Review

Recent progresses in analytical GC and LC mass spectrometric based-methods for the detection of emerging chlorinated and brominated contaminants and their transformation products in aquatic environment

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HIGHLIGHTS

- This paper is an overview of screening methods developed for emerging organohalogens.
- Target screening is available only for a limited number of emerging organohalogens.
- Non-target methods could be combined with biodegradation studies of contaminants.
- There is a need of further development of HRMS analytics for emerging organohalogens.

GRAPHICAL ABSTRACT
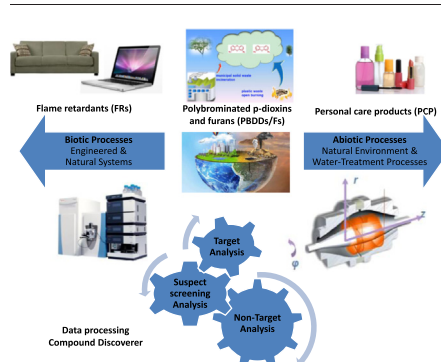
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ABSTRACT

This paper is an overview of screening methods recently developed for emerging halogenated contaminants and their transformation products. The target screening methods are available only for a limited number of emerging pollutants since the reference standards for these compounds are not always available, but a risk assessment of those micropollutants in environment must be performed anyhow. Therefore, the chromatographic techniques hyphenated with high resolution mass spectrometry (HRMS) trend to become indispensable methods for suspect and non-target screening of emerging halogenated contaminants. HRMS is also an effective tool for tentatively identification of the micropollutants' transformation products existing in much lower concentrations. To assess the transformation pathway of halogenated contaminants in environment, the non-target screening methods must be combined with biodegradation lab experiments and also with advanced oxidation and reduction processes that can mimic the transformation on these contaminants in environment. It is expected that in the future, the accurate-mass full-spectra of transformation products recorded by HRMS will be the basic information needed to elucidate the transformation pathways of emerging halogenated contaminants in aquatic environment.

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Contents

1. Introduction

Globally, the production and use of chemicals has increased and there is no doubt that society benefits from it (pharmaceuticals, food additives and health promoters, pesticides, synthetic fertilizers, material additives physical properties e.g. water/stain repellents, softeners and flame retardants). Nevertheless, many chemicals are of major environmental concern due to their occurrence upon screening in various environmental compartments, persistence, toxicity, potential for long range transport and tendency to bioaccumulate. Among them, the halogenated organic pollutants are of major concern in terms of human health and environmental issues due to their hazardous nature and recalcitrance to natural attenuation by biodegradation. Beside the group of legacy halogenated pollutants (like organochlorine insecticides 1,2,3,4,5,6-hexachlorocyclohexanes (HCHs) (Srivastava et al., 2019) or 2,2-bis(chlorophenyl)-1,1,1-trichlorethane and 2,4-bis(chlorophenyl)-1,1,1-trichlorethane (DDTs) (Ricking and Schwarzbauer, 2012) and polychlorinated biphenyls (Wang et al., 2019)), there are many emerging halogenated compounds that are not yet included in routine environmental monitoring programs and may be candidates for future regulations due to their adverse effects and/or persistency. As for halogenated contaminants of emerging concern (sometimes abbreviated as CEC), there are two classes of compounds that rise concern in environmental research: (*i*) flame retardants (FRs) (chlorinated and brominated), and (ii) polybrominated p-dioxins and furans (PBDDs/Fs). In the same time, the perfluoroalkyl substances (PFAS) are a distinct class of contaminants of emerging concern consisting in >3000 individual compounds (Ateia et al., 2019) and because of this they are out of the scope of this review paper.

Flame retardants (FRs) as contaminants of emerging concern consists mainly in the novel brominated flame retardants (NBFRs) like Tetrabromobisphenol A (TBBPA) (Lu et al., 2018), tetrabromocyclooctane (TBCO), tetrabromoethylcyclohexane (TBECH) (Arsenault et al., 2008) and hexachlorocyclopentenyl-dibromocyclooctane (HCDBCO) (Zhu et al., 2007), decabromodiphenyl ethane (DBDPE), 2,3-Dibromopropyl-2,4,6-tribromophenyl ether (TBP-DBPE) (von der Recke and Vetter, 2007), 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE) and Octabromotrimethylphenylindane (OBTMPI) (Melymuk et al., 2015). The use of these NBFRs in flame retardants industry appears after phasing out of polybrominated diphenyl ethers (PBDEs) in 2004 (Dodson et al., 2012).

Another class of emerging flame retardants is the chlorinated flame retardants of dechloranes which include the Dechlorane Plus (DP), a highly chlorinated flame retardant. It is a substitute for Dechlorane, which was also marketed under the name Mirex as a pesticide and was banned in the 1970s. DP comprises two pairs of isomers, *syn* and *anti*, which are present in the technical product in a ratio of about 1:3. Similarly to DP, dechlorane 602, dechlorane 603 and dechlorane 604 (Shen et al., 2012) were also patented as flame retardants (Feo et al., 2012). Despite its long production history, only in 2006 it was found in the environment (Sverko et al., 2011) and current knowledge about its environmental fate is still limited.

Regarding the PBDD/Fs, it was hypothesized that they can have both natural origin, being a class of marine toxins (Haglund et al., 2007), but also a man-made product from the uncontrolled combustion of PBDEs (Zhang et al., 2016), as well by the photochemical reactions given by their environmental transformation products hydroxylated polybrominated diphenyl ethers (OH-PBDEs) (Arnoldsson et al., 2012; Erickson et al., 2012). Although PBDD/Fs show similar toxicity as polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs), they can bioaccumulate more than PCDD/Fs and are more sensitive to UV

degradation due to the weaker bond energy of C—Br (276 kJ/mol) than that of C—Cl (328 kJ/mol). The knowledge about environmental fate of PBDD/Fs is still limited compared to PCDD/Fs (Zhou and Liu, 2018).

Beside the above mentioned and established classes of halogenated pollutants, there are two personal care products (PCP) that contain chlorine: 5-chloro-2-(2,4-dichlorophenoxy)phenol or triclosan (TCS) and 3-(4-chlorophenyl)-1-(3,4-dichlorophenyl)urea or triclocarban (TCC), that can be found in various cosmetic products (soaps, lotions, toothpastes, etc.). TCS and TCC can occur in the sewage systems due to the human used of above mentioned products (Sherburne et al., 2016). Since, TCC and TCS are incompletely removed during wastewater treatment processes, high concentrations of TCC (51 ± 15 mg/kg dry weight (Heidler et al., 2006)) and TCS (30 ± 11 mg/kg dry weight (Heidler and Halden, 2007)) were detected in digested sewage sludge.

To fingerprint exhaustively a wide range of halogenated contaminants new analytical strategies are needed, but these strategies differ from established screening strategies that are using a finite list of target analytes. Traditionally, the priority organic pollutants like above mentioned organochlorine pesticides were analysed by quantitative target screening methods that are using reference standard solutions to identify and quantify the target analytes (typically present at pg/L to ng/L levels) (Schymanski et al., 2015). In this case, the ordinary hyphenated analytical techniques, like gas chromatography (GC) or liquid chromatography (LC) coupled with low resolution mass spectrometry with single quadrupole (mass selective detector-MSD), as well with tandem mass spectrometry (MS-MS) that is using ion trap (IT) or triple quadrupole (QQQ) analyzers, are used in target screening methods (Hernández et al., 2019). Those target screening methods based on MSD or MS-MS (mostly QQQ) mass analyzers are well established and applied in environmental analysis of emerging compounds. Nevertheless, the evolution of hyphenated analytical techniques like GC or LC coupled with accurate mass (AM) high resolution mass spectrometry (HRMS) (especially as time of flight (TOF) and Orbitrap mass analyzers) has led to consolidation of suspect screening and non-target screening as analytical approaches that can overcome the large number of contaminants of emerging concern existing in the environment. The suspect/non-target screening methods are supposing the tentatively identification of compounds expected to be in an environmental sample, based on the information provided by their HRMS spectra, retention time (RT) and spectral library matching based a MS database search but for which reference standard solutions are not available. The difference between suspect and non-target screening is that in the 1st approach, the searching for a spectral library matching is restricted to a certain MS database search, while in the case on non-target screening the search for spectral library matching is not restricted to a database and the MS screening is performed using a wider mass acquisition range. A typically case of suspect screening is the identification of compounds based on existing lists of contaminants of emerging concern (i.e NORMAN suspect list exchange, https://www.norman-network.com/?q=node/236). Another case of suspect screening is the identification of a metabolite when the biodegradation pathway of parent organic pollutant is well-known (i.e. the anaerobic biodegradation of hexachlorocyclohexanes to benzene and chlorobenzene via intermediate metabolites of tetrachlorocyclohexanes (Zhang et al., 2014)). In this case, the identification of "suspect" analytes can be re-confirmed later via reference standards that provide in all cases the highest level of confidence. As suggested above, the non-target screening implies identification of all other compounds corresponding to the remaining features detected in a sample, for which there is no match with a compound in a database and is usually carried out after target and suspect screening. The identification of unknown features in non-target screening is based on the exact mass provided by full-scan HRMS analysis for providing a likely molecular formula and for reliable interpretation of the MS/MS spectra, on fragmentation ions, on the possible adducts ions formed, as well on the isotope patterns (especially in the case of compounds containing chlorine and bromine). Because of the tremendous amount of data generated by the HRMS instruments, the non-target screening usually requires sophisticated post-acquisition data-processing software (i.e. XCMS, EnviMass, Compound Discover, etc.).

