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An overview of analytical methods for enantiomeric determination of chiral pollutants in environmental samples and biota

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ABSTRACT

Chirality is a relevant topic in pharmaceutical, food and agrochemical fields because enantiomers, in spite of their similar physical-chemical properties, can exhibit different dynamics, kinetics and effects. Their enantiomeric determination implies a significant analytical challenge because of their identical physical-chemical properties, except light rotation. This review provides a state-of-the-art overview of analytical methods reported from 2010 to the date for the determination of chiral pollutants, including pharmaceuticals, pesticides, musk fragrances, perfluorinated compounds (PFCs), brominated flame retardants (BFRs) and polychlorinated biphenyls (PCBs), in environmental samples and biota. Recent reviews in this topic, mainly focused on pharmaceuticals and pesticides, have been also included. Special attention has been focused on analytical techniques most commonly applied for such determination. Finally, future trends and mainly challenges to be overcome are stated.

1. Introduction

Enantiomers of chiral compounds are mirror-images with identical physical-chemical properties [1], except light rotation, that can suffer different biotransformation and bioaccumulation patterns in a chiral environment [2–6]. This fact is a critical aspect in medicinal and agrochemical fields [1,7,8] and in food science [9]. Some reviews have stated the occurrence of chiral compounds in the aquatic environment [6,10] and their enantioselective behaviour in wastewater, aquatic and terrestrial environments and living organisms [11]. The importance of the enantiodetermination of chiral pollutants in the environment, for a proper evaluation of their toxicological effects and environmental behaviour (distribution, occurrence and (bio)degradation), was already stated by Armstrong et al. in 1992 [12]. A review from Ye et al. [13] revealed the significant differences on ecotoxicology of chiral insecticides and herbicides from different groups. An overview of such differences can be observed in Fig. 1. The most toxic enantiomers, which are those with lower median lethal concentration (LC50), are shown are black bars. The toxicities of some of them, as (+) enantiomers of leptophos and isocarbophos are up to 21 and 50-fold higher than the other enantiomer, respectively. In the last years, there is an increasing concern about the enantiomeric determination, or occurrence, of chiral pollutants in the environment. These studies have been mainly focused in pharmaceuticals, pesticides and, in a lower extent, in polychlorinated biphenyls as can be seen in Fig. 2. Nevertheless, to the date, most of the analytical methods for the determination of chiral pollutants ignore their enantiomeric determination [6]. The enantiomeric analysis of chiral compounds implies a significant analytical challenge because their identical physical-chemical properties considerably complicates their individual determination. Enantiomers can be designated as (+) or (−), depending on the clockwise or counterclockwise rotation of the polarised light, respectively, or as *R*- or *S*-, from the Latin *rectus* and *sinister*, respectively, depending on the spatial placement of the substituents of the stereogenic unit [6]. Enantioselectivity is usually expressed as enantiomeric fraction (EF), as proposed by Harner et al. [14]. Enantiomeric fraction is calculated using the following equation: $EF = A_+/(A_+ + A_-)$ or $EF = A_1/(A_1 + A_2)$ where A_+ and A_- represents (+) and (−) enantiomers, respectively, depending on the optical rotation caused on polarized light, or first and last eluting enantiomers on a chiral column, when the identity of (+) and (−) enantiomers is not known [14]. EF can be also expressed as $EF = A_S/(A_S + A_R)$ where A_R and A_R represent *R*- and *S*- enantiomers. In spite that most of the chiral compounds are provided in racemic forms, the EF can be altered in the environment mainly by different (bio) degradation pathways [6] and, in a lower extent, by interaction with other chiral compounds. In addition, enantioselectivity

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Abbreviations

ACE	acetone
ACN	acetonitrile
AcOH	acetic acid
$AcONH_4$	ammonium acetate
ACN	acetonitrile
BFR	brominated flame retardant
CBH	cellobiohydrolase
CD	cyclodextrine phases
CE	capillary electrophoresis
CEC	capillary electrochromatography
C-IRMS	combustion isotope ratio mass spectrometry
CLC	capillary liquid chromatography
CS	chiral selector
CSP	chiral stationary phase
CSIA	compound-specific isotope analysis
DTT	dichlorodiphenyltrichloroethane
DLLME	dispersive liquid-liquid microextraction
d-SPE	dispersive solid-phase extraction
dw	dry weight
ESI	electrospray ionisation
ESIA	enantioselective isotope analysis
EtOH	ethanol
FA	formic acid
GC	gas chromatography
GPC	gel permeation chromatography
HBCD	hexabromocyclododecane
HCH	hexachlorocyclohexane
HEX	hexane
IDL	instrumental detection limit
LC	liquid chromatography
LLE	liquid-liquid extraction
lw	lipid weight
MAE	microwave assisted extraction
MDL	method detection limit
MeOH	methanol
MS	mass spectrometry
MSPE	magnetic solid-phase extraction
MSPD	matrix solid-phase dispersion
MWCNTs	multi-walled carbon nanotubes
n.d.	no data
NH_4F	ammonium formate
NH_4OH	ammonium hydroxide
PCB	polychlorinated biphenyl
PDE5 inhibitor	phosphodiesterase type 5 inhibitor
PFC	perfluorinated compound
PFOA	perfluorooctanoic acid
PLE	pressurized liquid extraction
PUF	polyurethane foam
SFC	supercritical fluidic chromatography
SLE	solid-liquid extraction
SPE	solid-phase extraction
SUPRAS	supramolecular solvent
TBCO	tetrabromocyclooctane
TBECH	1,2-dibromo-4-(1,2-dibromoethly) cyclohexane
THF	tetrahydrofuran
UAE	ultrasound assisted extraction

depends not only on the nature of the process that a chiral contaminant undergoes but also on the interaction of the chiral contaminant with external agents (e.g. chiral molecules, chiral co-pollutants, humic acids and soil organominerals) and local environment conditions such as pH, redox conditions, organic carbon, organic nitrogen and redox conditions [15].

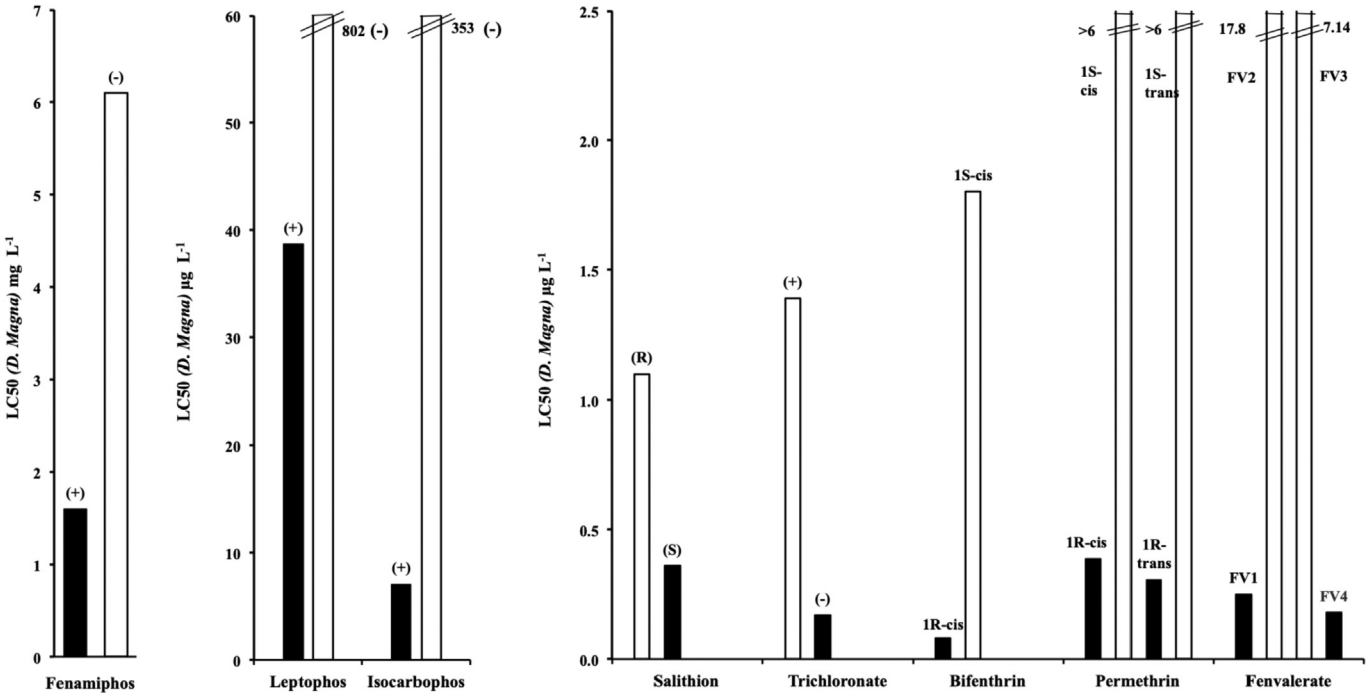

Fig. 1. Examples of enantioselective toxicity of chiral pesticides. Data from Ye et al., 2015 [13]. LC50: median lethal concentration.

