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Review

Critical review of analytical methods for the determination of flame retardants in human matrices

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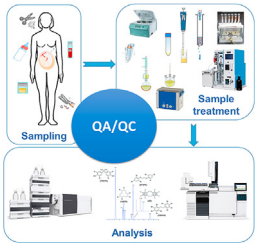
HIGHLIGHTS

- Humans are exposed to a variety of flame retardants (FRs) with different properties.
- Halogenated FRs are typically monitored as parent compounds in serum or milk.
- Phosphorous FRs are typically analyzed as metabolites in urine.
- Developments include wide-scope methods with selective and sensitive instruments.
- Quality assurance/quality control (QA/QC) is a key element in FR analysis.

GRAPHICAL ABSTRACT



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ABSTRACT

Human biomonitoring is a powerful approach in assessing exposure to environmental pollutants. Flame retardants (FRs) are of particular concern due to their wide distribution in the environment and adverse health effects. This article reviews studies published in 2009–2020 on the chemical analysis of FRs in a variety of human samples and discusses the characteristics of the analytical methods applied to different FR biomarkers of exposure, including polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCD), novel halogenated flame retardants (NHFRs), bromophenols, incl. tetrabromobisphenol A (TBBPA), and organophosphorous flame retardants (PFRs). Among the extraction techniques, liquid-liquid extraction (LLE) and solid phase extraction (SPE) were used most frequently due to the good efficiencies in the isolation of the majority of the FR biomarkers, but with challenges for highly lipophilic FRs. Gas chromatography-mass spectrometry (GC-MS) is mainly applied in the instrumental analysis of PBDEs and most NHFRs, with recent inclusions of GC-MS/MS and high resolution MS techniques. Liquid chromatography-MS/MS is mainly applied to HBCD, bromophenols, incl. TBBPA, and PFRs (including metabolites), however, GC-based analysis following derivatization has also been used for

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phenolic compounds and PFR metabolites. Developments are noticed towards more universal analytical methods, which enable widening method scopes in the human biomonitoring of FRs. Challenges exist with regard to sensitivity required for the low concentrations of FRs in the general population and limited sample material for some human matrices. A strong focus on quality assurance/quality control (QA/QC) measures is required in the analysis of FR biomarkers in human samples, related to their variety of physical-chemical properties, low levels in most human samples and the risk of contamination.

Contents

1. Introduction

Human biomonitoring is an important approach in assessing human exposure to pollutants and their potential health risks. Human biomonitoring can also evaluate time trends in concentrations, determine whether technological changes can affect human exposure, support epidemiological studies to investigate health effects or identify vulnerable groups, and evaluate the efficacy of regulatory actions [1,2]. It has been applied to a range of environmental pollutants, including flame retardants (FRs). FRs have been widely detected in humans and are related to exposure from food and the indoor environment, typically with intercontinental differences in levels in humans [3–5].

FRs are compounds added to consumer products or building materials with the aim of reducing their flammability. More than 175 chemicals are classified as FRs, which are divided into four main groups of inorganic, halogenated, organophosphorus and nitrogen-based organic FRs [6,7]. Within this group, brominated flame retardants (BFRs) have been widely used since the 1970s, due to their high trapping efficiency and suitable decomposing temperature. Additive BFRs, such as polybrominated diphenyl ethers (PBDEs) and hexabromocylododecane (HBCD), have chances of being released from the products due to their simple blending with the polymers. Reactive BFRs, on the contrary, are chemically bound to the plastic polymers. Tetrabromobisphenol A (TBBPA) is the most produced and globally consumed reactive FR [6]. Organophosphorous flame retardants (PFRs) and novel halogenated flame retardants (NHFRs) have emerged as replacements for PBDEs and HBCD since these were nationally and globally banned [8,9], and 94 different compounds were described as replacements [10].

FRs have been associated with several adverse human health effects, for instance neurotoxic effects (HBCD; PBDEs), endocrine disruption (PBDEs; TBBPA), carcinogenic effects (PBDEs; TBBPA; PFRs), cytotoxicity (PBDEs), DNA damage (HBCD), reproductive and behavioral effects (HBCD; PBDEs; TBBPA) and atopic dermatitis, asthma and allergic rhinitis (PFRs) [11–17]. PBDEs and HBCD are classified as Persistent Organic Pollutants (POPs) according to the UN Stockholm Convention, on the basis of their persistence, bioaccumulation, long-range transport and toxicity, and structurally similar FRs may also have similar properties [18]. Dechlorane plus (DDC-CO), a chlorinated FR, is currently under review for listing in the Stockholm Convention [19].

FRs have received much attention both in the research and in the policy-making communities, i.e. precise, accurate, sensitive and robust analytical methods are an important basis for research as well as decision-making in this field. However, FRs are a use-defined rather than a chemistry-defined group of compounds. Studying the human exposure to FRs includes the challenge of analyzing multiple chemically different compounds, typically involving different matrices, limited sample volumes and low analyte levels. Analytical capabilities have been constantly improved to enable detection of low levels of a variety of FRs in the environment and humans. Given the great importance of and resulting interest in FRs, several reviews on analytical methods used for the determination of FRs in biotic and abiotic samples have been published [2,8,20–22]. However, a recent comprehensive and up-to-date review of analytical methods for human biomonitoring of the vast and chemically diverse group of FRs is lacking. Such a review is useful in human biomonitoring programmes, such as HBM4EU, and in planning dedicated research projects that involve biomonitoring of FRs.

HBM4EU is a H2020 European Joint Programme which was

started in 2017 with the aim of coordinating and advancing human biomonitoring of chemicals in Europe, and minimizing the human health impact of the use of hazardous substances [23]. The programme includes FRs as a prioritized compound group [24]. It has established an external quality assurance/quality control (QA/QC) system for the substances prioritized in HBM4EU, including BFRs and PFRs [25,26], and studied the exposure to these environmental chemicals in the European population.

Based on information collected within HBM4EU, the main objective of this review is to summarize and discuss the state-of-the-art in the determination of FRs in human matrices and to create a better understanding of the analytical challenges related to the chemically diverse FR group. The review focuses on measurements in human specimens of biomarkers of exposure to FRs, including PBDEs, HBCD, bromophenols (including TBBPA), NHFRs, and PFRs (Table 1). Our manuscript updates previous reviews on FRs and addresses for the first time several types of FRs in human samples, which are traditionally analyzed separately, but increasingly combined in multi-methods.

2. Search method

2.1. Search strategy

The available literature has been reviewed on human biomonitoring and related method development studies on FRs of approximately the last ten years (2009–2020) to characterize the analytical methods used for the determination of different FR exposure biomarkers. Bibliographic searches were conducted in Web of Science and Google Scholar using the search terms flame retardant, novel flame retardant, dechlorane plus, PBDEs, HBCD, BFRs, PFRs and NHFRs, all of them in combination with "human". Web of Science was predominantly used because it has been recommended as the sole database for human-curated studies and the citation data are considered more accurate and reproducible [27].

2.2. Selection of articles for review

The database search returned a total of 162 articles. Their distribution over the search period is shown in Fig. 1. Each article was critically reviewed with a focus on detailed method descriptions. Articles lacking details on analytical techniques such as sample preparations and instrumental methods were excluded. Preference was given to articles containing quantitative QA/QC information, including for example method detection limits (MDLs) and recovery rates for specified FRs. In addition, relevant references extracted from the 162 articles of the bibliographic search were included to build up this review.

3. Biomarkers and matrices

In order to assess human exposure to environmental chemicals in human biomonitoring approaches, a selection of appropriate biomarkers and human specimens is required for the chemical analysis. Biomarkers of exposure can be the chemical substance itself, its metabolites, or products of interaction between the chemical and biomolecules (e.g. DNA-adducts). Recommendations for the most suitable biomarkers and matrices for human biomonitoring of the substances prioritized in HBM4EU, including FRs, were recently published [28]. Table 1 summarizes the broad range of FR metabolites and parent compounds recently analyzed in human biomonitoring programmes or described in method development studies. Although some primary publications used different compound names and acronyms, FR abbreviations have been harmonized according to Bergman et al. [29]. This review includes 99 biomarkers for FRs which have been monitored in human samples.

The various human specimens (here called matrix) used for determination of exposure to each class of FRs are also presented in Table 1. The selection of matrices for human biomonitoring of chemicals is mainly determined by the physical-chemical properties of the biomarker being monitored and its pharmacokinetics [30]. The most frequently used matrices for biomonitoring of FRs are serum and urine, while other matrices such as plasma, whole blood, cord blood, placenta, breast milk, hair, and nails have also been used for human biomonitoring (Table 1). PBDEs, HBCD and several NHFRs, which, generally speaking, are persistent compounds, typically accumulate in lipid-rich tissues after entering the human body, while PFRs are metabolized and eliminated in urine (Table 1). PFRs are metabolized to dialkyl and diaryl phosphate esters (DAPs) and hydroxylated metabolites (OH-PFRs). For example, tris(chloroisopropyl) phosphate (TCIPP) can be metabolized to the DAP bis(chloroisopropyl) phosphate (BCIPP) and the OH-PFR 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP) [21,31]. Both groups of PFR metabolites have been targeted in human biomonitoring studies; however, DAPs were the main PFR metabolites addressed in HBM4EU [25,31,32].

Due to geographical differences in use patterns of FRs, the types and concentrations of biomarkers differ in populations from different regions or countries. The higher levels in North America of BDE congeners originating from the PentaBDE product are well-known [5]. Despite their global ban in 2009 and indications of changes in PBDE exposure patterns towards more BDE-209 [33], the lower brominated BDE congeners are still included in many human biomonitoring studies on FRs. Furthermore, NHFRs are often analyzed together with PBDEs using the same or slightly adjusted methods. Many of the NHFRs have concentrations in human matrices that are similar to or lower than those of PBDEs, although exceptions exist, e.g. for DDC-CO and related compounds or bis(2-ethylhexyl)tetrabromophthalate (BEH-TEBP) (Tables 2–4). Little is known so far about spatial or temporal trends of NHFRs, possibly also hampered by analytical challenges. Likewise, the analysis of PFR metabolites presents a complex situation due to the number of possible metabolites (Table 1) and challenges with routine determinations of low concentrations [25]. The possible high inter-individual variability for metabolite formation should be considered in the interpretation of PFR exposure data to avoid misclassification of exposure.

The advantages of urine as a non-invasive biomonitoring matrix is the possibility of obtaining large sample volumes, minor ethical concerns, and the possibility of monitoring populations of all ages and both genders. The collection of urine spot samples, which is easier than 24-h samples, is usually employed in general population studies. An adjustment of exposure level is required based on the level of creatinine or specific gravity to compensate for the dilution of the urine in spot samples [120].

To monitor halogenated FRs (HFRs), biomonitoring studies have mainly used blood (serum or plasma) in studies of the general population and/or breast milk of women in the breastfeeding stage. Urine has also been used for biomonitoring of tetrabromobenzoic acid (TBBA), a metabolite of 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) [118,119]. Blood serum/plasma typically contains 0.5–0.8% lipids [121]. The reported concentrations of FRs in serum or plasma are typically normalized to the lipid content for comparison with other serum/plasma samples or other matrices [35]. Analysis of serum or plasma can be challenging due to high concentrations of proteins and low concentrations of target analytes, and often small volumes of sample, with the consequence of potentially elevated limits of quantification [122], as further discussed in section 4.1.

Table 1
Parent compounds and metabolites of flame retardants frequently determined in human samples.

	Biomarker (Abbreviation; CAS number)	Parent compound	Human specimens
PBDEs:	BDE-15 (2050-47-7)	[a]	Serum, plasma, cord blood, placenta, breast milk, hair, nails
	BDE-17 (147217-75-2)		
	BDE-28 (41318-75-6)		
	BDE-29 (337513-56-1)		
	BDE-30 (155999-95-4)		
	BDE-37 (147217-81-0)		
	BDE-47 (5436-43-1)		
	BDE-49 (243982-823)		
	BDE-66 (189084-615)		
	BDE-71 (189084-62-6)		
	BDE-77 (93703-48-1)		
	BDE-85 (32534-81-9)		
	BDE-99 (60348-60-9)		
	BDE-100 (189084-64-8)		
	BDE-138 (182677-30-1)		
	BDE-153 (68631-49-2)		
	BDE-154 (207122-15-4)		
	BDE-183 (207122-16-5)		
	BDE-196 (446255-39-6)		
	BDE-197 (117964-21-3)		
	BDE-203 (337513-72-1)		
	BDE-206 (63387-28-0)		
	BDE-207 (437701-79-6)		
	BDE-209 (1163-19-5)		
HBCDs:	α-HBCD (134237-50-6)	[a]	Serum, breast milk, hair
	β-HBCD (134237-51-7)		
	γ-HBCD (134237-52-8)		
NBFRs	2,4-Dibromophenol (615-58-7)	[a]	Serum, breast milk
	2,4,6-Tribromophenol (118-79-6)	[a]	Serum, breast milk
	5,6-Dibromo-1,10,11,12,13,13-hexachloro-11-tricyclo[8.2.1.02,9] tridecene (DBHCTD; 51936-55-1)	[a]	Serum, plasma
	Dechlorane 602 (31107-44-5)	[a]	Serum, plasma, placenta
	Dechlorane 603 (13560-92-4)	[a]	
	Dechlorane 604 (34571-16-9)	[a]	
	Pentabromobenzene (PBBz; 608-90-2)	[a]	Serum, breast milk, hair
	Pentabromobenzyl acrylate (PBB-Acr; 59947-55-1)	[a]	Serum, breast milk
	Octabromo-1,3,3-trimethyl-1-phenylindane (OBTMPI; 155613-93-7)	[a]	Serum, breast milk
	1,2,5,6-Tetrabromocyclooctane (TBCO; 3194-57-8)	[a]	Serum, breast milk
	Tetrabromo-o-chlorotoluene (TBCT; 39569-21-6)	[a]	Breast milk
	1,2-Bis(2,4,6-tribromophenoxy)-ethane (BTBPE; 37853-59-1)	[a]	Serum, cord blood, breast milk, hair, nails
	Decabromodiphenyl ethane (DBDPE; 84852-53-9)	[a]	Serum, cord blood, breast milk, nails
	Pentabromoethylbenzene (PBEB; 85-22-3)	[a]	Serum, breast milk, hair, nails
	Pentabromotoluene (PBT; 87-83-2)	[a]	Serum, breast milk, hair
	2,3,5,6,-Tetrabromo-p-xylene (TBX; 23488-38-2)	[a]	Serum, breast milk, hair
	2,3,4,5-Tetrabromobenzoic acid (TBBA; NA[b])	2-Ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB)	Urine
	Tetrabromobisphenol A (TBBPA; 79-94-7)	[a]	Serum, breast milk, hair
	Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-BDBPE; 21850-44-2)	[a]	Breast milk
	Di(2-ethylhexyl)tetrabromophthalate (BEH-TEBP; 26040-51-7)	[a]	Serum, cord blood, breast milk, hair, nails
	EH-TBB (183658-27-7)	[a]	Serum, cord blood, breast milk, hair, nails
	Hexabromobenzene (HBB; 87-82-1)	[a]	Serum, cord blood, breast milk, hair, nails
	Tetrabromoethylcyclohexane (DBE-DBCH; 3322-93-8)	[a]	Serum, breast milk
	Dechlorane Plus (135821-03-9)	[a]	Serum, cord blood, whole blood, breast milk, hair, nails
	Allyl-2,4,6-tribromophenyl ether (TBP-AE; 3278-89-5)	[a]	Breast milk
	2-Bromoallyl-2,4,6-tribromophenyl ether (TBP-BAE; NA)	[a]	Breast milk
	2,3-Dibromopropyl-2,4,6-tribromophenyl ether (TBP-DBPE; 35109-60-5)	[a]	Serum, Breast milk
	Pentabromophenol (PBP; 608-71-9)	[a]	Serum
PFRs:	2-Ethylhexyl diphenyl phosphate (EHDPP; 1241-94-7)	[a]	Urine, whole blood, hair, breast milk
	2-Ethyl-3-hydroxyhexyl diphenyl phosphate (3-OH-EHDPP; NA)	EHDPP	Urine, whole blood
	3-Hydroxy-4-methylphenyl di-p-tolyl phosphate (3-OH-MDTP; NA)	EHDPP	Urine, whole blood
	4-(Hydroxymethyl) phenyl di-p-tolyl phosphate (4-OH-MDTP; NA)	EHDPP	Urine, whole blood
	2-Ethyl-5-hydroxyhexyl diphenyl phosphate (5-OH-EHDPP; NA)	EHDPP	Urine, whole blood
	Triphenyl phosphate (TPHP; 115-86-6)	[a]	Urine, serum, whole blood, hair, nails
	3-Hydroxyphenyl diphenyl phosphate (3-HO-TPHP; NA)	TPHP	Urine, serum, hair
	4-Hydroxyphenyl diphenyl phosphate (4-HO-TPHP; NA)	TPHP	Urine, serum, hair
	Dibutyl phosphate (DBP; 107-66-4)	Tri-n-butylphosphate (TBP)	Urine
	Diphenyl phosphate (DPHP; 838-85-7)	TPHP	Urine, serum, whole blood, amniotic fluid, hair
	4-Hydroxyphenyl phenyl phosphate (4-HO-DPHP; NA)	TPHP	Urine
	Tert-butyl diphenyl phosphate (tbutyl-DPHP; 22433-83-6)	TPHP	Urine
	Tris(2-butoxyethyl) phosphate (TBOEP; 78-51-3)	[a]	Urine, serum, breast milk, hair, nails
	Bis(2-butoxyethyl) phosphate (BBOEP; 14260-97-0)	TBOEP	Urine, serum, amniotic fluid, hair
	2-Hydroxyethyl bis(2-butoxyethyl) phosphate (BBOEHEP; NA)	TBOEP	Urine, serum, hair
	Bis(2-butoxyethyl) 3′-hydroxy-2-butoxyethyl phosphate (3-OH-TBOEP; NA)	TBOEP	Urine
	Tris(chloroethyl) phosphate (TCEP; 115-96-8)	[a]	Urine, serum, hair, breast milk

