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Methods for the analysis of endocrine disrupting chemicals in selected environmental matrixes

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ABSTRACT

Endocrine disrupting chemicals (EDCs) are heterogenous in structure, chemical and physical properties, and their capacity to partition into various environmental matrixes. In many cases, these chemicals can disrupt the endocrine systems of vertebrate and invertebrate organisms when present at very low concentrations. Therefore, sensitive and varied analytical methods are required to detect these compounds in the environment. This review summarizes the analytical methods and instruments that are most used to monitor for EDCs in selected environmental matrixes. Only those matrixes for which there is a clear link between exposures and endocrine effects are included in this review. Also discussed are emerging methods for sample preparation and advanced analytical instruments that provide greater selectivity and sensitivity.

1. Introduction

As described in a previous article in this special issue by Metcalfe et al. there are many classes of endocrine disrupting chemicals (EDCs), and these chemicals are often ubiquitous in the environment. Because of the heterogeneity of these compounds, multiple analytical techniques are required to detect them. A further complication in the analyses of these substances is the variety of the matrixes in which they are present, including tissues and body fluids, soils, sediments and sludges, water, wastewater, and even the gases, aerosols and particulates that are present in indoor and outdoor atmospheres. Finally, many of these compounds are potent at low part per billion or even low part per trillion levels, so the methods for analysis of EDCs must be both sensitive and robust.

Other articles in this special issue focus on a range of topics related to EDCs, including endocrine effects in humans, wildlife, and fish. The focus of this article is to provide a general introduction to methods for the analysis of the EDCs that are discussed in these other articles in the special issue. An exhaustive review of analytical methods for EDCs in all environmental compartments is beyond the scope and the limits to the length of this article. Therefore, through cumulative knowledge in this field among the co-authors, we selected classes of EDCs for review that show a strong association between exposures and endocrine effects in humans, wildlife, or aquatic organisms. Similarly, we focused the chapter on describing analytical methods for chemicals in environmental media where there is a clear link between exposure and endocrine responses. Therefore, discussions are restricted to the analysis of the target EDCs in selected environmental matrixes. These chemicals and environmental matrixes were the subject of another article in this special issue by Metcalfe et al. that reviewed the sources, fate, transformations, and endocrine effects of selected EDCs. We are not aware of any other review article published in the peer-reviewed literature that provides a general introduction to analytical methods for such a broad range of EDCs in a variety of environmental matrixes.

Fig. 1 provides a general overview of the workflows required to prepare samples for analysis. These methods will vary depending upon the sample matrix (e.g., liquids, solids, tissues) and the target chemical, as described in this article. A key step in these analyses is the addition of internal standards to aid in accurate quantitation of the target analytes (Fig. 1). Where the internal standard is a stable isotope labelled homologue of the target compound, these are sometimes referred to as "surrogate standards".

The usual methods for analysis of EDCs involve initial chromatographic separation of analytes by gas chromatography (GC) or liquid chromatography (LC), as summarized in Table 1. The chromatography instruments are coupled to various types of ionization sources and

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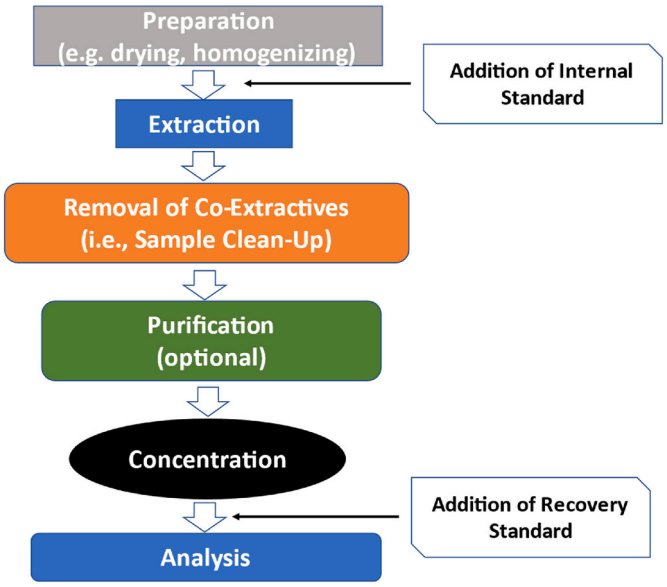

Fig. 1. Generalized workflows for the preparation of environmental samples for analysis of EDCs. The workflow is based on external calibration with corrections for recoveries of internal standards.

Table 1
Selected endocrine disrupting chemicals, the most commonly used analytical methods, and the priority environmental matrixes for analysis. Also listed are the analytical detection limits needed to meet regulatory requirements or toxicologically relevant thresholds.

Chemical Class	Analytical Methods	Priority Matrixes	Detection Limits
Organochlorine compounds	GC-MS GC-MS/MS	Tissues Urine and serum Breast milk	ng/g ng/mL ng/mL
Halogenated aromatic hydrocarbons	GC-MS GC-HRMS	Tissues Breast milk	ng/g or pg/g[a] ng/mLor pg/mL[a]
Brominated flame retardants	GC-MS LC-MS/MS	Tissues Urine and serum Breast milk	ng/g ng/mL ng/mL
Per- and polyfluoroalkyl compounds (PFAS)	LC-MS/MS LC-HRMS	Water and wastewater Soils and sediments Tissues Serum	ng/L ng/g dry wt. µg/g ng/mL
Alkylphenols	GC-MS LC-MS/MS	Water and wastewater	µg/L
Phthalates	LC-MS/MS	Food Beverages Urine and serum	ng/g ng/mL ng/mL
Bisphenol A and analogues	LC-MS/MS GC-MS	Food Beverages Urine and serum Hair	ng/g ng/mL ng/mL ng/g
Pharmaceuticals, illicit drugs, hormones	LC-MS/MS	Water and wastewater	ng/L
Personal care products	LC-MS/MS GC-MS	Water and wastewater	ng/L
Organotins	GC-MS (after derivatization) LC-MS/MS GC-ICP-MS LC-ICP-MS	Water Sediments	pg/L ng/g dry wt.

[a] Required detection limits for PCDD/Fs and dioxin-like PCBs.

positively or negatively charged ions are detected using mass spectrometers (MS) or tandem mass spectrometers (MS/MS) operated using a range of ion monitoring modes (Jeannot et al., 2002; Wille et al., 2012 Jimenez-Díaz, 2015). Increasingly, high resolution mass spectrometry (HRMS) is being used because of the sensitivity and specificity of these instruments (Hernández et al., 2011). Because of the variability in the efficiency of extraction of EDCs and the potential for interference from co-extractives with MS detectors (i.e., "matrix effects"), routine use of internal standards is recommended to aid in accurate quantitation of target analytes. In many cases, these internal standards are stable isotope homologs (i.e., "surrogate standard") of the target analytes.

The remainder of this article will focus on describing state-of-the-art techniques for the analysis of the classes of EDCs identified in Table 1, with a focus on analysis of samples of the "priority matrixes" identified in another article in this special issue by Metcalfe et al. The analytical detection limits required to meet regulatory limits or to detect EDCs in matrixes at toxicologically relevant thresholds are listed in Table 1. Only the methods that meet these requirements for analytical sensitivity and specificity are included in this article. Also included are descriptions of new or emerging analytical techniques. In some cases, these include non-targeted screening approaches to identify unknown transformation products and metabolites of the EDCs. Existing reviews on the subject are referenced as much as possible to provide additional sources of information and to limit the length of this article.

2. Organochlorine compounds

Many organochlorine compounds (OCs) have been recognized as priority pollutants for several decades, and so, environmental quality/food safety standards have been developed for many of these compounds. As a result, standard analytical test methods have been established for the targeted analysis of many OCs (e.g., US EPA methods 608 or 8081 B), and these methods support surveillance plans or biomonitoring programs. Standard reference materials with certified OC concentrations are available from organization such as the National Institute of Standards and Technology (NIST) or the Institute for Reference Materials and Measurements (IRMM), for example.

