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ABSTRACT

The major purpose of human biomonitoring is the mapping and assessment of human exposure to chemicals. The European initiative HBM4EU has prioritized seven substance groups and two metals relevant for human exposure: Phthalates and substitutes (1,2-cyclohexane dicarboxylic acid diisononyl ester, DINCH), bisphenols, per- and polyfluoroalkyl substances (PFASs), halogenated and organophosphorous flame retardants (HFRs and OPFRs), polycyclic aromatic hydrocarbons (PAHs), arylamines, cadmium and chromium. As a first step towards comparable European-wide data, the most suitable biomarkers, human matrices and analytical methods for each substance group or metal were selected from the scientific literature, based on a set of selection criteria. The biomarkers included parent compounds of PFASs and HFRs in serum, of bisphenols and arylamines in urine, metabolites of phthalates, DINCH, OPFRs and PAHs in urine as well as metals in blood and urine, with a preference to measure Cr in erythrocytes representing Cr (VI) exposure. High performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) was the method of choice for bisphenols, PFASs, the HFR hexabromocyclododecane (HBCDD), phenolic HFRs as well as the metabolites of phthalates, DINCH, OPFRs and PAHs in urine. Gas chromatographic (GC) methods were selected for the remaining compounds, e.g. GC-low resolution MS with electron capture negative ionization (ECNI) for HFRs. Both GC–MS and LC-MS/MS were suitable for arylamines. New developments towards increased applications of GC–MS/MS may offer alternatives to GC–MS or LC-MS/MS approaches, e.g. for bisphenols. The metals were best determined by inductively coupled plasma (ICP)-MS, with the particular challenge of avoiding interferences in the Cd determination in urine. The evaluation process revealed research needs towards higher sensitivity and non-invasive sampling as well as a need for more stringent quality assurance/quality control applications and assessments.

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1. Introduction

Human biomonitoring studies and programmes aim to generate reliable and robust data on the occurrence of a specific biomarker in human matrices, such as serum, urine, hair or human milk (WHO, 2015). Besides their overall objectives of providing data for risk assessments and policy making (Ganzleben et al., 2017; Zidek et al., 2017), human biomonitoring studies often target the exposure to specific chemicals, stratified by geography (Den Hond et al., 2015), age group (Choi et al., 2017), monitored over time (Koch et al., 2017; Zietz et al., 2008) or combinations of these (Schulz et al., 2007; Kolossa-Gehring et al., 2012). Biomonitoring data reflect the internal exposure (or dose), i.e. the actual uptake, accumulation and/or metabolism of a certain chemical, at the same time integrating multiple exposure routes (inhalation, ingestion, dermal uptake) and exposure sources, e.g. food, consumer products, industrial processes and occupational settings, and considering the individual exposure susceptibility.

With about 150,000 chemical substances pre-registered in the European Union (EU) under the EU legislation Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (Öberg and Iqbal, 2012), the general population as well as the work force of the EU can be exposed to a wide range of different chemicals. Biomonitoring in Europe was organised in national programmes or specific studies, with little coordination and incomplete geographical coverage before the EU-funded projects ESBIO, COPHES and DEMOCOPHES (Joas et al., 2015; Den Hond et al., 2015). In 2017, an initiative was started under the acronym HBM4EU that has brought together scientists from 30 countries and the European Environment Agency to coordinate and advance human biomonitoring in Europe (Ganzleben et al., 2017). Large-scale biomonitoring programmes for the general population have been in place outside of Europe for several years, including the National Health and Nutrition Examination Survey (NHANES) of the United States of America, the Canadian Health Measures Survey (CHMS) and the Japan Environment and Children's Study (JECS) (Ganzleben et al., 2017).

Based on policy-related research needs, evidence of exposure, concern for human health as well as financial and technical feasibility, the following seven substance groups and two metals were selected as the first set of prioritised substances in HBM4EU (Table 1): Phthalates (and the replacement 1,2-cyclohexane dicarboxylic acid diisononyl ester, DINCH), bisphenols, per- and polyfluoroalkyl substances (PFASs), halogenated and organophosphorous flame retardants (HFRs and OPFRs), polycyclic aromatic hydrocarbons (PAHs), arylamines, cadmium (Cd) and chromium (Cr). A list of acronyms is given in Table S1.

Several factors have to be considered in the design of a human biomonitoring programme or the use of biomonitoring data, for example whether the parent compound or a stable metabolite is the most suitable biomarker and in which matrix it should be determined. Analytical methods have to be sufficiently sensitive and selective to produce reliable data. The objective of this study was therefore i) to identify the most suitable biomarkers (parent compound vs. metabolites) for the selected substance groups and metals, ii) to describe the most suitable human matrix for their biomonitoring and iii) to discuss state-of-the-art analytical methods for the determination of this biomarker in this matrix. The prioritized biomarker and matrix combinations form the basis for further work in HBM4EU, including the sample selection and a comprehensive quality assurance/quality control (QA/QC) programme to ensure precise, accurate and comparable data across the EU.

2. Selected substances and metals

Phthalates and DINCH are plasticizers ubiquitously detected in the indoor environment and food as well as in humans (Wittassek et al., 2011; Schütze et al., 2017). Exposure to some phthalates has been associated with adverse effects in laboratory animals and epidemiological studies, caused by endocrine disruption (Table 1). Several phthalates have been classified as toxic for reproduction in the EU and are therefore listed as Substances of Very High Concern (SVHC) under EU REACH, triggering specific legislation (EU, 2006). Di(2-ethylhexyl) phthalate (DEHP), benzylbutylphthalate (BzBP), dibutylphthalate (DBP) and diisobutylphthalate (DIBP) are subject to EU authorization. DEHP, BzBP, DBP, diisononylphthalate (DINP), diisodecylphthalate (DIDP) and di-n-octylphthalate (DNOP) are further restricted to 0.1% in toys and childcare articles (EU, 2014a, 2014b). DEHP, BzBP, DBP and others are prohibited in cosmetics (EU, 2009). The updated Restriction of Hazardous Substances (RoHS) Directive limits the cumulative content of DEHP, BzBP, DBP and DIBP in electric and electronic equipment to 0.1% (EU, 2015). DINCH is currently regarded as a potential phthalate substitute with a preferred toxicological profile (Engel et al., 2018).

Bisphenol A (BPA) is mainly used in the manufacture of polycarbonate plastics and epoxy resins lining beverage and food cans. With more than 3 million tonnes produced every year, BPA is one of the

Table 1
Summary of substance groups and metals prioritized in HBM4EU and their (suspected) adverse effects. Chemical structures are given in Tables S2-S8.

Compound (group)	Main commercial use	(Suspected) Toxicity	References
Phthalates and 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH)	Plasticizers	Endocrine disruption, leading to reproduction toxicity and neurodevelopmental effects	CHAP (2014), EU (2006)
Bisphenols	Manufacture of polycarbonate, epoxy resins and other polymers	Endocrine disruption, associated with diabetes and cardiovascular diseases	EFSA (2015), Lang et al. (2008), vom Saal and Hughes (2005)
Per- and polyfluoroalkyl substances (PFASs)	Surfactants, stain repellents, dispersants	Hyperchlesterolemia, reproduction toxicity, immunosuppression; some substances are classified as persistent organic pollutants (POPs)	EFSA (2018), UNEP (2006a, 2016)
Halogenated flame retardants (HFRs)	Flame retardants in polymers	Thyroid homeostasis disruption, neurodevelopmental effects; some substances are classified as POPs	Lyche et al. (2015), UNEP (2006b, 2010)
Organophosphorous flame retardants (OPFRs)	Flame retardants and plasticizers in polymers	Cancer (chlorinated OPFRs), neurotoxicity	Reemtsma et al. (2008)
Polycyclic aromatic hydrocarbons (PAHs)	By-product of combustion processes, manufacture of pigments, dyes, pesticides, pharmaceuticals etc.	Cancer, mutagenicity, immunosuppression, endocrine disruption	Andersson and Achten (2015), EU (2013)
Arylamines	Manufacture of polymers, rubbers, adhesives, dyes, pharmaceuticals etc.	Methemoglobinemia; cancer	Neumann (2005), IARC (2010), Skipper et al. (2010)
Cadmium	Pigment production, solar panels	Cancer, effects on liver and kidney, bone mineralisation	EFSA (2009), IARC (2012)
Chromium	Stainless steel production, electroplating, paint additive, tanning agent	Cr (VI): Cancer, effects on liver and kidney, contact allergen	EFSA (2014), IARC (2012)

highest production volume chemicals in the world (Erler and Novak, 2010). BPA is widely detected in humans (Calafat et al., 2008; Koch et al., 2012; Ye et al., 2008) and shows an estrogenic mode of action (Table 1). In 2015, the European Food Safety Agency (EFSA) lowered the tolerable daily intake to 4 μg/kg bodyweight, subject to re-assessment (EFSA, 2015). In the EU, BPA has not been allowed in plastic infant feeding bottles since 2011 (EU, 2011), and has been phased out in thermal paper since 2020 (EU, 2016). It is also listed as an SVHC. Amongst its substitutes, **bisphenols S and F** are structurally similar to BPA, with similar toxicological concern (Eladak et al., 2015).

As **per- and polyfluoroalkyl substances (PFASs)** are both water and oil repellent, they have had a wide range of industrial and commercial applications, e.g. as surfactants, stain repellents and dispersants (Prevedouros et al., 2006). The main sub-groups are perfluoroalkyl sulfonic acids (PFSAs) and perfluoroalkyl carboxylates (PFCAs); among these the best studied compounds are perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Some PFASs bioaccumulate and biomagnify in the food chain, and incidents of PFASs in drinking water have been reported as well (de Vos et al., 2008; Post et al., 2012). PFASs are widely detected in humans, with decreasing tendencies for PFOS, but inconclusive developments for other PFASs (Kärrman et al., 2007; Gomis et al., 2017; Salthammer et al., 2018). They have been associated with various adverse effects (Table 1). PFOS and PFOA are globally restricted through the Stockholm Convention on Persistent Organic Pollutants (POPs), which currently also reviews perfluorohexane sulfonate (PFHxS). PFOA is also regulated in the EU, with a production ban effective in 2020 (EU, 2017a). Provisional tolerable weekly intake rates of 13 and 6 ng/kg body weight for PFOS and PFOA, respectively, were set by EFSA in 2018 (EFSA, 2018).

Halogenated flame retardants (HFRs) and **organophosphorous flame retardants (OPFRs)** account for the majority of organic FRs (Alaee et al., 2003). Most FRs are added to the polymer without covalent bonds and can be emitted to the environment more easily than reactive FRs, which are covalently bound to the polymer, e.g. tetrabromobisphenol A (TBBPA). FRs are frequently detected in the indoor environment, with OPFR concentrations in dust and air usually exceeding those of HFRs by at least an order of magnitude (Cequier et al., 2014a). However, OPFRs do not accumulate in food chains to the same extent as some HFRs (Greaves and Letcher, 2017). The chlorinated OPFRs tri(2-chloroethyl)phosphate (TCEP), tri(chloroisopropyl)phosphate (TCIPP) and tri(1,3-dichloroisopropyl)phosphate (TDCIPP) are carcinogenic or suspected to be carcinogenic; additional effects of HFRs and OPFRs are summarized in Table 1. Polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) are included in the Stockholm Convention on POPs. PBDEs are included with the three commercial mixtures Penta-, Octa- and Deca-BDE, mainly consisting of congeners with four/five, six/seven and ten bromine atoms, respectively. Dechlorane plus has been nominated to the Stockholm Convention. It was also recently added to the SVHC list of EU REACH. TCEP, TCIPP and TDCIPP are not allowed in toys in the EU (EU, 2014c).

Polycyclic aromatic hydrocarbons (PAHs) are emitted to the environment from incomplete combustion processes, which can be natural or anthropogenic, and petrogenic sources (Webster et al., 2009). To a minor extent, some PAHs are also used commercially, e.g. in the manufacture of pigments, dyes, pesticides and pharmaceuticals (Abdul-Shafy and Mansour, 2016). PAHs have raised a number of health concerns (Table 1). The commonly applied list of 16 priority PAHs originally set by the US Environmental Protection Agency in 1976 likely underestimates PAH toxicity as it does not include large molecule PAHs, alkylated PAHs and PAHs with heteroatoms (Andersson and Achten, 2015). Eight PAHs (benzo[a]pyrene, benzo[e]pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene and dibenzo[a,h]anthracene) are classified as carcinogenic in the EU (EU, 2013). Consumer products containing any of these PAHs in quantities above 1 mg/kg are prohibited in the EU, with a lower limit of 0.5 mg/kg for toys and childcare articles (EU, 2013).

Arylamines are intermediates in the production of agricultural and pharmaceutical chemicals, polyurethanes, dyes and pigments. 2,3-, 2,4-, 2,5- and 2,6-dimethylaniline (DMA), 2-, 3- and 4-ethylaniline (EA), 2-, 3- and 4-methylaniline (MA), 1- and 2-naphtylamine (NA), 2-, 3- and 4-aminobiphenyl (ABP) are present in cigarette smoke, and 2-NA and 4-ABP have also been found in fumes of cooking oils (Chung, 2015; Sabbioni, 2017). Several arylamines have been found in indoor and outdoor air where aniline usually was present at higher levels than other arylamines (Palmiotto et al., 2001). Other sources of exposure to arylamines are dyes in e.g. food, textiles, inks, hair dyes and tattoos, food packages or pesticides synthesized from arylamines (IARC, 2010; Chung, 2015; Sabbioni and Hauri, 2016). The analgesic Paracetamol (N-acetyl-4-aminophenol) is an aniline derivative, also formed from aniline in human metabolism (Dierkes et al., 2014). Arylamines are moderately to highly toxic (Table 1). Several arylamines and their metabolites (e.g. 4,4-methylenebis(2-chloroaniline) (MOCA), 4,4-methylenedianiline (MDA), 2,4-toluenediamine (2,4-TDA), 4-ABP, 2-MA and 2-methoxyaniline (2-MeOA)) are included on the SVHC list of EU REACH.

Cadmium and chromium occur naturally and have had many industrial applications: Cd has been used in the production of pigments for glass and plastics. Its former use in the anti-corrosion plating of steel and Ni-Cd rechargeable batteries has decreased, but it is newly used in cadmium telluride solar panels. Cr is mainly used for corrosion resistance in stainless steel production, electroplating and paint. Besides occupational situations, exposure mainly occurs through diet and cigarette smoke (Fagerberg et al., 2017; EFSA, 2014). While trivalent Cr is not toxic because it is poorly absorbed, hexavalent Cr is mutagenic and highly oxidative (Table 1). Both Cd and Cr (VI) have been evaluated as carcinogenic to humans (Table 1). Cadmium and several Cd salts are on the EU REACH list of SVHCs. Both Cd and Cr are severely restricted in their use in the EU (EU, 2006, 2015). For work places, an exposure limit value of 0.025 mg/m^3 has been set for Cr (VI), with a view to lower it to 0.005 mg/m^3 in the future (EU, 2017b).

3. Materials and methods

3.1. General approach

The first step of the study was to establish general criteria for the evaluation of most suitable biomarkers, matrices and analytical

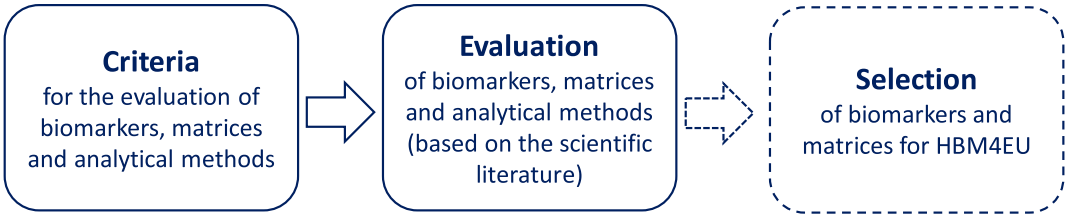

Fig. 1. Approach to identify the most suitable biomarkers, human matrices and analytical methods for the prioritised substance groups and metals. Based on the evaluation, specific biomarkers and matrices will be selected for further work in HBM4EU.

Table 2
Evaluation criteria for pairs of exposure biomarkers (EB) and matrices (M), not given in a ranked order. Categories A, B and C apply to sufficient, insufficient and very limited data availability, respectively, for a certain biomarker in human biomonitoring.

	Category A and B	Category C
Specificity	EB/M concentrations reflect exogenous exposure. The EB/M concentration is an exclusive consequence of environmental/ occupational exposure.	EB/M concentrations might not exclusively reflect exogenous exposure to the substance, but are a correct indication of exposure.
Biological sensitivity	The measured concentration of the EB/M correlates strongly with the substance intake dose. Variations of EB/M concentration reflect the variation of exposure to the substance of interest.	The measured concentration of the EB/M is an acceptable indication of the substance intake dose.
Half-life	The EB/M should preferably have a half-life sufficiently long to avoid an excessive intra-individual variability in EB/M concentration measurement.	
Stability after sample collection	The EB/M is stable in the sample for many hours during (refrigerated) transportation to the laboratory or before storage in a biobank. Transport conditions can be optimized easily to ensure the stability.	If stability data is missing, stability should be assessed. For compounds with low stability, sample degradation can be prevented by an adaptation of transportation conditions or implementation of particular sampling operating procedures.
Stability during storage	The cryo-preservability of EB/M is sufficient to guarantee a high stability during storage in the biobank, usually at −20 °C.	If stability of the EB/M is not guaranteed during storage in biobanks, it is recommended to analyse the sample as soon as possible.
Matrix availability and sample collection	The sample collection of the relevant matrix is not considered too invasive. Easy collection and transportation of the required amount of sample with a validated sampling protocol is beneficial. It is advantageous if it is possible to determine more than one EB in the same matrix.	It is relatively easy to obtain a sufficient sample volume for a required number of samples.
Method detection limits (MDL)	The MDL of a validated analytical method is lower than commonly measured concentrations in the general population. The EB/M with the highest frequency of quantified data available is preferable.	Only a few studies are available and the quantification might be based on insufficiently validated methods.
Measurement validity	The EB/M concentration in the sample is not likely to be altered by contamination with a ubiquitous parent substance from the environment preceding and during the analysis. Variations in matrix composition can be easily corrected for (e.g. creatinine in urine, lipids in serum).	Sample contamination by a ubiquitous parent substance might occur, but the level of contamination is low compared to expected levels and special precautions can be applied to minimize the amount of contamination.

methods (Fig. 1). In a second step, the literature was reviewed for each of the selected substance groups and metals, and the evaluation criteria were applied, resulting in a list of the most suitable biomarkers, matrices and analytical methods. Based on this evaluation, certain biomarker and matrix combinations will be selected for the studies in HBM4EU.

3.2. Criteria for the evaluation of biomarkers, matrices and analytical methods

The criteria established for the evaluation of biomarkers, matrices and analytical methods were intended to apply to all substance groups and metals, as well as to potential future additions, i.e. to a variety of compounds with different physical–chemical properties and exposure pathways. Most of the selected substance groups consist of multiple individual compounds (Tables S2-S8). Consequently, some analytical methods are still subject to research, while others have been applied routinely in human biomonitoring studies (e.g. Haines et al., 2017). To account for these differences, three operational levels were defined, representing categories of biomarkers with A) sufficient, B) insufficient, C) very limited data availability in human biomonitoring. Thus, the C category reflects emerging interest in a compound and/or technical limitations in the analytical chemistry. The criteria were based on literature information and expert knowledge.

