



# Recent advances in analytical methodologies based on mass spectrometry for the environmental analysis of halogenated organic contaminants

Juan F. Ayala-Cabrera, F. Javier Santos, Encarnación Moyano\*

Department of Chemical Engineering and Analytical Chemistry, University of Barcelona. Av. Diagonal 645, E-08028 Barcelona, Spain

## ARTICLE INFO

### Article history:

Received 24 November 2020

Received in revised form 13 February 2021

Accepted 16 February 2021

### Keywords:

Halogenated organic contaminants

Sample treatment

Chromatographic separation

Ionization techniques

Mass analyzers

Environmental samples

## ABSTRACT

Halogenated organic contaminants, including legislated and potential persistent organic pollutants and their precursors, represent a major environmental concern due to their hazardous effects in humans and wildlife as well as their ability to bioaccumulate through the food chain, their high resistance to environmental degradation, and their long-range atmospheric transport potential. The monitoring of these compounds in the environment at ultra-trace concentration levels requires highly selective and sensitive analytical methodologies. The lack of reference step-by-step methods led to a high number of reliable determinations depending on analytes, the complexity of the sample, and available instrumentation. Thus, this review article is mainly focused on the last advances in the analytical methodologies for the determination of halogenated organic contaminants. Methodologies regarding sample treatment, chromatographic separation, and mass spectrometry analysis have been reviewed to finally highlight the future perspectives for the improvement of the analytical determinations of these compounds and the throughput of environmental control laboratories in this field.

© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Abbreviations:** anti-DP, anti-Dechlorane Plus; CCS, Collision Cross Section; Cl<sub>10</sub>-DP, decachloropentacyclooctadecadiene or Cl<sub>10</sub>-Dechlorinated Dechlorane Plus; Cl<sub>11</sub>-DP, undecachloropentacyclooctadecadiene or Cl<sub>11</sub>-Dechlorinated Dechlorane Plus; CPs, Chlorinated Paraffins; Cy-PFAL, Cy-Perfluorinated Aldehyde; DP, Dechlorane Plus; Dec-602, Dechlorane 602; Dec-603, Dechlorane 603; Dec-604, Dechlorane 604; DTIMS, Drift Tube Ion Mobility Spectrometry; FBSA, *N*-Alquil Fluorobutane Sulfonamide; FBSE, *N*-Alquil Fluorobutane Sulfonamido-Ethanol; FOSA, *N*-Alquil Fluorooctane Sulfonamide; FOSE, *N*-Alquil Fluorooctane Sulfonamido-Ethanol; x:2 FTAL, x:2 Fluorotelomer Aldehyde; x:2 FTO, x:2 Fluorotelomer Olefin; x:2 FTOH, x:2 Fluorotelomer Alcohol; GC-APCI, Gas Chromatography-Atmospheric Pressure Chemical Ionization; GC-APPI, Gas Chromatography-Atmospheric Pressure Photoionization; GC×GC, Comprehensive Two-Dimensional Gas Chromatography; HBCDs, Hexabromocyclododecanes; α-HBCD, α-Hexabromocyclododecane; β-HBCD, β-Hexabromocyclododecane; γ-HBCD, γ-Hexabromocyclododecane; HS-SPME, Headspace Solid-Phase Microextraction; IM, Ion Mobility; LCCPs, Long-Chain Chlorinated Paraffins; MCCPs, Medium-Chain Chlorinated Paraffins; nPFAS, Neutral Per- and Polyfluoroalkyl Substances; PBDEs, Polybrominated Diphenyl Ethers; PCBs, Polychlorinated Biphenyls; PCDDs, Polychlorinated Dibenzo-*p*-dioxins; PCDFs, Polychlorinated Dibenzofurans; PCNs, Polychlorinated Naphthalenes; PFBSA, Perfluorobutane Sulfonamide; PFOSA, Perfluorooctane Sulfonamide; POPs, Persistent Organic Pollutants; PUF/XAD-2, Polyurethane Foams/Styrene-divinylbenzene Copolymer Resin; QuEChERS, Quick, Easy, Cheap, Effective, Rugged, and Safe; SBSE, Stir Bar Sorptive Extraction; SCCPs, Short-Chain Chlorinated Paraffins; *syn*-DP, *syn*-Dechlorane Plus.

\* Corresponding author.

E-mail address: [encarna.moyano@ub.edu](mailto:encarna.moyano@ub.edu) (E. Moyano).

## 1. Introduction

During the last decades, environmental pollution has become a severe threat to both human beings and wildlife. The economic and technological development of societies has led to an increase in industrial and agriculture activities, intensifying anthropogenic pollution, and severely affecting the quality of the atmosphere, water, and soil. Among the pollutants released into the environment, halogenated organic contaminants are of great concern since most of them are endocrine disruptors and can cause neurotoxicity, immunotoxicity as well as adverse effects on the reproductive system and organs, such as kidney, liver, and thyroid. Moreover, some of these halogenated organic contaminants have also been classified as persistent organic pollutants (POPs) because they can accumulate in fatty tissues and are highly resistant to degradation as well as prone to long-distance transportation in the environment [1]. Most of these halogenated POPs are pesticides (e.g., chlordane, lindane, and toxaphene) or industrial chemicals such as polychlorinated biphenyls (PCBs), polychlorinated naphthalenes (PCNs), and perfluorooctane sulfonic acid, while few others are unintentional by-products of industrial processes, such as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), among others.

In 1995, the United Nations Environment Programme (UNEP) expanded its research on halogenated organic contaminants,

focusing mainly on POPs [2]. Risk assessment results on these pollutants have forced many governments to establish restrictions or prohibitions on their production and use. Hence, reliable information about the environmental occurrence of these compounds is required to know their distribution, environmental fates, spatial and temporal trends as well as potential sources of release. Moreover, these chemicals are hazardous even at extremely low concentration levels, so powerful analytical methodologies are required to ensure their reliable monitoring in the environment. These methodologies need to meet some requirements, such as the high capacity for the detection/identification of pollutants at ultra-trace levels and high selectivity to avoid potential interferences. International organizations, such as the United States Environmental Protection Agency (US EPA), the European Committee for Standardization (CEN), or the Japanese Industrial Standards Committee (JISC), have proposed comprehensive analytical protocols for monitoring these compounds. However, the flexibility for the determination of these compounds in a wide variety of environmental samples leads to the development of many analytical methodologies, which are continuously increasing.

This review aims to provide readers with an overview of the most relevant advances in analytical methodologies used for the determination of legacy halogenated POPs, neutral per- and polyfluoroalkyl substances, and dechlorane plus and its related compounds (Table 1). Therefore, advances in sample preparation protocols, chromatographic separations, and mass spectrometry (MS) determinations/identifications are discussed based on the most relevant studies published in the last decades for these families of compounds.

## 2. Sample preparation

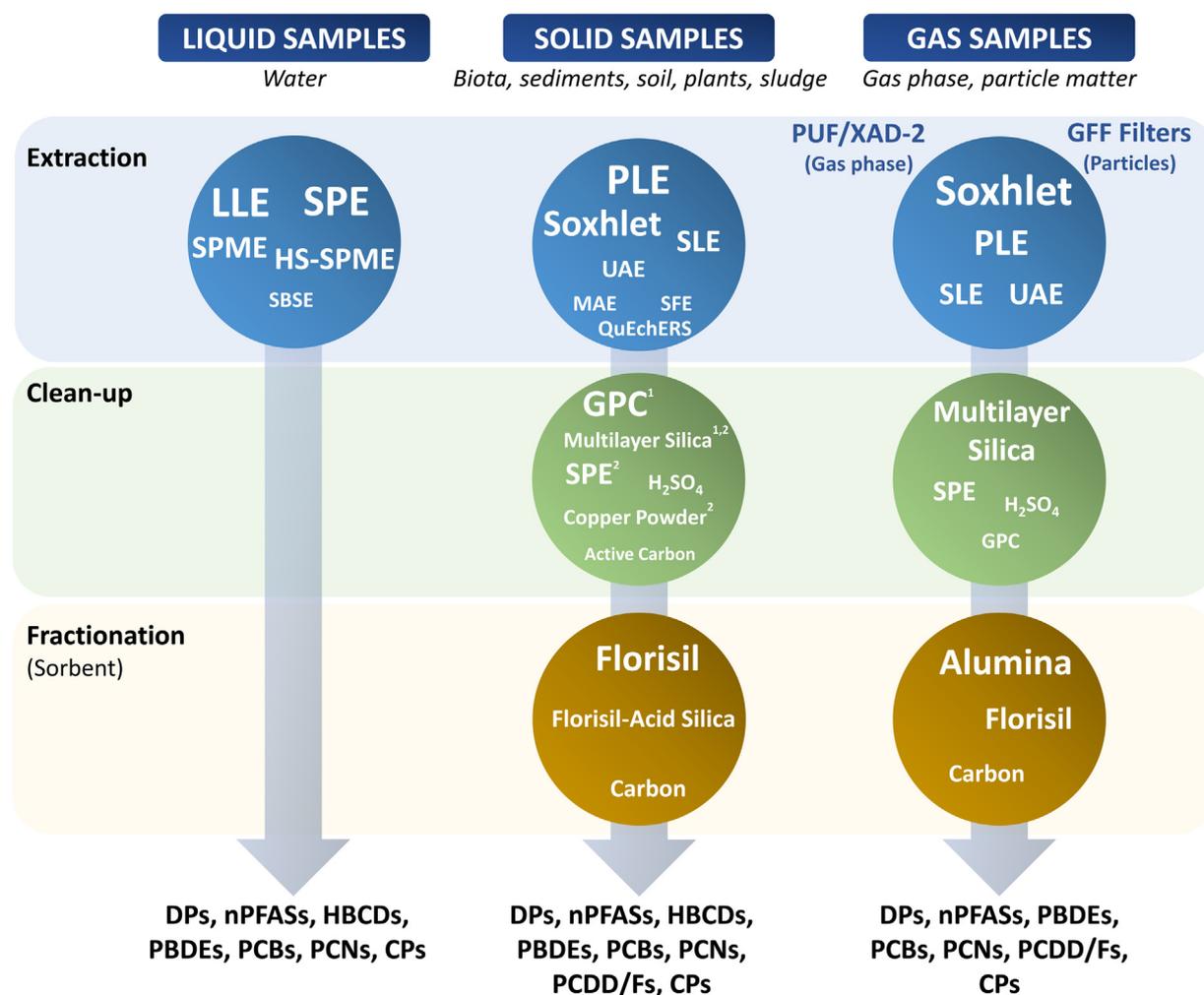
Sample preparation is a critical step in the analysis of halogenated organic contaminants in environmental samples. It often involves procedures to isolate target compounds from potential matrix interferences or structurally similar compounds, as well as to preconcentrate analytes to achieve their detection at

low concentration levels. Generally, sample preparation requires the use of extensive and laborious procedures, which are usually subjected to strict quality control protocols. To ensure the quality of the results and to control the recovery rates, surrogate internal standards, and isotopically labeled compounds are frequently added before the extraction step for achieving an accurate quantification of target compounds.

Regarding extraction techniques and clean-up procedures, many protocols have been proposed to analyze these target compounds in different environmental matrices. The most representative sample preparation methods applied to the analysis of halogenated organic contaminants in liquid, solid, and gas matrices are summarized in Fig. 1. Concerning liquid samples, liquid-liquid extraction (LLE) and solid-phase extraction (SPE) are the most commonly used techniques for the extraction of halogenated organic compounds from environmental water samples (e.g., surface water, river water, and wastewater). Dichloromethane has often been proposed as a solvent for liquid-liquid extraction of DPs, PBDEs and dioxin-like PCBs (dl-PCBs) from water samples [3,4], while methyl tert-butyl ether, hexane or ethyl acetate have been proposed for the extraction of FTOHs [5], PBDEs [6], and PCNs [7], respectively. This extraction technique has also been proposed for the analysis of serum as reported by Han et al. [8] for the determination of PCNs in blood from meat animals consumed by humans. Regarding SPE, Oasis HLB [9] and Oasis WAX [10] cartridges are often proposed for the extraction of neutral PFAS from river water and seawater samples, respectively. However, for the extraction of flame retardants, such as HBCD and PBDEs, as well as PCBs and PCNs compounds with dioxin-like toxicity, the use of C<sub>18</sub> cartridges followed by the elution of analytes with *n*-hexane-based mixtures is generally recommended [11,12]. Using these SPE procedures, recovery rates higher than 70 % for most of the target compounds have been reported [3,4,7,9,12], while for volatile compounds, such as neutral PFAS, lower values were achieved (35–55 %) [10]. This decrease on the recovery rate is sometimes caused by the adsorption of analytes on the polypropylene cartridge, as well as the losses of the

**Table 1**  
Families of halogenated organic contaminants included in this review.

Family of compounds	Classification	Linear structure
Chlorinated Paraffins (CPs)	Short-Chain Chlorinated Paraffins (SCCPs)	$C_xH_{2x+2-y}Cl_y$ ( $10 \leq x \leq 13$ , $3 \leq y \leq 14$ )
	Medium-Chain Chlorinated Paraffins (MCCPs)	$C_xH_{2x+2-y}Cl_y$ ( $14 \leq x \leq 17$ , $3 \leq y \leq 14$ )
	Long-Chain Chlorinated Paraffins (LCCPs)	$C_xH_{2x+2-y}Cl_y$ ( $x > 17$ , $3 \leq y \leq 14$ )
Dechlorane Plus (DP) and related compounds	<i>syn</i> -Dechlorane Plus ( <i>syn</i> -DP)	$C_{18}H_{12}Cl_{12}$
	<i>anti</i> -Dechlorane Plus ( <i>anti</i> -DP)	$C_{18}H_{12}Cl_{12}$
	Cl <sub>10</sub> -Dechlorinated Dechlorane Plus (Cl <sub>10</sub> -DP)	$C_{16}H_6Cl_{10}$
	Cl <sub>11</sub> -Dechlorinated Dechlorane Plus (Cl <sub>11</sub> -DP)	$C_{16}H_5Cl_{11}$
	Dechlorane 602 (Dec-602)	$C_{14}H_4Cl_{12}O$
	Dechlorane 603 (Dec-603)	$C_{17}H_8Cl_{12}$
	Dechlorane 604 (Dec-604)	$C_{13}H_4Br_4Cl_6$
Hexabromocyclododecanes (HBCDs)	$\alpha$ -Hexabromocyclododecane ( $\alpha$ -HBCD)	$C_{12}H_{18}Br_6$
	$\beta$ -Hexabromocyclododecane ( $\beta$ -HBCD)	$C_{12}H_{18}Br_6$
	$\gamma$ -Hexabromocyclododecane ( $\gamma$ -HBCD)	$C_{12}H_{18}Br_6$
Neutral per- and polyfluoroalkyl substances (nPFAS)	x:2 Fluorotelomer Alcohol (x:2 FTOH)	$C_xF_{2x+1}CH_2CH_2OH$ ( $4 \leq x \leq 12$ )
	x:2 Fluorotelomer Aldehyde (x:2 FTAL)	$C_xF_{2x+1}CH_2CHO$ ( $4 \leq x \leq 12$ )
	x:2 Fluorotelomer Olefin (x:2 FTO)	$C_xF_{2x+1}CH=CH_2$ ( $4 \leq x \leq 12$ )
	C <sub>y</sub> Perfluorinated Aldehyde (C <sub>y</sub> -PFAL)	$C_{y-1}F_{2y-1}CHO$
	N-Alkyl Fluorobutane Sulfonamide (FBSA)	$CF_3(CF_2)_3SO_2NHR$ (R: CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> )
	N-Alkyl Fluorobutane Sulfonamido-Ethanol (FBSE)	$CF_3(CF_2)_3SO_2N(R)CH_2CH_2OH$ (R: CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> )
	N-Alkyl Fluorooctane Sulfonamide (FOSA)	$CF_3(CF_2)_7SO_2NHR$ (R: CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> )
	N-Alkyl Fluorooctane Sulfonamido-Ethanol (FOSE)	$CF_3(CF_2)_7SO_2N(R)CH_2CH_2OH$ (R: CH <sub>3</sub> , C <sub>2</sub> H <sub>5</sub> )
	Perfluorobutane Sulfonamide (PFBSA)	$CF_3(CF_2)_3SO_2NH_2$
	Perfluorooctane Sulfonamide (PFOSA)	$CF_3(CF_2)_7SO_2NH_2$
	Polybrominated diphenyl ethers (PBDEs)	$C_{12}H_{10-x}Br_xO$ ( $1 \leq x \leq 10$ )
	Polychlorinated biphenyls (PCBs)	$C_{12}H_{10-x}Cl_x$ ( $1 \leq x \leq 10$ )
Polychlorinated dibenzo- <i>p</i> -dioxins (PCDDs)	$C_{12}H_{8-x}Cl_xO_2$ ( $4 \leq x \leq 8$ )	
Polychlorinated dibenzofurans (PCDFs)	$C_{12}H_{8-x}Cl_xO$ ( $4 \leq x \leq 8$ )	
Polychlorinated naphthalenes (PCNs)	$C_{12}H_{8-x}Cl_x$ ( $1 \leq x \leq 8$ )	



**Fig. 1.** Main sample preparation methods used for the determination of halogenated organic contaminants in environmental samples (<sup>1</sup>Biota samples; <sup>2</sup>Sediment, soil, plant, and sludge samples).

more volatile neutral PFAS during the evaporation step of the final extracts.

In the last decade, the use of rapid, inexpensive, and solvent-free alternative extraction techniques has been increased to improve recoveries and to avoid intensive sample handling. For instance, headspace solid-phase microextraction (HS-SPME) has been used for the analysis of neutral PFAS (FTOHs and FOSAs). Direct immersion SPME has also been proposed for the determination of SCCPs, PBDEs, and PCBs in water, while stir bar sorptive extraction (SBSE) has been reported for the analysis of SCCPs [13–16]. These extraction techniques allow *in-situ* preconcentration of analytes avoiding the use of evaporation steps that could lead to losses of the most volatile compounds.