The most widely monitored OC is dichlorodiphenyltrichloroethane (DDT) and its metabolic transformation products (i.e., DDE, DDD), but other classes of OCs include compounds from the cyclodiene, hexachlorocylohexane (HCH), endosulfan and pentacyclododecane classes of insecticides. Since OCs bioaccumulate in organisms and are often subject to biomagnification through food chains, analytical efforts are often focused on determining the concentrations of these compounds in biological matrices, such as tissues, cord blood and breast milk, with a focus on lipid-rich tissues that tend to be enriched with these compounds. There are often regulatory limits set for these compounds, such as consumption advisories for the levels of OCs and other persistent organic pollutants (POPs) in fish to protect human health (Binnington et al., 2014). In other cases, there are concerns over the endocrine disrupting hazards from the high concentrations of OCs that accumulate in the lipid-rich tissues of top predators, such as polar bears, *Ursus maritimus* (Routti et al., 2019). Therefore, the analytical priorities for OCs with regard to potential endocrine effects are the analysis of residues of these compounds in biological tissues.

Strategies for the analysis of OCs have been described in several previous reviews, including descriptions of the analysis in environmental samples (Muir and Sverko, 2006), in food (Chung and Chen, 2011) and in human tissues (Aprea et al., 2002). The conventional approach for sample preparation relies on solvent extraction of OCs followed by various cleanup and pre-concentration steps prior to instrumental analysis. As most OCs are nonpolar, extractions using nonpolar solvents (e.g., hexane, toluene, pentane) or solid phase materials (e.g., polydimethylsiloxane) are effective for extracting these compounds from biological samples. While Soxhlet extraction has been the standard approach for the solvent extraction of OCs, this method is

time consuming and uses large amounts of solvents, so other methods have been developed for a wide range of environmental, food and human matrixes, including microwave-assisted solvent extraction, pressurized liquid extraction or ultrasound-assisted extraction (Sun et al., 2012; Pico, 2013; Wang et al., 2016). Size-exclusion chromatography is often used to remove co-extracted interfering material, notably lipids. Further sample cleanup and fractionation often includes column chromatography with Florisil or silica gel. Prior to 2000, gas chromatography coupled with electron capture detection (GC-ECD) was the most commonly used analytical instrumentation (Aprea et al., 2002), but now, GC coupled to mass spectrometry (MS), tandem mass spectrometry (MS/MS) or high-resolution mass spectrometry (HRMS) are the gold standard for the analysis of hydrophobic contaminants, including OCs. Although GC-ECD instruments are sensitive, the detector responds to all halogenated compounds and so lacks the specificity of mass spectrometric instruments.

Although OCs have been monitored for nearly 60 years, their analysis remains relatively time-consuming and costly. Recent developments have focused on reducing sample size, time for sample preparation and costs. Rapid methods based on QuEChERS (i.e., quick, easy, cheap, effective, rugged, and safe) have been reported for sample preparation prior to the GC-MS analysis in several matrixes, including in eggs (Song et al., 2019), fish (Molina-Ruiz et al., 2015), soil Rashid et al. (2010), urine (Oenning et al., 2018) and human milk (Du et al., 2016). On-line solid-phase extraction and large volume injection for direct analysis by GC-HRMS have been reported for detection of OCs in serum and plasma with sample volumes of only 200 μL (Wittsiepe et al., 2014). Table 2 summarizes other recent analytical approaches for OCs in biological tissues. Direct sample introduction (DSI) for GC-MS/MS was recently reported for the analysis of DDT and other organochlorine compounds in mammalian tissues and blood (Baumer et al., 2020). Atmospheric Pressure Chemical Ionization (APCI) was recently introduced as an alternative to electron impact (EI) and chemical ionization (CI) for GC-MS analysis (Geng et al., 2016).

Analytical methods have also been developed to further elucidate the distribution and fate of the metabolites, breakdown products or specific isomers of OCs. For example, Reger et al. (2017) developed a method for the verification of the occurrence of hydroxylated metabolites of technical toxaphene in environmental samples. Liquid chromatography coupled with HRMS has also been reported for the identification of new metabolites of endosulfan sulfate in human liver preparations (Lee et al., 2020). Enantioselective estrogenicity has been reported for compounds such as *o,p′*-DDT, and therefore, multidimensional chromatographic methods have been developed for enantiomeric analysis (Naude and Rohwer, 2012).

In conclusion, efforts are still on-going to simplify the targeted analysis of OCs, as the standard methods are relatively complex, time consuming and costly. Recent analytical advances have also provided further insights into the degradation, metabolism and fate of specific OCs and isomers. Recently, "non-targeted analysis" has emerged as a tool for the screening of unknown or unexpected contaminants. Non-targeted screening was recently applied to study halogenated compounds in breast milk (Tran et al., 2020). Non-targeted analysis based on mass defect filtering on an H/Cl mass scale was also applied to data obtained from liquid chromatography coupled with HRMS and this technique facilitated the identification of compounds such as a constituent of toxaphene, nona-chlorobornane in marine mammal tissues (Cariou et al., 2021).

Table 2
Recently reported methods for the analysis of OCs in biological tissues. SPE (HLB) = Solid phase extraction with hydrophilic-lipophilic balance sorbent; DSI = direct sample introduction; EI = Electron impact ionization; APCI = Atmospheric pressure chemical ionization.

Matrix	Extraction/cleanup	Analysis	Reference
Urine	Disposable pipette extraction	GC-EI-MS	Oenning et al. (2018)
Human milk	QuEChERS	GC-EI-MS/MS	Du et al. (2016)
Mammalian tissues and blood	Passive sampling with PDMS	DSI-GC-MS/MS	Baumer et al. (2020)
Fish tissue	QuEChERS with dual dispersive solid phase extraction	GC-EI-MS	Molina-Ruiz et al. (2015)
Serum	SPE (HLB)/Acidified silica column	GC-APCI-MS/MS	Geng et al. (2016)

3. Halogenated aromatic hydrocarbons

Halogenated aromatic hydrocarbons (HAHs) are persistent, subject to bioaccumulation and toxic, and many of these compounds tend to biomagnify through food chains to reach very high concentrations in animals from upper trophic levels, such as killer whales, *Orcinus orca* (Desforge et al., 2018). Many congeners of polychlorinated biphenyls (PCBs) are present in the lipid-rich tissues of fish, wildlife, and humans at part per billion or even part per million concentrations. However, polychlorinated dibenzodioxins and dibenzofurans (PCDD/DFs) and the planar PCB congeners that are "dioxin-like" in terms of their toxic effects are usually present in tissues at part per trillion or even part per quadrillion concentrations. Since the co-contaminants in tissues are present at much higher concentrations, there are challenges associated with analyzing these highly toxic compounds in environmental matrixes. Therefore, this section is divided into a description of the analytical methods for PCB congeners and the methods used for analysis of PCDD/DFs.

3.1. PCBs

This section is based on a recent review of current knowledge on the procedures for sampling, extraction, and purification (i.e., "clean-up") for optimal quantification of PCBs in various matrixes (Vijaya Bhashar Reddy et al., 2019). When archiving sediment or tissue samples for PCB analysis, freezing the samples in their original wet state is the preferred approach. Alternatively, homogenized samples can be mixed with (PCB-free) desiccants such as sodium sulfate, Celite, or Hydromatrix® to bind water prior to extraction (Intrchom and Mitra, 2017). Depending on the matrix, samples can undergo different types of extraction, such as solid phase extraction (SPE), supercritical fluid extraction (SFE), Soxhlet, pressurized liquid extraction (PLE) or solvent extraction using recently developed microextraction methods (Vijaya Bhashar Reddy et al., 2019). Methods can also include QuEChERS approaches (Cloutier et al., 2017).

Priority matrixes for the analysis of PCBs are usually biological samples, including milk and lipid-rich tissues. In these matrixes, it is necessary to remove co-extracted lipids before analysis. It is necessary to perform purification procedures to remove these lipids before analysis so that these substances in the extract will not interfere with the resolution of the gas chromatographic column. Different techniques are available, and they can be used individually or in combination, depending on the selectivity and sensitivity of the final quantification technique. PCBs are stable in acids, so a cleanup step using sulfuric acid or acid impregnated silica columns will be effective for lipid removal while not causing any losses of the PCB analytes. However, several organochlorine compounds are acid-labile, so these lipid-removal methods should not be used if OCs are also included as target analytes. It is also necessary to remove sulfur from sediment or soil samples to minimize interferences when using ECD as a detector or to extend the life of an MS detector. Sulfur removal is typically accomplished by adding copper pellets or filings during extraction (Vijaya Bhashar Reddy et al., 2019).