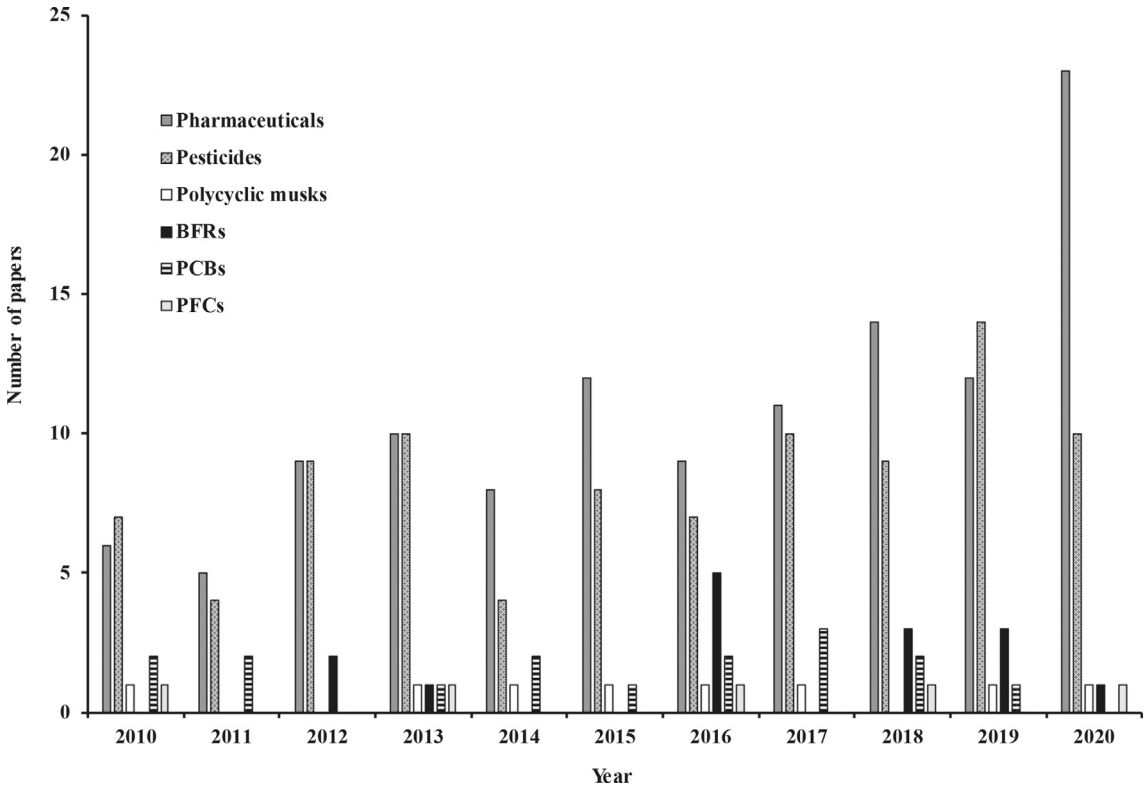

Fig. 2. Papers dealing with enantioseparation of chiral compounds in environmental samples. Data obtained from Scopus in May 2021 using the keywords: chiral, group name, and environment.

This review provides an overview of analytical methods and reviews, reported for the determination of chiral pollutants (pharmaceuticals, pesticides, musk fragrances, perfluorinated compounds (PFCs), brominated flame retardants (BFRs) and polychlorinated biphenyls (PCBs) in the environment and biota in the period from 2010 to the date. This overview is organized in two parts. In the first one, analytical techniques for enantiomer determination of chiral pollutants in the environment are reviewed and their advantages and disadvantages remarked. In the second one, an overview of analytical methods reported for each group of chiral pollutants and, when available, recent reviews for their determination is included. Finally, future trends, gaps to cover and drawbacks to be overcome are stated.

2. Analytical techniques for enantiomeric determination of chiral compounds in environmental matrices

Most of the analytical methods reported for the determination of chiral pollutants in environmental samples are based on liquid chromatography (LC) [16,17] and on gas chromatography (GC) [18], in most cases coupled to mass spectrometry (MS), because the high selectivity and sensitivity provided [6,10,19–21]. Other analytical techniques reported for such determinations are chiral supercritical fluid chromatography (SFC) [22–24], chiral capillary electrophoresis (CE) [19], chiral multidimensional liquid chromatography [25], nano- and capillary liquid chromatography (CLC) [26] and capillary electrochromatography (CEC) [17]. In addition, enantioselective stable isotope analysis (ESIA), has emerged as an innovative technique to assess the environmental fate of chiral pollutants by combining compound specific isotope analysis (CSIA) and enantioselective analysis mainly by chromatography [27,28]. It allows to differentiate between biotic and abiotic transformation pathways and even to distinguish between anaerobic and aerobic biotransformation pathways [27]. The main factors limiting the wide application of ESIA are matrix effects, trace concentrations and overlapping peaks [27].

Separation of enantiomers is carried out by using a chiral selector (CS), added to the chromatographic mobile phase or to the CE background electrolyte, or coated or immobilised onto the surface of a solid support (chiral stationary phases: CSP) (direct methods), or by using enantiomerically-pure derivatisation agents (indirect methods) [6]. Immobilised chiral selectors used as CSPs include cyclodextrins and their derivatives, polysaccharide derivatives, proteins, antibiotics, chiral ligands, cinchona alkaloids and amino acid derivatives, as well as molecularly imprinted polymers [29]. In the last 20 years, various monolithic CSPs, offering low flow-resistance, fast enantioseparation, and good enantioselectivity, have been developed for LC, SFC, CLS and CEC enantioseparation of a wide range of analytes. Nevertheless, many of these novel monolithic columns are lab-made columns and major challenges, such good reproducibility in terms of morphology, column efficiency, enantioselectivity and permeability, have to be overcome before being commercially available [29]. Their applications and limitations have been discussed in detail by Guo et al. [29].

LC and GC are the most used techniques for enantiomeric determination. Chiral LC has been widely applied for the enantiodetermination of chiral pharmaceuticals and pesticides whereas chiral GC has been applied to volatile and thermally-stable enantiomers of pesticides, polycyclic musks, BFRs, PCBs and PFCs. Some of their applications are listed in Table 1 [5,28,30–66] and are discussed in sections below. In sections below more information about the application of LC, GC and SFC in enantioseparation of

Table 1
Chiral stationary phases reported for enantiomeric analysis of chiral pollutants in environmental matrices by LC and GC.

LC columns				
CSP type	CSP	Commercial columns (Manufacturer)	Particle size (μm)	Application
Cyclodextrin-based	β-cyclodextrin	Nucleodex β-PM (Macherey-Nagel)	5	Pesticides [30]; BFRs [31–38]
Macrocyclic antibiotics	Teicoplanin	Chirobiotic T (Sigma-Aldrich)	5	Pharmaceuticals and illicit drugs [39]
	Vancomycin	Chirobiotic V (Sigma-Aldrich)	5	Pharmaceuticals and illicit drugs [5,40–42]
		Chirobiotic V2 (Sigma-Aldrich)	5	
		Poroshell 120 Chiral-V (Agilent)	2.7	Pharmaceuticals and illicit drugs [43,44[43,44]
				Pharmaceuticals and illicit drugs [45]
Pirkle-type	1-(3,5-dinitrobenzamido)- 1,2,3,4,-tetrahydrophenanthrene	Whelk-O 1 (Regis Technologies)	5	Pharmaceuticals [41]
	(R)-1-naphthyl glycine	Sumichiral OA-2500 (Sumika Chemical Analysis Service)	5	Pharmaceuticals [46]
Polysaccharide-based	Amylose tris(3,5-dimethylphenyl carbamate)	Chiralpak AD-RH (Daicel)	5	Pharmaceuticals [47]
	Amylose tris (3-chlorophenyl carbamate)	Chiralpak ID (Daicel)	3, 5	Pharmaceuticals [48]
	Amylose tris (3-chloro-5-methylphenyl carbamate)	Chiralpak IG (Daicel)	5	Pesticides [49]
	Amylose tris (5-chloro-2-methylphenyl carbamate)	Lux Amylose-2 (Phenomenex)	3	Pesticides [50]
	Cellulose tris (3,5-dimethylphenyl carbamate)	Chiralcel OD-RH (Daicel)	3, 5	Pharmaceuticals [51]; PCBs [84]
	Cellulose tris (3-chloro-4-methylphenyl carbamate)	Chiralcel OZ-RH (Daicel)	3, 5	Pharmaceuticals [52]
	Cellulose tris-(4-methylbenzoate)	Chiralcel OJ-H (Daicel)	5	PCBs [84]
Protein-based	α_1-Acid glycoprotein	Chiralpak AGP (Agilent)	5	Pharmaceuticals [53–55]
	Cellobiohydrolase	Chiralpak CBH (Agilent)	5	Pharmaceuticals and illicit drugs [56,57]
GC columns				
CSP type	CSP	Commercial columns (Manufacturer)	Column length (m)	Application
Cyclodextrin-based	Cyclodextrin bonded to dimethylpolysiloxane	Chiralsil-Dex (Agilent)	25, 50	PCBs [58–60]
	30% Heptakis (2,3-di-O-methyl-6-O-t-butyl dimethyl silyl)-β-cyclodextrin	Cyclosil-B (Agilent)	30	PCBs [28,60,61]; Polycyclic musks [62,63]
	tert-Butyldimethylsilyl β-cyclodextrin	BGB-172 (BGB Analytik)	30	Pesticides [59,64]; PCBs [58–60]; PFOAS [65]
	Heptakis-(2,3-di-O-methyl-6-O-t-butyldimethylsilyl)- β-cyclodextrin	Hydrodex-β-6TBDM (Macherey-Nagel)	25	Polycyclic musks [66]

chiral pollutants is provided. CE has been commonly applied to the determination of chiral drugs in pharmaceutical formulations and biological samples and to the determination of food components in food and food supplements [19] but it has been scarcely applied to the determination of chiral compounds in environmental matrices [68]. In such cases, β- and γ-cyclodextrins were added to the background electrolyte to be used as chiral selectors for the determination of pharmaceuticals [69,70] and pesticides [71] in wastewater and surface water. Nevertheless, as the application of CE, CLC and CEC for enantioseparation of chiral pollutants in environmental matrices is scarce and because of that no subsection has been included for such analytical techniques.

