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Review

A review of the analysis of novel brominated flame retardants

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ABSTRACT

This review provides a summary of various analytical methodologies applied to the determination of "novel" brominated flame retardants (NBFRs) in various environmental compartments, as reported in peer reviewed literature, either in print or online, until the end of 2010. NBFRs are defined here as those brominated flame retardants (BFRs) which are either new to the market or newly/recently observed in the environment. The preparation and extraction of sediment, water, sewage sludge, soil, air and marine biota samples, the extract clean-up/fractionation and subsequent instrumental analysis of NBFRs are described and critically examined. Generally, while the instrumental analysis step mainly relies on mass-spectrometric detection specifically developed for NBFRs, and hyphenated to liquid or gas chromatography, preceding steps tend to replicate methodologies applied to the determination of traditional BFRs such as polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD). Shortcomings and gaps are discussed and recommendations for future development are given.

Contents

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1. Introduction

Flame retardants are a diverse group of chemicals, mainly based on bromine, chlorine or phosphorus, which are added to a broad range of commercial products (such as televisions, computers, textiles and carpeting, building insulation and furniture) to provide fire protection. Some (such as tetrabromobisphenol A) may be covalently bound into materials during production, but most are simply additive. The latter types are more likely to leach from the finished products during use, following disposal or during recycling. Recently, concerns over the persistence, ability to bioaccumulate and potential for toxicity of some of the most widely used brominated flame retardants (BFRs), the polybrominated diphenyl ethers (PBDEs), have led to increasing regulation and restrictions on their production and use [1,2]. Their removal from markets has resulted in a need for their substitution with other non-PBDE, BFRs, in order to maintain the level of fire protection afforded to products. Tetrabromobisphenol A (TBBPA-A), polybrominated biphenyls (PBB), PBDE commercial mixtures and hexabromocyclododecane (HBCD, HBCDD) have for many years been high production brominated flame retardants. However, to date, more than 75 other different aliphatic, aromatic and cyclo-aliphatic compounds have been used as brominated flame retardants [3].

These "novel" BFRs–NBFRs: defined as those BFRs which are either new to the market or newly/recently observed in the environment [4] – are used in a wide range of products such as plastics, foams and fabrics [5]. Each compound has different applications as a result of their physico-chemical properties; there is no unique solution where protection of materials from fire is concerned. For many NBFRs, there is little information available on their levels of production and their uses. The total global NBFR production has however been estimated to range from 100,000 to 180,000 tonnes per annum [6]. The state of knowledge concerning NBFRs has been reviewed recently [4,7–9]. These articles summarise the levels and trends observed in the environment for some non-PBDE and novel brominated flame retardants. Covaci et al. [4] include also detailed information of production, use and physico-chemical properties for several NBFRs, and significant information about analytical aspects as well.

In this paper we specifically focus and review in detail the methodologies which have been used to date for the analysis of NBFRs in environmental samples, and make some recommendations regarding the need for further method development. The NBFRs for which information is given are listed in Table 1, with their chemical structures and abbreviations which are used in this paper to define the compounds studied.

2. Methods

2.1. Sample preparation

The different methods for extraction and clean-up of NBFRs in environmental samples are summarised in Supporting information, Table 1 and will be discussed in the following section.

2.1.1. Extraction of biota samples

Biological samples have typically been extracted using various organic solvent mixtures following a pre-treatment step. More specifically, the extraction of neutral aromatic brominated compounds is conducted using apolar solvents, while that of phenolic compounds and aliphatic alcohols is based on separating an aqueous phase containing the deprotonated phenolics, acidifying it to enable extraction with an apolar organic solvent and derivatising the phenolics to their methoxylated analogues [6]. Solvent extraction can be carried out using either a *Soxhlet* apparatus or, more recently, pressurised liquid extraction (PLE). Occasionally, microwave-assisted extraction (MAE) has also been used. In the determination of TBB and TBPH, blubber samples from dolphins and porpoises were extracted in a *Soxhlet* apparatus using dichloromethane (DCM)/*n*-hexane (3:1, v/v) [10]. TBECH was determined in beluga whale blubber samples using *n*-hexane/DCM/acetone (45:45:10, v/v) after homogenisation using a Polytron® hand blender [11]. In the determination of DPTE, ATE and BATE in seal blubber and brain samples, a variety of methods were used as some extracts were sourced from earlier studies. Some were extracted with hexane following acid digestion, others using MAE with hexane and Weflon® (microwave transformer) disks as the microwave adsorbent [12,13].

For the determination of BATE and DPTE in fish samples, closed-vessel MAE was used using ethyl acetate/cyclohexane under soft conditions (500 W energy) [14]. More recently, the use of PLE using DCM/hexane for tissues such as fish and mussels has been noted [15–18]. In the first of these studies [15], a broad range of NBFRs was studied (ATE, BATE, DPTE, OBIND, PBEB, HBB, BTBPE, DBDPE, HCDBCO, TBECH, TBCO, TBB and TBPH) in fish. In the determination of BTBPE, PBTo, DBDPE, PBEB and HBB in aquatic species from a pond close to an e-waste recycling site in China, biota samples were homogenised with sodium sulphate and extracted using *n*-hexane/acetone (1:1, v/v) in a *Soxhlet* apparatus for 48 h [19–21]. The same procedure was applied for the extraction of DBDPE from rat tissues [22]. HBB and TBECH were extracted from earthworms homogenised with sodium sulphate using an open column with acetone/hexane 5:2 followed by hexane/diethyl ether 9:1 or *Soxhlet* extracted using hexane/acetone [23]. PBEB, PBT and BTBPE were also determined in muscle tissue samples of five waterbird species, using *Soxhlet* extraction with hexane:acetone (1:1, v/v) for 48 h [24,25]. Pre-treatment of samples with anhydrous sodium sulphate was also conducted prior to column extraction of eggs from glaucous and herring gull eggs [26–28]. In the determination of BTBPE, PBEB, PBBB, DBDPE, PBPAE, TBPAE, PBTo, HBB, PBBA, pTBX, OBIND, TBCO, TBECH, TBBP-DBPE and TBBPA-DBPE, herring gull egg homogenates were ground with anhydrous sodium sulphate and extracted with DCM/*n*-hexane (1:1, v/v) [26]. HBB, BTBPE, PBEB and PBTo were determined in the yolks of glaucous gull and herring gull eggs using the column extraction technique and DCM/*n*-hexane (1:1, v/v) [27,28]. PLE was used for the analysis of TBBPA-S and TBBPA-A derivatives in herring gull eggs [9]. In this case, samples were mixed with diatomaceous earth and extracted with DCM/acetone (1:1, v/v). Samples of blood plasma from glaucous gulls and bald eagle were acidified, 2-propanol was added and finally extracted with methyl *tert*-butyl ether (MTBE)/*n*-hexane (1:1, v/v) [27,30]. In the first study [27], the denatured

Table 1
Structures and acronyms of novel brominated flame retardants (NBFRs).

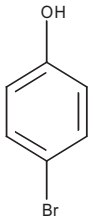
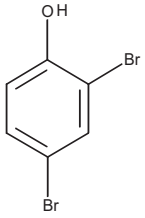
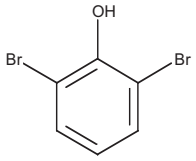
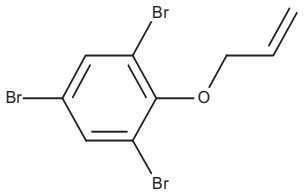
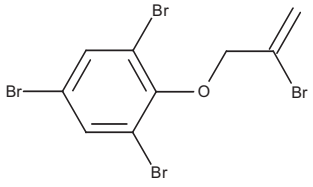
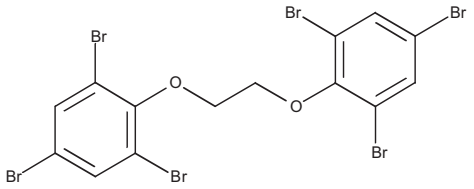
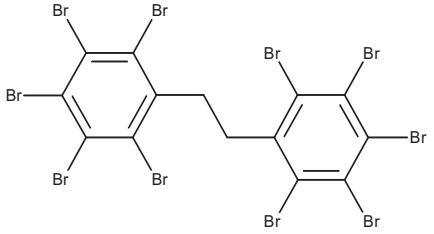
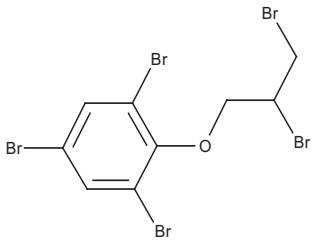
Compound	Name	CAS no.	Structure	MW
4-BP	4-Bromophenol	106-41-2		173.0
2,4-DBP	2,4-Dibromophenol	615-58-7		251.9
2,6-DBP	2,6-Dibromophenol	608-33-3		251.9
ATE (TBPAE)	Allyl 2,4,6-tribromophenyl ether	3278-89-5		370.9
BATE	2-Bromoallyl 2,4,6-tribromophenyl ether	–		449.8
BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane	37853-59-1		687.6
DBDPE	Decabromodiphenyl ethane	84852-53-9		971.2
DPTE	2,3-Dibromopropyl-2,4,6-tribromophenyl ether	35109-60-5		530.7