For solid matrices, pressurized liquid extraction (PLE) [17–22] and Soxhlet extraction [4,23–26] using dichloromethane or dichloromethane/hexane mixtures as solvent are the methods most commonly used for the efficient extraction of halogenated organic contaminants. For instance, Soxhlet extraction has been proposed for the extraction of PCBs, PCNs, and SCCPs from sediments [26] and PBDEs from sewage sludge [4], while PLE has also been applied to extract PBDEs, HBCDs and PCDD/Fs from sewage sludges and sediments. DPs and related compounds have also been extracted from sediments using both Soxhlet extraction [25] and PLE [21]. In some cases, the PLE extraction is carried out using sorbents such as alumina [27] or a mixture of silica/alumina/Florisil [22] as a fat retainer to allow a more selective extraction of

target compounds and simplify the further clean-up procedures. Besides, other extraction techniques such as solvent extraction (SE), ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE) and dispersive solid-phase extractions have also been successfully applied [28–33]. For instance, SE has been used to extract neutral PFAS from sediments and biota samples [28,29] and PBDEs, PCDD/Fs, and PCBs from fatty fish tissues [30]. Ultrasound-assisted extraction (UAE) has also been proposed to extract DPs, HBCDs, PBDEs, and PCBs from marine sediments [12,31], while microwave-assisted extraction (MAE) has shown to be also suitable to extract PBDEs from this matrix [32]. On the other hand, dispersive solid-phase extraction based on QuEchERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) procedures has been satisfactorily applied to extract HBCD from fish [33]. These procedures allow a faster extraction and similar recoveries of analytes than Soxhlet and PLE, becoming potential alternatives to improve laboratory throughput.

The analysis of samples with high lipid or hydrocarbon content requires the use of multilayer columns containing different sorbents, such as silica or silica modified with sulfuric acid or/and with sodium hydroxide, to remove these interferences [17,34], as well as to fractionate the extracts for the separation of the different families of halogenated contaminants. Direct treatment of sample extracts with concentrated sulfuric acid has been considered for lipid removal in the determination of PBDEs and DPs in biota and sludge samples [21,23,35], although for extracts from

biota samples, gel permeation chromatography (GPC) with porous styrene-divinylbenzene resin columns (e.g., Bio-beads S-X3) has also shown to be an efficient technique for lipid removal [18,19,23,24,30,31,36]. Moreover, GPC could be automated, offering an important advantage for increasing laboratory throughput although it also requires large amounts of solvents for both sample clean-up and recovering of column after use.

SPE sorbents such as silica, weak anion exchange (WAX), Florisil, or alumina have also been applied to remove matrix components that could interfere in the analysis of sediments and sludges [20,25,29,35]. For instance, a multi-layer silica column has been used to remove hydrocarbons during the isolation of HBCDs

from related halogenated compounds in sediments [17]. Additionally, activated copper powder is currently used for sulfur removal in sediment analysis, since its presence in the final extract cause distortions in baseline chromatograms [31]. The fractionation of extracts to separate different groups of compounds is usually required after the sample clean-up step to remove potential interferences. Moreover, the isolation of these families of target compounds into multiple fractions allows to carry out a multi-residue analysis that provides better monitoring of the contaminants present in an environmental sample. Florisil and sometimes Florisil combined with acidic silica are the sorbents most commonly used. To elute DP and related compounds, HBCDs,

**Table 2**  
Chromatographic techniques for the separation of halogenated organic contaminants.

Separation Technique	Analyte	Stationary Phase	Mobile Phase	Injection	Ref.
HPLC	DPs and analogs	Rtx Pinnacle DB Biphenyl (10 cm × 2.1 mm; 3 μm)	CH <sub>3</sub> OH/CH <sub>3</sub> OH-H <sub>2</sub> O (3:1 v/v) (0.3 mL min <sup>-1</sup> )	1 μL n.r. <sup>a</sup>	[66]
	PCBs	XSELECT HSS T3 (10 cm × 2.1 mm; 2.5 μm)	CH <sub>3</sub> OH/H <sub>2</sub> O (0.1 mL min <sup>-1</sup> )	5 μL Full Loop	[3]
	PCNs	Hypersil Green PAH (10 cm × 2.1 mm; 3 μm)	(5 % CH <sub>3</sub> OH) CH <sub>3</sub> CN/H <sub>2</sub> O (0.08 mL min <sup>-1</sup> )	5 μL Full Loop	[7]
UHPLC	FTOHs	Acquity BEH C18 (10 cm × 2.1 mm; 1.7 μm)	CH <sub>3</sub> OH/H <sub>2</sub> O (0.1% HCOOH) (0.3 mL min <sup>-1</sup> )	5 μL n.r. <sup>a</sup>	[29]
	FTOs, FTOHs, FOSAs and FOSEs FOSAs, FOSEs and PFOSA	Luna C18 (10 cm × 2.1 mm; 1.6 μm)	CH <sub>3</sub> CN/H <sub>2</sub> O (0.3 mL min <sup>-1</sup> )	10 μL Full Loop	[9]
		HSS T3 (10 cm × 2.1 mm; 1.8 μm)	CH <sub>3</sub> OH/H <sub>2</sub> O (5 mM NH <sub>4</sub> Ac <sup>b</sup> ) (0.3 mL min <sup>-1</sup> )	10 μL Full Loop	[71]
	HBCDs	Acquity CSH Phenyl-Hexyl (10 cm × 2.1 mm; 1.7 μm)	CH <sub>3</sub> CN/CH <sub>3</sub> OH/H <sub>2</sub> O (0.3 mL min <sup>-1</sup> )	1 μL n.r. <sup>a</sup>	[67]
	HBCDs	Acquity BEH C18 (5 cm × 2.1 mm; 1.7 μm)	CH <sub>3</sub> CN-CH <sub>3</sub> OH (1:1 v/v)/H <sub>2</sub> O (0.2 mL min <sup>-1</sup> )	1 μL n.r. <sup>a</sup>	[17]
	PBDEs	BEH C18 (15 cm × 2.1 mm; 1.7 μm)	CH <sub>3</sub> OH/H <sub>2</sub> O (0.25 mL min <sup>-1</sup> )	5 μL Partial Loop	[27]
	SCCPs, MCCPs and LCCPs	C18 Eclipse Plus (5 cm × 2.1 mm; 1.8 μm)	CH <sub>3</sub> OH/H <sub>2</sub> O (0.5 mM NH <sub>4</sub> Cl) (0.2 mL min <sup>-1</sup> )	5 μL n.r. <sup>a</sup>	[69]
pSFC GC	PCDD/Fs	Torus 1-AA (10 cm × 3.0 mm; 1.7 μm)	CO <sub>2</sub> /CH <sub>3</sub> OH (1 mL min <sup>-1</sup> )	n.r. <sup>a</sup> n.r. <sup>a</sup>	[46]
	DPs and analogs DPs	DB-5MS (30 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[56]
		DB-5HT (15 m × 0.25 mm; 0.1 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Pulsed Splitless	[51]
	FTOs, FTOHs, FOSAs; FOSEs, PFOSA, N-MeFBSA, N-MeFBSE	CP-Wax 57 CB (25 m × 0.25 mm; 0.2 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[47]
	FTOs, FTOHs, FOSAs and FOSEs FTOHs, FOSAs and FOSEs	DB-624 (60 m × 0.25 mm; 1.4 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[9]
		TG-WaxMS (30 m × 0.25 mm; 0.25 μm)	He (1.4 mL min <sup>-1</sup> )	2 μL Pulsed Splitless	[48]
	HBCDs	DB-1HT (15 m × 0.25 mm; 0.1 μm)	He (4.0 mL min <sup>-1</sup> )	1 μL Pulsed Splitless	[52]
	PBDEs	Rtx-1614 (15 m × 0.25 mm; 0.1 μm)	He or N <sub>2</sub> (3.0 mL min <sup>-1</sup> )	1 μL Splitless/ Split	[53]
	PBDEs	DB-5HT (15 m × 0.25 mm; 0.1 μm)	He (1.0 mL min <sup>-1</sup> )	10 μL PTV <sup>c</sup>	[54]
	PCDD/Fs and dl-PCBs	HP-5MS (30 m × 0.25 mm; 0.25 μm)	He (1.2 mL min <sup>-1</sup> )	1 μL Splitless, PTV	[50]
		DB-5MS (60 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[46]
	PCNs	DB-5 (60 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[38]
	PCNs	Rtx-5MS (60 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[38]
		RTX-Dioxin2 (40 m × 0.18 mm; 0.18 μm)	He (0.8 mL min <sup>-1</sup> )	1 μL Splitless	[72]
	SCCPs	DB-5 (15 m × 0.25 mm; 0.25 μm)	He (0.9 mL min <sup>-1</sup> )	2 μL Pulsed Splitless	[57]
SCCPs and MCCPs	TG-5SiIMS (15 m × 0.25 mm; 0.25 μm)	He (1.4 mL min <sup>-1</sup> )	n.r. <sup>a</sup> Pulsed Splitless	[58]	
GC×GC	PCNs	HP5-MS UI (15 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )	5 μL PTV <sup>c</sup>	[63]
		Rt-β DEXcst (30 m × 0.25 mm; 0.25 μm)	He (2.49 mL min <sup>-1</sup> )	1 μL Splitless, PTV	
	PCBs and PCNs	DB-WAX (2 m × 0.1 mm; 0.1 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[64]
		DB-XLB (20 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[64]
	PBDEs, PCBs and PCDD/Fs	BPX-70 (2 m × 0.1 mm; 0.1 μm)	He (488.8 kPa at 70 °C)	1 μL Splitless	[65]
SCCPs and MCCPs	InertCap-5MS/Sil (60 m × 0.25 mm; 0.1 μm)	He (1.0 mL min <sup>-1</sup> )	1 μL Splitless	[18]	
		SGE BPX-50 (1.5 m × 0.1 mm; 0.1 μm)	He (1.0 mL min <sup>-1</sup> )		
		DB-5MS (30 m × 0.25 mm; 0.25 μm)	He (1.0 mL min <sup>-1</sup> )		
		BPX-50 (1 m × 0.1 mm; 0.1 μm)	He (1.0 mL min <sup>-1</sup> )		

<sup>a</sup> Not reported.

<sup>b</sup> Ammonium acetate.

<sup>c</sup> Solvent vent mode.

PBDEs, and PCBs from these sorbents solvent mixtures with high *n*-hexane content are proposed, while for eluting CPs, PCDD/Fs, and PCNs solvent mixtures with high dichloromethane or toluene content are recommended. Additionally, carbon cartridges are usually backflushed with toluene to isolate planar compounds (PCNs, PCDD/Fs, and dioxin-like PCBs) from other related non-planar contaminants (DPs, *ortho*-PCBs, PBDEs or CPs, among others) [23,26,34,37].

For the analysis of gaseous samples (e.g., ambient air and emissions) in both gas-phase and particulate-phase are often collected using polyurethane foams/styrene-divinylbenzene copolymer resins (e.g., PUF/XAD-2) and glass-fiber filters (GFF), respectively. After sampling, these sorbents are generally extracted by Soxhlet or PLE and clean-up by multilayer silica [38–40]. Regarding PCNs, dioxin like-PCBs, and PCDD/Fs, which are often determined in fly ashes, the fractionation of the extracts is usually carried out on a multilayer silica column followed by alumina or Florisil ones [41,42]. It is important to highlight that with this protocol more volatile compounds such as mono- and diCNs led to low recoveries due to losses during the solvent evaporation process with a nitrogen stream. In this sense, Li et al. [38] have proposed to limit the evaporation steps to the use of rotary evaporation for improving the recoveries of mono- and diCN congeners.

### 3. Chromatographic separation

Mass spectrometry-based analytical strategies frequently require the use of a previous chromatographic separation to simplify and ensure the correct detection and quantification of analytes. Among them, gas chromatography (GC) and liquid chromatography (LC) are the separation techniques most commonly used for the analysis of these pollutants [43], although the use of packed column supercritical fluid chromatography (pSFC) has also been proposed for the analysis of PCDD/Fs, PCBs, DPs, and HBCDs [44–46]. This section reports an overview of the separation techniques currently employed for the determination of halogenated organic contaminants in environmental samples. Table 2 summarizes the chromatographic conditions of the most relevant articles published in the last years on this topic.

#### 3.1. Gas chromatography

Gas chromatography is the method of choice for the separation of most of these analytes due to their relatively high volatility. As most of them are non-polar or low-polar compounds, 5 % phenyl 95 % dimethylpolysiloxane (e.g., DB-5MS, DB-5HT, etc.) is the “gold standard” stationary phase that generally provides good chromatographic resolution for these families of compounds. However, other fused-silica capillary columns have also been proposed for the determination of specific families of halogenated organic contaminants. Poly(ethylene glycol)-based stationary phases are usually selected to achieve the simultaneous separation of FTOHs, PFOSA, FBSAs, FOSAs FBSEs, and FOSEs [47,48], while semi-polar stationary phases such as 6 % cyanopropylphenyl 94 % dimethylpolysiloxane (e.g., DB-624) are often used when non-polar FTOs are analyzed simultaneously with other more polar neutral PFAS. In that case, a thick stationary phase film (1.4  $\mu\text{m}$ ) is required to properly retain the FTOs providing good chromatographic peak shapes and enough separation from the other families of neutral PFAS [9]. Concerning HBCDs, 100 % dimethylpolysiloxane as well as 5 % phenyl 95 % dimethylpolysiloxane stationary phases are typically selected for gas chromatographic separation. GC-based methods are generally focused on the determination of the total concentration of the 16 potential HBCDs (six enantiomers and diastereomeric pairs) since the GC separation of HBCD isomers is not well resolved and interconversion between isomers generally

occurs due to the high temperatures applied in the GC inlet and/or in the MS ionization source [49]. The separation of dioxin-like compounds (PCDD/Fs, dioxin like-PCBs and PCNs) generally requires capillary columns of 60 m length and 0.18–0.25 mm internal diameter to achieve a satisfactory chromatographic separation of most representative isobaric compounds [38,46,50]. In contrast, the analysis of HBCDs, PBDEs, DP and related compounds are typically performed on capillary columns of 15 m, since they provide enough chromatographic resolution and a significant reduction on the analysis time [51–54], avoiding the decomposition of some thermolabile compounds, such as highly brominated PBDEs (e.g., BDE-209) during the GC analysis [55]. In this sense, the 15 m-Rtx<sup>®</sup>-1614 column, which consists of a 5 % phenyl 95 % dimethylpolysiloxane stationary phase is commonly recommended to improve the response of these thermally labile PBDEs [53]. Rjabova et al. [56] also indicated that the chromatographic behavior of Dec-604 can also be improved by using this stationary phase. On the other hand, even though the total separation of isobaric congener groups is not possible for CPs (more than 10,000 compounds), many authors reported the use of short fused-capillary columns for a total CP determination, since they increase the signal-to-noise (S/N) ratios and reduce analysis time [57,58].

Helium is by far the most widely used carrier gas for the GC separation of target compounds using flow rates around 1.0 mL  $\text{min}^{-1}$  when it is coupled to mass spectrometry using conventional ionization sources such as electron ionization (EI) and chemical ionization (CI). However, it is important to highlight that the use of atmospheric pressure ionization sources (API) for GC-MS analysis, especially with atmospheric pressure chemical ionization (APCI), requires relatively high flow rates (from 1.4 up to 4 mL  $\text{min}^{-1}$ ), probably to prevent potential post-column band broadening in the API source. This effect could also be avoided by using nitrogen as a make-up gas at the transfer line to improve the ion transmission from the capillary column to the ion source and mass spectrometer inlet [48,52,53,59–62]. Split/splitless injector port in splitless mode is generally preferred as most of the halogenated contaminants are present in environmental samples at very low concentration levels. In some cases, pulsed splitless injection mode has been proposed for the effective transfer of analytes with high molecular weights and low vapor pressures, like DP and related compounds, HBCDs, MCCPs, and LCCPs, from the inlet to the column head by increasing the carrier gas pressure during the splitless injection [51,52,57,58]. Programmed temperature vaporization (PTV) injection has also been proposed showing significant advantages over traditional split and splitless injection modes such as avoiding syringe discrimination and holding back of non-volatile compounds in the liner, as well as allowing large volume injections by removing solvent vapors (solvent purge) before the transfer of the analyte from the PTV inlet to the column head [54,58].

#### 3.2. Comprehensive two-dimensional gas chromatography

Comprehensive two-dimensional gas chromatography (GC $\times$ GC) is the multidimensional chromatographic separation technique most used for the determination of complex mixtures of halogenated pollutants. This technique significantly increases the peak capacity (selectivity) and the sensitivity over one-dimensional GC by connecting two columns through a modulator, which traps compounds eluting in the first column and efficiently transfers them onto the second column, often with an orthogonal selectivity [43]. GC $\times$ GC allows the separation of compounds closely eluting in one-dimensional GC. Generally, the GC $\times$ GC methods developed for the separation of complex mixtures of halogenated contaminants are based on the use of a long first-

dimension column (30–60 m length) with a low polarity stationary phase and a short second-dimension column (1–2 m length) with a more polar stationary phase. As an example, Hanari et al. [63] proposed a GC×GC separation for closely eluting PCNs (from tetraCNs to octaCN) based on a 14 % cyanopropylphenyl 86 % dimethylpolysiloxane stationary phase as first-dimension column with a poly(ethylene glycol)-based stationary phase as the second-dimension column using a modulation time of 8 s. This method achieved the separation of PCN congeners, but it required a slow-temperature program for the complete separation of tetra to hexaCN congeners, which led to a total run time of 204 min. The GC×GC separation of other families of contaminants with dioxin-like toxicity such as dioxin like-PCBs and PCDD/Fs, as well as PBDEs, have also been achieved by using the following combination of columns, DB-XLB×BPX-70 [64] and InertCap 5MS/Sil×SGE BPX-50 [65], respectively. The separation of overly complex mixtures such as SCCPs and MCCPs has also been evaluated by GC×GC. Xia et al. [18] proposed a method for their simultaneous analysis (chromatographic profile and quantitative data) that achieved good orthogonality on the separation of these families of compounds and allowed the determination of 48 CP congener groups in only one GC×GC run. This method also allowed the separation of SCCPs and MCCPs from other related compounds such as PCBs, PBDEs, organochlorine pesticides, or toxaphenes, minimizing potential interferences. Therefore, the high separation capacity of GC×GC combined with the high identification capacity of high-resolution mass spectrometers provides a powerful tool for the characterization of complex environmental samples. It also allows both the selective quantification of target compounds and the non-targeted approaches to detect suspect and new contaminants, although this may involve long-time and complex data treatment [18,64,65].