2.1. Liquid chromatography-mass spectrometry

Liquid chromatography is the most commonly used analytical technique for enantiomeric analysis of chiral compounds in environmental samples. This fact is due to the high number of commercially-available chiral columns [21] and the high versatility provided by the elution modes (normal, reverse, polar organic or polar ionic elution modes) [68] although reverse-phase mode is the preferred one because its better compatibility with MS detectors [21]. In Table 1, commercially available CSPs, together with brand names and available particle sizes are listed. Polysaccharide-based CSPs are the stationary phases most widely used on LC determination of chiral pollutants [17,29]. Such CSP are also the most widely used on nano-LC, SPC and CEC [72,74] This fact is due to presence of several stereogenic centers in the glucopyranose unit what allows a broad applicability to many structurally diverse compounds [72,73]. It has been reported that polysaccharide-based CSP columns are the commercially available chiral columns most widely used because they provide high selectivity, sensitivity and reproducibility [74]. It has been reported that 95% of chiral compounds have been resolved by using such polysaccharide phases [74]. These macromolecular CSPs are either amylose or cellulose-functionalised because native cellulose and amylose allows poor resolution and peak broadening due to slow diffusion of analytes through the polymer network [74]. Amilose and cellulose are commonly functionalised at the 2, 3 and 6 positions with phenylcarbamate (amilose and cellulose-based CSPs) or benzoate (cellulose-based CSPs) substituents [17]. A recent review from Chankvetadze [75] revealed an increasing interest for the

application of polysaccharide-based chiral stationary phases in chiral LC. This fact was explained by the development of more effective technologies for covalent immobilization of CSs onto silica and by the introduction of novel CS carriers, such as monolithic and superficially porous silica. Other CSPs used on LC are based on macrocyclic antibiotics, such as vancomycin, teicoplanin, ristocetin and avoparcin, and, in a lower extent, in cyclodextrin (CD) phases [72]; Brush-, Pirkle-type or donor-acceptor CSPs; derivatized cyclofructans; chiral synthetic macrocycles; chiral synthetic polymers; chiral imprinted polymers; protein-based CSPs and ligand- and ion-exchange CSPs [17,76]. Interaction of chiral compounds with polysaccharide derivative and cyclodextrin chiral selectors is described in detail in the review from Scriba [72]. Macrocyclic antibiotics allows enantiomer separation by the multiple molecular interaction of their diverse functional groups. For instance, vancomycin is useful for enantioseparation of amines because of its carboxylic acid group whereas teicoplanin is useful for enantioseparation of acids because of its amine group and its aglycone [17]. They are stable and efficient in both normal and reverse LC. Enantiomer separation by CD CSPs is carried out by non-covalent interactions into the hydrophobic cavity of CDs. Therefore, enantiomer separation by CD CSPs is limited to small molecules able to enter into the CDs cavity [17]. Brush-, Pirkle-type or donor-acceptor CSPs provide chiral recognition by dipole-dipole, van der Waals, aromatic and hydrogen bond interactions [29]. They are one of the most widely investigated CSPs but, to the date, their use is not so extended as that of polysaccharide-based and macrocyclic antibiotic CSPs. Molecularly imprinted polymers have been reported to provide a high selectivity [17,29] but, when used as CSPs, they provide low column efficiency and can suffer from swelling and shrinking when exposed to mobile phase [29]. Protein-based CSPs are not commonly used for chiral LC because they have low sampling loading capacity due to their limited binding sites and poor stability at high temperature and organic solvent environments [17]. Ligand CSPs are based on the higher retention of the enantiomer forming a more stable complex with the chiral ligands [17,29] whereas separation by ion-exchange CSPs is suitable for the enantioseparation of charged compounds [29]. In the last years, sub-5 μm LC columns have allowed narrower and more efficient chromatographic peaks and improving resolution and sensitivity. They can be used for high resolution separations or for faster separations with good resolution. Nevertheless, as can be seen in Table 1, only vancomycin (InfinityLab Poroshell 120 Chiral-V from Agilent), amylose-based (Chiralpak ID from Daicel, Lux Amylose-2 from Phenomenex) and cellulose-based (Chiralcel OD-RH and Chiralcel OZ-RH from Daicel) columns are commercially available with 3 μm stationary phase particle sizes.

As explained above, LC is commonly hyphenated with MS or MS/MS detectors because the high selectivity and sensitivity provided. LC-MS enantioseparation requires a thoughtfully optimisation of the type of organic solvent, organic solvent-water proportion and the concentration and type of modifiers. Different stationary phases should be previously tested as it remains difficult to predict enantiomer separation based on the chemical structure of the chiral compounds [48,74]. Multidimensional chromatography is applied when the chiral column does not provide good enantioseparation, especially in chiral separations involving compounds with several chiral centers [25,67] or enantiomers of several diastereoisomers [35,85]. In two-dimensional chiral chromatography, a chiral column is connected to a non-chiral column, or viceversa. Detailed information about the advances on multidimensional chromatography can be found in the review from Ali et al. [22].

LC-MS separations are carried out in reverse mode as normal mode solvents are not compatible with MS detectors using ESI or APCI sources [68,73]. Elution is commonly carried out in isocratic mode for a proper enantiomer separation, especially in multi-residue methods, resulting in long chromatographic run times. Mobile phase is often composed by ACN and MeOH, as organic modifiers, and an aqueous phase containing mobile phase additives, which have to be compatible with MS, to improve separation and sensitivity [74]. The type of organic modifier has to be optimised as it can significantly condition enantiomeric separation [9,48,49,76]. The influence of acidic additive types and mobile phase pH in enantiomeric separation should be also evaluated [48]. The mobile phase pH is often adjusted using formic acid (FA) (e.g., for basic compounds), which can enhance ionisation improving sensitivity, or lyophilic ions, such as ammonium acetate ($AcONH_4$) and ammonium trifluoroacetate, which promote interactions between the enantiomers and the stationary phase by lowering the column surface potential [21]. Nevertheless, $AcONH_4$ and FA have been reported to cause ion suppression in positive electrospray ionisation mode whereas ammonium trifluoroacetate can cause chiral column damage [21]. Other variables evaluated by some authors are the influence of flow rate and column temperature [49]. For instance, Zhao et al. [49] evaluated four types of cellulose-based chiral columns (Chiralpak IB, Chiralpak IC, Chiralcel OD-RH and Chiralcel OJ-RH) and three types of amylose-based chiral columns (Chiralpak IA, Chiralpak ID and Chiralpak IG), the organic modifier (MeOH and ACN) and it proportion with water, the concentration of mobile phase additives ($AcONH_4$ (0, 2, 5, 8 and 10 mM) and FA (0, 0.02, 0.05, 0.1 and 0.2%), flow rate (0.2, 0.4 0.6 mL min^{-1}) and column temperature (20, 25, 30, 35, 40°C) in the enantiomeric analysis of 18 chiral pesticides in water, soil and river sediment. They achieved enantioresolution above 1.45 for all the target pesticides, within a runtime of 55 min, by using Chiralpak IG column, isocratic elution with ACN and water containing 0.05% of FA and 5 mM of $AcONH_4$ as mobile phase, a flow rate of 0.6 mL min^{-1} and fixing column temperature at 30°C. In addition, matrix effect has to be carefully evaluated in LC-MS methods as both suppression and, less frequently signal enhancement, due to co-eluting compounds could affect the pair of enantiomers in a different extent because of their different retention times [40]. Lin et al. achieved the separation of eight stereoisomers of a pure pharmaceutical compound with 3 chiral centers by two-dimensional LC in a final analysis time of less than 24 min, including column equilibration time [67].

2.2. Gas chromatography-mass spectrometry

GC is one of the most used analytical technique for the analysis of chiral pesticides and volatile organic pollutants in environmental matrices [68]. This fact is due to its simplicity, high efficiency, short runtimes, good sensitivity, the absence of liquid mobile phases [18] and low organic solvent consumption (green analytical technique) and its easy hyphenation with MS. Nevertheless, non-volatile compounds require derivatisation, commercially-available GC chiral columns are still limited and the high temperatures required for large molecules, because of their high boiling points, could produce isomeric interconversion [77].