Table 1 (*Continued*)

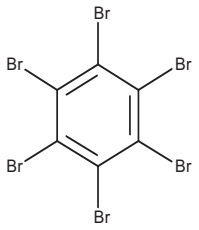
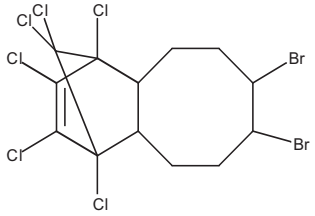
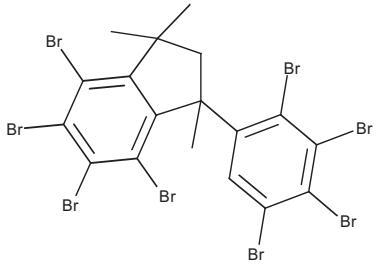
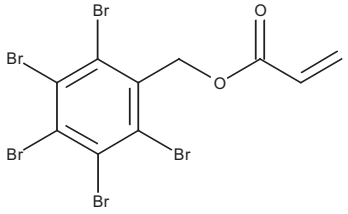
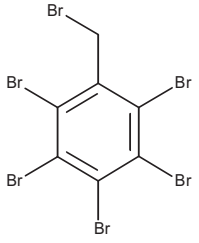
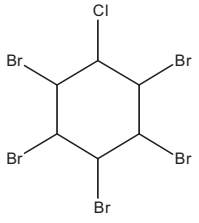
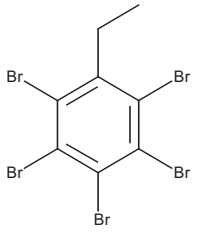
Compound	Name	CAS no.	Structure	MW
HBB	Hexabromobenzene	87-82-1		551.5
HCDBCO	Hexachlorocyclopentadienyl-dibromocyclooctane	51936-55-1		540.8
OBIND	Octabromotrimethyl-phenylindane	155613-93-7		867.5
PBBA	Pentabromobenzylacrylate	59447-55-1		556.7
PBBBr	Pentabromobenzylbro-mide	38521-51-6		565.5
PBCC	1,2,3,4,5-Pentabromo-6-chlorocyclohexane	87-84-3		513.1
PBEB	Pentabromoethylbenzene	85-22-3		500.7

Table 1 (*Continued*)

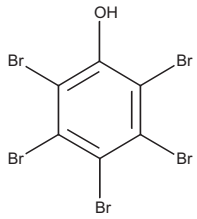
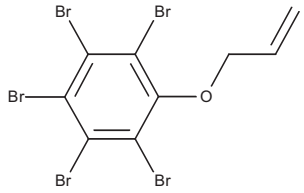
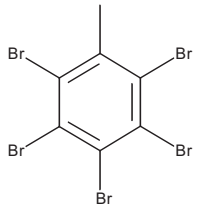
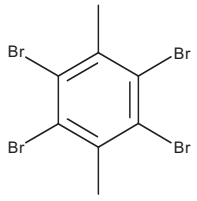
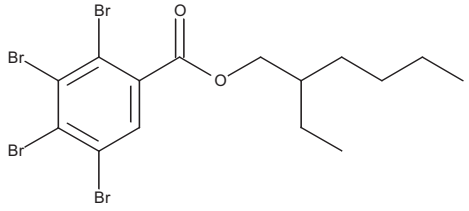
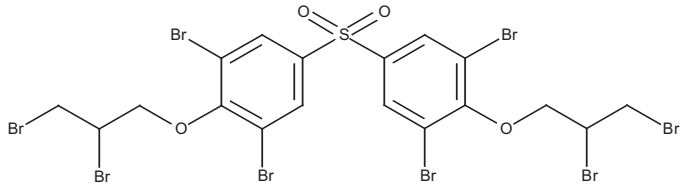
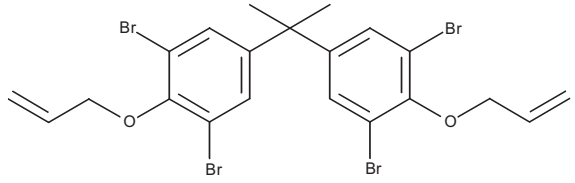
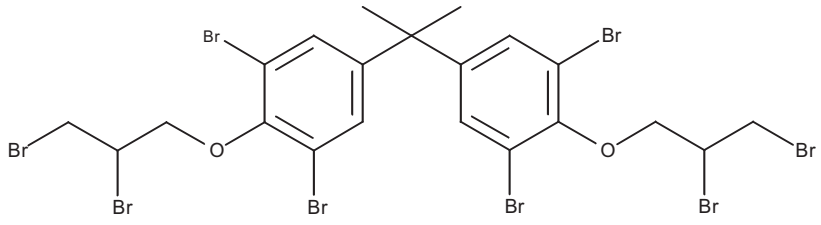
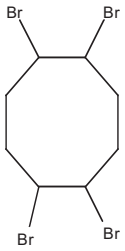
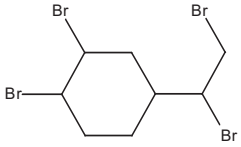
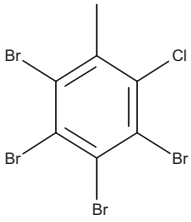
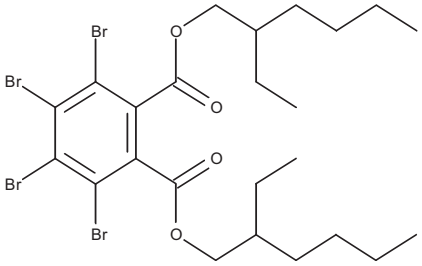
Compound	Name	CAS no.	Structure	MW
PBP	Pentabromophenol	608-71-9		488.6
PBPAE	Pentabromophenyl allyl ether	3555-11-1		528.7
PBTo (PBT)	2,3,4,5,6-Pentabromotoluene	87-83-2		486.6
pTBX	2,3,5,6,-Tetrabromo-p-xylene	23488-38-2		421.8
TBB (EHTeBB)	2-Ethylhexyl-2,3,4,5-tetrabromobenzoate	183658-27-7		549.9
TBBP-DBPE	Tetrabromobisphenol-*S*-bis(2,3-dibromopropyl) ether	42757-55-1		965.6
TBBPA-DAE	Tetrabromobisphenol-A diallyl ether	25327-89-3		624.1
TBBPA-DBPE	Tetrabromobisphenol-A 2,3-dibromopropyl ether	21850-44-2		943.9

Table 1 (*Continued*)

Compound	Name	CAS no.	Structure	MW
TBCO	1,2,5,6-Tetrabromo cyclooctane	3194-57-8		427.8
TBECH	Tetrabromoethylcyclohexane	3322-93-8		427.8
TBoCT	Tetrabromo-o-chlorotoluene	39569-21-6		442.2
TBPH (BEHTBP)	Bis-(2-ethylhexyl) tetrabromophtalate	26040-51-7		706.2

plasma from glaucous gulls was partitioned with potassium hydroxide solution to enable the determination of hydroxylated PBDE (OH-PBDEs). Two phases were obtained: an aqueous phase containing the deprotonated OH-PBDEs and an organic phase containing the non-polar BFRs, including HBB, BTBPE, PBEB, PBTo. BTBPE, DBDPE and TBBPA-DBPE were determined in freeze-dried farmed fish and wild birds, following *Soxhlet* extraction with *n*-hexane/acetone (1:1, v/v) for 48 h [31]. HBB, PBTo, 2,4-DBP, 2,4,6-TBP and PBP were determined in human adipose. Following homogenisation in a hexane/acetone 85:15 (v/v) solution, part of the lipid solution was dissolved in DCM/cyclohexane (1:1, v/v) and cleaned [32].