In recent years, a battery of analytical procedures has been developed to improve sensitivity and selectivity and to minimize the time

required for PCB analysis. Advances in the preparation of reference materials and the establishment of high-quality standards have contributed to the development of more precise and accurate analytical methods. Historically, the most common analytical technique for identification of PCBs was GC-ECD, but this detector responds to all halogenated compounds and so lacks the specificity for definitive identification of target PCB congeners. Now, GC-EI-MS is the most widely used analytical method. In recent years, more sensitive and selective instruments have been introduced for the analysis of dioxin-like PCB congeners (i.e., congeners 77, 81, 126, 169), with high-resolution gas chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS) being the most important. A range of high-resolution mass spectrometers such as magnetic sector, Orbitrap, ion trap (IT-MS), time-of-flight (TOF-MS), and triple quadrupole (QqQ-MS/MS) detectors are currently available and are connected to a GC or an LC for chromatographic separations (Vijaya Bhashar Reddy et al., 2019). However, the choice of mass detector depends on the adopted separation technique, required information, specificity governed by regulations and the mass accuracy (Grzeskowiak et al., 2016). Currently, GC-EI-MS is the detection technique that is best suited for the routine analysis of PCBs in a variety of environmental and biological matrices (Vijaya Bhashar Reddy et al., 2019).

3.2. PCDD/DFs

A literature review was recently published updating the analytical methods for PCDD/DFs in different environmental and human matrixes (Kanan and Samara, 2018). The sample preparation procedures are very similar to PCBs, with the same extraction and purification steps required prior to analysis. Once again, analytical priorities are generally for biological samples. However, PCDD/DFs are generally present in these environmental matrixes at concentrations at least an order of magnitude lower than the co-extracted PCBs, OCs and other halogenated compounds that may interfere with analysis. Therefore, traditionally, PCDD/DFs levels have been determined by HRGC/HRMS. Techniques incorporating GC-MS/MS offer excellent sensitivity and linearity. Recently, the European regulations for the official control of the levels of PCDD/DFs in food and feed have been amended (Regulations No. 589/2014 and 709/2014) with the recognition of GC-QqQ-MS/MS as the best analytical instrumentation to verify compliance. Other high-resolution methods have been developed, including GC-TOF-MS, and gas chromatography with Fourier transform ion cyclotron resonance mass spectrometry (GC-FT-ICR-MS), as reviewed by Kanan and Samara (2018). The concentrations of individual PCDD/Fs and dioxin-like PCBs are often multiplied by Toxic Equivalency Factors (TEFs) that reflect their toxic potency relative to the most toxic PCDD compound, 2,3,7,8-tetrachlorodibenzo-p-dioxin (i.e., TCDD) and these Toxic-Equivalent Quantities (TEQs) are summed to indicate the combined potential for these compounds to bind to the aryl-hydrocarbon (Ah) receptor (Lee et al., 2013).

4. Brominated flame retardants

The analytical approaches for some classes of brominated flame retardants (BFRs) such as polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBBs) are often similar to those developed for other hydrophobic chemicals such as OCs and PCBs (Covaci et al., 2011). In fact, these BFRs are often included in methods for the analysis of multiple classes of hydrophobic organic contaminants in environmental and biological samples (Zhang et al., 2015a; Svarcova et al., 2019). Several review papers have also described the various analytical approaches for novel BFRs (Covaci et al., 2011; Papachlimitzou et al., 2012).

The usual methods for extraction of BFRs from tissues or biota include solvent extraction (Zhong et al., 2018), ultrasound assisted extraction (Zhang et al., 2015b), microwave assisted extraction (Bayen et al., 2004) or pressurized liquid extraction (Neugebauer et al., 2018). Solid-phase extraction (SPE) has been reported to successfully extract a range of BFRs in blood serum (Megson et al., 2016) and some urinary biomarkers for exposure to BFRs (Lin et al., 2020). Since the hydroxy-metabolites of PBDEs disrupt thyroid function, methods have been developed for the extraction and analysis of PBDE metabolites in urine (Feng et al., 2016). Some of these methods are listed in Table 3.

For the analysis of BFRs in extracts from biological samples, GC-MS and GC-MS/MS remain the standard instruments to quantify these compounds. Some compounds, notably highly brominated PBDEs (e.g., BDE 209) can undergo thermal degradation, requiring specific attention during GC analysis, such as using a temperature programmable injector (e.g., 75–300 °C) and a short GC column (e.g., 15 m). Both Electron Capture Negative Ionization (ECNI) or EI are commonly used ionization techniques for the analysis of BFRs. The US EPA Method 1614 A describes methods for extraction of PBDEs from soil, sediment, water and biological tissues and analysis by HRGC/HRMS with ECNI or EI ionization. Megson et al. (2016) recently showed that the performances of an analytical method based on HRGC with APCI ionization and detection using a high-resolution qTOF/MS was comparable, and in some cases superior to existing HRGC-EI-HRMS methods. LC-MS/MS with electrospray ionization (ESI) is the analytical method of choice for the BFR compounds tetrabromobisphenol A (TBBPA), diastereoisomers of hexabromocyclododecane (α-HBCD, β-HBCD, γ-HBCD) or brominated phenols (Lankova et al., 2013). However, an LC-MS/MS method has been developed for the simultaneous analysis of PBDEs, HBCD isomers and other BFRs in wastewater (Zhou et al., 2010).

Recent developments for the analysis of BFRs have focused on reducing sample size, time for sample preparation and costs, and including BFRs as target compounds in multi-analyte methods (Table 3). These methods often aim at simultaneously analyzing the parent compounds with their transformation products/metabolites. For instance, Tan et al. (2020) established a simple and rapid method using LC-HRMS for the qualitative and quantitative analysis of TBBPA and its metabolites in fish. Finally, isotope ratio mass spectrometry (IRMS) has opened new perspectives for a better understanding of the fate of BFRs. For example, a method to determine the stable carbon isotope ratios of HBCD diastereoisomers using GC-IRMS was recently developed for tracking abiotic or biological transformation processes (Cheng et al., 2019). Compound-specific carbon isotope analysis using an off-line elemental analyzer was also employed to characterize the debromination of decabromodiphenyl ether (Zhu et al., 2020). Research is needed to develop analytical methods to measure novel BFRs in environmental matrixes (Zuiderveen et al., 2020).

5. Per- and polyfluoroalkyl substances

Per- and polyfluoroalkyl substances (PFAS) include a range of compounds in commercial and domestic products, the precursor compounds used in the manufacture of these products, and transformation products formed in the environment, as reviewed in the article by Metcalfe et al. in this special issue. Methods for the analysis of PFAS have been the subject of several recent review papers (Valsecchi et al., 2013; Liu et al., 2019; Mullin et al., 2019; Munoz et al., 2019; Nakayama et al., 2019). Historically, the shift from GC-MS to LC-MS methods in the early 2000s significantly improved the limits of detection (LODs) by more than three orders of magnitude, which allowed analysis of PFAS at the ultra-trace levels, while reducing sample volumes. For instance, the first reported method to analyze PFOA in blood required a 25,000 μL blood sample with an LOD of 15 ng/mL, while in comparison, a more recent method used a single drop of blood (<5 μL) for PFAS biomonitoring, with LODs of 0.05–0.10 ng/mL (Ma et al., 2013).

Background contamination from field equipment is considered to be of low concern for samples collected in contaminated areas as the PFAS levels in the samples are orders of magnitude higher than the maximum amounts released from sampling materials (Rodowa et al., 2020).

Table 3
Recently developed methods for the analysis of BFRs in biological tissues. ESI = electrospray ionization; QqQLIT = hybrid triple quadrupole/linear ion trap.

Matrix	BFR Class	Extraction/cleanup	Analysis	Reference
Human milk	HBCD TBBPA	Solvent extraction with sulfuric acid hydrolysis	LC- QqQLIT-MS	Inthavong et al. (2017)
Serum	PBDEs, TBBPA, brominated phenols	Solvent extraction, SPE/QuEChERS	HRGC–MS/MS LC-ESI-MS/MS	Svarcova et al. (2019)
Aquatic organisms	TBBPA	Ultrasound-dispersive liquid–liquid microextraction	LC-ESI-MS/MS	Macedo et al. (2020)
Aquatic organisms	PBDEs, HBB, TBBPA, HBCD	Ultrasound assisted extraction	HRGC–MS/MS LC-ESI-MS/MS	Zhang et al. (2015)
Urine	PBDE metabolites	SPE	HRGC–MS/MS	Feng et al. (2016)

However, where low concentrations in samples are expected, background contamination can become problematic and should be minimized, for instance by using washing protocols for sampling and laboratory materials. Selection of appropriate sample bottles should be made in accordance with EPA methods (e.g., Method 537.1, Method 533). To minimize the PFAS background from LC-MS/MS mobile phases or tubing, a PFAS trap column (or 'delay' column) is typically included after the mixing point in the the injector (Vestergren et al., 2012). Field blanks, laboratory blanks, and analytical injection blanks should be included in every batch of samples to minimize the risk of false positives.