The main parameters that influence GC chiral separation are the type of chiral column, temperature ramp rates and carrier gas linear velocity [62]. Once tested the separation by different chiral columns, temperature ramp rates and linear velocity of carrier gas are recommended to be systematically varied to optimise enantioseparation [62]. Nevertheless, special attention should be paid to high temperatures applied in GC because it has been reported to produce isomer interconversion of some chiral compounds such as HBCD [31]. Wang et al. reported a significant effect in enantioseparation due to temperature ramp rates whereas carrier gas flow rate had no significant effect in the range from 0.6 mL min^{-1} to 1.2 mL min^{-1}. In some cases, the chiral column does not allow a

good separation of enantiomers and multidimensional chromatography has to be applied. Two-dimensional chromatography has been reported for the determination of PFOAs in soil, sediments, and plants [65] and for the determination of polycyclic musks in drinking water and surface water [62] in both cases by combining a β-cyclodextrin-based chiral column and a non-chiral HP-5MS column. As can be seen in Table 1, cyclodextrin-based stationary phases are the CSP most frequently reported for GC determination of chiral pollutants. They have been applied to the determination of pesticides [59,64], polycyclic musks [62,63,66] and industrial compounds (PCBs [28,60,61], BFRs [35,78] and PFOAs [65]). In fact, it has been reported that CSPs based on cyclodextrin derivatives are by far the commercially available columns most widely used for enantioseparation by GC [9,18] probably due to their good long term thermal stability [29]. In the last years, novel chiral stationary phases, such as cyclofructan derivatives and chiral porous materials, have been developed for GC determination. They have been proven to be suitable for enantioseparation of amino acid derivatives, alcohols, amines, amino alcohols, organic acids, aldehydes, ketones, ethers, epoxides, and esters but, to the date, they have been scarcely applied in environmental analysis [18]. Information about their advantages, disadvantages and applications can be found in the review from Xie et al. [18].

2.3. Supercritical fluid chromatography

SFC provides several advantages in comparison to GC and LC such as shorter analysis time than LC, without affecting separation efficiency due to the lower viscosity and faster mass transfer properties of supercritical or subcritical carbon dioxide than traditionally used LC mobile phases [22]; it allows the separation of thermolabile and non-volatile compounds that cannot be analysed by GC; and it provides faster separations and requires lower organic solvent consumption than LC. In addition, most CSPs used in LC can be also applied in SFC [68]. Nevertheless, to the date, SFC has not been so widely applied to chiral analysis as LC and GC probably due to the fact of being a more recent technique what implies that SFC instrumentation is not so advanced and extended in laboratories as GC and LC. Deng et al. [24], have recently reviewed the application of SFC to pesticide analysis concluding that the advantages provided by SFC, such as high resolution in particular, short run time, low organic solvent consumption, and amenability with sample preparation procedures such as QuEChERS, have promoted its application on the enantioseparation of chiral pesticides. The recent advances in SFC instrumentation, in terms of variety of capillary columns and hyphenation to MS, are expected to increase its use for chiral separations [24].

3. Analytical methods for determination of chiral compounds in environmental samples

In Tables 2–6 it can be seen an overview of analytical methods for the determination of pharmaceuticals, pesticides, polycyclic musks and industrial compounds in the environment (Tables 2–5) and biota (Table 6). These methods are discussed below.

3.1. Determination of pharmaceutical compounds and illicit drugs

There is an increasing concern about stereoselectivity in environmental occurrence, phase distribution and degradation of chiral pharmaceuticals and illicit drugs in the environment [21]. Chiral pharmaceuticals have been detected in contaminated soil and aquatic ecosystems [8] to the point that remediation technologies are already being proposed to reduce their release to the environment [8]. More than 50% of pharmaceuticals in current use are chiral compounds. Nevertheless, the review by Sanganyado et al. [21] revealed that monitoring studies have been mainly focused on β-receptor antagonists, analgesics, antifungals and antidepressants. Analytical methods for their determination in environmental matrices have been recently reviewed by Ribeiro et al. [68]. Other authors have specifically reviewed analytical methods for their determination in wastewater [80] or in the aquatic environment [6] or for the determination of a specific therapeutic group, such as non-steroidal anti-inflammatory drugs [10]. The determination of chiral pharmaceuticals is commonly carried out by LC-MS/MS and, in a lower extent, by GC-MS and SFC [21,68] mainly due to the higher variety of commercially-available chiral columns. In Table 2, it can be seen an overview of analytical methods reported for the determination of chiral pharmaceuticals and illicit drugs. More information can be found in reviews mentioned above [6,10,67,79]. Some methods include the enantiomeric analysis of chiral metabolites of pharmaceutical compounds [5,40,41,52,53,55]. The CSP most commonly used in environmental analysis of chiral pharmaceuticals are proteins and macrocyclic antibiotics, particularly vancomycin and teicoplanin [21,68]. Protein-based cellobiohydrolase (CBH) columns are mainly used for basic pharmaceuticals [80]. CBH columns require mobile phase composition containing no more than 20% of organic modifier and pH values in the range from 3 to 7 [56]. Some authors, as Evans et al. [56] reported the use of two chromatographic columns. They separated β-blockers and antidepressants by means of a macrocyclic antibiotic column, with vancomycin as CSP, and amphetamines by means of a protein-based column with CBH as CSP. Coelho et al. [41] also used two columns for enantiomeric separation in reverse elution mode, a Chirobiotic V (vancomycin column) for basic compounds and a Pirkle type Whelk-O®1, for acidic compounds. Chirobiotic V column can be used in both reverse and normal phase [47]. López-Serna et al. [59] reported that Chirobiotic V stationary phase allowed the separation of basic compounds (with pKa >8) but not of enantiomers of acidic pharmaceuticals (with pKa <5) (ketoprofen, naproxen and flumequine) that, in addition, were eluted with very short retention times. Derivatisation can be required for chiral compounds with location of the functional groups preventing the interaction of the chiral center with the stationary phase, in such cases an achiral column is used for their separation [21,80].

Method optimisation has to be carefully optimised because mobile phase type and composition, modifier, and acidic/basic additives play an important role in the retention of enantiomers. The addition of a modifier to mobile phases generally reverses the enantiomer retention order and can cause a decrease in the sensitivity [80]. For instance, Caballo et al. [46] reported that $AcONH_4$, essential for enantioselectivity in the separation of ibuprofen, ketoprofen and naproxen, caused ion suppression in their determination when a turbo ion spray interface was used. Since most chiral pharmaceuticals are ionic compounds, their ionisation is conditioned by mobile phase pH. For instance, López-Serna et al. [40] tested the chromatographic separation of 18 pharmaceutical compounds from five therapeutic groups and two of their metabolites (see more information in Table 2) in a Chirobiotic V column by using i) MeOH and ACN (polar organic mode); ii) MeOH or ACN containing $AcONH_4$ in the range from 4 to 30 mM, FA in the range from 0.005 to 0.1% and water in the range from 0 to 5% (polar ionic mode); iii) MeOH containing $AcONH_4$ in the range from 4 to 30 mM, FA in the range from 0.005 to 1.48% and water in the range from 5 to 80% (reverse phase mode). They did not observe differences between using ACN or MeOH but in both cases additives such as $AcONH_4$, water and FA were needed for enantioselectivity and retention times. Nevertheless, the best results were obtained at low additive concentration: 4 mM $AcONH_4$ and 0.005% of FA in MeOH [40]. Some authors such as Caballo et al. [45] even propose

Table 2
Overview of analytical methods for enantiomeric analysis of chiral pharmaceuticals in environmental samples.