3.3. Evaluation of biomarkers, matrices and analytical methods

The literature search focused on studies on human biomonitoring, taking into account the compound-specific history of chemical analyses, for example transitions from single to triple quadrupole mass spectrometry, as well as important specifics for some compound groups, for example enzymes used for the deconjugation of glucuronides. No bioassays were included as analytical methods. In general, a non-systematic literature search was conducted in Web of Science, Scopus, ScienceDirect and/or PubMed, covering approximately the last 10 years. Search terms were the compound names, including typically used acronyms, combined with “biomonitoring”, “human” or “analytical method” or filtered for these terms subsequently. Priority was given to publications with exhaustive information on analytical methods and their quality. Reference lists were used to identify original publications with method validation data. The biomarkers were assigned to the A, B and C categories depending on data availability and the maturity of the analytical methods. For most substances, a second literature search was conducted with a focus on Category B and/or C compounds to ensure that recently published developments in their analytical determination were included. The initial literature search yielded between 47 (OPFRs) and 976 (Cr) articles, of which 21 and 45, respectively, were considered further for the evaluation of biomarkers, matrices and analytical methods. The highest number of articles was considered for PFASs, i.e. 69 publications.

Using the criteria for the evaluation of biomarkers, matrices and analytical methods, the information in the literature was evaluated with regard to the most suitable biomarker, matrix and analytical method for each of the selected compound groups and metals. Considering that some compounds occur at low levels in human matrices, particular attention was paid to sensitivity in terms of method detection limits (MDL), i.e. the limit of detection (LOD) related to a specific sample intake. If sensitivity was considered adequate for biomonitoring purposes, uncertainty and accuracy were assessed according to the criteria, including information on external QA/QC, i.e. interlaboratory comparisons and certified reference materials.

4. Results and discussion

4.1. Criteria for the evaluation of biomarkers and matrices

The criteria are summarized in Table 2, not presenting a ranked order. The first three criteria for the best biomarker/matrix combinations address the overall purpose of linking external and internal exposure. The qualitative criterion of specificity is extended to a quantitative one in the second criterion according to which the biomarker concentration should be correlated with intake dose. This knowledge is not always available for emerging compounds (Category C). For example, 2,4,6-tribromophenol was detected at a median concentration of

21.5 ng/g lipid weight in serum samples from Canada, but it could originate from multiple sources. Besides being a flame retardant, it can be a PBDE metabolite or formed naturally in aquatic ecosystems (Butt et al., 2016).

The half-life criterion bridges the purpose of linking external and internal exposure to the more technical criteria that need to be fulfilled to generate meaningful data. Prior knowledge of the half-life and toxicokinetics of a biomarker in a given matrix is essential for interpreting the biomonitoring data, but also for the sampling design. For example, phthalate diesters are rapidly cleaved into monoesters and can be oxidized prior to their excretion in urine, leading to primary and secondary metabolites as biomarkers in biomonitoring studies (Koch and Calafat, 2009).

The question of the most suitable matrix also involves issues of practicability, as described under "Matrix availability". Persistent organic pollutants are stable enough to accumulate in lipid-rich tissues and blood, making human milk and serum suitable matrices for these compounds (WHO, 2015). However, the invasive nature of blood sampling sometimes limits its applicability, and matrices like nails or hair have been subject of research into alternatives, e.g. for Cd and other metals as well as HFRs (Lemos and Carvalho, 2010; Liu et al., 2015). Nevertheless, non-invasive matrices might be in conflict with the criterion of specificity and biological sensitivity, thus not meeting criteria of suitable EB/M combinations. Non-persistent chemicals – or their metabolites - are readily excreted, making urine a more suitable matrix. Urinary metabolites typically reflect recent exposure and may be misguiding in case of intermittent exposure. Moreover, excretion rates vary for demographic groups and with bodyweight, and concentrations of chemicals in urine are affected by hydration status (Hays et al., 2015; Bevan et al., 2017). Therefore, they are typically corrected for creatinine content or specific gravity (WHO, 2015). As children's creatinine excretion increases with age, creatinine-correction would potentially introduce a bias into the data analysis of children's urine samples, making specific gravity a more robust and suitable correction factor for this age group (Pearson et al., 2009).

4.2. Criteria for the evaluation of analytical methods

Method detection limits, i.e. sensitivity, and measurement validity, both included in Table 2, also tie into the criteria for analytical methods, given without a ranking in Table 3. Potential contamination risks have to be considered for compounds of widespread commercial use, such as phthalates, bisphenols or flame retardants. BDE-209, the fully brominated PBDE congener, was a much discussed case as blank issues, in combination with limited stability, affected data quality and consequently, impeded reliable risk assessments (Alcock et al., 2011). Potential contamination issues affect the robustness and comparability of MDLs, as specified as additional criteria related to sensitivity (Table 3).

Given the low levels of many biomarkers in the general population, sensitivity was considered a key parameter in the evaluation criteria for analytical methods. It is determined by the instrumental technique, but also to a high degree by the sample amount available for analysis. For HFRs in serum, for example, MDLs in the pg/mL range usually require sample intakes greater than 1 mL (Cequier et al., 2013; Frederiksen et al., 2010a), which are not always available in biobanks or from multi-purpose sampling.

4.3. Evaluation of biomarkers, matrices and analytical methods

4.3.1. Literature summary

The priority substances in HBM4EU cover a wide range of chemical groups with different physical–chemical properties. Consequently, the scientific literature offers a variety of analytical methods between and sometimes within substance groups, as summarized in Table 4. The references in Table 4 are not exhaustive, but represent examples of studies including the matrices and analytical methods summarized in the table. Depending on the substance group, the biomarkers in human biomonitoring were either parent compounds or metabolites. A wide spectrum of matrices has been analyzed, sometimes with different purposes, e.g. method development towards non-invasive sampling (hair, nails) or exposure analyses of specific populations (human milk). The analytical methods that are summarized as gas chromatography (GC) with mass spectrometry (MS) in Table 4 included both GC with low resolution (GC-LRMS) and high resolution MS (GC-HRMS) as well as triple quadrupole MS (GC–MS/MS). It is important to highlight that the approach of this study did not target the most commonly used biomarker, matrix or analytical method, but those fulfilling the selection criteria (Table 2; Table 3). Although experiences from e.g. NHANES are included in Table 4, the approach did not intend to copy existing selections of biomarkers, matrices and analytical methods, but to apply the selection criteria to state-of-the-art methodology and to critically discuss potential challenges. This approach resulted in a number of recommendable EB/M combinations and analytical methods, as further discussed below.

4.3.2. Phthalates and DINCH

Phthalates are best monitored as their monoester metabolites, in oxidized form or without oxidative modification (Table 5). Uptake of phthalates is followed by their cleavage into monoesters, oxidation in phase I reactions, conjugation of this secondary metabolite with glucuronic acid in a phase II reaction and excretion with urine (Koch and Calafat, 2009). In the analysis, the conjugates are cleaved, and the (oxidized) monoester is a suitable biomarker. In general, the simple monoesters (without oxidative modification) will be the biomarkers of choice for low molecular weight phthalates, such as diethyl phthalate (DEP) and DBP, whereas oxidized secondary metabolites are the biomarkers of choice for phthalates with long alkyl chains, such as DEHP, DINP or DIDP (Koch et al., 2003; Koch and Calafat, 2009). This shift in target biomarkers (from simple to oxidized monoester metabolites) is mainly related to the lower water solubility of the monoesters with long alkyl chains, which needs to be further increased in phase I reactions (Koch and Calafat, 2009). Furthermore, the oxidized metabolites have longer elimination half-lives than the simple monoesters, which is in agreement with the criteria for half-lives in Table 2. The longer half-lives allow detection of exposures in the past or cumulative exposures (Wittassek et al., 2011). For DINCH, the oxidized monoesters are more suitable biomarkers than the simple monoesters, amongst other criteria because of half-lives of 12–24 h (Koch et al., 2013). In addition, the oxidized metabolites are not prone to external contamination (Wittassek et al., 2011). Otherwise the risk of external contamination during sampling and sample preparation is high, due to the wide use of phthalates as plasticizers, and needs to be considered in sampling and QA/QC strategies (Koch and Calafat, 2009).

For some phthalates, such as DINP and DIDP, several isomers exist. Their quantification is typically based on analytical standards of single isomers whereas all isomeric peaks are integrated in the urine sample. Having an isomeric composition of the alkyl side chain similar to DINP, the analysis of DINCH and its secondary oxidized metabolites is comparable to that of DINP (Koch et al., 2013). Quantification should integrate over all isomers with respective oxidative modifications, and the standards should be derived from the major alkyl chain isomer.

Based on the metabolism and elimination characteristics described above, urine is the preferred human matrix for biomonitoring of phthalates and DINCH (Esteban and Castaño, 2009). Phthalate metabolites correlate in serum and urine, indicating that serum would also be a suitable matrix. However, the concentrations in serum are considerably lower (Frederiksen et al., 2010b). Furthermore, degradation and external contamination need to be closely monitored in serum analyses (Koch and Calafat, 2009; Calafat et al., 2015), jeopardizing the criterion of measurement validity (Table 2). Phthalates and their metabolites were also detectable in human milk, but those studies were

Table 3
Evaluation criteria for analytical methods for human biomonitoring. Categories A, B and C apply to sufficient, insufficient and very limited data availability, respectively, in human biomonitoring. The criteria are not given in a ranked order. EB: Exposure biomarker. M: Matrix.

	Category A	Category B	Category C
Sample preparation	Sample preparation procedures are well established and applied on a routine basis for relevant biological matrices.	Appropriate sample preparation procedures may be available to some extent, but have not necessarily been established for all EB/M combinations. A certain level of development (mainly adaptation) could be necessary.	Sample preparation procedures are typically not yet available and have to be developed. The effort needed for this development will depend on the possible adaptation of an existing protocol (e.g. for adding new substances from an already known family).
Standards	The use of standards of target EBs and internal standards (among these isotopically labelled standards where relevant), is applied. They are commercially available at reasonable costs.	The use of standards of target EBs and internal standards (among these isotopically labelled standards where relevant), is applied where possible. Standards are not necessarily commercially available or might be offered by only one or few suppliers.	Determination of this substance might be the first tentative identification of the EB/M. Standards might not be commercially available.
Validation	The method is well-established in multiple laboratories. Comprehensive validations have been performed. Participation in inter-laboratory comparisons and/or use of certified materials is in place (if available for the EB/M).	The method is established and full within laboratory validation has been carried out in some research laboratories. Concentrations might still be reported using methods subjected to less rigorous validation procedures. Large-scale studies and interlaboratory comparisons are expected.	No method validation is expected. Assessment of critical parameters might be in progress.
Selectivity	A low extent of interferences has been demonstrated. The measured concentrations are that of the EB/M.	Potential interferences might not be fully controlled for some EB/M.	Selectivity has not necessarily been assessed.
Sensitivity			
- *Limits of detection (LOD)*	LODs have been determined for each EB/M and have usually been reported in comprehensive validations.	LODs are available for some individual EB/M, but not necessarily for all EBs and all matrices of interest for human biomonitoring.	Highly dependent on availability of standards. When available, the LODs might have been determined for individual studies, but not as part of a validation procedure.
- *Quantifiable compounds*	In general, LODs have been proven to be sufficiently below the concentrations in a high proportion of the samples of a population.	LODs may appear higher than the expected exposure, but enable quantification of most biomarkers in a reasonable number of samples of the population. Risk of low detection rates, and subsequent biased upper bound risk assessment.	Quantification is reliable only when the standard is available. For some compounds, only semi-quantitative determinations are possible.
- *Robustness*	Limited variation in the LODs between samples or over time. Controlled environment-laboratory conditions (e.g. low background levels).	Some variation in LODs can occur (e.g. variable blanks and/or instrument performance).	High variation in LODs can occur or absent/ insufficient information available to properly quantify this parameter. Interferences cannot be ruled out.
- *Comparability*	Similar LODs have been obtained by most laboratories.	Variability in LODs exists, for example due to different analytical approaches for the determination of the EB/M.	Low comparability of LODs or absence of information. Subject to method development and validation.
Accuracy			
- *Accuracy – availability of QC measures*	The accuracy has usually been assessed using external QC measures such as certified reference materials or relevant interlaboratory comparisons.	The accuracy has mainly been assessed using internal QC measures, recovery tests or comparisons with an independent analytical method, although some external QC measures might be available for some EB/M.	The accuracy has usually not been evaluated yet.
- *Accuracy - assessment*	The accuracy is within the limits given by guidelines for validation of analytical methods (e.g. $\leq$ 20% deviation, depending on the concentration level and EB/M).	The accuracy might be compromised by several factors (e.g. internal standards, blank contamination at low concentrations). A wider range of accuracies is expected (e.g. $\leq$ 40% deviation).	The accuracy has usually not been assessed, but indications from similar EB might be available. High uncertainty must be expected.
Recovery	The EB recoveries are usually in the range of 80–120%. If outside this range, the use of proper internal standards compensates the deviations.	Variable recoveries might be expected (e.g. 50–150%). There is a stronger need to compensate the deviations with a proper internal standard.	Recoveries have rarely been assessed.
Range/Linearity	The method provides acceptable precision and accuracy for the relevant concentration range. The linear range has been evaluated for the determination of the relevant EB/M.	The method mainly provides acceptable precision and accuracy for higher concentrations. Awareness exists of potential issues at low concentrations. The linear range has usually been evaluated for the relevant EB/M, although less attention might have been paid to keeping all determined concentrations within the linear range.	Optimal working range has rarely been evaluated.
Robustness			
- *Response to small changes in the analytical process*	The robustness has been assessed, and only small variations within acceptable limits have been identified due to minor changes in the analytical procedure/conditions.	The robustness has been assessed, and variations can occur due to several factors (e.g. EB stability, instrument performance, environment and/or operating conditions).	The robustness has likely not been assessed. Any significant variations, which could affect the analytical result, should be reported.
- *Method precision/ Repeatability*	The repeatability/intermediate precision has been evaluated according to common guidelines. It is within an acceptable range. Control charts are usually used for the assessment of precision.	The repeatability/intermediate precision has often been assessed, but the standard deviations can be higher than the recommendations given in the guidelines for validation of analytical methods.	The repeatability/intermediate precision has likely not been assessed.

Table 4
Summary of biomarkers, matrices and analytical methods commonly described in the scientific literature. SPE: Solid phase extraction. LLE: Liquid-liquid extraction. LC: Liquid chromatography. GC: Gas chromatography. MS: mass spectrometry. ICP: Inductively coupled plasma.

Compound (group)	Exposure biomarkers	Matrices	Analytical methods	References
Phthalates and DINCH	Metabolites	Urine, serum, hair, human milk, saliva	Deconjugation, extraction (SPE, LLE), clean-up optional, LC-MS/MS or GC–MS following derivatization	Chang et al. (2013), Hines et al. (2009), Kim et al. (2014), Koch et al. (2017), Schütze et al. (2012), (2017), Servaes et al. (2013), Silva et al. (2007)
Bisphenols	Parent compounds or conjugates	Serum/plasma/ whole blood, urine, human milk, hair, saliva, placenta	Deconjugation (for analysis of parent compounds), extraction (SPE, LLE, ultrasound or other techniques), LC-MS/MS or GC–MS (following derivatization)	Calafat et al. (2008), Cobellis et al. (2009), De Nys et al. (2018), Martín et al. (2016), Zhang et al. (2011), Zimmers et al. (2014)
Per- and polyfluoroalkyl substances (PFASs)	Parent compounds	Serum/plasma/whole blood, human milk, urine, hair, nails	Protein precipitation, extraction, clean-up, LC-MS/MS	Hartmann et al. (2017), Haug et al. (2009), Kärrman et al. (2007), Li et al. (2012)
Halogenated flame retardants (HFRs)	Parent compounds	Serum/plasma/whole blood, human milk, placenta, hair, nails	Extraction (SPE, LLE, pressurized liquid extraction), clean-up (incl. lipid removal), LC-MS/MS (for HBCDD, TBBPA and bromophenols), GC–MS (for other HFRs)	Butt et al. (2016), Čechová et al. (2017), Cequier et al. (2013), Frederiksen et al. (2009), Liu et al. (2015), Sochorová et al. (2017)
Organophosphorous flame retardants (OPFRs)	Metabolites; parent compounds in some studies	Urine, serum, hair, nails, human milk	Extraction (SPE, LLE), clean-up, LC-MS/MS, LC-HRMS or GC–MS (following derivatization for metabolite determination)	Alves et al. (2017), Bastiaensen et al. (2018), Cequier et al. (2014b), He et al. (2018), Li et al. (2017), Ospina et al. (2018), Schindler et al. (2009), Sundkvist et al. (2010), Van den Eede et al. (2013)
Polycyclic aromatic hydrocarbons (PAHs)	Parent compounds and metabolites	Urine, serum/plasma/whole blood, hair, human milk, placenta	Deconjugation, extraction (SPE, LLE), clean-up, LC-MS/MS or GC–MS (following derivatization for metabolite determination); LC-fluorescence detector	Boada et al. (2015), Lankova et al. (2016), Li et al. (2014), Motorykin et al. (2015), Romanoff et al. (2006), Schummer et al. (2009), Yamamoto et al. (2015), Yu et al. (2011)
Arylamines	Parent compounds and metabolites	Urine, plasma/ whole blood	Extraction (SPE, LLE), LC-MS/MS or GC–MS (following derivatization)	Marand et al. (2004), Dierkes et al. (2014), Shih et al. (2007), Weiss and Angerer (2002)
Cadmium	Elemental Cd	Urine, whole blood, hair	Dilution, acid dilution (urine) or microwave digestion (blood), ICP-MS	Bonberg et al. (2017), Ciesielski et al. (2012), Jursa et al. (2018)
Chromium	Total Cr, Cr (VI)	Urine, whole blood/plasma, red blood cells, exhaled breath condensate	Extraction (LLE, centrifugation), clean-up (strong acid), ICP-MS	Georgi et al. (2017), Goldoni et al. (2010), Leese et al. (2017)

Table 5
Prioritized biomarkers and analytical methods for phthalates and DINCH. Categories A, B and C apply to sufficient, insufficient and very limited data availability, respectively, of a certain biomarker in human biomonitoring. Urine was the matrix of choice for all biomarkers. LC-MS/MS: High performance liquid chromatography-tandem mass spectrometry. GC–MS: Gas chromatography-mass spectrometry. Further acronyms are explained in the text and in Table S1.