Current methods for the preparation of water samples typically involve off-line SPE with weak-anion exchange cartridges (e.g., Oasis WAX, Strata X-AW) to reach a suitable concentration factor. This is particularly useful for drinking water and surface water samples in view of the low levels and the stringent guidelines. For instance, the US EPA currently sets the drinking water health advisory level at 70 ng/L for PFOS, PFOA, and their sum, while the European Union sets an environmental quality standard of 0.65 ng/L for PFOS in inland surface waters (annual average). Direct injection is possible for contaminated samples collected near sources, but this requires addition of an organic co-solvent stabilizer (e.g., methanol) to reduce sorption artifacts (Martin et al., 2019). For this reason, the use of large-volume aqueous injection, for instance through on-line SPE methods, may be a questionable practice. Backe et al. (2013) circumvented this issue by employing large-volume non-aqueous injection using a set of orthogonal columns.

Sample preparation methods for soils present challenges, according to the characteristics of the targeted PFAS. Anionic PFAS are recovered well from soils using methanol (MeOH) mixed with a weak base, such as ammonium hydroxide (NH_4OH), or with acetonitrile (ACN) mixtures in water. However, the concentrations of zwitterionic and cationic PFAS in soils can be greatly underestimated using these approaches because stronger sorption results in extremely low (<10%) absolute recoveries (Mejia-Avendaño et al., 2017). Alternative methods using MeOH mixed with strong base (NaOH), strong acid (HCl), or salt (CH_3COONH_4) result in substantial improvements in recoveries (Liu et al., 2021; Nickerson et al., 2020), though enhanced extraction conditions could also lead to unwanted analyte interconversions. Following the extraction step, cleanup is typically performed using adsorption filtration through ENVI-Carb cartridges.

One of the most widely applied methods for extraction of PFAS from biota tissues is that of Hansen et al. (2001), based on ion-pairing extraction with tetrabutyl ammonium hydrogen sulfate (TBAHS) and methyl tert-butyl ether (MTBE). Extracts are usually evaporated to dryness and reconstituted in a suitable solvent for instrumental analysis. Other frequently reported methods include alkaline digestion with a strong base such as potassium hydroxide (KOH) or sodium hydroxide (NaOH) in methanol and ultrasonic extraction with methanol, acetonitrile, or methanol-water mixtures (Valsecchi et al., 2013). The subsequent purification step commonly involves solid phase dispersion methods with silica or graphite, SPE methods, or a combination of both (Bertin et al., 2014). Despite internal standard correction, matrix effects are occasionally reported in biota extracts and may be countered by matrix-matched calibration. Certified reference materials for biological tissues with PFAS values are available, for instance from NIST (Rodowa and Reiner, 2021).

In most cases, quantification of target PFAS involves isotopic dilution, with internal standards added at the beginning of the preparation procedure. Major PFCA and PFSA homologues nearly all have matched isotopologues. Matching stable isotope-labelled chemicals are also available for a few anionic and neutral precursors. However, the lack of commercially available internal standards for zwitterionic and cationic PFAS remains a challenge. In the commonly applied separation technique of reversed-phase liquid chromatography (RPLC), a C18 chromatographic column is used with mobile phases such as water and ACN or MeOH/ACN mixtures amended with acid (formic acid or acetic acid, 0.1–0.5%) or ammonium acetate (2–20 mM) modifiers. Pentafluorophenylpropyl stationary phases can also be used to improve LC separation of linear and branched PFOS isomers (Liu et al., 2019).

Most commercial and research labs target a select suite of anionic PFAS, with representative classes being PFCAs, PFSAs, FTSAs and precursors of the C8 electrochemical fluorination (ECF) manufacturing process, such as FOSA, Me/EtFOSA, Me/EtFOSAA. These classes of PFAS were reviewed in the article by Metcalfe et al. in this special issue. However, analysis of a more diverse range of PFAS classes may be needed to avoid underestimation of total PFAS levels. For instance, PFCA/PFSA may represent as little as 1–3% of the summed PFAS in soils contaminated by AFFF foams (Mejia-Avendaño et al., 2017; Nickerson et al., 2020). In addition to the lack of standardized analytical methods for emerging PFAS, the greatest limitation is the current lack of reference chemicals. Semi-quantitative approaches have been proposed, based on calibrants matched with related structures and retention times (Nickerson et al., 2020).

In addition to targeted PFAS analysis, total PFAS may be estimated using surrogate parameter approaches. These include analysis of total organofluorines (Koch et al., 2020; McDonough et al., 2019) and total fluorine, for instance using particle-induced gamma ray emission (PIGE) spectroscopy (Ritter et al., 2017). Houtz and Sedlak (2012) introduced the total oxidizable precursor (TOP) assay, based on persulfate chemistry. The TOP assay works in a strictly aqueous medium and under alkaline conditions. Using heat activation, persulfate thermolysis generates hydroxyl radicals, which in turn can oxidize precursors into the more easily measurable perfluoroalkyl carboxylic acids (PFCAs) listed in Table 4. The TOP assay has been used for applications for analysis of water samples, but application to more complex matrixes, such as solids, may require prior cleanup to avoid radical consumption by competing organic matter (Casson and Chiang, 2018).

The increasing availability of instruments for HRMS has also led to a rapid increase in investigations of PFAS using suspect-target and non-target approaches. Mass defect filtering is a key post-acquisition strategy applied in many workflows (Fig. 2), while other approaches, such as in-source fragmentation flagging, have also been reported (Liu et al., 2015). The high number of fluorine atoms in any given PFAS implies that their mass defect will be constrained within a specific range. In practice, only extracted peaks of CF_2-normalized Kendrick mass defects within 0–0.15 or 0.85–1.0 will be retained for PFAS analysis (Myers et al., 2014). Compounds within the same chemical class will have nearly equal mass defects and therefore line up horizontally in plots of KMD = f(m/z), while ascending retention times with increasing m/z in RPLC is another criterion to consider. Barzen-Hanson et al. (2017) applied homologue-based non-target screening to AFFFs and

Table 4
Major generated PFCA when applying the TOP assay (Houtz and Sedlak, 2012; Martin et al., 2019). Products with low yields (<10 mol%) are not shown in the table.

Precursor	Major perfluoroalkyl carboxylates generated from TOP assay							
	PFPrA	PFBA	PFPeA	PFHxA	PFHpA	PFOA	PFNA	PFDA
FBSA		X						
FHxSA				X				
FOSA						X		
EtFOSAA						X		
6:2 FTSA	X	X	X	X				
8:2 FTSA			X	X	X	X		
10:2 FTSA					X	X	X	X
6:2 diPAP		X	X	X	X			
AmPr-FHxSA				X				
AmPr-FOSA						X		
TAmPr-FHxSA				X				
TAmPr-FOSA						X		
6:2 FTSA-PrB	X	X	X					

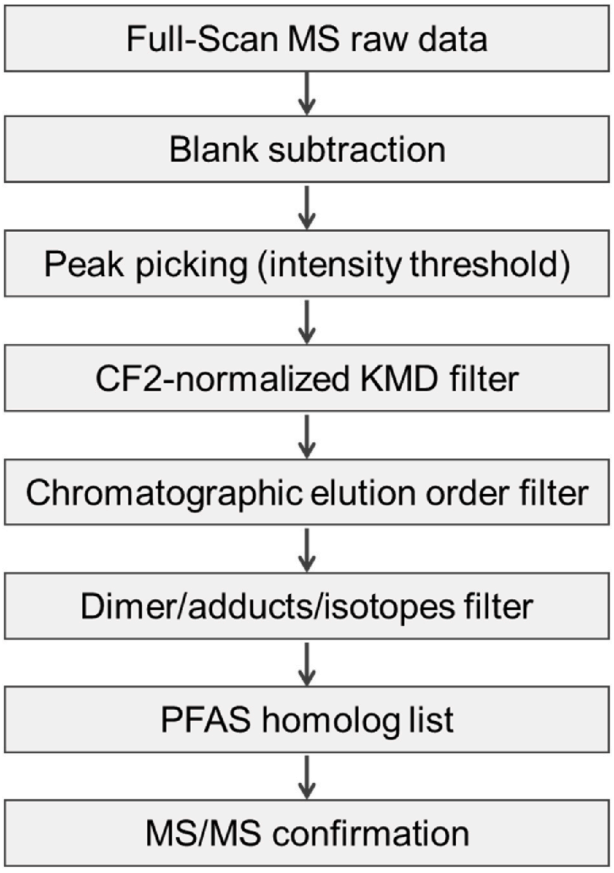

Fig. 2. Example workflow for homologue-based non-target PFAS screening with Kendrick mass defect filtering. This figure was adapted from Yu et al. (2018).