Table 1 (*continued*)

Biomarker (Abbreviation; CAS number)	Parent compound	Human specimens
Bis(chloroethyl) phosphate (BCEP; 3040-56-0)	TCEP	Urine
Tris(2-chloroisopropy) phosphate (TClPP; 13674-84-5)	[a]	Urine, breast milk, nail
Bis(1-chloro-2-propyl) phosphate (BClPP; 789440-10-4)	TClPP	Urine
1-Hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP; NA)	TClPP	Urine, serum, hair
Tris(1,3-dichloro-2-propyl) phosphate (TDClPP; 13674-87-8)	[a]	Urine, breast milk, hair
Bis(1,3-dichloro-2-propyl) phosphate (BDClPP; 72236-72-7)	TDClPP	Urine, serum, amniotic fluid, hair
Dibenzyl phosphate (DBzP; 1623-08-1)	Tribenzyl phosphate	Urine
Bis(methylphenyl) phosphate (BMPP; 843-24-3)	Tri-cresyl phosphate (TCP)	Urine
TCP (1330-78-5; 78-30-8)	[a]	Urine, hair
Di-cresyl phosphate (DCP; NA)	TCP	Urine, amniotic fluid
Diethyl phosphate (DEP; 598-02-7)	Triethyl phosphate (TEP)	Urine
Diisobutyl phosphate (DIBP; 84-69-5)	Tri-iso-butyl phosphate (TiBP)	Urine
Di-n-butyl phosphate (DNBP; NA)	Tri-n-butyl phosphate (TNBP)	Urine, serum, hair
TNBP (126-73-8)	[a]	Urine, serum, breast milk, hair
Isopropyl-phenyl phenyl phosphate (ip-PPP; NA)	4-tert-butylphenyl diphenyl phosphate (4tBPDPP)	Urine
Tert-butyl phenyl phenyl phosphate (tb-PPP; NA)	[a]	Hair, whole blood, serum, urine, breast milk
Tri-n-propyl phosphate (TPrP; 513-08-6)	[a]	Breast milk, hair
Triisopropyl phosphate (TiPrP; 5419-55-6)	[a]	Serum, whole blood, urine
Trimethyl phosphate (TMP; 512-56-1)	[a]	Urine, breast milk, whole blood
TEP (78-40-0)	Tris(2-ethylhexyl) phosphate (TEHP)	Urine, whole blood, serum
Bis(2-ethylhexyl) phosphate (BEHP; 298-07-7)	[a]	Urine, breast milk, hair, whole blood, serum
Tris(2-ethylhexyl) phosphate (TEHP; 78-42-2)		

[a] Biomarker in the first column is the parent compound.
[b] NA: not available

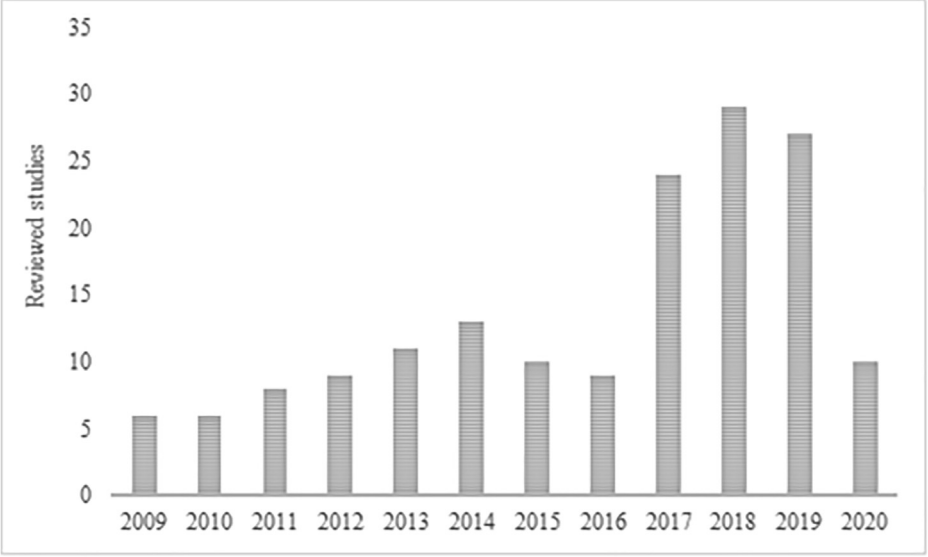

Fig. 1. Distribution over time of the studies reviewed in this article.

To avoid the difficulties related to invasive sampling of blood, research is ongoing on non-invasive matrices for biomonitoring. Human hair, as one of the non-invasive matrices, has the advantage of simple and cost-effective sampling, transport and storage, sample stability, the temporal exposure pattern by segmental analysis, and information on short- to long-term exposure to several environmental contaminants [123]. The hair root is irrigated with blood vessels, and chemical contaminants present in the blood stream are incorporated in the internal structure of hair during hair synthesis in the scalp. Exposure information stored in hair is very stable over time and analysis of 1 cm hair length is accepted to assess the average exposure over a 1-month period [124]. Hair can be a promising matrix for determination of lipophilic chemicals due to its relatively high lipid content (2–4%) [125]. However, some limitations prevent the wide application of hair as a matrix for human biomonitoring to FRs. For instance, only a low amount of hair can be sampled per individual (normally 0.05–0.2 g), and in addition, participants may not wish to donate hair. Furthermore, the interpretation of hair levels is not unambiguous as they reflect both external exposure (by deposition from air and dust) and internal exposure (through contact with blood at the hair follicle/root). Distinguishing between these exposure routes is difficult, especially when hair is used as indicator of exposure to FRs, where the contribution of atmospheric deposition cannot be ignored [126,127].

Due to the difficulty obtaining paired hair and serum samples, there are only few correlation studies. Zheng et al. [39] investigated the association between hair and serum levels of PBDEs and suggested the internal pathway as the major source of highly brominated BDE congeners in hair, while the exogenous pathway predominates for less-brominated BDEs. Associations found between PFR levels in hair and corresponding metabolites in urine of children suggested similar sources of exposure [80]. Significant correlations between levels of BFRs in hair and internal tissues (liver, kidney, muscle, and adipose tissue) of mammals were also reported [128].

Table 2
Overview of analytical methods used for analysis of PBDEs in human matrices.

Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μL)	Stationary phase/ Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
Serum	2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5/He	200 pg mL^{-1}	65–105	15	85	[34]
	2 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5MS/He	0.7–2.0 pg mL^{-1}	95–142	5–27	10	[35]
	3 mL	LLE/GPC	GC (ECNI)-MS	1	DB-5/He	0.1–10 pg mL^{-1}	82 ± 10	–	305 (pooled into 10)	[36]
	5 mL	Ultrasound/Sulfuric acid-silica	GC (ECNI)-MS	1	RTX-1614/He	–	75–110	–	72	[37]
	10 g	SPE/Sulfuric acid-silica	GC-HRMS	1	ZB-5/He	0.02–0.75 ng g^{-1} lipids	40–71	15–37	48	[38]
	2–4 mL	LLE/Silica-alumina	GC (ECNI)-MS	1	DB-5HT/DB-XLB/He	0.32–2.3 ng g^{-1} lipids	82–105	–	32	[39]
	1 mL	LLE	GC (ECNI)-MS	–	HP-5MS/He	50 pg mL^{-1}	–	–	–	[40]
	3 mL	LLE/GPC	GC (ECNI)-MS	1	DB-5MS/He	0.1–10 pg (instrumental detection limit)	72–110	–	305 (pooled into 12)	[41]
	3–4 g	SPE/Silica	GC (ECNI)-MS	–	DB-5HT/He	0.08 ng g^{-1} lipids	87 ± 15	–	43	[42]
	5 mL	QuEChERS or SPE	GC (ECNI)-MS	1	DB-5MS/He	0.5–50.8 pg mL^{-1}; 1.3–34.9 pg mL^{-1}	94–109; 82–123	0.69–4.6; 1.3–14	12	[43]
	3 g	SPE/Sulfuric acid-silica	GC (EI)-HRMS	–	DB-5HT/He	0.10–0.2 ng g^{-1} lipids	50–120	–	20 (pooled into 7)	[44]
	3 mL	SPE/Silica-acid silica	GC (ECNI)-MS	2	DB-5/He	0.1–0.6 ng g^{-1} lipids	78–92	–	67	[45]
	3–4 g	SPE/Silica	GC (ECNI)-MS	–	–	0.549–1.321 ng g^{-1} lipids	71–141	–	135	[46]
	3 mL	LLE/GPC-silica-alumina	GC (ECNI)-MS	–	DB-5MS/He	0.1–10.0 pg (instrumental detection limit)	89–95	–	595 (pooled into 10)	[47]
	2 mL	SPE/Acidified diatomaceous earth- GPC	GPC-GC-(ECNI)-MS	10	ShodexCLNpak EV-200AC/acetone-cyclohexane	0.6–16 pg mL^{-1}	67–127	–	10	[48]
	3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	5–100 pg mL^{-1}	80–109	–	300	[49]
	5 g	SPE/Acid silica	GC (ECNI)-MS	–	DB-5/He	12.6–13.8 pg g^{-1}	79 ± 32	–	145	[50]
	3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	TG-5HT/He	0.05–20 pg (instrumental detection limit)	55–109	–	942 (pooled into 20)	[51]
	5 mL	MAE	GC (ECNI)- MS	–	DB-XLB/He	20–100 pg g^{-1}	–	–	9	[52]
	5 mL	Ultrasound/ Multilayer, acid silica	GC (ECNI)-MS	50	RTX-1614/He	150–720 pg g^{-1} lipids	61–109	–	72	[53]
	1 mL	LLE/Florisil	GC-ICP-MS	2	-/He	1.6–3.9 pg mL^{-1}	96–101	–	Method validation	[54]
	4.5 mL	SPE	GC (ECNI)-MS	1	DB-5HT/He	0.42–4.8 ng g^{-1} lipids	67 ± 18	–	174	[55]
	2–3 mL	LLE	GC-MS	–	Dual capillary column	0.002–0.008 ng g^{-1} lipids	92–98	–	63	[56]
	3 mL	SPE/Silica	GC (ECNI)-MS	1	DB-5HT/He	0.1–0.5 ng g^{-1} lipids	82.4–97.3	–	103	[57]
	2 mL	LLE/Sulfuric acid-silica	GC-MS	–	HP-5MS/He	0.1 ng mL^{-1}	95 ± 5	–	110	[58]
	1 mL	LLE	GC (ECNI)-MS	2	RTX-1614/He	2.5–6.0 pg mL^{-1}	56–81	8.0–19.0	Method development and validation	[59]
	5 mL	Soxhlet/Florisil	GC (ECNI)-MS	1	DB-XLB/He	0.0001–72.6 ng g^{-1} lipids	83.1–110	–	43	[60]
	0.5 mL	SPE	GC (APCI)-MS/MS	1	DB-5MS/He	0.06–1.08 pg mL^{-1}	98.7–112	2.61-11.2	60	[61]
	0.5–2 g	SPE	GC (ECNI)-MS	1	RTX-5MS/He	0.03–0.1 ng g^{-1}	66–97	–	25	[62]
	1 mL	LLE	GC-HRMS	2	DB-5MS/He	2–10 pg mL^{-1}	73 ± 17	–	86	[63]
	5 g	PLE	GC-HRMS	–	DB-5MS/He	0.1–0.15 ng g^{-1} lipids	90–116	–	800	[64]
	5 g	SPE/Florisil	GC-HRMS	–	RTX-1614/He	–	28.4–109.1	–	91	[12]
	3 mL	LLE/Florisil	GC (EI)-MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.1–2.5 ng g^{-1} lipids	72–112	1.0–20.0	Method development (38)	[65]
	5 mL	LLE/GPC-sulfuric acid	GC (ECNI)-MS	–	DB-5MS/He	1.8–35.0 pg g^{-1}	80–108	<15	103	[66]
	1 mL	LLE/Silica	GC-MS	1	DB-5MS/He	0.1–0.25 ng mL^{-1}	72–98	–	293	[67]
	0.2 mL	QuEChERS	GC (EI)-MS/MS	2	DB-5MS/He	2–20 pg g^{-1}	85–112	1.4–28.2	25	[68]
	1 mL	SPE	HPLC-ICP-MS	5	C18/water-MeOH-ACN	0.06–0.081 ng mL^{-1}	79–89	–	20	[69]
	5 mL	QuEChERS/SPE	GC (ECNI)- MS/MS	1	DB-5MS/He	300 pg g^{-1} lipids	82–121	11.5	111	[70]
Plasma	–	SPE	GC (EI)- MS	–	RXI-5HT/He	0.2–2.5 ng mL^{-1}	–	–	159	[71]
	1 mL	SPE/Silica	GC (ECNI)-MS	–	HP-5MS/He	0.16–0.69 ng g^{-1} lipids	59–125	4.1–7.2	414	[72]
	5 g	LLE/Silica	GC (ECNI)-MS	–	HP-5MS UI/He	1.5–480 pg g^{-1}	86–104	–	113	[73]
Cord blood	10 mL	Ultrasound/Sulfuric acid-silica	GC (ECNI)-MS	1	RTX-1614/He	–	–	–	72	[37]
	10 mL	Ultrasonic/ Multilayer- acid silica	GC (ECNI)-MS	20	RTX-1614/He	90–440 pg g^{-1} lipids	61–109	–	72	[53]
	500 mg	LLE/Florisil-multilayer silica	GC (ECNI)-MS	–	–	0.011–0.070 ng mL^{-1}	58–112	–	300	[74]
	2 mL	SPE/Silica	GC-HRMS		DB-5MS/He	0.17 ng g^{-1} lipids	87 ± 13	–	108	[75]
	–	SPE/Acid silica	GC (ECNI)-MS/MS	2	ZB semivolatiles/He	0.05–6 pg g^{-1}	–	–	Method development	[76]

Table 2 (*continued*)

Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μL)	Stationary phase/ Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
Hair	2 g	LLE/Silica-alumina	GC (ECNI)-MS	1	DB-5HT/He	0.01–2.59 ng g^{-1}	85–101	13.00	173	[77]
	200 mg	Ultrasound/Florisil	GC (ECNI)-MS	1	DB-5HT/He	0.1–15.9 ng g^{-1} dry weight	83–110	31		[78]
	1 g	MAE/GPC	GC (EI)-MS/MS	5	DB-5MS/He	15–375 pg g^{-1}	62–121	2.0–19	13	[75]
	2 g	LLE/Silica-alumina	GC (ECNI)-MS	1	DB-5HT; DB-XLB/He	0.05–2.5 ng g^{-1}	82–105	–	32	[39]
	100 mg	LLE/Florisil	GC (ECNI)-MS	1	RTX -1614/He	0.06–1.2 ng g^{-1}	64–108	4.0–13.0	5	[79]
	200 mg	LLE/Florisil	GC (ECNI)-MS	5	DB-5MS/He	0.8 ng g^{-1}	82.112	2–9	Method development (102)	[80,81]
	3 g	Soxhlet/Sulfuric acid-silica	GC (ECNI)-MS	–	DB-5MS/He	17–1697 pg g^{-1}	–	–	13	[82]
	25 mg	Ultrasound/Sulfuric acid-silica	GC (ECNI)-MS	-	DB-5MS/He	0.1–10.0 pg g^{-1}	89–95	–	34	[83]
	2 g	Soxhlet/Florisil	GC (ECNI)-MS	1	DB-XLB/He	0.001–0.26 ng g^{-1}	77.3–163	–	43	[60]
	1 g	Ultrasound, LLE/ GPC, SPE	GC (ECNI)-MS	1	DB-5HT/He	0.05–0.5 pg g^{-1}	62–145	3–18	20	[84]
	300 mg	LLE/SPE	GC (ECNI)- MS/ MS	1	DB-5MS/He	20 ng g^{-1}	98–139	12.6	111	[70]
	100 mg	LLE/Florisil	GC (ECNI)-MS	1	DB-5HT/He	0.06–7.48 ng g^{-1}	88–115	2–14	14	[85]
Breast milk	2 g	LLE/GPC	GC (ECNI)- MS/ MS	1	DB-1MS/He	0.08–4.6 ng g^{-1}	52–101	–	87	[86]
	30 mL	Soxhlet/GPC-sulfuric acid	GC (ECNI)-MS	1	DB-5MS/He	2.3–35.8 pg g^{-1} lipids	75–125	<15	103	[87]
	10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)-HRMS	2	RTX-1614/He	0.006–0.029 ng g^{-1} lipids; 0.001–0.137 ng g^{-1} lipids	82–115; 75–115	2–20; 8–30	120; 458	[88,89]
	5 mL	SPE/GPC	GC (ECNI)-MS	1	DB-5HT/He	0.13–1.76 pg mL^{-1}	–	–	20	[90]
	20 –25 mL	Soxhlet/GPC-sulfuric acid	GC (ECNI)-MS	1	DB-5MS/He	10 pg g^{-1}	80–120	–	29	[91]
	0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)-MS	2	TraceGOLD (TG)/He	0.003–0.07 ng g^{-1}	83–95	–	35	[92]
	30 mL	Soxhlet	GC (ECNI)-MS	1	DB-5MS/He	0.1–10 pg mL^{-1}	75–125	–	111	[93]
	20 mL	Soxhlet/GPC-sulfuric acid	GC (APCI)-MS/ MS	1	DB-5MS/He	0.05–3 pg g^{-1}	70–125	<15	20	[94]
	10 ml	LLE	GC (ECNI)-MS	–	HP-5MS/He	50 pg mL^{-1}	–	–	–	[40]
	1 g	PLE/Florisil-sulfuric acid	GC (EI)-MS	1	Restek Rxi5Sil MS/He	0.06–0.6 ng g^{-1}	–	–	16 pooled	[95]
Nails	10 finger nails	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	0.12–2.4 ng g^{-1}	71–109	7–12	5	[79]
	50 mg	LLE	GC (ECNI)-MS	1	DB-5MS/He	0.3–0.5 ng g^{-1}	82–118	–	50	[96]
	100 mg	LLE/Florisil	GC (ECNI)- MS/ MS	1	DB-5MS/He	0.27–0.85 ng g^{-1}	60–111	–	94	[97]
	300 mg	LLE/SPE	GC (ECNI)- MS/ MS	1	DB-5MS/He	50 ng g^{-1}	98–139	12.6	66	[70]
Placenta	2 g dry weight	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	1	RTX-1614/He	–	72–107	–	72	[37]
	2 g dry weight	Ultrasonic/ Multilayer, acid silica	GC (ECNI)- MS	50	RTX-1614/He	40–220 pg g^{-1} lipids	–	68–107	72	[53]

The use of human nail samples in assessing exposure to FRs is scarce. Recent studies have suggested the use of nails as a non-invasive matrix in biomonitoring of PBDEs, NHFRs and PFRs [126,70,79,96,97]. The study by Alves et al. [126] identified diphenyl phosphate (DPHP) as the major metabolite detected in nail and hair with very high (mg g^{-1}) and relatively constant levels over two months for the female volunteer, and the high levels of DPHP in fingernails suggested both internal and external contributions. Zhao et al. [70] reported high levels of BDE-209 in paired hair-serum and nail-serum samples collected from chemical manufacturing workers. The results showed significant and positive correlations of BDE-209 in hair and fingernails to BDE-209 in serum, indicating that both hair and nails can be used as non-invasive proxy to determine internal exposure to BDE-209. Meng et al. [97] also identified BDE-209 as the major congener of PBDEs (92–98%) in human nails, especially in e-waste-dismantling workers. The current literature indicates that hair and nails are suitable matrices for screening purposes, while precise quantifications of FR exposure, e.g. for risk assessments or epidemiological studies, may require less ambiguity in the data interpretation [123,129].

Due to their highly lipophilic properties, HFRs accumulate in matrices associated with perinatal exposure, i.e. breast milk, cord blood, placenta and fetal membranes [74,130–134]. Even though sampling is challenging, cord blood and amniotic fluid have been used for monitoring the child's exposure to FRs (Table 1). Breast milk is typically used for monitoring mother and child exposure to HFRs and some PFRs [91,94]. Breast milk, beside serum, was also used for human biomonitoring of bromophenols, such as TBBPA [91,66,98,100,101]. Breast milk is easy to obtain in large volumes

Table 3
Overview of analytical methods used for analysis of HBCDs and bromophenols in human matrices.

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/ Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
HBCDs: α-HBCD β-HBCD γ-HBCD	Serum	5 mL	LLE/GPC-sulfuric acid	LC (ESI)-MS/MS	10	BEH C18/ACN-water-MeOH	20–40 pg g^{-1} lipids	94–101	<15	103	[66]
		3–4 g	SPE/Silica	LC (ESI)-MS/MS	20	C18/ACN- water	0.08 ng g^{-1} lipids	87 ± 15	–	43	[42]
		2 mL	SPE/Acidified diatomaceous earth	LC (ESI)-MS/MS	10	DiKMA Endeavorsil/ Water-MeOH	1.3–3.2 pg mL^{-1}	82.8–145	–	10	[48]
		3 g	LLE/Silica	LC (ESI)-MS/MS	5	HSS T3/Ammonium acetate in water-MeOH	0.036 ng mL^{-1}	80–109	–	300	[49]
		2–3 mL	LLE	GC-MS		Dual capillary column	0.033 ng g^{-1} lipids	95	–	63	[56]
		5 g	PLE	LC (ESI)-MS	–	Kinetex XB C18/ Water-MeOH	0.1 ng g^{-1} lipids	87–91	–	800	[64]
		3 mL	LLE	LC (ESI)-MS/MS	5	HSS T3/Ammonium acetate in water-MeOH	0.33 ng g^{-1} lipids	92–116	14–18	Method development (38)	[65]
	Breast milk	15 mL	Shaking/C18	LC(ESI)-MS/MS	5	C18/Water-MeOH	6.0 –30.0 pg mL^{-1}	108–111	4.0–7.0	50	[98]
		30 mL	PLE/GPC	LC (ESI)- MS/MS	10	BEH C18/ACN-Water-MeOH	20–50 pg g^{-1} lipids	86–102	<15	103	[66]
		5 mL	SPE/GPC	LC (ESI)-MS/MS	20	SB-C18/Water-MeOH-ACN	0.31 –1.18 pg mL^{-1}	88.1 –98.8	–	20	[99]
		5 mL	LLE/Sulfuric acid	LC (ESI)-MS/MS	5	C18/Water-MeOH	2.5 ng g^{-1} lipids	76	–	106	[100]
		20 –25 mL	Soxhlet/GPC-sulfuric acid	LC (ESI)-MS/MS	–	BEH C18/ACN-water-MeOH	5.0–10.0 pg g^{-1}	80–120	–	29	[91]
		0.5 g	PLE/Florisil-sulfuric acid	LC (ESI)-MS/MS	10	C18/Water-ACN	0.02–0.03 ng g^{-1} lipids	–	–	35	[92]
		5 g	LLE/GPC	LC (ESI)-MS/MS	–	XRS C18/Water-MeOH	20 pg g^{-1} lipids	68–90	–	64	[101]
		3 g	Soxhlet/GPC	LC (ESI)-MS/MS	10	C18/Water-ACN	0.13–0.32 ng g^{-1}	115–134	–	180	[102]
		20 mL	Soxhlet/GPC-sulfuric acid	LC (ESI)-MS/MS	10	BEH C18/ACN-water-MeOH	5 pg g^{-1}	70–125	<15	20	[94]
		1 g	PLE/Florisil-sulfuric acid	LC-MS/MS	1	Pursuit XRS3 C18/ Water-MeOH	0.05 ng g^{-1} lipids	–	–	16 pooled	[95]
	Hair	0.5 g	Ultrasound/Silica	LC (ESI)-MS/MS	–	C18/Water-MeOH-ACN	0.04–0.09 ng g^{-1}	–	95–111	Method development	[103]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/Water-MeOH-ACN	0.04–0.23 ng g^{-1}	82–117	4–10	14	[85]
2,4-Dibromophenol; 2,4,6-Tribromophenol	Serum	2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5MS/He	0.5–5.0 ng mL^{-1} (Unit uncertain)	103–158	7–15	85	[34]
		3–4 g	SPE/Silica	GC (ECNI)-MS	–	DB-5HT/He	1.8 ng g^{-1} lipids	93 ± 5	–	43	[42]
		1 mL	SPE	GC (ECNI)-MS	2	HP-5MS/He	15 pg mL^{-1}	68–84	8–9	20	[104]
		3 g	LLE/Silica	LC (ESI)-MS/MS	5	HSS T3/Ammonium acetate in water-MeOH	0.333 –0.364 ng mL^{-1}	80–109	<20	300	[49]
		3 mL	LLE/QuEChERS	LC (ESI)-MS/MS	5	HSS T3/Ammonium acetate in water-MeOH	0.33 ng mL^{-1}	72–104	2–19	Method development (38)	[65]
	Breast milk	15 mL	Shaking/C18	LC (ESI)-MS/MS	5	C18/Water-MeOH	30 pg mL^{-1}	80–109	4–5	50	[98]
		5 g	LLE/GPC	LC (ESI)-MS/MS	–	XRS C18/Water-MeOH	31 pg g^{-1}	68–90	–	64	[101]
Tetrabromobisphenol A (TBBPA)	Serum	0.5 –1 mL	SPE	LC (ESI)- MS/MS	20	PFP(2)/Water-ACN	0.02 ng g^{-1}	94–95	2	–	[105]
		1 mL	LLE	GC (ENCI)-MS	–	HP-5MS/He	0.2 ng mL^{-1}	–	–	–	[40]
		1 mL	SPE	GC (ECNI)-MS	2	HP-5MS/He	1.24 pg mL^{-1}	75–80	5	20	[104]
		2 mL	SPE/Acidified diatomaceous earth	LC (ESI)- MS/MS	10	DiKMA Endeavorsil/ Water-MeOH	4.2 pg mL^{-1}	84 ± 4	–	10	[48]
		3 g	LLE/Silica	LC (ESI)- MS	5	HSS T3/Ammonium acetate in water-MeOH	0.333 ng mL^{-1}	80–109	<20	300	[106]
		5 mL	LLE/GPC-sulfuric acid	LC (ESI)-MS/MS	10	BEH C18/ACN-water-MeOH	30 pg g^{-1} lipids	91–102	2.65 –7.18	42	[66]
		3 mL	LLE/QuEChERS	LC (ESI)- MS/MS	5	HSS T3/Ammonium acetate in water-MeOH	0.33 ng mL^{-1}	85–113	6	Method development (38)	[106]

Table 3 (*continued*)

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/ Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
	Breast milk	2 g	PLE/In-cell cleanup-SPE	LC (ESI)- MS/MS	–	C18/MeOH-water	9 pg g^{-1} lipids	82–95	3.6–4.7	12	[107]
		15 mL	Shaking/C18	LC (ESI)- MS/MS	5	C18/Water-MeOH	60 pg mL^{-1}	103	–	50	[98]
		30 mL	PLE/GPC-sulfuric acid	LC (ESI)- MS/MS	10	BEH C18/ACN-water-MeOH	60 pg g^{-1} lipids	88–95	2.97–6.57	12	[66]
		5 mL	LLE/Sulfuric acid	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.06 ng g^{-1} lipids	125	–	106	[100]
		20–25 mL	Soxhlet/GPC-sulfuric acid	LC (ESI)- MS/MS	–	DB-5MS/He	5 pg g^{-1}	80–120	–	29	[91]
		10 mL	LLE	GC (ECNI)-MS	–	HP-5MS/He	0.2 ng mL^{-1}	–	–	–	[40]
		5 g	LLE/GPC	LC (ESI)- MS/MS	–	XRS C18/Water-MeOH	34 pg g^{-1} lipids	68–90	–	64	[101]
	Hair	0.5 g	Ultrasound/Silica	LC (ESI)- MS/MS	–	C18/Water-MeOH-ACN	0.15 ng g^{-1}	89	5–16	Method development	[103]

and does not require help from medical staff, as is the case with blood sampling; this is advantageous in e.g. developing countries. Due to variable lipid concentrations in human milk, a lipid adjustment is necessary to compare the contaminant levels [135]. Nevertheless, breast milk provides information on the exposure of only limited population groups, compared to blood samples.

4. Analytical methods

4.1. Sample intake

Sample intake is one of the key parameters in the human biomonitoring of FRs, as the low concentrations of FRs in human matrices in combination with challenges in obtaining large sample amounts or volumes might lead to insufficient MDLs. Based on the sample intake, diverse MDLs have been reported for FRs in human matrices and will be further discussed in connection with the instrumental techniques in section 4.4 (Tables 2–5). According to the literature and expected concentrations, sample intakes of 1–5 mL are typically required for measurements of PBDEs in serum and plasma at MDLs in the pg mL^{-1} range, depending on the target compounds and the selected analytical method [36,43,47,50,59,72,73,111,113,136]. However, in a method developed for PBDEs and NBFRs (1,2-bis(2,4,6-tribromophenoxy)-ethane (BTBPE), decabromodiphenyl ethane (DBDPE), pentabromoethylbenzene (PBEB), pentabromotoluene (PBT) and hexabromobenzene (HBB)) in serum, MDLs in the pg mL^{-1} range were achieved with 0.5 mL of sample [61]. Likewise, MDLs of 2–20 pg g^{-1} were achieved for 23 PBDEs with a serum volume of only 0.2 mL [68]. In both cases, atmospheric pressure chemical ionization techniques (APCI) were used and found particularly sensitive. Sample intake of breast milk ranged from 2 to 30 mL for human biomonitoring of PBDEs and HBCD. The sample intake ranges are summarized in Fig. 2.

Sample intakes of 1–3 g hair were generally required to detect biomarkers of PBDEs at MDLs in the pg g^{-1} range [39,60,77,82,84]. However, Li et al. [83] achieved low MDLs (0.1–10 pg g^{-1}) for PBDEs in hair with a sample intake as low as 0.025 g. Barghi et al. [103] reported MDLs of 40–90 pg g^{-1} for HBCD diastereoisomers in hair with a sample intake of 0.5 g.

For urine as the matrix of choice for PFR biomonitoring, sample intakes of 0.4–10 mL have been reported (Table 5). Based on a sample intake of 0.5 mL, MDLs of 1–100 pg mL^{-1} have been achievable [140,106]. Whole blood (0.5 mL) and serum (0.5–3 mL) have also been used in some studies to investigate the relationship between PFR metabolite concentrations in urine and blood [47,65,106,140,143]. Sample intake of breast milk ranged from 2 to 30 mL for biomonitoring of PFR metabolites. To achieve low MDLs (20–90 pg g^{-1}) for PFR metabolites in breast milk, a minimum sample intake of 2 mL was required [137]. Sample intakes of 0.1–0.2 g hair have been reported to detect PFR parent compounds and metabolites at MDLs in the pg g^{-1} range [126,80,140,81]. For the determination of TBBA in urine, 0.4 mL urine was sufficient to achieve an MDL in the pg mL^{-1} range [118].

The current literature shows that typically available blood volumes can be a limitation in the biomonitoring of FRs, in addition to the challenges related to invasive sampling. However, the literature review shows noticeable trends in sample reduction over the last ten years. Sample intakes have been reduced by a factor of ten for serum and breast milk samples, and by a factor of 25 for urine samples, while still achieving required MDLs. MDLs might be lowered to some extent, possibly by a factor of five, if instrumental sensitivity is further optimized. However, this might require focus on specific compounds in question and prevent extension to multi-methods at the same time. Furthermore, as PBDEs and HBCD have been banned, their levels will likely further decrease in humans and possibly challenge current MDLs. The US National Health and Nutrition Examination Survey (NHANES) has used pooled serum samples since 2004 to increase the sample amount for PBDE analysis [161]. While this provides average exposure data for e.g. time trends, inter-individual variation is lost, which could e.g. be linked to health outcomes. As sensitivity will remain an issue with serum-based HFR monitoring, research into practical and conceptual possibilities and limitations of non-invasive matrices such as hair and nails, will be particularly relevant for FRs.