Therapeutic class	Pharmaceutical compounds	Matrix	Sample treatment	Analytical determination	Chromatographic separation	Recovery (%)	MDL	Ref.
Analgesics, psychiatric drugs, antibiotics, cardiovascular drugs, β-agonists and metabolites	Ibuprofen, fluoxetine, atenolol, sotalol, metoprolol, propranolol, timolol, betaxolol, carazolol, pindolol, albuterol and clenbuterol *Metabolites*: 4-OH propranolol and norfluoxetine	Influent and effluent wastewater River water	SPE (Oasis HLB)	LC-MS/MS	Chirobiotic V (250 mm × 2.1 mm, 5 μm) Isocratic: 0.005% FA in 4 mM $AcONH_4$:MeOH (0.005:99.995; v/v)	Influent wastewater: 43.8–115.8 Effluent wastewater: 75.4–113.1 River water: 55.9–105.9	Influent wastewater: 0.11–10.03 ng L^{-1} Effluent wastewater: 0.09–2.91 ng L^{-1} River water: 0.09 –0.62 ng L^{-1}	[40]
Antibiotics and metabolites	Besifloxacin, ofloxacin, lomefloxacin, moxifloxacin, prulifloxacin, flumequine and nadifloxacin *Metabolites:* ofloxacin-N-oxide, desmethyl-ofloxacin, ulifloxacin and moxifloxacin-N-sulfate; and 4 achiral compounds	Influent and effluent wastewater River water Suspended particulate matter	Aqueous samples: SPE (Oasis HLB) Solid samples: MAE and SPE (Oasis MAX)	LC-MS/MS	Chiralcel OZ-RH (150 mm × 2.1 mm, 5 μm) Isocratic: 0.05% FA in 10 mM NH_4F:MeOH (1:99; v/v)	70–120	Aqueous samples: 0.1–81.4 ng L^{-1} Solid samples: 0.01–22.73 ng g^{-1}	[52]
Antidepressants, β-blockers, β-agonist, antihistamines and stimulants	Amphetamine, methamphetamine, atenolol, chlorpheniramine, citalopram, desmethylcitalopram, fluoxetine, propranolol, salbutamol, venlafaxine, desmethylvenlafaxine, bisoprolol, acebutolol, metoprolol and sotalol	Sediments	PLE + SPE (Oasis HLB)	LC-MS/MS	Poroshell 120 Chiral-V (150 mm × 2.1 mm, 2.7 μm) Isocratic: 2 mM $AcONH_4$ in MeOH containing 0.01% AcOH	22–93	0.1–3.0 ng g^{-1}	[45]
Antidepressants, analgesics, anxiolytics, and illicit drugs	Opioid analgesics, amphetamines, cocaine, heroin, stimulants, anaesthetics, sedatives, anxiolytics, designer drugs, PDE5 inhibitors, amphetamine and methamphetamine drug precursors	Wastewater	SPE (Oasis HLB)	LC-MS/MS	Chiralpak CBH (100 mm × 2.0 mm, 5 μm) Isocratic: 1 mM $AcONH_4$:MeOH (85:15; v/v)	>90	0.03–61 ng L^{-1}	[57]
Anti-inflammatories, anthelmintics, cytostatic, gastrointestinal, antibacterial, antifungal, antiepileptics, antihistamines and metabolites	Chloramphenicol, fexofenadine, ibuprofen, ifosfamide, ketoprofen, naproxen, praziquantel and tetramisole. *Metabolites:* aminorex, 3-N-dechloroethylifosfamide, 10,11-dihydro-10-hydroxycarbamazepine and dihydroketoprofen	River water Effluent wastewater	SPE (Oasis HLB-MAX)	LC-MS/MS	Chiralpak AGP (100 mm × 2 mm, 5 μm) Isocratic: 10 mM $AcONH_4$:ACN (99:1; v/v)	n.d.	0.04–34.7 ng L^{-1}	[53]
Illicit drugs	Amphetamine and methamphetamine	Wastewater	SPE (Oasis HLB)	LC-MS/MS	Chirobiotic V2 (250 mm × 2.1 mm, 5 μm) Isocratic: MeOH:AcOH:NH_4OH (100:0.1:0.025; v/v/v)	69–90	0.6–1 ng L^{-1}	[43]
Non-steroidal anti-inflammatory drugs	Ibuprofen, naproxen and ketoprofen	Wastewater	SUPRAS microextraction	LC-MS/MS	Sumichiral OA-2500 (250 mm × 4.6 mm, 5 μm) Isocratic: THF:50 mM $AcONH_4$ in MeOH (90:10; v/v)	97–103	0.5–1.2 ng L^{-1}	[46]
Non-steroidal anti-inflammatory drugs	Ibuprofen, naproxen and flurbiprofen	River water	SPE (Oasis HLB)	LC-MS/MS	Chiralpak AD-RH (150 mm × 4.6 mm, 5 μm) Isocratic: 10 mM $AcONH_4$ (pH 5 FA adjusted):ACN (65:35; v/v)	74.1–89.9	0.35–11.1 ng L^{-1}	[47]

(*continued on next page*)

Table 2 (*continued*)

Therapeutic class	Pharmaceutical compounds	Matrix	Sample treatment	Analytical determination	Chromatographic separation	Recovery (%)	MDL	Ref.
β-Blockers, antidepressants and metabolites	Metoprolol, propranolol, atenolol, venlafaxine and fluoxetine. *Metabolites:* metoprolol acid, α-hydroxymetoprolol, 4-hydroxypropranolol, norfluoxetine, O-desmethylvenlafaxine and N,O-didesmethylvenlafaxine	Surface water	SPE (Oasis HLB)	LC-MS/MS	Chirobiotic V (250 mm × 4.6 mm, 5 μm) Isocratic: 10 mM $AcONH_4$buffer (pH 4 FA adjusted):MeOH (10:90; v/v)	75−94	0.1−2.2 ng L^{-1}	[5]
β-Blockers, antidepressants, β-2-adrenergic agonist, steroidal anti-inflammatory drugs, illicit drugs and metabolites	Fluoxetine, alprenolol, metoprolol, tramadol propranolol, salbutamol benzoylecgonine, mirtazapine, ibuprofen, ketoprofen, naproxen, warfarin, bisoprolol, nebivolol, venlafaxine, flurbiprofen, amphetamine, methamphetamine and cocaine *Metabolites*: O-desmethylvenlafaxine, O-desmethyltramadol, N-desmethyltramadol, norcocaine	Surface water	SPE (Oasis MCX)	LC-MS/MS	Chirobiotic V (150 mm × 2.1 mm, 5 μm). Isocratic: 10 mM $AcONH_4$ (pH 6.8):EtOH (7.5:92.5, v/v) Pirkle type Whelk-O 1 (250 mm × 4.6 mm, 5 μm) Isocratic: MeOH:0.1% FA in H_2O (60:40; v/v)	54−117	0.01−2.66 ng L^{-1}	[41]
β-Blockers, β-agonists, antidepressants, stimulants and antihistamines	Atenolol, propranolol, salbutamol, fluoxetine, citalopram, amphetamine and chlorpheniramine	Septic tank wastewater	SPE (Oasis HLB)	LC-MS/MS	Chirobiotic V2 (250 mm × 2.1 mm, 5 μm) Isocratic:1 mM $AcONH_4$ in MeOH containing 0.01% AcOH	83−115	0.001−0.43 ng L^{-1}	[44]
β-Blockers	Atenolol, metoprolol, esmolol, pindolol and arotinolol	Influent and effluent wastewater River water	MSPE (MWCNTs)	LC-MS/MS	Chiralpak AGP (100 mm × 4 mm, 5 μm) Gradient, 0.5 mL min^{-1}. Solvent A: 10 mM $AcONH_4$ (pH 7 FA adjusted). Solvent B: ACN	82.9−95.6	0.50−1.45 ng L^{-1}	[54]
β-Blockers, antidepressants, amphetamines and metabolites	Amphetamine, methamphetamine, 3,4-methylenedioxy-amphetamine, 3,4-methylenedioxy-methamphetamine, 3,4-methylenedioxy-N-ethyl-amphetamine, 1R,2S (+)-ephedrine, 2R,2S (−)-ephedrine, 1S,2S (+)-pseudoephedrine, 2S,2S (−)-pseudoephedrine, norephedrine, venlafaxine, fluoxetine, tramadol, atenolol, metoprolol, propranolol, alprenolol, sotalol, salbutamol, mirtazapine, citalopram, mexiletine and terbutaline *Metabolites:* norfluoxetine, O-desmethylvenlafaxine and desmethylcitalopram	Influent and effluent wastewater Digested sludge	Wastewater: SPE (Oasis HLB) Sludge: MAE + SPE (Oasis MAX)	LC-MS/MS	β-Blockers and antidepressants: Chirobiotic V (250 mm × 2.1 mm, 5 μm). Isocratic: MeOH:0.005% FA in 4 mM $AcONH_4$ Amphetamines: Chiralpak CBH (100 mm × 2 mm 5 μm). Isocratic: 1 mM $AcONH_4$:2-propanol (90:10; v/v)	Wastewater: 46.9 −187.3 Sludge: 9.0−323.7	Influent: 0.05−28.74 ng L^{-1} Effluent: 0.01−32.73 ng L^{-1} Sludge: 0.08−7.12 ng g^{-1}	[56]

Table 3
Overview of analytical methods for enantiomeric analysis of chiral pesticides in environmental samples.

Group	Analyte	Matrix	Sample treatment	Analytical determination	Chromatographic separation	Recovery (%)	MDL	Ref.
Fungicides	Metalaxyl	Soil	UAE + d-SPE	GC-C-IRMS	BGB-172 (30 m × 0.25 mm, 0.25 μm)	n.d.	7000 ng L^{-1} (IDL)	[64]
Fungicides	Zoxamide	Soil	QuEChERS	LC-MS/MS	Lux Amylose-2 (150 mm × 2 mm, 3 μm) Isocratic: ACN:H_2O (70:30; v/v)	89.4–117.4	0.5 ng g^{-1}	[50]
Fungicides	Uniconazole and diniconazole	Soil Earthworms	QuEChERS	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Isocratic: H_2O:ACN -Uniconazole: (40:60; v/v) -Diniconazole: (73:27; v/v)	n.d.	5000 ng L^{-1} (IDL)	[30]
Fungicides, herbicides, insecticides	Diniconazole, metalaxyl, paclobutrazol, epoxiconazole, myclobutanil, hexaconazole, napropamide and isocarbophos	Soils and river sediments	MSPD + DLLME	LC-MS/MS	Chiralcel OD-RH (150 mm × 4.6 mm, 5 μm) Isocratic: 0.1% FA in H_2O:ACN (60:40, v/v)	87.0–104.1	0.22–1.54 ng g^{-1}	[51]
Fungicides, herbicides, insecticides	Triadimenol, triazolone, tebuconazole, fenamiphos, metalaxyl, epoxiconazole, hexaconazole, napropamide, isocarbophos, diniconazole, paclobutrazol, imazalil, fenbuconazole, propiconazole, difenoconazole, profenofos, dinotefuran and fipronil	Soil and river sediments River water Wastewater	Solid samples: UAE + MSPE Liquid samples: MSPE	LC-MS/MS	Chiralpak IG (250 mm × 4.6 mm, 5 μm) Isocratic: ACN:0.05% FA in 5 mM $AcONH_4$ (53:47; v/v)	80.3–106.3	Soil and sediments: 0.02–0.17 ng g^{-1} Water samples: 0.11–0.62 ng L^{-1}	[49]
Organochlorine insecticides	α-HCH o,p-DDT	Air, soil, sediment, mosh and lichen	Air: PUF disk + PLE Solid samples: PLE	GC-MS	BGB-172 (30 m × 0.25 mm, 0.25 μm)	n.d.	Air: 0.0004–0.0077 pg m^{-3} Vegetation: 0.03–1.19 ng g^{-1} Soil and sediment: 0.01–1.07 pg g^{-1}	[59]

increasing mobile-phase flow-rate for the separation of enantiomers.