AFFF-impacted groundwater, leading to the discovery of 40 novel classes of PFAS. Key to higher levels of confidence in identification is the acquisition of MS/MS spectra. Commonly observed MS/MS fragmentation patterns of newly identified PFAS are available as searchable Excel files (Barzen-Hanson et al., 2017).

Current analytical approaches provide a range of techniques and tools to analyze an ever-increasing number of PFAS compounds in a variety of environmental matrixes. However, much remains to be determined about identifying and quantifying a range of precursor compounds and transformation products in the environment.

6. Alkylphenol compounds

Most analytical studies for alkylphenol compounds (APEs) have focused only on the compound that has the greatest potential for endocrine disruption, which is nonylphenol (NP) or more specifically, the 4-NP or *para*-isomer of this compound. The concentrations of another alkylphenol, octylphenol (OP) are reported less often because this compound is typically found in environmental matrixes at much lower concentrations than NP. However, restricting analyses to just NP may result in a severe underestimation of the total concentration of this class of compounds. As discussed in another article in this special issue by Metcalfe et al., water and sediment quality guidelines in some jurisdictions apply to the sum of NP and any nonylphenol ethoxylates (NPEOs) and nonylphenol ethoxycarboxylates (NPECs) that are also analyzed in water or sediment matrixes. Thus, the analytical monitoring requirements will vary with the regulatory jurisdiction. The following description of analytical methods will focus on the most common techniques used to monitor this class of compounds in water and sediments.

Table 5 summarizes the most reported methods used for sample preparation and analysis of APEs in water and sediment samples. Blank contamination is the primary problem associated with the analysis of APEs in environmental samples. These compounds are often present at ultra-trace levels in plasticware, reagents and solvents. Supercritical fluid extraction (SFE) with supercritical CO_2 has been used as a method for extracting these compounds from sediments to reduce contamination from solvents (Bennett and Metcalfe, 1998). Therefore, rigorous quality control procedures are essential for these analyses. Because standard reference materials are not available for APEs in environmental samples, spiked real samples should be used to define recoveries (%) and method detection and quantitation limits.

Table 5
Commonly used methods for sample preparation and analysis of APEs in water and in sediments. SPE = Solid phase extraction; LLM = Liquid-liquid microextraction; PLE = pressurized liquid extraction; UASE = ultrasonic assisted liquid extraction.

Class of APEs	Extraction		Analysis
	Water	Sediments	
Alkylphenols (NP, OP)	SPE, LLM	Soxhlet, PLE, UASE	GC-MS after derivatization; LC-MS/MS (+)
Alkylphenol ethoxylates (e.g., NPEOs)	SPE	PLE, UASE	LC-MS/MS (+)
Alkylphenol ethoxycarboxylates (e.g., NPECs)	SPE	PLE, UASE	LC-MS/MS (−)

6.1. Alkylphenols

The methods for analysis of NP and OP in water/wastewater and in sediments and other solid matrixes have been thoroughly reviewed by Salgueiro-Gonzalez et al. (2017) and Salgueiro-Gonzalez et al. (2018), respectively. As indicated in Table 5, the usual methods for extraction of these compounds from water are SPE using various sorbents or liquid-liquid microextraction (LLM). A variety of techniques have been used to extract these compounds from sediments, but the most common are Soxhlet, PLE and ultrasonic assisted liquid extraction (UASE). Cleanup of the extracts is generally done using SPE with various sorbents. For the analysis of APEs in extracts from both water and sediments, the most common method is derivatization followed by GC-MS. Although some researchers skip the derivatization step, this leads to poor peak resolution and low sensitivity (Gonzalez et al., 2018). Acylation and silylation are the most common derivatization methods used for these analyses. LC-MS/MS is becoming a more common analytical technique (Table 5). The advantages of this instrumentation are that a derivatization step is not necessary, and all of the isomers elute in only one peak. This contrasts with the resolution by GC of a group of peaks representing isomers with branched and linear alkyl chains. Analytical standards of 4-NP and 4-OP compounds are available commercially and an isotopically labelled NP-$^{13}C_6$ compound is available as an internal standard.

6.2. Alkylphenol ethoxylates and ethoxycarboxylates

The alkylphenol ethoxylates (APEOs) and alkylphenol ethoxycarboxylates usually monitored in the environment are NPEOs and NPECs, respectively. These compounds are usually extracted from water using SPE with various sorbents (Table 5). However, the SPE methods that are used for extracting NPEOs from water are not efficient at extracting NPECs, so separate liquid-liquid extraction procedures are necessary (Loyo-Rosales et al., 2007b). For sediment samples, PLE and USAE are the most widely reported methods for extracting both NPEOs and NPECs, followed by SPE cleanup. For the analysis of these classes of compounds in extracts from both water and sediments, LC-MS/MS with electrospray ionization (ESI) is the method of choice. For the analysis of NPEOs, ammonium acetate is often added to the HPLC mobile phase to generate $[M + NH_4]^+$ adducts. Monitoring of these adducts allows greater sensitivity and selectivity for the analytes of interest (DeArmond and DiGregorio, 2013). For analysis of NPECs, the LC-MS/MS is operated in negative ion mode and deprotonated compounds are monitored (Table 5).

The greatest problem for the analysis of both NPEOs and NPECs in environmental samples is the selection of appropriate analytical standards. Commercial mixtures of NPEOs are often used as standards, but the relative proportions of the individual ethoxy-oligomers must be defined to provide accurate quantitative data. Some individual NPEOs and NPECs are available commercially, such as NP1EO and NP2EO and NP1EC (Loyo-Rosales et al., 2007a and b). Therefore, these compounds are the most widely reported in the literature. A lack of commercially available isotopically labelled standards is also a challenge for analysis by LC-MS/MS because of the effects of sample co-extractives on the efficiency (i.e., "matrix effects") of the ESI source.

Despite the fact that APEs have been targeted for several decades as an important group of endocrine disrupting compounds in the environment, there are still significant challenges associated with their analysis. To improve the accurate quantitation of APEs, there is a need for a more extensive range of commercially available analytical standards and isotopically labelled surrogates, as well as CRMs for various environmental matrixes.

7. Phthalates

Over the last 15 years, the number of phthalic acid esters (PAEs) included for monitoring in environmental matrixes has increased from the eight most analyzed compounds (i.e., DMP, DEP, DiBP, DBP, BBP, DCHP, DnOP, DEHP) to include phthalate compounds more recently developed by industry as additives in plastics and resins. These more recently developed compounds include, di-isodecyl phthalate (DiDP), di-isononyl phthalate (DiNP), di-isodecyl phthalate (DiDP), and di-n-octyl phthalate (DnOP). Because of their potential for causing endocrine disruption, priority analytes now also include several monoester metabolites of phthalates, such as mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), monocarboxy-isononly phthalate (MCNP), monocarboxyoctyl phthalate (MCOP), mono-(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-ethyl phthalate (MEP), monoisobutyl phthalate (MiBP), monoisononyl phthalate (MiNP), mono-methyl phthalate (MMP), ND mono-methyl phthalate (MNOP). Analytical methods are thus required for the more recently developed phthalates, as well as for the metabolites that are confirmed or suspected EDCs (Kahn et al., 2020; Net et al., 2015).