2.1.2. Extraction of aqueous samples

For NBFRs, the extraction method of choice is Solid-Phase Extraction (SPE), except in one case in which Stir-Bar Sorptive Extraction (SBSE) was used [33]. These authors cited an enhanced extraction efficiency and the robustness and simplicity of the method for the simultaneous determination of a range of acidic and polar organic pollutants, including 2,4,6-TBP and PBP, in various water types from tap water to wastewater. The method involved an extraction time of 4 h for 15 mL samples with pH adjusted to 2 and NaCl added. Analytes were desorbed for 30 min using ethyl acetate as solvent and derivatised using N-(*tert*-butyldimethylsilyl)-N-methyltrifluoroacetamide (MTBSTFA). Mean extraction efficiencies varied in the various matrices, from 79% to 102% for TBP and 76% to 86% for PBP. In a different study, water samples were acidified to pH < 3 and NBFRs were extracted using a preconditioned Empore™ Speed Disk [15]. An ethanol/toluene mixture was used as the elution solvent. The same technique was used by Zhou et al. for the determination of ATE, BTBPE, BATE, PBEB, DPTE, EHTeBB, HBB, HCDBCO, TBPH and OBIND in wastewater [34]. For small brominated phenol NBFRs (4-BP, 2,4-DBP and 2,6-DBP), SDB-XC, a poly(styrenedivinylbenzene) copolymer, was preferred as a reverse phase sorbent for SPE [35]. This sorbent has been shown to provide unique selectivity, especially in the retention of moderately polar, water-soluble analytes. The authors also recommended not filtering water samples prior to extraction so that determination of the more hydrophobic analytes, such as PBTo, would not be affected by removal of suspended particulate material from the samples. Headspace solid phase micro-extraction (SPME) has been used to extract brominated phenol NBFRs (2-BP, 2,4-DBP, 2,6-DBP, 2,4,6-TBP and PBP) from water samples [36]. 10 mL of water was placed in headspace vials of 22 mL, adding potassium hydrogen carbonate and NaCl. Derivatisation was carried out using acetic anhydride as an acetylating agent. The extraction was carried out in the headspace mode at 100 °C. Experiments showed that the best results for PBP were achieved using a polydimethylsiloxane (PDMS) fiber, while, for the other phenols, the best results were obtained using a Carboxen/polydimethylsiloxane (CAR-PDMS) fiber. Amberlite XAD-2 resin was also used for the collection of NBFRs (DBDEP, BTBPE and PBEP, HBB, PBTo) from melted ice cores [37] and

from larger volume water samples [17,20], and then sequentially extracted using methanol and DCM.

2.1.3. Extraction of solid samples

Solid samples, such as sediment, soil and sewage sludge, have been extracted using *Soxhlet* or PLE. PBEB and BTBPE were determined in 20 g soil samples extracted by *Soxhlet* with hexane/acetone (1:1) over a period of 24 h [5]. ATE, BATE, DPTE, OBIND, PBEB, HBB, BTBPE, DBDPE, HCDBCO, TBECH, TBCO, TBB and TBPH were determined in sewage sludge, soils and sediment following extraction overnight with toluene [15]. BTBPE, DBDPE and TBBPA-DBPE were determined in freeze-dried sediment, sewage sludge and soil, following *Soxhlet* extraction with *n*-hexane/acetone (1:1, v/v) for 48 h [31]. BTBPE and DBDPE have also been *Soxhlet* extracted from sediment in a 24 h extraction with the same solvent mixture [38]. This technique was also used for the extraction of HBB and TBECH from soil samples using *n*-hexane/acetone 2:5 [23]. TBB, TBPH, DBDPE and BTBPE were extracted from dried sewage sludge using PLE with DCM [39]. BTBPE and DBDPE were extracted using PLE from freeze dried sediment using a mixture of *n*-hexane/DCM (1:1, v/v) [17]. This technique was also used for the analysis of DBDPE, PBEB and HBB in freeze dried sediment, using the same solvents but with copper and neutral alumina inside the extraction cell for the simultaneous extraction and clean-up of the samples [40].

2.1.4. Extraction of air and dust

As for biota samples, extraction either using *Soxhlet* apparatus or PLE is the most common method used for the analysis of air and dust samples for NBFRs. BTBPE, DBDPE and TBBPA-DBPE were determined in freeze-dried dust following *Soxhlet* extraction with *n*-hexane/acetone (1:1, v/v) for 48 h [31]. HBB, PBEB and PBTo were determined in air following *Soxhlet* extraction of polyurethane foam (PUF) plugs for 20 h using DCM/*n*-hexane (1:1, v/v) [41], while DBDPE was extracted from PUF disks using hot *Soxhlet* extraction with hexane for 8 h [42]. *n*-Hexane/acetone (1:1, v/v) was used in a 24 h *Soxhlet* extraction for BTBPE and PBEB [38] and in a 48 h *Soxhlet* extraction for BTBPE and DBDPE [43] that had been captured in PUF plugs. In a study of indoor environments in Ottawa, Canada, PUF plugs from passive air samplers were also analysed following *Soxhlet* extraction for 21 h using petroleum ether [44]. Dust samples were extracted by repeated shaking with aliquots of DCM/*n*-hexane (1:1, v/v), followed by centrifugation and decanting of the solvent [43]. HCDBCO was detected and quantified in both types of samples [44]. BTBPE, PBT, PBEB, HBB and DBDPE in dust samples from recycling and urban areas were extracted using *Soxhlet* extraction with acetone/hexane (1:1, v/v) for 48 h [45]. DBDPE and BTBPE were also found in dust samples from offices, using for the extraction hot *Soxhlet* with acetone/hexane (1:3, v/v) for 2 h [46]. PLE was used for the analysis of TBECH, TBCO, ATE, BATE, DPTE and OBIND in dust collected in houses and offices from Belgium [47] and DBDPE in electronic waste storage facilities in Thailand [42]. Extraction was carried out using 1.5 g of Florisil® inside the cell and *n*-hexane as the extraction solvent. PLE using DCM was used to extract DBDPE, TBB, TBPH and BTBPE from dust collected in homes from the US [48].

2.2. Clean-up/fractionation

The methods used to clean-up and/or fractionate samples are summarised in detail in SI, Table 1, including quantities of sorbent, solvent elution volumes, etc., where reported.

2.2.1. Clean-up of biota sample extracts

In most cases, the clean-up/fractionation of biota sample extracts is a two stage process. The sample extracts can first be subjected to gel permeation chromatography (GPC), primarily to remove lipids, followed by adsorption chromatography on a variety of columns, containing alumina, silica or Florisil® as an additional clean-up/fractionation step. For the latter, the elution solvent most often used is a mixture of DCM and *n*-hexane. In the analysis undertaken by von der Recke and Vetter [12], purified extracts obtained from previous studies were used. Some of these had been treated with sulphuric acid, followed by clean-up on deactivated silica with *n*-hexane as the elution solvent. Others had simply been cleaned up using silica adsorption chromatography. Lipids were removed from beluga whale blubber samples using GPC followed by chromatography on Florisil®, eluted first with *n*-hexane (containing DBDPE) then DCM/*n*-hexane (15:85%, v/v) [11]. A similar method was used for fish and zooplankton samples [17,18] with a second fraction collected which was eluted with DCM/*n*-hexane (15:85%, v/v) followed by DCM/*n*-hexane (50:50%, v/v) which contained BTBPE. PBEB was split across the two fractions collected [18]. Lipids were removed from human adipose tissue using GPC followed by Florisil®, with elution with hexane followed by DCM/*n*-hexane (20:80%, v/v) to obtain HBB and PBTo [32]. The Florisil® step was omitted for determination of 2,4-DBP, 2,4,6-TBP and PBP, with a derivatisation step using *bis*-(trimethylsilyl)-trifluoroacetamide taking its place [32]. For lipid removal from dolphin, whale, seal and porpoise blubber samples, GPC as well as purification with activated silica gel was used [10,49]. In this case, DCM/*n*-hexane (1:1 and 15:85, v/v) was used as the GPC elution solvent. During silica gel chromatography, HCDBCO, TBP and TBPH were eluted with *n*-hexane followed by DCM/*n*-hexane (1:1, v/v). For the clean-up of herring gull extracts, GPC was employed initially followed by SPE using a silica adsorption extraction cartridge eluted with DCM/*n*-hexane (15:85, v/v) [26,28,29]. Waterbird muscle [25], liver and kidney [24] extracts were cleaned up by GPC followed by silica SPE. Herring gull egg and glaucous gull egg yolk extracts used GPC followed by the use of a silica SPE cartridge [27]. For their plasma samples, these authors [27] employed two different techniques, one for the organic phase containing the non-polar analytes (including all NBFRs studied) and one for the aqueous phase containing the methoxylated analogues of the phenolic compounds (i.e. OH-PBDEs in this case). The organic phase was put through a Florisil® column, while the aqueous phase was cleaned-up using an acidified silica gel column. For the analysis of PBEB, the extracts obtained from bald eagle plasma were cleaned up using an alumina column eluted with hexane and hexane/DCM 4:6 [30]. Extracts of earthworms were cleaned using GPC, Florisil® and acid silica [23]. Kolic et al. used an automated two-column system to clean-up their mussel extracts [15]. This used a pre-packed Teflon silica column followed by a carbon column to fractionate the target compounds. A similar approach (acid silica column followed by carbon column) was used by Zhou et al. [16]. Clean-up of fish sample extracts was achieved using GPC with ethyl acetate/cyclohexane (1:1, v/v) followed by adsorption chromatography on deactivated silica gel with *n*-hexane as the elution solvent [14]. Freeze-dried bird and fish tissue samples were cleaned-up using GPC, followed by a passage of the extract through a silica or a mixed silica/alumina column [19–22,31].