Biomarker	Parent compound	Category	Instrumental analysis	References
Low molecular weight / short alkyl chain phthalates → Monoester metabolites				
Monoethyl phthalate (MEP)	DEP	A	LC-MS/MS	Černa et al. (2015), Frederiksen et al. (2010b), Koch et al. (2017), Myridakis et al. (2015), Sabaredzovic et al. (2015), Saravanabhavan et al. (2013), Servaes et al. (2013), Silva et al. (2007)
Monobenzyl phthalate (MBzP)	BzBP	A	LC-MS/MS	
Mono-n-butyl phthalate (MNBP)	DBP [a] and BzBP	A	LC-MS/MS	
Monoisobutyl phthalate (MIBP)	DIBP [a]	A	LC-MS/MS	Černa et al. (2015), Frederiksen et al. (2010b), Koch et al. (2017), Myridakis et al. (2015), Sabaredzovic et al. (2015), Servaes et al. (2013), Silva et al. (2007)
Monomethyl phthalate (MMP)	Dimethyl phthalate (DMP)	B	LC-MS/MS	Cerna et al. (2015), Koch et al. (2017), Saravanabhavan et al. (2013), Silva et al. (2007)
Mono-n-pentyl phthalate (MNPeP)	Di-n-pentyl phthalate (DNPeP)	B	LC-MS/MS	Koch et al. (2017)
Monocyclohexyl phthalate (MCHP)	Dicyclohexyl phthalate (DCHP)	B	LC-MS/MS	Cerna et al. (2015), Koch et al. (2017), Saravanabhavan et al. (2013), Silva et al. (2007)
Mono-isopentyl phthalate (MIPeP)	Di-isopentyl phthalate (DIPeP)	C	LC-MS/MS	Souza et al. (2018)
Mono-n-hexyl phthalate (MNHxP)	Di-n-hexyl phthalate (DNHxP)	C	LC-MS/MS	Rocha et al. (2017)
High molecular weight / long alkyl chain phthalates → Oxidized monoester metabolites				
Mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP, MEHHP)	DEHP [b]	A	LC-MS/MS	Černa et al. (2015), Frederiksen et al. (2010b), Koch et al. (2017), Myridakis et al. (2015), Sabaredzovic et al. (2015), Saravanabhavan et al. (2013), Servaes et al. (2013), Silva et al. (2007)
Mono(2-ethyl-5-oxo-hexyl) phthalate (5oxo-MEHP, MEOHP)	DEHP [b]	A	LC-MS/MS	
Mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP, MECPP)	DEHP [b]	A	LC-MS/MS	Frederiksen et al. (2010b), Koch et al. (2017), Sabaredzovic et al. (2015), Silva et al. (2007)
Mono-n-octyl phthalate (MNOP)	DNOP	B	LC-MS/MS	Frederiksen et al. (2010b), Koch et al. (2017), Saravanabhavan et al. (2013), Silva et al. (2007)
OH-mono-isononyl phthalate [c] (OH-MINP)	DINP	B	LC-MS/MS	Frederiksen et al. (2010b), Koch et al. (2017), Sabaredzovic et al. (2015), Saravanabhavan et al. (2013), Silva et al. (2007)
Oxo-mono-isononyl phthalate [c] (oxo-MINP)	DINP	B	LC-MS/MS	Frederiksen et al. (2010b), Koch et al. (2017), Sabaredzovic et al. (2015), Silva et al. (2007)
Carboxy-(mono-isononyl) phthalate [c] (cx-MINP)	DINP	B	LC-MS/MS	
OH-mono-isodecyl phthalate [c] (OH-MIDP)	DIDP	B	LC-MS/MS	Koch et al. (2017)
Oxo-mono-isodecyl phthalate [c] (oxo-MIDP)	DIDP	B	LC-MS/MS	
Carboxy-(mono-isodecyl) phthalate [c] (cx-MIDP)	DIDP	B	LC-MS/MS	
OH-mono-2-propyl-heptyl phthalate (OH-MPrHpP)	DPrHpP	B	GC–MS [d]	Gries et al. (2012)
Oxo-mono-2-propyl-heptyl phthalate (oxo-MPrHpP)	DPrHpP	B	GC–MS [d]	
Carboxy-(mono-2-propyl-heptyl) phthalate (cx-MPrHpP)	DPrHpP	B	GC–MS [d]	
Phthalate substitutes (DINCH)				
Cyclohexane-1,2-dicarboxylate-mono-hydroxyisononyl ester (OH-MINCH)	DINCH	B	LC-MS/MS	Fromme et al. (2016), Schütze et al. (2012), Silva et al. (2013)
Cyclohexane-1,2-dicarboxylate-mono-oxoisononyl ester (oxo-MINCH)	DINCH	B	LS-MS/MS	
Cyclohexane-1,2-dicarboxylate-mono-carboxyisononyl ester (cx-MINCH)	DINCH	B	LC-MS/MS	

[a] The oxidized monoesters 3-OH-mono-n-butyl phthalate (OH-MnBP) and 2-OH-mono-*iso*-butyl phthalate (OH-MiBP) are additional useful biomarkers.
[b] The monoester metabolite mono(2-ethyl-5-hexyl) phthalate (MEHP) is also commonly measured, but a less suitable biomarker according to the selection criteria for half-lives and measurement validity.
[c] Simplified abbreviations for complex, isomeric structures. For identification and quantification purposes specific isomeric standards are used, e.g. omega and omega-1 oxidation products of the 4-methyl-octyl side chain of DINP. For details see Table S1 and Koch and Calafat (2009) or Koch et al. (2017).
[d] Gas chromatography with high-resolution mass spectrometry (GC-HRMS) was used by Gries et al. (2012).

related to the specific exposure of infants (Fromme et al., 2011).

The analysis of the phthalate and DINCH metabolites is best performed by LC-MS/MS, offering sufficient sensitivity for biomonitoring of the general population. The generally low levels in the general population require MDLs of approximately 100–300 pg/mL, which is technically feasible with state-of-the-art instrumentation and sample volumes of ≤ 1 mL. All relevant metabolites can be covered with a single LC-MS/MS method. GC–MS analysis after derivatization has been applied to separate metabolites of di(2-propylheptyl) phthalate (DPrHpP) from DIDP metabolites (Gries et al., 2012).

The compounds can be extracted and separated by solid phase extraction (SPE), either online or off-line, or the deconjugated samples are directly analysed by LC-MS/MS (Müllerová et al., 2016). Deconjugation is best achieved by enzymatic hydrolysis with arylsulfatase-free *E.coli K12* β-glucuronidase. Some glucuronidase enzymes might hydrolyse phthalate ester bonds in the parent phthalates due to arylsulfatase or esterase side activities, which has to be avoided (Blount et al., 2000; Feng et al., 2015; Koch et al., 2018). Thus, the use of *Helix pomatia* β-glucuronidase might lead to false positives when monoester metabolites are analysed. Native and labelled standards are commercially available for most of the prioritized biomarkers, as are certified reference materials (Schantz et al., 2015).

4.3.3. Bisphenols

The bisphenol parent compounds were identified as the most suitable biomarkers for human biomonitoring (Table 6), determined after hydrolysis of conjugates, typically using *H. pomatia* or *E. coli K12* β-glucuronidase enzymes, some of which also present arylsulfatase activity. Most bisphenols are rapidly metabolized, mainly to their glucuronidated form, and excreted as conjugates. The half-lives of bisphenol A and S conjugates in humans were determined to be less than six and seven hours, respectively (Dekant and Völkel, 2008; Oh et al., 2018). However, deconjugation can take place in the body, and since only the parent compound can bind to the estrogen receptor, the presence of unconjugated bisphenols is discussed as a measure of toxic potential (Ginsberg and Rice, 2009). Separate analyses of free and conjugated bisphenols at trace levels have been attempted, but proven challenging due to the very low levels of the free forms requiring maximum sensitivity and posing a risk of external contamination (Markham et al., 2010; Liao and Kannan, 2012). However, for means of quantitative exposure assessments, the analyses of total bisphenol levels appear sensitive and robust (Dekant and Völkel, 2008).

For bisphenol F, more specifically the isomer 4,4′-bisphenol F, a natural occurrence in mustard has been reported, leading to a daily intake similar to that of BPA and posing the question of a distinction between natural and anthropogenic sources of bisphenol F (Dietrich and Hengstler, 2016). The isomer 2,2′-bisphenol F is a biomarker of non-natural exposure to bisphenol F (Zoller et al., 2016). Bisphenols S and F have been analysed more frequently than the remaining bisphenols in Table 6 and have been included in the NHANES since 2013 (CDC, 2018), hence their Category B classification.

Urine was the matrix of choice to study exposure of the general population. Techniques are available to analyse bisphenols in other human matrices (Table 4), but these studies have usually been directed at specific populations or research questions (Gerona et al., 2013; Zimmers et al., 2014). However, urine analyses alone have been considered unsuitable to assess the full toxicokinetics of bisphenols (Vandenberg et al., 2014).

The selected analytical methods are based on LC-MS/MS, combined with a variety of extraction and clean-up methods, for example online-solid phase extraction (SPE). However, GC–MS approaches, in particular GC–MS/MS, appear equally suitable according to the selection criteria (Table 3), as they provide low detection limits and low external contamination levels (Zhang et al., 2011; Deceuninck et al., 2014). Isotope-labelled standards of bisphenols are increasingly available including those for bisphenols A, S, F and B.

Based on sample intakes of 100–500 µl, MDLs of 20–100 pg/mL are achievable for bisphenols A, S and F (Liao et al., 2012; Ye et al., 2015; Wang et al., 2019); however, higher and lower sample intakes have been described as well (Heffernan et al., 2016; Rocha et al., 2016). The Category C bisphenols are generally present in lower levels (Ye et al., 2015). However, an MDL of 5 pg/mL has been reported for bisphenol AF (Heffernan et al., 2016; Rocha et al., 2016).

Thus, analytical methods published today will benefit from further development towards higher sensitivity, greater accuracy (by using labelled standards) and the more frequent inclusion of other bisphenols. Given the widespread use of bisphenols, control of external contamination is important at all pre-analytical and analytical stages to ensure measurement validity. Based on the human biomonitoring information currently available, only BPA was considered a category A compound.

4.3.4. Per- and polyfluoroalkyl substances (PFASs)

Most PFSAs and PFCAs are persistent and can be measured directly as biomarkers of exposure (Table 7). However, PFSAs and PFCAs can also be transformation products of less persistent precursors, e.g. fluorotelomer alcohols (FTOHs), perfluoroalkyl sulfonamides (FOSAs) and perfluoroalkyl sulfonamidoethanols (FOSEs) (Table S4). Thus, detection of PFSAs and PFCAs in human samples integrates direct exposure to these compounds and exposure to precursors, which implies that strictly speaking, the first EB/M criterion of specificity is not met for all PFSAs and PFCAs. Furthermore, the precursors are not always transformed quantitatively, and some can also be detected in human samples (Vorkamp et al., 2014). Finally, other transformation products than PFSAs and PFCAs are detectable in human samples, for example N-methyl-perfluorooctane sulfonamidoacetate (MeFOSAA) or N-ethyl-perfluorooctane sulfonamidoacetate (EtFOSAA), which are transformation products of N-methyl-perfluorooctane sulfonamidoethanol (MeFOSE) and N-ethyl-perfluorooctane sulfonamidoethanol (EtFOSE) (Buck et al., 2011; Vorkamp et al., 2014). For 8:2 FTOH, 8:2 FTOH sulfate has been suggested as an applicable biomarker (Dagnino et al., 2016). While half-lives of serum elimination are in the order of years for

Table 6
Prioritized biomarkers for bisphenols. Categories A, B and C apply to sufficient, insufficient and very limited data availability, respectively, of a certain biomarker in human biomonitoring. Matrix and analytical method of choice were urine and high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS), respectively, for all biomarkers.

Biomarker	Category	Reference
Bisphenol A	A	Calafat et al. (2008), Heffernan et al. (2016), Koch et al. (2012), Rocha et al. (2016), Wang et al. (2019), Ye et al. (2015)
Bisphenol S	B	Heffernan et al. (2016), Liao et al. (2012), Ndaw et al. (2018), Rocha et al. (2016), Wang et al. (2019)
Bisphenol F	B	Heffernan et al. (2016), Rocha et al. (2016), Wang et al. (2019), Ye et al. (2015)
Bisphenol B	C	Heffernan et al. (2016)
Bisphenol P	C	Rocha et al. (2016)
Bisphenol Z	C	
Bisphenol AP	C	
Bisphenol AF	C	Heffernan et al. (2016), Rocha et al. (2016), Ye et al. (2015)

Table 7
Prioritized biomarkers and human matrices for per- and polyfluoroalkyl substances (PFASs). Categories A, B and C apply to sufficient, insufficient and very limited data availability, respectively, of a certain biomarker in human biomonitoring. The analytical method of choice was high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) for all biomarkers.

Biomarker	Category	Matrix	Reference
PFSAs: PFBS; PFHxS; PFHpS; PFOS; PFDS [a]	A	Serum; plasma; whole blood	Gao et al. (2018), Haug et al. (2009), Nilsson et al. (2013), Poothong et al. (2017)
PFCAs: PFBA; PFPeA; PFHxA; PFHpA; PFOA; PFNA; PFDA; PFUnDA; PFDoDA; PFTrDA; PFTeDA [b]	A	Serum; plasma; whole blood	
Perfluoro-1-octaperfluoro-1-octane sulfonamide (FOSA); N-methyl-perfluoro-1-octane sulfonamide (N-MeFOSA)	B	Serum; plasma; whole blood	Gao et al. (2018), Haug et al. (2009), Kuklenyik et al. (2005), Nilsson et al. (2013), Poothong et al. (2017)
N-methyl-perfluorooctane sulfonamidoacetate (MeFOSAA); N-ethyl-perfluorooctane sulfonamidoacetate (EtFOSAA)	B	Serum	Gao et al. (2018), Kato et al. (2018), Kuklenyik et al. (2005), Vorkamp et al. (2014)
8:2 polyfluoroalkyl phosphoric acid diesters (8:2 diPAP)	B	Serum; plasma, whole blood	Gao et al. (2018), Poothong et al. (2017)
Fluorotelomer sulfonic acids (FTSAs): 4:2 FTSA; 6:2 FTSA; 8:2 FTSA	B	Serum	Gao et al. (2018)
Fluorotelomer carboxylic acids (FTCAs): 5:3 FTCA; 7:3 FTCA	B	Whole blood [c]	Nilsson et al. (2013)
Fluorotelomer unsaturated carboxylic acids (FTUCAs): 6:2 FTUCA; 8:2 FTUCA; 10:2 FTUCA	B	Whole blood [c]	
Ammonium 4,8-dioxa-3H-perfluorononanoate (ADONA)	B	Serum	Kato et al. (2018)
Perfluoroalkyl phosphoric acid monoesters (monoPAPs): 6:2 monoPAP; 8:2 monoPAP	C	Serum; plasma	Gao et al. (2018), Poothong et al. (2017)
Perfluoroalkyl phosphoric acid diesters (diPAPs): 6:2 diPAP; 6:2/8:2 diPAP	C	Serum; plasma; whole blood	
N-ethyl-perfluoro-1-octanesulfonamide (N-EtFOSA)	C	Serum	Gao et al. (2018), Haug et al. (2009), Kuklenyik et al. (2005)
N-methyl-perfluorooctane sulfonamidoethanol (MeFOSE); N-ethyl-perfluorooctane sulfonamidoethanol (EtFOSE)	C	Serum	Kuklenyik et al. (2005)
Perfluoroalkyl phosphonic acid: PFHxPA; PFOPA; PFDPA [d]	C	Serum; plasma; whole blood	Gao et al. (2018), Poothong et al. (2017)
PFCAs: PFHxDA; PFODA [e]	C	Serum	Gao et al. (2018)
FTCAs: 6:2 FTCA; 8:2 FTCA; 10:2 FTCA	C	Serum	Dagnino et al. (2016) [g]
8:2 fluorotelomer alcohol sulfate (8:2 FTOH sulfate) [f]	C	Serum	
Bis(perfluorohexyl)phosphinic acid (C6/C6 PFPiA); bis(perfluorohexyloctyl)phosphinic acid (C6/C8 PFPiA); bis(perfluorooctyl)phosphonic acid (C8/C8 PFPiA)	C	Serum	Gao et al. (2018)
Ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoate (GenX)	C	Serum	Kato et al. (2018)

[a] Perfluorobutane sulfonate (PFBS); perfluorohexane sulfonate (PFHxS); perfluoroheptane sulfonate (PFHpS); perfluorooctane sulfonate (PFOS); perfluorodecane sulfonate (PFDS).
[b] Perfluorobutanoic acid (PFBA); perfluoropentanoic acid (PFPeA); perfluorohexanoic acid (PFHxA); perfluoroheptanoic acid (PFHpA); perfluorooctanoic acid (PFOA); perfluorononanoic acid (PFNA); perfluorodecanoic acid (PFDA); perfluoroundecanoic acid (PFUnDA); perfluorododecanoic acid (PFDoDA); perfluorotridecanoic acid (PFTrDA); perfluorotetradecanoic acid (PFTeDA).
[c] Serum or plasma would likely be suitable matrices as well, but insufficient information is available at present.
[d] Perfluorohexyl phosphonic acid (PFHxPA); perfluorooctyl phosphonic acid (PFOPA); perfluorodecyl phosphonic acid (PFDPA).
[e] Perfluorohexadecanoic acid (PFHxDA); perfluorooctadecanoic acid (PFODA).
[f] Biomarker for 8:2 FTOH.
[g] Dagnino et al. (2016) used LC-Time of Flight (TOF)-MS instead of LC-MS/MS.

PFHxS, PFOS and PFOA, short-chain PFASs, such as perfluorobutane sulfonate (PFBS) and perfluorobutanoic acid (PFBA), appear less persistent and bioaccumulative (Gomis et al., 2018; Olsen et al., 2007). As PFASs differ in their toxicity (Gomis et al., 2018) it is advisable for risk assessment purposes to address a suite of substances, while bearing in mind that transformation processes take place which limit EB specificity.

Serum, plasma or whole blood are the matrices of choice for all PFAS compounds, and relatively small volumes are necessary for acceptable MDLs. In general, published detection limits are sufficiently low for human biomonitoring. Based on sample intakes of 25–150 µl, MDLs for most PFASs are usually as low as 2–100 pg/mL (Haug et al., 2009; Gao et al., 2018; Kato et al., 2018). For the analysis of fluorotelomer acids and 8:2 FTOH sulfate, 500 µl of serum were used, with corresponding MDLs < 100 pg/mL (Dagnino et al., 2016; Nilsson et al., 2013). Slightly higher MDLs of 400 pg/mL were reported for MeFOSE and EtFOSE (Kuklenyik et al., 2005), but further method development might improve the currently documented sensitivity. PFSAs and PFCAs can also be measured in blood spots (Kato et al., 2009; Ma et al., 2013; Poothong et al., 2019), which would improve sample availability for infants. Table 7 includes a reference to whole blood for the analysis of fluorotelomer saturated and unsaturated carboxylic acids. Serum and plasma would likely be suitable matrices for these compounds as well, however, a method with full validation and QA/QC information is not yet available in the literature.

PFASs have also been analysed in human milk (Kärrman et al., 2007; Thomsen et al., 2010). However, the concentrations in milk are usually considerably lower than in serum, which might challenge MDLs, besides the obvious drawback of only presenting a part of the general population. For these reasons, human milk is not evaluated as the primary matrix in this context. Some studies exist on PFSAs and PFCAs in urine (Hartmann et al., 2017). This might be a relevant matrix for the short-chain PFSAs and PFCAs with shorter half-lives, but more information will be needed prior to a re-evaluation of this EB/M combination.

The analytical methods are rather uniform for all PFASs and include protein precipitation, clean-up and LC-MS/MS analysis using isotope-labelled internal standards where available. The literature survey indicates that multi-methods addressing many PFASs together are feasible for this compound group. All biomarkers except 8:2 FTOH sulfate are commercially available and isotope-labelled standards are obtainable for some representatives of each PFAS-subgroup. However, QA/QC measures lack the availability of interlaboratory comparisons and certified reference materials beyond the most commonly measured PFSAs and PFCAs. Contamination from fluorine-containing materials such as polytetrafluoroethylene (PTFE) has to be avoided during sampling and sample processing. In addition to compound-specific analyses, sum parameters, e.g. total, inorganic or extractable organic fluorine, can be

Table 8
Prioritized biomarkers, human matrices and analytical methods for halogenated flame retardants (HFRs). Categories A, B and C apply to sufficient, insufficient and limited data availability, respectively, of a certain biomarker in human biomonitoring. GC–MS (ECNI): Gas chromatography-low resolution mass spectrometry with electron capture negative ionization. LC-MS/MS: High performance liquid chromatography-tandem mass spectrometry.