Because of the widely reported exposure of humans to phthalates and their metabolites, and the growing evidence of their impacts as EDCs, there are now regulations in several jurisdictions on tolerable daily intake (TDI) from the consumption of foods and beverages contaminated with several phthalate compounds, including MMP, DEHP, BBP, DNBP, and DIBP. Therefore, foods and beverages are a priority environmental matrix for the analysis of these compounds. Contamination commonly occurs from leaching of phthalates from plastic packaging and containers. Considering the importance of evaluating exposure of humans to phthalates, methods have also been developed to estimate exposures through the concentrations of phthalate metabolites in the human body. In humans, phthalates are rapidly metabolized to monoesters within a few hours (Kumar and Sivaperumal, 2016). Studies have demonstrated that the levels of phthalate metabolites are several orders of magnitude (30–100 fold) higher in urine than in blood (Calafat et al., 2013) and that the metabolites are detectable in urine for longer periods due to the presence of enzymes in blood that degrade these compounds (Calafat et al., 2015). Because of these factors and because of the complexity of collecting blood samples, most analytical methods have been developed to monitor these compounds in urine (63%) rather than in serum (21%) and in other body fluids, such as breast milk, seminal plasma, and saliva (Tsochatzis et al., 2016). Therefore, urine is a priority analytical matrix for evaluating exposures of humans to phthalates and particularly the monoester metabolites.

One of the important aspects to consider for the analysis of phthalates is the high risk of contamination due to the laboratory environment and the activities of analytical personnel, as well as contamination from glassware, solvents and reagents which may contain traces of phthalates. Due to the ubiquitous nature of phthalates, precautions are necessary to avoid contamination, including minimizing sample manipulation, careful selection of sample preparation materials (e.g., tubing, vial caps, filters, cartridges, stir bars, etc.), as well as optimized protocols for glassware cleaning and/or baking of glassware at high temperatures prior to use. It is important to have methods with a minimum number of steps, requiring less solvents and changes of glassware and minimizing exposure to air. It is also particularly important to have field blanks and to run procedural blanks routinely to detect contamination that may occur during sampling, sample preparation, extraction and/or instrumental analysis. Several of these aspects are discussed in the methodologies presented in the articles listed in Table 6. This risk of contamination is less important when monitoring metabolites, but still must be considered when there is a possibility of the original diesters being transformed into metabolites (Guo and Kannan, 2012).

Phthalates have been chemicals of concern for a few decades and so there is abundant literature on sample preparation and analytical methods for several matrixes, including in foods and beverages, and in

Table 6
Summary of the methods for preparing samples of body fluids, food and beverages for analysis of phthalates.

Matrix	Sample Preparation Methods
Body fluids	- Off-line SPE extraction preceded by de-glucuronidation step. - On-line SPE extraction - SPE is often based on a two-step process to first remove endogenous components before extraction of the phthalate metabolites. - For urine, stable isotope internal standards used to account for the effect of the salts on SPE efficiency. - LLE and SPME sometimes used. - More advanced sample preparation techniques such as magnetic Solid Phase Extraction (mSPE) used to a lesser extent.
Foods and beverages	*Non-alcoholic and alcoholic beverages* - LLE - SPE using relatively non-polar stationary phases (e.g., C18) - SPME - SBSE - Dispersive liquid-liquid microextraction (DLLME) and ultrasound-assisted DLLME *Foods* - Homogenization as a first step. - LLE - Soxhlet extraction - SBSE and ultrasonic extraction. - Clean-up procedures needed for the removal of fats and oils from fatty foods.

body fluids. The following section summarizes methods for the analysis of phthalates in foods and beverages, which is the main route of human exposure to these contaminants and represents the clearest link between the concentrations of the target analytes and endocrine effects in humans. In addition, methods are discussed for analysis of phthalates and their monoester metabolites in body fluids, and mainly urine. The overall approach includes sample preparation, extraction and cleanup and concentration, and quantification by chromatography coupled with mass spectrometry. Table 6 summarizes the various approaches reported in the literature for these matrixes.

For analysis of phthalates and metabolites in body fluids, SPE methods are often used (Table 6). Note that a significant proportion of the monoester metabolites in urine are conjugated with glucuronide and so a step involving treatment with glucuronidase is usually required prior to extraction to release the bound metabolites (Tsochatzis et al., 2016). Online extraction with column switching provides the advantage of minimal sample handling and high sensitivity. However, dispersive SPE might provide a quick and one-step extraction and clean-up procedure that warrants attention (Tsochatzis et al., 2016). Additional reviews on this topic have been published by Kumar and Sivaperumal (2016) and Guo and Kannan (2013).

Haji Harunarashid et al. (2017) provided a detailed summary of the advantages and disadvantages of various sample preparation methods for the analysis of phthalates in foods and beverages. Overall, this review indicated that liquid-liquid extraction (LLE) methods using large amounts of organic solvents are being replaced by more advanced sample preparation methods (Table 6) For beverages, LLE and SPE are the usual extraction methods. For foods, LLE is the most common extraction technique, although Soxhlet extraction or microwave assisted extraction have also been used. Stir-bar sorptive extraction (SBSE) whereby the solutes are extracted into a polymer coating (e.g., polydimethylsiloxane) on a magnetic stirring rod has the advantage of not requiring organic solvents that could be contaminated with phthalates. Several additives have been proposed to complement the LLE approach. These include addition of aluminum oxide and sodium chloride solution to decrease interference from proteins, fats and other components, addition of sodium chloride to eliminate water from fresh food items, and addition of potassium hydroxide or potassium oxalate as destabilizing agents to damage the phospholipid-protein membrane of fat globules (Haji Harunarashid et al., 2017). QuEChERS was identified as a promising sample preparation method, considering that it is simple, requires low quantities of organic solvent and a short amount of time, in addition to being a low-cost method. Other methods identified in the review by Haji Harunarashid et al. (2017) include SPME techniques, and more recent methods including headspace or direct immersion SPME methods (Table 6). These recent changes to the methods of sample preparation have allowed the development of approaches based on "greener" extractants and smaller amounts of solvents. For oily or fatty foods, a step is required to remove lipids co-extracted with the target analytes. Methods must include a clean-up procedure for the removal of fats and oils; commonly partitioning with gel permeation chromatography (GPC), based on size exclusion chromatography (SEC).

After sample preparation, the literature indicates that GC and LC are the preferred methods for chromatographic separation of these compounds, independent of the matrix analyzed. Based on the review by Tsochatzis et al. (2016), LC-MS/MS is the dominant analytical technique for the analysis of both phthalates and their metabolites in body fluids, with 64% of studies using this technique, relative to 18% using GC-MS, or other techniques, such as liquid chromatography coupled to other detectors, or Enzyme Linked Immunoassays (ELISA). This might be explained by the time-consuming and expensive derivatization step required prior to analysis by GC to decrease the polarity and increase the volatility of phthalate metabolites. The extensive review indicates that both techniques provide comparable precision and accuracy (Tsochatzis et al., 2017). However, the sensitivity of the GC-MS seems higher, considering the lower limits of detection (0.004–0.2 ng/mL) compared to the limits of 0.5–2 ng/mL for LC-MS or LC-MS/MS, or limits of 0.01 ng/mL for ultra-high pressure liquid chromatography (UPLC) with MS/MS detection. Another review article by Kumar and Sivaperumal (2016) also reported that LC-MS/MS is the most commonly used technique for the quantitation of phthalate metabolites in body fluids.

Haji Harunarashid et al. (2017) reviewed 45 articles describing the methods that have been used for the analysis of phthalates in foods and beverages. Unlike the predominant LC-MS/MS analysis of urine and blood samples that contain metabolites, 73% of these studies used GC-MS instrumentation for the analysis. This might be explained by the fact that phthalates are more suited to chromatographic separation by GC because of their relatively low polarity, thermal stability and high volatility, which means that a derivatization step is not needed prior to analysis. In addition, some studies indicate that, notwithstanding the differences between the pre-treatment steps and instrumental conditions, lower LODs for phthalates in food items can be achieved using GC-MS methods relative to LC-based methods (Moret et al., 2012; Ostrovský et al., 2011).