4.2. Sample pre-treatment

A pre-treatment of biological samples is often required to remove interferences or to hydrolyze the conjugated forms of the target biomarkers. Deconjugation (by an enzymatic or acid hydrolysis treatment) to selectively deconjugate glucuronides or sulfated conjugates, is suggested before analysis of PFR metabolites [162]. However, only hydroxylated PFR metabolites which are excreted as glucuronide and sulfate conjugates in urine require conjugation before excretion [30]. The pre-treatment can also be a simple

Table 4
Overview of analytical methods used for determination of novel halogenated flame retardants (NHFRs) in human matrices.

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
Dechlorane plus	Serum	5 g	LLE/Strong acid	GC (ECNI)- MS	1	DB-5HT/He	–	91–108	–	40	[108]
		5 mL	LLE/Strong acid	GC (ECNI)- MS	1	DB-5HT/He	0.4–0.7 ng mL^{-1}	90	–	20	[109]
		2–4 mL	LLE/GPC	GC (ECNI)- MS	1	DB-5MS/He	0.6 ng g^{-1} lipids	90 ± 7	–	11	[110]
		5 mL	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	1	RTX-1614/He	34.5–131 pg g^{-1} lipids	86.7–104.9	–	45	[111]
		3 mL	LLE/GPC	GC (ECNI)- MS	1	DB-5/He	0.2 pg (instrumental detection limit)	92 ± 8	–	10	[36]
		2 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5MS/He	1.1–2.3 pg mL^{-1}	65–84	3–13	10	[35]
		10 g	SPE/Sulfuric acid-silica	GC (EI)-HRMS	1	ZB-5/He	0.08–0.16 ng g^{-1} lipids	33–61	27.0–31.6	48	[38]
		2 mL	LLE/GPC	GC (ECNI)- MS	1	DB-1MS/He	0.04–0.12 ng g^{-1} lipids	44–84	29–38	102	[112]
		3 mL	LLE/GPC	GC (ECNI)-MS	1	DB-5MS/He	0.2 pg (instrumental detection limit)	84–100	–	12	[41]
		_	LLE/Silica-alumina	GC (ECNI)-MS	1	DB-XLB/He	1.3–3.1 ng g^{-1} lipids	80–98	–	34	[113]
		3 g	SPE/Sulfuric acid-silica	GC (EI)- HRMS	–	DB-5HT/He	0.02–0.4 ng g^{-1} lipids	50–120	–	7	[44]
		3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–0.5 pg (instrumental detection limit)	82–113	–	20	[51]
		4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	0.66–42 ng g^{-1} lipids	67–97	–	174	[55]
		5 mL	Soxhlet/Florisil	GC (ECNI)- MS	1	DB-XLB/He	0.37–5.14 ng g^{-1} lipids	–	–	43	[60]
	Whole blood; Cord blood	5 g	Open column/Sulfuric acid-silica	GC (ECNI)- MS	1	DB-5MS/He	0.592–0.846 ng g^{-1} lipids	89.7 ± 9.4	–	48	[114]
		10 mL	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	20	RTX-1614/He	124–131 pg g^{-1} lipids	60–103	–	72	[37]
		_	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	0.03–0.05 pg g^{-1}	–	–	Method development	[76]
	Placenta	2 g	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	50	RTX-1614/He	56.6–60.1 pg g^{-1} lipids	66–109	–	72	[37]
	Breast milk	3 g	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	1	RTX-1614/He	46.0–34.5 pg g^{-1} lipids	60–97	–	44	[111]
		8–10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.021–0.044 ng g^{-1} lipids	104–113	–	120	[37,88]
		0.5 g	PLE/Florisil sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
		5 g	LLE/GPC	GC (ECNI)-MS	1	DB-5MS/He	0.01–0.02 ng g^{-1} lipids	44	–	105	[112]
	Hair	2 g	LLE/Silica-alumina	GC (ECNI)- MS	1	DB-5HT/He	2.8–3.1 pg g^{-1}	91–98	≤10	173	[115]
		2 g	ASE/Sulfuric acid-silica	GC (ECNI)- MS	1	DB-5MS/He	0.013–0.018 ng g^{-1} dry weight	92.3 ± 15.2	–	48	[114]
		2 g	LLE/Silica-alumina	GC (ECNI)-MS	1	DB-XLB/He	2.6–2.9 pg g^{-1}	78–103	–	34	[113]
		100 mg	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	0.10–0.28 ng g^{-1}	93–95	5	5	[79]
		2 g	Soxhlet/Florisil	GC (ECNI)- MS	1	DB-XLB/He	0.02–0.14 ng g^{-1} dry weight	–	–	43	[60]
	Nails	10 finger nails	LLE/Florisil	GC (ECNI)- MS	1	RTX -1614/He	0.20–0.56 ng g^{-1}	93–95	7–8	5	[79]
		50 mg	LLE	GC (ECNI)-MS	1	DB-5HT/He	0.30 ng g^{-1}	99 ± 4.1	–	50	[96]
Dechlorane 602, 603 and 604	Serum	2 mL	SPE/Sulfuric acid-silica	GC (ECNI)- MS	2	DB-5MS/He	0.64–1.7 pg mL^{-1}	78–99	4–11	10	[35]
		10 g	SPE/Sulfuric acid-silica	GC (EI)- HRMS	1	ZB-5/He	0.04–0.4 ng g^{-1} lipids	–	14.7–19.5	48	[38]
		2 g	LLE/GPC	GC (ECNI)- MS/MS	1	DB-1MS/He	0.02–3.6 ng g^{-1} lipids	–	15–45	102	[112]
		3 g	SPE/Sulfuric acid-silica	GC (EI)-HRMS	–	DB-5HT/He	0.02–0.10 g g^{-1} lipids	–	–	7	[44]
	Plasma	1 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	–	HP-5/MS/He	0.02–0.04 g g^{-1} lipids	103.8 –140.7	27.9–28.1	414	[72]
	Cord blood	–	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	1 pg g^{-1}	–	–	Method development	[76]
	Breast milk	5 g	LLE/GPC	GC (ECNI)- MS/MS	1	DB-1MS/He	0.01–0.10 ng g^{-1} lipids	–	15–45	105	[112]

Pentabromobenzene (PBBz); Pentabromobenzyl acrylate (PBB-Acr)	Serum	3 mL	LLE/GPC-silica- alumina	GC (ECNI)-MS	–	DB-5MS/He	0.6–10 pg (instrumental detection limit)	–	–	10	
		3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg (instrumental detection limit)	–	–	20	[51]
		3 mL	LLE/GPC	GC (ECNI)-MS	1	DB-5MS/He	0.11 pg (instrumental detection limit)	–	–	12	[41]
	Breast milk	8–10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX -1614/He	0.002 ng g^{-1} lipid	94–110	7–16	120	[88]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
	Hair	25 mg	Ultrasound/GCP, sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg (instrumental detection limit)	–	–	34	[83]
		3 g	Soxhlet/Sulfuric acid-silica	GC (ECNI)-MS	–	DB-5MS/He	18.8–727 pg g^{-1} dry weight	–	–	13	[82]
Octabromo-1,3,3-trimethyl-1-phenylindane (OBTMPI, OBIND)	Serum	2 g	LLE/GPC	GC (ECNI)- MS/MS	1	DB-1MS/He	1.5 ng g^{-1} lipids	–	–	102	[116]
		3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	0.2 ng mL^{-1}	80–109	<20	300	[49]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	2.5 ng g^{-1} lipids	71–89	7–15	Method development (38)	[65]
	Breast milk	5 g	LLE/GPC	GC (ECNI)- MS/MS	–	DB-1MS/He	0.20 ng g^{-1} lipids	33 ± 22	–	35	[116]
1,2,5,6-Tetrabromocyclooctane (TBCO); Tetrabromo-o-chlorotoluene (TBCT)	Serum	3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.05 ng g^{-1} lipids	105–107	8–9	Method development (38)	[65]
	Breast milk	8–10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.002–0.030 ng g^{-1} lipids	65–114	10–41	120	[88]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
1,2-Bis(2,4,6-tribromophenoxy)-ethane (BTBPE)	Serum	2–4 mL	LLE/GPC	GC (ECNI)- MS	1	DB-5MS/He	1.2 ng g^{-1} lipids	91.8 ± 6.9	–	11	[110]
		2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5/He	0.2 ng g^{-1} lipids	84–92	3–4	85	[34]
		2 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5MS/He	2.3 pg mL^{-1}	67–94	1–5	10	[35]
		2 g	LLE/GPC	GC (ECNI)- MS/MS	1	DB-1MS/He	3.2 ng g^{-1} lipids	77 ± 49	–	102	[116]
		5 mL	QuEChERS or SPE	GC (ECNI)- MS	1	DB-5MS/He	1.4 pg mL^{-1}; 4.3 pg ml^{-1}	63–75; 96–106	1.1–13.2; 4.2–14.9	12	[43]
		3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	0.01 ng mL^{-1}	80–109	<20	300	[49]
		4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	0.48–1.5 ng g^{-1} lipids	67–97	–	174	[55]
		5 mL	Soxhlet/Florisil	GC (ECNI)- MS	1	DB-XLB/He	35.2 ng g^{-1} lipids	–	–	43	[60]
		1 mL	LLE	GC (ECNI)- MS	2	RTX-1614/He	1.7 pg mL^{-1}	76	17	Method development	[59]
		0.5 mL	QuEChERS	GC (APCI)-MS/MS	1	DB-5MS/He	0.07 pg mL^{-1}	97–112	4.59–11.9	60	[61]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.1 ng g^{-1}	73–87	2.0–3.0	Method development (38)	[65]
	Cord blood	–	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	0.24 pg g^{-1}	–	–	Method Development	[117]
	Breast milk	5 g	LLE/GPC	GC (ECNI)- MS/MS	–	DB-1MS/He	0.86 ng g^{-1} lipids	77 ± 49	–	105	[116]
		20–25 mL	Soxhlet/GPC-sulfuric acid	GC (ECNI)- MS	1	DB-5MS/He	1.5 pg g^{-1}	80–115	<15	29	[10]
		8–10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.006 ng g^{-1}; 0.001 ng g^{-1}	110–114; 69 ± 24	7–12	120; 458	[88,89]
		0.5 g	PLE/Florisil - Sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	0.03 ng g^{-1} dry weight	89 ± 37	–	35	[92]
		20 mL	Soxhlet/GPC-sulfuric acid	GC (APCI)-MS/MS	1	DB-5MS/He	0.05–0.3 pg g^{-1}	70–125	<15	20	[94]
	Hair	2 g	LLE/Silica-alumina	GC (ECNI)- MS	1	DB-5HT/He	0.01–0.83 ng g^{-1}	–	–	173	[77]
		100 mg	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	0.24 ng g^{-1}	139	5	5	[79]
		2 g	Soxhlet/Florisil	GC (ECNI)- MS	1	DB-XLB/He	0.01 ng g^{-1} dry weight	–	–	43	[82]
		200 mg	Ultrasound/Florisil	GC (ECNI)- MS	1	DB-5HT/He	0.20 ng g^{-1} dry weight	102–126	–	31	[78]
	Nails	10 finger nails	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	0.48 ng g^{-1}	178 ± 10	10	5	[79]

(*continued on next page*)

Table 4 (*continued*)

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
Decabromodiphenyl ethane (DBDPE)	Serum	2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5/He	2.0 ng mL^{-1} (unit uncertain)	84–91	10–15	85	[34]
		2 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5MS/He	20 pg mL^{-1}	34–36	8–13	10	[35]
		2 g	LLE/GPC	GC (ECNI)- MS/MS	–	DB-1MS/He	3.5 ng g^{-1} lipids	30 ± 15	–	102	[116]
		5 mL	QuEChERS or SPE	GC (ECNI)- MS	1	DB-5MS/He	472 pg mL^{-1}; 330 pg mL^{-1}	43–55; 59–71	33–42; 49–50	12	[43]
		3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	0.20 ng mL^{-1}	80–109	<20	300	[49]
		4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	23–73 ng g^{-1} lipids	67–97	–	174	[55]
		1 mL	LLE	GC (ECNI)- MS	2	RTX-1614/He	–	82	18	Method development	[59]
		5 mL	Soxhlet/Florisil	GC (ECNI)- MS	1	DB-XLB/He	5.59 ng g^{-1} lipids	–	–	43	[60]
		0.5 mL	QuEChERS	GC (APCI)-MS/MS	1	DB-5MS/He	30 pg mL^{-1}	100-115	10.2–16.3	60	[61]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	2.5 ng g^{-1} lipids	71–87	10–18	Method development (38)	[65]
	Cord blood	–	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	13 pg g^{-1}	–	–	Method development	[76]
	Breast milk	5 g	LLE/GPC	GC (ECNI)- MS		DB-1MS/He	1.7 ng g^{-1} lipids	15 ± 11		105	[116]
		20–25 mL	Soxhlet/GPC-sulfuric acid	GC (ECNI)- MS	1	DB-5MS/He	27 pg g^{-1}	70–130	<30	29	[10]
		0.5 g	PLE/Florisil- sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	0.25 ng g^{-1} dry weight	–	–	35	[92]
	Nails	50 mg	LLE	GC (ECNI)-MS	1	DB-5MS/He	1.51 ng g^{-1}	79 ± 6.8	–	50	[96]
Pentabromoethylbenzene (PBEB)	Serum	5 mL	QuEChERS or SPE	GC (ECNI)- MS	1	DB-5MS/He	0.5 pg mL^{-1}; 2.3 pg mL^{-1}	101–106; 78–89	1.7–2.1; 1.9–7.3	12	[43]
		3 mL	LLE/GPC-silica- alumina	GC (ECNI)-MS	–	DB-5MS/He	0.6–10 pg (instrumental detection limit)	–	–	10	[47]
		3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg (instrumental detection limit)	–	–	20	[51]
		3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	0.01 ng mL^{-1}	80–109	<20	300	[49]
		1 mL	LLE	GC (ECNI)- MS	2	RTX-1614/He	0.9 pg mL^{-1}	70	6	Method Development	[59]
		0.5 mL	QuEChERS	GC (APCI)-MS/MS	1	DB-5MS/He	0.06 pg mL^{-1}	102–117	4.49–10.2	60	[61]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.1 ng g^{-1} lipids	75–79	2–5	Method development (38)	[65]
	Breast milk	8–10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.003 ng g^{-1} lipids; 0.001 ng g^{-1} lipids	120–121; 121	7–17; 10	120; 458	[88,89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–		35	[92]
	Hair	100 mg	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	0.1 ng g^{-1}	95	5	5	[79]
	Nails	10 finger nails	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	0.2 ng g^{-1}	98	8	5	[79]
Pentabromophenol (PBP)	Serum	3 mL	LLE/QuEChERS	LC (ESI)-MS/MS	5	HSS T3/ammonium acetate in water-MeOH	0.33 ng mL^{-1}	71–78	2–15	Method development (38)	[65]