### 3.3. Liquid chromatography and supercritical fluid chromatography

In the last decades, liquid chromatography has allowed expanding the environmental analysis of a wider range of halogenated contaminants, including polar, ionic, non-volatile and thermally labile compounds, which were more difficult to analyze by GC [43]. Reversed phases, mainly  $C_{18}$ , are the stationary phases most widely used to achieve the chromatographic separations of many of these compounds. Other columns based on biphenyl-embedded stationary phases have also been proposed to improve the separation of DP isomers since these columns also allow  $\pi$ - $\pi$  and steric interactions of analytes in addition to the hydrophobic ones exhibited by the conventional  $C_{18}$  columns. Thus, the  $\pi$ - $\pi$  interactions may improve the separation between those species with and without  $\pi$  electrons, while steric interactions may yield shape recognition of the different chemical structures [66]. As a result of the general trend observed in the last decade towards the widespread use of ultra-high performance liquid chromatography (UHPLC) columns (sub-2  $\mu$ m particle size), many LC methodologies developed for the analysis of halogenated organic contaminants already propose the use of these UHPLC columns taking advantage of the high chromatographic efficiency and short analysis time they provide. For instance, Ayala-Cabrera et al. [9] suggested the use of a  $C_{18}$  column packed with 1.6  $\mu$ m totally porous particles to improve the chromatographic separation of neutral PFAS (FTOs, FTOHs, FOSAs and FOSEs), thus achieving faster separation than GC-based methods. LC-based methods are frequently chosen to separate diastereomers of HBCDs. For instance, Zhao et al. [17] proposed a UHPLC method for the selective separation of  $\alpha$ -HBCD,  $\beta$ -HBCD, and  $\gamma$ -HBCD using a reversed-phase stationary phase ( $C_{18}$ ) and a ternary mobile phase (methanol/acetonitrile/water), while for the base line separation of these three diastereomers and  $\delta$ -HBCD and  $\epsilon$ -HBCD (recently

detected in industrial mixtures) a phenyl-hexyl stationary phase and a ternary mobile phase was required [67]. However, when the separation of HCBD enantiomers is considered, the use of a chiral stationary phase such as the permethylated  $\beta$ -cyclodextrin column has been proposed requiring a linear gradient of water/methanol/acetonitrile to achieve their baseline separation [68]. For PBDEs, PCBs and PCNs, the LC separation is usually achieved using stationary phases that favor hydrophobic ( $C_{18}$ ) as well as  $\pi$ - $\pi$  interactions (Hypersil Green PAH) [3,7,27]. Moreover, even though the separation of CPs has also been investigated by liquid chromatography, the chromatographic resolution achieved was lower than in GC columns [69].

Standard hydro-organic mobile phase mixtures mainly without the presence of acidic or basic species are generally employed providing enough elutropic strength and satisfactory peak shape for the retention and separation of the halogenated organic contaminants. An aspect to highlight is the effect of the mobile phase composition in the ionization efficiency of analytes when working with API sources. This fact makes necessary a careful optimization of the mobile phase composition to fulfil the minimum requirements in terms of sensitivity for the adequate determination of these compounds. As an example, Zhou et al. [66] proposed the use of methanol/water mixtures instead of acetonitrile/water as mobile phase to achieve better response of DP and related compounds when using API sources. Ayala-Cabrera et al. [70] also evaluated this effect in APCI and atmospheric pressure photoionization (APPI) response of FTOHs, FOSAs and FOSEs. They concluded that only methanol/water mixtures allowed the ionization of FTOHs by deprotonation when using APCI, whereas acetonitrile/water mixtures provided the highest responses for the deprotonated molecule using APPI negative ion mode. On the other hand, when neutral PFAS are determined simultaneously with legacy PFAS, ammonium acetate is usually added to the mobile phase to ensure the retention of the polar and ionic compounds, but this can negatively affect the ionization of neutral PFAS [71].

Packed column supercritical fluid chromatography (pSFC) has also been reported to facilitate the simultaneous analysis of different families of compounds or thermally labile compounds, such as DPs, PCBs, PCDD/Fs or HBCDs [44–46]. For instance, PCDD/Fs have been separated in a column based on a two-stage functionalization stationary phase containing a 2-(propyloxy) ethanol chain and a 1-aminoanthracene group (Torus 1-AA column from Waters) employing supercritical  $CO_2$  and methanol as a cosolvent. The aromaticity of this stationary phase allows the retention of PCDD/Fs through the  $\pi$  electrons. Even though the elution profile of this chromatographic separation was similar to that achieved in GC using a DB-5 column, the resolution was worse [46]. This technique could be a complementary analytical tool for the analysis of halogenated pollutants, although further investigation to improve resolution would be required to propose pSFC as a potential alternative to conventional GC separations.

## 4. Mass spectrometry

Mass spectrometry is a powerful technique, especially when coupled with chromatography, allowing to overcome the lack of confirmation of classical selective detection systems (e.g., electron capture detector, fluorescent detection, or even electrochemical detection) for the determination of halogenated organic contaminants. Some of the important advantages offered by mass spectrometry techniques over classical detection systems are the unequivocal identification/confirmation, the structural and isotope information needed for analyte characterization, the selectivity to prevent interferences and to differentiate isobaric coeluting compounds as well as to reduce the background noise improving sensitivity. Additionally, recent advances in mass

**Table 3**  
Mass spectrometry systems used for the determination of halogenated organic contaminants.

Analyte	Inlet System	Ionization Technique	Ion Source Conditions	Precursor Ion	Mass Analyzer	iLOD (pg $\mu\text{L}^{-1}$ )	Ref.		
CPs	GC	EI	70 eV	$[\text{C}_7\text{H}_7]^+ / [\text{C}_5\text{H}_7\text{Cl}]^{+\bullet}$	QqQ	90–230	[16,34,75,76]		
			70 eV	$[\text{M}]^{+\bullet}$ (deuterodechlorinated analogs)	QTOF	1.5 <sup>a,d</sup>	[79]		
		NICI	Methane/ $\text{NH}_3^b$	$[\text{M}-\text{Cl}]^- / [\text{M}-\text{HCl}]^{-\bullet}$	QqQ	n.r. <sup>c</sup>	[75,76]		
			n.r. <sup>c</sup>	$[\text{M}-\text{Cl}]^- / [\text{M}-2\text{Cl}]^{-\bullet}$	QTOF	24–170	[80]		
			Methane <sup>b</sup>	$[\text{M}-\text{Cl}]^- / [\text{M}-\text{HCl}]^{-\bullet}$	Q-Orbitrap	0.03–2.02 <sup>d</sup>	[58]		
			Methane <sup>b</sup>	$[\text{M}-\text{Cl}]^-$	Q	100–700	[34]		
		GC $\times$ GC	NICI	Methane <sup>b</sup>	$[\text{M}-\text{Cl}]^- / [\text{M}-\text{HCl}]^{-\bullet}$	TOF	n.r. <sup>c</sup>	[18]	
				LC	ESI (–)	$\text{NH}_4\text{Cl}^e$	$[\text{M}+\text{Cl}]^-$	QTOF	10–20
		FIA <sup>f</sup>	ESI (–)	ESI (–)	$\text{CH}_2\text{Cl}_2^g$	$[\text{M}+\text{Cl}]^-$	QTOF	50–400	[81]
				APCI (–)	$\text{CH}_2\text{Cl}_2^g$	$[\text{M}+\text{Cl}]^-$	QTOF	30–1200/0.2–100 <sup>d</sup>	[82,83,84]
DPs	GC	EI	$\text{CHBr}_3^g$	$[\text{M}+\text{Br}]^-$	QTOF	0.1–160 <sup>d</sup>	[85]		
			35 eV	$[\text{C}_5\text{Cl}_6]^{+\bullet} / [\text{C}_7\text{H}_2\text{Cl}_5]^+ / [\text{C}_5\text{H}_x\text{Cl}_y]^{+\bullet \ddagger}$	QqQ	n.r. <sup>c</sup>	[31]		
		NICI	35 eV	$[\text{C}_5\text{Cl}_6]^{+\bullet} / [\text{C}_7\text{H}_2\text{Cl}_5]^+ / [\text{C}_5\text{H}_x\text{Cl}_y]^{+\bullet \ddagger}$	Sectors	0.003–0.064	[51,56]		
			Methane <sup>b</sup>	$[\text{M}]^{-\bullet} / [\text{Br}]^-$	Q	0.005–0.096 <sup>a</sup>	[21]		
			Methane <sup>b</sup>	$[\text{M}]^{-\bullet} / [\text{Br}]^-$	QqQ	0.017–0.075 <sup>a</sup>	[21]		
			–	$[\text{C}_7\text{H}_2\text{Cl}_5]^+ / [\text{M}+\text{H}-\text{Cl}]^{+\bullet}$	QTOF	n.r. <sup>c</sup>	[19]		
		LC	GC-APCI (+)	–	$[\text{M}+\text{Cl}]^-$	QqQ	n.r. <sup>c</sup>	[66]	
			ESI (–)	$\text{NH}_4\text{Cl}^g$	$[\text{M}+\text{H}]^- / [\text{M}-\text{X}+\text{O}]^{-\ddagger}$	QqQ	n.r. <sup>c</sup>	[66]	
		APCI (–)	–	$-\text{NH}_4\text{Cl}^g$	$[\text{M}+\text{H}]^- / [\text{M}-\text{Br}+\text{O}]^- / [\text{M}-\text{xH}+\text{yCl}-\text{zO}]^{-\square}$	QqQ	25–50 <sup>a</sup>	[66]	
			APPI (–)	Acetone <sup>g</sup>	$[\text{M}-\text{Br}-4\text{HBr}]^+$	QqQ	n.r. <sup>c</sup>	[86]	
HBCDs	GC	EI	70 eV	$[\text{M}-\text{Br}]^+$	QqQ	0.1	[52]		
			–	$[\text{M}-\text{Br}]^+$	QqQ	0.09–0.19	[17,86,87]		
		GC-APCI (+)	–	$[\text{M}-\text{H}]^-$	Orbitrap	0.39–0.90 <sup>a</sup>	[88]		
			–	$[\text{M}-\text{H}]^-$	QqQ	0.3–0.4 <sup>a</sup>	[89]		
		APCI (–)	–	$[\text{M}-\text{H}]^-$	QqQ	4.3–23	[90]		
			APPI (–)	Toluene + 1,4-DBB <sup>g,h</sup>	$[\text{M}+\text{Br}]^-$	Q	n.r. <sup>c</sup>	[44]	
		pSFC	APPI (–)	Fluorobenzene <sup>g</sup>	$[\text{M}-\text{H}]^-$	Q	n.r. <sup>c</sup>	[44]	
			–	FAPA (–)	Helium	QIT	10,000	[91]	
		nPFAS	GC	EI	70 eV	$[\text{C}_3\text{H}_2\text{F}_3]^+ / [\text{C}_3\text{H}_3\text{F}_2]^+ / [\text{NSO}_2\text{HR}]^{+\ddagger} / [\text{M}-\text{CH}_3\text{O}]^+$	Q	0.2–6	[9]
					–	$[\text{M}+\text{H}]^+ / [\text{M}-\text{F}]^+$	Q	0.06–4	[9,47,78]
PCI	Methane <sup>b</sup>			$[\text{M}-\text{xHF}]^{+\ddagger} / [\text{NSO}_2\text{HR}]^{-\ddagger} / [\text{C}_2\text{H}_5\text{ONSO}_2\text{R}]^{+\ddagger}$	Q	n.r. <sup>c</sup>	[9,78]		
	Methane <sup>b</sup>			$[\text{M}+\text{H}]^+$	QqQ	0.001–0.005 <sup>a</sup>	[48]		
GC-APCI (+)	$\text{H}_2\text{O}^i$			$[\text{M}+\text{O}_2]^{-\bullet} / [\text{M}-\text{H}]^- / [\text{M}-\text{CH}_3\text{F}_2]^-$	Orbitrap	0.03–0.2	[92]		
	GC-APPI (–)			Acetone <sup>i</sup>	$[\text{M}+\text{CH}_3\text{COO}]^-$	QqQ	n.r. <sup>c</sup>	[71]	
LC	ESI (–)			$\text{NH}_4\text{Ac}^c$	$[\text{M}-\text{H}]^-$	QqQ	n.r. <sup>c</sup>	[5]	
	–			–	$[\text{M}-\text{H}]^- / [\text{M}-\text{C}_2\text{H}_4\text{OF}]^- / [\text{M}-\text{xHF}]^{-\ddagger}$	QqQ	0.3–1	[9]	
APCI (–)	–			Acetonitrile/ $\text{H}_2\text{O}^c$	$[\text{M}-\text{H}]^- / [\text{M}-\text{C}_2\text{H}_4\text{OF}]^-$	QqQ	0.7–75	[70]	
	–			Methanol/ $\text{H}_2\text{O}^c$	$[\text{M}-\text{H}]^- / [\text{M}+\text{O}_2]^{-\bullet}$	QqQ	0.08–1	[28,70]	
PBDEs	GC	EI	70 eV	$[\text{M}]^{+\bullet}$	Q	0.2–200 <sup>a</sup>	[40]		
			65 eV	$[\text{M}]^{+\bullet} / [\text{M}-\text{Br}_2]^{+\bullet}$	QqQ	0.04–24 <sup>a</sup>	[74]		
		NICI	45 eV/–	$[\text{M}]^{+\bullet} / [\text{M}-\text{Br}_2]^{+\bullet}$	Sectors	0.010–11	[36,73,93]		
			Methane/ $\text{NH}_3^b$	$[\text{Br}]^-$	Q	n.r. <sup>c</sup>	[35,94]		
		GC-APCI (+)	–	$[\text{M}+\text{H}]^+ / [\text{M}]^{+\bullet}$	QTOF	0.013–2.5	[93]		
			–	$[\text{M}+\text{H}]^+ / [\text{M}]^{+\bullet}$	QqQ	0.001–0.01	[95]		
		–	$\text{H}_2\text{O}/\text{HCOOH}$ (1%) <sup>i</sup>	$[\text{M}+\text{H}]^+$	QqQ	0.001–0.025	[95]		
			–	–	$[\text{M}]^{+\bullet}$	TOF	n.r. <sup>c</sup>	[53]	
		GC-APPI (+)	–	$[\text{M}-\text{Br}+\text{O}]^-$	QqQ	0.10–0.72 <sup>a</sup>	[27]		
			APCI (–)	Toluene <sup>g</sup>	$[\text{M}]^{+\bullet}$	QqQ	n.r. <sup>c</sup>	[96]	
APPI (+)	–	Toluene <sup>g</sup>	$[\text{M}-\text{Br}+\text{O}]^- / [\text{M}-2\text{Br}+\text{O}]^{-\bullet}$	QqQ	0.11–6.3 <sup>a</sup>	[6,27]			
	APPI (–)	Toluene/Acetone <sup>g</sup>	$[\text{M}-\text{Br}+\text{O}]^-$	Q-Orbitrap	0.2–2.2 <sup>a</sup>	[24]			
–	APCI (–)	–	$[\text{M}-\text{Br}+\text{O}]^-$	DTIMS-QTOF	n.r. <sup>c</sup>	[97]			
	APPI (–)	Toluene/Acetone <sup>e</sup>	$[\text{M}-\text{Br}+\text{O}]^-$	DTIMS-QTOF	n.r. <sup>c</sup>	[97]			
PCBs	GC	EI	70 eV	$[\text{M}]^{+\bullet}$	QqQ	0.05–0.63	[50]		
			32 eV	$[\text{M}]^{+\bullet}$	Sectors	0.004–0.007	[50]		
		NICI	Methane <sup>b</sup>	$[\text{M}]^{-\bullet}$	Q	n.r. <sup>c</sup>	[22]		
			–	$[\text{M}]^{+\bullet}$	QqQ	0.0025	[60,61,98]		
		GC-APCI (+)	–	$[\text{M}]^{+\bullet}$	QTOF	0.02–0.5	[99]		
			–	$[\text{M}-\text{Cl}+\text{O}]^-$	IT	1–1000	[100]		
		GC- $\mu$ APCI (–)	–	$[\text{M}-\text{Cl}+\text{O}]^-$	Orbitrap	0.0005–0.01 <sup>a</sup>	[101]		
			GC-APPI (–)	Diethyl ether <sup>i</sup>	$[\text{M}-\text{Cl}+\text{O}]^-$	IT	1–2000	[100]	
		GC- $\mu$ APPI (–)	–	Toluene <sup>i</sup>	$[\text{M}-\text{Cl}+\text{O}]^-$	QqQ	0.29–8.3 <sup>a</sup>	[3]	
			APPI (–)	Toluene <sup>g</sup>	$[\text{M}-\text{Cl}+\text{O}]^-$	DTIMS-QTOF	n.r. <sup>c</sup>	[97]	
–	APCI (–)	–	$[\text{M}-\text{Cl}+\text{O}]^-$	DTIMS-QTOF	n.r. <sup>c</sup>	[97]			
	APPI (–)	Toluene/Acetone <sup>e</sup>	$[\text{M}-\text{Cl}+\text{O}]^-$	DTIMS-QTOF	n.r. <sup>c</sup>	[97]			
PCDD/Fs	GC	EI	70 eV	$[\text{M}]^{+\bullet}$	QqQ	0.07–0.75 <sup>a</sup>	[50]		
			70 eV	$[\text{M}]^{+\bullet}$	IT	0.04–0.86 <sup>a</sup>	[30]		
		–	32 eV	$[\text{M}]^{+\bullet}$	Sectors	0.007–0.026 <sup>a</sup>	[50]		
			70 eV	$[\text{M}]^{+\bullet}$	Orbitrap	0.009–0.055 <sup>a</sup>	[102]		
		GC-APCI (+)	–	$[\text{M}]^{+\bullet}$	QqQ	0.001–0.002 <sup>a</sup>	[59,103,104]		
			GC-APPI (–)	Benzene	$[\text{M}-\text{Cl}+\text{O}]^-$	Orbitrap	0.0005–0.025 <sup>a</sup>	[101]	
		LC	APCI (+)	Benzene <sup>g</sup>	$[\text{M}]^{+\bullet}$	IT	n.r. <sup>c</sup>	[105]	
			APPI (+)	Fluorobenzene <sup>g</sup>	$[\text{M}]^{+\bullet}$	QqQ	n.r. <sup>c</sup>	[44]	
		pSFC	APPI (+)	Fluorobenzene <sup>g</sup>	$[\text{M}-\text{Cl}+\text{O}]^-$	QqQ	0.17–4.61 <sup>a</sup>	[106]	
			–	APPI (–)	Toluene <sup>e</sup>	$[\text{M}]^{+\bullet}$	QqQ	n.r. <sup>c</sup>	[38]
PCNs	GC	EI	70 eV	$[\text{M}]^{+\bullet}$	Sectors	0.06–0.13 <sup>a</sup>	[72]		
		EI	70 eV	$[\text{M}]^{+\bullet}$	QqQ	n.r. <sup>c</sup>	[38]		

Table 3 (Continued)

Analyte	Inlet System	Ionization Technique	Ion Source Conditions	Precursor Ion	Mass Analyzer	iLOD (pg $\mu\text{L}^{-1}$ )	Ref.
		NICI	$\text{NH}_3^{\text{b}}$	$[\text{M}]^{\text{+}}/[\text{M}-\text{HCl}]^{\text{+}}$	Q	n.r. <sup>c</sup>	[107]
	GC×GC	EI	70 eV	$[\text{M}]^{\text{+}}$	TOF	0.09–0.6	[64]
	LC	APPI (–)	Toluene <sup>g</sup>	$[\text{M}-\text{Cl}+\text{O}]^{\text{+}}$	QqQ	0.8–16 <sup>a</sup>	[7]

<sup>a</sup> pg injected on column.