Biomarker	Category	Matrix	Instrumental analysis	Reference
Polybrominated diphenyl ethers (PBDEs): BDE-47, BDE-153, BDE-209	A	Serum [a]	GC–MS (ECNI)	Ali et al. (2013), Butt et al. (2016), Cequier et al. (2013), Gao et al. (2016), Guo et al. (2018), He et al. (2013), Li et al. (2017), van den Berg et al. (2017)
Hexabromocyclododecane (HBCDD) isomers	A	Serum [a]	LC-MS/MS	Butt et al. (2016)
Tetrabromobisphenol A (TBBPA)	A	Serum	LC-MS/MS	Hayama et al. (2004), Sochorová et al. (2017)
Dechlorane plus isomers	B	Serum [a]	GC–MS (ECNI)	Cequier et al. (2013), Guo et al. (2018), He et al. (2013)
2-Ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB)	B	Serum [a]	GC–MS (ECNI)	Butt et al. (2016), Guo et al. (2018)
Bis(2-ethylhexyl) tetrabromophthalate (BEH-TEBP)	B	Serum [a]	GC–MS (ECNI)	Ali et al. (2013), Butt et al. (2016), Guo et al. (2018), He et al. (2013)
1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE)	B	Serum [a]	GC–MS (ECNI)	Ali et al. (2013), Cequier et al. (2013), Gao et al. (2016), Guo et al. (2018)
Decabromodiphenyl ethane (DBDPE)	B	Serum [a]	GC–MS (ECNI)	Ali et al. (2013), Cequier et al. (2013), Gao et al. (2016), Guo et al. (2018), Sochorová et al. (2017)
Hexabromobenzene (HBB)	B	Serum [a]	GC–MS (ECNI)	Cequier et al. (2013), Gao et al. (2016), Li et al. (2017), Sochorová et al. (2017)
Pentabromotoluene (PBT)	B	Serum [a]	GC–MS (ECNI)	Gao et al. (2016), Li et al. (2017), Sochorová et al. (2017)
Pentabromoethylbenzene (PBEB)	B	Serum [a]	GC–MS (ECNI)	
2,3,5,6-Tetrabromo-p-xylene (p-TBX)	C	Serum [a]	GC–MS (ECNI)	Li et al. (2017)
Tetrabromoethylcyclohexane (DBE-DBCH)	C	Serum [a]	GC–MS (ECNI)	Guo et al. (2018)
Dechloranes 602 and 603	C	Serum [a]	GC–MS (ECNI)	Cequier et al. (2013)
2,4,6-Tribromophenol	C	Serum	LC-MS/MS	Ali et al. (2013), Butt et al. (2016), Sochorová et al. (2017)

[a] Human milk has been evaluated as an equally suitable matrix for lipophilic HFRs.

determined including total oxidizable precursor analysis (TOPA) (Houtz and Sedlak, 2012). These can provide supplementary information if standardized for analysis.

4.3.5. Halogenated flame retardants (HFRs)

The evaluation included 14 biomarkers (or groups of biomarkers) for HFRs which had been determined in human samples and for which quality assurance information was available (Table 8). All biomarkers were identical with the parent compounds. Regarding the PBDEs, BDE-47, BDE-153 and BDE-209 were considered the main biomarkers, reflecting a combination of highest exposure and strongest bioaccumulation (Geyer et al., 2004; Thuresson et al., 2006). However, it is debatable if the half-life of BDE-209 of approximately 15 days is sufficiently long to avoid large variation among individuals (Table 2) (Thuresson et al., 2005). In contrast, the elimination half-lives of BDE-47 and BDE-153 in humans were calculated as 1.8 and 6.5 years, respectively (Geyer et al., 2004). However, lower brominated PBDE congeners will not fully meet the EB/M criteria (Table 2) if they also are transformation products of higher brominated congeners in addition to reflecting exogenous exposure.

Of the HBCDD isomers, α- and γ-HBCDD were determined most frequently in human samples. However, the EB/M criterion of biomarker concentrations reflecting exogenous exposure is also challenged in this case since bioisomerization has been shown (Szabo et al., 2010), leading to differences in HBCDD profiles between exposure sources and human samples. Thus, HBCDD only fulfills the EB/M criteria if ΣHBCDD is considered. The elimination half-life of ΣHBCD was 64 days (Geyer et al., 2004). Little is known of the transformation of other HFRs, which were all categorized as B or C compounds, i.e. compounds with insufficient biomonitoring or exposure data. 2,3,4,5-Tetrabromobenzoic acid has been analysed as a biomarker for EH-TBB in urine (Hoffman et al., 2014). Thus, re-evaluations of the B and C cases might lead to changes in the prioritized biomarkers and matrices as new knowledge becomes available.

Serum was evaluated to be the matrix of choice for the biomonitoring of HFRs in the general population. Human milk has also been analysed widely and its higher lipid content favours accumulation of lipophilic HFRs (Čechova et al., 2017; Siddique et al., 2012). Furthermore, larger sample volumes can be available, which reduces sensitivity issues. The serum analyses are based on relatively large sample amounts of roughly 1–5 mL in order to reach acceptable MDLs, which usually are 0.1–1 ng/g lipids, sometimes with MDLs of BDE-209 exceeding those of lower brominated PBDEs (Butt et al., 2016; Gao et al., 2016; He et al., 2018). Higher MDLs of 2–20 ng/g lipids usually exist for decabromodiphenyl ethane (DBDPE) (Cequier et al., 2013; Gao et al., 2016). Likewise, higher MDLs have been reported for other B and C compounds for which little information is available and that will benefit from further method development (Butt et al., 2016; Li et al., 2017). In the NHANES programme, pooled serum samples have been used since 2004 for the analysis of PBDEs to increase the sample amount (CDC, 2018).

Lipids should be removed from the extracts by e.g. acid silica or gel permeation chromatography (GPC), the latter being suitable for acid-sensitive HFRs, e.g. BEH-TEBP (Covaci et al., 2011). ^{13}C-labelled standards are used increasingly when other masses than those of bromine ions (m/z 79 and 81) are targeted. While GC-LRMS (ECNI) is a suitable method for PBDEs and other HFRs (Table 8), except HBCDD and phenolic compounds, recent developments also include the use of GC-HRMS or GC–MS/MS (e.g. Čechová et al., 2017; Sochorová et al., 2017), offering low MDLs, high specificity, and if run in Electron Ionization (EI) mode, the possibility to use ^{13}C-labelled standards. For HBCDD isomers, TBBPA and other bromophenols, the analytical methods evaluated as state-of-the-art include LC-MS/MS with negative electrospray ionisation

It was a general outcome of the HFR evaluation that QA/QC information was insufficient, even for PBDEs which are generally perceived as well-studied compounds. The analysis of BDE-209 often resulted in lower precision and accuracy than that of other PBDEs, combined with more frequently occurring blanks (e.g. Alcock et al., 2011; Guo et al., 2018). External contamination can also be an issue for current-use HFRs analysed as parent compounds, which would challenge the method validity criterion (Table 2). Developments are ongoing towards alternative, non-invasive matrices, but concentrations in e.g. hair and nails are difficult to interpret and thus in conflict with criteria of specificity and biological sensitivity in Table 2. The number of HFRs for which analytical methods are available is still small considering the large number of brominated FRs currently in use (Covaci et al., 2011). Because of the chemical heterogeneity of the HFR group, method extensions or multi-methods are not easily possible, but each compound requires its own method optimization.

Table 9
Prioritized biomarkers for organophosphorous flame retardants (OPFRs). Categories B and C apply to insufficient and very limited data availability, respectively, of a certain biomarker in human biomonitoring. Matrix and analytical method of choice were urine and high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS), respectively, for all biomarkers.

Biomarker	Parent compound	Category	Reference
Bis(2-chloroethyl) phosphate (BCEP)	Tri(2-chloroethyl) phosphate (TCEP)	B	Bastiaensen et al. (2018), Chen et al. (2018), Fromme et al. (2014), He et al. (2018), Ospina et al. (2018), Sun et al. (2018), Van den Eede et al. (2013)
Bis(chloroisopropyl) phosphate (BCIPP)	Tri(chloroiso-propyl) phosphate (TCIPP) [a]	B	Bastiaensen et al. (2018), Carignan et al. (2017), Chen et al. (2018), Fromme et al. (2014), He et al. (2018), Ospina et al. (2018), Sun et al. (2018), Van den Eede et al. (2013)
Bis(1,3-dichloro-isopropyl) phosphate (BDCIPP)	Tri(1,3-dichloro-isopropyl) phosphate (TDCIPP)	B	Bastiaensen et al. (2018), Carignan et al. (2017), Chen et al. (2018), He et al. (2018), Ospina et al. (2018), Sun et al. (2018), Van den Eede et al. (2013)
Diphenyl phosphate (DPHP) [b]	Triphenyl phosphate (TPHP)	B	
Biscresyl phosphate (BMPP)	Tricresyl phosphate (TMPP)	B	Chen et al. (2018), Fromme et al. (2014), He et al. (2018), Ospina et al. (2018), Sun et al. (2018)
Bis(2-butoxyethyl) phosphate (BBOEP)	Tris(2-butoxyethyl) phosphate (TBOEP) [a]	B	Bastiaensen et al. (2018), Chen et al. (2018), Fromme et al. (2014), He et al. (2018), Sun et al. (2018), Van den Eede et al. (2013)
Diethyl phosphate (DEP)	Triethyl phosphate (TEP)	B	Sun et al. (2018)
Di-n-butyl phosphate (DNBP)	Tri-n-butyl phosphate (TNBP)	B	Bastiaensen et al. (2018), Chen et al. (2018), Fromme et al. (2014), He et al. (2018), Ospina et al. (2018), Sun et al. (2018), Van den Eede et al. (2013)
Bis(2-ethylhexyl) phosphate (BEHP)	Tris(2-ethylhexyl) phosphate (TEHP)	B	He et al. (2018), Sun et al. (2018)
Mono-substituted isopropylphenyl phenyl phosphate (i,p-PPP)	Isopropyl triphenyl phosphate (i,p-TPP)	C	Carignan et al. (2017), Phillips et al. (2018)

[a] Additional biomarkers exist for this parent compound, see text for details.
[b] Unspecific biomarker, see text for details.

4.3.6. Organophosphorous flame retardants (OPFRs)

The trialkyl and triarylphosphate esters are less persistent than the HFRs and readily metabolized. Their dialkyl or diarylphosphate esters have been analyzed as the main biomarkers for human biomonitoring (Cequier et al., 2014b; Van den Eede et al., 2013) (Table 9). Although the group of OPFRs has been studied in the environment for many years (Reemtsma et al., 2008), their biomonitoring is still an issue of research and development.

Recent studies have revealed a more complex group of metabolites and thus potential biomarkers for biomonitoring, besides the dialkyl and diarylphosphate esters: For example, bis(chloroisopropyl) phosphate (or bis(1-chloro-2propyl) phosphate; BCIPP) and 1-hydroxy-2-propyl-bis(1-chloro-2-propyl)phosphate (BCIPHIPP) are both metabolites of TCIPP (He et al., 2018; Phillips et al., 2018; Van den Eede et al., 2013). For tris(2-butoxyethyl) phosphate (TBOEP), hydroxylated metabolites have also been identified as metabolites besides the diester bis (2-butoxyethyl) phosphate (BBOEP) (van den Eede et al., 2013). Additional phase I and phase II metabolites were observed for all OPFRs (van den Eede et al., 2013). The presence of several metabolites does not necessarily conflict with the criteria in Table 2, as long as the metabolites qualitatively and quantitatively reflect exogeneous exposure of a defined parent compound. However, the current identification of most suitable biomarkers (Table 9) might be preliminary as research into metabolite identification continues.

Regarding the criteria in Table 2, it is more problematic that some biomarkers are metabolites of several OPFRs and thus not reflective of exposure to a specific parent compound. Diphenyl phosphate (DPHP) was found to be a biomarker of several aryl-OPFRs rather than of triphenyl phosphate (TPHP) specifically, as it could also result from 2-ethylhexyl diphenyl phosphate (EHDPHP), resorcinol bis(diphenyl) phosphate, isopropyl triphenyl phosphate (i,p-TPHP) and probably other aryl-OPFRs (van den Eede et al., 2016; He et al., 2013; Phillips et al., 2018). Thus, DPHP does not fully meet the criterion of specificity. In addition, the current literature is not always specific with regard to isomers of tricresyl phosphate (TMPP) and their metabolites. Little is known about the stability of the OFPR urinary biomarkers, but indications exist of half-lives in the order of hours (Hammel et al., 2016).

According to the current state of knowledge and applying the criteria in Table 2 and Table 3, urine is the preferred matrix and LC-MS/MS a suitable instrumental technique for most OPFRs. Sample intakes varied considerably between studies, e.g. 400 µl in the NHANES programme (Ospina et al., 2018) and 5 mL in a German biomonitoring study (Fromme et al., 2014). Resulting MDLs ranged between approximately 50 and 3000 pg/mL for most metabolites, in the studies referred to in Table 9. For some metabolites, such as bis(2-chloroethyl) phosphate (BCEP) and BCIPP, GC–MS/MS might reach comparable sensitivity after derivatization (Schindler et al., 2009).

Other matrices than urine have also been analysed, targeting both parent compounds and metabolites, but usually in studies addressing specific research questions, for example comparisons between matrices or compound groups (Li et al., 2017; Sundkvist et al., 2010). Deuterated standards are commercially available for many diester metabolites. The NHANES studies, for example, include deuterated standards of all target analytes (Ospina et al., 2018).

4.3.7. Polycyclic aromatic hydrocarbons (PAHs)

PAHs undergo oxidation and conjugation in phase I and phase II reactions, similarly to the metabolism reactions described for phthalates. 1-Hydroxypyrene is the main phase I metabolite of pyrene (Table 10) and has been used as general surrogate urinary biomarker for PAH exposure from both environmental and occupational sources (Esteban and Castaño, 2009; Jongeneelen, 2014). Analogously, hydroxylated metabolites of naphthalene, fluorene, phenanthrene and chrysene are suitable PAH urinary biomarkers (Li et al., 2014; Onyemauwa et al., 2009). However, 1-hydroxynaphthalene can also be a metabolite of the insecticide carbaryl and should be assessed in combination with 2-hydroxynapthalene, which is a specific biomarker for naphthalene exposure (Meeker et al., 2007). The hydroxylated metabolites of benzo [a]pyrene and benz[a]anthracene have been detected in urine as well (Barbeau et al., 2014; Onyemauwa et al., 2009; Xu et al., 2004), however, they are excreted to a minor extent in urine, with the consequence of generally low concentrations (Jacob and Seidel, 2002). Haemoglobin and albumin adducts of benzo[a]pyrene have been analysed and detected in workers (e.g. Pastorelli et al., 2000).

A variety of parent PAHs have also been monitored in serum (Boada et al., 2015). The authors concluded that serum was a less suitable matrix for PAH biomonitoring because of large inter-individual variability in the metabolism of PAHs. This might challenge the half-life criterion in Table 2. Furthermore, the risk of contamination conflicts with the measurement validity (Table 2). The analysis of metabolites in

Table 10
Prioritized biomarkers for polycyclic aromatic hydrocarbons (PAHs). Categories A and B apply to sufficient and insufficient data availability, respectively, of a certain biomarker in human biomonitoring. Matrix and analytical method of choice were urine and high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS), respectively, for all PAH biomarkers.

Biomarker	Parent compound	Category	Reference
1-Hydroxypyrene	Pyrene	A	Barbeau et al. (2014), Fan et al. (2012), Jacob III et al. (2007), Lankova et al. (2016), Onyemauwa et al. (2009), Xu et al. (2004)
Hydroxynapthalenes [a]	Naphthalene	A	Fan et al. (2012), Jacob III et al. (2007), Lankova et al. (2016), Onyemauwa et al. (2009), Xu et al. (2004)
Hydroxyfluorenes [b]	Fluorene	A	
Hydroxyphenanthrenes [c]	Phenanthrene	A	Fan et al. (2012), Jacob III et al. (2007), Onyemauwa et al. (2009)
Hydroxychrysenes [d]	Chrysene	B	Onyemauwa et al. (2009), Xu et al. (2004)
3-Hydroxybenzo[a]-pyrene	Benzo[a]pyrene	A	Barbeau et al. (2014), Lankova et al. (2016), Onyemauwa et al. (2009), Xu et al. (2004)
1-Hydroxybenz[a]-anthracene	Benz[a]-anthracene	B	Onyemauwa et al. (2009), Xu et al. (2004)

[a] 1- and 2-Hydroxynaphthalene
[b] 2-, 3- or 9-Hydroxyfluorene
[c] 1-, 2-, 3-, 4- or 9-Hydroxyphenanthrene
[d] 1-, 3- or 6-Hydroxychrysene

urine minimizes the contamination risks and is therefore the preferred approach, besides the obvious disadvantage of the invasive sampling of serum (Table 10). Half-lives of PAH metabolites in urine were given with a range of 5 hours to 17 days (Esteban and Castaño, 2009).

While HPLC in combination with fluorescence detection is still applied in the analysis of PAH metabolites (Yamamoto et al., 2015), the current method of choice providing highest sensitivity and selectivity is LC-MS/MS with electrospray ionisation in negative mode (Table 10). Based on sample intakes of 3–10 mL, MDLs of 1–50 pg/mL were achieved (Lankova et al., 2016; Onyemauwa et al., 2009; Xu et al., 2004). GC-based methods can offer comparable sensitivity, but require an additional derivatization step (Li et al., 2014).

The urine samples are first subjected to enzymatic conjugate cleavage, for example using β-glucuronidase/arylsulfatase (Lankova et al., 2016). Both serum and urine samples can then be further processed by common extraction techniques, e.g. solid-phase extraction, and clean-up steps (Jacob and Seidel, 2002). Labelled standards are commercially available for many parent PAHs and their metabolites. Certified reference materials are available for PAH metabolites in urine (Schantz et al., 2015).

4.3.8. Arylamines

The major metabolites of arylamines are aminophenols and N-acetylated aminophenols excreted as conjugates (glucuronides and sulfates) or free compounds in urine. Extraction with organic solvents without enzymatic or acid pre-treatment at neutral pH yields free arylamines, aminophenols, N-acetylated arylamines and N-acetylated aminophenols since the conjugates are too polar to be extractable in sufficient amounts under these conditions. Enzymatic treatment of urine cleaves glucuronides and sulfates, yielding arylamines, N-acetylated arylamines and aminophenols. Boiling of urine in base or acid yields the parent arylamines and aminophenols (Sabbioni, 2017).

The biomarkers included in Table 11 reflect the multiple potential exposure sources that exist for arylamines. MDA, MOCA, 2,4-TDA and 2,6-TDA mainly reflect the exposure to plastic products. 4-Chloroaniline (CA) and 3,4-dichloroaniline (DCA) are metabolically released from pesticides. Aniline, 4-ABP, 2-NA, 2-MA, 4-MA and 2-MeOA appear to be ubiquitously present in the environment according to former biomonitoring studies (Sabbioni, 2017) and are thus markers to monitor the general exposure to arylamines. The aniline biomarker N-acetyl-4-aminophenol included in Table 11 can also result from Paracetamol intake and does thus not meet the criteria in Table 2 as it is no specific biomarker for aniline (or Paracetamol) (Dierkes et al., 2014).

N-Hydroxyarylamines are toxic intermediates of arylamines and nitroarenes and can form adducts with hemoglobin (Hb-adducts), albumin, proteins and DNA in a dose-dependent manner (Sabbioni and Jones, 2002). Most of the arylamine Hb-adducts can be cleaved *in vitro*, by mild acid or base, to release the arylamines. Hb-adducts are a marker of the biological availability of the toxic N-hydroxyarylamine and have been analyzed in biomonitoring studies (Bryant et al., 1988; Sabbioni, 2017).

While the biomonitoring of urinary metabolites (Table 11) is a less invasive process than blood monitoring, it only represents recent exposure to arylamines, i.e. of the past 24–48 h (Sabbioni, 2017). For 2,5-TDA, for example, a half-life of 8 h was reported (Gube et al., 2011). In case of intermittent exposure, urinary metabolites may not be detected and subjects may be misclassified as non-exposed. In addition, the quantification of arylamines in urine, which can originate from several products, does not give information about the biologically active N-hydroxyarylamine. Measuring the parent arylamine in urine does not indicate how much of the toxic intermediate is bioavailable since the yields of N-hydroxyarylamines resulting from different derivatives are unknown. Thus, Hb-adduct values have the potential to be a better exposure marker for the risk assessment of arylamines than urinary levels of metabolites.