The objective of this paper is an overview of the analytical screening methods recently developed for detection of the above-mentioned classes of emerging organohalogenated contaminants, as well of the screening methods recently applied to identify the metabolites of the respective classes of compounds.

2. Challenges in development of screening methods for emerging organohalogen contaminants

Due to the diversity of halogenated contaminants of emerging concern, both GC and LC methods are used for separation of compounds from above mentioned three classes of compounds. With respect of halogenated flame retardants and PBDDs/Fs, the main challenges in developing GC–MS methods for those compounds are thermal degradation (which can transform also PBDEs into PBDDs/Fs) (Hagberg, 2009) and isomeric interconversion. For developing of target screening GC–MS methods, the available standards must be used to carefully optimize several parameters including injection technique, stationary phase, column dimensions, GC system parameters and mass spectrometer parameters.

2.1. Gas chromatography–mass spectrometry analytical methods for emerging organohalogen contaminants

2.1.1. Sample preparation
Sample preparation of in the environmental analysis of halogenated contaminants performed by GC–MS includes both extraction and clean-up. The pressurised liquid extraction techniques (PLE) (Veenaas and Haglund, 2017), accelerated solvent extraction (ASE) (Tohidi and Cai, 2015), matrix solid-phase dispersion (MSPD) (Portolés et al., 2015) were the most frequent methods currently used for the extraction of solid samples (see Table 1). As for aquatic samples, beside the classically liquid-liquid extraction (LLE), the new trends include solid phase extraction (SPE) and solid phase microextraction (SPME) (Lopez et al., 2009), the latter one used to increase the detection limit of the GC–MS (low resolution) methods. Nevertheless, the SPME methods are time consuming procedures, so the detection limits of the respective methods can be increase also by using HRMS. The clean-up of the aquatic and solid samples includes a variety of columns (florisil, alumina, multi-silica layers, etc.). Generally, there is the paradox between the need for purification/clean-up and the need for an exhaustive extraction method meaning that techniques like PLE require less clean-up afterwards comparing with classical Soxhlet extraction, but a lot of optimisation efforts before they can be reliable used for extraction of halogenated contaminants.

2.1.2. Injection technique
The environmental samples containing halogenated flame retardants and PBDDs/Fs in relatively low levels (especially for PBDDs/Fs), are usually injected into inlet by split/splitless injection, and more recently by programmed temperature vaporization (PTV) injection (Butt et al., 2011), while on-column injection (where the sample is delivered directly to the entrance of the capillary column) is less and less used. Particularly in the case of legacy and novel BFRs, the PTV injector can improve the response factor of higher molecular weight BFRs, while assuring minimal degradation of thermolabile compounds and operating large volume injections (5–10 μL), thus improving the sensitivity of the GC method (Hagberg, 2009). Nevertheless, large volume injections assured by PTV injectors might result in peak tailing and possible in loss of chromatographic resolution. While for the analysis of novel BFRs, lower injection temperatures are preferred, for the analysis of PBDEs (particularly for PBDE-209) and PBDDs/Fs, generally a range of

Table 1
Summary of the target screening methods used for the detection of emerging organohalogen contaminants.

Class of halogenated contaminants	Specific contaminants	Extraction/Preparative method used	Hyphenated technique used	Type of ionization used in mass spectrometry involved	Type of mass spectrometer analyser used	IDLs/MDLs/instrumental LOQs/method LOQs	Reference
FRs	PBDEs, DBDPE, BTBPE	Matrix solid-phase dispersion (MSPD)/multilayer silica clean-up	GC–MS/MS	APPI	QQQ	<10 fg on-column for 14 PBDEs (IDL)	(Portolés et al., 2015)
	Mirex, Dec602, Dec603, Dec604, and DP	Solvent extraction/GPC	GC-HRMS and GC-QQQ-FT-ICR-MS	EI	Magnetic Sector and QQQ-FT-ICR-MS	From 5 to 15 pg g^{-1} (MDL) (for mirex, Dec602, Dec603, Dec604, and DP)	(Shen et al., 2012)
	HBCDs	Solvent extraction/GPC/Florisil column chromatography	UHPLC–Orbitrap-HRMS and UHPLC–TOF-HRMS	ESI	Orbitrap-HRMS and TOF-HRMS	5.0 pg g^{-1} for UHPLC–QqQ-MS/MS (SIM), 4.0 pg g^{-1} for UHPLC–Orbitrap-HRMS and 29 pg g^{-1} for UHPLC–TOF-MS (SCAN) (all of them method LOQ for α-HBCD)	(Zacs et al., 2014)
PBDDs/Fs	PBDDs/Fs	High speed solvent extraction/multilayer silica clean-up	GC–HRMS	EI	Magnetic Sector	n.a.	(Goto et al., 2017)
	PBDDs/Fs, PXDD/F	Soxhlet extraction multilayer silica clean-up	GC-Q-TOF-HRMS	APCI$^-$	TOF-HRMS	5 to 10 fg (IDL)	(Fernando et al., 2016)
PCP	TCS, TCC	Liquid-Liquid Extraction (LLE) and SPE/ultrasonic-assisted extraction (UAE)	LC- MS/MS	ESI	QQQ	n.a.	(Lehutso et al., 2017)
	TCS, 2,4-DCP, 2,8-DCDD, MTCS	LLE, accelerated solvent extraction (ASE)/silica clean-up	GC–MS	EI	Quadrupole	30.0 ng/L for TCS, 12.0 ng/L for 2,4-DCP, 18.0 ng/L for 2,8-DCDD and 27.0 ng/L for MTCS (method LOQs in wastewater)	(Tohidi and Cai, 2015)
	TCS, TCC	Solvent extraction/cartridge clean-up	UPLC-MS/MS	ESI	QQQ	0.495 ng/g for TCS and 0.381 ng/g for TCC (method LOQs in sewage sludge)	(Zhu et al., 2019)
	TCS, MTCS	Stir bar sorptive extraction (SBSE)/sonication	APGC–TOF-HRMS	APCI	TOF-HRMS	0.04 μg/L for TCS and 0.04 μg/L for MTCS (method LOQs)	(Pintado-Herrera et al., 2014)

between 240 and 280 ° C is employed in order to get the optimal yield for the target compounds.

2.1.3. Stationary phase and column dimensions

Many GC analysis method of emerging halogenated compounds (NBFRs, dechloranes and PBDDs/Fs), employed DB-5-like GC columns that are containing a stationary phase composed of 5% phenyl and 95% dimethyl polysiloxane (e.g., DB5-MS from J&W), in most cases with a thin film thickness (0.1 or 0.25μm). While for the target analysis of legacy organochlorine pesticides, a 30 m length column with internal diameter (ID) of 0.25 mm and with film thickness of 0.25μm, is enough to achieve a good separation, the analysis of BFRs and PBDDs/Fs usually needs a 10–15 m length column to minimize the possibility of decomposition or isomerization. For the same brominated compounds, a thin film thickness 0.1 μm is preferred to decrease elution temperature of the target compounds and the time spent by analytes (especially those with high M.W., like DBDPE, BTBPE, BBE-209) at higher temperatures (Hagberg, 2009). Due to the increase of retention factor (k), smaller ID columns (i.e. 0.18 mm) are more suitable for samples originated from complex environmental matrices (i.e. soil from contaminated sites) where a range of low to high molecular weight emerging halogenated compounds may exist in the samples.

2.1.4. GC system parameters

Like in any other GC analysis, the oven temperature program, the flow of carrier gas and the average velocity are key parameters for the separation of emerging halogenated contaminants. While novel BFRs with relatively low M.W. (i.e. TBECH) can be analysed with GC columns that have maximum operating temperatures <300 °C, high M.W.

compounds like BBE-209, DBDPE, BTBPE, and higher congeners of PBDDs/Fs require GC column with maximum operating temperatures up to 340 °C (Liu et al., 2018). The optimal flow of helium carrier gas depends on the ID columns: smaller ID columns require a low flow (i.e. 0.6 mL/min for 10 mm ID column), while larger ID columns require a higher flow (i.e. 1.8 mL/min or higher for 32 mm ID column). Since most of the modern GC–MS instruments are using helium as carrier gas, a wider range for optimal linear velocity exists in GC separation of emerging halogenated contaminants, with a near optimum linear velocity at 25 cm/s. Nevertheless, the efficiency of chromatographic separation remains high when using higher linear velocities.