2.2.2. Clean-up of aqueous sample extracts

Extracts obtained from ice core samples were cleaned using a 10% deactivated silica column, using methanol/DCM 1:10 (v/v) for elution [37]. The more complex wastewater sample extracts were subjected to a multi-stage silica clean-up, in a column using layers of silica treated with silver nitrate, sodium hydroxide and sulphuric acid [15,34]. Elution was with *n*-hexane followed by DCM/*n*-hexane (1:1, v/v). The concentrated eluates were then passed through an alumina column, eluted sequentially with *n*-hexane, carbon tetrachloride/*n*-hexane (1:9, v/v) and DCM/methanol (4:1, v/v),

only the final eluate being retained for analysis. Larger volume water samples also require extensive clean-up [17,20]. Law et al. [17] concentrated the methanol and DCM used to elute their SPE cartridges to 100 mL, added 10 mL of NaCl and conducted a liquid:liquid extraction (LLE) using hexane (3 times). This was followed by clean-up using the same Florisil® column used for fish and zooplankton samples. Wu et al. [20] also performed a liquid:liquid extraction of their SPE eluant, followed by clean-up using the multilayer silica/alumina column used for biota clean-up. Phenolic NBFRs require little additional clean-up, with those collected by SBSE [33] and SPME [36] desorbed straight into the injection port of the analytical instrument, while those collected by SPE were eluted with 10 mL ethyl acetate, 10 mL DCM and 10 mL ethyl acetate/DCM – 1:1 (v/v), which was combined and concentrated and passed through an anhydrous sodium sulphate column [35].

2.2.3. Clean-up of solid sample extracts

Similar clean-up schemes to that outlined for wastewaters are also typically applied to extracts of solid samples. The same technique as outlined above was applied in the case of soil, sediment and sludge samples [15], and a similar approach was applied to the extracts of sediments, sewage sludge, and aerial particulates [31]. In the latter case, a layered column of alumina, silica and silica treated with sodium hydroxide or sulphuric acid was eluted, firstly with *n*-hexane then with DCM/*n*-hexane (1:1, v/v). Multi-stage clean-up beginning with GPC has been used to clean-up sediment [17] and soil [23] samples, with Florisil® used as the 2nd clean-up step (same method described for biota above [17]), and acidified silica was used in a 3rd column for soils [23]. La Guardia et al. utilised size exclusion chromatography (SEC) on an Envirosep-ABC column followed by a silica column for sewage sludge samples [39]. Elution was with hexane, hexane/DCM (60:40%) and DCM. Hoh et al. had an acid treatment step followed by silica clean-up (3.5%, w/w water deactivated silica gel) eluted with DCM and alumina fractionation for sediment samples [38]. Fractions were eluted with hexane, 3:2 (v/v) hexane/DCM, and DCM. PBEB was in F1 and BTBPE in both F2 and F3. Others have used a simple silica column eluted with DCM/*n*-hexane (1:1, v/v) [5].

2.2.4. Clean-up of air and dust sample extracts

Extracts of air and dust samples are commonly cleaned-up with a combination of columns, such as alumina, silica and Florisil®. Shi et al. [31] and Wang et al. [45] applied the same scheme as that outlined above for solid and biota samples in the case of air and dust, using a silica/alumina column eluted with *n*-hexane followed by DCM/*n*-hexane (1:1, v/v). Dust extracts were cleaned-up on deactivated alumina using DCM/petroleum ether (1:9, v/v) as elution solvent [41], or using alumina and DCM/*n*-hexane (7:93, v/v) [44]. Harrad et al. used acid silica for the clean-up of dust extracts, using hexane and DCM for the elution of BTBPE and DBDPE [46]. Geens et al. also used Florisil® and modified silica (acid 44% and basic 40%) for the clean-up of dust samples, eluting with hexane and DCM [47]. Stability studies carried out in this work showed problems with degradation of ATE and BATE following the clean-up with acidified silica. Using basic silica, γ-TBECH, δ-TBECH, α-TBCO and DPTE were completely degraded, only β-TBCO, ATE and OBIND being stable. Florisil® was the only sorbent that incurred no degradation for the target compounds. Similarly, Ali et al. [50,51] studied the use of several solid phase sorbents for the clean up of dust samples. They finally selected acid silica (44%) and Florisil® cartridges for this purpose. After the fractionation using activated silica, DBDPE and HCDBCO were collected in hexane while TBB, BTBPE, TBPH and TBBPA-DBPE were eluted using DCM. The hexane fraction was cleaned-up by passage through an acid silica cartridge and the DCM fraction by passage through a Florisil cartridge, eluting in both cases with *n*-hexane and DCM. For the analysis of DBDPE in air and dust samples, extracts were treated with concentrated sulphuric acid and added to a Florisil® column, using hexane for elution [42]. Hoh et al. [38] and Venier and Hites [43] cleaned-up and fractionated air samples on a column containing 3.5% (w/w) water deactivated silica gel, eluted with *n*-hexane and 1:1 (v/v) *n*-hexane/DCM [38] or DCM [43]. Stapleton et al. used two different methods for cleaning-up dust extracts, depending on target analyte [48]. For analysis of BTBPE, SPE eluted with *n*-hexane was used, and for DBDPE, TBB and TBPH, 2.5% deactivated Florisil®, eluted with *n*-hexane/DCM – (50:50, v/v) was used.

2.3. Instrumental analysis

The different techniques of instrumental analysis used for determining NBFRs in environmental samples are summarised in Supporting information, Table 2, and will be discussed in the following section. Halogenated flame retardants have been most commonly analysed using gas chromatography–mass spectrometry (GC–MS) in the electron capture negative ion mode (GC–ECNI-MS) [5,10–14,17,18,20–22,24–28,30,31,34,35,37,39–43,45,47,48,52]. Quantification is usually achieved using the selected ion monitoring (SIM) mode by monitoring the bromide ion isotopes (*m*/*z* 79 and *m*/*z* 81), essentially using the GC–MS as a bromine-selective detector. If the electron ionisation mode is used (GC–EI-MS) instead, quantification is usually based on molecular ions [14]. GC–EI-MS offers greater selectivity and an increased ability to confirm a compound's identity using full scan data [35], however, GC–ECNI-MS offers higher sensitivity for compounds with more than one bromine atom. The exception is for derivatised phenolic NBFRs such as 2,4,6-TBP and PBP [33,36]. Care must be taken using GC, however, as some compounds may be subject to thermal decomposition (such as BDE209, TBBPA-DBPE and DBDPE) or isomeric interconversion (such as TBECH [11,53] and TBCO [54]) during gas-chromatography. Shorter GC columns can be used (10–15 m column length is commonly used for the analysis of BDE209 [27,40]) to reduce the analytes' residence time on a column and so minimise such degradation. However, most NBFRs should exhibit sufficient thermal stability to be analysed using GC–MS [15,26]. An alternative method which can be applied to compounds which are thermolabile is liquid chromatography–mass spectrometry (LC–MS). A number of different ionisation modes have been applied, including electrospray ionisation (ESI) [53,54], atmospheric pressure chemical ionisation (APCI) [34] and atmospheric pressure photoionisation (APPI) [16,26,29]. Enantioselective techniques have also been used for the analysis of chiral compounds such as DPTE. The technique most frequently used has been GC using a chiral stationary phase based on modified cyclodextrins. Due to the high molecular weights of many NBFRs, high elution temperatures are required, reducing the resolving power of the phases [13]. In view of this limitation, liquid chromatographic techniques have also been employed [34,53,54]. Analytical problems are further complicated by the lack of commercially available reference standards [9,14]. Compounds for which reference standards are not available or where only technical mixtures are available can only be semi-quantified using response factors derived for structurally similar compounds; although in some cases, even these cannot be obtained [6].

2.3.1. Gas chromatography–mass spectrometry

Specific examples of the application of GC–MS to NBFR analysis are presented below, along with discussion of some of the issues and challenges.

2.3.1.1. Gas chromatography. GC columns with low-polarity phases were systematically used to separate various NBFRs, except for a couple of studies that reported the use of mid-polarity columns

[24,36]. Almost all the shorter columns (10–15 m) had stationary phases predominantly composed of 5% phenyl/95% dimethyl polysiloxane or equivalent (i.e. DB5-MS from J&W), in most cases with a 0.10 μm film thickness. This particular combination of column length and stationary phase allows relatively short column residency times for the analytes of interest while affording a small degree of retention (compared to less polar stationary phases). This is a particularly attractive characteristic for NBFRs that have relatively high molecular weight/high boiling points (e.g. DBDPE, BTBPE, HBB, PBEB, etc.) or for those compounds that are prone to on-column thermal decomposition or isomer interconversion. Compounds separated using this combination included BTBPE [15,17,20,21,26,28,31,45,48,49,51], DBDPE [15,17,19,20,25,26,31,40,42,45,48,51], PBEB [15,18,26,28,40,49], HBB [15,23,26,28,40,49], TBECH diastereoisomers [15,23,26,45,53], TBCO diastereoisomers [15,26,45,53], PBTo [26–28,49], and to a lesser extend OBIND [15,26,45], ATE [15,26,44], TBB [15,48,51], TBBPA-DBDPE [26,31,51], BATE [15,45], DPTE [15,45], TBPH [48,51], HCDBCO [15,51], BEHTBP [15], TBBP-DBPE [26], PBBB [26], PBPAE [26], PBBA [26] and pTBX [26]. However, coelution of TBB with BDE 99 has been described using this type of column [48]. Only another two types of stationary phases were used with short columns in all of the literature reviewed. A 15 m Rtx-1614 column (proprietary stationary phase by Restek) was used by Venier and Hites [43] to determine BTBPE and DBDPE and by Venier et al. [30] to analyse a range of BFRs including PBEB, HBB, BTBPE and DBDPE (in addition to PBDEs and Dechlorane Plus). Zhang et al. used a short (12.5 m) mid-polarity CP-Sil 13CB column to successfully analyse BTBPE (and Dechlorane Plus) [24].