<sup>b</sup> Reagent gas.

<sup>c</sup> Not reported.

<sup>d</sup> Individual CP homologues.

<sup>e</sup> Mobile phase component.

<sup>f</sup> Flow injection analysis.

<sup>g</sup> Post-column addition.

<sup>h</sup> 1,4-Dibromobutane.

<sup>i</sup> Modifier in the source.

<sup>‡</sup> x = 1–2, y = 4–5.

<sup>∗</sup> X = Cl, Br.

<sup>□</sup> x = 2–3, y = 4–5, z = 4–5.

<sup>§</sup> R = –CH<sub>3</sub>, –C<sub>2</sub>H<sub>5</sub>; <sup>†</sup> x = 1–4.

spectrometry have increased the number of commercially available instruments that provide high sensitivity and selectivity while being easy to handle with reduced cost and maintenance. Thus, mass spectrometry has become a universal and specific technique for targeted and non-targeted analysis of these contaminants in environmental applications.

#### 4.1. Ionization techniques

In addition to the sample introduction, ionization is one of the first steps in the mass spectrometric analysis. Table 3 summarizes the main ionization techniques employed in the analysis of halogenated organic contaminants by chromatography-mass spectrometry.

Regarding high-vacuum ionization techniques (applied in GC–MS determinations), electron ionization (EI) has been widely used for compounds such as PCDD/Fs, PCBs, and PCNs. These compounds generally yield the molecular ion  $[\text{M}]^{\text{+}}$  in EI. However, low ionization energies have often been used to reduce the fragmentation of PCDD/Fs and PCBs. This also happens for PBDEs, although highly brominated congeners still show the ion  $[\text{M}-\text{Br}_2]^{\text{+}}$  as the base peak of the mass spectrum even at low ionization energies [54,73,74]. On the other hand, the ionization of CPs, DPs, HBCDs, and neutral PFAS under EI conditions has shown a high fragmentation that hinders the detection capability and the selectivity of the method. This fact is especially critical for the determination of CPs, where the highly fragmented mass spectra make difficult the quantitation of the congener groups. Thus, the EI-based methods are generally focused on the determination of total CPs concentration. In contrast to EI, chemical ionization techniques are typically proposed to reduce fragmentation of these compounds improving both selectivity and sensitivity. Among them, few of the target compounds are usually determined using positive ion chemical ionization (CI)-based methods. For instance, FTOHs, FOSAs and FOSEs were ionized leading to the protonated molecule  $[\text{M}+\text{H}]^{\text{+}}$  while FTOs show the  $[\text{M}-\text{F}]^{\text{+}}$  ion as the base peak of the mass spectra improving both selectivity and sensitivity [9]. Regarding negative-ion chemical ionization (NICI), different ionization trends can be observed. CPs were primarily ionized generating the  $[\text{M}-\text{Cl}]^{\text{+}}$  and  $[\text{M}-\text{HCl}]^{\text{+}}$  ions that facilitate the individual quantitation of each congener group [75]. Despite the advantages of NICI, Zencak et al. [76] reported that EI combined with tandem mass spectrometry (MS/MS) was still more selective than NICI-MS to overcome potential interferences such as PCBs or PBDEs, which enable the use of simple clean-up procedures. A similar ionization pattern was observed by NICI for PCDD/Fs, PCBs, PCNs, and even DP and related compounds, where the molecular ion

$[\text{M}]^{\text{+}}$  is typically monitored although losses of Cl or HCl are also observed. This kind of fragmentation may hinder the selectivity on the determination of these analytes in front of other structurally similar compounds. Additionally, low chlorinated congener groups of PCDD/Fs, dl-PCBs, and PCNs show a relatively low response. At the same time, significant differences in the intensity have also been observed for compounds from the same homologue group of congeners [77], which makes necessary the isotope dilution for correcting quantitation problems. Sometimes, NICI also provides highly fragmented mass spectra. For instance, FOSAs and FOSEs show high fragmentation with low characteristic ions while the mass spectra of FTOs and FTOHs are characterized by fragment ions originated by losses of HF units from the molecular ion [9]. Therefore, NICI is usually employed for confirmation purposes in the analysis of neutral PFAS [47,78]. This disadvantage in the selectivity is also manifested for brominated organic contaminants. For instance, an intense but low selective  $[\text{Br}]^{\text{+}}$  ion is normally selected to determine Dec-604 [21] and tri- to heptaBDEs whereas highly brominated PBDEs show a lower fragmentation being possible to select more characteristic ions at high  $m/z$  values in the mass spectra [35].

Concerning API sources, the number of publications that propose these techniques for the ionization of halogenated pollutants has exponentially increased in the last years. These ionization sources are mainly used for LC–MS systems, but in this last decade, the number of applications using the API sources for GC–MS has greatly increased. API techniques provide a soft ionization promoting the formation of molecular or quasi-molecular ions (protonated or deprotonated molecule) and, therefore, reducing the in-source fragmentation. Among the API sources, APCI and APPI are the most widely used for the analysis of these compounds using both LC–MS and GC–MS. These sources ionize both moderate-polar and non-polar compounds, while electrospray (ESI) is mainly applied for the ionization of ionic, polar, and less volatile halogenated compounds. Regardless of the coupling used (LC–MS, GC–MS, etc.), the ions observed for each family of compounds are generally similar in each API source. The nature of these ions will only depend on the liquid-phase (ESI) or gas-phase composition (APCI and APPI), leading to small variations in the mass spectra.

Halogenated aromatic contaminants (PBDEs, PCBs, PCDD/Fs, and PCNs) have been widely analyzed by APCI and APPI, for LC–MS and pSFC–MS couplings, yielding the molecular ion  $[\text{M}]^{\text{+}}$  and the phenoxide ion  $[\text{M}-\text{X}+\text{O}]^{\text{+}}$  (X: Cl, Br) in positive and negative ion mode, respectively, regardless of the mobile phase composition in APCI or the dopant used in APPI. However, the gas-phase composition can have a significant effect over the ionization

efficiency. For instance, Perazzolli et al. [105] reported the post-column addition of benzene in LC-APCI to dramatically increase the ionization efficiency of TCDD/Fs in positive ion mode. Besides, Debrauwer et al. [96] used the post-column addition of toluene as dopant in LC-APPI (positive ion mode) to favor the formation of the molecular ion for PBDEs. In contrast, Riddell et al. [44] proposed the use of fluorobenzene, instead of the more toxic toluene, to promote charge-exchange reactions in the ionization of PCDD/Fs in pSFC-APPI positive ion mode. Concerning LC-APCI and LC-APPI negative ion mode, the formation of  $[M-X+O]^-$  ion occurs by the gas-phase reaction of analyte neutral molecules with superoxide ions, which are generated in these ionization sources even when oxygen is present at trace concentration level [106]. In dopant-assisted negative APPI ionization, toluene has been often used for PCBs [3], PCDD/Fs [106] and PCNs [7] yielding the  $[M-Cl+O]^-$  ion, while for PBDEs [6,24] the best results have been reported using toluene and acetone, which favor the formation of  $[M-Br+O]^-$  ion for highly brominated PBDEs. In contrast, di- and triBDEs showed a very low response working in negative ion APPI mode [96,108]. In the case of BDE-209 the ion  $[C_6Br_5O]^-$  was the base peak of the mass spectrum instead of the phenoxide ion observed for other highly brominated BDEs [24,27,109]. Furthermore, when using  $[M-X+O]^-$  ions as precursor ions in tandem mass spectrometry experiments, they yielded product ions due to losses of chlorine or bromine atoms, providing high selectivity for the corresponding LC-MS/MS methods [3,7,106]. Product ion mass spectra of the  $[M-Br+O]^-$  precursor ion also yielded a non-specific intense  $[Br]^-$  ion as reported by Bacaloni et al. for BDE-153 [6].

The atmospheric pressure ionization of non-aromatic halogenated contaminants has also been evaluated in negative ion mode for LC-MS determinations. HBCDs yielded the deprotonated molecule when using ESI [17,86], while neutral PFAS and DP have shown a high tendency to form adduct ions. For neutral PFAS, ammonium acetate is employed in the mobile phase to favor the chromatographic retention of ionic PFAS. Under these conditions, FOSAs generated the deprotonated molecule, while FTOHs and FOSEs yielded  $[M+CH_3COO]^-$  ions, which only led to an unselective acetate ion in the tandem mass spectrum [70]. To overcome this lack of selectivity, the ammonium acetate must be removed to favor the formation of the deprotonated molecule for FTOHs [5]. Peng et al. [29] proposed dansyl derivatization of FTOHs to improve the ionization, preventing the adduct formation. Regarding DP and related compounds, Zhou et al. [66] reported that ESI only allows the ionization of Dec-603, *syn*- and *anti*-DP in the negative ion mode through the generation of  $[M+Cl]^-$  ions when  $NH_4Cl$  is added to the mobile phase. In contrast, negative ion APCI and APPI (dopant: acetone) showed similar results mainly consisting in displacement products ions such as  $[M-Br+O]^-$  and  $[M-xH+yCl-zO]^-$  (where  $x=2-3$ ,  $y=4-5$ ,  $z=4-5$ ) or association product ions  $[M+H]^-$ , although negative ion APPI provided the best sensitivity. The use of LC-APCI and LC-APPI in negative ion mode also improved the ionization efficiency of neutral PFAS and HBCDs. Ayala-Cabrera et al. reported that FTOs were ionized yielding odd-electron fragment ions while FTOHs led to deprotonated molecules or odd-electron fragment ions depending on the mobile phase composition [70,92]. Chu et al. [28] reported that when analyzing biota samples, negative ion APPI (gas-phase ionization) showed the additional advantage of a significantly lower matrix effect over FTOHs response compared to ESI (liquid-phase ionization). Feng et al. [89] indicated that APCI achieved 2–3 times higher sensitivity for HBCDs than ESI for the formation of the deprotonated molecule, thus becoming an interesting alternative to overcome potential matrix effect. In the last few years, the use of API sources has also been deeply evaluated to achieve the ionization of CPs by promoting stable adduct ions through anion-attachment ionization mechanism. Thus, Bogdal et al. [82] proposed the post-column addition of dichloromethane to an acetonitrile mobile

phase, which allowed the generation of an APCI plasma of  $Cl^-$  ions to promote the formation of  $[M+Cl]^-$  adduct ions. The chlorine-enhanced ionization conditions suppressed the formation of multiple fragment ions, which improved the sensitivity and the selectivity for the determination of CPs by negative ion APCI [82]. However, under these ionization conditions, Yuan et al. [85] observed that  $[M+Cl]^-$  ions of  $C_{10}Cl_5$  to  $C_{10}Cl_8$  congeners overlapped with  $[M+Cl-HCl]^-$  ions coming from the ionization of  $C_{10}Cl_6$  to  $C_{10}Cl_9$  congener groups. In contrast, the post-column addition of bromoform produced an APCI plasma of  $[Br]^-$  ions that favored the formation of nearly exclusive  $[M+Br]^-$  ions for  $C_{10}Cl_5$  to  $C_{10}Cl_9$  congeners that increased the selectivity and avoided complex data deconvolution processes. Recently, this anion-attachment ionization strategy is being applied in ESI. For instance, Li et al. [81] have evaluated the use of negative ion ESI for the analysis of CPs by using a post-column addition of dichloromethane to promote the formation of  $[M+Cl]^-$  ions. Zheng et al. [69] also proposed the use of  $NH_4Cl$  in a methanol mobile phase to form the chloride adduct ions thus increasing 3-fold the response of  $[M+Cl]^-$  ions compared to the use of  $CH_2Cl_2$ . The authors suggested that the concentration of  $Cl^-$  ion would be enhanced by the decomposition of  $NH_4Cl$  into ammonia and HCl (at 300 °C), whereas volatilization of dichloromethane would reduce the presence of  $Cl^-$  ions in the ESI source.

The use of API techniques has significantly increased in the last decades not only for LC-MS determinations but also for GC-MS analysis due to the development of atmospheric pressure chemical ionization (GC-APCI) and photoionization (GC-APPI) sources for the GC-MS coupling [110,111]. Among them, positive ion GC-APCI has been extensively used owing to its great sensitivity for the determination of halogenated contaminants. The use of GC-APCI source significantly prevented the fragmentation observed in EI as it could be observed in Fig. 2 for CB-156. PCDD/Fs as well as di-PCBs show very intense molecular ion with negligible APCI in-source fragmentation, thus allowing the detection of the target compounds at the low fg level (ca. 2–25 fg injected on column) [59–61,103].

Sales et al. [52] reported that HBCDs efficiently formed the  $[M-Br]^+$  ion in GC-APCI, that allowed the selective and sensitive screening of these compounds up to 100 fg  $\mu L^{-1}$ , while Portolés et al. [48] indicated that FTOHs, FOSEs and FOSAs were efficiently ionized by yielding the protonated molecule as base peak in GC-APCI-MS. The addition of an uncapped vial with water into the ion source has been proposed to increase water vapors inside the source and promote proton-transfer reactions, which allowed the detection of neutral PFAS at low fg level (1–5 fg on column). This strategy has also been evaluated to ionize PBDEs, which formed both the molecular ion and the protonated molecule. However, it was observed that the absence of water or other substances such as formic acid in the gas-phase to prevent proton-transfer reactions provided the highest sensitivity for PBDEs by monitoring product ions coming from the  $[M]^{**}$  ion [95].

The GC-APPI source has been commercialized in the last years and it has demonstrated a great potential to efficiently ionize halogenated pollutants. In fact, Di Lorenzo et al. [53] demonstrated that under dopant-assisted photoionization PBDEs only yielded the molecular ion in contrast to the ion mixture  $[M]^{**}/[M+H]^+$  observed in the GC-APCI source. Besides, some photooxidation products such as  $[M-Br+O]^+$  or  $[M-Br+O_2]^+$  were also observed working in positive ion GC-APPI mode which allowed the differentiation between coeluting BDE isomers like BDE-49 and BDE-71. Luosujärvi et al. [100] evaluated the ionization of PCBs using both GC-APCI and GC-APPI in negative ion mode and observed the generation of the corresponding phenoxide ions as happen in LC-APCI and LC-APPI sources. Moreover, Ayala-Cabrera et al. [92] achieved a high ionization efficiency by negative ion GC-APPI ionization for neutral PFAS, which yielded the formation of the deprotonated molecule for

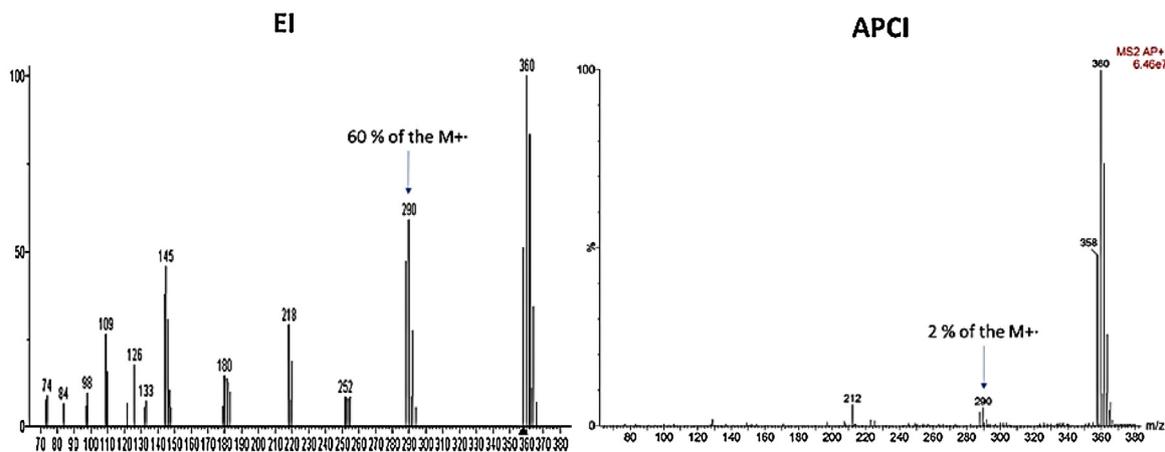


Fig. 2. Comparison of the EI and GC-APCI mass spectra obtained for the 2,3,3',4,4',5-hexachlorobiphenyl (CB-156). Reprinted from [60], Copyright (2016), with permission from Elsevier.