2.1.5. Spectrometric parameters

While target screening of emerging halogenated contaminants by GC can be performed routinely using low resolution mass spectrometry (LRMS) detection, the suspect and non-target screening analyses require usually HRMS detection. In the target screening of NBFRs performed using GC-ECNI-MS, usually only bromide ions (79 and 81) are monitored (Ali et al., 2011), since many NBFRs do not produce abundant stable molecular or fragment ions in the ECNI source. Nevertheless, currently, the target methods based on ECNI are more and more adapted to monitor also other fragments. For example, recently Pomata et al. (2019) used 80.9 and 251.8 and 331.7 ions to quantify the BTBPE in particulate matter collected within an electronic waste recycling facility. In case of ECNI-based screening of dechloranes, the molecular ions 653.8 and 651.8 are usually used (Liu et al., 2018). For target analysis by GC-EI-QQQ-MS, there are three critical factors that should be optimized in developing selected reaction monitoring (SRM) methods for emerging halogenated contaminants: (*I*) the selection of the precursor ions; (*II*)

the optimisation of collision energy in the 2nd quadrupole (the collision cell, actually a hexapole using a mixture of nitrogen and helium as make-up gas) of the mass analyser; and (III) the optimal adjustment of Dwell time (duration in which each m/z ion signal is collected) which is a critical parameter in SRM transitions since increasing the dwell time can improve ion counting of the detector (therefore the sensitivity), but in the same time will decrease the number of points available for each specific peak. The negative chemical ionization was applied also for the target analysis of dechloranes, since Barón et al. (2012) used GC–NCI–MS–MS and methane as moderating gas to quantify dechloranes in biota and environmental samples (i.e. by using 654 > 35 transition in SRM method used to quantify syn-DP and anti-DP). For the target analysis of PBBDs/Fs, usually the magnetic sector (HRMS) is preferred by using EI configured to standard electron energy of 70 eV, while for the magnetic sector analysis or NBFRs lower electron energies are preferred (Shen et al., 2012). More recently Fernando et al. (2016) used [M-Br + O]⁻ ions formed during APCI to detected the PBBDs/Fs using a Q-TOF-HRMS (for example 750.41 ion in the case of octabromo-DD). In the case of suspect and non-target screening, the resolution, scan rate (expressed in Hz) and mass acquisition range of the HRMS analyzers employed are the most critical parameters, the last parameter being important to tentatively identify as many as possible compounds.

2.2. Liquid chromatography–mass spectrometry analytical methods for emerging organohalogen contaminants

Due to the thermolability of many of the emerging halogenated contaminants (for example isomerization and decomposition of TBECH (Eljarrat et al., 2008) around 120 °C) and due to the increasing need to analyze polar contaminants of emerging concern (i.e. TBBPA, TCS, etc.), as well their hydroxylated metabolites (i.e. HBCDs metabolites (Heeb et al., 2012), the LC-MS-MS methods emerged as alternative techniques in target and non-target analysis of emerging halogenated contaminants. Without neglecting the composition of the stationary phase, it can be stated that the mobile phase in LC contributes more to the chromatographic separation, in comparison to GC, and therefore the parameters of mobile phase play a crucial role in LC separation of emerging halogenated contaminants. Nevertheless, due to the fact that some halogenated contaminants can be found in environment in low concentrations (i.e. pg to ng/L), some pre-concentration steps using absorbents are needed. Therefore, the following factors must be taken into account in developing LC-MS-MS methods for halogenated contaminants: selecting of absorbents for pre-concentration steps, composition of the stationary phase and column dimensions, mobile phase composition, influence of pH, ion strength and flow rate, and especially mass spectrometric parameters for MS-MS tandem system (Lacorte and Fernandez-Alba, 2006).

2.2.1. Selecting of absorbents

The pre-concentration steps performed on aquatic samples containing the halogenated emerging pollutants involved solid phase extraction (SPE) performed in many cases on cartridges using C18 as absorbent. More recently, new absorbents materials have been developed and used in this pre-concentration process. For example, Wang et al. (2013) used silicon dioxide/polystyrene composite microspheres to performed SPE followed by elution with 3 × 5 mL mixture methanol/acetone (1:1) for quantification of TCC, TCS and its metabolite MTCS by LC-ESI-MS (quadrupole mass analyser). As an alternative to C18–based cartridges, Blum et al. (2017) used Oasis HLB (200 mL solvent/6 cm³) cartridges installed on a SmartPrep automated cartridge extractor (Horizon Technology, Salem, NH, USA), in the pre-concentration steps, prior to NTS. Then Blum et al. (2017) used 8 mL dichloromethane/acetonitrile (4:1, v/v) followed by 10 mL dichloromethane (DCM) to elute the analytes from the HLB cartridges. More recently, Ccanccapa-Cartagena et al. (2019) used also Oasis HLB (200 mL solvent/

6 cm³) cartridges to preconcentrate water samples (in volume of 200 mL), prior to NTS. Ccanccapa-Cartagena et al. (2019) eluted the analytes using 10 mL of methanol-DCM mixture but they enriched the samples by evaporation to dryness and to final volume of 1 mL, respectively (enrichment factor of 200). The choice of the absorbent material and of the elution solvent depends on the polarity of the target analytes. Nevertheless, methanol and acetonitrile are preferred due to their compatibility with the columns used in reversed phase LC.

2.2.2. Stationary phase and column dimensions

Usually, the reversed-phase LC (based of hydrophobic interactions) columns are preferred for the separation of emerging halogenated contaminants discussed in this paper since they have M.W. <2000., while the columns based on octadecylsilane (C_{18} type) are by far the most frequently used. Nevertheless, in the case of selected personal care products (TCS, TCC and their metabolites), the reversed-phase C8 columns (octylsilane-based) are also used (Liu and Wu, 2012; Wang et al., 2013). Regarding the column dimensions, for lab experiments involving firstly a development of LC methods, a short column (e.g. 100 mm) with small particles (e.g., ~2 μm) might be preferred. Nevertheless, in the case of complex environmental samples containing a wide range of contaminants of emerging concern, a longer column (e.g. 150–250 mm) packed with small particles might be selected. Also, a LC column with a small internal diameter (e.g. I.D. = 2.1 mm), appears to be the best in the case of screening of emerging halogenated contaminants, due to the lower flow rates used in conjunction with various high or low resolution MS detectors. In order to interact with the stationary phase packed in the LC column, the molecules of analyte must 'fit' into the porous structure. Smaller pore size packings (pore size ranged from 80 to 120 Å) appear to be ideal for separation of emerging halogenated contaminants (M.W. <2000). For example, Wang et al. (2013) used a Agilent Eclipse XDB-C8 column, (150 mm length × 4.6 mm I.D. × 5 μm particle size) for separation of TCS, MTCS and TCC, while Ganci et al. (2019) separated PBDEs and NBFRs from the sediments of Thames river using a Thermo Scientific Accucore™ RP-MS column (100 mm length × 2.1 mm I.-D. × 2.6 μm particle size).

2.2.3. Mobile phase composition

Since many of the emerging halogenated contaminants have hydrophobic functional groups, the reversed phase LC is usually preferred, so a combination of weak solvents (i.e. water) and stronger solvents (i.e. acetonitrile) is the basis of the LC separation of such target analytes. The development of such LC methods is almost always based on a solvent gradient (a slow one when a wide range of contaminants of emerging concern has to be separated) and this approach has the advantage of sharper peaks because of the compression effects induced by the gradient, as well the one of minimizing the build-up of contamination in the LC column since the column is continuously exposed to an increasing solvent strength. A gradient based of combination of acetonitrile/water/methanol is often applied for the separation of emerging halogenated contaminants (Harrad et al., 2009, Wang et al., 2013, Ganci et al., 2019), while solvents like isopropanol or tetrahydrofuran are not often used.

2.2.4. pH, ion strength and flow rate

The pH and ionic strength of the mobile phase can influence the LC separation in multiple ways. The pH can influence the peak shape and retention, as well the selectivity of a LC method. The pH influence is less relevant for the LC separation of emerging halogenated contaminants, but more relevant for the separation of their metabolites that have basic functional groups (i.e. hydroxyl). The pH can also influence the stationary phase by deprotonation of silanols from the column, which might increase the retention time for positively-charged compounds (i.e. triclocarban that contains two amine groups). When volatile mobile phase additives are used in ESI of emerging halogenated contaminants, the resulted pH can be either slightly acidic (for

HCOOH, CH$_3$COOH, NH$_4$Cl), slightly alkaline (NH$_4$OH) or even neutral (when CH$_3$COONH$_4$ is used) (Galindo-Iranzo et al., 2009). Nevertheless, when a wide range of contaminants of emerging concern is present in an environmental matrix, a pH around 6 is preferred for the mobile phase. Also, a high value of ionic strength can influence the LC separation by increasing the competition for ionic or adsorptive sites, between the mobile phase and the analytes.

Theoretically, the optimization of flow rates can be performed using the van Deemter plots since they evaluate the efficiency (expressed as H,) as a function of linear velocity (u) or flow rate (also taking into consideration the maximum pump pressure). In practice, higher flow rates are decreasing the retention times and producing sharper peaks, thus shortening the LC analysis time. However, high flow rates can also decrease the LC resolution. To balance the retention times and LC resolution a optimum flow rate must be used. The flow rates of LC-MS systems can be ranged typically between 1 μL/min to 1 mL/min, with a maximum 600 μL/min in the case of LC-ESI-MS-MS analysis (Zhou et al., 2010).