The analysis of Hb-adducts has shown better agreement between laboratories than the analysis of urinary metabolites, probably related to differences in hydrolysis conditions (Sabbioni, 2017). Therefore, in order to improve comparability, the methods for urinary analyses might have to be standardized to a greater extent. Regarding the instrumental analysis, the most sensitive methods include the derivatization of the amino group with perfluorinated anhydride and analysis by GC–MS (ECNI). LC-MS/MS and GC–MS/MS (EI) have been used as well, with high sensitivity and large sample throughputs (Bhandari et al., 2016; Mazumder et al., 2019). Based on sample intakes of 0.2–5 mL, MDLs of 2–1000 pg/mL could be achieved (Table 11). As with other widely used chemicals, external contaminations risks have to be considered in the sampling and processing strategies.

4.3.9. Cadmium and chromium

Cadmium has been included in many human biomonitoring studies. It is preferably monitored in whole blood or urine (Table 12), with urinary Cd reflecting cumulative exposure and accumulation in the kidney, while the Cd concentration in blood also reflects more recent exposure (Jarrett et al., 2008; Vacchi-Suzzi et al., 2016; Wiseman et al., 2017). Chromium analyses in urine are common, but possess a number of disadvantages, such as a short half-life (Paustenbach et al., 1997), conflicting with the criteria in Table 2.

Erythrocytes are the current matrix of choice to quantify Cr (VI) exposure, since Cr (VI), mainly as chromate CrO_4^{2-}, can cross the cell membrane through active anion channels, whereas Cr (III) is unable to cross membranes (Goldoni et al., 2010; Devoy et al., 2016). Thus, although total Cr is determined in erythrocytes, it is assumed to only reflect Cr (VI). Targeting occupational exposure to Cr (VI), exhaled breath condensate has also been used, with selective determination of Cr (VI) (Goldoni et al., 2006; Leese et al., 2017).

Table 11
Prioritized biomarkers and analytical methods for arylamines. The categories A, B and C apply to sufficient, insufficient and limited data availability, respectively, of a certain biomarker in human biomonitoring. Urine was the matrix of choice for all biomarkers. LC-MS/MS: High performance liquid chromatography-tandem mass spectrometry. GC–MS (ECNI/EI): Gas chromatography-mass spectrometry with electron capture negative ionization / electron impact ionization.

Biomarker	Parent compound [a]	Category	Instrumental analysis	Reference
4,4-Methylenedianiline (MDA)		A	LC-MS/MS; GC–MS (ECNI)	Bhandari et al. (2016), Cocker et al. (2017), Lépine et al. (2019)
4,4-Methylenebis(2-chloroaniline) (MOCA)		A	LC-MS/MS[b]	Marand et al. (2004), Shih et al. (2007)
2,4-Toluoenediamine (2,4-TDA)		B	LC-MS/MS; GC–MS (ECNI)	Bhandari et al. (2016), Cocker et al. (2017), Lépine et al. (2020), Marand et al. (2004)
2,6-Toluenediamine (2,6-TDA)		B	LC-MS/MS; GC–MS (ECNI)	
2,5-Toluenediamine (2,5-TDA)		B	GC–MS [c, d]	Gube et al. (2011)
1,4-Phenylenediamine (1,4-PDA)		B	LC-MS/MS; GC–MS [d]	Bhandari et al. (2016), Gube et al. (2011)
4-Aminobiphenyl (4-ABP)		B	LC-MS/MS; GC–MS (ECNI); GC–MS/MS (EI)	Mazumder et al. (2019), Riedel et al. (2006), Weiss and Angerer (2002), Yu et al. (2014)
2-Naphthylamine (2-NA)		B	LC-MS/MS; GC–MS (ECNI); GC–MS/MS (EI)	
2-Methylaniline (2-MA)		B	GC–MS (ECNI); GC–MS (EI); GC–MS/MS (EI)	Mazumder et al. (2019), Riedel et al. (2006), Weiss and Angerer (2002)
4-Methylaniline (4-MA)		C	GC–MS (EI); GC–MS/MS (EI)	Mazumder et al. (2019), Weiss and Angerer (2002)
2-Methoxyaniline (2-MeOA)		C	GC–MS (EI); GC–MS/MS (EI)	
4-Chloroaniline (4-CA)		C	GC–MS (EI)	Weiss and Angerer (2002)
3,4-Dichloroaniline (3,4-DCA)		C	GC–MS (EI)	
Acetanilide	Aniline	B	LC-MS/MS	Dierkes et al. (2014)
N-Acetyl-4-aminophenol	Aniline	B	LC-MS/MS	

[a] Also biomarkers for diisocyanates.
[b] GC–MS primarily used in older studies, e.g. Vaughan and Kenyon (1996).
[c] Analysis by LC-MS/MS likely possibly, by analogy to 2,4-TDA and 2,6-TDA.
[d] Ionization technique not specified.

Inductively coupled plasma (ICP)-MS is state-of-the-art instrumentation to reach the detection limits required in human biomonitoring. MDLs for Cd in blood and urine are typically 10–100 pg/mL (Aoki et al., 2017; Bonberg et al., 2017; Ciesielski et al., 2012; Garner and Levallois, 2017). For Cr in erythrocytes, MDLs of 10–250 pg/mL have been reported (Goldoni et al., 2010; Heitland et al., 2017). For trace level quantification of Cd in urine via ICP-MS, special precautions apply: Interferences from molybdenum oxides and molybdenum hydroxide need to be eliminated (Jarrett et al., 2008) and other interferences from tin (^{114}Sn) have to be corrected for. The Mo interferences could be overcome by ICP-dynamic reaction cell (DRC)-MS, a single-element technique which can be combined with the multi-element ICP-MS analysis (Jarrett et al., 2008; Cañas et al., 2013). The Mo-induced bias was not observed in blood analyses, presumably due to lower Mo levels in blood (Jarrett et al., 2008). Speciation of Cr can be achieved if ICP-MS is preceded by HPLC (Séby et al., 2003).

The sample preparation for Cd can consist of a simple acid or alkaline dilution of urine or blood (Bonberg et al., 2017; Jarrett et al., 2008). Microwave digestion with HNO_3 and/or H_2O_2 is an alternative, following dilution of the sample, especially for frozen blood, which may contain micro clots (Henríquez-Hernández et al., 2017). Quantification should be based on isotope dilution (Heumann, 2004). It must be borne in mind that the results in urine should be adjusted for creatinine (Garner and Levallois, 2017; Middleton et al., 2016). For Cr, erythrocyte samples are diluted with acid and heated prior to ICP-MS analysis (Goldoni et al., 2010). In order to avoid contamination, it is important to use metal-free tubes for sample collection and to be aware of stainless steel needles as potential contamination sources.

4.4. Need for developments

Biomonitoring of the general population requires analytical methods of high selectivity and high sensitivity, due to low concentrations and limited sample volumes. The most common matrices are urine and blood (serum), and for the latter in particular increases in sensitivity cannot always be achieved by increases in sample amount. Triple quadrupole MS techniques have increased sensitivity in many fields of human biomonitoring, and further developments towards lower MDLs can be expected within analytical chemistry.

The quest for lower MDLs should be accompanied by an increased awareness of contamination issues or other interferences in the chemical analyses. These issues should find reflection in the pre-analytical and the analytical phase of human biomonitoring studies. Some biomarkers are more prone to external contamination than others, i.e. parent compounds widely distributed in products and the environment (e.g. flame retardants, PFASs) as opposed to specific metabolites formed in human metabolism. A better understanding of toxicokinetics and metabolism might provide novel and more robust biomarkers of exposure.

The collection of blood requires invasive sampling, which is difficult for sensitive populations such as children, and always accompanied by volume limitations. Non-invasive matrices such as hair, nails and saliva show promising results in terms of detectable concentrations, and might offer additional advantages regarding stability during transport and storage (Table 2). However, the interpretation of these results can be ambiguous and needs further research, for example related to internal exposure, individual variability, contamination and other parameters

Table 12
Prioritized biomarkers, human matrices and analytical methods for cadmium and chromium. The categories A and B apply to sufficient and insufficient data availability, respectively, of a certain biomarker in human biomonitoring. ICP-MS: Inductively coupled plasma-mass spectrometry.

Biomarker	Matrix	Category	Instrumental analysis	Reference
Cd	Blood	A	ICP-MS	Aoki et al. (2017), Bonberg et al. (2017), González-Atuña et al. (2017), Wiseman et al. (2017)
Cd	Urine	A	ICP-MS [a]	Ciesielski et al. (2012), Garner and Levallois (2017), Jarrett et al. (2008), Middleton et al. (2016)
Cr [b]	Erythrocytes (red blood cells)	B	ICP-MS [c]	Devoy et al. (2016), Goldoni et al. (2010), Heitland et al. (2017)

[a] Dynamic reaction cell (DRC)-ICP-MS can overcome the interferences with molybdenum.
[b] As a measure of Cr (VI) exposure as only Cr (VI) can cross the cell membrane.
[c] The study by Devoy et al. (2016) used Atomic Absorption Spectroscopy (AAS).

listed in Table 2 and Table 3. The technical ability to analyse a chemical in a human matrix alone does not guarantee a suitable EB/M combination.

For substances in Category B, some EB/M combinations and analytical methods have been published, but are not widely or routinely used. Further work in HBM4EU and other initiatives, with an integrated focus on QA/QC, will likely lead to a broader dissemination and use of these methods while keeping a critical approach to analytical quality. Compounds of the C category require more research, and this category is continuously extended in HBM4EU as new chemicals are placed on the market or knowledge of new exposure issues and situations increases. This includes, for example, short-chain PFSAs and PFCAs, which bioaccumulate to a lesser extent than the longer-chain PFASs, but might have other toxicokinetics. No analytical method was specified for the metabolites of the Category C phthalates (DIPeP, DnHxP) and method development is needed, especially as these phthalates are classified as SVHCs on account of their reproductive toxicity. Experiences in HBM4EU with the development of analytical methods for less-studied compounds and preparations towards their routine analyses will also be relevant for other biomonitoring programmes, e.g. NHANES and CHMS, and vice versa.

For the HFRs, no category A compounds were identified beyond PBDEs, HBCDD and TBBPA, implying need for further research on other current-use compounds. For OPFRs, discussion of most suitable biomarkers should continue, as little knowledge is available on the main stable (and oxidative) metabolites. PAH biomonitoring is established well, but does not involve alkylated and heterocyclic PAHs on a routine basis, which also leaves room for developments within HBM4EU and other biomonitoring programmes.

For arylamines, the EB/M requirement for specificity is only fulfilled in an occupational environment. The general population can be exposed to several products with the same urinary biomarkers. Therefore, possible health effects should be related to the biologically active metabolite, the N-hydroxyarylamine, which are measured as Hb-adducts. The determination of Hb-adducts requires more time than the analysis of urine, but is established in e.g. NHANES and CHMS.

In general, the extension from initiatives focusing on method development to a large-scale human biomonitoring study such as HBM4EU is substantial and challenging. It includes aspects of capacity building in terms of a wider geographical coverage of analyses of Category A compounds as well as work towards the establishment of analyses of Category B and C compounds, all accompanied by QA/QC programmes. The objective of high-quality and comparable human biomonitoring data across Europe is ambitious, but necessary to be able to detect agreements and differences in sub-groups of the European population.

5. Conclusions

The project HBM4EU has prioritized a first set of seven substance groups and two metals of relevance for human health. With the long-term objective of harmonized and quality-assured biomonitoring, this study addressed the most suitable biomarkers, human matrices and analytical methods for the priority substance groups and metals. It attempted an objective approach of defining criteria for suitable biomarker/matrix combinations as well as analytical methods and applying these to the currently available scientific literature. The evaluation resulted in a list of recommended parent compounds, metabolites and metal (species), each in a preferred human matrix, and state-of-the art methodology for their determination, with a focus on sensitivity. However, it also became obvious that the consistent application of the criteria was compromised in some cases. For example, some common biomarkers can be metabolites of several parent compounds and thus do not reflect exogenous exposure in a quantitative way. In addition, the maturity of analytical methods varied considerably among and within the priority substances and metals, with nearly each compound group including a number of Category C compounds with limited data availability. Thus, the study also revealed multiple needs for development, mainly in terms of higher sensitivity, non-invasive sampling and more stringent QA/QC. Research activities in these fields are ongoing and show promising results, which, however, do not yet possess the maturity for large-scale biomonitoring applications. These developments should be followed closely. They will likely also be relevant for other biomonitoring programmes outside of Europe.

CRediT authorship contribution statement

Katrin Vorkamp: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing. **Argelia Castaño:** Conceptualization, Data curation, Methodology, Project administration, Validation, Writing - review & editing. **Jean-Philippe Antignac:** Project administration, Validation, Writing - review & editing. **Luis D. Boada:** Data curation, Investigation, Methodology, Writing - review & editing. **Enrique Cequier:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Adrian Covaci:** Data curation, Investigation, Methodology, Project administration, Writing - review & editing. **Marta Esteban López:** Conceptualization, Data curation, Methodology, Project administration, Validation, Writing - review & editing. **Line S. Haug:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Monika Kasper-Sonnenberg:** Data curation, Investigation, Methodology, Writing - review & editing. **Holger M. Koch:** Data curation, Investigation, Methodology, Project administration, Writing - review & editing. **Octavio Pérez Luzardo:** Data curation, Investigation, Methodology, Project administration, Writing - review & editing. **Agnese Osīte:** Investigation, Methodology, Project administration. **Loïc Rambaud:** Investigation, Methodology, Project administration. **Maria-Teresa Pinorini:** Data curation, Validation, Writing - review & editing. **Gabriele Sabbioni:** Data curation, Investigation, Methodology, Project administration, Writing - review & editing. **Cathrine Thomsen:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing - review & editing.

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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Appendix A. Supplementary data

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References

Abdel-Shafy, H.I., Mansour, M.S.M., 2016. A review on polycyclic aromatic hydrocarbons: Source, environmental impact, effect on human health and remediation. Egypt. J. Petrol. 25, 107–123.

Alaee, M., Arias, P., Sjödin, A., Bergman, Å., 2003. An overview of commercially used