8. Bisphenol A and analogues

Because tolerable daily intake (TDI) levels have been set under several regulatory jurisdictions for the consumption of bisphenol A (BPA), foods and beverages are the priority environmental matrix for the analysis of this compound. Contamination of food and beverages commonly occurs from leaching of BPA from polycarbonate plastic bottles and containers, and from the resins and coatings that are used to line bottle caps and metal cans. Analytical methods have also been developed to estimate exposures of humans to BPA by determining the concentrations of this compound in body fluids, and especially urine. Because of the expanded use of structural analogues of BPA (e.g., bisphenol S) in plastics and resins, analytical methods have been adapted to include these novel compounds. Since polycarbonate plastics and resins containing BPA and analogues are often used for labware or to line the caps of solvent bottles, care must be taken to reduce background contamination, and analysis of field blanks and procedural blanks are key QA/QC procedures.

The methods for the preparation of samples and the analysis of BPA in various matrixes have been reviewed previously (Sun et al., 2016; Cao, 2012), and the most common methods are summarized in Table 7. For liquid samples, off-line SPE is by far the most common extraction method, but SPME and online SPE methods have also been developed. An interesting application is the use of molecularly imprinted polymer SPE (MIP-SPE) which have been used successfully to extract BPA from liquids with complex matrixes (Sun et al., 2016). As is the case for the extraction of phthalates from urine, pre-treatment with glucuronidase is required to release conjugated metabolites of BPA prior to extraction. Methods for the extraction of BPA in urine do not require adaptation to also extract a range of structural analogues (Heffernan et al., 2016). For extraction of BPA from solid samples, such as foods, LLE has been the most used method, but recent developments to reduce solvent use include Liquid-Phase Microextraction (LPME) and Dispersive Liquid--Liquid Microextraction (DLLME). Microwave assisted extraction (MAE) has also been widely used for foods (Table 7).

LC-MS and LC-MS/MS are currently the primary methods for analysis of BPA in urine and liquid samples (Table 7). Analysis of BPA and analogues in human hair by LC-MS/MS may be a better indicator than urine analysis for assessing exposure in humans (Lee et al., 2017). GC-MS is also often applied to detect BPA and its analogues. Since BPA and analogues are slightly polar, derivatization is required before GC analysis to decrease polarity and increase the volatility of the of the analytes. The most widely used derivatizing reagents are N, O bis-(-trimethylsilyl)-trifluoroacetamide (BSTFA) and N-methyl--N-(trimethylsilyl)trifluoro-acetamide (MSTFA). An essential step in the analysis of BPA in these matrixes is the addition of internal standards to the samples before preparation. Matrix effects may result in inhibition or enhancement of ionization in the source of LC-MS, LC-MS/MS or GC-MS instruments, so internal standards must be used to generate accurate quantitative results.

9. Pharmaceuticals, drugs of abuse and hormones

As discussed in another article in this special issue by Metcalfe et al. a wide range of pharmaceuticals, illicit drugs and natural hormones have been detected in the aquatic environment. The compounds discharged in wastewater into surface waters that have been most widely studied for endocrine disrupting effects are natural estrogens (i.e., 17β-estradiol, estrone) and the synthetic estrogen that is the active ingredient in oral contraceptives (i.e., 17α-ethinylestradiol). Several pharmaceuticals, such as antidepressants from the serotonin reuptake inhibitor class (e.g., fluoxetine, venlafaxine) have been identified as causing disruption of the neuroendocrine system in aquatic organisms. Fibrate drugs that reduce blood cholesterol (e.g., gemfibrozil) are agonists for peroxisome proliferator-activated receptors (PPARs) and cause changes in lipid metabolism. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen that reduce inflammation by inhibiting prostaglandin synthesis can reduce levels of testosterone. Some illicit drugs, including cocaine and metabolites and opioid drugs can affect the endocrine system of both humans and lower vertebrates.

Several methods have been developed to quantify these compounds in rivers, streams, lakes, the marine environment and even in groundwater at concentrations ranging from ng/L up to μg/L. These low concentrations, in addition the effects of co-extractives on the sensitivity of analysis (i.e., "matrix effects") can be significant analytical challenges. Developing methods that address these low concentrations and matrix effects is essential to ensure accurate quantification of these drugs in environmental samples.

9.1. Sample preparation

Because of the low concentrations of drugs usually found in waters, analytical methods must include sample preparation techniques to concentrate the analytes to detectable levels. In a recent review, Daniels et al. (2020) reported that off-line SPE is by far the most popular method, with about 70% of the publications up to 2018 reporting this method, although on-line SPE has attracted increasing attention. With the availability of more sensitive analytical instruments, direct injection of water samples without extraction has become more widely used.

Table 8 provides a summary of the methods for sample preparation, based on several recent reviews of analytical methods (Daniels et al., 2020; Ohoro et al., 2019; Patel et al., 2019; Sosa-Ferrera et al., 2013; Baker and Kasprzyk-Hordern, 2011). Choosing an SPE adsorbent requires consideration of the physiochemical properties of both the target analyte(s) and other constituents within the sample matrix. The materials used for SPE range from the popular Oasis® HLB cartridges with a balance of hydrophilic and lipophilic properties to sorbents with cation (e.g., Oasis® MCX) or anion (e.g., Oasis® MAX) exchange capability. Other commercial sorbents have been developed for strong acids (Oasis® WAX) or bases (Oasis® WCX), and other sorbent materials for more non-polar compounds include C8 or C18 organic groups chemically bonded to silica. The most widely used SPE sorbent is Oasis HLB because it can extract acidic, neutral, and basic polar analytes at a wide range of pH values and is less sensitive to drying. Off-line SPE provides adequate results, but this method is time-consuming. Other more rapid methods are being increasingly used, such as on-line SPE or direct injection, or the microscales approaches (Table 8). In addition to reducing the time required for analysis, these methods use smaller amounts of solvents and consumables. The most commonly used approaches for microscale approaches include hollow fiber protected liquid-phase microextraction (HF-LPME), DLLME, SPME and magnetic solid-phase extraction (MSPE). These more rapid preparative techniques may become more widely used now that regulations have been introduced in the EU (i.e., REACH) for routine monitoring of these target compounds in surface waters and drinking water.

An essential step in the analysis of drugs in complex matrixes is the addition of internal standards to the samples before preparation. Because co-extractives in the sample matrix may inhibit or enhance ionization of the target analytes in the source of MS instruments, the

Table 7
Summary of the methods for preparing samples of body fluids, food and beverages for analysis of bisphenol A and structural analogues. Information taken from Sun et al. (2016) and Cao (2012).

Sample Matrix	Sample Preparation Method	Analytical Method
Liquid samples and urine	SPE (off-line and on-line). Urine samples require pre-treatment with glucuronidase prior to extraction. SPME MIP-SPE	LC-MS LC-MS/MS GC-MS (after derivatization)
Foods and solid samples Hair	LLE LPME DLLME MAE	

Table 8
Overview of extraction methods for preparation of aqueous samples for quantification of pharmaceuticals, illicit drugs and natural hormones.

Methods	Sample Preparation Methods
Conventional off-line SPE	SPE cartridges are packed with an appropriate sorbent with a high affinity for the compounds of interest.
Complexed off-line SPE	Methods based on multi-step SPE to minimize matrix effects.
On-line SPE	Method based on the use of SPE cartridge installed on the analytical instrument and the preconcentrated analytes are eluted directly onto the analytical column.
Large volume injection	No extraction necessary. Direct injection of larger volumes of sample (e.g., 20 μL for GC and 100–200 μL for LC) without prior pre-concentration
Miniaturized extraction	Methods based on reducing the scale of extraction, as well as the size of the extraction devices.

signal generated by these internal standards can be used to compensate for these matrix effects and provide more accurate quantitative results. Stable isotope surrogates that match the target analyte should be added as internal standards (e.g., carbamazepine-d_3 as a surrogate for carbamazepine).