2.2.5. Spectrometric parameters

In order to obtain the best detection conditions of target analytes, in ESI mode, the parameters of the tandem MS-MS analysers (i.e. flow of nebulizer and heater gases, IonSpray voltage, declustering potential, temperature of Turbo-IonSpray source, collision energy, dwell time, etc.), must be optimized. Among those parameters, the use of higher temperature of Turbo-IonSpray source (i.e. up to 500 °C) gives a higher analytical signal (relative intensity), but this strategy has limitations when it applied to enantioselective analyses of chiral brominated flame retardants (Badea et al., 2016). Here too, in the case of suspect and non-target screening by LC-HRMS/MS, the resolution, scan rate and mass acquisition range of the HRMS analyzers are the most critical parameters to be taken into consideration. As demonstrated by Rostkowski et al. (2019), ESI in both negative and positive mode remains the most used ion source used for HRMS mass analyser, being extremely sensitive for polar compounds, therefore usefully in the analysis of metabolites of emerging halogenated compounds as well in analysis of more polar PCP like TCS and TCC and more polar NBFRs like TBBPA. For example, recently Zhu et al. (2019) used multiple reaction monitoring (MRM) induced by ESI in negative mode and a QQQ-MS-MS analyser for target screening of TCS, TCC, TBBPA from municipal sewage sludge using the folllowing transitions: 289.0 to 35.0 for TCS, 315.0 to 62.0 for TCC and 542.8 to 418.0 for TBBPA. Nevertheless, many legacy and NBFRs like HBCDs and HCDBCO are non-polar and while ESI in negative mode (formation of [M−H]$^-$ molecular ion) can be still apply for them, it gives low signals. One approach to enhance the sensitivity of LC-ESI-QQQ-MS-MS methods for such compounds is to use the formation of adducts ions for quantification (i.e. acetate adduct (m/z 700.6) and chlorine adduct (m/z 676.6) for quantification of HBCDs diastereoisomers) (Galindo-Iranzo et al., 2009). Nevertheless, a more promising approach more and more used, is to employ atmospheric pressure photoionization (APPI) operated in negative mode for the target screening of NBFRs. Zacs and Bartkevics (2015) used either molecular ion [M − H]$^-$ (m/z = 640.6369 for HBCDs, and m/z = 542.7452 for TBBPA), or the adducts [M − Br + O]$^-$ (for example m/z = 384.7898 for BATE) and [M + O$_2$]$^-$ (m/z = 571.7285 for HCDBCO) for HPLC-Q-Orbitrap-MS target screening of BFRs.

3. Screening methods for the detection of emerging organohalogen contaminants in aquatic environment

3.1. Target screening methods

3.1.1. Flame retardants

Many routine target screening methods applied for the detection of novel brominated flame retardants (NBFRs) are still involving gas chromatography coupled with low resolution mass spectrometry with single quadrupole, that is using electron-capture negative ionization (GC-ECNI-MS), since the impact electron ionization mass spectrometry (EI-MS) has a low sensitivity in determining higher brominated compounds (with >6 bromine atoms) (for an overview of target methods see Table 1). Nevertheless, the ECNI-MS method is not specific and requires a very good gas chromatography separation. To overcome the limitations of ECNI-MS and EI-MS (low specificity in ECNI-MS and high fragmentation in EI-MS), Portolés et al. (2015) developed a GC-tandem MS method (involving a triple quadrupole (QQQ) mass analyser), using atmospheric pressure chemical ionization methods (GC-APPI-MS/MS), method which was subsequently applied in target screening of NBFRs. More specifically, Portolés et al. (2015) achieved a very low limit of detection (lower than 10 f. on-column) for the detection of 14 PBDEs (congeners 28, 47, 66, 85, 99, 100, 153, 154, 183, 184, 191, 196, 197, and 209) two novel BFRs, decabromodiphenyl ethane (DBDPE) and 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE)). In the last years, accurate high resolution mass spectrometry was also applied in the GC analysis of NBFRs and dechloranes. de la Torre et al. (2012) applied GC-EI-HRMS (magnetic sector analyser) in the target analysis of dechloranes (as well of the legacy contaminants mirex) from the tissues of Franciscana Dolphin (Pontoporia blainvillei), while decabromodiphenylethane (DBDPE) and legacy PBDEs were analysed using low resolution mass spectrometry (GC-EI-MS and GC-EI-MS/MS). Ions monitored in HRMS analysis (SIM mode) using a resolution >10,000 were: 262.8570/264.8540 for dechlorane 603 (Dec 603); 417.7026/419.7006 for dechlorane 604 (HCTBPH); 271.8102/273.8072 for mirex, dechlorane 602 (Dec 602) and chlordene plus; 201.8911/203.8881 for decachloropentacyclooctadecadiene (aCl$_{10}$DP), and 237.8491/239.8462 for undecachloropentacyclooctadecadiene (aCl$_{11}$DP), the last two compounds, being presumably degradation products of dechloranes isomers. For the analysis of PBDEs and emerging halogenated contaminants, such target GC-EI-HRMS methods using magnetic sector analyser were developed since 2009 (Kolic et al., 2009), particularly for a wide range of NBFRs, including compounds with high molecular weight (M.W.) like: hexabromobenzene (HBB), TBP-DBPE, 2,2′,4,4′,5,5′-hexabromobiphenyl (BB-153), HBCD, HCDBCO, DBDPE, BTBPE, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EHTeBB), octabromotrimethylphenylindane (OBIND), Dechlorane Plus, and bis(2-ethly-1-hexyl)tetrabromophthalate (BEHTBP). (Shen et al., 2012) compared the target GC-EI-HRMS method with a gas chromatography-tandem triple quadrupole-Fourier transform mass spectrometry (GC-QQQ-FT-ICR-MS) method for quantification of dechloranes and their dechlorination products in Great Lakes fish (Canada) and Arctic beluga whales (see Table 1). The magnetic sector mass analyser was configured to 10,000 resolution (10% valley definition), using a electron energy of 38 eV (EI mode), while the FT-ICR-MS analyser was tuned to a actual mass resolution of 30,000–60,000 (10% valley definition), using the standard electron energy of 70 eV (EI mode too). The method detection limits for the target compounds (mirex, Dec602, Dec603, Dec604, and DP) ranged from 5 to 15 pg g^{-1} lipid for fish and beluga samples. Shen et al. (2012) was also the first study reporting the identification of hydroDec602 isomers in biota (both in fish and Arctic beluga whales), as possible metabolites of dechloranes. More recently, Zacs et al. (2019) performed the screening of novel brominated and chlorinated flame retardants in food, both in target and in non-target analysis by using GC coupled with atmospheric pressure chemical ionization Fourier transform ion cyclotron resonance mass spectrometry (GC-APCI-FT-ICR-MS), thus employing FT-ICR-MS, a mass analyser that was less used until now in environmental analysis of organic pollutants. Among the current available mass analyser, Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR-MS) proven among the best mass accuracies (<100 ppb) and by far the highest spectrometric resolution (>1,000,000) (Zacs et al., 2019). In target analysis, Zacs et al. (2019) employed FT-ICR-MS to calculated the instrumental LOQs for the target compounds (PBDEs and the following emerging compounds: Dechloranes (Dec 602, Dec 603), BATE, PBEB,

HBB, EH-TBB and BTBPE), values that varied from ~1 pg to ~5 pg injected on-column, while the method LOQs were in the range of 0.002–0.04 ng/g sample. The GC-APCI-FT-ICR-MS method was validated by using reference material, and the results were similarly with those obtained by GC-HRMS with magnetic sector. With respect of target LC-MS-MS methods for NBFRs, Zacs et al. (2014) found that ultrahigh performance liquid chromatography coupled with time-of flight high resolution mass spectrometry (UHPLC–TOF-HRMS) method (using ESI in negative way) operated in scan mode over a *m/z* range of 600–700 and at high resolution (15,000 full width at half maximum (FWHM)) and UHPLC–Orbitrap-HRMS method (see Table 1) operated in targeted-SIM mode at even higher resolution (35,000 FWHM) proved to be at least at the same level of performance, if not superior to LC–MS/MS methods for target analysis of HBCDs diastereomers and these methods could be also applied for the less studied emerging BFRs. For example, the instrumental LOQs calculated for α-HBCD ranged from 1.3 pg for UHPLC–QQQ-MS/MS, to 1.1 pg for UHPLC–Orbitrap-HRMS method and to 4.5 pg for UHPLC–TOF-MS method, while the corresponding method LOQs for the same compound were: 5.0 pg g^{-1} for UHPLC–QqQ-MS/MS, 4.0 pg g^{-1} for UHPLC–Orbitrap-HRMS and 29 pg g^{-1} for UHPLC–TOF-MS full scan method (taking into consideration that the SIM methods are usually more sensitive than full scan methods). Moreover, Zacs and Bartkevics (2015) quantified 27 BFRs, including NBFRs ones in fish tissue, using the same UHPLC–Orbitrap-HRMS target technique operated here too in targeted-SIM at high resolution (17,500 FWHM), buy employing atmospheric pressure photoionization (APPI) interface operated in negative mode instead of electrospray ionization (ESI). For example, among the NBFRs, the instrumental LOQ for HCDBCO, calculated by Zacs and Bartkevics (2015) was 59 pg on-column, while the method LOQ was 0.19 ng/g. Overall, Zacs and Bartkevics (2015) confirmed the findings for the previously study (Zacs et al., 2014) showing that the LC–Orbitrap-HRMS methods are superior in sensitivity and selectivity to conventional LC–MS/MS methods, especially for the target screening of a wide range of NBFRs originating from a broad variety of matrices. Very recently, Ganci et al. (2019) used liquid chromatography coupled to a high resolution Orbitrap mass spectrometer (LC-Orbitrap HRMS) operated in negative atmospheric pressure chemical ionization (APCI) mode for the target analysis of legacy PBDEs and NBFRs in river sediments. In the above mentioned study (Ganci et al., 2019), the LODs were calculated for PBDEs in sediment matrix and the values ranged from 0.001 ng/g (for PBDE-209) to 0.37 ng/g (for BDE-17), while in general the interval of LODs varied from 0.0001 ng/g (the lowest for HBCDDs) to 1.1 ng/g (the highest for DBE-DBCH).