Longer columns (from 25 m up to 60 m) were used to achieve better analyte separation, often when other brominated compounds such as PBDEs were simultaneously analysed or for confirmation purposes. Again, the vast majority of columns used had a low-polarity stationary phase composed of either 5% phenyl/95% dimethyl polysiloxane (or the equivalent DB5-MS from J&W) or the proprietary DB-XLB phase from J&W. Vetter and Rosenfelder managed to analyse a total of 118 brominated chemicals, including BFRs and NBFRs such as 2,4-DBP, 2,6-DBP, 2,4,6-TBP, ATE, BATE, DPTE, BTBPE and HBB using a 30 m HP-5MS column [14]. Possible co-elutions were reported and while DPTE eluted just prior to BDE75, ATE co-eluted with BDE10 [14]. A few studies used a nonpolar, 100% dimethylpolysiloxane column successfully to analyse TBB, TBPH, DBDPE, and BTBPE (along with PBDEs including BDE209, DP and HBCD) [37], HCDBCO [44] and HBB, PBTo, 2,4-DBP, 2,4,6-TBP and PBP [32]. Geens et al. used a mid-polarity 30 m HT-8 column to analyse a suite of NBFRs (TBECH diastereoisomers, TBCO diastereoisomers, ATE, BATE, DPTE and OBIND), but OBIND could not be eluted [47].

Phenolic NBFRs tend to be analysed following derivatisation, which means separate GC methods are often required to those used for other NBFRs. When applying a newly developed methodology involving extraction of water samples using SBSE, analysis of a range of compounds (including PBP) was conducted using large volume injection with in port derivatisation and separation using a 60 m DB-XLB column [33]. A 30 m HP-1 column was used for the analysis of HBB, PBTo, 2,4-DBP, 2,4,6-TBP and PBP [32], the phenolic NBFRs being first silylated with *bis*-(trimethylsilyl)-trifluoroacetamide (BSTFA). Phenolic NBFRs were also analysed using a 25 m CPSil8 column following derivatisation with acetic anhydride [36]. A method for the simultaneous determination of underivatised phenolic BFRs as well as their by-products, formulation intermediates and decomposition products used a 60 m CPSil8-CB column [35].

Tomy et al. [11] developed a GC–MS method for the detection of TBECH diastereoisomers. Although baseline separation of the two dominant isomers was achieved using short GC columns, co-elution of the β-isomer with BDE19 was observed. Using longer columns in order to improve resolution resulted in thermal interconversion of the α- and β-isomers, due to the longer residence time on the column [11]. Separation of the γ- and δ-isomers was not possible in either case. A combination of a short 10 m DB-5 GC column and EI-MS allowed selective monitoring of the β-TBECH isomer. Arsenault et al. successfully separated all four TBECH diastereoisomers with a 15 m DB-5HT column [53]. They investigated a range of injection temperatures, and observed that the interconversion of α- and β-TBECH to γ- and δ-TBECH occurred at temperatures above 120 °C [53]. Riddell et al. [54] studied the analysis of the two TBCO diastereoisomers, and concluded that it is possible to separate them if due attention is given to the column length (15 m) and injector temperature, otherwise thermal interconversion takes place both in the injector (<200 °C) and on column. Geens et al. compared three columns (a 15 m DB-5 column, a 25 m HT-8 column and a 30 m DB-5 column) to analyse a suite of NBFRs including ATE, BATE, DPTE, OBIND and diastereoisomers of TBECH and TBCO [47]. Only the 15 m column was able to separate all of the diastereoisomers [47] and this was attributed to the thinner film thickness of the 15 m column (i.e. 0.10 μm) compared to the 25 m and 30 m columns (0.25 μm).

2.3.1.2. MS detection. ECNI-MS was the detection mode the most applied across the literature reviewed and used for the determination of BTBPE [5,12,17–20,26–28,30,31,37–39,43,45,48,49,51], DBDPE [17,19–21,24–26,30,31,37,39,40,42,43,45,48,51], PBEB [5,18,24,27,28,30,37,38,40,41,49] HBB [12,26–28,30,40,41,49], TBPH [10,39,48,51], PBT [24,27,28,41,49], TBB [39,48,51], HCDBCO [10,44,51], TBBPA-DBDPE [31,51], ATE [12,47] BATE [12,47], DPTE [12,47], TBECH [26,47], TBCO [47], OBIND [47] and TBB [10]. Although bromide ions (*m*/*z* 79, 81) were almost always monitored in GC–ECNI-MS, in rare cases ions other then *m*/*z* 79, 81 were monitored. For example, TBPH was determined using *m*/*z* 463, 461 [39] and *m*/*z* 463, 515 [48]. Also, in one study, TBB co-eluted with BDE99 and the use of fragment ions (*m*/*z* 357,471) was necessary to improve selectivity [48].

Interestingly, Rosenfelder and Vetter chose N_2 as the ion source reaction gas for ECNI in preference to the traditional CH_4 which had been used in all other studies [52]. They observed that the use of CH_4 results in varying response for different polybrominated compounds (even isomers) caused by the carbonisation of the filament and ion source. The use of NH_3, an alternative reaction gas, resulted in varying peak responses like for CH_4 and changing mass spectra between injections due to the difficulty of maintaining a constant pressure in the ion source. Additionally, NH_3 is corrosive and therefore necessitates the use of special tubing and pressure regulator, and also causes corrosion of the standard gas valves and connection, thus posing a safety risk. N_2 has a similar proton affinity to CH_4 and supports the fragmentation of molecules. Its use was also found to reduce instrument maintenance and to give higher and more uniform responses for many polybrominated compounds (though not TBP and DPTE).

Both ECNI-MS and EI-MS were investigated as possible ionisation modes for the detection of TBECH diastereoisomers by Tomy et al. [11]. The authors observed that using ECNI-MS, there is a likelihood that too few or no diagnostic ions (other than the bromine ion isotopes) will be present to allow discrimination between co-eluting brominated compounds, so peak resolution is essential. Low-resolution and high-resolution EI-MS detection were also evaluated and data comparison showed that values acquired using low resolution-MS were slightly overestimated, indicating an interference at the nominal mass.

Detectors in EI-MS mode were often used for confirmation [19,20,27,28], with $[M]^+$ and $[M–C_6H_2Br_3O]^+$ monitored for BTBPE, $[M]^+$ and $[M/2]^+$ monitored for DBDPE, $[M]^+$ and $[M–Br]^+$ for HBB and PBTo, $[M]^+$ and $[M–CH_3]^+$ for PBEB [19,20]. The identification of

HCDBCO was confirmed in dust samples using GC–EI-MS by comparison of its mass spectrum with that of a synthesised standard [44] and TBBPA-DBPE was confirmed using GC–EI-MS [31]. Nyholm et al. used GC–EI-MS to quantify TBECH and HBB, the ions monitored being respectively *m*/*z* 264.9, 266.9 and *m*/*z* 547.5, 549.5 [23]. The detection of a wide range of NBFRs including ATE, TBCO, TBB, BATE, PBEB, DPTE, HBB, HCDBCO, DP, TBECH, BTBPE, BEHTBP, OBIND and DBDPE was described by Kolic et al. [15] with all analyses conducted using gas chromatography–high resolution mass spectrometry (GC–HR-EI-MS).