3.2. Determination of pesticides

The enantioseparation of pesticides has been recently reviewed by Carrão et al. [73] and Petrie et al. [74]. The enantiomeric analysis of pyrethroids and organophosphorus insecticides has been specifically reviewed by Jiménez-Jiménez et al. [81]. The stereoselectivity of chiral pesticides is an issue of great concern because they can play a significant role in the fate and effects of active substances resulting in differences in exposure, toxicity/bioactivity, and bioavailability [3]. LC and GC are the analytical techniques most commonly used for enantioselective pesticide analysis [73]. Nevertheless, LC is the first choice for enantioselective pesticide analysis because the large number of commercially-available columns. The most used CSP for LC chiral pesticide analysis are polysaccharide-based, cyclodextrin-based, and Pirkle-type phases [73] although polysaccharide derivative phases are the ones that offer the wide scope for pesticide separations [74]. Stereoselective LC-MS/MS determination often requires run times higher than 30 min [74].

SFC provides several advantages such as high resolution, short run time [74], low organic solvent consumption, and amenability with sample preparation procedures such as QuEChERS what make it a promising tool for chiral pesticide analysis [24,73]. For instance, Tao et al. [82] proposed an analytical method based on SFC-MS/MS for the determination of fencubonazole and two chiral metabolites in fruits, vegetables, cereals and soils. They achieved the separation of the six stereoisomers in an amylose-based column in just 4.0 min using a mobile phase composed of CO_2/ethanol (EtOH) at a flow rate of 1.8 mL min^{-1}. SFC, not suitable for polar pesticides, has been mainly applied for triazole fungicides whereas GC has been mostly used for volatile pesticides, such as pyrethroids and organochlorines [73]. More information about the application of SFC, using UV, DAD, MS and MS/MS detectors, to the determination of several types of pesticides mainly in vegetables can be found in the review from Deng et al. [24]. ESIA has been proposed by several authors to trace the origin, degradation and transformation of chiral pesticides in environmental samples [28,64,83]. For instance, Badea et al. [83], applied ESIA to characterise by gas chromatography-combustion-isotope ratio mass spectrometry (GC-C-IRMS) the biodegradation of α-hexachlorocyclohexane (HCH) in a HCH-contaminated field whereas Masbou et al. [64] applied ESIA to evaluate the degradation of metalaxyl in soils by GC-C-IRMS.

In Table 3, it can be seen an overview of analytical methods reported for enantioseparation of pesticides in environmental samples. Most of the methods have been developed for the determination of fungicides which are commonly analysed by LC-MS/MS using chiral columns and mobile phase composed of ACN and pure water or water containing FA or $AcONH_4$ [30,50,51]. More information about analytical methods for pesticide enantiomer separation of chiral acaricides, fungicides, herbicides and insecticides can be found in the recent review from Carrão et al. [73].

3.3. Determination of polycyclic musks

Polycyclic musks are widely used as synthetic fragrances in personal care products and in other everyday products [66]. According to Ribeiro et al. [6] only three papers had been published in 2017 about the occurrence of chiral polycyclic musks in surface water and wastewater. This fact can be due to the limited number of analytical methods available for their determination. An overview of such methods can be seen in Table 4. Their

Table 4
Analytical methods for the enantiomeric analysis of chiral polycyclic musks in environmental samples.

Polycyclic musks	Matrix	Sample treatment	Analytical determination	Chromatographic separation	Recovery (%)	MDL	Ref.
Galaxolide, galaxolidone and tonalide	Sewage sludge	Soxhlet (CH_2Cl_2; 72h)	GC-MS/MS	Hydrodex-β-6TBDM (25 m × 0.25 mm, 0.25 μm)	n.d.	10–45 ng L^{-1} (IDL)	[66]
Galaxolide, tonalide, phantolide, traseolide and cashmeran	Drinking water, surface water, effluent wastewater and advanced treated recycled water	SPE (Oasis HLB)	GC-MS/MS	Achiral HP-5MS (30 m × 0.25 mm, 0.25 μm) connected to the outlet of a Cyclosil-B column (30 m × 0.25 mm, 0.25 μm)	84–116	1.0–2.0 ng L^{-1}	[62]
Galaxolide, tonalide, phantolide, traseolide and cashmeran	River water, effluent and influent wastewater	LLE (CH_2Cl_2-HEX)	GC-MS/MS	Cyclosil-B (25 m × 0.25 mm, 0.25 μm)	n.d.	18–34 ng L^{-1}	[63]

enantioseparation is especially difficult to overcome in the case of galaxolide and traseolide because of their two chiral centers. Because of that, the connection of a chiral and an achiral column has been proposed [62]. Extraction methods proposed require high volumes of toxic chlorinated solvents [63,66] and non-automatable and labour consuming extraction techniques such as Soxhlet [66] and liquid-liquid extraction (LLE) [62]. The extraction method proposed by Wang et al. [61] was easy to perform, as it was based on the use of solid-phase extraction (SPE) cartridges (OASIS HLB), but required a chiral column connected to an achiral column for enantioseparation of 5 polycyclic musks. All of them are based on GC-MS/MS determination with chiral columns based on modified dimethylsilyl β-cyclodextrin (Cyclosil- β column (Agilent) [63]; Hydrodex β-6TBDM (Macheray-Nagel) [66]). Wang et al. [62] tested four chiral cyclodextrin-based columns (α-DEX 120, β-DEX 120 and γ-DEX from Supelco (Castle Hill, NSW, Australia) and a Cyclosil-B column (Agilent Technologies) for the enatioseparation of galaxolide, tonalide, phantolide, traseolide and cashmeran in water. All of them had the same dimensions (30 m × 0.25 mm, 0.25 μm). The α-DEX 120 and γ-DEX columns did not allow the separation of any of the enantiomers. The β-DEX 120 column allowed the separation of the enantiomers except those of tonalide and two of galoxide. Cyclosil-B column provided not only the best chiral resolution but also allowed the faster oven temperature gradient rate (10°C/min), except for tonalide enantiomers separation (0.3°C/min). Nevertheless, to achieve an accurate determination of all tonalide enantiomers the combination of two columns, an achiral HP-5MS column connected to the outlet of a chiral Cyclosil-B column and a chromatographic run time of 4h was required. They also tested a Rt-βDEXcst (RESTEK) column specifically developed for fragrance industry but a run time of 5h was needed and poor resolution of tonalide was achieved. Gao et al. [66] achieved the enantioseparation of galaxolide, tonalide and galoxidone, the main degradation product of galaxolide, by using a Hydrodex-β-6TBDM chiral column (25 m × 0.25 mm, 0.25 μm, Macherey-Nagel, Düren, Germany). Their enantioseparation was achieved in a run time of 4.5h. Lee et al. [62] proposed the use of a Cyclosil-B (30 m × 0.25 mm; 0.25 μm) column, and a low temperature gradient rate (2°C/min), for the enantioseparation of galaxolide, tonalide, trasolide, phantolide and cashmeran. Nevertheless, in spite that they reported a short run time (49 min), poor resolution was achieved for most of the enantiomers, especially those of tonalide.

3.4. Determination of industrial compounds

Chiral organolides are widely used industrial compounds which have been reported to be environmental recalcitrant pollutants. Most of such organolides are used in agriculture, as insecticides, herbicides, acaricides, and as flame retardants (hexabromocyclododecane: HBCD), fluorosurfactants (PFCs) and as dielectric and coolant fluids (PCBs) [4]. Nevertheless, to the date, only a few analytical methods have been reported for their enantiomeric determination in the environment. In Table 5 it can be seen an overview of such analytical methods.

3.4.1. Brominated flame retardants

Badea et al. [77], in their review published in 2016 about advances in enantioselective analysis of chiral BRFs, reported that enantioselective methods were available only for a limited number of BFRs and, after that, only a few methods have been reported (Table 5) [32,33,35,37,38,78]. Such methods have been mainly developed for the determination of α-HBCD, β-HBCD and γ-HBCD enantiomers, which is commonly carried out by LC-MS/MS [32,33,35,37,38], whereas methods reported for novel BFR (tetrabromocyclooctane (TBCO) and tetrabromoethylcyclohexane (TBECH)) are based on GC-MS/MS [35,78]. GC-MS/MS parameters should be carefully optimised to avoid thermal degradation and isomeric interconversion of BFRs [77]. For instance, racemic interconversion of HBCDs has been reported at temperatures higher than 160°C [77]. Because of that, LC-MS/MS is commonly applied for their determination [32,33,35,37,38]. The application of supramolecular solvents (SUPRAS), containing XB donors in their structure, has been proposed for the determination α-HBCD, β-HBCD and γ-HBCD in fish [31], soils and sediments [32] and river water [33]. SUPRASs are nanostructured liquids made up of three-dimensional aggregates of amphiphilic compounds [31]. SUPRAS used for HBCD extraction was synthetized by a self-assembly process by mixing decanoic acid, tetrahydrofuran and water [31]. For their application to soils and sediments, sample extraction (400 mg) was carried out by vortex extraction with just 250 μL. After centrifugation, extracts were directly injected into an LC-MS/MS system. A method for the determination of novel BFRs has been recently proposed by Zhao et al. [78] and applied to their determination in Antarctic atmosphere. Target compounds are retained in a glass fibre filter and polyurethane foam (PUF), extracted by pressurized liquid extraction (PLE) and subjected to SPE clean-up with Florisil sorbent. More details can be found in Table 5.