Pentabromotoluene (PBT)	Serum	3 mL	LLE/GPC	GC (ECNI)-MS	1	DB-5MS/He	0.6 pg (instrumental detection limit)	–		12	[41]
		5 mL	QuEChERS or SPE	GC (ECNI)- MS	1	DB-5MS/He	0.3 pg mL^{-1}; 1.6 pg mL^{-1}	102–111; 83–101	1.5–12.4; 1.8–5.1	12	[43]
		3 mL	LLE/GPC-silica- alumina	GC (ECNI)-MS	–	DB-5MS/He	0.6–10 pg (instrumental detection limit)	–	–	10	[47]
		3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg (instrumental detection limit)	–	–	20	[51]
		3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	0.01 ng mL^{-1}	80–109	<20	300	[49]
		1 mL	LLE	GC (ECNI)-MS	2	RTX-1614/He	1.4 pg mL^{-1}	82	1	Method development	[59]
		0.5 mL	QuEChERS	GC (APCI)-MS/MS	1	DB-5MS/He	0.11 pg mL^{-1}	92.3–103	5.51–8.59	60	[61]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.1 ng g^{-1} lipids	78–91	5–10	Method development (38)	[65]
	Breast milk	20 –25 mL	Soxhlet/GPC-sulfuric acid	GC (ECNI)- MS	1	DB-5MS/He	0.2 pg g^{-1}	80–115	15	29	[10]
		10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.003 ng g^{-1} lipids; 0.001 ng g^{-1} lipids	104–121; 121 ± 23	15–22; 23	120; 458	[88,89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
		20 mL	Soxhlet/GPC-sulfuric acid	GC (APCI)-MS/MS	1	DB-5MS/He	0.05–0.3 pg g^{-1}	70–125	<15	20	[94]
	Hair	3 g	Soxhlet/Sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	18.8–727 pg g^{-1} dry weight	–	–	13	[82]
		25 mg	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg	–	–	34	[83]
2,3,5,6,-Tetrabromo-p-xylene (TBX)	Serum	3 mL	LLE/GPC-silica- alumina	GC (ECNI)-MS	–	DB-5MS/He	0.6–10 pg (instrumental detection limit)	–	–	10	[47]
		3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg (instrumental detection limit)	–	–	20	[51]
	Breast milk	8–10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.001 ng g^{-1} lipids	80–87; 80 ± 15	10–18; 15	120; 458	[88,89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
	Hair	3 g	Soxhlet/Sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	18.8–727 pg g^{-1} dry weight	–	–	13	[82]
2,3,4,5-Tetrabromobenzoic acid (TBBA)	Urine	0.4 mL	SPE	LC (ESI)- MS/MS	–	–	0.05 ng mL^{-1}	90–113	<10	59	[118]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-water	0.05 ng mL^{-1}	–	2.7–7.5	2666	[119]
Tetrabromobisphenol A-bis(2,3-dibromopropyl ether) (TBBPA-BDBPE)	Breast milk	0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
Di(2-ethylhexyl) tetrabromophthalate (BEH-TEBP)	Serum	2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5/He	1.0 ng mL^{-1} (unit uncertain)	61–65	8–13	85	[34]
		3 mL	LLE/GPC	GC (ECNI)- MS	1	DB-5/He	0.25 pg (instrumental detection limit)	111 ± 27.4	–	10	[36]
		2 g	LLE/GPC	GC (ECNI)- MS	–	DB-1MS/He	7.3 ng g^{-1} lipids	–	–	102	[116]
		3–4 g	SPE/Silica	GC (ECNI)-MS	–	DB-5HT/He	24 ng g^{-1} lipids	101 ± 5	–	43	[42]
		4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	0.48–1.5 ng g^{-1} lipids	67–97		174	[55]
	Cord blood	–	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	5 pg g^{-1}	–	–	Method development	[76]
	Breast milk	5 g	LLE/GPC	GC (ECNI)- MS/MS	–	DB-1MS/He	0.15 ng g^{-1} lipids	–	–	105	[116]
		10 mL	PLE/Dialysis. basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.023 ng g^{-1} lipids	87 ± 18	18	458	[89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	0.003 ng g^{-1} dry weight	88 ± 11; 75–83	11	35	[92]
	Hair	100 mg	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	8.4 ng g^{-1}	120	7	5	[79]
		25 mg	Ultrasound/Sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg	–	–	34	[83]
	Nails	50 mg	LLE	GC (ECNI)-MS	1	DB-5HT/He	0.55 ng g^{-1}	115 ± 8.3	–	50	[96]
		10 finger nails	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	16.8 ng g^{-1}	141	13	5	[79]

(continued on next page)

Table 4 (*continued*)

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
2-Ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB)	Serum	2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5/He	1.0 ng mL^{-1} (unit uncertain)	112–117	9–15	85	[34]
		2 g	LLE/GPC	GC (ECNI)- MS/MS	–	DB-1MS/He	0.38 ng g^{-1} lipids	–	27	102	[116]
		3–4 g	SPE/Silica	GC (ECNI)-MS	–	DB-5HT/He	56 ng g^{-1} lipids	111 ± 4	–	43	[42]
		4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	0.74–2.4 ng g^{-1} lipids	67–97	15–42	174	[55]
		1 mL	LLE	GC (ECNI)- MS	2	RTX-1614/He	–	55	13	Method development	[59]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.05 ng g^{-1} lipids	113–115	7–12	Method development (38)	[65]
	Cord blood	–	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	10 pg g^{-1}	–	–	Method development	[117]
	Breast milk	5 g	LLE/GPC	GC (ECNI)- MS/MS	–	DB-1MS/He	0.03 ng g^{-1} lipids	–	–27	105	[116]
		10 mL	PLE/GPC, dialysis, basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.006 ng g^{-1} lipids; 0.001 ng g^{-1} lipids	105–109; 109 ± 21	12–21; 21	120; 458	[88,89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	0.003 ng g^{-1} dry weight	81–90	–	35	[92]
	Hair	100 mg	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	4.6 ng g^{-1}	136	9	5	[79]
	Nails	10 finger nails	LLE/Florisil	GC (ECNI)- MS	1	RTX-1614/He	9.2 ng g^{-1}	136	15	5	[79]
		50 mg	LLE	GC (ECNI)-MS	1	DB-5HT/He	0.51 ng g^{-1}	107 ± 7.3	–	50	[96]
Hexabromobenzene (HBB)	Serum	2 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5MS/He	0.30 pg mL^{-1}	93–102	5–8	10	[35]
		5 mL	QuEChERS or SPE	GC (ECNI)- MS	1	DB-5MS/He	0.8 pg mL^{-1}; 3.6 pg mL^{-1}	100–110; 98–104	1.2–2.9; 2.4–5.9	12	[43]
		3 mL	LLE/GPC-silica- alumina	GC (ECNI)-MS	–	DB-5MS/He	0.60–10 pg (instrumental detection limit)	–	–	10	[47]
		3 mL	LLE/GPC-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg (instrumental detection limit)	67–92	–	20	[51]
		3 g	LLE/Silica	GC (ECNI)- MS	2	DB-XLB/He	0.010 ng mL^{-1}	80–109	–	300	[49]
		0.5 mL	QuEChERS	GC (APCI)-MS/MS	1	DB-5MS/He	0.13 pg mL^{-1}	83.4–89.7	12.6–21.1	60	[61]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.1 ng g^{-1} lipids	71–83	6–10	Method development (38)	[65]
	Cord blood	–	SPE/Acidified silica	GC (ECNI)- MS/MS	2	ZB semivolatiles/He	5 pg g^{-1}	–	–	Method development	[76]
	Breast milk	20–25 mL	Soxhlet/GPC-sulfuric acid	GC (ECNI)- MS	1	DB-5MS/He	–	80–115	<15	29	[10]
		8–10 mL	PLE/GPC, dialysis. basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.060 ng g^{-1} lipids; 0.002 ng g^{-1} lipids	100–110; 110 ± 8	2–18; 8	120; 458	[88,89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35	[92]
		20 mL	Soxhlet/GPC-sulfuric acid	GC (APCI)-MS/MS	1	DB-5MS/He	0.05–0.3 pg g^{-1}	70–125	<15	20	[94]
	Hair	2 g	LLE/Silica-alumina	GC (ECNI)- MS	1	DB-XLB/He	0.01–0.83 ng g^{-1}	–	–	173	[77]
		100 mg	LLE/Florisil	GC (ECNI)-MS	1	RTX-1614/He	0.10 ng g^{-1}	60 ± 10	10	5	[79]
		3 g	Soxhlet/Sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	18.8–727 pg g^{-1} dry weight	–	–	13	[82]
		25 mg	Ultrasound/GPC, sulfuric acid-silica	GC (ECNI)- MS	–	DB-5MS/He	0.1–5 pg g^{-1}	77–122	–	34	[83]
	Nails	10 finger nails	LLE/Florisil	GC (ECNI)-MS	1	RTX-1614/He	0.2 ng g^{-1}	86 ± 7	7	5	[79]
		50 mg	LLE	GC (ECNI)-MS	1	DB-5HT/He	0.08 ng g^{-1}	106 ± 3.2	–	50	[96]

Tetrabromoethylcyclohexane (DBE-DBCH)	Serum	4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	0.78–2.5 ng g^{-1} lipids	67–97	15–42	174		[55]
		3 mL	LLE/Florisil	GC (EI)- MS/MS; GC (ECNI)-MS	2	DB-XLB/He	0.05 ng g^{-1} lipids	89–107	12–16	Method development (38)		[65]
	Breast milk	10 mL	PLE/Dialysis. basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.007–0.008 ng g^{-1} lipids; 0.001 ng g^{-1} lipids	64–105; 105 ± 20	13–24; 20	120; 458		[88,89]
		0.5 g	PLE/Florisil-sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	0.04 ng g^{-1} dry weight	–	–	35		[92]
5,6-Dibromo-1,10,11,12,13,13-hexachloro-11-tricyclo [8.2.1.02,9] tridecene (DBHCTD)	Serum	2–3 mL	SPE/Sulfuric acid-silica	GC (ECNI)-MS	2	DB-5/He	1 ng mL^{-1} (unit uncertain)	99–102	1–2	85		[34]
		2 g	LLE/GPC	GC (ECNI)- MS	1	DB-1MS/He	0.21 ng g^{-1} lipids	–	23	102		[112]
		4.5 mL	SPE	GC (ECNI)- MS	1	DB-5HT/He	0.48–1.5 ng g^{-1} lipids	67–97	15–42	174		[55]
		3 mL	LLE/Florisil	GC (EI)- MS/MS	2	DB-XLB/He	0.05 ng g^{-1} lipids	86–104	11–15	Method development (38)		[65]
	Plasma	1 mL	SPE/Sulfuric acid-silica	GC (ECNI)- MS	–	HP-5MS/He	0.28 ng g^{-1} lipids	199.6	19.9	414		[72]
	Breast milk	5 g	LLE/GPC	GC (ECNI)-MS	1	DB-1MS/He	0.05 ng g^{-1} lipids	–	23	105		[112]
Allyl-2,4,6-tribromophenyl ether (TBP-AE); 2-Bromoallyl-2,4,6-tribromophenyl ether (TBP-BAE); 2,3-Dibromopropyl-2,4,6-tribromophenyl ether (TBP-DBPE)	Serum	3 mL	LLE/Florisil	GC (EI)- MS/MS	2	DB-XLB/He	0.05 ng g^{-1} lipids	89–100	4–10	Method development (38)		[65]
	Breast milk	8–10 mL	PLE/GPC, dialysis. basic alumina and C18	GC (EI)- HRMS	2	RTX-1614/He	0.006–0.731 ng g^{-1} lipids; 0.001–0.004 ng g^{-1}	40–98; 55 –96	14–26; 20 –25	120; 458		[88,89]
		0.5 g	PLE/Florisil- sulfuric acid	GC (ECNI)- MS	2	TraceGOLD (TG)/He	–	–	–	35		[92]

dilution of the urine with water or formic acid, which reduces matrix effects and thus between-sample variability potentially affecting analyte recovery [2].

Protein precipitation (with acetonitrile, methanol or freeze-drying) or protein denaturation (with strong inorganic acids such as HCl, or a weak organic acid, such as formic acid in combination with 2-propanol and water) is normally used to disrupt the protein-compound interaction in matrices with high protein contents such as blood, serum, plasma, hair, nail and breast milk [70,92,95,163–165].

In order to distinguish between internal and external sources of PBDEs, hair washing procedures were suggested [166]. In a series of studies, Kucharska et al. [80,81,167] and Poon et al. [168] investigated the distinctions between internal and external FRs in the hair matrix. They claimed that there was no washing medium that was able to entirely and exclusively remove external contamination. Therefore, it seems impossible to distinguish external from internal sources of FRs in hair samples by applications of pre-treatment procedures. Water and shampoo could not sufficiently remove all external contamination, while solvents (such as n-hexane, dichloromethane (DCM) and methanol) might penetrate to the inner part of the hair and extract compounds from the inner structure of hair.

4.3. Extraction and clean-up

Several techniques have been applied for the extraction of FRs from human samples, optimized for the matrix and group of FRs to be analyzed (Tables 2–5). They include liquid-liquid extraction (LLE), here encompassing all solvent-based extractions without additional instrumentation, solid-phase extraction (SPE), cavity-dispersed microwave-assisted extraction (MAE), pressurized liquid extraction (PLE), ultrasound and Soxhlet. LLE and SPE are the most widely used methods to extract FRs from human samples. Both techniques showed good extraction efficiencies for the isolation of the majority of the FR compounds although challenges may exist for highly lipophilic compounds.

Because of similar interaction between lipids and the non-polar solvents or stationary phases, lipids are co-extracted with the targeted HFRs. Therefore, clean-up is normally required after extraction for matrices containing lipids such as serum, plasma, milk and hair. Various clean-up techniques have been employed for human samples, among them silica acidified with sulfuric acid, silica-alumina, basic alumina, gel permeation chromatography (GPC), in-cell SPE, C18 SPE, and dialysis (Tables 2–5). The acid treatment removes lipids efficiently, but is not suitable for acid-labile compounds, such as BEH-TEBP.

4.3.1. Halogenated flame retardants

LLE has been broadly used for extraction of HFRs from human matrices. It is typically performed with non-polar solvents (e.g. hexane, DCM, diethylether, ethyl acetate, and methyl-tert-butyl ether (MTBE)). More specifically, the isolation of neutral aromatic brominated compounds is conducted with non-polar solvents, while extraction of phenolic compounds is based on separating an aqueous phase containing the deprotonated phenols, acidifying it to enable extraction with a non-polar organic solvent. For analysis with gas chromatographic methods, derivatising phenols to their methoxylated analogues is needed [22].

LLE has been used for the extraction of PBDEs, HBCD, and NHFRs from serum [39,36,113,47,59,40,41,49,51,54,56,58,63,65,67,109,110,112,116], plasma [73], breast milk [100,101,116,86], hair [39,80,79,70,113,115,77,84,81,167,85], and nails [70,79,96,97]. Reported recoveries of most PBDEs and HBCDs extracted with LLE in all human matrices are in acceptable ranges

of 80–110% (Table 2; Table 3). However, LLE is not equally efficient for the isolation of highly lipophilic FRs (Tables 2–4). For instance, recoveries of ^{13}C-labelled BDE-209 in serum extracted with a hexane/MTBE mixture were only 55–88% [51], and its extraction with a hexane/acetone mixture followed by elution on a PHREE (Phospholipid Removal) cartridge was 56% [59]. Recoveries of 52 ± 22% and 59 ± 17% were achieved for $^{13}C_{12}$-BDE-209 and $^{13}C_{10}$-syn-DDC-CO in breast milk with LLE using a DCM/hexane mixture [86]. Recoveries of the spiked surrogates in serum and breast milk samples extracted with LLE using ethanol/diethylether/pentane were 49 ± 6%, 42 ± 20%, 46 ± 8%, and 30 ± 15%, for $^{13}C_{12}$-BDE-153, $^{13}C_{12}$-BDE-209, $^{13}C_{10}$-anti-DDC-CO, and $^{13}C_{14}$-decabromodiphenyl ethane (DBDPE), respectively [116,112]. Recoveries of EH-TBB in serum were 55% [59] and 67–92% [116] with LLE using hexane/acetone and hexane/MTBE mixtures, respectively, but higher recoveries were achieved with other methods (Table 4).

SPE, among the other methods, has been reported as the technique of choice for the extraction of numerous HFRs from serum, plasma, cord blood, whole blood, and breast milk. SPE sorbents commonly used include weak anion-exchange, molecularly imprinted polymers (MIP) or hydrophilic–lipophilic balanced polymers. Commercial sorbents, such as Oasis HLB, Oasis MAX, Oasis WAX, C18, Florisil, Isolute 101, Isolute Phenyl, ENV$^+$, Strata-X, StrataSI-1 Silica, Strata-NH_2, and Strata-CN have been used. The main advantages of SPE are the low solvent volumes required, the potential for automation, good reproducibility and time saved. Besides, the wide range of stationary phases makes SPE a useful technique for different groups of compounds. Oasis HLB (divinylbenzene based stationary phase) has been reported as the preferred sorbent for extraction of the seven most abundant PBDEs (BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183) from serum and plasma. The recoveries obtained for these BDE congeners were in the range of 65–105% [34], 95–142% [35], 50–120% [44,57], 87 ± 15% [42], 78–92% [45], 71–141% [46], 67–127% [48], 59–125% [72], and 71–89% [69]. Oasis HLB has also been used for the extraction of HBCD diastereoisomers from serum. The recoveries achieved were 87 ± 15% [42] and 83–145% [48]. Acceptable recoveries (95–118%) were also reported for extraction of 2,4-dibromophenol and 2,4,6-tribromophenol from human serum [34,42].

The poor recoveries for highly lipophilic compounds (e.g. BDE-209, DBDPE, DDC-CO) were explained by irreversible adsorption [3,169] or incomplete protein denaturation [122]. Investigations by Cequier et al. [170] on the recoveries of NHFRs from human serum using Oasis HLB reported very low recoveries for DBDPE, BDE-209, and DDC-CO, averaging 24%, 38%, and 49%, respectively. The poor recoveries were negatively associated with the lipid content of the serum, which indicates that interactions between highly lipophilic FRs and lipids might have affected the extraction efficiencies. Cequier et al. [170] recommended the use of isotopically labelled analogues as internal standards, in order to avoid erroneous concentrations of the highly lipophilic HFRs in serum.

A C18 sorbent used for extraction of PBDEs by several studies showed lower extraction efficiency compared to Oasis HLB. The recoveries obtained for PBDEs from serum were 40–71% for BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154 [38], 67–123% for BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, and BDE-209 [43], and 29–109% for BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, and BDE-209 [12]. C18 was also used for the extraction of NHFRs such as BTBPE, DBDPE, PBT and HBB with more acceptable ranges of recoveries [43,61]. The reported recoveries were 63–75% for BTBPE [43], 103–115% for DBDPE [61], 92–103% and 83–101% for PBT [43,61], as well as 87–90% and 98–104% for HBB [43,61].