3.1.2. Polybrominated p-dioxins and furans

With respect to PBDD/Fs determined from environmental samples, most of target screening methods were developed until present using GC-EI-HRMS with magnetic sector analyser configured in selected ion monitoring (SIM) mode (Zhou and Liu, 2018), while few studies used GC–MS/MS (for example GC-IT-MS/MS like (Wang et al., 2007)) to analyze PBDD/Fs.

Zhou et al. (2012), performed the target analysis of polybrominated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs) in surface sediment samples from Taihu Lake, China, by GC-EI-HRMS with magnetic sector operated in SIM mode with a resolution >10,000. Zhou et al. (2012) found the levels of PBDD/Fs in sediment ranged from 0.16 to 1.6 pg toxic equivalency (TEQ)/g dry weight. More recently, Goto et al. (2017) determined the levels of PBDD/Fs in sediment cores (covering the period 1895–2000) from Tokyo Bay, Japan, using the same magnetic sector high resolution mass spectrometer (GC–EI-HRMS) (see Table 1), but coupled with a solvent cut large volume injection system. Using the above mentioned target method, Goto et al. (2017) found the concentration of PBDD/Fs in sediment ranged from 2.2 to 66 pg g^{-1} dw, with a mean value of 16 pg g^{-1} dw. Regarding other types of HRMS instruments, Fernando et al. (2016) used gas chromatography coupled quadrupole-time-of-flight (GC-Q-TOF-HRMS) mass spectrometry using negative ion atmospheric

pressure chemical ionization (APCI^{-}) employing a resolution of 20,000 FWHM and a mass acquisition range of 30–1000 *m/z*, for the target analysis of PBDD/Fs (see Table 1). Using the above mentioned novel target method, Fernando et al. (2016) calculated the instrument detection limits (IDLs) (defined versus a signal-to-noise ratio (S/N) of 10) of tetrabromodibenzo p-dioxins (TBDDs) as ranged between 5 and 10 fg, similarly with those of a magnetic sector analyser.

3.1.3. Personal care products

The target screening of halogenated PCP was performed also in various studies and particularly for triclosan (TCS) and triclocarban (TCC) the target analysis is performed usually (but not exclusively) based on LC-MS/MS methods (see Table 1). Lehutso et al. (2017) performed the target screening of TCS and TCC in different type of liquid and solid samples collected from selected wastewater treatment plants in Gauteng Province, South Africa, using a LC-ESI-QQQ-MS/MS method. For example, Lehutso et al. (2017) found the levels of TCS and TCC in influent wastewater ranged from 2.01 to 17.6 μg/L for TCS, and from 0.0860 to 2.84 μg/L for TCC, while the levels in raw sludge ranged from 3.65 to 15.0 μg/kg for TCS and from 3.65 to 11.8 μg/kg for TCC, respectively. In the same time, Lehutso et al. (2017) recorded also the concentrations in biosolids as ranged from 2.16 to 13.5 μg/kg for TCS, and from 2.59 to 8.23 μg/kg for TCC, values that might limit the application of biosolids to agriculture land. In another study, Tohidi and Cai (2015) used a GC-EI-MS in SIM mode method (see Table 1) for the target analysis of triclosan and its degradation by-products (namely 2,4-dichlorophenol (2,4-DCP), 2,8-dichlorodibenzo-p-dioxin (2,8-DCDD), and methyl triclosan (MTCS)) in wastewater and sludge samples. Tohidi and Cai (2015) calculated the method LOQs for the above mentioned compounds in wastewater as ranged from 30.0 ng/L for TCS, 12.0 ng/L for 2,4-DCP, 18.0 ng/L for 2,8-DCDD and 27.0 ng/L for MTCS, while the LOQs values in sludge ranged from 30.0 ng/g for TCS, 3.0 ng/g for 2,4-DCP, 6.0 ng/g for 2,8-DCDD and 15.0 ng/g for MTCS, respectively. While Tohidi and Cai (2015) detected by not quantified 2,4-DCP and 2,8-DCDD in real samples, the highest influent wastewater level of TCS was 512.8 ± 52.1 ng/L (with correspond level in dewatered sludge 2505.9 ± 253.4 ng/g, after treatment), while the highest concentration of MTCS was 129.3 ± 17.2 ng/g of dewatered sludge. Very recently, Zhu et al. (2019) performed the target screening of triclosan and triclocarban from municipal sewage sludge across China by UPLC-QQQ-MS/MS analysis, using multiple reaction monitoring (MRM) in negative ion electrospray mode (see Table 1). Zhu et al. (2019) calculated the method LOQs to 0.495 ng/g for TCS and to 0.381 ng/g for TCC, respectively. Furthermore, Zhu et al. (2019) found the concentration of above mentioned two PCP in sludge ranged from 107 to 3890 ng/g dw for TCS and from 26.1 to 7760 ng/g dw for TCC, respectively, values that were similarly to those recoded by Lehutso et al. (2017) in variously types of sludge samples. With respect of HRMS target methods, Pintado-Herrera et al. (2014) determined triclosan and methyl triclosan using a atmospheric pressure gas chromatography–time-of-flight-high resolution mass spectrometry (APGC–TOF-HRMS) target method (see Table 1). Pintado-Herrera et al. (2014) calculated the instrumental LODs that were 0.074 μg/L for TCS and 0.024 for MTCS, while the method LODs were 0.04 μg/L for TCS and 0.04 μg/L for MTCS, respectively. Once developed, Pintado-Herrera et al. (2014) used the target screening method for real water samples upon stir bar sorptive extraction (SBSE), the highest concentrations being detected in wastewater: 95 ± 8 μg/L for TCS and 52 ± 1 μg/L for MTCS, respectively.

3.2. Suspect screening methods

3.2.1. Flame retardants

The hyphenated two-dimensional gas chromatography coupled with time-of-flight high resolution mass spectrometry (GC × GC-TOF HRMS) has been used recently for developing of suspect screening methods for emerging halogenated contaminants (for an overview of

suspect and non-target screening methods see Table 2). Phillips et al. (2018) performed suspecting screening of a wide range of chemicals in consumer products by GC × GC-TOF HRMS analysis and identified tentatively 1602 chemicals of which 198 compounds were existing in a database of known consumer product chemicals. Among these 198 compounds, 119 target compounds were latter identified using reference standards. With respect to flame retardants, Phillips et al. (2018) searched for 67 compounds from in source list of known consumer products, and they identified 9 flame retardants based of their HRMS spectra. Among the flame retardants, Phillips et al. (2018) identified tentatively the legacy brominated flame retardant 2,2′4,4′-tetrabromodiphenyl ether (BDE-47), and the emerging monobromoalkanes (1-bromodecane, 1-bromododecane, 1-bromopentadecane, 1-bromo-tridecane, and 1-bromopentadecane) that originate from carpet type products. More recently, Rostkowski et al. (2019) conducted an intercompared suspect screening of NBFRs from house dust. Rostkowski et al. (2019) performed the suspect screening of NBFRs in several labs using a combination of GC–MS (with (Q)TOF (most of them HRMS), QQQ, and single-quadrupole analysers), GC × GC-TOF-HRMS and LC-MS-MS methods (involving Orbitrap, TOF and even ion mobility-quadrupole-time-of-flight mass spectrometry (IM-Q-TOF-HRMS) analysers) (see Table 2). Most of the GC–MS analyses performed by the laboratories involved in the intercomparison test used EI, while four of them used CI and two used APCI. In the case of LC-HRMS/MS analyses, Rostkowski et al. (2019) used ESI for most of the labs (one single lab used ACPI and APPI), while resolution of the Orbitrap-based systems ranged from 70,000 to 120,000 and the resolution of the TOF systems from 10,000 to 42,000. Among the BFRs tentatively identified by Rostkowski et al. (2019) were four legacy PBDEs (BDE-47, BDE-99, BDE-100, BDE-153) based on the GC–MS methods, and HBCD based on LC-MS-MS methods. Jobst et al. (2013) performed suspect screening to identify novel halogenated contaminants from sediment and specific biota (lake trout) of Lake Ontario, by gas chromatography-tandem triple quadrupole-

