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# Occurrence of Chiral Bioactive Compounds in the Aquatic Environment: A Review

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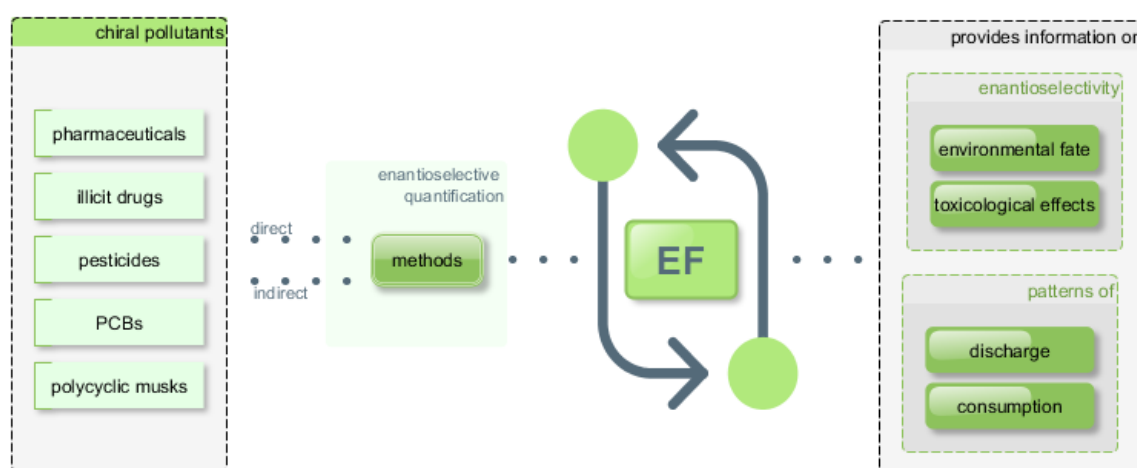
**Abstract:** In recent decades, the presence of micropollutants in the environment has been extensively studied due to their high frequency of occurrence, persistence and possible adverse effects to exposed organisms. Concerning chiral micropollutants in the environment, enantiomers are frequently ignored and enantiomeric composition often neglected. However, enantioselective toxicity is well recognized, highlighting the need to include enantioselectivity in environmental risk assessment. Additionally, the information about enantiomeric fraction (EF) is crucial since it gives insights about: (i) environmental fate (i.e., occurrence, distribution, removal processes and (bio)degradation); (ii) illicit discharges; (iii) consumption pattern (e.g., illicit drugs, pharmaceuticals used as recreational drugs, illicit use of pesticides); and (iv) enantioselective toxicological effects. Thus, the purpose of this paper is to provide a comprehensive review about the enantioselective occurrence of chiral bioactive compounds in aquatic environmental matrices. These include pharmaceuticals, illicit drugs, pesticides, polychlorinated biphenyls (PCBs) and polycyclic musks (PCMs). Most frequently analytical methods used for separation of enantiomers were liquid chromatography and gas chromatography methodologies using both indirect (enantiomerically pure derivatizing reagents) and direct methods (chiral stationary phases). The occurrence of these chiral micropollutants in the environment is reviewed and future challenges are outlined.

**Keywords:** chiral drugs; pharmaceuticals; illicit drugs; pesticides; chiral chromatography; environment

## 1. Introduction

In recent decades, thousands of synthetic and naturally occurring compounds have been constantly released into the environment, becoming an issue of serious concern to public, scientists and regulatory authorities [1–4]. Among various environmental pollutants, organic contaminants as pesticides, polychlorinated biphenyls (PCBs), and pharmaceuticals are of most concern due to their high toxicity, persistence and constant release. In addition, many of these pollutants are chiral and commercialized as racemic mixtures or enantiomerically pure [5]. Enantiomers of chiral

bioactive compounds may exhibit different biological and toxicological properties as a result of their enantioselective interaction with other naturally occurring chiral molecules [6–8]. Therefore, when released into the environment, enantiomers can suffer different degradation and biodegradation pathways and conduct to a wider variety of compounds [8–10]. Selective microbial degradation of the enantiomers was observed in either field applications or laboratory microcosms [10–13], as recently reviewed by Maia et al. [14]. However, most environmental regulations, occurrence or ecotoxicological studies consider these compounds as unique molecular entities. These can lead to inaccurate data since enantiomers of the same chiral compound may differ in its environmental behavior (e.g., occurrence, distribution, (bio)degradation) and toxicological effects. Therefore, understanding the environmental behavior (i.e., occurrence, distribution and toxicity) of the individual enantiomers is important for determining their environmental damage, ecological risk and for the implementation of safety regulations. Additionally, enantiomeric analysis of chiral compounds in the environment may give insights about illicit discharges, consumption pattern of substances as illicit drugs, pharmaceuticals used as recreational drugs or illegal use of pesticides (Figure 1). Hence, this paper intends to (a) summarize basic concepts of chirality; (b) offer a brief review of the chromatographic methods used for the analysis of chiral bioactive drugs in environmental matrices; and (c) summarize the occurrence of chiral bioactive compounds, namely pharmaceuticals, illicit drugs, pesticides, PCBs and polycyclic musks (PCMs). The search was based in ScienceDirect and ISI web of Knowledge databases, considering articles up to 2017 that comprise surface waters, ground and drinking waters and wastewaters as aquatic environmental matrices.



**Figure 1.** Schematic representation of the importance of determination of enantiomeric fraction (EF) in environmental analysis of chiral pollutants.