3.4.2. Polychlorinated biphenyls

PCBs are a group of 209 chlorinated hydrocarbons, 78 of them chiral in nature [1]. The determination of PCBs is commonly carried out by GC-MS [58–60] by using β-cyclodextrin based columns (Chiralsil-Dex [58,59,84] and BGB-172 [58,59]) (Table 5). Nevertheless, Guo et al. [84], recommended their determination by LC

Table 5
Analytical methods for the enantiomeric analysis of chiral industrial compounds in environmental samples.

Group	Analytes	Matrix	Sample treatment	Analytical determination	Chromatographic separation	Recovery (%)	MDL	Ref.
BFRs	α-HBCD, β-HBCD and γ-HBCD	Soil and sediment	SUPRAS-based extraction	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Gradient; 0.3 mL min^{-1}. Solvent A: ACN:MeOH(70:30; v/v). Solvent B: H_2O:MeOH (70:30; v/v)	93–102	0.18–0.67 ng g^{-1}	[32]
BFRs	α-HBCD, β-HBCD and γ-HBCD	River water	SUPRAS-based microextraction	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Gradient; 0.3 mL min^{-1}. Solvent A: ACN:MeOH (70:30; v/v). Solvent B: H_2O:MeOH (70:30; v/v)	89–106	0.02–0.26 ng L^{-1}	[33]
BFRs	α-HBCD, β-HBCD and γ-HBCD	River water and sediments	Water: SPE Sediments: SLE + SPE	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Gradient; 0.6 mL min^{-1}. Solvent A: MeOH:H_2O (30:70, v/v). Solvent B: MeOH:ACN (30:70, v/v)	61–125	n.d.	[37]
BFRs	α-HBCD, β-HBCD and γ-HBCD	Sediments	Soxhlet (48h, ACE:HEX) + GPC	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Gradient; 0.5 mL min^{-1}. Solvent A: MeOH:H_2O (30:70, v/v). Solvent B: MeOH:ACN (30:70, v/v)	81–100	0.18–0.38 pg g^{-1} (dw)	[38]
BFRs	α-, β-, γ-, δ-, and ε-HBCD, and β-, γ-, α/β-, and γ/δ-TBECH	Wastewater and fresh sludge	SPE (Waters Sep-Pak tC18 for extraction; silica for clean up)	LC-MS/MS (for HBCD) GC-MS/MS (for TBECH)	HBCD: Eclipse Plus C18 column (4.6 mm × 100 mm, 3.5 μm) coupled to a Nucleodex β-PM column (4 mm × 200 mm, 5 μm). Isocratic: $AcONH_4$10 mM in H_2O: $AcONH_4$ in ACN:MeOH (1:1. v/v) (10:90, v/v) TBECH: Chiraldex B-TA column (30 m × 0.25 mm, 0.12 μm)	HBCD: 62–94 TBECH: 61–86	Dissolved phase: 0.05–0.8 ng L^{-1} Solid phase: 0.2–1.0 ng g^{-1} (dw)	[35]
Novel BFRs	α-TBECH, β-TBECH and β-TBCO	Air	PUF plug and filter + PLE + SPE (Florisil)	GC-MS	MEGA-176 MS (10 m × 0.25 mm, 0.18 μm)	n.d.	0.0001–0.1 pg m^{-3}	[78]
PCBs	PCBs (95, 136, 149, 174, 176, 183)	Air, soil, sediment, Mosh and lichen	Air: PUF disk + PLE Solid samples: PLE	GC-MS	BGB-172 (30 m × 0.25 mm, 0.25 μm) for PCB-183 Chirasil-Dex (25 m × 0.25 mm, 0.25 μm) for PCB 95, 136, 149, 174, 176	n.d.	Air: 0.0004–0.0077 pg m^{-3} Vegetation: 0.00003–0.00119 ng g^{-1} Soil and sediment: 0.00001–0,00107 ng g^{-1}	[59]
PCBs	PCBs (84, 95, 132, 136, 149, 183)	Eucalyptus leaves, pine needles, air and soil	Air: PUF plug and filter + Soxhlet Solid samples: Soxhlet	GC-MS	ChiraSil-Dex (25 m × 0.25 mm, 0.25 μm) for PCB 95, 136, 149 BGB-172 (30 m × 0.25 mm, 0.18 μm) for PCB 84, 132, 183	Air samples: 76.9–129 Soil samples: 88.7–112	Air samples: 0.04–0.15 pg m^{-3} Soil samples: 0.01–0.04 ng g^{-1}	[58]
PFOAs	3m-, 4m- and 3,5 dm-PFOA	River water	SPE (Oasis WAX)	GC-MS	HP-5MS (30 m × 0.25 mm, 0.25 μm) Chiral derivatisation agent: (S)-1-phenethyl chloride	95	0.05–50 ng L^{-1}	[79]
PFOAs	3m-, 4m-PFOA	Soil, sediment, grass and sludge-amended soil	SLE	GC-MS	DB-5MS (30 m × 0.25 mm, 0.25 μm) followed by BGB-172 (30 m × 0.25 mm, 0.25 μm)	n.d.	n.d.	[65]

Table 6
Analytical methods for the enantiomeric analysis of chiral pollutants in biota.

Group	Analytes	Matrix	Sample treatment	Analytical determination	Chromatographic separation	Recovery (%)	MDL	Ref.
Pharmaceuticals	Venlafaxine *Metabolite:* O-desmethylvenlafaxine	Loach liver	SLE + SPE (Silica)	LC-MS/MS	Chirobiotic V (250 mm × 4.6 mm, 5 μm) Isocratic: MeOH:10 mM $AcONH_4$ (pH 4 FA adjusted) (90:10; v/v)	72–108	1.97–2.31 ng g^{-1}	[42]
Pharmaceuticals	Indoprofen, flurbiprofen, carprofen and naproxen	Fish tissues	UAE + SPE (Clearnert S C18)	LC-MS/MS	Chiralpak ID (250 mm × 4.6 mm, 5 μm) Isocratic: 20 mM $AcONH_4$ (pH 3.5 FA adjusted):ACN (60:40, v/v)	82.6–106.7	1–8 ng g^{-1}	[48]
Pharmaceuticals	Atenolol, metoprolol, venlafaxine and chloramphenicol	Marine organisms (4 mollusc species, 5 crustacean species, and 15 fish species)	UAE + SPE (Oasis MCX)	LC-MS/MS	Chiralpak AGP (150 mm × 3 mm, 5 μm) Gradient, 0.35 mL min^{-1}. Solvent A: 10 mM $AcONH_4$. Solvent B: 10 mM $AcONH_4$ in isopropanol:H_2O (15:85, v/v)	68–96	0.05–0.25 ng g^{-1} dw	[55]
Fungicides	Uniconazole and diniconazole	Earthworms	QuEChERS	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Isocratic: H_2O:ACN -Uniconazole: (40:60; v/v) -Diniconazole: (73:27; v/v)	n.d.	5000 ng L^{-1} (IDL)	[30]
BFRs	α-HBCD, β-HBCD and γ-HBCD	Fish	SUPRAS-based extraction	LC-MS/MS	Nucleodex β-PM (200 mm × 4.0 mm, 5 μm) Gradient, 0.3 mL min^{-1}. Solvent A: ACN:MeOH (70:30; v/v). Solvent B: H_2O:MeOH (70:30; v/v)	87–114	0.1–1.7 ng g^{-1}	[31]
BFRs	α-HBCB, β-HBCB and γ-HBCB	Duck	UAE + d-SPE	LC-MS/MS	Nucleodex β-PM (200 mm × 4 mm, 5 μm) Gradient, 0.25 mL min^{-1}. Solvent A: MeOH:ACN (80:20, v/v). Solvent B: 5 mM $AcONH_4$	71–110	0.02–0.03 ng g^{-1}	[33]
BFRs	α-HBCD, β-HBCD, γ-HBCD, α-TBECH and β-TBECH	Marine organisms: 5 mollusk species, 6 crustacean species, and 19 fish species	PLE + GPC (for lipid removal) + elution through anhydrous sodium sulfate, activated aluminum oxide, and activated silica gel successively	LC-MS/MS (for HBCD) GC-MS (for TBECH)	Eclipse Plus C18 (4.6 mm × 100 mm, 3.5 μm) coupled to a Nucleodex β-PM (4 mm × 200 mm, 5 μm) for HBCD Isocratic: 10 mM $AcONH_4$ in H_2O:10 mM $AcONH_4$ in ACN:MeOH (1:1, v/v) (1:99, v/v) Chiraldex B-TA (30 m × 0.25 mm,0.12 μm) for TBECH	72–106	0.3–0.8 ng g^{-1} lw for HBCD 0.1–0.5 ng g^{-1} lw for TBECH	[85]
BFRs	α-HBCD, β-HBCD and γ-HBCD	Earthworm	Soxhlet (HEX:ACE 1:1, v/v, 24h) + SPE	LC-MS/MS	Nucledex β-PM (200 mm × 4 mm, 5 μm) Isocratic: ACN:10 mM $AcONH_4$ (80:20, v/v)	83.8–97.6	0.004–0.016 ng g^{-1}	[36]
BFRs	α-HBCD, β-HBCD and γ-HBCD	Fish	Soxhlet (HEX:ACE 1:1, v/v, 24h) + SPE	LC-MS/MS	Nucledex β-PM (200 mm × 4 mm, 5 μm) Gradient, 0.25 mL min^{-1}.Solvent A: MeOH:H_2O (30:70, v/v). Solvent B: MeOH:ACN (30:70, v/v)	90–93	n.d.	[37]
BFRs	α-HBCD, β-HBCD and γ-HBCD	Striped mullet, mud crab, red eelgoby, Chinese black sleeper and blue-spotted mudskipper	Soxhlet (HEX:ACE 1:1, v/v, 48h) + GPC	LC-MS/MS	Nucledex β-PM (200 mm × 4.0 mm, 5 μm) Gradient, 0.5 mL min^{-1}. Solvent A: MeOH:H_2O (30:70, v/v). Solvent B: MeOH:ACN (30:70, v/v)	75–105	0.09–0.19 pg g^{-1} lw	[38]