FOSAs, the  $[M+O_2]^-$  ion for FTOHs and FOSEs and odd-electron fragment ions for FTOs and allowed their detection up to low fg injected.

#### 4.2. Mass analyzers

Halogenated organic contaminants have been analyzed using both low-resolution (LRMS) and high-resolution mass spectrometry (HRMS) (Table 3). Low-resolution mass analyzers, especially quadrupoles (Q), have been used for both GC-MS and LC-MS determinations. Earlier GC-MS applications were quadrupole-based using EI due to the rich information that it could provide and the capability for library searching. For instance, the analysis of neutral PFAS in animal plasma and tissues [112], as well as PBDEs in long-finned pilot whale [113], have been proposed by GC-EI-MS working in selected ion monitoring (SIM) mode. In contrast to ion traps (IT), where sensitive full-scan acquisition mode could be performed, quadrupole analyzers often operate in SIM mode to enhance the selectivity and sensitivity, especially for quantitative purposes when analytes are present at very low concentration levels. The use of single quadrupoles is more limited when using soft ionization techniques (CI, NICI and API sources) [9,34,48] since the low fragmentation observed in the mass spectra does not allow to obtain chemical structural information necessary for confirming purposes by searching in the mass library. However, the lower fragmentation and the promotion of molecular and quasi-molecular ions provide better sensitivity than EI-SIM methods using single quadrupoles. For instance, neutral PFAS showed low fragmentation by GC-CI-MS (Q) with intense quasi-molecular ions. However, the few fragment ions observed were very low in abundance, requiring the positive samples to reanalyze by an alternative technique as GC-NICI-MS to confirm the identification of the target compounds [47]. Thus, Iozza et al. [34] determined SCCPs by GC-NICI-MS (based on the monitoring of  $[M-Cl]^-$  ions) although an extensive clean-up was required to avoid interferences from other related halogenated compounds that can elute with them at the same retention time. Thereby, tandem mass spectrometry (MS/MS) with triple quadrupole (QqQ) instruments has been often chosen to improve the selectivity and detection capability of the methods, as well as to offer significant structural information for confirmation purposes. To overcome the lack of fragment ions in soft ionization sources, MS/MS is carried out to generate product ions that allow the improvement of the capabilities of the methods. For instance, new advances on QqQ instruments have allowed the fast and sensitive determination of PCDD/Fs and PCBs through the use of EI and positive-ion APCI ionization modes without sacrificing the selectivity

required for their determination and avoiding some isobaric interferences from other dioxin-like compounds [50,59,60,103,104]. However, variations in the measurement of the ion transition ratios (for MS/MS systems) could be higher than those ion ratios estimated for GC-HRMS systems (in SIM mode) [50], which could reduce method precision. LC-MS and GC-MS applications using soft API sources have been performed exclusively in MS/MS when working with low-resolution mass spectrometers. For example, Sales et al. [52] proposed a GC-APCI-MS/MS method to determine HBCDs by monitoring product ions from the  $[M-Br]^+$  precursor ion in multiple reaction monitoring (MRM) mode. Moukas et al. proposed the LC-APPI-MS/MS (QqQ) methods to determine PCBs [3] and PCNs [7] by monitoring selective transitions such as  $[M-Cl+O]^- \rightarrow [M-2Cl+O]^-$  and  $[M-Cl+O]^- \rightarrow [M-3Cl+O]^-$ . LC-MS/MS methods have also been proposed for other halogenated organic contaminants such as DP [66], PBDEs [27] and HBCDs [87,89]. Although MRM mode generally improves both selectivity and sensitivity for the analysis of these halogenated compounds,  $[Cl]^-$  and  $[Br]^-$  ions are usually selected as product ions for their monitoring. However, these transitions are not selective enough and can compromise the selectivity of these methods against other coeluting chlorinated or brominated isobaric interferences. In the case of the MS/MS determination of neutral PFAS, especially FTOHs and FOSEs, the product ions monitored in negative ion APCI and APPI [9,70] or positive ion GC-APCI [48] (combined losses of HF, fluoroalkyl chain or functional group moieties) are more selective than the non-characteristic acetate product ion observed in negative ion ESI since only  $[M+CH_3COO]^-$  ions are generally formed in electrospray for these families of compounds.

Additionally, with the advances in modern triple quadrupoles, MS/MS has also been used to reduce background noise even for analytes showing high fragmentation. For instance, Barón et al. [21] observed that QqQ instrument increased the S/N ratio of DPs compared to a single quadrupole system when analyzing biota samples by GC-NICI-MS(/MS). Furthermore, the GC-EI-MS/MS analysis of CPs, which are based on the monitoring of common fragment ions at low  $m/z$  values, allows that isobaric interferences could be filtered, thus increasing method sensitivity by acquiring data in MRM mode [34]. On the other hand, although ion traps offered better sensitivity than quadrupoles working in full-scan, it surprises the reduced number of applications for the determination of these substances. This fact can be due to the slow scanning rate of these mass analyzers in tandem mass spectrometry compared with new QqQ and quadrupole-time-of-flight (QTOF) instruments, which could hinder the adequate monitoring of narrow chromatographic peaks. Nonetheless, some works have reported the used of an ion-trap mass analyzer for the screening of

HBCDs using an ambient ionization mass spectrometry technique such as flowing atmospheric pressure afterglow (FAPA)-MS/MS [91] and for the determination of PCDD/Fs by GC-MS/MS [30].

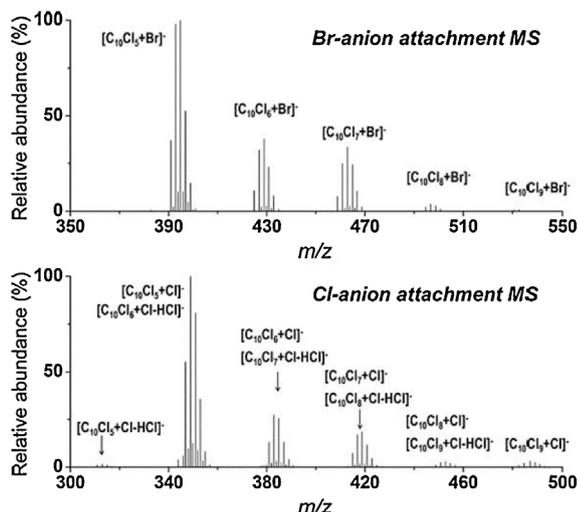
The ability of tandem mass spectrometry to study the fragmentation pathway for identifying common fragmentation patterns, product ions or even mass losses of closed related compounds has been applied to some families of halogenated contaminants. For instance, Ayala-Cabrera et al. [114] tentatively proposed fragmentation pathways for neutral PFAS, identifying general fragmentation trends (losses of HF, CF<sub>2</sub> or functional group moieties) and common product ions for FTOs, FTOHs, FOSAs, and FOSEs, using API sources in LC-MS methods. The fragmentation studies may assist in the identification of new and unknown related compounds, as well as in the development of non-targeted strategies, such as fragmentation flagging approaches or mass defect plots.

Despite the advantages of tandem mass spectrometry, the difficulties of LRMS to differentiate isobaric ions may hinder the quantitation of some complex mixtures. For instance, the LRMS analysis of CPs is mainly based on the determination of the total CP concentration due to the limitations in separating the individual response of each CP homologue group without the contribution of CP groups with different chlorination degree and/or carbon chain-length or other halogenated contaminants like pesticides or PCBs [34]. Most of the problems and limitations observed in the LRMS determination of CPs can be overcome by using HRMS coupled to both GC and LC, with the additional advantage of reducing the number of false positives and negatives. Traditionally, the environmental occurrence of PBDEs [93] and compounds with dioxin-like toxicity (PCDD/Fs, dioxin like-PCBs and PCNs) [50,72] has been addressed through the GC-EI-HRMS analysis with the double-focusing magnetic sector to overcome isobaric interferences from coeluting congeners and/or matrix components. Regarding DPs, EI leads to low-specific fragment ions such as [C<sub>5</sub>Cl<sub>6</sub>]<sup>+</sup> or [C<sub>5</sub>HCl<sub>5</sub>]<sup>+</sup> and the use of HRMS (sectors) affords the selective determination [56]. The use of double-focusing magnetic sectors mass analyzers not only could improve selectivity by removing potential interferences, but also could increase the sensitivity on the analysis of complex matrices by reducing the background noise. Nonetheless, these HRMS instruments have to work in SIM mode due to the low sensitivity that they show when they operate in full-scan acquisition mode. In this sense, the new generation of HRMS analyzers like time-of-flight (TOF) and Orbitrap offers important advantages, such as high scanning speed and sensitivity over traditional double-focusing magnetic sectors mass analyzers. Thus, Hayward et al. [102] proposed a GC-EI-Orbitrap method to determine PCDD/Fs in cow and human milk samples, since Orbitrap could keep a high selectivity operating at a resolution of 120,000 (FWHM, full width at half maximum at *m/z* 200) with high sensitivity in full-scan acquisition mode. These advantages allowed achieving instrumental limits of detection (iLODs) comparable to those obtained using double-focusing magnetic sectors. The easy operation of modern HRMS instruments, but keeping and enhancing the HRMS capabilities, have exponentially increased the number of publications using TOF and Orbitrap analyzers in the field of the analysis of halogenated pollutants during the last decades. For instance, Zacs et al. [24,88] proposed highly sensitive and selective UHPLC-ESI-Orbitrap and UHPLC-APPI-Orbitrap methods for the determination of HBCDs and PBDEs, respectively. These authors highlighted that a compromise between selectivity and sensitivity might be considered due to the reduced scanning speed of Orbitrap compared with TOF instruments. These mass analyzers have been particularly relevant for the determination of CPs. Typically, GC-NICI-HRMS (TOF and Orbitrap) methods have been usually carried out for both the determination of the total CP content and the characterization

of individual CP homologue groups [58,80], achieving with the GC-NICI-Orbitrap technique the lowest iLODs for SCCPs (0.03–2.02 pg μL<sup>-1</sup>) and MCCPs (0.11–0.41 pg μL<sup>-1</sup>). Working at a resolution of 60,000 FWHM authors observed that relative deviation between experimental and theoretical ion ratios was lower than 10 % when the response of the homologue CP group was lower than 1 % of the total 'hump' area, demonstrating the high selectivity of the method [58]. However, a mass resolution of 94,000 FWHM is required to solve some overlapping signals due to the high number of CP isomers. The rich CP isotope clusters and the multiple fragmentations of CP congeners lead to overly complex mass spectral data, which may result in mass interferences between CPs from the same and different homologue groups [83]. In the last few years, flow injection analysis (FIA)-HRMS (TOF) methods have also been developed for the determination of CPs, showing important advantages. As mentioned above, the use of anion-attachment APCI and ESI through the formation of [M+Cl]<sup>-</sup> ions led to less complex mass spectra than those obtained by NICI [84], and the combination with a mathematical deconvolution approach and the TOF mass analyzer has made possible the selective and sensitive determination of CPs. The deconvolution approach allowed the identification of ion signals within a pull of overlapping masses since [M+Cl]<sup>-</sup> ions of C<sub>n</sub>Cl<sub>m</sub> homologue groups were not resolved from other ions, especially [M+Cl-HCl]<sup>-</sup> ions coming from C<sub>n</sub>Cl<sub>m+1</sub> homologue groups (Fig. 3), thus avoiding an overestimation of 1.4–39 % [85]. A minimum mass resolution of 10,000 FWHM was required to overcome other potential interferences before the deconvolution step [83]. This procedure was even simplified by Yuan et al. [85] by using a bromide-attachment APCI-TOF method where the measured isotopic distributions of the [M+Br]<sup>-</sup> ions perfectly matched with the theoretical values because there was no fragmentation (Fig. 3). Thus, these results would suggest that using this methodology there would be no need to use the deconvolution approach, which simplifies the data treatment analysis and even it would open the door for the application of this methodology using LRMS.

The highly sensitive full-scan acquisition provided by HRMS mass analyzers like TOF or Orbitrap allows not only target analysis but also non-targeted approaches such as screening analysis of a large number of suspect analytes and the identification of new related pollutants, among others. For instance, Ieda et al. [115] proposed a workflow for the targeted and non-targeted screening of contaminants in environmental samples based on GC×GC-EI-HRMS (TOF) analysis. Regarding the non-targeted approach, the authors propose the use of specialized software (NMF with DBcreator) to achieve the deconvolution of the mixture of components and improve the mass spectral library searching. Mass defect plots are another useful tool based on full-scan HRMS data that can simplify and make faster the identification of halogenated pollutants in complex mixtures. In this strategy, the whole set of acquired *m/z* values are transformed into the H/Cl mass scale by multiplying each ion mass by the exchange factor 1.0011 (34/33.96102). A mass defect graph is then built by plotting the ion nominal mass in front of the H/Cl mass defect. This graph shows ion series aligned in different classes ("bands") indicating that all ions within the same series have the same repeating unit. In this example, hydrocarbon ions, silicon-containing ions and halogen-containing ions were separated in different "bands" [116].

As mentioned before, the use of API source for GC-MS has become very popular in the last few years and this methodology is often used in combination with HRMS. The use of GC-APCI-HRMS (TOF) has shown significant advantages over GC-EI-HRMS (double-focusing magnetic sector). For instance, Portolés et al. [117] proposed a multiclass screening of organic pollutants, including PBDEs, PCBs, and PCNs in water by GC-APCI-HRMS (QTOF) facilitating a rapid, wide-scope, more sensitive and effective screening based on molecular ion and/or protonated molecule



**Fig. 3.** Bromine- and chlorine-enhanced APCI mass spectra of five CP congeners in a standard mixture (MIX-2). Reprinted with the permission from [85]. Copyright 2018 American Chemical Society.

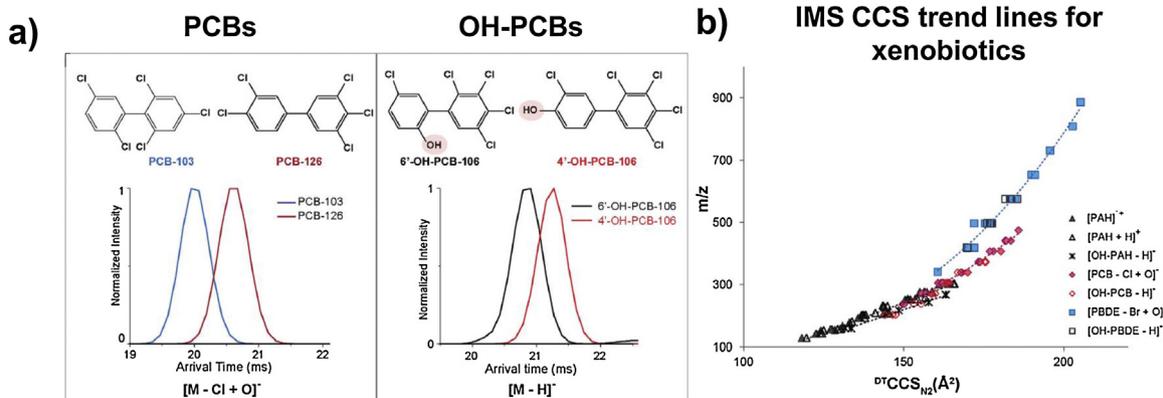
searching. The possibility of performing both full-scan and product ion scan in hybrid instruments such as QTOF or quadrupole-Orbitrap (Q-Orbitrap) provides useful chemical structural information to support the tentative analyte identification. In this way, Liu et al. [19] reported the use of a QTOF mass analyzer using the GC-APCI source in the positive ion mode and combining HRMS and MS/HRMS experiments to identify two novel dechlorane analogues, structurally related to Dec-603.

GC-HRMS and LC-HRMS methods can provide accurate determinations of halogenated contaminants, but in some cases, the separation of isomeric compounds that have an identical or very close elemental composition is difficult. GC×GC could overcome this problem, but long analysis times and complex data processing may limit its use when very complex mixtures have to be analyzed. A promising alternative technique is the ion mobility (IM) combined with HRMS because it could provide a selective and fast determination of closed related halogenated organic contaminants by separating isobaric/isomeric compounds in very complex samples and improving environmental laboratory throughput. In IM separation, ions travelling through a drift cell filled with a buffer gas (e.g., N<sub>2</sub>) and under the influence of a weak electric field are separated according to their shape and volume

(collision cross-section, CCS) in addition to their  $m/z$  value. Despite having an identical elemental composition, compounds with a compact structure (lower CCS) will travel faster through the IM cell than compounds with more extended shapes (higher CCS). Zheng et al. [97] evaluated the capabilities of IM-QTOF (using APCI and APPI) and demonstrated that isobaric PCBs and PBDEs can be almost baseline separated. For instance, IM is a powerful technique to separate *ortho* and *non-ortho* PCB congeners (Fig. 4a). *Non-ortho* PCBs mainly exist in a planar structure leading to a larger size and, therefore, a higher CCS value than that observed for *ortho* PCBs, which are more likely to adapt to more compact three-dimensional structures and consequently show lower CCS values. The authors also reported that the CCS values measured for PCBs in the drift tube IM (DTIMS) are larger than those obtained for PBDEs with the same  $m/z$  values (Fig. 4b). This fact indicates that PCBs have a larger structure than PBDEs, which may be explained because the electron density conjugation between the phenyl rings and the oxygen allows PBDEs to form a more stable planar structure. Finally, it must be considered that despite the advantages that HRMS and IM instruments can offer for both targeted and non-targeted analysis, the high cost and maintenance of these high-standing equipment could prevent their use in routine laboratories.