Fourier transform mass spectrometry (GC-QQQ-FT-ICR-MS) at a mass resolving power of 50,000–100,000 (FWHM), using the standard electron energy of 70 eV (EI mode) (see Table 2). They used mass defect plots (by plotting H/Cl mass defect vs. m/z) for the identification of dibromo and tribromo analogues of Dechlorane 604 (i.e. 5-tetrabromophenyl-1,2,3,4,7,7-hexachloro-2-norbornene) in lake trout. More specifically, Jobst et al. (2013) applied the Kendrick mass scale which used a specific Kendrick mass being equal to 34.000 Da, as is defined by the substitution of a hydrogen atom by a chlorine atom (H/Cl). Thus, the conversion to Kendrick scale involves multiplying the IUPAC mass by 34/33.96102, while in this case the mass defect from the above mentioned plots was calculated as difference between the nominal and exact mass of brominated analogues of Dec 604 (also standard abbreviated as HCTBPH (Bergman et al., 2012)). For example, recording a H/Cl mass defect of 0.16, for dibromo analogue of HCTBPH, $C_8H_5ClBr_2^+$ ($m/z = 295.8420$) and $C_7H_3Cl_2Br_2^+$ ($m/z = 316.7951$) are obtained as major fragments, after the loss of $C_6H_2Cl_5^+$ ($m/z = 250.8566$) fragment. The identification of dibromo and tribromo analogues of HCTBPH was later confirmed by Jobst et al. (2013) using a technical mixture of HCTBPH containing also the dibromo and tribromo analogues of HCTBPH. Also, Cariou et al. (2016) performed suspect screening for the identification of BFRs in biota based on isotopic pattern and Kendrick mass plot (also using H/Cl-scale mass defect) by analysis samples using an UHPLC-Q-Orbitrap MS (configurated in ESI) operated at a resolving power of 70,000 full width half maximum (FWHM) at m/z 200 and using a full scan mode over the m/z range of 250 to 900. Using these suspect screening approach, Cariou et al. (2016) identified HBCDD in biota samples. Using a similar UHPLC-Q-Orbitrap MS system, Leon et al. (2019) performed suspect and non-target screening using the H/Cl-scale mass defect plot. A series of 21 homologue clusters, with a putative general formula of $C_{12}H_xBr_yCl_zO_2$ were revealed by H/Cl-scale plots. Leon et al. (2019) he found that triclosan and 3,4,5-tribromo-2-(2,4-dibromophenoxy)phenol were later confirmed by injection of authentically standards. Very recently, Zhang et al. (2019) used isotope

Table 2
Summary of the suspect/non-target screening methods used for the detection of emerging organohalogen contaminants.

Class of halogenated contaminants	Tentatively identified contaminants	Extraction/Preparative method used	Hyphenated technique used	Type of ionization used in mass spectrometry involved	Type of mass spectrometer analyser used	Reference
FRs	BDE-47, monobromoalkanes	Soxhlet extraction	GC × GC-TOF HRMS	EI	TOF HRMS	(Phillips et al., 2018)
	BDE-47, BDE-99, BDE-100, BDE-153, HBCDs	Soxhlet extraction, PLE, ASE	GC–MS; GC–MS/MS; GC-TOF HRMS; GC × GC-TOF HRMS; LC-Q-Orbitrap HRMS; LC-IM-Q-TOF-HRMS	EI, CI, APCI, ESI and APPI	Quadrupole, QQQ, TOF HRMS, Q-Orbitrap HRMS, IM-Q-TOF-HRMS	(Rostkowski et al., 2019)
	Dibromo and tribromo analogues of Dechlorane 604	Solvent extraction/multilayer silica	GC-QQQ-FT-ICR-MS	EI	QQQ-FT-ICR-MS	(Jobst et al., 2013)
PBDDs/Fs	PBDEs, BTBPE and TBBA	Ultrasound assisted extraction/solvent vortexing	Q-TOF-HRMS	ESI and APCI	TOF-HRMS	(Ionas et al., 2015)
	PBDEs	PLE with off-line GPC, SPLE	GC × GC-TOF-HRMS	EI	TOF-HRMS	(Veenaas and Haglund, 2017)
	PBDEs, PBBs, tribromophenol	GPC cleanup	GC × GC-TOF HRMS and GC-FT-ICR-MS	EI	TOF-HRMS FT-ICR-MS	(Hoh et al., 2012)
	PXDFs,	high speed solvent extraction/multilayer silica/carbon columns	GC × GC-EI-TOF HRMS	EI	TOF HRMS	(Tue et al., 2019)
	PXDF	Soxhlet extraction/multilayer silica/alumina/carbon columns	GC × GC-TOF-HRMS and GC-QQQ-FT-ICR-MS APGC-APCI-QQQ-MS-MS	EI and APCI	QQQ TOF-HRMS QQQ-FT-ICR-MS	(Myers et al., 2014)
PCP	TCS, MTCS, TCC, DCC	PLE/clean-up/microfiltration	LC-APPI-Orbitrap HRMS	APPI	Orbitrap HRMS	(Chiaia-Hernandez et al., 2013)
	TCS	PLE with off-line GPC, SPLE	GC × GC-TOF-HRMS	EI	TOF-HRMS	(Veenaas and Haglund, 2017)
	TCS	LLE/Soxhlet extraction	GC × GC-TOF-HRMS	EI	TOF-HRMS	(Blum et al., 2017)

clustering and Kendrick mass plot (also using H/Cl-scale) to perform suspect and non-target screening of halogenated contaminants. Zhang et al. (2019) used GC-Q-TOF HRMS operated using APCI and mass resolution higher than 20,000 FWHM (the mass acquisition range *m/z* was from 50 to 1000 at 4 Hz) to perform dust sample analysis, and to discover the presence of chlorofluoro flame retardants.

3.2.2. Polybrominated p-dioxins and furans

Due to the toxicity analogy (van den Berg et al., 2013) with chlorinated dioxins and furans (PCDDs/Fs), and due to the relatively low availability of standards, the suspect and non-target screening of PBDDs/Fs are much less performed comparing with other two classes of halogenated contaminants of emerging concern discussed in this paper. Tue et al. (2019) performed suspect screening of mixed brominated/chlorinated furans (PXDFs) from soils near a e-waste deposit site (located in Ghana) using a GC × GC-EI-TOF HRMS instrument configured at a resolution of >5000 (FWHM) (see Table 2). Beside the molecular ion cluster (M^+), Tue et al. (2019) used theoretically predicted $[M-COBr]^+$ ions for tentatively identification of low brominated PXDFs (<6 Br atoms), as suggested by (Fernando et al., 2016), while due to thermal degradation in the GC × GC modulator, highly brominated PXDFs could not be identified.

3.2.3. Personal care products

Chiaia-Hernandez et al. (2013) performed suspect screening of contaminants of emerging concern extracted from Greifensee lake (Switzerland) sediments by LC-APPI-Orbitrap HRMS (as well using the more classical ESI) operated using a resolution of 60,000 referenced to *m/z* 400 (at FWHM) for full scan mode and a resolution of 7500 for recording high resolution product ion spectra (HR-MS/MS) (see Table 2). Upon suspect screening, Chiaia-Hernandez et al. (2013) identified TCS and tentatively its metabolites MTCS, as well TCC and tentatively its dechlorination product dichlorocarbanilide (DCC) in lake sediments. Overall, Chiaia-Hernandez et al. (2013) concluded that LC-APPI-Orbitrap HRMS is a powerful tool in identification of metabolites of triclosan and triclocarban without using reference standards.