brominated flame retardants, their applications, their use patterns in different countries/regions and possible modes of release. Environ. Int. 29, 683–689.
Alcock, R.E., MacGillivray, B.H., Busby, J.S., 2011. Understanding the mismatch between the demands of risk assessment and practice of scientists – The case of Deca-BDE. Environ. Int. 37, 216–225.
Ali, N., Eqani, S.A.M.A.S., Malik, R.N., Neels, H., Covaci, A., 2013. Organohalogenated contaminants (OHCs) in human serum of mothers and children from Pakistan with urban and rural residential settings. Sci. Total Environ. 461–462, 655–662.
Alves, A., Covaci, A., Voorspoels, S., 2017. Method development for assessing the human exposure to organophosphate flame retardants in hair and nails. Chemosphere 168, 692–698.
Andersson, J.T., Achten, C., 2015. Time to say goodbye to the 16 EPA PAHs? Toward an up-to-date use of the PACs for environmental purposes. Polycycl. Aromat. Compd. 35, 330–354.
Aoki, Y., Yee, J., Mortensen, M.E., 2017. Blood cadmium by race/hispanic origin: The role of smoking. Environ. Res. 155, 193–198.
Barbeau, D., Persoons, R., Marques, M., Hervé, C., Laffitte-Rigaud, G., Maitre, A., 2014. Relevance of urinary 3-hydroxybenzo(a)pyrene and 1-hydroxypyrene to assess exposure to carcinogenic polycyclic aromatic hydrocarbon mixtures in metallurgy workers. Ann. Occup. Hyg. 58, 579–590.
Bastiaensen, M., Xu, F., Been, F., Van den Eede, N., Covaci, A., 2018. Simultaneous determination of 14 urinary biomarkers of exposure to organophosphate flame retardants and plasticizers by LC-MS/MS. Anal Bioanal Chem. 410, 7871–7880.
Bevan, R., Brown, T., Matthies, F., Sams, C., Jones, K., Hanlon, J., La Vedrine, M., 2017. Human biomonitoring data collection from occupational exposure to pesticides. EFSA Supporting Publication 2017: EN-1185.
Bhandari, D., Ruhl, J., Murphy, A., McGahee, E., Chambers, D., Blount, B.C., 2016. Isotope dilution UPLC-APCI-MS/MS method for the quantitative measurement of aromatic diamines in human urine: Biomarkers of diisocyanate exposure. Anal. Chem. 88, 10687–10692.
Blount, B.C., Milgram, K.E., Silva, M.J., Malek, N.A., Reidy, J.A., Needham, L.L., Brock, J.W., 2000. Quantitative detection of eight phthalate metabolites in human urine using HPLC-APCI-MS/MS. Anal. Chem. 72, 4127–4134.
Boada, L.D., Henríquez-Hernández, L.A., Navarro, P., Zumbado, M., Almeida-González, M., Camacho, M., Álvarez-León, E.E., Valencia-Santana, J.A., Luzardo, O.P., 2015. Exposure to polycyclic aromatic hydrocarbons (PAHs) and bladder cancer: evaluation from a gene-environment perspective in a hospital-based case-control study in the Canary Islands (Spain). Int. J. Occup. Environ. Health 21, 23–30.
Bonberg, N., Pesch, B., Ulrich, N., Moebus, S., Eisele, L., Marr, A., Arendt, M., Jöckel, K.-H., Brüning, T., Weiss, T., 2017. The distribution of blood concentrations of lead (Pb), cadmium (Cd), chromium (Cr) and maganese (Mn) in residents of the German Ruhr area and its potential association with occupational exposure in metal industry and/or other risk factors. Int. J. Hyg. Environ. Health 220, 998–1005.
Bryant, M.S., Vineis, P., Skipper, P.L., Tannenbaum, S.R., 1988. Hemoglobin adducts of aromatic amines: associations with smoking status and type of tobacco. Proc. Natl. Acad. Sci. USA 85, 9788–9791.
Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., de Voogt, P., Jensen, A.A., Kannan, K., Mabury, S.A., van Leeuwen, S.P.F., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. Integr. Environ. Assess. Manag. 7, 513–541.
Butt, C.M., Miranda, M.L., Stapleton, H.M., 2016. Development of an analytical method to quantify PBDEs, OH-BDEs, HBCDs, 2,4,6-TBP, EH-TBB, and BEH-TEBP in human serum. Anal. Bioanal. Chem. 408, 2449–2459.
Calafat, A.M., Ye, X., Wong, L.-Y., Reidy, J.A., Needham, L.L., 2008. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ. Health Perspect. 116, 39–44.
Calafat, A.M., Longnecker, M.P., Koch, H.M., Swan, S.H., Hauser, R., Goldman, L.R., Lanphear, B.P., Rudel, R.A., Engel, S.M., Teitelbaum, S.L., Whyatt, R.M., Wolff, M.S., 2015. Optimal exposure biomarkers for nonpersistent chemicals in environmental epidemiology. Environ. Health Perspect. 123, A166–A168.
Cañas, A.I., Estaban, M., Cutanda, F., Castaño, A., 2013. Risk of overestimation of urinary cadmium concentrations: interference from molybdenum. E3S Web of Conferences 1. https://doi.org/10.1051/e3sconf/20130121003.
Carignan, C.C., Mínguez-Alarcón, L., Butt, C.M., Williams, P.L., Meeker, J.D., Stapleton, H.M., Toth, T.L., Ford, J.B., Hauser, R., for the EARTH Study Team, 2017. Urinary concentrations of organophosphate flame retardant metabolites and pregnancy outcomes among women undergoing in vitro fertilization. Environ. Health. Persp. 125 (8) 087018–1.
CDC, 2018. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2018, Volume One. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
Čechová, E., Vojta, Š., Kukučka, P., Kočan, A., Trnovec, T., Murínová, L.P., de Cock, M., van de Bor, M., Askevold, J., Eggesbø, M., Scheringer, M., 2017. Legacy and alternative halogenated flame retardants in human milk in Europe: Implications for children's health. Environ. Int. 108, 137–145.
Cequier, E., Marcé, R.M., Becher, G., Thomsen, C., 2013. Determination of emerging halogenated flame retardants and polybrominated diphenyl ethers in serum by gas chromatography mass spectrometry. J. Chromatogr. A 1310, 126–132.
Cequier, E., Ionas, A.C., Covaci, A., Marcé, R.M., Becher, G., Thomsen, C., 2014a. Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. Environ. Sci. Technol. 48, 6827–6835.
Cequier, E., Marcé, R.M., Becher, G., Thomsen, C., 2014b. A high-throughput method for determination of metabolites of organophosphate flame retardants in urine by ultra performance liquid chromatography-high resolution mass spectrometry. Anal. Chim. Acta 845, 98–104.
Černa, M., Malý, M., Rudnai, P., Középesy, S., Náray, M., Halzlová, K., Jajcaj, M., Grafnetterová, A., Krsková, A., Antošová, D., Forysová, K., Den Hond, E., Schoeters, G., Joas, R., Casteleyn, L., Joas, A., Biot, P., Aerts, D., Angerer, J., Bloemen, L., Castaño, A., Esteban, M., Koch, H.M., Kolossa-Gehring, M., Gutleb, A.C., Javlošková, J., Vrbík, K., 2015. Case study: Possible differencs in phthalates exposure among the Czech, Hungarian, and Slovak populations identified based on the DEMOCOPHES pilot study results. Environ. Res. 141, 118–124.
Chang, Y.-J., Lin, K.-L., Chang, Y.-Z., 2013. Determination of di-(2-ethylhexyl)phthalate (DEHP) metabolites in human hair using liquid chromatography-tandem mass spectrometry. Clin. Chim. Acta 420, 155–159.
CHAP, 2014. Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives, U.S. Consumer Product Safety Commission, Directorate for Health Sciences.
Chen, Y., Fang, J., Ren, L., Fan, R., Zhang, J., Liu, G., Zhou, L., Chen, D., Yu, Y., Lu, S., 2018. Urinary metabolites of organophosphate esters in children in South China: Concentrations, profiles and estimated daily intake. Environ. Pollut. 235, 358–364.
Choi, J., Knudsen, L.E., Mizrak, S., Joas, A., 2017. Identification of exposure to environmental chemicals in children and older adults using human biomonitoring data sorted by age: Results from a literature review. Int. J. Hyg. Environ. Health 220, 282–298.
Chung, K.-T., 2015. Occurrence, uses, and carcinogenicity of arylamines. Front. Biosc. (Elite Ed.) 7, 367–393.
Ciesielski, T., Weuve, J., Bellinger, D.C., Schartz, J., Lanphear, B., Wright, R.O., 2012. Cadmium exposure and neurodevelopmental outcomes in U.S. children. Environ. Health Perspect. 120, 758–763.
Cobellis, L., Colacurci, N., Trabucco, E., Carpentiero, C., Grumetto, L., 2009. Measurement of bisphenol A and bisphenol B levels in human blood sera from healthy and endometriotic women. Biomed. Chromatogr. 23, 1186–1190.
Cocker, J., Jones, K., Leng, G., Gries, W., Budnik, L.T., Müller, J., Göen, T., Hartwig, A., 2017. Hexamethylene diisocyanate, 2,4-toluene diisocyanate, 2,6-toluene diisocyanate, isophorone diisocyanate and 4,4'-methylene diphenyl diisocyanate – Determination of hexamethylenediamine, 2,4-toluenediamine, 2,6-toluenediamine, isophoronediamine and 4,4'-methylenedianiline in urine using gas chromatography-mass spectrometry. The MAK Collection for Occupational. In: Health and Safety. 2 No. 3, Wiley-VCH Verlag GmbH & Co. KGaA.
Covaci, A., Harrad, S., Abdallah, M.-A.-E., Ali, N., Law, R.J., Herzke, D., de Wit, C.A., 2011. Novel brominated flame retardants: a review of their analysis, environmental fate and behaviour. Environ. Int. 37, 532–556.
Dagnino, S., Strynar, M.J., McMahen, R.L., Lau, C.S., Ball, C., Garantziotis, S., Webster, T.F., McClean, M.D., Lindstrom, A.B., 2016. Identification of biomarkers of exposure to FTOHs and PAPs in humans using a targeted and nontargeted analysis approach. Environ. Sci. Technol. 50, 10216–10225.
Den Hond, E., Govarts, E., Willems, H., Smolders, R., Casteleyn, L., Kolossa-Gehring, M., Schwedler, G., Seiwert, M., Fiddicke, U., Castaño, A., Esteban, M., Angerer, J., Koch, H.M., Schindler, B.K., Sepai, O., Exley, K., Bloemen, L., Horvat, M., Knudsen, L.E., Joas, A., Joas, R., Biot, P., Aerts, D., Koppen, G., Katsonouri, A., Hadjipanayis, A., Krskova, A., Maly, M., Mørck, T.A., Rudnai, P., Kozepesy, S., Mulcahy, M., Mannion, R., Gutleb, A.C., Fischer, M.E., Ligocka, D., Jakubowski, M., Reis, M.F., Namorado, S., Gurzau, A.E., Lupsa, I.-R., Halzlova, K., Jajcaj, M., Mazej, D., Tratnik, J.S., López, A., Lopez, E., Berglund, M., Larsson, K., Lehmann, A., Crettaz, P., Schoeters, G., 2015. First steps towards harmonized human biomonitoring in Europe: Demonstration project to perform human biomonitoring on a European scale. Children's Health 123, 255–263.
de Nys, S., Putzeys, E., Vervliet, P., Covaci, A., Boonen, I., Elskens, M., Vanoirbeek, J., Godderis, L., van Meerbeek, B., van Landuyt, K.L., Duca, R.C., 2018. A novel high sensitivity UPLC-MS/MS method for the evaluation of bisphenol A leaching from dental materials. Sci. Rep. 8, 6981.
de Vos, M.G., Huijbregts, M.A.J., van den Heuvel-Greve, M.J., Vethaak, A.D., van de Vijver, K.I., Leonards, P.E.G., van Leeuwen, S.P.J., de Voogt, P., Hendriks, A.J., 2008. Accumulation of perfluorooctane sulfonate (PFOS) in the food chain of the Western Scheldt estuary: Comparing field measurements with kinetic modelling. Chemosphere 70, 1766–1773.
Deceuninck, Y., Bichon, E., Durand, S., Bemrah-Aouachria, N., Zendong, Z., Morvan, M.L., Marchand, P., Dervilly-Pinel, G., Antignac, J.-P., Leblanc, J.C., Le Bizec, B., 2014. Development and validation of a MIP/GC-MS/MS method for the determination of bisphenol A residues in wide range of food items. J. Chromatogr. A 1362, 241–249.
Dekant, W., Völkel, W., 2008. Human exposure to bisphenol A by biomonitoring: Methods, results and assessment of environmental exposures. Toxicol. Appl. Pharmacol. 228, 114–134.
Devoy, J., Géhin, A., Müller, S., Melczer, M., Remy, A., Antoine, G., Sponne, I., 2016. Evaluation of chromium in red blood cells as an indicator of exposure to hexavalent chromium: An *in vitro* study. Toxicol. Lett. 255, 63–70.
Dierkes, G., Weiss, T., Modick, H., Käfferlein, H.U., Brüning, T., Koch, H.M., 2014. N-Acetyl-4-aminophenol (paracetamol), N-acetyl-2-aminophenol and acetanilide in urine samples from the general population, individuals exposed to aniline and paracetamol users. Int. J. Hyg. Environ. Health 217, 592–599.
Dietrich, D.R., Hengstler, J.G., 2016. From bisphenol A to bisphenol F and a ban of mustard due to chronic low-dose exposures? Arch. Toxicol. 90, 489–491.
Eladak, S., Grisin, T., Moison, D., Guerquin, M.-J., N'Tumba-Byn, T., Pozzi-Gaudin, S., Benachi, A., Livera, G., Rouiller-Fabre, V., Habert, R., 2015. A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound. Fertil. Steril. 103, 11–21.
Engel, A., Buhrke, T., Kasper, S., Behr, A.-C., Bräuning, A., Jessel, S., Seidel, A., Völkel, W., Lampen, A., 2018. The urinary metabolites of DINCH® have an impact on the activities of the human nuclear receptors ERα, ERβ, AR, PPARα and PPARγ. Toxicol. Lett. 287, 83–91.
Erler, C., Novak, J., 2010. Bisphenol A exposure: Human risk and health policy. J. Pediatr.

Nurs. 25, 400–407.
EFSA, 2009. Scientific opinion: Cadmium in food. Scientific opinion of the Panel on Contaminants in the Food Chain (Question no. EFSA-Q-2007-138). European Food Safety Agency, EFSA Journal 980, 1–139.
EFSA, 2014. Scientific opinion on the risks to public health related to the presence of chromium in food and drinking water. EFSA Panel on Contaminants in the Food Chain (CONTAM). European Food Safety Agency, EFSA Journal 12 (3), 3595.
EFSA, 2015. Scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive Summary. EFSA Panel on Food Contact Meterials, Enymes, Flavourings and Processing Aids (CEF), European Food Safety Agency, EFSA Journal 13 (1), 3978.
EFSA, 2018. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. European Food Safety Agency, EFSA Journal 16 (12), 5194.
Esteban, M., Castaño, A., 2009. Non-invasive matrices in human biomonitoring: A review. Environ. Int. 35 483–449.
EU, 2006. Regulation (EC) no. 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the registration, evaluation, authorisation and restriction of chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) no. 793/93 and commission regulation (EC) no. 1488/94 as well as council directive 76/769/EEC and commission directives 91/155/EEC, 83/67/EEC, 93/105/EC and 2000/21/EC. Official Journal of the European Union L396,1-849.
EU, 2009. Regulation (EC) no. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Official Journal of the European Union L342, 59-209.
EU, 2011. Commission implementing regulation (EU) no. 321/2011 of 1 April 2011 amending regulation (EU) no. 10/2011 as regards the restriction of use of bisphenol A in plastic infant feeding bottles. Official Journal of the European Union L87, 1-2.
EU, 2013. Commission implementing regulation (EU) no. 1272/2013 of 6 December 2013 amending regulation (EU) no. 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards polycyclic aromatic hydrocarbons. Official Journal of the European Union L328, 69–71.
EU, 2014a. Phthalates in entry 51 (DEHP, DBP, BBP) of Annex XVII to REACH - the Commission services' conclusions on the review and follow-up actions, 15th Meeting of Competent Authorities for REACH and CLP (CARACAL), European Commission, Environment Directorate, Green Economy, Chemicals, Brussels, Belgium, 8-9 July 2014, Doc. CA/42/2014, Ref. Ares(2014)2285796 - 09/07/2014.
EU, 2014b. Phthalates entry 52, Commission conclusions on the review clause and next steps, European Commission, Environment Directorate, Green Economy, Chemicals, Ref. Ares(2015)4340306 - 16/10/2015.
EU, 2014c. Commission Directive 2014/79/EU of 20 June 2014 amending Appendix C of Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys, as regards TCEP, TCPP and TDCP. Official Journal of the European Union L182/49.
EU, 2015. Commission Delegated Directive (EU) 2015/863 of 31 March 2015 amending Annex II to Directive 2011/65/EU of the European Parliament and of the Council as regards the list of restricted substances. Official Journal of the European Union L137, 10-12.
EU, 2016. Commision regulation (EU) 2016/2235 of 12 December 2016 amending Annex XVII to regulation (EC) no. 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards bisphenol A. Official Journal of the European Union L337, 3–5.
EU, 2017a. Commission regulation (EU) 2017/1000 of 13 June 2017 amending Annex XVII to regulation (EC) no. 1907/2006 of the European Parliament and of the Council concerning the the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards perfluorooctanoic acid (PFOA). Official Journal of the European Union L150, 14-18.
EU, 2017b. Directive (EU) 2017/2398 of the European Parliament and of the Council of 12 December 2017 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. Official Journal of the European Union L345, 87–95.
Fagerberg, B., Borné, Y., Barregard, L., Sallsten, G., Forsgard, N., Hedblad, B., Persson, M., Engström, G., 2017. Cadmium exposure is associated with soluble urikinase plasminogen activator receptor, a circulating marker of inflammation and future cardiovascular disease. Environ. Res. 152, 185–191.
Fan, R., Ramage, R., Wang, D., Zhou, J., She, J., 2012. Determination of ten monohydroxylated polycyclic aromatic hydrocarbons by liquid-liquid extraction and liquid chromatography/tandem mass spectrometry. Talanta 93, 383–391.
Feng, Y.-L., Liao, X., Grenier, G., Nguyen, N., Chan, P., 2015. Determination of 18 phthalate metabolites in human urine using a liquid chromography-tandem mass spectrometer equipped with a core-shell column for rapid separation. Anal. Methods 7, 8048–8059.
Frederiksen, M., Thomsen, M., Vorkamp, K., Knudsen, L.E., 2009. Patterns and concentration levels of polybrominated diphenyl ethers (PBDEs) in placental tissue of women in Denmark. Chemosphere 76, 1464–1469.
Frederiksen, M., Thomsen, C., Frøyshaug, M., Vorkamp, K., Thomsen, M., Becher, G., Knudsen, L.E., 2010a. Polybrominated diphenyl ethers in paired samples of maternal and umbilical cord blood plasma and associations with house dust in a Danish cohort. Int. J. Hyg. Environ. Health 213, 233–242.
Frederiksen, H., Jørgensen, N., Andersson, A.M., 2010b. Correlations between phthalate metabolites in urine, serum, and seminal plasma from young Danish men determined by isotope dilution liquid chromatography tandem mass spectrometry. J. Anal. Toxicol. 34, 400–410.
Fromme, H., Gruber, L., Seckin, E., Raab, U., Zimmermann, S., Kiranoglu, M., Schlummer, M., Schwegler, U., Smolic, S., Völkel, W., 2011. Phthalates and their metabolites in breast milk – results from the Bavarian monitoring of breast milk (BAMBI). Environ. Int. 37, 715–722.
Fromme, H., Lahrz, T., Kraft, M., Fembacher, L., Mach, C., Dietrich, S., Burkardt, R., Völkel, W., Göen, T., 2014. Organophosphate flame retardants and plasticizers in air and dust in German daycare centers and human biomonitoring in visiting children (LUPE 3). Environ. Int. 71, 158–163.
Fromme, H., Schütze, A., Lahrz, T., Kraft, M., Fembacher, L., Siewering, S., Burkardt, R., Dietrich, S., Koch, H.M., Völkel, W., 2016. Non-phthalate plasticizers in German daycare centers and human biomonitoring of DINCH metabolites in children attending the centers (LUPE 3). Int. J. Hyg. Environ. Health 219, 33–39.
Gao, L., Li, J., Wu, Y., Yu, M., Chen, T., Shi, Z., Zhou, X., Sun, Z., 2016. Determination of novel brominated flame retardants and polybrominated diphenyl ethers in serum using gas chromatography-mass spectrometry with two simplified sample preparation procedures. Anal. Bioanal. Chem. 408, 7835–7844.
Gao, K., Fu, J., Xue, Q., Li, Y., Liang, Y., Pan, Y., Zhang, A., Jiang, G., 2018. An integrated method for simultaneously determining 10 classes of per- and polyfluoroalkyl substances in one drop of human serum. Anal. Chim. Acta 999, 76–86.
Ganzleben, C., Antignac, J.-P., Barouki, R., Castaño, A., Fiddicke, U., Klánova, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G.R., Sepai, O., Tolonen, H., Kolossa-Gehring, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int. J. Hyg. Environ. Health 220, 94–97.
Garner, R.E., Levallois, P., 2017. Associations between cadmium levels in blood and urine, blood pressure and hypertension among Canadian adults. Environ. Res. 155, 64–72.
Georgi, J.C., Sommer, Y.L., Ward, C.D., Cheng, P.-Y., Jones, R.L., Caldwell, K.L., 2017. Biomonitoring method for the analysis of chromium and cobalt in human whole blood using inductively coupled plasma – kinetic energy distrimination – mass spectrometry (ICP-KED-MS). Anal. Methods 9, 3463–3476.
Gerona, R.R., Woodruff, T.J., Dickenson, C.A., Pan, J., Schwartz, J.M., Sen, S., Friesen, M.W., Fujimoto, V.Y., Hunt, P.A., 2013. Bisphenol A (BPA), BPA glucuronide, and BPA sulfate in midgestation umbilical cord serum in a Northern and Central California population. Environ. Sci. Technol. 47, 12477–12485.
Geyer, H.J., Schramm, K.-W., Darnerud, P.O., Aune, M., Feicht, E.A., Fried, K.W., Henkelmann, B., Lenoir, D., Schmid, P., McDonald, T.A., 2004. Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans. Organohal. Comp. 66, 3820–3825.
Ginsberg, G., Rice, D.C., 2009. Does rapid metabolism ensure negligible risk from bisphenol A? Environ. Health Perspect. 117, 1639–1643.
Goldoni, M., Caglieri, A., Poli, D., Vettori, M.V., Corradi, M., Apostoli, P., Mutti, A., 2006. Determination of hexavalent chromium in exhaled breath condensate and environmental air among chrome plating workers. Anal. Chim. Acta 562, 229–235.
Goldoni, M., Caglieri, A., De Palma, G., Acampa, O., Gergelova, P., Corradi, M., Apostoli, P., Mutti, A., 2010. Chromium in exhaled breath condensate (EBC), erythrocytes, plasma and urine in the biomonitoring of chrome-plating workers exposed to soluble Cr(VI). J. Environ. Monit. 12, 442–447.
Gomis, M.I., Vestergren, R., MacLeod, M., Mueller, J.F., Cousins, I.T., 2017. Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. Environ. Int. 108, 92–102.
Gomis, M.I., Vestergren, R., Borg, D., Cousins, I.T., 2018. Comparing the toxic potency *in vivo* of long-chain perfluoroalkyl acids and fluorinated alternatives. Environ. Int. 113, 1–9.
González-Antuña, A., Camacho, M., Henríquez-Hernández, L.A., Boada, L.D., Almeida-González, M., Zumbado, M., Luzardo, O.P., 2017. Simultaneous quantification of 49 elements associated to e-waste in human blood by ICP-MS for routine analysis. MethodsX 4, 328–334.
Greaves, A.K., Letcher, R.J., 2017. A review of organophosphate esters in the environment from biological effects to distribution and fate. Bull. Environ. Contam. Toxicol. 98, 2–7.
Gries, W., Ellrich, D., Küpper, K., Ladermann, B., Leng, G., 2012. Analytical method for the sensitive determination of major di-(2-propylheptyl)-phthalate metabolites in human urine. J. Chromatogr. B 908, 128–136.
Gube, M., Heinrich, K., Dewes, P., Brand, P., Kraus, T., Schettgen, T., 2011. Internal exposure of haidressers to permanent hair dyes: a biomonitoring study using urinary aromatic diamines as biomarkers of exposure. Int. Arch. Occup. Environ. Health 84, 287–292.
Guo, L.-C., Xiao, J., Zhang, Y., Yu, S., Lin, H., Su, G., Liu, T., Li, X., Lv, S., Rutherford, S., Ma, W., 2018. Association between serum polybrominated diphenyl ethers, new flame retardants and thyroid hormone levels for school students near a petrochemical complex, South China. Chemosphere 202, 476–482.
Haines, D.A., Saravanabhavan, G., Werry, K., Khoury, C., 2017. An overview of human biomonitoring of environmental chemicals in the Canadian Health Measures Survey: 2007–2019. Int. J. Hyg. Environ. Health 220, 13–28.
Hammel, S.C., Hoffman, K., Webster, T.F., Anderson, K.A., Stapleton, H.M., 2016. Measuring personal exposure to organophosphate flame retardants using silicone wristbands and hand wipes. Environ. Sci. Technol. 50, 4483–4491.
Hartmann, C., Raffesberg, W., Weiss, S., Scharf, S., Uhl, M., 2017. Perfluoroalkylated substances in human urine: results of a biomonitoring pilot study. Biomonit. 4, 1–10.
Haug, L.S., Thomsen, C., Becher, G., 2009. A sensitive method for determination of a broad range of perfluorinated compounds in serum suitable for large-scale human biomonitoring. J. Chromatogr. A 1216, 385–393.
Hayama, T., Yoshida, H., Onimaru, S., Yonekura, S., Kuroki, H., Todoroki, K., Nohta, H., Yamaguchi, M., 2004. Determination of tetrabromobisphenol A in human serum by liquid chromatography-electrospray ionization tandem mass spectrometry. J. Chromatogr. B 809, 131–136.