Soxhlet extraction, as a robust and affordable method, has been used to extract PBDEs, HBCD and NHFRs from serum, breast milk and hair with acceptable ranges of recoveries of 75–125% (Table 3; Table 4). To extract liquid matrices such as serum and milk using Soxhlet, samples were commonly dried using freeze-drying or drying agents, such as sodium sulfate and hydromatrix [94,60,102]. A mixture of hexane/acetone was the solvent of choice for the extraction of PBDEs, HBCD and NHFRs using Soxhlet [91,94,82,60,87,93,102]. However, the main disadvantages of Soxhlet extraction are the long extraction time and the larger solvent volumes needed compared to other techniques.

PLE with solvent mixtures of hexane/acetone [66,92]; hexane/DCM [95,107,64] and hexane/DCM/methanol [88] has been used as the method of choice for extraction of PBDEs, HBCD and NHFRs, mainly from breast milk and serum samples. Good recoveries were achieved for PBDEs (75–116%), HBCDs (75–125%), with a slightly larger range for dechloranes 602, 603 and 604 (53–113%) (Table 3; Table 4). Ultrasonication has been used for the extraction of PBDEs, HBCDs and NHFRs from serum, blood, placenta, breast milk and hair. Mixtures of MTBE/hexane [111,37,53], hexane/DCM [103,78] and hexane/acetone [83] were used as extraction solvents. Ultrasonication showed acceptable extraction efficiencies for PBDEs (61–110%), dechloranes 602, 603 and 604 (60–109%) and TBBPA (89%) (Tables 2–4).

QuEChERS (quick, easy, cheap, effective, rugged, and safe) has also been introduced for the analysis of less lipophilic compounds (e.g. pentabromophenol (PBP), TBBPA) in serum. Gao et al. [43] introduced QuEChERS as a simple and efficient method for simultaneous extraction and clean-up of six NHFRs and eight PBDEs in human serum. They used an acetone/hexane mixture to isolate the lipids and analytes from serum with a combination of $MgSO_4$ and NaCl, followed by a dispersive SPE using C18 particles as a sorbent. QuEChERS generally showed higher efficiency in recovering PBDEs and NHFRs compared to SPE extraction and clean-up using Oasis HLB column (Table 2; Table 4). For BDE-209, however, this only applied for higher spike levels. Svarcova et al. [65] reported 92–116% of recoveries for PBP and TBBPA in cleaning up serum samples using a QuEChERS fat dispersive-SPE EN kit (PSA, C18 and $MgSO_4$) (Table 4). In a recent study by Lee et al. [68], QuEChERS was validated to extract 23 PBDEs in human serum with detection limits of 2–20 pg mL^{-1} and recoveries of 85–112%.

Acid digestion and LLE followed by SPE clean-up were reported as suitable methods to extract HFRs from hair and nails. Liu et al. and Zhao et al. [79,70] achieved acceptable recoveries for several PBDEs and NHFRs using LLE (with hexane/DCM) and Florisil SPE clean-up. Reported extraction recoveries ranged between 71 and 109% (PBDEs), 93–95% (dechloranes 602, 603, 604), 178% (BTBPE), 98% (PBEB), 141% (BEH-TEBP), 136% (EH-TBB), and 86% (HBB).

Lin et al. [84] developed a method that addressed the challenge of distinguishing PBDEs in hair originating from internal and external sources. They extracted the external analytes under ultrasonication using acetone, while the internal target analytes were resolved with further digestion and LLE. Alkaline digestion with LLE in combinations of alkaline and re-acidification conditions was suggested as the key procedure to successfully extract both parent and metabolic compounds from hair. Recoveries of 62–145% and 60–88% were achieved for PBDEs and hydroxylated PBDEs metabolites, respectively.

The literature shows that multiple extraction and clean-up methods achieve comparable results with efficiencies close to 100%. With the techniques presented here, and assuming suitable solvents, differences in extraction efficiency seems to be larger between compounds than between extraction and clean-up methods. The complete extraction of highly lipophilic compounds remains challenging and should be quality assured by the use of labelled internal standards. The lipid content of the sample seems

to be an important factor in the quantitative extraction, although interactions between lipids, target analytes and sorbents are not fully understood.

4.3.2. Organophosphorous flame retardants

Since PFRs are readily excreted from the body, they are rarely measured in blood-related matrices. However, some studies reported analyses of PFR compounds and metabolites in whole blood and serum [47,65,106,140,143,139]. LLE was used for extraction of PFR compounds and metabolites from serum [47,143,49,139], urine [143,144], breast milk [159], hair [80,84,81,167,85] and nails [96].

Extraction of PFR metabolites from urine is mainly performed using SPE techniques. SPE with anion exchange sorbents, such as Oasis WAX, Strata X-AW, Oasis MAX and ENV$^+$ are reported to be suitable for isolation of PFR metabolites from urine samples [140,106,137,138,147,150–153,158]. These sorbents contain positively charged groups that can interact with the analytes through anion interactions. To remove this interaction and recover the analytes, an organic solvent containing a small percentage of base (mainly ammonia) is used. Oasis WAX and StrataX-AW, which are weak anion exchange sorbents, showed best performance in extracting PFR metabolites from urine samples [106,137,150] (Table 5). Oasis MAX, which is a mixed-mode polymeric sorbent, has also been used to isolate various PFR metabolites from urine samples. This SPE sorbent produced recoveries from 75 to 113% [31,32,140,153,141,152,157,158]. Application of an ENV$^+$ sorbent in isolating PFR metabolites from urine resulted in recoveries of 84–110% [142].

Bastiaensen et al. [31] reported a method for the determination of 14 urinary PFRs metabolites (covering eight DAPs and six OH-PFRs) using Bond-Elut C18 SPE, which produced recoveries from 87 to 112%. The method was applied to the biomonitoring of PFR metabolites in urine samples of children, adults and a particular target group of intensive care patients [32,141,157,171]. Hu et al. [172] introduced a rapid and robust multi-analyte method for biomonitoring of 15 urinary PFR metabolites using a solvent induced phase transition extraction (SIPTE) technique. SIPTE is a novel LLE technology which uses a hydrophobic solvent (MTBE) to induce better phase separation of an acetonitrile (ACN) aqueous solution [172]. The method was described as simple and rapid and achieved high recoveries, i.e. 71-118% for 15 urinary PFRs metabolites.

Direct injection of untreated urine samples into the analytical instrument (ultraperformance liquid chromatography (UPLC) with quadrupole time-of-flight (Q-TOF) mass spectrometry (MS)) has also been a rapid method for analyses of DAPs [170]. The method performed well with high accuracy (58–125%) and precision (1–8%) for monitoring of DPHP, di-n-butyl phosphate (DNBP), bis(2-butoxyethyl) phosphate (BBOEP), and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) in urine samples. Low MDLs were reported, i.e. 0.1, 0.4, 0.6 and 0.4 ng mL^{-1} for DPHP, DNBP, BBOEP and BDCIPP, respectively. However, MDLs were not sufficiently low for the most polar DAPs; i.e. bis(chloroethyl) phosphate (BCEP) (12 ng mL^{-1}) and BCIPP (25 ng mL^{-1}). The direct injection of urine reduced the risk for background contamination and showed insignificant matrix effects evaluated using deuterated internal standards.

A QuEChERS approach has also been applied to PFR parent compounds in breast milk. Beser et al. [159] achieved recoveries of 94–110% for PFR compounds (trimethyl phosphate (TMP), triethyl phosphate (TEP), tris(chloroethyl) phosphate (TCEP), triisopropyl phosphate (TiPrP), tri-n-propyl phosphate (TPrP), TCIPP, triphenyl phosphate (TPHP), tri-n-butyl phosphate (TNBP)) in breast milk with QuEChERS clean-up using NaCl and $MgSO_4$ (Table 5).

Acid digestion followed by SPE clean-up was reported as the method of choice to monitor PFR biomarkers in hair and nails. Alves et al. [126] developed a method for monitoring of four PFR metabolites (DPHP, Dibutyl phosphate (DBP), BDCIPP, and BBOEP) in hair and nails. They used acid digestion followed by Oasis Wax SPE for clean-up of hair and nail samples which produced recoveries of 74–102% in hair and 85–110% in nail matrices (Table 5).

The urine analysis of PFR metabolites, the most common biomonitoring approach for determination of PFR exposure, indicates high extraction efficiencies, and promising results exist for extension to further compounds, covering both DAPs and OH-PFRs. High MDLs might pose a challenge, but these seem to be related to instrumental analysis rather than to extraction and clean-up techniques.

4.3.3. Multi-analyte methods

Due to the typically small amounts of sample material available, it is advantageous to apply methods, which enable the simultaneous analysis of several contaminants in different matrices. Several multi-analyte methods for simultaneous determination of FRs in human matrices have been developed.

Shi et al. [66] developed a method for the simultaneous analysis of PBDEs, HBCD diastereoisomers, and TBBPA in human serum and breast milk. The method uses PLE as extraction technique and GPC and SPE as clean-up techniques and performed well with recoveries from 79 to 109%. Sahlström et al. [173] introduced a method for the measurement of multiple HFRs in human serum. The method separated acid-resistant BFRs and acid-sensitive BFRs on silica SPE columns, followed by aminopropyl columns for clean-up. The average method recoveries ranged from 57 to 101%. Huang et al. [90] developed a method for the simultaneous determination of multiple POPs, including FRs in human breast milk using LLE for extraction and GPC and SPE for clean-up. Reported recoveries were 89–93% for HBCD diastereoisomers and 89–99% for PBDEs.

Svarcova et al. [65] developed a novel multi-analyte procedure for the determination of organohalogen contaminants including HFRs and PFRs in serum. The sample preparation procedure included the extraction of non-polar compounds, based on a three-step solvent extraction, followed by purification using a Florisil SPE. For the isolation of more polar and hydrophilic analytes, the remaining fraction was further processed using a modified QuEChERS method. Recoveries of 71–115% were achieved for FRs (Tables 2–5). Tang et al. [85] recently introduced a solvent-saving method for the simultaneous determination of eight PBDEs, HBCD diastereoisomers, and twelve PFRs in human hair (Table 2; Table 3; Table 5). The reported accuracies ranged between 88 and 115%, 82–117%, and 81–128% for PBDEs, HBCD diastereoisomers, and PFR parent compounds, respectively. Chen et al. [96] applied LLE using n-hexane/DCM to extract PBDEs, NHFRs and PFRs from nails. Their approach produced recoveries of 81–118% (PBDEs), 103–109% (HBB), 100–114% (EH-TBB), 107–123% (BEH-TEBP), 95–103% (DDC-CO), and 68–107% for several PFR compounds (TCEP, TPHP, TCIPP, TPrP, Tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), Tris(2-butoxyethyl) phosphate (TBOEP), and TNBP (Tables 2–5).

These examples show that the combination of several FR compounds in one extraction and clean-up method is possible, even from groups with different physical-chemical properties, applying fractionation approaches in the clean-up procedures and subsequent instrumental analysis techniques that are optimized for the different compound groups. Considering the challenges related to limited sample amounts and the potentially time-consuming sample processing and analysis, the development of multi-methods will have a relevant place in the human biomonitoring of FRs, possibly also in combination with high resolution instrumental techniques.

Table 5
Overview of analytical methods used for determination of organophosphorous flame retardants (PFRs) in human matrices.

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
2-Ethyl-3-hydroxyhexyl diphenyl phosphate (3-OH-EHDPP); 3-Hydroxy-4-methylphenyl di-p-tolyl phosphate (3-OH-MDTP); 4-(Hydroxymethyl) phenyl di-p-tolyl phosphate (4-OH-MDTP)	Whole blood	0.5 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/MeOH/Water	0.001–0.01 ng mL^{-1}	74–86	–	259	[106]
	Urine	2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.66 ng mL^{-1}	107	21.5	128	[31,32]
		0.5 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.001–0.008 ng mL^{-1}	67–85	–	259	[106]
Trimethylphenyl phosphate (TMPP); Tri-p-tolyl phosphate (p-TMPP); Tri-m-tolyl phosphate (m-TMPP); Tri-o-tolyl phosphate (o-TMPP)	Serum	3 mL	LLE/GPC-silica-alumina	GC (ECNI)-MS	–	DB-5MS/He	–	–	–	595 (pooled into 10)	[47]
		3 mL	LLE/GPC-silica-alumina	GC (EI)- MS/MS	2	DB-XLB/He	–	–	–	Method development (38)	[65]
	Urine	2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.01 ng mL^{-1}	72–93	–	20	[137]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.01 ng mL^{-1}	63–92	–	51	[138]
	Breast milk	2 mL	ASE/GPC-silica-alumina	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.034 ng mL^{-1}	–	–	3	[137]
Triphenyl phosphate (TPHP); 3-Hydroxyphenyl diphenyl phosphate (3-HO-TPHP); 4-Hydroxyphenyl diphenyl phosphate (4-HO-TPHP)	Serum	3 mL	LLE/GPC-silica-alumina	GC (ECNI)-MS		DB-5MS/He	-	93 ± 15	–	595 (pooled into 10)	[47]
		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	64–175	28.9	99	[139]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	760–3800 pg mL^{-1}	–	–	61	[140]
	Whole blood	0.5 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.14 ng mL^{-1}	76–96	–	259	[106]
	Urine	2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	0.004–0.29 ng mL^{-1}	93–100	10.3–30.5	128; 400	[31,32,141]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.31 ng mL^{-1}	89–117	–	20	[137]
		2 mL	SPE	LC (ESI)-MS/MS	-	Synergi Fusion-RP/Water-MeOH	0.5 ng mL^{-1}	63–92	–	51	[138]
		10 mL	SPE/Silica	GC (EI)- MS/MS	1	TG-5HT/He	–	84–110	–	48	[142]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	23–57 pg mL^{-1}	–	–	61	[140]
	Hair	200 mg	LLE/Florisil-acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	4 ng g^{-1}	104	4	Method development (102)	[80,81]
		200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	10.8 ng g^{-1} dry weight	–	–	31	[78]
		100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	–	–	–	55	[140]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/Water-MeOH-ACN	0.30 ng g^{-1}	75–95	3	14	[85]
	Nails	50 mg	LLE	UPLC (ESI)- MS/MS	10	SPP C18/ACN-Water	0.03 ng g^{-1}	81 ± 4.9	–	50	[96]

Dibutyl phosphate (DBP); Diphenyl phosphate (DPhP);	Serum	0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	517 pg mL^{-1}	107	–	61	[140]
4-Hydroxyphenyl phenyl phosphate (4-HO-DPHP); 2-Ethylhexyldiphenyl phosphate (EHDPP); 2-Ethyl-5-hydroxyhexyl diphenyl phosphate (5-OH-EHDPP); *Tert*-butyl diphenyl phosphate (t-butyl-DPHP); Bis(1,3- and bis(2-butoxy ethyl) phosphate (BBEP)		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	60–100	9.9	99	[139]
		0.5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.006–0.173 ng mL^{-1}	63–68	–	57	143
	Whole blood	0.5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.006–0.173 ng mL^{-1}	62–68	–	57	[143]
		0.5 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.12 ng mL^{-1}	69–94	–	259	[106]
	Amniotic fluid	2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.1 ng mL^{-1}	–	–	15	[144]
	Urine	2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.005–0.66 ng mL^{-1}	101–107	2.9–21.5	128 400	[31,32,141]
		2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	25–130 pg mL^{-1}	119 ± 0.75	–	211	145
		5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	0.33 ng mL^{-1}	71.9–82.4	–	310	[146]
		0.4 mL	SPE	LC (ESI)- MS/MS	–	–	0.16 μg mL^{-1}	–	–	59	[118]
		1 mL	SPE	LC (ESI)- MS/MS	5	Synergi Polar-RP/Water-MeOH	0.06–0.5 ng mL^{-1}	–	–	41	[147]
		2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	25–130 pg mL^{-1}	119 ± 0.75	–	276	[148]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.22 ng mL^{-1}	103–115	2.9–21.5	20	[137]
		0.4 mL	SPE	LC (ESI)-MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.05–0.6 ng mL^{-1}	63–92	–	51	[138]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-water	0.16 μg L^{-1}	93.5–108	–	2666	[119]
		5 mL	SPE	LC (ESI)- MS/MS	5	Hypersil Gold C18/ACN-water	0.12 ng mL^{-1}	103 ± 3.02	–	203	[149]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	2.55 pg mL^{-1}	103 ± 3.02	–	180	[150]
		2 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	0.03 ng mL^{-1}	–	–	118	[151]
		2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.1 ng mL^{-1}	–	–	15	[144]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-ACN	0.41 ng mL^{-1}	–	–	84	[152]
		5 mL	SPE	LC (ESI)- MS/MS	20	Luna C18/Water-MeOH	–	–	–	100	[153]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Kinetex XBC18/Water-MeOH	0.08–0.45 ng mL^{-1}	–	–	32	[154]
		1 mL	SPE	LC (ESI)- MS/MS	–	C18/Water-MeOH	3.5 pg mL^{-1}	–	–	19	[155]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	10 pg mL^{-1}	75–90	–	61	[140]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	–	–	–	227	[156]
		0.5 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.15 ng mL^{-1}	84–97	–	259	[106]
		5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.016–0.047 ng mL^{-1}	61–73	–	52	[143]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	0.66 ng mL^{-1}	99.7 ± 15.8	–	46	[157]
	Hair	100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	130 pg mL^{-1}	–	–	55	[140]
		200 mg	LLE/Florisil-acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	2 ng g^{-1}	109	9	Method development (102)	[80,81]
		200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	10.8 ng g^{-1} dry weight	–	–	31	[78]
		100 mg	Acid digestion/SPE	LC (ESI)- MS/MS	5	Kinetex Biphenyl/Water-MeOH	46.4 ng g^{-1}	74–102	11	Method development	[126]
	Nails	30 mg	Acid digestion/SPE	LC (ESI)- MS/MS	5	Kinetex Biphenyl/Water-MeOH	2.8 ng g^{-1}	77–87	17	Method development	[126]
	Breast milk	2 mL	ASE/GPC-silica-alumina	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.084 ng mL^{-1}	–	–	259	[106]