## 5. Quantification methods

The methods applied for the determination of halogenated pollutants in environmental samples depend on the family of compounds, the objective of the quantification (total content or congener-specific determination) and the instrumental methodology applied (chromatographic separation and ionization techniques used in GC-MS and LC-MS). One of the main advantages of working with mass spectrometry is the ability to quantify using isotope-labeled compounds regardless of the mass analyzer employed. These isotopically labeled analogues are generally used to guarantee accurate and precise quantitative data since they behave similarly to native analytes during sample processing (surrogates), chromatographic separations (internal standards) and mass spectrometry analysis (internal standards and isotope dilution). Traditionally, the determination of 2,3,7,8-PCDD/Fs and dl-PCBs have been performed by isotope dilution, providing accurate results despite the high cost of labeled standards for all the compounds [30,50]. Nowadays, isotopically labeled compounds are also commercially available for broader families of compounds such as DP [93], HBCDs [87] and neutral PFAS [15,92]. In the case of PBDEs, the applicability of the isotope dilution



**Fig. 4.** a) IMS separations of isobaric PCBs and OH-PCBs and b) CCS values versus  $m/z$  trend lines for PAHs, PCBs, PBDEs and their metabolites. Reprinted from [97], Copyright (2018), with permission from Elsevier.

method depends on the ionization source selected. For instance, the monitoring of non-specific  $[\text{Br}]^-$  ions in NICI make the isotope dilution method unsuitable for quantitative purposes. In contrast, when ionization techniques such as EI and API are used, more specific ions are monitored that often keep up the  $^{13}\text{C}$  atoms in their chemical structure [27]. There are 75 potential congeners of PCNs and it is unfeasible to have labeled compounds for all of them, therefore, the quantitation is generally performed by using only one  $^{13}\text{C}$ -labeled compound for each homologue group [72,118]. Although the use of isotopically labeled compounds provides significant advantages, they are expensive and for some of them like SCCPs are not available for each specific group of congeners. Consequently, compounds with similar properties are often used as internal standards for quantitation purposes and/or calculate recovery rates [43]. For instance, in the determination of CPs,  $^{13}\text{C}$ -trans chlordane [18,34,76], Dec-603 [75] or pentachlorobenzene [16], among others, have been proposed as internal standards for quantification purposes, while  $\epsilon$ -hexachlorohexane has been used as recovery standard [18,34]. Regarding PCN determination, the  $^{13}\text{C}_{12}$ -PCB indicators [38,107] and  $^{13}\text{C}_6$ -hexachlorobenzene [26] have been proposed as injection internal standards for quantification purposes whereas tetrabromobenzene and CB-209 have been applied as surrogates to estimate recovery rates [107]. When surrogates and/or internal standards are not used, which often occurs when working with API sources in LC-MS/MS determinations, matrix effect takes significant relevance because it may lead to underestimated or overestimated results. In these cases, the matrix effect could be corrected by using a matrix-matched calibration approach [70]. The use of APCI or APPI sources (gas-phase ionization) instead of ESI (liquid-phase ionization) could also help to overcome matrix effects (compared to ESI) as it was reported by Chu et al. for neutral PFAS [28].

Special attention must be paid in the determination of CPs. Mixtures with different chlorine content and the lack of isotope-labeled compounds lead to different quantitative approaches according to the ionization technique used. For instance, the EI response factors of different SCCP mixtures are not dependent on the chlorine content, although the low selectivity only allows the determination of the total SCCP content [34]. In contrast, NICI responses of these compounds are strongly affected by the chlorine content, which requires the use of a different approach like Reth's method to overcome quantification errors [119]. A similar quantitative method has been carried out when using APCI-HRMS but with a previous deconvolution approach [84]. Nevertheless, this methodology has important advantages over NICI-based methods such as lower quantitation errors and the ability to detect a larger number of homologue groups (from  $\text{Cl}_3$  to  $\text{Cl}_{12}$ -homologue groups) than those observed in NICI based-methods (from  $\text{Cl}_5$  to  $\text{Cl}_{10}$ -homologue groups), becoming a reliable alternative to reduce quantification errors in the analysis of SCCPs.

## 6. Concluding remarks

The recent advances in the mass spectrometry analysis of halogenated organic contaminants have been reviewed in this work to show the trends in this field. Furthermore, sample treatment procedures and chromatographic separation methods most frequently required for GC-MS and LC-MS analysis have also been discussed.

Regarding the sample treatment, the use of fast solvent-free extraction techniques, such as SPME or SBSE, that allow *in-situ* preconcentration and avoid evaporation steps are increasing their popularity in the last decade for the analysis of liquid samples. Soxhlet and PLE, followed by clean-up and fractionation steps, remain to be the most common procedures for sample preparation

of both solid samples and sorbents used for gas and particulate sampling.

Concerning chromatographic techniques, GC with non-polar stationary phases is still the separation method of choice. Nonetheless, the interest in UHPLC separations is growing to take advantage of the chromatographic efficiency and resolution they provide. However, mobile phase composition must be carefully selected to optimize both the chromatographic separation and the ionization efficiency with the API source. Multidimensional techniques have also been proposed to increase the separation capacity when analyzing complex mixtures of halogenated organic contaminants. GC $\times$ GC and ion mobility provide an additional dimension to the GC-MS separations opening a new field of applications that may overcome some of the challenges in the analysis of structurally similar compounds, especially isobaric/isomeric substances, difficult to separate by both chromatographic techniques and high-resolution mass spectrometry.

The interest in the determination of halogenated organic contaminants by both LC-MS and GC-MS using API sources such as APCI and APPI is increasing mainly to solve ionization problems observed with EI, CI and ESI such as low ionization efficiency, high fragmentation or generation of poorly selective fragment ions, but also to widen the range of compounds that can be ionized and detected in a single run. In this sense, the determination of CPs by API-HRMS through the formation of chloride/bromide adduct ions has been of relevance overcoming the ionization challenges observed for these compounds and allowing a more selective and sensitive determination. Furthermore, tandem mass spectrometry is generally recommended with API techniques to provide structural information, but it has been also proposed to overcome potential interferences from other halogenated compounds. Thereby, these new LC-API-MS/MS and GC-API-MS approaches enable simplified clean-up procedures that can help to improve the performance and throughput of control laboratories. Moreover, the advances in modern triple quadrupoles have also allowed the reduction of the background noise to develop more sensitive methods. Furthermore, when operating with API sources their use becomes essential to obtain structural information and avoid interferences such as in the analysis of PCDD/Fs. Because there is a lack of MS/MS libraries, fragmentation studies of halogenated contaminants are of great importance to assist in the development of non-targeted strategies and the identification of new and unknown related compounds. However, the increasing interest in the development of methods able to screen many contaminants including target, suspect and unknown compounds makes more necessary the use of high-resolution mass analyzers which can also overcome the limitation of low-resolution mass analyzers to differentiate between isobaric compounds. Nowadays, the easy operation, the high sensitivity of full-scan acquisition modes and the fast-scanning rates of modern mass spectrometers based on TOF or Orbitrap mass analyzers are approaching the HRMS to control laboratories. Moreover, the combination of these HRMS analyzers and the use of H/Cl mass defect plots provides a useful tool that could help on the identification of these compounds, especially when working with soft GC-APCI and GC-APPI techniques. As mentioned before, the use of ion mobility offers an additional dimension that could improve non-targeted approaches facilitating analyte identification through the establishment of CCS values, becoming a potential tool to overcome the determination of halogenated organic contaminants.

## Declaration of Competing Interest

The authors report no declarations of interest.

## Acknowledgements

Authors acknowledge the financial support received from Spanish Ministry of Science, Innovation and Universities under the project PGC2018-095013-B-I00 and from the Generalitat of Catalonia under the project 2017-SGR-310. Juan F. Ayala-Cabrera also thanks to the Spanish Ministry of Education, Culture and Sports for the PhD FPU fellowship (FPU14/05539).

## References

- [1] W. Xu, X. Wang, Z. Cai, Analytical chemistry of the persistent organic pollutants identified in the Stockholm Convention: a review, *Anal. Chim. Acta* 790 (2013) 1–13, doi:<http://dx.doi.org/10.1016/j.aca.2013.04.026>.
- [2] UNEP Decision 18/32 of the UNEP Governing Council: Persistent Organic Pollutants (POPs), (1995).
- [3] A.I. Moukas, N.S. Thomaidis, A.C. Calokerinos, Determination of polychlorinated biphenyls by liquid chromatography-atmospheric pressure photoionization-mass spectrometry, *J. Mass Spectrom.* 49 (2014) 1096–1107, doi:<http://dx.doi.org/10.1002/jms.3427>.
- [4] N. Xiang, L. Chen, X.Z. Meng, Y.L. Li, Z. Liu, B. Wu, L. Dai, X. Dai, Polybrominated diphenyl ethers (PBDEs) and dechlorane plus (DP) in a conventional wastewater treatment plant (WWTP) in Shanghai: seasonal variations and potential sources, *Sci. Total Environ.* 487 (2014) 342–349, doi:<http://dx.doi.org/10.1016/j.scitotenv.2014.04.014>.
- [5] B. Szostek, K.B. Prickett, R.C. Buck, Determination of fluorotelomer alcohols by liquid chromatography/tandem mass spectrometry in water, *Rapid Commun. Mass Spectrom.* 20 (2006) 2837–2844, doi:<http://dx.doi.org/10.1002/rcm.2667>.
- [6] A. Bacaloni, L. Callipo, E. Corradini, P. Giansanti, R. Gubbiotti, R. Samperi, A. Laganà, Liquid chromatography-negative ion atmospheric pressure photoionization tandem mass spectrometry for the determination of brominated flame retardants in environmental water and industrial effluents, *J. Chromatogr. A* 1216 (2009) 6400–6409, doi:<http://dx.doi.org/10.1016/j.chroma.2009.07.039>.
- [7] A.I. Moukas, N.S. Thomaidis, A.C. Calokerinos, Novel determination of polychlorinated naphthalenes in water by liquid chromatography-mass spectrometry with atmospheric pressure photoionization, *Anal. Bioanal. Chem.* 408 (2016) 191–201, doi:<http://dx.doi.org/10.1007/s00216-015-9092-5>.
- [8] Y. Han, W. Liu, H. Li, R. Lei, G. Liu, L. Gao, G. Su, Distribution of polychlorinated naphthalenes (PCNs) in the whole blood of typical meat animals, *J. Environ. Sci.* 72 (2018) 208–212, doi:<http://dx.doi.org/10.1016/j.jes.2018.01.008>.
- [9] J.F. Ayala-Cabrera, E. Moyano, F.J. Santos, Gas chromatography and liquid chromatography coupled to mass spectrometry for the determination of fluorotelomer olefins, fluorotelomer alcohols, perfluoroalkyl sulfonamides and sulfonamido-ethanols in water, *J. Chromatogr. A* 1609 (2019) 460463, doi:<http://dx.doi.org/10.1016/j.chroma.2019.460463>.
- [10] S. Taniyasu, K. Kannan, K.S. Man, A. Gulkowska, E. Sinclair, T. Okazawa, N. Yamashita, Analysis of fluorotelomer alcohols, fluorotelomer acids, and short- and long-chain perfluorinated acids in water and biota, *J. Chromatogr. A* 1093 (2005) 89–97, doi:<http://dx.doi.org/10.1016/j.chroma.2005.07.053>.
- [11] M. Qiao, W. Cao, B. Liu, X. Zhao, J. Qu, Simultaneous detection of chlorinated polycyclic aromatic hydrocarbons with polycyclic aromatic hydrocarbons by gas chromatography-mass spectrometry, *Anal. Bioanal. Chem.* 409 (2017) 3465–3473, doi:<http://dx.doi.org/10.1007/s00216-017-0290-1>.
- [12] N. Barco-Bonilla, A.J. Nieto-García, R. Romero-González, J.L. Martínez Vidal, A. G. Frenich, Simultaneous and highly sensitive determination of PCBs and PBDEs in environmental water and sediments by gas chromatography coupled to high resolution magnetic sector mass spectrometry, *Anal. Methods* 7 (2015) 3036–3047, doi:<http://dx.doi.org/10.1039/c5ay00017c>.
- [13] F. Gandolfi, L. Malleret, M. Sergent, P. Doumenq, Parameters optimization using experimental design for headspace solid phase micro-extraction analysis of short-chain chlorinated paraffins in waters under the European water framework directive, *J. Chromatogr. A* 1406 (2015) 59–67, doi:<http://dx.doi.org/10.1016/j.chroma.2015.06.030>.
- [14] I. Domínguez, F.J. Arrebola, R. Romero-González, A. Nieto-García, J.L. Martínez Vidal, A. Garrido Frenich, Solid phase microextraction and gas chromatography coupled to magnetic sector high resolution mass spectrometry for the ultra-trace determination of contaminants in surface water, *J. Chromatogr. A* 1518 (2017) 15–24, doi:<http://dx.doi.org/10.1016/j.chroma.2017.08.061>.
- [15] C. Bach, V. Boiteux, J. Hemard, A. Colin, C. Rosin, J.F. Muñoz, X. Dauchy, Simultaneous determination of perfluoroalkyl iodides, perfluoroalkane sulfonamides, fluorotelomer alcohols, fluorotelomer iodides and fluorotelomer acrylates and methacrylates in water and sediments using solid-phase microextraction-gas chromatography/mass spectrometry, *J. Chromatogr. A* 1448 (2016) 98–106, doi:<http://dx.doi.org/10.1016/j.chroma.2016.04.025>.
- [16] P. Tölgyessy, S. Nagyová, M. Sládkovičová, Determination of short chain chlorinated paraffins in water by stir bar sorptive extraction-thermal desorption-gas chromatography-triple quadrupole tandem mass spectrometry, *J. Chromatogr. A* 1494 (2017) 77–80, doi:<http://dx.doi.org/10.1016/j.chroma.2017.03.012>.
- [17] Y. Zhao, Q. Li, X. Miao, X. Huang, B. Li, G. Su, M. Zheng, Determination of hexabromocyclododecanes in sediments from the Haihe River in China by an optimized HPLC-MS-MS method, *J. Environ. Sci.* 55 (2017) 174–183, doi:<http://dx.doi.org/10.1016/j.jes.2016.07.013>.
- [18] D. Xia, L. Gao, M. Zheng, Q. Tian, H. Huang, L. Qiao, A novel method for profiling and quantifying short- and medium-chain chlorinated paraffins in environmental samples using comprehensive two-dimensional gas chromatography-electron capture negative ionization high-resolution time-of-flight mass spectrometry, *Environ. Sci. Technol.* 50 (2016) 7601–7609, doi:<http://dx.doi.org/10.1021/acs.est.6b01404>.
- [19] X. Liu, Y. Wu, X. Zhang, L. Shen, A.L. Brazeau, D.H. Adams, H. Marler, B.D. Watts, D. Chen, Novel dechlorane analogues and possible sources in peregrine falcon eggs and shark livers from the Western North Atlantic regions, *Environ. Sci. Technol.* 53 (2019) 3419–3428, doi:<http://dx.doi.org/10.1021/acs.est.8b06214>.
- [20] F. Li, J. Jin, D. Tan, J. Xu, Dhanjai, Y. Ni, H. Zhang, J. Chen, High performance solid-phase extraction cleanup method coupled with gas chromatography-triple quadrupole mass spectrometry for analysis of polychlorinated naphthalenes and dioxin-like polychlorinated biphenyls in complex samples, *J. Chromatogr. A* 1448 (2016) 1–8, doi:<http://dx.doi.org/10.1016/j.chroma.2016.04.037>.
- [21] E. Barón, E. Eljarrat, D. Barceló, Analytical method for the determination of halogenated norbornene flame retardants in environmental and biota matrices by gas chromatography coupled to tandem mass spectrometry, *J. Chromatogr. A* 1248 (2012) 154–160, doi:<http://dx.doi.org/10.1016/j.chroma.2012.05.079>.
- [22] L. Aguilar, E.S. Williams, B.W. Brooks, S. Usenko, Development and application of a novel method for high-throughput determination of PCDD/Fs and PCBs in sediments, *Environ. Toxicol. Chem.* 33 (2014) 1529–1536, doi:<http://dx.doi.org/10.1002/etc.2579>.
- [23] D. Zacs, V. Bartkevics, A. Viksna, Content of polychlorinated dibenzo-p-dioxins, dibenzofurans and dioxin-like polychlorinated biphenyls in fish from Latvian lakes, *Chemosphere* 91 (2013) 179–186, doi:<http://dx.doi.org/10.1016/j.chemosphere.2012.12.041>.
- [24] D. Zacs, V. Bartkevics, Analytical capabilities of high performance liquid chromatography - Atmospheric pressure photoionization - Orbitrap mass spectrometry (HPLC-APPI-Orbitrap-MS) for the trace determination of novel and emerging flame retardants in fish, *Anal. Chim. Acta* 898 (2015) 60–72, doi:<http://dx.doi.org/10.1016/j.aca.2015.10.008>.
- [25] Z. Zhao, G. Zhong, A. Möller, Z. Xie, R. Sturm, R. Ebinghaus, J. Tang, G. Zhang, Levels and distribution of dechlorane plus in coastal sediments of the Yellow Sea, North China, *Chemosphere* 83 (2011) 984–990, doi:<http://dx.doi.org/10.1016/j.chemosphere.2011.02.011>.
- [26] P. Castells, J. Parera, F.J. Santos, M.T. Galceran, Occurrence of polychlorinated naphthalenes, polychlorinated biphenyls and short-chain chlorinated paraffins in marine sediments from Barcelona (Spain), *Chemosphere* 70 (2008) 1552–1562, doi:<http://dx.doi.org/10.1016/j.chemosphere.2007.08.034>.
- [27] G. Mascolo, V. Locaputo, G. Mininni, New perspective on the determination of flame retardants in sewage sludge by using ultrahigh pressure liquid chromatography-tandem mass spectrometry with different ion sources, *J. Chromatogr. A* 1217 (2010) 4601–4611, doi:<http://dx.doi.org/10.1016/j.chroma.2010.05.003>.
- [28] S. Chu, R.J. Letcher, Analysis of fluorotelomer alcohols and perfluorinated sulfonamides in biotic samples by liquid chromatography-atmospheric pressure photoionization mass spectrometry, *J. Chromatogr. A* 1215 (2008) 92–99, doi:<http://dx.doi.org/10.1016/j.chroma.2008.10.103>.
- [29] H. Peng, K. Hu, F. Zhao, J. Hu, Derivatization method for sensitive determination of fluorotelomer alcohols in sediment by liquid chromatography-electrospray tandem mass spectrometry, *J. Chromatogr. A* 1288 (2013) 48–53, doi:<http://dx.doi.org/10.1016/j.chroma.2013.02.085>.
- [30] M. Roszko, K. Szymczyk, R. Jedrzejczak, Separation of polychlorinated dibenzo-p-dioxins/furans, non-ortho/mono/di/tri/tetra-ortho-polychlorinated biphenyls, and polybrominated diphenyl ethers groups of compounds prior to their determination with large volume injection gas chromatography-Quadrupole ion storage tandem mass spectrometry, *Anal. Chim. Acta* 799 (2013) 88–98, doi:<http://dx.doi.org/10.1016/j.aca.2013.08.053>.
- [31] H. Zhang, S. Bayen, B.C. Kelly, Co-extraction and simultaneous determination of multi-class hydrophobic organic contaminants in marine sediments and biota using GC-ESI-MS/MS and LC-ESI-MS/MS, *Talanta* 143 (2015) 7–18, doi:<http://dx.doi.org/10.1016/j.talanta.2015.04.084>.
- [32] V. Yusà, O. Pardo, A. Pastor, M. De La Guardia, Optimization of a microwave-assisted extraction large-volume injection and gas chromatography-ion trap mass spectrometry procedure for the determination of polybrominated diphenyl ethers, polybrominated biphenyls and polychlorinated naphthalenes in sediments, *Anal. Chim. Acta* 557 (2006) 304–313, doi:<http://dx.doi.org/10.1016/j.aca.2005.10.041>.
- [33] D. Lankova, M. Kockovska, O. Lacina, K. Kalachova, J. Pulkabova, J. Hajslova, Rapid and simple method for determination of hexabromocyclododecanes and other LC-MS-MS-amenable brominated flame retardants in fish, *Anal. Bioanal. Chem.* 405 (2013) 7829–7839, doi:<http://dx.doi.org/10.1007/s00216-013-7076-x>.