Phenolic NBFRs tend to be analysed by GC–EI-MS following derivatisation, which means separate methods are often required to those used for other NBFRs. When applying a newly developed methodology involving extraction of water samples using SBSE, analysis of a range of compounds (including PBP) was conducted using GC–EI-MS [33]. Derivatisation was accomplished using the silylation reagent MTBSTFA. The derivatives yield very characteristic EI mass spectra, dominated by ions produced by the loss of the *tert*-butyl moiety $[M-57]^+$. EI-MS was used for the analysis of HBB, PBT, 2,4-DBP, 2,4,6-TBP and PBP [32]. The phenolic NBFRs were first silylated with BSTFA and the $[M-CH_3]^+$ ions were monitored. For HBB and PBT, the $[M+4]^+$ and $[M+6]^+$ ions were used for quantification [32]. Phenolic NBFRs were also analysed in EI-MS mode following derivatisation with acetic anhydride [36]. Ions monitored were 2-BP: *m*/*z* 172, 174, 2,4-DBP: *m*/*z* 250, 252, 254, 2,6-DBP: *m*/*z* 250, 252, 254, 2,4,6-TBP: *m*/*z* 328, 330, 332, 334, PBP: *m*/*z* 486, 488, 490, and TBBPA: *m*/*z* 527, 529, 530. A method for the simultaneous determination of underivatised phenolic BFRs as well as their by-products, formulation intermediates and decomposition products in water, used GC–ECNI-MS, as it was more sensitive than GC–EI-MS [35].

2.3.2. Liquid chromatography–mass spectrometry

Zhou et al. [16] developed a comprehensive, sensitive and high throughput LC–APPI-MS method using tandem mass spectrometry mode (MS/MS) for the analysis of 36 halogenated flame retardants (HFRs) in fish. This was optimised for a number of parameters, including the type of column, temperature and flow rate of operation, dopant, and the operating parameters of the APPI ion source. An Ultra II C18 column operated at 25 °C at a flow rate of 400 μL/min gave the best separation of the compounds determined. In a comparison of acetone with toluene as the dopant reagent, toluene provided around 10% higher ion intensity for those HFRs that were less hydrophobic, and acetone offered about 10% stronger signal for those analytes that were more hydrophobic. When tested using fish samples, the method proved to have excellent limits of detection, even for high molecular weight compounds (unlike GC–HR-EI-MS) [16]. LC–MS/MS using an APCI source was also investigated for the analysis of 38 halogenated flame retardants in wastewater [34]. For the LC separation, the authors evaluated several different columns, column temperatures and mobile phase compositions. For the APCI ion source, the temperature, the composition of the LC eluent and the addition of a 10 mM ammonium acetate buffer to the mobile phase was studied. For the MS/MS detection, a relatively high collision energy was found to be required in order to produce bromide product ions, and the authors suggested that increasing the collision gas pressure may assist the generation of more of these ions. The method proved to be rapid and highly sensitive, and applicable to compounds with a wide range of physical and chemical properties and of varying polarity. Its advantages over the LC–APPI-MS/MS method was its simplicity, and the fact that APCI is available in more laboratories than APPI. Also, it does not require a dopant or UV lamps that have a finite lifetime. For BDEs, it yielded similar results to those obtained using GC–HR-EI-MS. Letcher and Chu [29] solved the problem of the dopant using the same solvent as LC mobile phase and dopant. The method developed for the analysis of TBBPA-S-DBPE, TBBPA-AE and TBBPA-DBPE used LC-APPI(−)-MS/MS with acetone as mobile phase, showing an improvement in the sensitivity compared with classical solvents, such as methanol. However, LC does not seem to be an ideal alternative for the analysis of TBCOs, due to a poor resolution of both α and β isomers and the failure of ESI, APCI and APPI ionisation to produce the molecular ion with sufficient intensity for identification [54]. Similarly, for the TBECHs, the use of ESI and APCI produced no or very weak molecular ion adducts, and the use of a BEH C_{18} column did not allow the separation of α/β isomers and gave an extremely low signal compared with that for γ/δ isomers [53].

2.3.3. Enantioselective techniques

Von der Recke and Vetter [12] identified an unknown pentabrominated compound from hooded seal blubber using GC–ECNI-MS and GC–EI-MS to compare its spectra with those of synthesised DPTE. The column used was a 30 m Factor Four VF5-MS column (of similar polarity to DB-5). The latter compound was confirmed by its enantioseparation using gas chromatography with an electron capture detector (GC–ECD) (25 m column coated with permethyl-β-cyclodextrin covalently bonded to dimethyl polysiloxane (β-PMCD, Chirasil-Dex)). Other compounds studied included ATE and BATE. The enantioselective separation of DPTE was achieved using three different techniques [13]: normal-phase LC (NP-LC), GC–ECD and GC–ECNI-MS. The two enantiomers were resolved within 30 minutes using NP-LC with a mobile phase of *n*-hexane/2-propanol (9:1, v/v) as well as one of decreased polarity *n*-hexane/2-propanol (98:2, v/v). Finally, GC–ECNI-MS with a 25 m Chirasil-Dex CB column was used to analyse marine mammal brain and blubber samples. The authors also explored the possibility of using a different column consisting of β-PMCD dissolved in polysiloxane, but concluded that the DPTE enantiomers could be only partially resolved even at the cost of a very long elution time.

2.3.4. Instrument limits of detection (iLODs) and limits of quantitation (iLOQs)

Quantitative details about instrumental performance for the analysis of NBFRs are rarely reported in the literature. From the works reviewed, only five give instrumental limits of quantification [40] or detection [16,29,34,44]. These iLOD values have been converted to iLOQs for discussion below. To obtain further data concerning instrumental sensitivity, additional iLOQs have been calculated, where possible, from method LOQs when sufficient information was given in the papers to do so [26–28,33,35]. Most works use GC-ECNI-MS for the analysis of NBFRs. Some of the lowest iLOQs found were those reported by Guerra et al. [40] for PBEB: 5.6 pg, HBB: 5.4 pg and DBDPE: 39 pg. These iLOQs were similar to that found for PBTo: 3 pg by Gauthier et al. [28], although their iLOQs for BTBPE, PBEB and HBB were higher: around 30 pg. The same compounds were analysed by Verrault et al. [27], who found similar iLOQs for PBEB: 20–30 pg, HBB: 60–90 pg and PBTo: 20–40 pg, while for BTBPE, iLOQs were one order of magnitude higher: 200–270 pg. Generally, iLOQs from 150 to 300 pg were found for BTBPE, PBEB, PBBB, ATE, PBT, HBB, PBBA, pTBX, OBIND, α-TBCO, β-TBCO, α-TBECH, β-TBECH, γ-TBECH, δ-TBECH, TBBPA-DBPE, while that for DBDPE was 900 pg [26]. Of the same order was the iLOQ reported for HCDBCO: 228 pg [44] and also those for 2,4-DBP, 2,6-DBP and PBTo: 333 pg [35]. Quitana et al. [33] found iLOQs for 2.4-DP: 550 pg and 2,6-DP: 650 pg using GC-EI-MS. These results suggest that the use of chemical ionisation would be slightly better than electronic ionisation for the analysis of these phenolic compounds. Some authors use LC for the analysis of NBFRs. Zhou et al. [16,34] obtained the same iLOQs using APPI-MS/MS and APCI-MS/MS for ATE: 13.3 pg, HBB: 1.7 pg, BEHTBP: 1.7 pg and DBDPE: 13.3 pg. For other NBFRs, the iLOQs obtained using APPI

were around half of those obtained using APCI: BTBPE: 1.7 vs. 13.3 pg, BATE: 6.7 vs. 13.3 pg, PBEB: 6.7 vs. 13.3 pg, DPTE: 66.7 vs. 133 pg, EHTeBB: 3.3 vs. 6.7, OBIND: 3.3 vs. 13.3 pg, with the exception of HCDBCO: 66.7 vs. 33 pg. These iLOQs are similar to, or sometimes even lower than, the ones found by Guerra et al., and much lower than the ones from other studies conducted using GC–MS. Letcher and Chu [29] used LC–APPI-MS/MS also for the analysis of TBBPA-DBPE, TBBPA-AE and TBBPA-DBPE. In this case, iLOQs were 40 pg, 107 pg and 406 pg for TBBPA-AE, TBBPA-DBPE and TBBPS-DBPE, respectively.

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

An important part of reporting of any study should be the documentation of method quality and performance characteristics. There are a number of studies on NBFRs that have reported extensive QA/QC and method validation, although for many others such important information is lacking. Several studies used retrospective analysis of existing extracts [14,20,44] and therefore the extraction and clean-up methods used were not optimised for NBFRs. Some authors reported recoveries for certain parts of their method, but not whole method recoveries, e.g. [47]. Recoveries from acid silica columns were reported, but not for the overall method. A few authors have reported that recoveries of the NBFRs in their studies were similar to those of PBDEs, e.g. [26] and this has been used as justification by others to report NBFR concentrations without any method recovery information, giving instead the recoveries of PBDEs, PCBs or PCDEs [5,15,17,18,21,22,25,27,28,30,34,37–39,41–44]. Some authors did not report any QA data at all [12]. Of these authors, only a few correctly assert that their method is only semi-quantitative due to the lack of method recovery and validation data [34] or report their results on a qualitative basis [16,52]. For this reason there remain doubts about the accuracy of some of the data produced to date on levels of NBFRs in the environment.