(*continued on next page*)

Table 5 (*continued*)

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
Bis(2-butoxyethyl) phosphate (BBOEP); 2-Hydroxyethyl bis(2-butoxyethyl) phosphate (BBOEHEP); Tris(2-butoxyethyl) phosphate (TBOEP); Bis(2-butoxyethyl) 3′-hydroxy-2-butoxyethyl phosphate (3OH-TBOEP)	Serum	0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	17–204 pg mL^{-1}	–	–	61	[140]
		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	76–149	13.5	99	[139]
		3 mL	LLE/GPC-silica-alumina	GC (EI)- MS	–	DB-5MS/He	–	–	–	10	[47]
		0.5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.027–0.07 ng mL^{-1}	101–118	4.1–10.2	57	143
	Whole blood	0.5 mL	LLE/SPE	LC (ESI)-MS/MS	5	C18/Water-MeOH	0.027–0.07 ng mL^{-1}	108–122	3.1–4.8	57	[143]
	Urine	5 mL	LLE/SPE	LC (ESI)-MS/MS	5	C18/Water-MeOH	0.013–0.016 ng mL^{-1}	101–110	4.7–9.3	52	[143]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	0.002–0.03 ng mL^{-1}	104–109	2.2–22.7	128 400	[31,32,141]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Bipheny-lRP/Water-MeOH	5–103 pg mL^{-1}	–	–	61	[140]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.0025–0.26 ng mL^{-1}	93–128	–	20	[137]
		2 mL	SPE	LC (ESI)-MS/MS	-	Sznergi Fursion-RP/Water-MeOH	0.01 ng mL^{-1}	63–92	–	51	[138]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.339 μg L^{-1}	83.9–113.9	–	411	[158]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	21.9 pg mL^{-1}	101 ± 4.10	–	180	[150]
		2 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	0.23 ng mL^{-1}	–	–	118	[151]
		2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.1 ng mL^{-1}	–	–	15	[144]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-ACN	0.33 ng mL^{-1}	81.4–113	–	84	[152]
		1 mL	SPE	LC (ESI)- MS/MS	–	C18/Water-MeOH	11 pg mL^{-1}	–	–	19	[155]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	–	–	–	227	[156]
	Hair	200 mg	LLE/Florisil-Acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	5 ng g^{-1}	113	5	Method development (102)	[80,81]
		200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	40 ng g^{-1}	–	–	31	[78]
		100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	–	–	–	55	[140]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/Water-MeOH-ACN	1.03 ng g^{-1}	–	10	14	[85]
	Nails	50 mg	LLE	UPLC (ESI)- MS/MS	10	SPP C18/ACN-water	0.04 ng g^{-1}	101 ± 6.7	–	50	[96]
Bis(chloroethyl) phosphate (BCEP); Tris(chloroethyl) phosphate (TCEP)	Serum	0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	194 pg mL^{-1}	–	–	61	[140]
		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	80–150	14.2	99	[139]
	Urine	0.4 mL	SPE	LC (ESI)- MS/MS	–	–	0.08 μg L^{-1}	90–113	10	59	[118]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	0.01 ng mL^{-1}	112	–	128	[31,32]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	1.648 μg L^{-1}	–	–	411	[158]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.014–0.022 ng mL^{-1}	69–131	–	20	[137]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-water	0.08 μg L^{-1}	–	–	2666	[119]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	2.51 pg mL^{-1}	89.3 ± 5.23	–	180	[150]
		2 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	0.38 ng mL^{-1}	80 ± 10	–	118	[151]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.001–0.02 ng mL^{-1}	73–139	–	227	[156]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-ACN	1.60 ng mL^{-1}	–	–	84	[152]
		10 mL	SPE	GC (EI)- MS/MS	1	TG-5HT/He	0.02 pg g^{-1}	68–102	–	48	[142]
		1 mL	SPE	LC (ESI)- MS/MS		C18/Water-MeOH	2.7 pg mL^{-1}	–	–	19	[155]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex Biphenyl-RP/Water-MeOH	0.05 ng mL^{-1}	–	–	46	[157]
	Breast milk	2 mL	ASE/GPC-silica-alumina	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.02 ng mL^{-1}	–	–	3	[137]
		2 mL	QuEChERs/SPE	LC (ESI)- MS/MS	10	Hypersil Gold/Water-MeOH-ACN	1.02 ng g^{-1} lipids	89–94	–	20	[159]
	Hair	200 mg	LLE/Florisil/acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	33 ng g^{-1}	109	4	Method development (102)	[80,81]
		200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	12.1 ng g^{-1} dry weight	–	–	31	[78]
		100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	–	–	–	55	[140]
		100 mg	LLE/Florisil	LC(ESI)-MS/MS	10	C18/Water-MeOH-ACN	3.47 ng g^{-1}	80–119	3	14	[85]
	Nail	50 mg	LLE	UPLC (ESI)- MS/MS	10	SPP C18/ACN-Water	0.13 ng g^{-1}	64 ± 4.6	–	50	[96]
Bis(1-chloro-2-propyl) phosphate (BCIPP); 1-Hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP Tris(2-	Serum	0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	182 pg mL^{-1}	–	–	61	[140]
		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	–	–	99	[139]
	Urine	2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	68–180 pg mL^{-1}	–	–	211	[145]
		5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	0.13 ng mL^{-1}	–	–	310	[146]

chloroisopropy) phosphate (TCIPP)		0.4 mL	SPE	LC (ESI)- MS/MS	–	–	0.1 μg mL^{-1}	–	–	59	[118]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.02–0.4 ng mL^{-1}	85–101	5.7–21.6	128 400	[31,32,141]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	1.123 μg L^{-1}	–	–	411	[158]
		5 mL	SPE	LC (ESI)- MS/MS	20	Luna C18/Water-MeOH	–	–	–	100	[153]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.002–0.039 ng mL^{-1}	82–119	–	20	[137]
		2 mL	SPE	LC (ESI)- MS/MS	-	Synergi Fusion-RP/Water-MeOH	2.8 ng mL^{-1}	63–92	–	51	[138]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-Water	0.1 μg L^{-1}	–	–	2666	[119]
		5 mL	SPE	LC (ESI)- MS/MS	5	Hypersil Gold C18/ACN-Water	0.18 ng mL^{-1}	–	–	203	[149]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	68–180 pg mL^{-1}	–	–	180	[150]
		2 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	20.5 ng mL^{-1}	80.5 ± 2.21	–	118	[151]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-ACN	1.20 ng mL^{-1}	–	–	84	[152]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Kinetex XBC18/Water-MeOH	0.15–0.64 ng mL^{-1}	–	–	32	[154]
		10 mL	SPE	GC (EI)- MS/MS	1	TG-5HT/He	–	–	–	48	[142]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	55 pg mL^{-1}	–	–	61	[140]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.05 ng mL^{-1}	–	–	46	[157]
		5 mL	SPE	LC (ESI)- MS/MS	5	Kinetex core shell/Water-MeOH	0.06 ng mL^{-1}	93.6–100.5	3.1–6.5	40	[160]
		1 mL	SPE	LC (ESI)- MS/MS	5	Synergi Polar-RP/Water-MeOH	0.05–0.1 ng mL^{-1}	–	–	41	[147]
	Breast milk	2 mL	ASE/GPC-silica-alumina	LC (ESI)- MS/MS		Synergi Fusion-RP/Water-MeOH	2.4 ng mL^{-1}	–	–	3	[137]
		10 mL	QuEChERs/SPE	LC (ESI)- MS/MS	10	Hypersil Gold/Water-MeOH-ACN	0.13 ng g^{-1} lipids	92–103	10–23	20	[159]
	Hair	100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	–	–	–	55	[140]
		100 mg	Acid digestion/SPE	LC (ESI)- MS/MS	5	Kinetex Biphenyl/Water-MeOH	286 pg g^{-1}	75	18	Method development	[126]
		200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	13.4 ng g^{-1} dry weight	–	–	31	[78]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/Water-MeOH-ACN	1.11 ng g^{-1}	75–90	4	14	[85]
	Nail	50 mg	LLE	UPLC (ESI)- MS/MS	10	SPP C18/ACN-Water	0.66 ng g^{-1}	99 ± 5.2	–	50	[96]
		30 mg	Acid digestion/SPE	LC (ESI)- MS/MS	5	Kinetex Biphenyl/Water-MeOH	286 pg g^{-1}	110	20	Method development	[126]
Bis(1,3-dichloro-2-propyl) phosphate (BDCIPP); tris(1,3-dichloro-2-propyl) phosphate (TDCIPP)	Serum	0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	406 pg mL^{-1}	–	–	61	[140]
		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	64–184	20.1	99	[139]
	Amniotic fluid	2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.5 ng mL^{-1}	69–125	–	15	[144]
	Urine	2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	31–300 pg mL^{-1}	152 ± 2.1	15 ± 35	211	[145]
		5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	0.03 ng mL^{-1}	115.6 ± 116.5		310	[146]
		2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	31–300 pg mL^{-1}	152 ± 2.2	–	276	[148]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.04 ng mL^{-1}	99	3.4–15.3	128 400	[31,32,141]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.848 μg L^{-1}	–	–	411	[158]
		5 mL	SPE	LC (ESI)- MS/MS	20	Luna C18/Water-MeOH	–	–	–	100	[153]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.0034–0.014 ng mL^{-1}	71–106	–	20	[137]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.024–3.3 ng mL^{-1}	63–92	–	51	[138]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-water	0.11 μg L^{-1}	–	–	2666	[119]
		5 mL	SPE	LC (ESI)- MS/MS	5	Hypersil Gold C18/ACN-Water	0.07 ng mL^{-1}	–	–	203	[149]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	4.45 pg mL^{-1}	85.8 ± 7.98	–	180	[150]
		2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.5 ng mL^{-1}	69–125	–	15	[144]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Kinetex XBC18/Water-MeOH	0.19 ng mL^{-1}	107	–	32	[154]
		10 mL	SPE	GC (EI)- MS/MS	1	TG-5HT/He	–	–	–	48	[142]
		1 mL	SPE	LC (ESI)- MS/MS		C18/Water-MeOH	10 pg mL^{-1}	–	–	19	[155]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	–	–	–	227	[156]
	Breast milk	2 mL	ASE/GPC-silica-alumina	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.053 ng mL-1	–	–	3	[137]
	Hair	200 mg	LLE/Florisil/acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	9 ng g^{-1}	107	8	Method development (102)	[80,81]
		100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	10 pg g^{-1}	–	–	55	[140]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/Water-MeOH-ACN	5.59 ng g^{-1}	79–100	2	14	[85]
Dibenzyl phosphate (DBzP)	Urine	0.4 mL	SPE	LC (ESI)- MS/MS	–	–	0.05 μg mL^{-1}	–	–	59	[118]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-Water	0.05 μg L^{-1}	–	–	2666	[119]
Bis(methylphenyl) phosphate (BMPP)	Urine	2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.0022 ng mL^{-1}	122–123	–	20	[137]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.004 ng mL^{-1}	63–92	–	51	[138]

(continued on next page)

Table 5 (*continued*)

Analytes	Matrix	Sample intake	Extraction/Clean up	Instrumental analysis	Inj. vol. (μl)	Stationary phase/Mobile phase	Method detection limit	Recovery (%)	RSD (%)	Study size	Reference
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	0.84 pg mL^{-1}	112 ± 2.89	–	180	[150]
Di-o-cresyl phosphate (DoCP); Di-p-cresyl phosphate (DpCP); Tricresyl phosphate (dTCP)	Urine	2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	–	–	–	227	[156]
		2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.1 ng mL^{-1}	–	–	15	[144]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-ACN	0.06 ng mL^{-1}	–	–	84	[152]
	Amniotic fluid	2 mL	LLE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.1 ng mL^{-1}	–	–	15	[144]
	Hair	200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	–	–	–	31	[78]
Diethyl phosphate (DEP); Diisobutyl phosphate (DIBP); Di-n-butyl phosphate (DNBP); Tri-n-butyl phosphate (TNBP)	Serum	3 mL	LLE/GPC-silica-alumina	GC (ECNI)-MS	–	DB-5MS/He	–	–	–	595 (polled into 10)	[47]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	314 pg mL^{-1}	–	–	61	[140]
		0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	–	–	99	[139]
	Urine	0.4 mL	SPE	LC (ESI)- MS/MS	–	–	0.05 μg mL^{-1}	–	–	59	[118]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.05 ng mL^{-1}	102	2.1–16.7	128 400	[31,32,141]
		2 mL	SPE	LC (ESI)- MS/MS	10	XTerra-C18/Water-MeOH	0.881 μg L^{-1}	–	–	411	[158]
		2 mL	SPE	LC (ESI)- MS/MS		Synergi Fusion-RP/Water-MeOH	0.051–7.5 ng mL^{-1}	92–128	–	20	[137]
		0.4 mL	SPE	LC (ESI)- MS/MS	10	XDB-C8/ACN-Water	0.05 μg L^{-1}		–	2666	[119]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	2.04–9.05 pg mL^{-1}	93.4 ± 4.63	–	180	[150]
		2 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	0.03 ng mL^{-1}	80.5 ± 2.21	–	118	[151]
		1 mL	SPE	LC (ESI)- MS/MS	–	C18/Water-MeOH	1.7–29 pg mL^{-1}	74.8–113	–	19	[155]
		0.5 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	239 pg mL^{-1}	–	–	61	[140]
		10 mL	SPE	GC (EI)- MS/MS	1	TG-5HT/He	–	–	–	48	[142]
		2 mL	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	0.05 ng mL^{-1}	–	–	46	[157]
	Breast milk	2 mL	ASE/GPC-silica-alumina	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.03 ng mL^{-1}	–	–	3	[137]
		10 mL	QuEChERS/SPE	LC (ESI)- MS/MS	10	Hypersil Gold/Water-MeOH-ACN	0.03 ng g^{-1} lipids	93–97	19–23	20	[159]
	Hair	200 mg	LLE/Florisil/acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	2 ng g^{-1}	106	4	Method development (102)	[80,81]
		200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	4.99 ng g^{-1} dry weight	–	–	31	[78]
		100 mg	SPE	LC (ESI)- MS/MS	5	Phenomenex Kinetex BiphenylRP/Water-MeOH	46 pg g^{-1}	–	–	55	[140]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/water-MeOH-ACN	3.62 ng g^{-1}	–	12	14	[85]
Isopropyl-phenyl phenyl phosphate (ip-PPP); *Tert*-butyl phenyl phenyl phosphate (tb-PPP)	Urine	2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	10–150 pg mL^{-1}	–	20–25	211	[145]
		5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	0.08–0.14 ng mL^{-1}	–	–	310	[146]
		1 mL	SPE	LC (ESI)- MS/MS	5	Synergi Polar-RP/Water-MeOH	0.02 ng mL^{-1}	–	–	41	[147]
		2.5–5 mL	SPE	LC (ESI)- MS/MS	5	Luna C18/Water-MeOH	23–120 pg mL^{-1}	–	–	276	[148]
		5 mL	SPE	LC (ESI)- MS/MS	20	Luna C18/Water-MeOH	–	–	–	100	[153]
		5 mL	SPE	LC (ESI)- MS/MS	5	Hypersil Gold C18/ACN-Water	0.02–0.08 ng mL^{-1}	–	–	203	[149]
Tri-o-cresyl phosphate (TOCP); Tri-p-cresyl phosphate (dTPCP)	Urine	10 mL	SPE/Silica	GC (EI)- MS/MS	1	TG-5HT/He	–	–	–	48	[142]
Tri-n-propyl phosphate (TPrP); Triisopropyl phosphate (TiPrP); Trimethyl phosphate (TMP); Triethyl phosphate (TEP)	Serum	0.5 mL	LLE	UPLC (ESI)- MS/MS	5	C18/Water-MeOH	0.05–0.5 ng mL^{-1}	62–114	11.4	99	[139]
		0.5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.016–0.485 ng mL^{-1}	101–109	–	57	[143]
	Whole blood	0.5 mL						99–11	–		
	Urine	5 mL					0.003–0.097 ng mL^{-1}	112–127	–	52	
		10 mL	SPE/Silica	GC (EI)- MS/MS	1	TG-5HT/He	–	–	–	48	[142]
	Breast milk	10 mL	QuEChERs/SPE	LC (ESI)- MS/MS	10	Hypersil Gold/Water-MeOH-ACN	0.02–0.32 ng g^{-1} lipids	92–110	7–19	20	[159]
	Hair	200 mg	Ultrasound/Florisil	GC (EI)- MS	1	DB-5MS/He	0.03–0.11 ng g^{-1} dry weight	–	–	31	[78]
		100 mg	LLE/Florisil	LC (ESI)-MS/MS	10	C18/Water-MeOH-ACN	0.11 ng g^{-1}	–	12	14	[85]
Bis(2-ethylhexyl) phosphate (BEHP); Tris(2-ethylhexyl) phosphate (TEHP)	Urine	2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.03–0.16 ng mL^{-1}	74–94	–	20	[137]
		2 mL	SPE	LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.01–0.41 ng mL^{-1}	63–92	–	51	[138]
		5 mL	SPE	LC (ESI)- MS/MS	5	Poroshell 120 EC-C18/Water-MeOH	0.53 pg mL^{-1}	105 ± 6.81	–	180	[150]
		1 mL	SPE	LC (ESI)- MS/MS	–	C18/Water-MeOH	2.3 pg mL^{-1}	–	–	19	[155]
		5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.003–0.097 ng mL^{-1}	112–127	–	52	[143]
	Breast milk	2 mL		LC (ESI)- MS/MS	–	Synergi Fusion-RP/Water-MeOH	0.66 ng mL^{-1}	–	–	3	[137]