PCBs	PCBs 91, 95, 132, 136 and 149	Common carp	Soxhlet (HEX:ACE 1:1, v/v, 72h) +lipid removal + LLE + SPE	CSIA GC-MS	Chiralsil-Dex (25 m × 0.25 mm, 0.25 μm)	81–116	0.16–0.59 ng g^{-1} lw	[28]
PCBs	PCBs (45, 91, 95, 132, 149, 174, 183)	Carp organs	Solid samples: Soxhlet (HEX:ACE 1:1, v/v, 72h + column chromatography (silica gel) Serum: LLE + column chromatography	CSIA GC-MS	Chiralsil-Dex (25 m × 0.25 mm, 0.25 μm) for PCB 91, 95, 132, 149, 174 BGB-172 (30 m × 0.25 mm, 0.18 μm) for PCB 183 Cyclosil-B (30 m × 0.25 mm, 0.25 μm) for PCB 45	n.d.	0.16–0.59 ng g^{-1} lw	[60]
PCB	PCB-91	Earthworm Soil	QuEChERS	GC-MS/MS	Cyclosil-B (30 m × 0.25 mm, 0.25 μm)	Earthworm: 94-99 Soil: 95–105	Earthworm and soil: 0.03 ng g^{-1}	[61]

because of the higher interconversion observed at the high temperatures applied in GC as explained above for HBCD enantiomers [77]. Guo et al. [84], evaluated PCB isomer conversion in solvents used in HPLC and at temperatures applied in GC. They did not detect isomer conversion in a 15-day experiment carried out with racemic PCBs solved in pure water, ACN, dichloromethane, acetone (ACE), EtOH, MeOH, isopropanol, and ethyl acetate but observed isomer conversion with the increase of inlet temperature from 200°C to 400°C [84]. The higher isomer conversion was reported for PCB45, PCB95 and PCB149. In case of using GC, they recommend inlet temperatures in the range from 200 to 280°C because they caused ignorable conversion rates. LC analysis was carried out with cellulose-based columns (Chiralcel OD-H and Chiralcel OJ-H).

3.4.3. *Perfluorinated compounds*

PFCs are produced by electrochemical fluorination what produces multiple linear and branched isomers some of them with chiral centers [64]. To the date, only a few methods have been reported for the determination of chiral PFCs in the environment (Table 5). Such methods are based on GC determination and requires derivatisation [79] or multidimensional chromatography with a chiral and achiral column [65]. Naile et al. [65] proposed a method for the determination of PFOA isomers and enantiomers based on multidimensional chromatography by using an achiral column connected to a ß-cyclodextrin-based chiral column (BGB-172) and applying derivatisation with diazomethane for the determination of non-volatile PFCs. In 2020, Zhu et al. [79] afforded the enantioseparation of enantiomers of PFOA isomers (perfluoro-3-methyl-heptanoic acid (3m-PFOA), perfluoro-4-methyl-heptanoic acid (4m-PFOA), perfluoro-5-methyl- heptanoic acid (5m-PFOA), perfluoro-4,5-dimethyl-hexanoic acid (4,5 dm-PFOA), and perfluoro-3,5-dimethyl-hexanoic acid (3,5 dm-PFOA). Derivatives of the enantiomers of 3m-PFOA, 4m-PFOA, and 3,5 dm-PFOA were separated in a HP-5 MS GC achiral column prior reaction with a chiral derivatisation agent ((S)-1-phenetyl chloride) whereas derivatives of 5m-PFOA and 4,5 dm-PFOA could not be separated.

4. Analytical methods for biota samples

To the date, methods for the enantiomeric analysis of chiral pollutants in biota are scarce in spite that they are of great relevance for an accurate risk assessment [67]. In Table 6, it can be seen that most of such analytical methods have been focused on HBCD flame retardants which have been determined by LC-MS/MS [31,33,36–38] as isomer interconversion has been reported at temperatures higher than 160°C and they do not elute from GC columns at lower temperatures [31]. Lara et al. [31] proposed a fast and effective extraction method for the enantiodetermination of HBCD stereoisomers. The extraction method required just 750 mg of fish sample, 600 μL of supramolecular solvent (SUPRAS) and 5 min of extraction time. No extract clean-up was required and recoveries in the range from 87 to 114% were achieved. Nevertheless, most of the extraction methods for the enantiodetermination of HBCD stereoisomers are based on Soxhlet extraction [36–38] requiring extraction times up to 48h. Recently, some methods have been proposed for the determination of chiral pharmaceuticals in fish [42,48] and marine organisms [55]; fungicides in earthworms [30] and PCBs in common carp [28,60] and earthworms [61].

Tang et al. [28] applied the combination of chiral analysis and compound specific stable isotope analysis (CSIA) as a promising approach for investigating biotransformation of PCBs in common carp. They obtained interesting results for achiral PCBs but, due to

the low concentrations of chiral PCB congeners, they were not available for CSIA measurement and further work in this field is still needed. No method has been found for the determination of chiral polycyclic musks, neither chiral PFOAs, in biota.

5. Conclusions and future prospects

The enantiomeric analysis of chiral pollutants in the environment is scarce and mainly focused on pharmaceuticals and pesticides. Enantioselective analysis of other chiral pollutants such as PFCs, BFRs, PCBs, polycyclic musks, illicit drugs and chiral metabolites or degradation products of the above-mentioned pollutants has been scarcely evaluated. No analytical method has been reported in the last 10 years for the enantiomeric analysis of chiral UV filters, such as 2-ethylhexyl 4-methoxycinnamate, octocrylene and 3-(4′-methylbenzylidene) camphor.

In addition, most of the analytical methods have been reported for the determination of chiral pollutants in aqueous samples (wastewater and surface water) whereas methods for their determination in air samples and biota are even scarcer. Most of the analytical methods are based on chiral LC-MS/MS or GC-MS. Nevertheless, poor resolution is reported by several authors and then multidimensional LC or GC chromatography is applied by connecting an achiral column and a chiral column. This fact is of special relevance for enantioseparation of chiral compounds with several chiral centers such as polycyclic musks. An advantage of chiral separation by LC are the wide variety of commercially-available CSPs but, on the other hand, enantioseparation by LC-MS/MS often requires long run times, as enantioseparation commonly requires long columns (250 mm) and isocratic elution. This problem could be overcome in the next future with the new 3 μm particle size columns. In addition, interconversion of enantiomers in polar solvents should be evaluated although it is not so frequent as interconversion by the high temperatures in GC. Matrix effect should be carefully evaluated as signal suppression or enhancement can be different for each enantiomer [74]. Stable isotope analogues should be used not only to correct instrument and matrix effects but also to consider chiral inversion during analysis. Nevertheless, to the date, there is a lack of deuterated surrogate standards for chiral pollutants, or they are cost prohibitive, and matrix effect has to be accounted by matrix-matched calibration curves [74,86].

With respect to enantioseparation by chiral GC, its main advantages are the high efficiency and easy hyphenation with MS, as well as the absence of organic solvent consumption (green analytical technique) in comparison to LC determinations. Nevertheless, only a few of chiral columns are commercially available, mainly cyclodextrin-based columns. If they do not allow enantiomer separation a chiral derivatisation agent and an achiral column are used. In addition, interconversion of the enantiomers at the high temperatures applied in GC has to be properly evaluated. Such effect is of especial relevance in the determination of HBCDs and PCBs. Nevertheless, interconversion can also occur by solvents and temperatures used in several stages of the analytical process such as extraction, purification, concentration and detection [84]. Therefore, solvent and thermal stability of enantiomers should be carefully evaluated to minimise EF biases [84] and stable isotope analogues should be used as internal standards whenever possible. SFC seems to be a promising analytical technique for enantioseparation of chiral compounds because, due to the viscosity and diffusivity of CO_2, which is the main component of the mobile phase, analytical method run times are considerably reduced whilst achieving improved separation of chiral enantiomers.

In the next years it is expected an increase of multiresidue analytical methods for the determination of chiral pollutants based on LC, because of the wide variety of commercially-available columns, the increase of high resolution columns (<3 μm) and the low temperatures required what minimise isomeric conversion, and on SFC because of the recent instrumental advances in CSPs and hyphenation to MS that allows taking advantage of its short run times, high separation efficiency and low solvent consumption.

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CRediT authors statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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