Hays, S.M., Aylward, L.L., Blount, B.C., 2015. Variation in urinary flow rates according to demographic characteristics and body mass index in NHANES: Potential confounding of associations between health outcomes and urinary biomarker concentrations. Environ. Health Perspect. 123, 293–300.
He, S., Li, M., Jin, J., Wang, Y., Bu, Y., Xu, M., Yang, X., Liu, A., 2013. Concentrations and trends of halogenated flame retardants in the pooled serum of residents of Laizhou Bay. China. Environ. Toxicol. Chem. 32, 1242–1247.
He, C., Toms, L.-M.L., Thai, P., Van den Eede, N., Wang, X., Li, Y., Baduel, C., Harden, F.A., Heffernan, A.L., Hobson, P., Covaci, A., Mueller, J.F., 2018. Urinary metabolites of organophosphate esters: Concentrations and age trends in Australian children. Environ. Int. 111, 124–130.
Heffernan, A.L., Thompson, K., Eaglesham, G., Vijayasarathy, S., Mueller, J.F., Sly, P.D., Gomez, M.J., 2016. Rapid, automated online SPE-LC-QTRAP-MS/MS method for the simultaneous analysis of 14 phthalate metabolites and 5 bisphenol analogues in human urine. Talanta 151, 224–233.
Heitland, P., Blohm, M., Breuer, C., Brinkert, F., Achilles, E.G., Pukite, I., Köster, H.D., 2017. Application of ICP-MS and HPLC-ICP-MS for diagnosis and therapy of a severe intoxication with hexavalent chromium and inorganic arsenic. J. Trace Elem. Med. Biol. 41, 36–40.
Henríquez-Hernández, L.A., Boada, L.D., Carranza, C., Pérez-Arellano, J.L., González-Antuña, A., Camacho, M., Almeida-González, M., Zumbado, M., Luzardo, O.P., 2017. Blood levels of toxic metals and rare earth elements commonly found in e-waste may exert suble effects on hemoglobin concentration in sub-Saharan immigrants. Environ. Int. 109, 20–28.
Heumann, K.G., 2004. Isotope-dilution ICP-MS for trace element determination and speciation: from a reference method to a routine method? Anal. Bioanal. Chem. 378, 318–329.
Hines, E.P., Calafat, A.M., Silva, M.J., Mendola, P., Fenton, S.E., 2009. Concentrations of phthalate metabolites in milk, urine, saliva, and serum of lactating North Carolina women. Environ. Health Perspect. 117, 86–92.
Hoffman, K., Fang, M., Horman, B., Patisaul, H.B., Garantziotis, S., Birnbaum, L.S., Stapleton, H.M., 2014. Urinary tetrabromobenzoic acid (TBBA) as a biomarker of exposure to the flame retardant mixture Firemaster® 550. Environ. Health Perspect. 122, 963–969.
Houtz, E.F., Sedlak, D.L., 2012. Oxidative conversion as a means of detection precursors to perfluoroalkyl acids in urban runoff. Environ. Sci. Technol. 46, 9342–9349.
IARC, 2010. In: Some aromatic amines, organic dyes, and related exposures. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 99. International Agency for Research on Cancer, World Health Organization. ISBN 978-92-832-1299-7. www.iarc.fr.
IARC, 2012. A review of human carcinogens. Part C: Arsenic, metals, fibres and dust. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 100C, International Agency for Research on Cancer, World Health Organization. ISBN 978-92-832-1320-8. www.iarc.fr.
Jacob, J., Seidel, A., 2002. Biomonitoring of polycyclic aromatic hydrocarbons in human urine. J. Chromatogr. B 778, 31–47.
Jacob III, P., Wilson, M., Benowitz, N.L., 2007. Determination of phenolic metabolites of polycyclic aromatic hydrocarbons in human urine as their pentafluorobenzyl ether derivatives using liquid chromatography-tandem mass spectrometry. Anal. Chem. 79, 587–598.
Jarrett, J.M., Xiao, G., Caldwell, K.L., Henahan, D., Shakirova, G., Jones, R.L., 2008. Eliminating molybdenum oxide interference in urine cadmium biomonitoring using ICP-DRC-MS. J. Anal. At. Spectrom. 23, 962–967.
Joas, A., Knudsen, L.E., Kolossa-Gehring, M., Sepai, O., Casteleyn, L., Schoeters, G., Angerer, J., Castaño, A., Aerts, D., Biot, P., Horvat, M., Bloemen, L., Reis, F.M., Lupsa, I.-R., Katsonouri, A., Cerna, M., Berglund, M., Crettaz, P., Rudnai, P., Halzlova, K., Mulcahy, M., Gutleb, A.C., Fischer, M.E., Becher, G., Fréry, N., Jensen, G., Van Vliet, L., Koch, H.M., Den Hond, E., Fiddicke, U., Esteban, M., Exley, K., Schwedler, G., Seiwert, M., Ligocka, D., Hohenblum, P., Kyrtopoulos, S., Botsivali, M., DeFelip, E., Guillou, C., Reniero, F., Grazuleviciene, R., Veidebaum, T., Mørck, T.A., Nielsen, J.K.S., Jensen, J.F., Rivas, T.C., Sanchez, J., Koppen, G., Smolders, R., Kozepesy, S., Hadjipanayis, A., Krskova, A., Mannion, R., Jakubowski, M., Fucic, J.A., Pereira-Miguel, J., Gurzau, A.E., Jajcaj, M., Mazej, D., Tratnik, J.S., Lehmann, A., Larsson, K., Dumez, B., Joas, R., 2015. Policy recommendations and cost implications for a more sustainable framework for European human biomonitoring surveys. Environ. Res. 141, 42–57.
Jongeneelen, F.J., 2014. A guidance value of 1-hydroxypyrene in urine in view of acceptable occupational exposure to polycyclic aromatic hydrocarbons. Toxicol. Lett. 231, 239–248.
Jursa, T., Stein, C.R., Smith, D.R., 2018. Determinants of hair manganese, lead, cadmium and arsenic levels in environmentally exposed children. Toxics 6, 19.
Kärrman, A., Ericson, I., van Bavel, B., Darnerud, P.O., Aune, M., Glynn, A., Lignell, S., Lindström, G., 2007. Exposure of perfluorinated chemicals through lactation: Levels of matched human milk and serum and a temporal trend, 1996–2004, in Sweden. Environ. Health Perspect. 115, 226–230.
Kato, K., Wanigatunga, A.A., Needham, L.L., Calafat, A.M., 2009. Analysis of blood spots for polyfluoroalkyl chemicals. Anal. Chem. Acta 6565, 51–55.
Kato, K., Kalathil, A.A., Patel, A.M., Ye, X., Calafat, A.M., 2018. Per- and polyfluoroalkyl substances and fluorinated alternatives in urine and serum by on-line solid phase extraction-liquid chromatography-tandem mass spectrometry. Chemosphere 209, 338–345.
Kim, M., Song, N.R., Choi, J.-H., Lee, J., Pyo, H., 2014. Simultaneous analysis of urinary phthalate metabolites of residents in Korea using dilution gas chromatography-mass spectrometry. Sci. Total Environ. 470–471, 1408–1413.
Koch, H.M., Rossbach, B., Drexler, H., Angerer, J., 2003. Internal exposure of the general population to DEHP and other phthalates – determination of secondary and primary phthalate monoester metabolites in urine. Environ. Res. 93, 177–185.
Koch, H.M., Calafat, A.M., 2009. Human body burdens of chemicals used in plastic manufacture. Phil. Trans. R. Soc. B 364, 2063–2078.
Koch, H.M., Kolossa-Gehring, M., Schröter-Kermani, C., Angerer, J., Brüning, T., 2012. Bisphenol A in 24 h urine and plasma samples of the German Environmental Specimen Bank from 1995 to 2009: A retrospective exposure evaluation. J. Expo. Sci. Environ. Epidemiol. 22, 610–616.
Koch, H.M., Schütze, A., Pälmke, C., Angerer, J., Brüning, T., 2013. Metabolism of the plasticizer and phthalate substitute diisononyl-cyclohexane-1,2-dicarboxylate (DINCH®) in humans after single oral doses. Arch. Toxicol. 87, 799–806.
Koch, H.M., Rüther, M., Schütze, A., Conrad, A., Pälmke, C., Apel, P., Brüning, T., Kolossa-Gehring, M., 2017. Phthalate metabolites in 24-h urine samples of the German Environmental Specimen Bank (ESB) from 1988 to 2015 and a comparison with US NHANES data from 1999 to 2012. Int. J. Hyg. Environ. Health 220, 130–141.
Koch, H.M., Lessmann, F., Swan, S.H., Hauser, R., Kolossa-Gehring, M., Frederiksen, H., Andersson, A.M., Thomsen, C., Sakhi, A.K., Bornehag, C.G., Mueller, J.F., Rudel, R.A., Braun, J.M., Harth, V., Brüning, T., 2018. Analyzing terephthalate metabolites in human urine as biomarkers of exposure: Importance of selection of metabolites and deconjugation enzyme. J. Chromatogr. B 1100–1101, 91–92.
Kolossa-Gehring, M., Becker, K., Conrad, A., Schröter-Kermani, C., Schulz, C., Seiwert, M., 2012. Environmental surveys, specimen bank and health related environmental monitoring in Germany. Int. J. Hyg. Environ. Health 215, 120–126.
Kuklenyik, Z., Needham, L.L., Calafat, A.M., 2005. Measurement of 18 perfluorinated organic acids and amides in human serum using on-line solid-phase extraction. Anal. Chem. 77, 6085–6091.
Lang, I.A., Galloway, T.S., Scarlett, A., Henley, W.E., Depledge, M., Wallace, R.B., Melzer, D., 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA 300, 1303–1310.
Lankova, D., Urbancova, K., Sram, R.J., Hajslova, J., Pulkrabova, J., 2016. A novel strategy for the determination of polycyclic aromatic hydrocarbon monohydroxylated metabolites in urine using ultra-high-performance liquid chromatography with tándem mass spectrometry. Anal. Bioanal. Chem. 408, 2515–2525.
Leese, E., Morton, J., Gardiner, P.H.E., Carolan, V.A., 2017. The simultaneous detection of trivalent & hexavalent chromium in exhaled breath condensate: A feasibility study comparing workers and controls. Int. J. Hyg. Environ. Health 220, 415–423.
Lemos, V.A., de Carvalho, A.L., 2010. Determination of cadmium and lead in human biological samples by spectrometric techniques: a review. Environ. Monit. Assess. 171, 255–265.
Lépine, M., Sleno, L., Lesage, J., Gagné, S., 2019. A validated liquid chromatography/tandem mass spectrometry method for 4,4'-methylenedianiline quantitation in human urine as a measure of 4,4'-methylene diphenyl diisocyanate exposure. Rapid Commun. Mass Spectrom. 33, 600–606.
Lépine, M., Sleno, L., Lesage, J., Gagné, S., 2020. A validated UPLC-MS/MS method for the determination of aliphatic and aromatic isocyanate exposure in human urine. Anal. Bioanal. Chem. 412, 753–762.
Li, J., Guo, F., Wang, Y., Liu, J., Cai, Z., Zhang, J., Zhao, Y., Wu, Y., 2012. Development of extraction methods for the analysis of perfluorinated compounds in human hair and nail by high performance liquid chromatography tandem mass spectrometry. J. Chromatogr. A. 1219, 54–60.
Li, P., Jin, J., Wang, Y., Hu, J., Xu, M., Sun, Y., Ma, Y., 2017. Concentrations of organophosphorus, polybromobenzene, and polybrominated diphenyl ether flame retardants in human serum, and relationships between concentrations and donor ages. Chemosphere 171, 654–660.
Li, Z., Romanoff, L.C., Trinidad, D.A., Pittman, E.N., Hilton, D., Hubbard, K., Carmichael, H., Parker, J., Calafat, A.M., Sjödin, A., 2014. Quantification of 21 metabolites of methylnaphthalenes and polycyclic aromatic hydrocarbons in human urine. Anal. Bioanal. Chem. 406, 3119–3129.
Liao, C., Kannan, K., 2012. Determination of free and conjugated forms of bisphenol A in human urine and serum by liquid chromatography-tandem mass spectrometry. Environ. Sci. Technol. 46, 5003–5009.
Liao, C., Liu, F., Alomirah, H., Loi, V.D., Mohd, M.A., Moon, H.-B., Nakata, H., Kannan, K., 2012. Bisphenol S in urine from the United States and seven Asian countries: Occurrence and human exposures. Environ. Sci. Technol. 46, 6860–6866.
Liu, L.-Y., Salamova, A., Hites, R.A., 2015. Analysis of polybrominated diphenyl ethers and emerging halogenated and organophosphate flame retardants in human hair and nails. J. Chromatogr. A 1406, 251–257.
Lyche, J.L., Rosseland, C., Berge, G., Polder, A., 2015. Human health risk associated with brominated flame-retardants (BFRs). Environ. Int. 74, 170–180.
Ma, W., Kannan, K., Wu, Q., Bell, E.M., Druschel, C.M., Caggana, M., Aldous, K.M., 2013. Analysis of polyfluoroalkyl substances and bisphenol A in dried blood spots by liquid chromatography tandem mass spectrometry. Anal. Bioanal. Chem. 405, 4127–4138.
Markham, D.A., Waechter Jr., J.M., Wimber, M., Rao, N., Connolly, P., Chuang, J.C., Hentges, S., Shiotsuka, R.N., Dimond, S., Chappelle, A.H., 2010. Development of a method for the determination of bisphenol A at trace concentrations in human blood and urine and elucidation of factors influencing method accuracy and sensitivity. J. Anal. Toxicol. 34, 293–303.
Marand, Å., Karlsson, D., Dalene, M., Skarping, G., 2004. Determination of amines as pentafluoropropionic acid anhydride derivatives in biological samples using liquid chromatography and tandem mass spectrometry. Analyst 129, 522–528.
Martín, J., Santos, J.L., Aparicio, I., Alonso, E., 2016. Analytical method for biomonitoring of endocrine-disrupting compounds (bisphenol A., parabens, perfluoroalkyl compound and a brominated flame retardant) in human hair by liquid chromatography-tandem mass spectrometry. Anal. Chim. Acta. 945, 95–101.
Mazumder, S., Ahamed, R.A., McGahee, E., Wang, L., Seyler, T.A., 2019. A new automated method for the analysis of aromatic amines in human urine by GC-MS/MS. J. Anal. Toxicol. 43, 25–35.