2.4.1. Method recoveries

2.4.1.1. Biota samples. Recoveries of spiked HCDBCO, TBB, and TBPH in blubber using *Soxhlet* extraction followed by GPC and silica clean-up extraction ranged from 70% to 120%, and the resulting relative standard deviations (RSDs) ranged from 10% to 15% [10]. Average recoveries of TBECH from spiked blanks at 3 different levels in a blubber method, extracted by *Soxhlet* and cleaned-up with GPC and Florisil®, ranged from 69% to 92% for α-TBECH and from 59% to 98% for β-TBECH [11]. The average recoveries of HBB, BTBPE, PBT, PBEB and DBDPE in spiked biota samples that were *Soxhlet* extracted and cleaned-up using GPC and a multilayer silica/alumina column were 99 ± 3% (n = 5), 103 ± 1% (n = 5), 94 ± 2% (n = 5), 94 ± 3% (n = 5), 101 ± 8% (n = 5), respectively [20]. The RSD for DBDPE among triplicate rat tissue samples that were *Soxhlet* extracted and cleaned-up using GPC and SPE were on average 3–10% for all target compounds [22]. Recovery of BDE77, BDE181, $^{13}C_{12}$-CB141 and $^{13}C_{12}$-BDE209 standards, but not DBDPE, were reported and averaged from 66% to 102% in all the samples. Method validation data for TBECH and HBB in earthworm tissues were not presented, but the average recovery of ^{13}C-HBB during sample analysis was 82%, following solvent extraction and clean-up with GPC, Florisil® and acid silica [23]. This was a rare example of the use of mass-labelled NBFRs and reflects the lack of available standards. The average recovery of phenolic NBFRs from spiked adipose tissue that was solvent extracted and cleaned-up using GPC was 76% (n = 4) for 2,4-DBP and 88% (n = 3) for PBP, with RSDs <20% [32]. In a method for the analysis of bird tissues that were *Soxhlet* extracted and cleaned-up using GPC and SPE, the average recoveries from spiked blanks (n = 5) for PBEB, PBT and BTBPE were 95%, 94% and 103%, respectively; and the RSD for all target compounds were below 5%. The RSD of duplicates (n = 3) were less than 15% for all contaminants [24]. Recoveries of NBFRs from spiked herring gull eggs (n = 4) that were *Soxhlet* extracted and cleaned-up using GPC and SPE were reported as similar to BDE30 for which an average value of 90% was given, but without specific details shown [26]. The average recoveries from spiked chicken eggs (n = 5) that were extracted using PLE and cleaned-up using GPC and SPE for TBBPS-DBPE, TBBPA-AE and TBBPA-DBPE were 89%, 55% and 63%, respectively [29]. Shi et al. analysed a spiked blank with every batch of 10 bird and fish samples that were *Soxhlet* extracted and cleaned-up with GPC and a multilayer silica/alumina column, with recoveries of TBBPA-DBPE and DBDPE, between 88% and 106% and 72% and 89%, respectively [31].

2.4.1.2. Aqueous samples. Several studies on phenolic NBFRs in water have presented comprehensive method performance data (including limits of detection (LODs), trueness, repeatability) for the suite of compounds [33,35,36]. Extraction efficiencies for 2,4-DBP, 2,6-DBP, 2,4,6-TBP and PBP using SBSE were 41%, 72%, 93% and 88%, respectively. Accuracy of the method in 5 different water sample types was also reported [33]. Recoveries from spiked influent and effluent samples of 2-BP, 2,4-DBP, 2,6-DBP, 2,4,6-TBP, PBP using headspace SPME were between 96% and 113%, but for TBBPA this was only 13%. RSD (n = 3) was <10% for all apart from PBP which was ~20% [36].

2.4.1.3. Solid samples. Duplicate sample analysis of sewage sludge, following extraction by PLE and clean-up with SEC and a silica column, had relative percent differences of 28%, 4%, 37% and 25% for TBB, TBPH, BTBPE and DBDPE, respectively [39]. Recoveries were not reported. Recoveries from spiked sediments (n = 5) using PLE with in-cell clean-up using copper and alumina of 58%, 62% and 102% were found for PBEB, HBB and DBDPE, respectively, with RSDs of 3%, 5% and 6%, respectively [40]. Duplicate sample analysis of soil had RSDs ranging from 5% to 33% for BFRs including BTBPE, after *Soxhlet* extraction and silica column clean-up, but recoveries were only given for PBDEs [5].

2.4.1.4. Air and dust samples. Wang et al. looked at a range of BFRs in dust samples including PBDEs, PBBs, BTBPE, PBTo, PBEB, HBB and DBDPE [45]. Recoveries from spiked blanks that were *Soxhlet* extracted and cleaned-up using a multilayer silica/alumina column (n = 3) ranged from 65% to 114% for all BFRs, but details for individual chemicals were not reported. Stapleton et al. reported average recoveries from spiked blanks for TBB, TBPH, BTBPE, and DBDPE to be 103%, 46%, 93% and 94%, respectively for their dust analysis method using PLE and Florisil column clean-up [48].

2.4.1.5. Recovery correction. Although recoveries have been determined in some studies, final concentrations are rarely corrected, even when they are significantly different to 100% recovery. Exceptions were the works of Smeds and Saukko [32] and Ali et al. [51], who reported final concentrations corrected using the average recovery percentages. In a few others studies, sample concentrations were corrected based on the recoveries of the non-NBFR surrogate standards, e.g. [27,39,42].

2.4.2. Reference materials

Certified reference materials with either certified and/or indicative mass fractions for NBFRs are scarce as their demand is low due to the 'emerging' status of NBFRs, and more CRMs are needed for both method validation and quality control purposes. However, a few authors have reported the presence of NBFRs in some available reference materials. Stapleton et al. analysed NIST dust SRM 2585 and found TBPH at 145 ng/g. BTBPE and DBDPE were reported to be

below 0.8 ng/g and 10 ng/g, respectively and could not be quantified [48]. The lack of certified materials or even consensus values makes it difficult to compare methods and studies.

2.4.3. Method blanks

Typically authors report that NBFRs are absent in method blanks, although there were some exceptions. Law et al. found BTBPE with a mean concentration of 3 pg/g in biota blanks and of 0.4 pg/L in water blanks, whereas DBDPE was below LOQs [17]. In contrast, BTBPE was not found in biota blanks by Ismail et al., but PBEB was [18]. Wu et al. found traces of HBB and PBEB (but no BTBPE, DBDPE and PBT) in the procedural blanks when analysing biota samples, but the levels were less than 1% of the mass in the samples [20]. Smeds and Saukko reported finding most of the phenolic NBFRs in the blanks from their adipose tissue method, in amounts ranging from 0.6 to 5.9 ng [32]. In a water sample analysis method, 2,4,6-TBP and PBP were also detected in method blanks [33]. Hermanson et al. reported finding NBFRs in ice cores in layers which predated their production, and these were at levels close to those found in more recent layers [37]. These cores may have been contaminated during sample handling, rather than during sample analysis. Zhu et al. found HCDBCO in lab and field blank samples when analysing dust samples. The average blank level of HCDBCO was 48 pg/g for a 1 g dust sample [44]. Stapleton et al. also found NBFRs in blanks when analysing dust samples. TBB was detected in field/laboratory blanks (average 1150 pg). Minor levels of TBPH and BTBPE (60 and 440 pg, respectively) were also detected in field and laboratory blanks. DBDPE was below detection limits in all the blank samples [48]. Other articles have reported the presence of NBFRs in blanks below limits of detection. These findings suggest that the pattern of use of NBFRs is quite varied and is not dominated by one or two chemicals.

2.4.4. Method limits of detection (LODs) or quantification (LOQs)

The presence of NBFRs in blanks is reflected by higher method limits of detection (LODs) or quantification (LOQs). More studies report method detection limits or limits of quantitation than method validation data. The majority of studies utilised GC–ECNI-MS for quantification as this is usually the most sensitive technique.