		ASE/GPC-silica-alumina								
Hair	200 mg	LLE/Florisil/acidified silica	LC (ESI)- MS/MS	5	BEH C18/Water-MeOH	1 ng g^{-1}	101	5	Method development (102)	[80,81]
	200 mg	Ultrasound/florisil	GC (EI)- MS	1	DB-5MS/He	0.09 ng g^{-1} dry weight	–	–	31	[78]
	100 mg	LLE/Florisil	LC(ESI)-MS/MS	10	C18/Water-MeOH-ACN	0.67 ng g^{-1}	–	8	14	[85]
Serum, Whole blood	0.5 mL	LLE/SPE	LC (ESI)- MS/MS	5	C18/Water-MeOH	0.016–0.485 ng mL^{-1}	101–109 99–11	–	57	[143]

4.4. Instrumental analysis

As for all other chemicals, the selection of the instrumental technique for the analysis of FRs depends on the physical-chemical properties of the target analytes and their concentrations in matrices of interest. Tables 2–5 present the instruments commonly used in the human biomonitoring of FRs. Mass spectrometric techniques have played an essential role in the detection of FR biomarkers, due to their high sensitivity, selectivity and powerful identification ability. PBDEs have mainly been analyzed using gas chromatography (GC)-MS in the electron capture negative ionization mode (ECNI). GC-low resolution MS has been state-of-the-art in the detection of PBDEs for the last ~20 years. However, there has been a recent development toward GC-MS/MS and GC-high resolution MS with electron ionization (EI) or ECNI. Except for more polar compounds, like phenolic BFRs (PBP, TBBA, TBBPA, 2,4-dibromophenol, and 2,4,6-tribromophenol) and HBCD, NHFRs are also mainly analyzed using GC (ECNI)-MS. While GC (ECNI)-MS provides higher sensitivity for compounds with more than one bromine atom, GC (EI)-MS offers greater selectivity, the use of labelled standards and an increased ability to confirm the compounds' identity using full scan data in samples with high analyte concentrations [99]. The soft ionization provided by APCI has resulted in low MDLs for PBDEs and NHFRs in GC-APCI-MS/MS approaches [61,94].

PBDEs and most NHFRs exhibit sufficient thermal stability to be analyzed using GC–MS. However, some compounds may be subject to thermal decomposition (e.g. BDE-209, TBBPA-bis(2,3-dibromopropyl ether (TBBPA-BDBPE) and DBDPE) or isomeric interconversion (e.g. tetrabromoethylcyclohexane (DBE-DBCH) and 1,2,5,6-tetrabromocyclooctane (TBCO)) during GC analysis [174,175]. In order to minimize such degradation, shorter GC columns (10–15 m column length) are typically used to reduce the analytes' residence time on a column. During the last decade, GC approaches have used a wide range of capillary columns such as

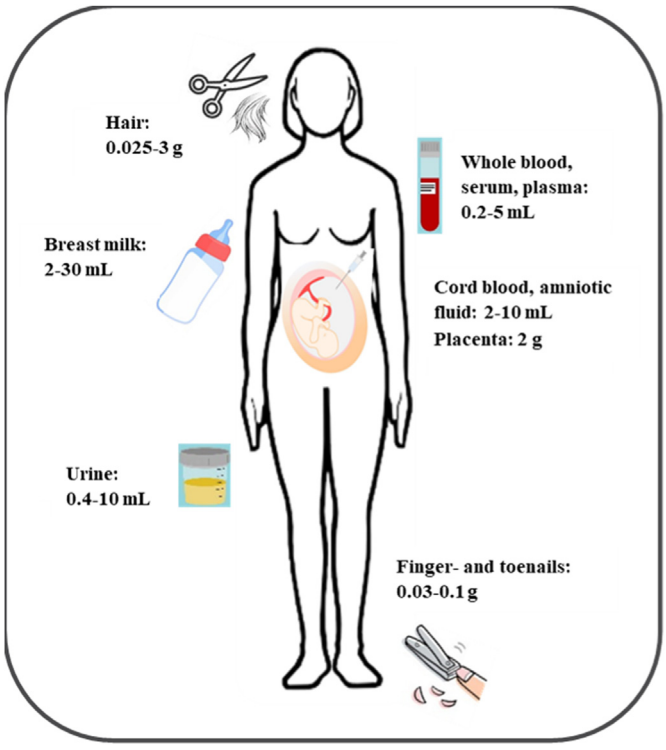

Fig. 2. Sample amounts and volumes typically used for the determination of flame retardants in human matrices.

DB-5, DB5-MS, DB-5HT, DB-1MS, DB-XLB, TG-5HT, HP5-MS, RXI-5HT, RTX-1614, TraceGOLD (TG), and ZB semivolatiles. Among them, DB-5MS (phenyl arylene polymer) and DB-5HT (5%-phenyl-methylpolysiloxane) are the most frequently used stationary phases in separating FRs (Tables 2–5). Helium (He) is generally used as GC carrier gas.

The analysis of HBCD diastereoisomers in all human matrices is commonly performed with high performance liquid chromatography (HPLC)-MS/MS. If analyzed by GC-MS, no diastereoisomer-specific results can be obtained. GC-MS is commonly used for the analysis of bromophenols in human samples, usually involving derivatization. However, LC-MS/MS has also been applied (Table 3). Some studies also introduced unconventional instruments for analysis of FRs. Bergant et al. [54] developed a method for PBDE analysis in serum using GC attached to Inductively Coupled Plasma (ICP)-MS achieving low MDLs of 1.6–3.9 pg mL^{-1}. Song et al. [69] recently developed an HPLC-ICP-MS method for simultaneous determination of four PBDEs (BDE-47, BDE-99, BDE-153 and BDE-209) and hydroxylated analogues (3-OH-BDE-47, 5-OH-BDE-47, 6-OH-BDE-47, 5-OH-BDE-99) in serum. Due to the characteristics of ICP, organic matrix effects were effectively eliminated. The achieved MDL ranged from 66 to 81 pg mL^{-1}.

Analysis of PFRs and their metabolites in human matrices are commonly carried out using LC-MS/MS (Table 5). However, some studies used GC (ECNI)-MS and GC (EI)-MS/MS for the determination of PFR metabolites after derivatization [47,65,78,142]. The sensitivity obtained using EI is generally higher than that obtained with ECNI. However, the reported MDLs for PFR metabolites in urine were always lower using LC-MS. LC-MS/MS with electrospray ionization (ESI) is the preferred analysis technique for PFR metabolites, especially for DAPs in urine due to higher MDLs produced by LC-MS with single quadrupole analyser. The main disadvantage of the ESI source is the strong matrix effect on the analytes in the ion source. Therefore, it is recommended to quantify the metabolites using the internal standard addition method or application of isotopically labelled internal standards. LC approaches for FR analysis mainly use silica-based reversed-phase columns, such as C18, XDB-C8, HSS-T3, PFP, Kinetex Biphenyl, Synergi Fusion-RP, Synergi Polar-RP. Among them, C18 is the most frequently used phase (Tables 2–5). Acetonitrile and methanol are commonly used solvents for the mobile phases in analyzing PFRs. Solvent modifiers (mainly formic acid and ammonium acetate) are also added to enhance ionization efficiencies or improve peak separation or peak shape of target analytes.

4.5. Trends in analytical methods

Analytical methods for the determination of FR biomarkers have undergone rapid development in the last few years. As FR levels in the general population are low, generally requiring MDLs in the pg ml^{-1} or lower ng ml^{-1} range for HFRs and PFR metabolites, respectively [25,28], sensitivity is a key parameter in the human biomonitoring of FRs. The last ten years covered by this review have seen an increase in instrumental sensitivity, accompanied by reductions in sample volumes. However, as banned BFRs have decreased in concentrations over time [176] and current-use HFRs have often shown lower concentrations than PBDEs in humans [35], MDLs will also be a challenge in the future for serum-based HFR determinations. Research into the use of non-invasive matrices for HFR determinations has increased in the last ten years, but does not seem mature for human biomonitoring purposes yet, mainly because of ambiguity in data interpretation.

Analyses of novel HFRs have often been based on established PBDE methods. Extending the scope from PBDEs with similar physical-chemical properties to a diverse group of HFRs has initiated developments towards multi-methods in the fields of FRs, eventually also including PFRs and/or their metabolites if targeted in the same matrix. Multi-methods are interesting for reasons of efficiency, both with regard to maximum outputs in time and from often limited sample material. As known from other fields, it is challenging to optimize method performance equally for all components in a multi-method. The use of labelled internal standards is an important QA/QC element in this respect, which has been included increasingly in the last ten years. The increasing availability of high resolution instruments may initiate developments that move optimization towards higher selectivity from sample processing to the instrument stage. However, while GC-MS/MS and GC-HRMS instruments are increasingly used in the human biomonitoring of FRs, they are still usually combined with target-optimized extraction and clean-up steps. The diastereoisomer-specific analysis of HBCD by LC-MS/MS is the established technique today and has fully replaced former GC-MS analyses of HBCD.

Developments towards efficient methods can also be seen among the extraction and clean-up methods where QuECHERS have established themselves in the human biomonitoring of FRs, extraction and clean-up steps have been combined in single SPE applications and solvent volumes have been reduced. While SPE is the method of choice in the analyses of PFR metabolites in urine samples, multiple extraction techniques, e.g. LLE, SPE, ultrasonication, Soxhlet and PLE, seem to give comparable results for HFRs, with indications of larger differences between compounds than between methods. This generates robustness in the HFR determination, which can be based on several methods of similar performances.

5. Quality assurance/quality control (QA/QC)

Quality control (QC) which is a part of quality assurance (QA) procedures, includes activities which are undertaken to affirm the quality of data produced [177]. Important quality parameters of an analytical method include method sensitivity (MDLs), accuracy, precision, and robustness. Since the levels of many FR biomarkers are low in the general population, method sensitivity is considered a key parameter in the quality of analytical methods, which is mainly determined by the sensitivity of the instrumental technique and the sample volume available. There have been advances in lowering MDLs for FR biomarkers owing to both sensitive instruments and extraction methods developed recently. Extraction recoveries are commonly reported in biomonitoring and research studies, while important information on precision and robustness of the methods is often lacking. It should be considered that variations in accuracy and precision are largely introduced by matrix effects and/or losses in the sample processing, rather than instrumental analysis [178].

The accuracy of the analytical method is normally determined by the analysis of certified reference materials, which are commercially available for some FR compounds (e.g. NIST SRM1954 and SRM1958 for PBDEs in human milk and serum, respectively). However, the application of such materials for QC purposes was rarely reported in the reviewed studies. Proficiency testing schemes are available for e.g. PBDEs in serum and two PFR metabolites (DPHP and BDCIPP) in urine (AMAP ring test), and both PBDEs, HBCD diastereoisomers, the NHFRs DBDPE and DDC-CO in serum as well as four PFR metabolites (BCEP, BCIPP, BDCIPP, DPHP) were included in recent interlaboratory comparison investigations and external quality assurance schemes organized by HBM4EU [25,26]. In an interlaboratory exercise in 2015, four PFRs metabolites (BDCIPP, DPHP, BCEP, BCIPP) in urine (SRM3673) were measured by nine expert laboratories from Belgium, the USA, Canada, China, and Australia [179].

Standard addition is commonly applied as an approach to compensate for variable matrix effects. The use of deuterated or ^{13}C-labelled internal standards compensating for losses during extraction, clean-up and incomplete derivatization is common practice in the analysis of HBCD diastereoisomers, bromophenols incl. TBBPA, and increasingly for NHFRs, for example DDC-CO isomers [76]. Labelled standards are also frequently used in methods for PBDE determination involving GC-MS/MS or GC-HRMS rather than GC (ECNI)-MS [76,117]. Potential contamination risks have to be considered for FRs as many FRs are compounds of widespread commercial use. Use of laboratory blanks ensures the monitoring of possible contamination. Long-term in-house quality control samples should also be applied to check for precision and robustness in control charts.

6. Concluding remarks and outlook

Due to their lipophilic properties, PBDEs, HBCD and NHFRs are usually measured in blood (serum or plasma), while PFRs are most commonly monitored through their metabolites in urine. In addition to these classical human matrices, other matrices are increasingly being tested for use in the human biomonitoring of FRs in the general populations, avoiding invasive sampling and/or limitations in sample material. Some applications may be most useful for screening purposes, while others allow quantitative measurements over time. More knowledge is needed on correlations between a chemical in a non-invasive matrix and its levels in blood to ensure that the non-invasive matrix represents the total body burden without interferences with external exposure levels.

Recently, interest in fast, reliable and economical analytical methods for FR biomarkers in human samples has increased. There have been efforts to develop extraction techniques that allow efficient extraction with reduced solvent volumes in shorter times, and the detection of more compounds. Although conventional methods of sample preparation, such as SPE, are still widely used in routine analysis, human biomonitoring may shift towards more universal extraction methods, such as QuEChERS, that enable extended method scopes, reduction in sample volume, and simplification of sample treatment for high-throughput analysis and optimum use of the sample material, which is particularly important for large scale biomonitoring programmes. The availability of reference materials for these human matrices is an import issue to consider during the validation of the analytical method. MDLs have been significantly reduced in recent years due to the tremendous increases in the sensitivity of the analytical instruments. For most of the studies reviewed here, the MDLs were as low as the pg mL^{-1} level, which is a requirement for human biomonitoring of FRs in the general population. However, challenges remain with regard to sensitivity mainly due to the low concentrations of FRs in the general population, limited sample material for some human matrices and the high risk of contamination.

Analysis of polar FR biomarkers is generally carried out by LC-MS/MS which provides enough sensitivity required in human biomonitoring studies. GC (ECNI)-MS is the main analytical system currently employed for analysis of non-polar FRs in human matrices, with developments towards more frequent use of GC-MS/MS and GC-HRMS. The introduction of recently developed high-resolution MS instruments, such as Q-TOF or Orbitrap, might offer equally sensitive alternative techniques in biomonitoring programmes, and connect the targeted and highly specialized FR human biomonitoring with suspect or non-target screening approaches. There is a general need for more focus on QA/QC measures, including both in-house measures and proficiency testing exercises, in the analysis of FR biomarkers in human samples at the levels found in the general population, particularly for NHFRs and PFRs, as well as recently introduced analytical methods and instruments.

Declaration of competing interest

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

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Further reading

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