Meeker, J.D., Barr, D.B., Serdar, B., Rappaport, S.M., Hauser, R., 2007. Utility of urinary 1-naphthol and 2-naphthol levels to assess environmental carbaryl and naphthalene exposure in an epidemiology study. J. Expos. Sci. Environ. Epidemiol. 17, 314–320.
Middleton, D.R.S., Watts, M.J., Lark, R.M., Milne, C.J., Polya, D.A., 2016. Assessing urinary flow rate, creatinine, osmolality and other hydration adjustment methods for urinary biomonitoring using NHANES arsenic, iodine, lead and cadmium data. Environ. Health 15, 68.
Motorykin, O., Schrlau, J., Jia, Y., Harper, B., Harris, S., Harding, A., Stone, D., Kile, M., Sudakin, D., Simonich, S.L.M., 2015. Determination of parent and hydroxyl PAHs in personal $PM_{2.5}$ and urine samples collected during native American fish smoking activities. Sci. Total Environ. 505, 694–703.
Müllerová, D., Bouchalová, V., Matějková, D., Kovářová, K., Svačina, S., Vrbík, K., Pavloušková, J., Dvořáková, J., Müller, L., 2016. Phthalates exposure indicators determined by urinary phthalate metabolites in healthy non-obese Czech adults: FANTOM study. Food Add. Contam. A 33, 1817–1825.
Myridakis, A., Balaska, E., Gkaitatzi, C., Kouvarakis, A., Stephanou, E.G., 2015. Determination and separation of bisphenol A, phthalate metabolites and structural isomers of parabens in human urine with conventional high-pressure liquid chromatography combined with electrospray ionisation tandem mass spectrometry. Anal. Bioanal. Chem. 407, 2509–2518.
Ndaw, S., Remy, A., Denis, F., Marsan, P., Jargot, D., Robert, A., 2018. Occupational exposure of cashiers to bispehnol S via thermal paper. Toxicol. Lett. 298, 106–111.
Neumann, H.G., 2005. Monocyclic aromatic amino and nitro compounds. The MAK-Collection Part I: MAK Value Documentations 21 Deutsche Forschungsgemeinschaft. Wiley-VCH Verlag GmbH & Co. KBaA, Weinheim3-527-31134-3.
Nilsson, H., Kärrman, A., Rotander, A., van Bavel, B., Lindström, G., Westberg, H., 2013. Biotransformation of fluorotelomer compound to perfluorocarboxylates in humans. Environ. Int. 51, 8–12.
Öberg, T., Iqbal, M.S., 2012. The chemical and environmental property space of REACH chemicals. Chemosphere 87, 975–981.
Oh, J., Choi, J.W., Ahn, Y.-A., Kim, S., 2018. Pharmacokinetics of bisphenol S in humans after single oral administration. Environ. Int. 112, 127–133.
Olsen, G.W., Burris, J.M., Ehresman, D.J., Froehlich, J.W., Seacat, A.M., Butenhoff, J.L., Zobel, L.R., 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ. Health Perspect. 115, 1298–1305.
Onyemauwa, F., Rappaport, S.M., Sobus, J.R., Gajdošová, D., Wu, R., Waidyanatha, S., 2009. Using liquid chromatography-tandem mass spectrometry to quantify monohydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. J. Chromatogr. B 877, 1117–1125.
Ospina, M., Jayatilaka, N.K., Wong, L.-Y., Restrepo, P., Calafat, A.M., 2018. Exposure to organophosphate flame retardant chemicals in the U.S. general population: Data from the 2013–2014 National Health and Nutrition Examination Survey. Environ. Int. 110, 32–41.
Palmiotto, G., Pieraccini, G., Moneti, G., Dolara, P., 2001. Determination of the levels of aromatic amines in indoor and outdoor air in Italy. Chemosphere 43, 355–361.
Pastorelli, R., Guanci, M., Cerri, A., Minoia, C., Carrer, P., Negri, E., Fanelli, R., Airoldi, L., 2000. Benzo(a)pyrene diolepoxide-haemoglobin and albumin adducts at low levels of benzo(a)pyrene exposure. Biomarkers 5, 245–251.
Paustenbach, D.J., Panko, J.M., Fredrick, M.M., Finley, B.L., Proctor, D.M., 1997. Urinary chromium as a biological marker of environmental exposure: What are the limitations? Regul. Toxicol. Pharmacol. 26, S23–S34.
Pearson, M.A., Lu, C., Schmotzer, B.J., Waller, L.A., Riederer, A.M., 2009. Evaluation of physiological measures for correcting variation in urinary output: Implications for assessing environmental chemical exposure in children. J. Expo. Sci. Environ. Epidemiol. 19, 336–342.
Phillips, A.L., Hammel, S.C., Hoffman, K., Lorenzo, A.M., Chen, A., Webster, T.F., Stapleton, H.M., 2018. Children's residential exposure to organophosphate ester flame retardants and plasticizers: Investigating exposure pathways in the TESIE study. Environ. Int. 116, 176–185.
Poothong, S., Thomsen, C., Padilla-Sanchez, J.A., Papadopoulou, E., Haug, L.S., 2017. Distribution of novel and well-known poly- and perfluoroalkyl substances (PFASs) in human serum, plasma, and whole blood. Environ. Sci. Technol. 51, 13388–13396.
Poothong, S., Papadopoulou, E., Lundanes, E., Padilla-Sánchez, J.A., Thomsen, C., Haug, L.S., 2019. Dried blood spots for reliable biomonitoring of poly- and perfluoroalkyl substances (PFASs). Sci. Total Environ. 655, 1420–1426.
Post, G.B., Cohn, P.D., Cooper, K.R., 2012. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: A critical review of recent literature. Environ. Res. 116, 93–117.
Prevedouros, K., Cousins, I.T., Buck, R.C., Korzeniowski, S.H., 2006. Sources, fate and transport of perfluorocarboxylates. Environ. Sci. Technol. 40, 32–44.
Reemtsma, T., Quintana, J.B., Rodil, R., García-López, M., Rodríguez, I., 2008. Organophosphorus flame retardants and plasticizers in water and air. I. Occurrence and fate. Tr. Anal. Chem. 27, 727–737.
Riedel, K., Scherer, G., Engl, J., Hagedorn, H.-W., Tricker, A.R., 2006. Determination of three carcinogenic aromatic amines in urine of smokers and nonsmokers. J. Anal. Toxicol. 30, 187–195.
Rocha, B.A., da Costa, B.R.B., de Albuquerque, N.C.P., de Oliveira, A.R.M., Souza, J.M.O., Al-Tameemi, M., Capiglia, A.D., Barbosa Jr., F., 2016. A fast method for bisphenol A and six analogues (S, F, Z, P, AF, AP) determination in urine samples based on dispersive liquid-liquid microextraction and liquid chromatography-tandem mass spectrometry. Talanta 154, 511–519.
Rocha, B.A., Asimakopoulos, A.G., Barbosa Jr., F., Kannan, K., 2017. Urinary concentrations of 25 phthalate metabolites in Brazilian children and their association with oxidative DNA damage. Sci. Total Environ. 586, 152–162.
Romanoff, L.C., Li, Z., Young, K.J., Blakely, N.C.I.I.I., Patterson, D.G., Sandau, C.D., 2006. Automated solid-phase extraction method for measuring urinary polycyclic aromatic hydrocarbon metabolites in human biomonitoring using isotope-dilution gas chromatography high-resolution mass spectrometry. J Chromatog B 835, 47–54.
Sabaredzovic, A., Sakhi, A.K., Brantsæter, A.L., Thomsen, C., 2015. Determination of 12 urinary phthalate metabolites in Norwegian pregnant women by core-shell high performance liquid chromatography with on-line solid-phase extraction, column switching and tandem mass spectrometry. J. Chromatogr. B 1002, 343–352.
Sabbioni, G., Jones, C., 2002. Biomonitoring of arylamines and nitroarenes. Biomarkers 7, 347–421.
Sabbioni, G., Hauri, U., 2016. Carcinogenic tattoos? Epidemiol. Biostat. Public Health 13 (4), e12018.
Sabbioni, G., 2017. Hemoglobin adducts and urinary metabolites of arylamines and nitroarenes. Chem. Res. Toxicol. 30, 1733–1766.
Salthammer, T., Zhang, Y., Mo, J., Koch, H.M., Welscher, C.J., 2018. Assessing human exposure to organic pollutants in the indoor environment. Angew. Chem. (Int. Ed.) 57, 12228–12263.
Saravanabhavan, G., Guay, M., Langlois, É., Giroux, S., Murray, J., Haines, D., 2013. Biomonitoring of phthalate metabolites in the Canadian population through the Canadian health Measures Survey (2007–2009). Int. J. Hyg. Environ. Health 216, 652–661.
Schantz, M.M., Benner Jr., B.A., Heckert, N.A., Sander, L.C., Sharpless, K.E., Vander Pol, S.S., Vasquez, Y., Villegas, M., Wise, S.A., Alwis, K.U., Blount, B.C., Calafat, A.M., Li, Z., Silva, M.J., Ye, X., Gaudreau, E., Patterson Jr., D.G., Sjödin, A., 2015. Development of urine standard reference materials for metabolites of organic chemicals including polycyclic aromatic hydrocarbons, phthalates, phenols, parabens, and volatile organic compounds. Anal. Bioanal. Chem. 407, 2945–2954.
Schindler, B.K., Förster, K., Angerer, J., 2009. Determination of human urinary organophosphate flame retardant metabolites by solid-phase extraction and gas chromatography-tandem mass spectrometry. J. Chromatogr. B 877, 375–381.
Schulz, C., Conrad, A., Becker, K., Kolossa-Gehring, M., Seiwert, M., Seifert, B., 2007. Twenty years of the German Environmental Survey (GerES): Human biomonitoring - Temporal and spatial (West Germany/East Germany) differences in population exposure. Int. J. Hyg. Environ. Health 210, 271–297.
Schummer, C., Appenzeller, B.M.R., Millet, M., Wennig, R., 2009. Determination of hydroxylated metabolites of polycylic aromatic hydrocarbons in human hair by gas chromatography-negative chemical ionization mass spectrometry. J. Chromatogr. A 1216, 6012–6019.
Schütze, A., Pälmke, C., Angerer, J., Weiss, T., Brüning, T., Koch, H.M., 2012. Quantification of biomarkers of environmental exposure to di(isononyl)cyclohexane-1,2-decarboxylate (DINCH) in urine via HPLC-MS/MS. J. Chromatogr. B 895–896, 123–130.
Schütze, A., Otter, R., Modick, H., Langsch, A., Brüning, T., Koch, H.M., 2017. Additional oxidized and alkyl chain breakdown metabolites of the plasticizer DINCH in urine after oral dosage to human volunteers. Arch. Toxicol. 91, 179–188.
Séby, F., Charles, S., Gagean, M., Garraud, H., Donard, O.F.X., 2003. Chromium speciation by hyphenation of high-performance liquid chromatography to inductively coupled plasma-mass spectrometry - study of the influence of interfering ions. J. Anal. At. Spectrom. 18, 1386–1390.
Servaes, K., Voorspoels, S., Lievens, J., Noten, B., Allaerts, K., van de Weghe, H., Vanermen, G., 2013. Direct analysis of phthalate ester biomarkers in urine without preconcentration: Method validation and monitoring. J. Chromatogr. A 1294, 25–32.
Shih, W.-C., Chen, M.-F., Huang, C.-C.J., Uang, S.-N., Shih, T.-S., Liou, S.-H., Wu, K.-Y., 2007. Simultaneous analysis of urinary 4,4'-methylenebis(2-chloroaniline) and N-acetyl 4,4'-methylenebis(2-chloroaniline) using solid-phase extraction and liquid chromatography/tandem mass spectrometry. Rapid Commun. Mass Spectrom. 21, 4073–4078.
Siddique, S., Xian, Q., Abdelouahab, N., Takser, L., Phillips, S.P., Feng, Y.-L., Wang, B., Zhu, J., 2012. Levels of dechlorane plus and polybrominated diphenylethers in human milk in two Canadian cities. Environ. Int. 39, 50–55.
Silva, M.J., Samandar, E., Preau Jr., J.L., Reidy, J.A., Needham, L.L., Calafat, A.M., 2007. Quantification of 22 phthalate metabolites in human urine. J. Chromatogr. B 860, 106–112.
Silva, M.J., Jia, T., Samander, E., Preau Jr., J.L., Calafat, A.M., 2013. Environmental exposure to the plasticizer 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH), un US adults (2000–2012). Environ. Res. 126, 159–163.
Skipper, P.L., Kim, M.Y., Sun, H.-L.P., Wogan, G.N., Tannenbaum, S.R., 2010. Monocyclic aromatic amines as potential human carcinogens: old is new again. Carcinogenesis 21 (1), 50–58.
Sochorová, L., Hanzlíková, L., Černá, M., Drgáčová, A., Fialová, A., Švarcová, A., Grambličkа, T., Pulkrabová, J., 2017. Perfluorinated alkylated substances and brominated flame retardants in serum of the Czech adult population. Int. J. Hyg. Environ. Health 220, 235–243.
Souza, M.B., Passoni, M.T., Pälmke, C., Meyer, K.B., Venturelli, A.C., Araújo, G., de Castilhos, B.S., Morais, R.N., Dalsenter, P.R., Swan, S.H., Koch, H.M., Martino-Andrade, A.J., 2018. Unexpected, ubiquitous exposure of pregnant Brazilian women to diisopentyl phthalate, one of the most antiandrogenic phthalates. Environ. Int. 119, 447–454.
Sundkvist, A.M., Olofsson, U., Haglund, P., 2010. Organophosphorus flame retardants and plasticizers in marine and fresh water biota and in human milk. J. Environ. Monit. 12, 943–951.
Sun, Y., Gong, X., Lin, W., Liu, Y., Wang, Y., Wu, M., Kannan, K., Ma, J., 2018. Metabolites of organophosphate flame retardants in urine from Shanghai, China. Environ. Res. 164, 507–515.
Szabo, D.T., Diliberto, J.J., Hakk, H., Huwe, J.K., Birnbaum, L.S., 2010. Toxicokinetics of the flame retardant hexabromocyclododecane gamma: Effect of dose, timing, route, repeated exposure, and metabolism. Toxicol. Sci. 117, 282–293.

Thomsen, C., Haug, L.S., Stigum, H., Frøshaug, M., Broadwell, S.L., Becher, G., 2010. Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation. Environ. Sci. Technol. 44, 9550–9556.

Thuresson, K., Bergman, Å., Jakobsson, K., 2005. Occupational exposure to commercial decabromodiphenyl ether in workers manufacturing or handling flame-retarded rubber. Environ. Sci. Technol. 39, 1980–1986.

Thuresson, K., Höglund, P., Hagmar, L., Sjödin, A., Bergman, Å., Jakobsson, K., 2006. Apparent half-lives of hepta- to decabrominated diphenyl ethers in human serum as determined in occupationally exposed workers. Environ. Health Perspect. 114, 176–181.

UNEP, 2006a. Report of the Persistent Organic Pollutants Review Committee on the work of its second meeting. Addendum: Risk profile on perfluorooctane sulfonate. Stockholm Convention on Persistent. In: Organic Pollutants, Geneva, Switzerland, 6-10 November 2006. United Nations Environment Programme. UNEP/POPS/POPRC.2/17/Add.5.

UNEP, 2006b. Report of the Persistent Organic Pollutants Review Committee on the work of its second meeting. Addendum: Risk profile on commercial pentabromodiphenyl ether. Stockholm Convention on Persistent Organic Pollutants, Geneva, Switzerland, 6-10 November 2006, United Nations Environment Programme. UNEP/POPS/POPRC.2/17/Add.1 www.pops.int.

UNEP, 2010. Report of the Persistent Organic Pollutants Review Committee on the work of its sixth meeting. Addendum: Risk profile on hexabromocyclododecane. Stockholm Convention on Persistent Organic Pollutants, Geneva, Switzerland, 11-15 October 2010, United Nations Environment Programme. UNEP/POPS/POPRC.6/13/Add.2 www.pops.int.

UNEP, 2016. Report of the Persistent Organic Pollutants Review Committee on the work of its twelfth meeting. Addendum: Risk profile on pentadecafluorooctanoic acid (CAS No: 335-67-1, PFOA, perfluorooctanoic acid), its salts and PFOA-related compounds. Stockholm Convention on Persistent Organic Pollutants, Rome, Italy, 19-23 September 2016, United Nations Environment Programme. UNEP/POPS/POPRC.12/11/Add.2 www.pops.int.

Vacchi-Suzzi, C., Kruse, D., Harrington, J., Levine, K., Meliker, J.R., 2016. Is urinary cadmium a biomarker of long-term exposure in humans? A review. Curr. Environ. Health Rep. 3, 450–458.

Van den Berg, M., Houba, R., Leslie, H.A., Canton, R.F., Thomsen, C., Becher, G., Alvarez-Pedrerol, M., Deu, J.S., Steiner, M., van Tongeren, M., Brunekreef, B., de Boer, J., 2017. Serum levels of decabromodiphenyl ether (BDE-209) in women from different European countries and possible relationships with lifestyle and diet. Environ. Int. 107, 16–24.

Van den Eede, N., Neels, H., Jorens, P.G., Covaci, A., 2013. Analysis of organophosphate flame retardant diester metabolites in human urine by liquid chromatography electrospray ionisation tandem mass spectrometry. J Chromatogr A 1303, 48–53.

Van den Eede, N., Ballesteros-Goméz, A., Neels, H., Covaci, A., 2016. Does biotransformation of aryl phosphate flame retardants in blood cast a new perspective on their debated biomarkers? Environ. Sci. Technol. 50, 12439–12445.

Vandenberg, L.N., Gerona, R.R., Kannan, K., Taylor, J.A., van Breemen, R.B., Dickenson, C.A., Liao, C., Yuan, Y., Newbold, R.R., Padmanabhan, V., vom Saal, F.S., Woodruff, T.J., 2014. A round robin approach to the analysis of bisphenol A (BPA) in human blood samples. Environ. Health 13, 25.

Vaughan, G.T., Kenyon, R.S., 1996. Monitoring for occupational exposure to 4,4'-methylenebis(2-chloroaniline) by gas chromatographic-mass spectrometric analysis of haemoglobin adducts, blood, plasma and urine. J. Chromatogr. B 678, 197–204.

vom Saal, F.S., Hughes, C., 2005. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environ. Health Perspect. 113, 926–933.

Vorkamp, K., Nielsen, F., Kyhl, H.B., Husby, S., Nielsen, L.B., Barington, T., Andersson, A.-M., Jensen, T.K., 2014. Polybrominated diphenyl ethers (PBDEs) and perfluoroalkyl substances (PFASs) in serum of pregnant women – levels, correlations and potential health implications. Arch. Environ. Contam. Toxicol. 67, 9–20.

Wang, Y.-X., Liu, C., Shen, Y., Wang, Q., Pan, A., Yang, P., Chen, Y.-J., Deng, Y.-L., Lu, Q., Cheng, L.-M., Maio, X.-P., Xu, S.-Q., Lu, W.-Q., Zeng, Q., 2019. Urinary levels of bisphenol A, F and S and markers of oxidative stress among healthy adult men: Variability and association analysis. Environ. Int. 123, 301–309.

Webster, L., Tronczynski, J., Korytar, P., Booij, K., Law, R., 2009. Determination of parent and alkylated polycyclic aromatic hydrocarbons (PAHs) in biota and sediment. ICES Techniques in Marine Environmental Sciences 45 26–pp.

Weiss, T., Angerer, J., 2002. Simultaneous determination of various aromatic amines and metabolites of aromatic nitro compounds in urine for low level exposure using gas chromatography–mass spectrometry. J. Chromatogr. B 778, 179–192.

WHO, 2015. Human biomonitoring: Facts and figures. WHO Regional Office for Europe, Copenhagen. www.euro.who.int.

Wiseman, C.L.S., Parnia, A., Chakravartty, D., Archbold, J., Zawar, N., Copes, R., Cole, D.C., 2017. Blood cadmium concentrations and environmental exposure sources in newcomer South and East Asian women in the Greater Toronto Area. Canada. Environ. Res. 154, 19–27.

Wittassek, M., Koch, H.M., Angerer, J., Brüning, T., 2011. Assessing exposure to phthalates – the human biomonitoring approach. Mol. Nutr. Food Res. 55, 7–31.

Xu, S., Zhang, J., Zhang, L., Liu, W., Weisel, C.P., 2004. Selective detection of monohydroxy metabolites of polycyclic aromatic hydrocarbons in urine using liquid chromatography/triple quadrupole tandem mass spectrometry. Rapid Commun. Mass Spectrom. 18, 2299–2308.

Yamamoto, Y., Ishizaki, A., Kataoka, H., 2015. Biomonitoring method for the determination of polycyclic aromatic hydrocarbons in hair by online in-tube solid-phase microextraction coupled with high performance liquid chromatography and fluorscence detection. J. Chromatogr. B 1000, 187–191.

Ye, X., Pierik, F.H., Hauser, R., Duty, S., Angerer, J., Park, M.M., Burdorf, A., Hofman, A., Jaddoe, V.W.V., Mackenbach, J.P., Steegers, E.A.P., Tiemeier, H., Longnecker, M.P., 2008. Urinary metabolite concentrations of organophosphorous pesticides, bisphenol A, and phthalates among pregnant women in Rotterdam, the Netherlands: The Generation R study. Environ. Res. 108, 260–267.

Ye, X., Wong, L.-Y., Kramer, J., Zhou, X., Jia, T., Calafat, A.M., 2015. Urinary concentrations of bisphenol A and three other bisphenols in convenience samples of U.S. adults during 2000–2014. Environ. Sci. Technol. 49, 11834–11839.

Yu, J., Wang, S., Zhao, G., Wang, B., Ding, L., Zhang, X., Xie, J., Xie, F., 2014. Determination of urinary aromatic amines in smokers and nonsmokers using a MIPs-SPE coupled with LC-MS/MS method. J. Chromatogr. B 958, 130–135.

Yu, Y., Wang, X., Wang, B., Tao, S., Liu, W., Wang, X., Cao, J., Li, B., Lu, X., Wong, M.H., 2011. Polycyclic aromatic hydrocarbon residues in human milk, placenta, and umbilical cord blood in Beijing. China. Environ. Sci. Technol. 45, 10235–10242.

Zhang, J., Cooke, G.M., Curran, I.H.A., Goodyer, C.G., Cao, X.-L., 2011. GC-MS analysis of bisphenol A in human placental and fetal liver samples. J. Chromatogr. B 879, 209–214.

Zidek, A., Macey, K., MacKinnon, L., Patel, M., Poddalgoda, D., Zhang, Y., 2017. A review of human biomonitoring data used in regulatory risk assessment under Canada's Chemicals Management Program. Int. J. Hyg. Environ. Health 220, 167–178.

Zietz, B.P., Hoopmann, M., Funcke, M., Huppmann, R., Suchenwirth, R., Gierden, E., 2008. Long-term biomonitoring of polychlorinated biphenyls and organochlorine pesticides in human milk from mothers living in northern Germany. Int. J. Hyg. Environ. Health 211, 624–638.

Zimmers, S.M., Browne, E.P., O'Keefe, P.W., Anderton, D.L., Kramer, L., Reckhow, D.A., Arcaro, K.F., 2014. Determination of free bisphenol A (BPA) concentrations in breast milk of U.S. women using a sensitive LC/MS/MS method. Chemosphere 104, 237–243.

Zoller, O., Brüschweiler, B.J., Magnin, R., Reinhard, H., Rhyn, P., Rupp, H., Zeltner, S., Felleisen, R., 2016. Natural occurrence of bisphenol F in mustard. Food Addit. Contam. A 33, 137–146.