3.3. Non-target screening methods

The non-target screening (NTS) method applied to environmental samples has to follow a certain workflow in order to generate reliable results. As usually, in the environmental monitoring, the NTS starts with sampling of different matrices (Hollender et al., 2017) that can be collected from surface water, wastewater treatment plants (WWTPs), or even from lab experiments (see Fig. 1). Upon sampling, the next step in NTS is analysis, where some method developments and sample enrichment (concentration) are needed prior to the chromatographic separation and HRMS detection. Pre-processing of data upon data acquisition is of high importance to reduce the volume and complexity of data. Upon peaks' detection, the instrumental noise can be subtracted by performing replicate measurements, and the signals given by the compounds present in blanks can be subtracted as well. Also, it is important to group all signal that might belong to a certain compound. In the prioritization step, the isotope patterns, adducts and Kendrick mass defects are used to define components. Furthermore, in order to handle the huge number of signals, the multivariate analysis (MVA) and particularly principal components analysis (PCA) are essentially for prioritization of the most relevant signals from the sample sets. Identification of unknown compounds in the samples requires almost always sophisticated MS libraries (in many cases MS/MS libraries) and evaluation of exact *m/z* features obtained by HRMS (molecular ion, fragment ions, isotope patterns) in order to tentatively assign formulas. Beside the existing databases with such unknown compounds, the information about the environmental context (origin of samples or emissions) can be also essentially for identification. The final step in NTS is the confirmation that can be performed by analysing the sample sets on different HRMS instruments from the same lab (i.e. Orbitrap, TOF, Magnetic sector, ICR) and even by intercomparing the findings with HRMS instruments other labs, as well by comparing the results with those obtained from *in silico* predictions. Afterwards, the features identified in NTS can be searched in a certain MS database and the NTS is converted into suspect screening. Finally, by using reference standards, the suspect screening methods can be eventually routinized as target screening methods. The transition between non-target screening to target screening via suspect screening was also described theoretically by Schymanski confidence levels (Schymanski et al., 2015). According to this concept, the non-target screening starts at lowest level of confidence (level 5) with the *m/z* features of interest, the suspect screening at level 3 meaning tentative candidates (via unequivocally molecular formula-level 4), while the target screening starts at level 1 (confirmed structure) via level 2 (probable structure).

Regarding the NBFRs, by using a in-house database and monoisotopic accurate masses, Ionas et al. (2015) developed a non-target
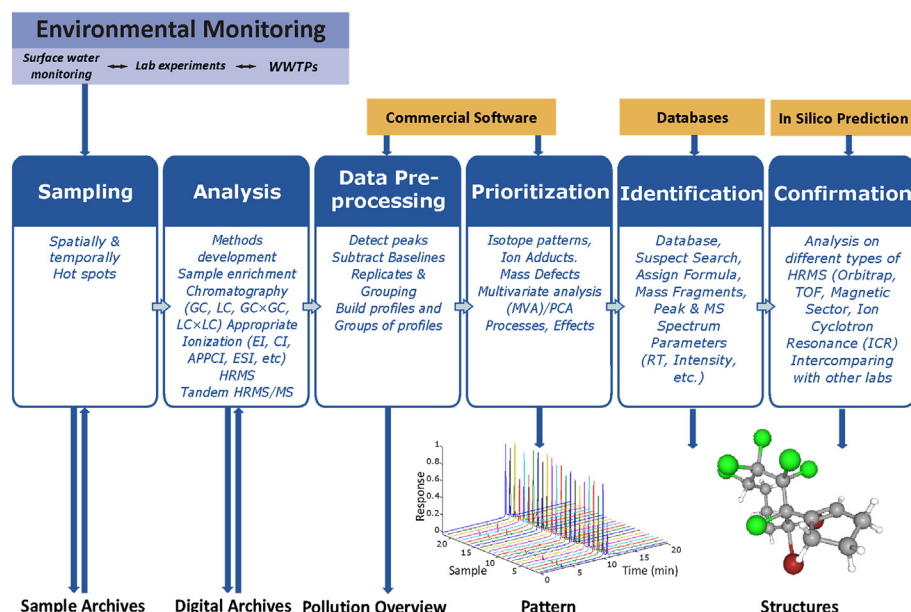

Fig. 1. The workflow of non-target screening (figure modified and adapted from Hollender et al. (2017)).

screening method for the legacy PBDEs and NBFRs (BTBPE and Tetrabromobisphenol A) from dust samples using one LC-TOF-MS and one LC-Q-TOF HRMS instruments (see Table 2), providing a resolution >16,500, respectively >20,000 (both recorded at FWHM).

Hoh et al. (2012) used a comprehensive GC × GC-EI-TOF HRMS method (mass resolution 7000 FWHM), as well a GC-EI-FT-ICR-MS approach to performed non-target screening for the identification of bioaccumulative halogenated contaminants from relevant marine fauna (common dolphin (*Delphinus delphis*) blubber). In total 271 compounds belonging to 24 classes were tentatively identified by Hoh et al. (2012), which all of them were halogenated (excepting one compound). Among the halogenated contaminants identified by Hoh et al. (2012) were 16 legacy PBDEs, and 10 polybrominated biphenyls (PBBs), as well the emerging tribromophenol. Also, Myers et al. (2014) performed non-targeted screening analysis (beside target) to identify toxic halogenated contaminants in a bioaccumulation experiment involving three freshwater organisms (*Lumbriculus variegatus*, *Hexagenia* spp., and *Pimephales promelas*) by GCxGC- TOF-HRMS and GC-QQQ-FT-ICR-MS (resolution of 40,000 at m/z 400 full width at half maximum (FWHM)), but also by atmospheric pressure gas chromatography tandem mass spectrometry (APGC-APCI-QQQ-MS-MS) (see Table 2). The following mixed brominated/chlorinated dioxins and furans (PXDFs) were identified by non-target GCxGC-TOF-HRMS analysis: $C_{12}OH_5BrCl_2$, $C_{12}OH_4BrCl_3$, $C_{12}OH_3BrCl_4$, $C_{12}OH_4Br_2Cl_2$, $C_{12}OH_3Br_2Cl_3$, $C_{12}O_2H_5BrCl_2$, and $C_{12}O_2H_4BrCl_3$.

More recently, Veenaas and Haglund (2017) performed non-target screening of Swedish sewage sludge by GC × GC-EI-TOF-HRMS (see Table 2) and they found 1865 features of which 321 were tentatively identified and later confirmed upon validation of a pressured liquid extraction (PLE) method. Among them were six PBDEs (4-Bromodiphenyl ether, BDE-28, BDE-47, BDE-99, BDE-154, and BDE-153) and one PCP (triclosan) (see Table 2). Using the same GC × GC-EI-TOF-HRMS instrument, Blum et al. (2017) performed non-target screening in wastewater from 17 different on-site sewage treatment facilities from Sweden (see Table 2). Upon peaks' extraction and alignment, Blum et al. (2017) detected >200,000 features of which 300 compounds were tentatively identified, from which 46 compounds were finally classified as of environmental concern and were semi-quantified using chrysene-d$_{12}$ (among them was the previously detected triclosan).

4. Screening methods applied to characterize the biodegradation of emerging organohalogen contaminants in aquatic environment

4.1. Flame retardants

In the case of emerging organohalogen contaminants, various metabolites can form via reaction like dehydrohalogenation, hydrolysis, hydroxylation, formation of oxy-derivates, methylation (in the case of TCS), hydrogenolysis, vicinal reduction, the last two reaction mechanisms being characteristic usually to anaerobic microorganisms. Huang et al. (2019) performed aerobic biodegradation of α-, β- and γ-

HBCD by *Pseudomonas aeruginosa HS9* and investigated the metabolites formed by both GC-EI-MS, and UPLC-ESI-TOF-MS-MS. The proposed degradation pathway found (see Fig. 2) leads initially to the formation of both 2,5,6,9,10-pentabromocyclododecanols (PBCDOHs) (by hydrolysis) and also to tetrabromocyclododecene (TBCD) (via dehydrobromination). The PBCDOHs are final metabolites, while TBCD are further degraded by dehydrobromination to dibromocyclododecadiene (DBCD), followed by a 3rd dehydrobromination to cis, trans, trans-1,5,9-cyclododecatriene (1,5,9-CDT). The last step of the degradation pathway is the oxidation of 1,5,9-CDT to 1,2-epoxy-5,9-cyclododecadiene (ECDD). In the case of UPLC-ESI-TOF-MS-MS analysis, the target and suspect screening of metabolites was performed using [M − H]⁻ and [M − Cl]⁻ adduct ions. Thus, while many detected metabolites are similar to the ones detected previously by Peng et al. (2015) by LC-ESI-Q-MS, the aerobic nature of *Pseudomonas aeruginosa HS9* (comparing with anaerobic nature of HBCD-1 used by Peng et al. (2015)) creates a different metabolic pathway. As mentioned above, Sverko et al. (2015) used GC-ECNI-MS for the target screening of anaerobic metabolites of dechloranes in sewage sludge upon reductive dechlorination and the following metabolites were detected: *syn*-DP-Cl (*exo*), *anti*-DP-Cl (*endo*), and *anti*-DP-Cl (*exo*). In this study, Sverko et al. (2015) used 649.8, 651.8, and 653.8 ions for the detection of syn-DP and anti-DP (parent compounds) and 615.7/617.7/619.7 ions for the detection of above mentioned metabolites.

4.2. Polybrominated p-dioxins and furans

Little is known about the environmental biodegradation pathways of PBDDs/Fs (van den Berg et al., 2013) and further studies are needed. It is expected that the reductive debromination to be the dominant anaerobic pathway similarly to PCCDs/Fs.

