. Nørgaard-Pedersen, G. Toft, D.M. Hougaard, J.P. Bonde, A. Cohen, A.M. Thulstrup, R. Ivell, R. Anand-Ivell, C.H. Lindh, B.A.G. Jönsson, Phthalates and perfluorooctanesulfonic acid in human amniotic fluid: temporal trends and timing of amniocentesis in pregnancy, Environ. Health Perspect. 120 (2012) 897–903.
[138] L.X. Li, L. Chen, X.Z. Meng, B.H. Chen, S.Q. Chen, Y. Zhao, L.F. Zhao, Y. Liang, Y.H. Zhang, Exposure levels of environmental endocrine disruptors in mother-newborn pairs in China and their placental transfer characteristics, PLoS one 8 (2013) e62526 1–9.

[139] I. Jiménez-Díaz, J.M. Molina-Molina, A. Zafra-Gómez, O. Ballesteros, A. Navalón, M. Real, J.M. Sáenz, M.F. Fernández, N. Olea, Simultaneous determination of the UV-filters benzyl salicylate, phenyl salicylate, octyl salicylate, homosalate, 3-(4-methylbenzylidene) camphor and 3-benzylidene camphor in human placental tissue by LC–MS/MS. Assessment of their *in vitro* endocrine activity, J. Chromatogr. B 936 (2013) 80–87.
[140] T. Zhang, H. Sun, X. Qin, Q. Wu, Y. Zhang, J. Ma, K. Kannan, Benzophenone-type UV filters in urine and blood from children, adults, and pregnant women in China: partitioning between blood and urine as well as maternal and foetal cord blood, Sci. Total Environ. 461–462 (2013) 49–55.
[141] C. Philippat, M.S. Wolff, A.M. Calafat, X. Ye, R. Bausell, M. Meadows, J. Stone, R. Slama, S.M. Engel, Prenatal exposure to environmental phenols: concentrations in amniotic fluid and variability in urinary concentrations during pregnancy, Environ. Health Perspect. 121 (2013) 1225–1231.
[142] L. Mathiesen, G. Zuri, M.H. Andersen, L.E. Knudsen, A proposed study on the transplacental transport of parabens in the human placental perfusion model, ATLA 41 (2013) 473–482.
[143] Y. Huang, J. Li, J.M. Garcia, H. Lin, Y. Wang, P. Yan, L. Wang, Y. Tan, J. Luo, Z. Qiu, J. Chen, W. Shu, Phthalate levels in cord blood are associated with preterm delivery and foetal growth parameters in Chinese women, PLoS One 9 (2014) 1–8 e87430.
[144] A. Cappiello, G. Famiglini, P. Palma, V. Termopoli, A.M. Lavezzi, L. Matturri, Determination of selected endocrine disrupting compounds in human foetal and newborn tissues by GC–MS, Anal. Bioanal. Chem. 406 (2014) 2779–2788.
[145] A. Aris, Estimation of bisphenol A (BPA) concentrations in pregnant women, fetuses and nonpregnant women in Eastern Townships of Canada, Reprod. Toxicol. 45 (2014) 8–13.
[146] F. Vela-Soria, I. Rodríguez, O. Ballesteros, A. Zafra-Gómez, L. Ballesteros, R. Cela, A. Navalón, Simplified matrix solid phase dispersion procedure for the determination of parabens and benzophenone-ultraviolet filters in human placental tissue samples, J. Chromatogr. A 1371 (2014) 39–47.
[147] F. Vela-Soria, O. Ballesteros, F.J. Camino-Sánchez, A. Zafra-Gómez, L. Ballesteros, A. Navalón, Matrix solid phase dispersion for the extraction of selected endocrine disrupting chemicals from human placental tissue prior to UHPLC-MS/MS analysis, Microchem. J. 118 (2015) 32–39.
[148] H. Otaka, A. Yasuhara, M. Morita, Determination of bisphenol A and 4-nonylphenol in human milk using alkaline digestion and cleanup by solid-phase extraction, Anal. Sci. 19 (2003) 1663–1666.
[149] Y. Sun, M. Irie, N. Kishikawa, M. Wada, N. Kuroda, K. Nakashima, Determination of bisphenol A in human breast milk by HPLC with column-switching and fluorescence detection, Biomed. Chromatogr. 18 (2004) 501–507.
[150] A.M. Calafat, A.R. Slakman, M.J. Silva, A.R. Herbert, L.L. Needham, Automated solid phase extraction and quantitative analysis of human milk for 13 phthalate metabolites, J. Chromatogr. B 805 (2004) 49–56.
[151] G.K. Mortensen, K.M. Main, A.M. Andersson, H. Leffers, N.E. Skakkebæk, Determination of phthalate monoesters in human milk, consumer milk, and infant formula by tandem mass spectrometry (LC-MS-MS), Anal. Bioanal. Chem. 382 (2005) 1084–1092.
[152] X. Ye, Z. Kuklenyik, L.L. Needham, A.M. Calafat, Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry, J. Chromatogr. B 831 (2006) 110–115.
[153] R. Kuruto-Niwa, Y. Tateoka, Y. Usuki, R. Nozawa, Measurement of bisphenol A concentrations in human colostrum, Chemosphere 66 (2007) 1160–1164.
[154] X. Ye, A.M. Bishop, L.L. Needham, A.M. Calafat, Automated on-line column-switching HPLC–MS/MS method with peak focusing for measuring parabens, triclosan, and other environmental phenols in human milk, Anal. Chim. Acta 622 (2008) 150–156.