2.4.4.1. Biota samples. For biota samples, LODs/LOQs are in the sub ng/g range, although authors normalise to different parameters depending on the sample matrix. LODs for HCDBCO, TBB and TBPH in blubber were 40 pg/g of lipid (lw) [10]. LOQs for BTBPE, PBEB, HBB and PBTo for winter flounder, seals and right whales were 810, 20 and 110 pg/g lw, respectively [49]. LODs for β-TBECH in blubber were determined to be 0.8 pg/g wet weight (ww) by HR-MS and 4 pg/g ww by LR-MS in EI mode [11]. LOQs in fish using an LC–APPI-MS method were: ATE: 37, BTBPE: 11, BATE: 320, PBEB: 18, DPTE: 110, EHTeBB: 6.1, HBB: 4.5, HCDBCO: 390, BEHTBP: 42, OBIND: 8.8, DBDPE: 20 pg/g ww [16]. These values are equivalent to those obtained by GC methods. LODs in fish and zooplankton for BTBPE and DBDPE were 50 pg/g [17]. LODs for BTBPE and PBEB in fish homogenate were 5 and 210 pg/g ww, respectively [18]. LOQs in a range of biota were 580, 530, 980, 2490 and 380 pg/g lw for PBT, PBEB, HBB, BTBPE and DBDPE, respectively [20]. In another study, LODs for HBB, PBT, PBEB and BTBPE in biota ranged from 10 to 50 ng/g lw [21]. LODs for BTBPE, TBBPA-DBPE and DBDPE in bird and fish tissue were 8–16, 1500 and 2500 pg/g dry wt (dw), respectively, or 12–24, 2300 and 3800 pg/g lw, respectively [31]. LOQs for PBEB, PBT and BTBPE in bird tissues were 120, 170 and 600 pg/g, respectively [24]. LOQs for NBFRs in gull eggs were between 50 and 100 pg/g ww, excluding DBDPE for which the LOQ was about 300 pg/g ww [26]. LOQs for HBB, BTBPE, PBEB and PBTo were 60, 200, 30 and 40 pg/g ww respectively in bird plasma and 90, 270, 20 and 20 pg/g ww respectively in egg yolk [27]. Also in gull eggs, LOQ was 10 pg/g ww for PBEB, BTBPE, HBB, PBBA, PBBB and DBDPE and 1 pg/g ww for PBTo [28], and for TBBPS-DBPE, TBBPA-AE and TBBPA-DBPE (by LC–APPI-MS/MS) were 4270, 80 and 250 ng/g ww, respectively [29]. Typical LODs in rat tissues ranged from 6.2 to 1043 pg/g lw for DBDPE, depending on the sample size [22]. The LODs in human adipose using GC–EI-MS for 2,4-DP and 2,4,6-TBP was 500 pg/g, and for PBP was 2000 pg/g. No method performance statistics were reported for HBB and PBTo as they could not be detected in samples [32].

2.4.4.2. Aqueous samples. For water analysis, LODs/LOQs are in the ng/L range, although one study using large volume (~100 L) water samples concentrated on XAD columns had LODs of 1 and 15 pg/L for BTBPE and DBDPE, respectively [17]. In contrast, LODs in small volume (0.015 L) samples extracted using SBSE followed by thermal desorption were 11,000, 13,000, 22,000 and 106,000 pg/L for 2,4-DBP, 2,6-DBP, 2,4,6-TBP and PBP, respectively [33]. LODs for 10 mL samples using SPME and thermal desorption were better, with values of 2100, 2200, 2000, 1300, 46,000 and 12,000 pg/L, for 2-BP, 2,4-DBP, 2,6-DBP, 2,4,6-TBP, PBP and TBBPA, respectively [36]. Both these methods used GC–EI-MS [33,36]. LOQs for 0.8 L wastewater samples extracted by SPE with multi-stage clean-up and analysis by LC–APPI-MS/MS were 2200, 3300, 600, 600, 3400, 1400, 400, 2600, 300, 3200, 1700 and 1300 pg/L for ATE, BTBPE, BATE, PBEB, DPTE, HBB, EHTeBB, HCDBCO, BEHTBP, OBIND, 4PC-BDE208 and DBDPE, respectively [34]. Another SPE method with 0.5 L water samples had better LODs for 2,4-DBP and 2,6-DBP of 100 pg/L [35]. In this study, samples were analysed in both EI and ECNI modes and the latter method was 3–5 times more sensitive.

2.4.4.3. Solid samples. For analysis of soil and sediment, LODs/LOQs are in the 100 s of pg/g range. LODs in sediment for BTBPE and DBDPE were 100 pg/g [17] and for PBEB and BTBPE in soil were 90 pg/g and 340 pg/g respectively [5]. LOQs in sediment were 60, 30 and 288 pg/g for PBEB, HBB and DBDPE, respectively [40], and in another study was 200 pg/g for BTBPE [38].

2.4.4.4. Air and dust samples. For dust samples, sample size is generally smaller (<1 g), which has a predictable effect on detection limits, which are not as low. LODs for BTBPE, PBTo, PBEB, HBB, DBDPE and PBDEs ranged from 200 to 4000 pg/g of dust [45] with individual values not reported, and for HCDBCO the LOD was 240 pg/g of dust [44]. LOQs were 20,000 pg/g dust for TBECH and TBCO isomers, 25,000 pg/g for ATE, BATE, DPTE and 40,000 pg/g for OBIND [47], 40,000 pg/g of dust for DBDPE [42], 5000 pg/g dust for DBDPE and BTBPE [46] and in another study were 500 pg/g dust for BTBPE, 2000 pg/g dust for TBB and TBPH and 20,000 pg/g dust for DBDPE and TBBPA-DBPE [51]. For air samples LODs varied between 0.005 and 0.01 pg/m^3 for PBEB, HBB and PBTo [41], and LOQs for PBEB and BTBPE were 20 and 40 pg, respectively [38].

3. Conclusions

This review has focused on the various methods currently available for the extraction, clean-up and instrumental analysis of different environmental samples that might contain NBFRs, such as marine biota, sediments, sludge, soil, air and dust. The environmental presence of these novel compounds, which are gradually replacing classic BFRs such as the PBDEs, is becoming more and more evident. Currently, the information available on the sources, temporal and spatial distribution and ultimate fate of the compounds in the environment is limited. As a result, conducting future risk assessments and determining the exposure of both humans and organisms to these chemicals is a complicated procedure which

would benefit from the development of accurate and comprehensive methods of analysis.

So far, the methods in use have generally not been targeted specifically at NBFRs, but were developed for the determination of classical BFRs, such as PBDEs and HBCD. Mainly, they involve the detection and analysis of a limited number of NBFR compounds using GC–ECNI-MS. This technique is associated with several problems such as thermal decomposition and isomerization of some of the compounds of interest, lack of standards and certified reference materials, and co-elution of relevant pairs of organobromine compounds. As a result, in most cases, structural confirmation of the compounds in question needs to be achieved using GC-HREIMS, a technique that is not widely available in all labs. An alternative and quite comprehensive method of analysis of novel BFRs involves the use of LC–MS/MS, although the APPI technology used by Zhou et al. [16] is again not widely available.

Covaci et al. [4] in their recent review selected the most important NBFRs as BTBPE, TBPH, DBDPE, HBB, PBTo, PBEB, TBBPA-DAE, TBBPA-DBPE, 2,4,6-TBP, ATE, ethylene *bis*(tetrabromophthalimide) (EBTPI), tetrabromophthalic anhydride (TPA) and 2,4,6-*tris*(2,4,6-tribromo-phenoxy)-1,3,5-triazine (TBTP). This selection of compounds was based on criteria such as commercial production and use, occurrence in the environment, persistence, bioavailability and toxicity (where such information is available) of these NBFRs. No information was available on methods for the analysis of the latter three chemicals. For the other chemicals, methods have more frequently been reported, but not always with sufficient detail to allow an assessment of their effectiveness.

4. Recommendations

(a) There is considerable variability in the methods used for the determination of NBFRs. In order to assess the comparability of these methods, there is an urgent need for interlaboratory comparison exercises to be carried out.
(b) More certified reference materials and labelled-standards are required to confirm and improve the accuracy of analytical methods. The materials analysed in an interlaboratory comparison exercise could be the first reference materials produced.
(c) Data have frequently been published without sufficient evidence that the method used was fit for purpose, and peer reviewing of future papers where NBFRs are analysed needs to put more emphasis on demonstrating that this important aspect of any study has been considered, and suitable validation carried out.
(d) Investigation should be carried out into the source of contamination in blanks. Once knowledge of where NBFRs are being used within the lab environments is attained, it will be easier to prevent their interaction with samples.
(e) Results observed from studies show the importance of choosing an appropriate method for the clean-up of the samples. Some compounds seem to be sensitive to degradation, as is the case of ATE, BATE and TBPH to acids and γ-TBECH, δ-TBECH, α-TBCO and DPTE to bases. DBDPE, TBB and TBPH have been found to be susceptible of photodegradation and measures must be taken to avoid this. Solvent selection has also an important part in analyte recoveries, since TBB, BTBPE, TBPH and TBBPA-DBPE seem to need more polar solvents to be eluted from silica and Florisil® columns than other NBFRs. Phenolic NBFRs usually require derivatisation before analysis.
(f) Better results for some compounds can be achieved with specific instrumental analyses. The use of short columns for their analysis by GC–MS will prevent the degradation of thermally labile compounds, like DBDPE, and TBECH and TBCO isomers, although longer columns may give better separation of other NBFRs. LC–MS is the preferred method for the analysis of TBBPA derivatives, such as TBBPA-DBPE and TBBPA-DAE. LC–APCI, and especially LC–APPI, have shown good results for the analysis of some NBFRs (ATE, HBB, TBPH, DBDPE, BTBPE, BATE, PBEB, EHTeBB, OBIND, TBBPA-AE, TBBPA-DBPE and TBBPS-DBPE). However, LC–MS does not seem to be an ideal alternative for the analysis of isomers of TBCO and TBECH.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2011.11.029.

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