9.2. Analysis

Analytical techniques to detect pharmaceuticals have been widely reviewed, including in recent articles by Ohoro et al. (2019), Patel et al. (2019) and Locatelli et al. (2016). Table 9 provides an overview of the approaches used for the quantification of drugs in environmental samples. The pharmaceuticals present in environmental samples were initially analyzed by GC-MS, but since these analyses typically required a derivatization step prior to analysis to increase volatility and reduce the polarity of the analytes, LC-MS/MS is now the dominant analytical technique (Siddiqui et al., 2017). The use of ultra-high pressure LC (UHPLC) has become more popular as it uses shorter columns and smaller-diameter particles (<2 μm) in the stationary phase, leading to sharper chromatographic peaks (5–10 μs width) and improved chromatographic separations (Sosa-Ferrera et al., 2013). UHPLC also shortens analysis times to often <10 min. Recent reviews cite many studies that describe a range of analytical methods for drugs and hormones (Patel et al., 2019; Omar et al., 2016; Sosa-Ferrera et al., 2013; Baker and Kasprzyk-Hordern, 2011; Wong and McLeod, 2009). Several detectors have been used, including single quadrupole mass spectrometers (MS), tandem mass spectrometers (MS/MS), as well as ultraviolet (UV), diode-array (DAD) and fluorescence detectors. However, MS/MS is the preferred detection techniques because it provides information on the molecular structure of the compounds and has superior sensitivity and selectivity. ESI and APCI are the two most used ionization methods, depending on the analyte and the severity of matrix effects. Due to the increasing interest in detecting trace contaminants in complex matrices, several technologies have been improved and developed. These include QqQ-MS that provides high selectivity and unequivocal identification of the target analytes, TOF-MS or LIT-MS, which have been introduced as a powerful new tool, as well as the hybrid mass spectrometers (e.g., Qq-TOF-MS) and Orbitrap instruments. These advanced instruments provide data on the accurate mass of the product ions and allow structural elucidation of unknown compounds, as well as identification with a high degree of certainty.

10. Personal care products

Personal care products are chemicals that are added to consumer goods such as soaps, shampoos, toothpaste, mouthwashes, perfumes and other cosmetics, insect repellents and sunscreens. There chemicals may be adsorbed through the skin in humans or can be released into the aquatic environment when washed off the body during bathing, then transported through sewage into wastewater treatment plants. Insect repellants and sunscreens may wash off the skin at bathing beaches. The chemical and physical properties of the chemicals in personal care products are variable, and so analytical methods differ according to chemical class (Brausch and Rand, 2011). For instance, many antibacterial compounds (e.g., triclosan) and fragrances (e.g., Galaxolide) have potential for bioaccumulation in aquatic organisms and so methods are needed to measure these compounds in lipid-rich tissues. Other chemicals in personal care products, such as the preservatives from the paraben class are relatively hydrophilic and so analytical methods focus on analysis in water and wastewater.

Table 9
Analytical techniques and instrumentation used for the quantification of pharmaceuticals, illicit drugs and natural hormones in environmental samples.

Chromatography	Detector	Examples of Analytes
Gas Chromatography: GC; usually with derivatization prior to analysis.	MS MS/MS	- Estrogens - Anti-anxiety medications - Analgesics - Cholesterol reducing drugs
Liquid Chromatography: HPLC UHPLC	MS MS/MS HRMS DAD FD	- Cocaine, amphetamines, opioids, cannabinoids - Antidepressants, and anti-anxiety medications - Anti-epileptics - Analgesics and anti-inflammatory drugs - Beta-blocker drugs - Synthetic estrogens, and natural estrogens and androgens - Diabetes therapy drugs - Cholesterol reducing drugs

There have been several reviews published on the analysis of chemicals added to personal care products in various matrixes, including in sewage sludge (Pérez-Lemus et al., 2019), in human body fluids and tissues (Jiménez-Diaz et al., 2014) and in human breast milk (Jiménez-Diaz et al., 2013). However, the priority environmental matrix for this review of analytical methods is water and wastewater. The methods for analysis of several classes of chemicals in personal care products (i.e., UV-filters, insect repellents antimicrobials, preservatives, synthetic musk fragrances) in water, wastewater and other environmental samples was reviewed by Buchberger (2011), As with the analytical procedures for many of the other classes of EDCs, care is needed to avoid background contamination. Field and laboratory personnel may be applying insect repellants, soaps and shampoos, cosmetics and fragrances on their hair and skin than can contaminate samples. Toothpastes and mouth washes, and some detergents and surface cleaners used in the laboratory can contain antibacterial compounds, such as triclosan and triclocarban.

Although the chemicals in personal care products are often analyzed in water and wastewater in conjunction with pharmaceuticals, several classes of these compounds differ in their physicochemical properties from pharmaceuticals and so require different or modified methods for sample preparation and analysis. For instance, while the most widely used method for extracting pharmaceuticals from water and wastewater is SPE with various sorbents, SBSE is widely used to extract the chemicals in personal care products from aqueous samples (Buchberger, 2011). Instead of SPE, SPME and LLE are also used to prepare water and wastewater samples for analysis of the chemicals in personal care products. While the methods for quantifying pharmaceuticals in water and wastewater generally involve analysis using LC-MS/MS, the preferred analytical method for many more non-polar analytes, such as N,N-diethyl-meta-toluamide (DEET) insect repellent, UV-filters, triclosan and synthetic musk fragrances is GC-MS (Buchberger, 2011).

11. Organotins

The regulatory limits for tributyltin (TBT) established in many jurisdictions are for the concentrations in water and in sediments, which are usually in the low ng/L range in water and in the low μg/kg dry weight range in sediments. Thus, sensitive analytical methods are needed to detect TBT and other organotin compounds in water and sediments. The methods used to analyze organotins in various environmental matrixes have been recently reviewed by Cole et al. (2015), so only a summary of these methods will be provided here. For extraction of these analytes from freshwater and saltwater, SPE using C18 sorbent is a commonly used method. However, LLME and SPME methods have been reported. For extraction from sediments, PLE and microwave assisted extraction methods have been widely used.

The separation method of choice for analysis of TBT and other butyltins (i.e., dibutyltin, monobutyltin) is GC because of its high peak resolving power. The analytes are typically derivatized by ethylation prior to analysis using sodium tetraethyl borate (NaBEt4). Various systems have been used for detection of the compounds after GC separation,

including MS and atomic absorption spectrometry (AAS). Hyphenated systems such as GC with inductively coupled plasma emission mass spectrometric (GC-ICP-MS) and microwave induced plasma-atomic emission (GC-MIP-AED) systems have been used, but these require specialized equipment and modified operating parameters (Cole et al., 2015). However, to meet the pg/L analytical detection limits required for some surface water regulations, it may be necessary to use these hybrid systems. Analytical methods using LC with an ICP-MS detector have been reported, but these systems typically have poor sensitivity relative to GC instrumentation (Cole et al., 2015).

Quantification is usually by external calibration using commercially available standards. Isotopically enriched (i.e., ^{119}Sn) MBT, DBT and TBT are available as internal standards. When using derivatization, the use of internal standards is essential to correct for the efficiency of this step. Pre-derivatized standards (i.e., ethylated organotin compounds) are available commercially but are expensive in comparison to their non-derivatized analogues. Despite the advancements in analytical methods, analysis of organotins is still a complex and time-consuming process, with extraction and derivatization procedures accounting for the highest sources of analytical error.

12. Summary

In this article, a variety of sample preparation methods and instrumental techniques were described for a range of EDCs in priority environmental matrixes. The environmental matrixes were selected based on the most likely route of exposure and known linkages to endocrine effects that have been observed in organisms and/or in humans. Recent advances in the preparation of samples from these matrixes are focused on simplifying the process, avoiding background contamination and reducing solvent use, while maintaining low analytical limits of detection. Because many of these EDCs can cause effects at very low concentrations and are often present in complex matrixes (e.g., sediments, tissues, urine), the analytical techniques that are required must have high sensitivity and specificity for the target analytes.

Therefore, the instruments of choice for these analyses use LC or GC separation with mass spectrometric detection. Ionization techniques vary according to the analytes and the type of MS instrument. Challenges to the analysis of EDCs include the lack of commercially available standards and isotopically labelled surrogates for the quantitation of many target analytes. Now that high resolution instruments are becoming more readily available to research and analytical services laboratories, various HRMS instruments (e.g., Qq-TOF-MS, Orbitrap, FT-ICR-MS) are being applied for the analysis of EDCs in environmental samples. The advent of non-targeted approaches for identifying potential EDCs in the environment will challenge analytical chemists to develop new quantitative methods for the novel compounds that are sure to be detected and identified in environmental samples, tissues and body fluids.

Credit author statement

All co-authors that contributed to this manuscript were involved in the conceptualization; data curation; formal analysis; investigation; methodology; resources; visualization; and writing of the original draft and the revised article.

Author contributions statement

The co-authors of this manuscript declare that they contributed different subsections of the article and were responsible for writing these subsections in the original draft and in the revised version of the article. None of this material has been published elsewhere.

Declaration of competing interest

The authors declare that they have no financial, professional or other interest relevant to the work described in this manuscript.

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