4.3. Personal care products

Chen et al. (2015) studied the aerobic biodegradation pathways of TCS in activated sludge by target and suspect screening performed using HPLC-ESI-QQQ-MS and by LC-ESI-Orbitrap HRMS, the later operated at resolution of 100,000. 2,4-Dichlorophenol ([M − H]⁻ as $m/z = 143$ and 143 to 107 transition in MRM) and 4-Chlorocatechol ([M − H]⁻ as $m/z = 161$, and 161 to 125 transition) were identified as resulting metabolites, upon C—O cleavage reaction (see pathway (I) from Fig. 3A). The methylation reaction produced MTCS, the hydroxylation reaction of one aromatic ring produced Hydroxy-Triclosans (detected as 303 to 161 transition in MRM) and Dihydroxy-Triclosans (detected as 321 to 163 transition), with the structure of 5-Hydroxy Triclosan identified also by nuclear magnetic resonance (NMR). Beside HPLC-ESI-QQQ-MS (367 to 287 transition), Triclosan-O-Sulfate (by ions 366.9002, 286.9434 and 79.95676 for O$_3$S group detected in scan mode) was identified as the metabolite of sulfation reaction (belonging to phase II metabolism) also by HRMS/MS analysis. In a more recent study, Wang et al. (2018) studied the aerobic degradation of triclosan by *Dyella* sp. WW1 strain (see pathway (II) from Fig. 3A) by suspect
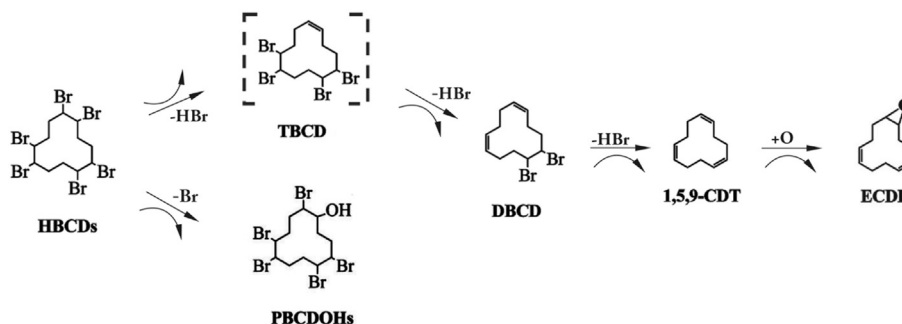

Fig. 2. Biodegradation pathway of α-, β- and γ-HBCD by *Pseudomonas aeruginosa HS9* (figure modified from Huang et al. (2019)).
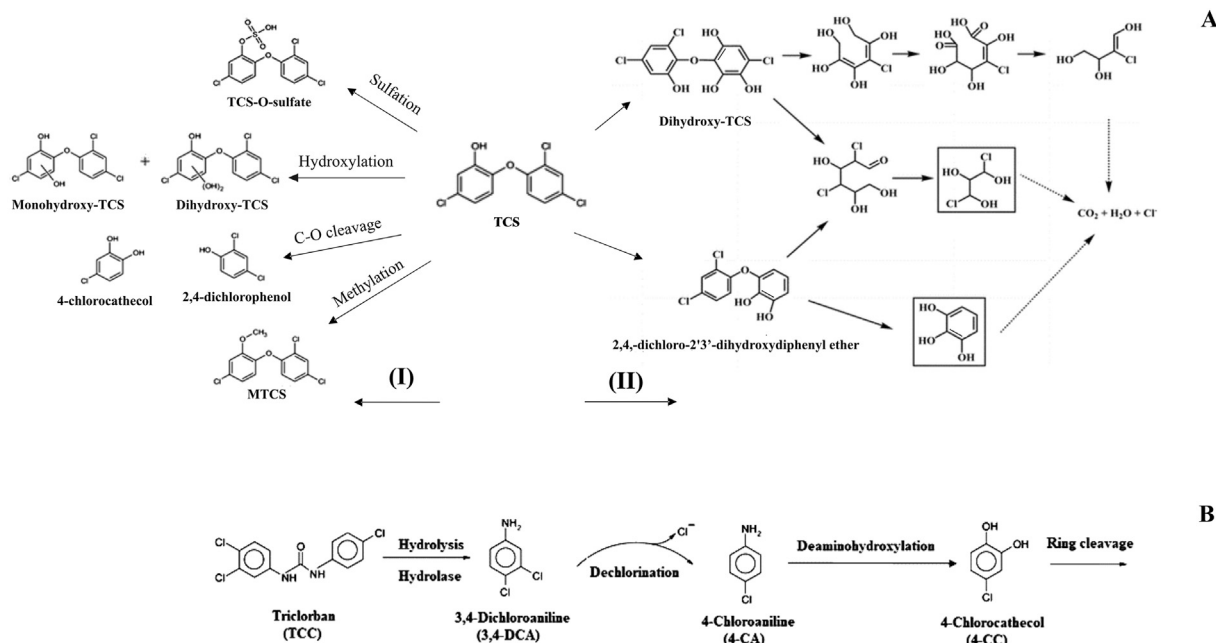
Fig. 3. Aerobic biodegradation pathways of triclosan (TCS): pathway (I) in activated sludge (modified figure from Chen et al. (2015)), and pathway (II) by *Dyella sp.* WW1 strain (modified figure from Wang et al. (2018)) (A). Aerobic biodegradation pathway of triclocarban (TCC) by *Sphingomonas* sp. strain YL-JM2C (modified figure from Mulla et al. (2016)) (B).

screening performed using HPLC-ESI-Q-MS, and two degradation sub-pathways were proposed. The 1st sub-pathway involved the formation of dihydroxy-triclosan ($m/z = 337$) by hydroxylation of both aromatic rings, metabolite identified also in a previously study by Lee et al. (2012), followed by a meta-cleavage (ring opening), reactions that might be catalysed by mono- or dioxygenases enzymes and this is demonstrated by the formation of metabolites with m/z of 195, 225, and $m/z = 215$ respectively. The 2nd sub-pathway suggested by Wang et al., (2018) is different from the 1st one by involving also of reductive dechlorination (hydrogenolysis) as shown by the formation of metabolite with m/z of 273 (2,4,-dichloro-2′3′-dihydroxydiphenyl ether). Beside the ring cleavage and the formation of a metabolite with $m/z = 215$, Wang et al. (2018) suggested also the formation of 1,2,3-Trihydroxybenzene (pyrogallol), but they were not able to detect it. Further studies using HRMS screening are needed to elucidate more properly the biodegradation of TCS by *Dyella sp.* WW1. Although reductive dechlorination of TCC in anaerobic sediment has been shown since 2008 Miller et al. (2008), there are very few studies on HRMS screening of its metabolites. Possible metabolites of TCC include 4,4′-dichlorocarbilide (DCC), 1-(3-chlorophenyl)-3-phenylurea (MCC), carbanilide (NCC) and 4-chloroaniline (4-CA) (Vimalkumar et al., 2019). Mulla et al. (2016) studied the aerobic degradation of TCC by *Sphingomonas* sp. strain YL-JM2C by target screening using GC-EI-MSD (single quadrupole). Mulla et al. (2016) deduced that a 1st degradation step of TCC is the formation 3,4-dichloroaniline by hydrolase enzyme, followed by dechlorination and formation of 4-chloroaniline, followed by deaminohydroxylation and formation of 4-chlorocatechol, and followed finally by the ring opening (see Fig. 3B). Further studies are needed to elucidate the biodegradation pathways of TCC in aquatic environment.

5. Conclusions

The screening of emerging halogenated micropollutants (target, suspect or non-target) using GC and LC coupled with HRMS became a major tool for risk assessment of those micropollutants in groundwater, surface water, wastewater, marine water, sewage sludge, sediments, contaminated soils or atmospheric depositions. Particularly, the screening of halogenated micropollutants in groundwater and surface water is of maximum important due to the used of these water sources by human inhabitants. While parent emerging halogenated contaminants can be often detected by low resolution mass spectrometry (i.e. single quadrupole, QQQ, or IT)., their transformation products are present in much lower concentrations, and therefore requires a much extensive clean-up and often HRMS to be reliable detected and even quantified in environmental samples. Therefore, the involvement of advanced hyphenated analytical techniques by GC and LC coupled with high-resolution (HR) hybrid mass spectrometers (Q-TOF HRMS, Q-Orbitrap MS, QQQ-FT-ICR-MS, or even ion mobility-quadrupole-time-of-flight mass spectrometry (IM-Q-TOF-HRMS) might be the key for identification of such transformation products by suspect and non-target screening. In spite all these, the analytical screening cannot establish alonely the degradation pathways of emerging halogenated contaminants in environment and it needs further laboratory experiments. In the lab, advanced oxidation processes (AOPs) or biodegradation experiments must be performed to create profiles of transformation products for the target contaminants of emerging concern since they mimic the transformation of those compounds in environment and these profiles can be latter used to apply the analytical screening to field samples. Within these lab experiments, compound specific isotope analysis (CSIA), enantioselective analysis, or even enantioselective stable isotope analysis (ESIA) (the last two only for chiral compounds) can be applied to characterize the degradation pathways. Therefore, in the future it is expected that a combination between non-target screening using HRMS and stable isotope techniques will be applied more extensively for identification of contaminants of emerging concern and for elucidation of their environmental fate.

Declaration of competing interest

The authors have no conflict of interests.

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