- [34] S. Iozza, P. Schmid, M. Oehme, Development of a comprehensive analytical method for the determination of chlorinated paraffins in spruce needles applied in passive air sampling, *Environ. Pollut.* 157 (2009) 3218–3224, doi: <http://dx.doi.org/10.1016/j.envpol.2009.06.033>.
- [35] M. Gorga, E. Martínez, A. Ginebreda, E. Eljarrat, D. Barceló, Determination of PBDEs, HBB, PBEB, DBDPE, HBCD, TBBPA and related compounds in sewage sludge from Catalonia (Spain), *Sci. Total Environ.* 444 (2013) 51–59, doi: <http://dx.doi.org/10.1016/j.scitotenv.2012.11.066>.
- [36] S. Pizzini, E. Marchiori, R. Piazza, G. Cozzi, C. Barbante, Determination by HRGC/HRMS of PBDE levels in edible Mediterranean bivalves collected from north-western Adriatic coasts, *Microchem. J.* 121 (2015) 184–191, doi: <http://dx.doi.org/10.1016/j.microc.2015.03.010>.
- [37] Y.H. Zeng, X.J. Luo, B. Tang, B.X. Mai, Habitat- and species-dependent accumulation of organohalogen pollutants in home-produced eggs from an electronic waste recycling site in South China: levels, profiles, and human dietary exposure, *Environ. Pollut.* 216 (2016) 64–70, doi: <http://dx.doi.org/10.1016/j.envpol.2016.05.039>.
- [38] F. Li, J. Jin, X. Sun, X. Wang, Y. Li, S.M. Shah, J. Chen, Gas chromatography-triple quadrupole mass spectrometry for the determination of atmospheric polychlorinated naphthalenes, *J. Hazard. Mater.* 280 (2014) 111–117, doi: <http://dx.doi.org/10.1016/j.jhazmat.2014.07.060>.
- [39] Y. Moussaoui, L. Tuduri, Y. Kerchich, B.Y. Meklati, G. Eppe, Atmospheric concentrations of PCDD/Fs, dl-PCBs and some pesticides in northern Algeria using passive air sampling, *Chemosphere* 88 (2012) 270–277, doi: <http://dx.doi.org/10.1016/j.chemosphere.2012.02.025>.
- [40] R. Piazza, A. Gambaro, E. Argiriadis, M. Vecchiato, S. Zambon, P. Cescon, C. Barbante, Development of a method for simultaneous analysis of PCDDs, PCDFs, PCBs, PBDEs, PCNs and PAHs in Antarctic air, *Anal. Bioanal. Chem.* 405 (2013) 917–932, doi: <http://dx.doi.org/10.1007/s00216-012-6464-y>.
- [41] R. Man, P. Ping-an, Z. Su-kung, D. Yun-yun, M. Bi-xian, S. Guo-ying, Determination of 2,3,7,8-substituted polychlorinated dibenzo-p-dioxins-dibenzofurans and dioxin-like polychlorinated biphenyls in environmental samples by gas chromatography/high resolution mass spectrometry, *Chinese J. Anal. Chem.* 35 (2007) 176–180.
- [42] Y. Fan, H. Zhang, D. Wang, M. Ren, X. Zhang, L. Wang, J. Chen, Simultaneous determination of chlorinated aromatic hydrocarbons in fly ashes discharged from industrial thermal processes, *Anal. Methods* 9 (2017) 5198–5203, doi: <http://dx.doi.org/10.1039/c7ay01545c>.
- [43] D. Megson, E.J. Reiner, K.J. Jobst, F.L. Dorman, M. Robson, J.-F. Focant, A review of the determination of persistent organic pollutants for environmental forensics investigations, *Anal. Chim. Acta* 941 (2016) 10–25, doi: <http://dx.doi.org/10.1016/j.aca.2016.08.027>.
- [44] N. Riddell, B. van Bavel, I. Ericson Jogsten, R. McCrindle, A. McAlees, B. Chittim, Coupling supercritical fluid chromatography to positive ion atmospheric pressure ionization mass spectrometry: ionization optimization of halogenated environmental contaminants, *Int. J. Mass Spectrom.* 421 (2017) 156–163, doi: <http://dx.doi.org/10.1016/j.ijms.2017.07.005>.
- [45] N. Riddell, B. van Bavel, I. Ericson Jogsten, R. McCrindle, A. McAlees, B. Chittim, Coupling of supercritical fluid chromatography to mass spectrometry for the analysis of Dechlorane Plus: examination of relevant negative ion atmospheric pressure chemical ionization mechanisms, *Talanta* 171 (2017) 68–73, doi: <http://dx.doi.org/10.1016/j.talanta.2017.04.066>.
- [46] N. Riddell, B. Van Bavel, I.E. Jogsten, R. McCrindle, A. McAlees, D. Potter, C. Tashiro, B. Chittim, Comparative assessment of the chromatographic separation of 2,3,7,8-substituted polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans using supercritical fluid chromatography and high resolution gas chromatography, *Anal. Methods* 7 (2015) 9245–9253, doi: <http://dx.doi.org/10.1039/c5ay01644d>.
- [47] J.L. Barber, U. Berger, C. Chaemfa, S. Huber, A. Jahnke, C. Temme, K.C. Jones, Analysis of per- and polyfluorinated alkyl substances in air samples from Northwest Europe, *J. Environ. Monit.* 9 (2007) 530–541, doi: <http://dx.doi.org/10.1039/b701417a>.
- [48] T. Portolés, L.E. Rosales, J.V. Sancho, F.J. Santos, E. Moyano, Gas chromatography-tandem mass spectrometry with atmospheric pressure chemical ionization for fluorotelomer alcohols and perfluorinated sulfonamides determination, *J. Chromatogr. A* 1413 (2015) 107–116, doi: <http://dx.doi.org/10.1016/j.chroma.2015.08.016>.
- [49] R. Köppen, R. Becker, C. Jung, I. Nehls, On the thermally induced isomerisation of hexabromocyclododecane stereoisomers, *Chemosphere* 71 (2008) 656–662, doi: <http://dx.doi.org/10.1016/j.chemosphere.2007.11.009>.
- [50] Á. García-Bermejo, M. Ábalos, J. Sauló, E. Abad, M.J. González, B. Gómara, Triple quadrupole tandem mass spectrometry: a real alternative to high resolution magnetic sector instrument for the analysis of polychlorinated dibenzo-p-dioxins, furans and dioxin-like polychlorinated biphenyls, *Anal. Chim. Acta* 889 (2015) 156–165, doi: <http://dx.doi.org/10.1016/j.aca.2015.07.039>.
- [51] P. Xu, B. Tao, Z. Ye, L. Qi, Y. Ren, Z. Zhou, N. Li, Y. Huang, J. Chen, Simultaneous determination of three alternative flame retardants (dechlorane plus, 1,2-bis(2,4,6-tribromophenoxy) ethane, and decabromodiphenyl ethane) in soils by gas chromatography-high resolution mass spectrometry, *Talanta* 144 (2015) 1014–1020, doi: <http://dx.doi.org/10.1016/j.talanta.2015.07.031>.
- [52] C. Sales, T. Portolés, J.V. Sancho, E. Abad, M. Ábalos, J. Sauló, H. Fiedler, B. Gómara, J. Beltrán, Potential of gas chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry for screening and quantification of hexabromocyclododecane, *Anal. Bioanal. Chem.* 408 (2016) 449–459, doi: <http://dx.doi.org/10.1007/s00216-015-9146-8>.
- [53] R.A. Di Lorenzo, V.V. Lobodin, J. Cochran, T. Kolic, S. Besevic, J.G. Sled, E.J. Reiner, K.J. Jobst, Fast gas chromatography-atmospheric pressure (photo) ionization mass spectrometry of polybrominated diphenylether flame retardants, *Anal. Chim. Acta* 1056 (2019) 70–78, doi: <http://dx.doi.org/10.1016/j.aca.2019.01.007>.
- [54] A. Piersanti, T. Tavoloni, E. Bastari, C. Lestingi, S. Romanelli, R. Rossi, G. Saluti, S. Moretti, R. Galarini, A GC-EC-MS/MS method for the determination of 15 polybrominated diphenyl ethers (PBDEs) in fish and shellfish tissues, *Food Anal. Methods* 11 (2018) 355–366, doi: <http://dx.doi.org/10.1007/s12161-017-1006-z>.
- [55] H.M. Stapleton, Instrumental methods and challenges in quantifying polybrominated diphenyl ethers in environmental extracts: a review, *Anal. Bioanal. Chem.* 386 (2006) 807–817, doi: <http://dx.doi.org/10.1007/s00216-006-0400-y>.
- [56] J. Rjabova, A. Viksna, D. Zacs, Development and optimization of gas chromatography coupled to high resolution mass spectrometry based method for the sensitive determination of Dechlorane plus and related norbornene-based flame retardants in food of animal origin, *Chemosphere* 191 (2018) 597–606, doi: <http://dx.doi.org/10.1016/j.chemosphere.2017.10.095>.
- [57] T.P. Rusina, P. Korytár, J. de Boer, Comparison of quantification methods for the analysis of polychlorinated alkanes using electron capture negative ionisation mass spectrometry, *Int. J. Environ. Anal. Chem.* 91 (2011) 319–332, doi: <http://dx.doi.org/10.1080/03067311003602583>.
- [58] K. Krätschmer, C. Cojocariu, A. Schächtle, R. Malisch, W. Vetter, Chlorinated paraffin analysis by gas chromatography orbitrap high-resolution mass spectrometry: method performance, investigation of possible interferences and analysis of fish samples, *J. Chromatogr. A* 1539 (2018) 53–61, doi: <http://dx.doi.org/10.1016/j.chroma.2018.01.034>.
- [59] B. Van Bavel, D. Geng, L. Cherta, J. Nächer-Mestre, T. Portolés, M. Ábalos, J. Sauló, E. Abad, J. Dunstan, R. Jones, A. Kotz, H. Winterhalter, R. Malisch, W. Traag, J. Hagberg, I. Ericson Jogsten, J. Beltran, F. Hernández, Atmospheric-pressure chemical ionization tandem mass spectrometry (APGC/MS/MS) an alternative to high-resolution mass spectrometry (HRGC/HRMS) for the determination of dioxins, *Anal. Chem.* 87 (2015) 9047–9053, doi: <http://dx.doi.org/10.1021/acs.analchem.5b02264>.
- [60] T. Portolés, C. Sales, M. Abalos, J. Sauló, E. Abad, Evaluation of the capabilities of atmospheric pressure chemical ionization source coupled to tandem mass spectrometry for the determination of dioxin-like polychlorobiphenyls in complex-matrix food samples, *Anal. Chim. Acta* 937 (2016) 96–105, doi: <http://dx.doi.org/10.1016/j.aca.2016.06.038>.
- [61] D. Geng, I.E. Jogsten, J. Dunstan, J. Hagberg, T. Wang, J. Ruzzin, R. Rabasa-Lhoret, B. van Bavel, Gas chromatography/atmospheric pressure chemical ionization/mass spectrometry for the analysis of organochlorine pesticides and polychlorinated biphenyls in human serum, *J. Chromatogr. A* 1453 (2016) 88–98, doi: <http://dx.doi.org/10.1016/j.chroma.2016.05.030>.
- [62] J. Stubleski, P. Kukucka, S. Salihovic, P.M. Lind, L. Lind, A. Kärrman, A method for analysis of marker persistent organic pollutants in low-volume plasma and serum samples using 96-well plate solid phase extraction, *J. Chromatogr. A* 1546 (2018) 18–27, doi: <http://dx.doi.org/10.1016/j.chroma.2018.02.057>.
- [63] N. Hanari, J. Falandysz, T. Nakano, G. Petrick, N. Yamashita, Separation of closely eluting chloronaphthalene congeners by two-dimensional gas chromatography/quadrupole mass spectrometry: an advanced tool in the study and risk analysis of dioxin-like chloronaphthalenes, *J. Chromatogr. A* 1301 (2013) 209–214, doi: <http://dx.doi.org/10.1016/j.chroma.2013.05.070>.
- [64] D. Xia, L. Gao, M. Zheng, S. Wang, G. Liu, Simultaneous analysis of polychlorinated biphenyls and polychlorinated naphthalenes by isotope dilution comprehensive two-dimensional gas chromatography high-resolution time-of-flight mass spectrometry, *Anal. Chim. Acta* 937 (2016) 160–167, doi: <http://dx.doi.org/10.1016/j.aca.2016.07.018>.
- [65] S. Hashimoto, Y. Takazawa, A. Fushimi, K. Tanabe, Y. Shibata, T. Ieda, N. Ochiai, H. Kanda, T. Ohura, Q. Tao, S.E. Reichenbach, Global and selective detection of organohalogenes in environmental samples by comprehensive two-dimensional gas chromatography-tandem mass spectrometry and high-resolution time-of-flight mass spectrometry, *J. Chromatogr. A* 1218 (2011) 3799–3810, doi: <http://dx.doi.org/10.1016/j.chroma.2011.04.042>.
- [66] S.N. Zhou, E.J. Reiner, C.H. Marvin, P.A. Helm, L. Shen, I.D. Brindle, Liquid chromatography/atmospheric pressure photoionization tandem mass spectrometry for analysis of Dechloranes, *Rapid Commun. Mass Spectrom.* 25 (2011) 436–442, doi: <http://dx.doi.org/10.1002/rcm.4874>.
- [67] S.Y. Baek, S. Lee, B. Kim, Separation of hexabromocyclododecane diastereomers: application of C18 and phenyl-hexyl ultra-performance liquid chromatography columns, *J. Chromatogr. A* 1488 (2017) 140–145, doi: <http://dx.doi.org/10.1016/j.chroma.2017.01.047>.
- [68] K. Janák, A. Covaci, S. Voorspoels, G. Becher, Hexabromocyclododecane in marine species from the Western Scheldt Estuary: diastereoisomer- and enantiomer-specific accumulation, *Environ. Sci. Technol.* 39 (2005) 1987–1994, doi: <http://dx.doi.org/10.1021/es0484909>.
- [69] L. Zheng, L. Lian, J. Nie, Y. Song, S. Yan, D. Yin, W. Song, Development of an ammonium chloride-enhanced thermal-assisted-ESI LC-HRMS method for the characterization of chlorinated paraffins, *Environ. Pollut.* 255 (2019) 113303, doi: <http://dx.doi.org/10.1016/j.envpol.2019.113303>.
- [70] J.F. Ayala-Cabrera, F. Javier Santos, E. Moyano, Negative-ion atmospheric pressure ionisation of semi-volatile fluorinated compounds for ultra-high-performance liquid chromatography tandem mass spectrometry analysis,