[155] M. Schlumpf, K. Kypke, C.C. Vökt, M. Birchler, S. Durrer, O. Faassb, C. Ehnes, M. Fuetsch, C. Gaille, M. Henseler, L. Hofkamp, K. Maerkel, S. Reolon, A. Zenker, B. Timms, J.A.F. Tresguerres, W. Lichtensteiger, Endocrine active UV filters: developmental toxicity and exposure through breast milk, Chimia 62 (2008) 345–351.
[156] B. Yia, C. Kim, M. Yang, Biological monitoring of bisphenol A with HPLC/FLD and LC/MS/MS assays, J. Chromatogr. B 878 (2010) 2606–2610.
[157] A. Cariot, A. Dupuis, M. Albouy-Llaty, B. Legube, S. Rabouana, V. Migeot, Reliable quantification of bisphenol A and its chlorinated derivatives in human breast milk using UPLC–MS/MS method, Talanta 100 (2012) 175–182.
[158] V. Migeot, A. Dupuis, A. Cariot, M. Albouy-Llaty, F. Pierre, S. Rabouan, Bisphenol A and its chlorinated derivatives in human colostrum, Environ. Sci. Technol. 47 (2013) 13791–13797.
[159] L.P. Melo, M.E.C. Queiroz, A molecularly imprinted polymer for microdisc solid- phase extraction of parabens from human milk samples, Anal. Methods 5 (2013) 3538–3545.
[160] B. Yi, C. Kim, M. Park, Y. Han, J.Y. Park, M. Yang, Association between endocrine disrupting phenols in colostrums and maternal and infant health, Int. J. Endocrinol. 2013 (2013) 1–7.
[161] S.M. Zimmers, E.P. Browne, P.W. O'Keefe, D.L. Anderton, L. Kramer, D.A. Reckhow, K.F. Arcaro, Determination of free Bisphenol A (BPA) concentrations in breast milk of U.S. women using a sensitive LC/MS/MS method, Chemosphere 104 (2014) 237–243.
[162] R. Rodríguez-Gómez, I. Jiménez-Díaz, A. Zafra-Gómez, O. Ballesteros, A. Navalón, A multi-residue method for the determination of selected endocrine disrupting chemicals in human breast milk based on a simple extraction procedure, Talanta 130 (2014) 561–570.
[163] X.L. Cao, S. Popovic, T.E. Arbuckle, W.D. Fraser, Determination of free and total bisphenol A in human milk samples from Canadian women using a sensitive and selective GC–MS method, Food Addit. Contam. A (2014) 1–6.
[164] K. Mendonca, R. Hauser, A.M. Calafat, T.E. Arbuckle, S.M. Duty, Bisphenol A concentrations in maternal breast milk and infant urine, Int. Arch. Occup. Environ. Health 87 (2014) 13–20.
[165] V.F. Samanidou, M.A. Frysali, I.N. Papadoyannis, Matrix solid phase dispersion for the extraction of Bisphenol A from human breast milk prior to HPLC analysis, J. Liq. Chromatogr. R. T 37 (2014) 247–258.
[166] R. Rodríguez-Gómez, A. Zafra-Gómez, N. Dorival-García, O. Ballesteros, A. Navalón, Determination of benzophenone-UV filters in human milk samples using ultrasound-assisted extraction and clean-up with dispersive sorbents followed by UHPLC–MS/MS analysis, Talanta 134 (2015) 657–664.
[167] E.P. Hines, P. Mendola, O.S. von Ehrenstein, X. Ye, A.M. Calafat, S.E. Fenton, Concentrations of environmental phenols and parabens in milk, urine and serum of lactating North Carolina women, Reprod. Toxicol. 54 (2015) 120–128.
[168] Y. Deceuninck, E. Bichon, P. Marchand, C.Y. Boquien, A. Legrand, C. Boscher, J.P. Antignac, B. Le Bizec, Determination of bisphenol A and related substitutes/analogues in human breast milk using gas chromatography-tandem mass spectrometry, Anal. Bioanal. Chem. 407 (2015) 2485–2497.
[169] B. Sellergren, Noncovalent molecular imprinting: antibody-like molecular recognition in polymeric network materials, TRAC-Trends Anal. Chem. 16 (1997) 310–320.
[170] E. Baltussen, P. Sandra, F. David, C. Cramers, Stir bar sorptive extraction (SBSE), a novel extraction technique for aqueous samples: theory and principles, J. Microcolumn Sep. 10 (1999) 737–747.
[171] E. Psillakis, N. Kalogerakis, Developments in liquid-phase microextraction, TRAC-Trends Anal. Chem. 22 (2003) 565–574.
[172] M. Rezaee, Y. Yamini, M. Faraji, Evolution of dispersive liquid–liquid microextraction method, J. Chromatogr. A 1217 (2010) 2342–2357.
[173] M.C. Alcudia-León, R. Lucena, S. Cárdenas, M. Valcárcel, Stir membrane extraction: a useful approach for liquid sample pretreatment, Anal. Chem. 81 (2009) 8957–8961.
[174] S.A. Barker, A.R. Long, C.R. Short, Isolation of drug residues from tissues by solid-phase dispersion, J. Chromatogr. 475 (1989) 353–361.
[175] J.L. Tadeo, C. Sánchez-Brunete, B. Albero, A.I. García-Valcárcel, Application of ultrasound-assisted extraction to the determination of contaminants in food and soil samples, J. Chromatogr. A 1217 (2010) 2415–2440.
[176] F.J. Camino-Sánchez, R. Rodríguez-Gómez, A. Zafra-Gómez, A. Santos-Fandila, J.L. Vílchez, Stir-bar sorptive extraction. Recent applications, limitations and future trends, Talanta 130 (2014) 388–399.

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