- Anal. Bioanal. Chem. 410 (2018) 4913–4924, doi:<http://dx.doi.org/10.1007/s00216-018-1138-z>.
- [71] O. Lacina, P. Hradkova, J. Pulkrabova, J. Hajslova, Simple, high throughput ultra-high performance liquid chromatography/tandem mass spectrometry trace analysis of perfluorinated alkylated substances in food of animal origin: milk and fish, *J. Chromatogr. A* 1218 (2011) 4312–4321, doi:<http://dx.doi.org/10.1016/j.chroma.2011.04.061>.
- [72] R. Lega, D. Megson, C. Hartley, P. Crozier, K. MacPherson, T. Kolic, P.A. Helm, A. Myers, S.P. Bhavsar, E.J. Reiner, Congener specific determination of polychlorinated naphthalenes in sediment and biota by gas chromatography high resolution mass spectrometry, *J. Chromatogr. A* 1479 (2017) 169–176, doi:<http://dx.doi.org/10.1016/j.chroma.2016.11.054>.
- [73] N. Barco-Bonilla, P. Plaza-Bolaños, N.M.V. Tarifa, R. Romero-González, J.L.M. Vidal, A.G. French, Highly sensitive determination of polybrominated diphenyl ethers in surface water by GC coupled to high-resolution MS according to the EU Water Directive 2008/105/EC, *J. Sep. Sci.* 37 (2014) 69–76, doi:<http://dx.doi.org/10.1002/jssc.201300757>.
- [74] S.A. Mackintosh, A. Pérez-Fuentetaja, L.R. Zimmerman, G. Pacepavicius, M. Clapsadl, M. Alae, D.S. Aga, Analytical performance of a triple quadrupole mass spectrometer compared to a high resolution mass spectrometer for the analysis of polybrominated diphenyl ethers in fish, *Anal. Chim. Acta* 747 (2012) 67–75, doi:<http://dx.doi.org/10.1016/j.aca.2012.08.021>.
- [75] U.E. Fridén, M.S. McLachlan, U. Berger, Chlorinated paraffins in indoor air and dust: concentrations, congener patterns, and human exposure, *Environ. Int.* 37 (2011) 1169–1174, doi:<http://dx.doi.org/10.1016/j.envint.2011.04.002>.
- [76] Z. Zencak, A. Borgen, M. Reth, M. Oehme, Evaluation of four mass spectrometric methods for the gas chromatographic analysis of polychlorinated n-alkanes, *J. Chromatogr. A* 1067 (2005) 295–301, doi:<http://dx.doi.org/10.1016/j.chroma.2004.09.098>.
- [77] E. Jakobsson, L. Asplund, Polychlorinated naphthalenes (PCNs), in: J. Paasivirta (Ed.), *Handb. Environ. Chem. Vol. 3 Anthropol. Compd. Part K New Types Persistent Halogenated Compd.*, Springer-Verlag, Berlin, 2000, pp. 97–126, doi:[http://dx.doi.org/10.1007/3-540-48915-0\\_5](http://dx.doi.org/10.1007/3-540-48915-0_5).
- [78] J.J. Ellington, J.W. Washington, J.J. Evans, T.M. Jenkins, S.C. Hafner, M.P. Neill, Analysis of fluorotelomer alcohols in soils: optimization of extraction and chromatography, *J. Chromatogr. A* 1216 (2009) 5347–5354, doi:<http://dx.doi.org/10.1016/j.chroma.2009.05.035>.
- [79] Y. Gao, H. Zhang, L. Zou, P. Wu, Z. Yu, X. Lu, J. Chen, Quantification of short-chain chlorinated paraffins by deuterodechlorination combined with gas chromatography-mass spectrometry, *Environ. Sci. Technol.* 50 (2016) 3746–3753, doi:<http://dx.doi.org/10.1021/acs.est.5b05115>.
- [80] W. Gao, J. Wu, Y. Wang, G. Jiang, Quantification of short- and medium-chain chlorinated paraffins in environmental samples by gas chromatography quadrupole time-of-flight mass spectrometry, *J. Chromatogr. A* 1452 (2016) 98–106, doi:<http://dx.doi.org/10.1016/j.chroma.2016.04.081>.
- [81] T. Li, Y. Wan, S. Gao, B. Wang, J. Hu, High-throughput determination and characterization of short-, medium-, and long-chain chlorinated paraffins in human blood, *Environ. Sci. Technol.* 51 (2017) 3346–3354, doi:<http://dx.doi.org/10.1021/acs.est.6b05149>.
- [82] C. Bogdal, T. Alsberg, P.S. Diefenbacher, M. Macleod, U. Berger, Fast quantification of chlorinated paraffins in environmental samples by direct injection high-resolution mass spectrometry with pattern deconvolution, *Anal. Chem.* 87 (2015) 2852–2860, doi:<http://dx.doi.org/10.1021/ac504444d>.
- [83] B. Yuan, T. Alsberg, C. Bogdal, M. MacLeod, U. Berger, W. Gao, Y. Wang, C.A. De Wit, Deconvolution of Soft ionization mass spectra of chlorinated paraffins to resolve congener groups, *Anal. Chem.* 88 (2016) 8980–8988, doi:<http://dx.doi.org/10.1021/acs.analchem.6b01172>.
- [84] B. Yuan, C. Bogdal, U. Berger, M. MacLeod, W.A. Gebbink, T. Alsberg, C.A. De Wit, Quantifying short-chain chlorinated paraffin congener groups, *Environ. Sci. Technol.* 51 (2017) 10633–10641, doi:<http://dx.doi.org/10.1021/acs.est.7b02269>.
- [85] B. Yuan, J.P. Baskin, C.E.L. Chen, A. Bergman, Determination of chlorinated paraffins by bromide-anion attachment atmospheric-pressure chemical ionization mass spectrometry, *Environ. Sci. Technol. Lett.* 5 (2018) 348–353, doi:<http://dx.doi.org/10.1021/acs.estlett.8b00216>.
- [86] X. Wang, X. Zhang, Z. Wang, Y. Chen, X. Li, Z. Cui, Determination of hexabromocyclododecane in soil by supercritical fluid extraction and gas chromatography mass spectrometry, *Anal. Methods* 10 (2018) 1181–1189, doi:<http://dx.doi.org/10.1039/c8ay00018b>.
- [87] F.L. Chiriac, L. Crueru, M. Niculescu, L.F. Pascu, C.B. Lehr, T. Galaon, Simultaneous determination of  $\alpha$ -,  $\beta$ - and  $\gamma$ -hexabromocyclododecane diastereoisomers in sewage sludge using liquid chromatography tandem mass spectrometry, *Rev. Chim.* 68 (2017) 1685–1689.
- [88] D. Zacs, J. Rjabova, V. Bartkevics, New perspectives on diastereoselective determination of hexabromocyclododecane traces in fish by ultra high performance liquid chromatography-high resolution orbitrap mass spectrometry, *J. Chromatogr. A* 1330 (2014) 30–39, doi:<http://dx.doi.org/10.1016/j.chroma.2014.01.023>.
- [89] J. Feng, Y. Wang, T. Ruan, G. Qu, G. Jiang, Simultaneous determination of hexabromocyclododecanes and tris (2,3-dibromopropyl) isocyanurate using LC-APCI-MS/MS, *Talanta* 82 (2010) 1929–1934, doi:<http://dx.doi.org/10.1016/j.talanta.2010.08.014>.
- [90] M.S. Ross, C.S. Wong, Comparison of electrospray ionization, atmospheric pressure photoionization, and anion attachment atmospheric pressure photoionization for the analysis of hexabromocyclododecane enantiomers in environmental samples, *J. Chromatogr. A* 1217 (2010) 7855–7863, doi:<http://dx.doi.org/10.1016/j.chroma.2010.09.083>.
- [91] M. Smoluch, J. Silberring, E. Reszke, J. Kuc, A. Grochowalski, Determination of hexabromocyclododecane by flowing atmospheric pressure afterglow mass spectrometry, *Talanta* 128 (2014) 58–62, doi:<http://dx.doi.org/10.1016/j.talanta.2014.04.042>.
- [92] J.F. Ayala-Cabrera, A. Contreras-Llin, E. Moyano, F.J. Santos, A novel methodology for the determination of neutral perfluoroalkyl and polyfluoroalkyl substances in water by gas chromatography-atmospheric pressure photoionisation-high resolution mass spectrometry, *Anal. Chim. Acta* 1100 (2019) 97–106, doi:<http://dx.doi.org/10.1016/j.aca.2019.12.004>.
- [93] D. Megson, M. Robson, K.J. Jobst, P.A. Helm, E.J. Reiner, Determination of halogenated flame retardants using gas chromatography with atmospheric pressure chemical ionization (APCI) and a high-resolution quadrupole time-of-flight mass spectrometer (HRqTOFMS), *Anal. Chem.* 88 (2016) 11406–11411, doi:<http://dx.doi.org/10.1021/acs.analchem.6b01550>.
- [94] V. Hloušková, D. Lanková, K. Kalachová, P. Hrádková, J. Poustka, J. Hajšlová, J. Pulkrabová, Brominated flame retardants and perfluoroalkyl substances in sediments from the Czech aquatic ecosystem, *Sci. Total Environ.* 470–471 (2014) 407–416, doi:<http://dx.doi.org/10.1016/j.scitotenv.2013.09.074>.
- [95] T. Portolés, C. Sales, B. Gómara, J.V. Sancho, J. Beltrán, L. Herrero, M.J. González, F. Hernández, Novel analytical approach for brominated flame retardants based on the use of gas chromatography-atmospheric pressure chemical ionization-tandem mass spectrometry with emphasis in highly brominated congeners, *Anal. Chem.* 87 (2015) 9892–9899, doi:<http://dx.doi.org/10.1021/acs.analchem.5b02378>.
- [96] L. Debrauer, A. Riu, M. Jouahri, E. Rathahao, I. Jouanin, J.P. Antignac, R. Cariou, B. Le Bizec, D. Zalko, Probing new approaches using atmospheric pressure photo ionization for the analysis of brominated flame retardants and their related degradation products by liquid chromatography-mass spectrometry, *J. Chromatogr. A* 1082 (2005) 98–109, doi:<http://dx.doi.org/10.1016/j.chroma.2005.04.060>.
- [97] X. Zheng, K.T. Dupuis, N.A. Aly, Y. Zhou, F.B. Smith, K. Tang, R.D. Smith, E.S. Baker, Utilizing ion mobility spectrometry and mass spectrometry for the analysis of polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polybrominated diphenyl ethers and their metabolites, *Anal. Chim. Acta* 1037 (2018) 265–273, doi:<http://dx.doi.org/10.1016/j.aca.2018.02.054>.
- [98] G. ten Dam, I.C. Pussente, G. Scholl, G. Eppe, A. Schaechtele, S. van Leeuwen, The performance of atmospheric pressure gas chromatography-tandem mass spectrometry compared to gas chromatography-high resolution mass spectrometry for the analysis of polychlorinated dioxins and polychlorinated biphenyls in food and feed samples, *J. Chromatogr. A* 1477 (2016) 76–90, doi:<http://dx.doi.org/10.1016/j.chroma.2016.11.035>.
- [99] F. Hernández, M. Ibáñez, T. Portolés, M.I. Cervera, J.V. Sancho, F.J. López, Advancing towards universal screening for organic pollutants in waters, *J. Hazard. Mater.* 282 (2015) 86–95, doi:<http://dx.doi.org/10.1016/j.jhazmat.2014.08.006>.
- [100] L. Luosujärvi, M.-M. Karikko, M. Haapala, V. Saarela, S. Huhtala, S. Franssila, R. Kostiainen, T. Kotiaho, T.J. Kauppila, Gas chromatography/mass spectrometry of polychlorinated biphenyls using atmospheric pressure chemical ionization and atmospheric pressure photoionization microchips, *Rapid Commun. Mass Spectrom.* 22 (2008) 425–431, doi:<http://dx.doi.org/10.1002/rcm.3379>.
- [101] J.F. Ayala-Cabrera, M. Ábalos, E. Abad, E. Moyano, F.J. Santos, Feasibility of gas chromatography-atmospheric pressure photoionization – high-resolution mass spectrometry for the analysis of polychlorinated dibenzo-p-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls in environmental and feed sample, *Anal. Bioanal. Chem.* 412 (2020) 3703–3716, doi:<http://dx.doi.org/10.1007/s00216-020-02615-7>.
- [102] D.G. Hayward, J.C. Archer, S. Andrews, R.D. Fairchild, J. Gentry, R. Jenkins, M. McLain, U. Nasini, S. Shojae, Application of a high-resolution Quadrupole/orbital trapping mass spectrometer coupled to a gas chromatograph for the determination of persistent organic pollutants in cow's and human milk, *J. Agric. Food Chem.* 66 (2018) 11823–11829, doi:<http://dx.doi.org/10.1021/acs.jafc.8b03721>.
- [103] K.L. Organtini, L. Haimovici, K.J. Jobst, E.J. Reiner, A. Ladak, D. Stevens, J.W. Cochran, F.L. Dorman, Comparison of atmospheric pressure ionization gas chromatography-triple quadrupole mass spectrometry to traditional high-resolution mass spectrometry for the identification and quantification of halogenated dioxins and furans, *Anal. Chem.* 87 (2015) 7902–7908, doi:<http://dx.doi.org/10.1021/acs.analchem.5b01705>.
- [104] J. Rivera-Austrui, K. Martínez, M. Ábalos, C. Sales, T. Portolés, J. Beltrán, J. Sauló, B.H. Aristizábal, E. Abad, Analysis of polychlorinated dibenzo-p-dioxins and dibenzofurans in stack gas emissions by gas chromatography-atmospheric pressure chemical ionization-triple-quadrupole mass spectrometry, *J. Chromatogr. A* 1513 (2017) 245–249, doi:<http://dx.doi.org/10.1016/j.chroma.2017.07.039>.
- [105] C. Perazzolli, I. Mancini, G. Guella, Benzene-assisted atmospheric-pressure chemical ionization: a new liquid chromatography/mass spectrometry approach to the analysis of selected hydrophobic compounds, *Rapid Commun. Mass Spectrom.* 19 (2005) 461–469, doi:<http://dx.doi.org/10.1002/rcm.1807>.
- [106] R. McCulloch, A. Alvaro, A.M. Astudillo, J.C. del Castillo, M. Gómez, J.M. Martín, M. Amo-González, A novel atmospheric pressure photoionization – mass spectrometry (APPI-MS) method for the detection of polychlorinated dibenzo P- dioxins and dibenzofuran homologues in real environmental samples collected within the vicinity of industrial incinerators, *Int. J. Mass*

- Spectrom. 421 (2017) 135–143, doi:<http://dx.doi.org/10.1016/j.ijms.2017.05.016>.
- [107] D. Carrizo, J.O. Grimalt, Rapid and simplified method for the analysis of polychloronaphthalene congener distributions in environmental and human samples by gas chromatography coupled to negative ion chemical ionization mass spectrometry, *J. Chromatogr. A* 1118 (2006) 271–277, doi:<http://dx.doi.org/10.1016/j.chroma.2006.03.108>.
- [108] A. Riu, D. Zalko, L. Debrauwer, Study of polybrominated diphenyl ethers using both positive and negative atmospheric pressure photoionization and tandem mass spectrometry, *Rapid Commun. Mass Spectrom.* 20 (2006) 2133–2142, doi:<http://dx.doi.org/10.1002/rcm>.
- [109] M.A.E. Abdallah, S. Harrad, A. Covaci, Isotope dilution method for determination of polybrominated diphenyl ethers using liquid chromatography coupled to negative ionization atmospheric pressure photoionization tandem mass spectrometry: validation and application to house dust, *Anal. Chem.* 81 (2009) 7460–7467, doi:<http://dx.doi.org/10.1021/ac901305n>.
- [110] C.N. McEwen, R.G. McKay, LC / MS: GC / MS ion source: advantages of dual AP-LC / MS: GC / MS instrumentation, *J. Am. Soc. Mass Spectrom.* (2005) 1730–1738, doi:<http://dx.doi.org/10.1016/j.jasms.2005.07.005>.
- [111] I.A. Revelsky, Y.S. Yashin, T.G. Sobolevsky, A.I. Revelsky, B. Miller, V. Oriedo, Electron ionization and atmospheric pressure photochemical ionization in gas chromatography-mass spectrometry analysis of amino acids, *Eur. J. Mass Spectrom. Chichester (Chichester)* 9 (2003) 497–507, doi:<http://dx.doi.org/10.1255/ejms.581>.
- [112] B. Szostek, K.B. Prickett, Determination of 8:2 fluorotelomer alcohol in animal plasma and tissues by gas chromatography-mass spectrometry, *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 813 (2004) 313–321, doi:<http://dx.doi.org/10.1016/j.jchromb.2004.10.031>.
- [113] G. Lindström, H. Wingfors, M. Dam, B. van Bavel, Identification of 19 polybrominated diphenyl ethers (PBDEs) in long-finned pilot whale (*Globicephala melas*) from the Atlantic, *Arch. Environ. Contam. Toxicol.* 36 (1999) 355–363, doi:<http://dx.doi.org/10.1007/s002449900482>.
- [114] J.F. Ayala-Cabrera, F.J. Santos, E. Moyano, Fragmentation studies of neutral per- and polyfluoroalkyl substances by atmospheric pressure ionization-multiple-stage mass spectrometry, *Anal. Bioanal. Chem.* 411 (2019) 7357–7373, doi:<http://dx.doi.org/10.1007/s00216-019-02150-0>.
- [115] T. Ieda, S. Hashimoto, T. Isobe, T. Kunisue, S. Tanabe, Evaluation of a data-processing method for target and non-target screening using comprehensive two-dimensional gas chromatography coupled with high-resolution time-of-flight mass spectrometry for environmental samples, *Talanta*. 194 (2019) 461–468, doi:<http://dx.doi.org/10.1016/j.talanta.2018.10.050>.
- [116] K.J. Jobst, L. Shen, E.J. Reiner, V.Y. Taguchi, P.A. Helm, R. McCrindle, S. Backus, The use of mass defect plots for the identification of (novel) halogenated contaminants in the environment, *Anal. Bioanal. Chem.* 405 (2013) 3289–3297, doi:<http://dx.doi.org/10.1007/s00216-013-6735-2>.
- [117] T. Portolés, J.G.J. Mol, J.V. Sancho, F. Hernández, Use of electron ionization and atmospheric pressure chemical ionization in gas chromatography coupled to time-of-flight mass spectrometry for screening and identification of organic pollutants in waters, *J. Chromatogr. A* 1339 (2014) 145–153, doi:<http://dx.doi.org/10.1016/j.chroma.2014.03.001>.
- [118] N.D. Dat, K.-S. Chang, C.P. Wu, Y.-J. Chen, C.-L. Tsai, K.H. Chi, M.-B. Chang, Measurement of PCNs in sediments collected from reservoir and river in northern Taiwan, *Ecotoxicol. Environ. Saf.* 174 (2019) 384–389, doi:<http://dx.doi.org/10.1016/j.ecoenv.2019.02.087>.
- [119] M. Reth, Z. Zencak, M. Oehme, New quantification procedure for the analysis of chlorinated paraffins using electron capture negative ionization mass spectrometry, *J. Chromatogr. A* 1081 (2005) 225–231, doi:<http://dx.doi.org/10.1016/j.chroma.2005.05.061>.