## 2. Basic Concepts of Chirality

According to IUPAC definition, chirality is “The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image; such an object has no symmetry elements of the second kind (a mirror plane,  $\sigma = S_1$ , a center of inversion,  $i = S_2$ , a rotation-reflection axis,  $S_{2n}$ ). If the object is superposable on its mirror image the object is described as being achiral” [15]. When an atom holds a set of ligands in a spatial arrangement that is not superposable on its mirror image, it originates a chirality center with a stereoelement (stereogenic unit), the most common type of chirality [15]. The interchange of any two of the substituents leads to its enantiomer [15], defined by IUPAC as “one of a pair of molecular entities which are mirror images of each other and non-superposable” [15]. In an achiral environment, enantiomers have identical properties except for their chiroptics (polarimetry, circular dichroism (CD) and optical rotatory dispersion (ORD)). The stereogenic unit is frequently generated by a tetrahedron carbon

with four different groups of substituents, or other atoms (e.g., sulfur, phosphorous, silicon) [16]. The presence of a unique chirality center in a molecule guarantees that it is chiral and enantiomeric forms are possible; however, molecules with more than one stereogenic center may not be chiral [17]. Other forms of chirality exist, namely axial, planar, and helical [18]. Enantiomers normally have similar physical and chemical characteristics (e.g., boiling point, melting point, solubility, pH, partition coefficient) except for the fact that they rotate the plane of polarized light in opposite direction (optical activity). Thus, the conventional and straightest way to distinguish enantiomers is polarimetry based on the different rotation of polarized light (i.e., to the right or clockwise in the case of dextrorotatory, (d) or (+)-enantiomers; and to the left or counterclockwise in the case of levorotatory, (l) or (-)-enantiomers). Enantiomers can be designated as (*R*)- and (*S*)- from the Latin *rectus* and *sinister*, respectively, depending on the spatial placement of the substituents of the stereogenic unit. They can be present in different proportions, as enantiomerically pure substances or as racemate or racemic mixture, when they are equimolar and consequently do not rotate the polarized light [19]. The equivalent thermodynamic properties are observed in an achiral medium, however in a chiral medium (e.g., biological system or reaction with other chiral compound), enantiomers usually have different behavior. Biological structures are often chiral due to the “intrinsic chirality” of their constituents (e.g., amino acids and carbohydrates) [20]. This is the reason why enantiomers of a chiral compound can lead to different biological effects. Thus, enzymes, receptors, membrane proteins or other binding molecules in organisms can discriminate enantiomers, a selective mechanism called chiral recognition [5]. The interaction chiral compound-receptor may result in different effects and consequently, in the case of micropollutants, enantioselective toxicity [5,21–23].

Chiral compounds such as pharmaceuticals, as well as illicit drugs, and pesticides, among others, are administrated/used as racemates or as enantiomerically pure forms, despite the desired pharmacological/biological activity is normally exclusive of one enantiomer. Often the other enantiomer has less or no activity, a different activity, originates adverse effects of variable intensity, or differs in their kinetic parameters [24]. Natural chiral compounds are frequently pure enantiomers such as morphine, epinephrine, hyoscine, levothyroxine, levodopa, among others [20,25]. Currently, the use of enantiomerically pure compounds is a trend, however there are many pharmaceuticals and pesticides still commercialized as racemates [8,20]. Some approaches have been employed as possible solutions to deal with chiral bioactive environmental contaminants, using strategies conducting to enantioselectivity. For example, biodegradation studies using activated sludge have been shown enantioselectivity for the removal of some pharmaceuticals [26–30]. Enantioselectivity can also be dependent on the pH when different microorganisms and enzymes are involved in the degradation, as verified recently in a work reporting the enantioselective degradation of fungicides in soils [31]. A recent work highlighted the importance of studying the effect of achiral additives that can be present in soils and alter the community of microorganisms, leading to changes in the enantioselective degradation [32]. Another completely different approach is the recovery of enantiomers from wastewaters. For instance, wastewater effluents from the pharmaceutical industry can be treated using membrane technology, in order to recover high-value enantiomeric pure forms of pharmaceuticals (e.g., (*S*)-amlodipine) [33].

### 3. Analytical Methodologies for Enantioseparation of Chiral Bioactive Compounds

Enantioselective discrimination of chiral molecules has received a great attention in the last decade, namely using new enantiopure crown ethers [34], functionalized nanoporous graphene [35], chiral imprinted polymers [36], enantioselective inclusion complexation–organic solvent nanofiltration membranes [37], and chiral optical force [38]. Another useful approach for the investigation of enantiomerization processes is the stopped-flow multidimensional gas chromatography (GC) technique (stopped-flow MDGC) employing CSP for enantioseparation. This technique was applied for the determination of the rotational barriers of atropisomeric PCBs via on-line enantiomerization kinetics [39–41]. However, the most-used methodologies to analyze and quantify enantiomers

include liquid chromatography (LC) [42], GC [43,44], capillary electrophoresis (CE), supercritical fluid chromatography (SFC), among others [45–47]. Among these technologies, chromatography has been the most used technique for the analysis of chiral pollutants, by two different approaches: direct and indirect methods [48,49]. The direct method using chiral stationary phases (CSPs) has demonstrated many advantages and many applications [50,51]. Many types of CSPs are available, but Pirkle-type, polysaccharide derivatives, cyclodextrin (CD), protein, macrocyclic glycopeptides antibiotics-based, and polymeric-based [50,52,53] are mostly applied.

The central challenges in the analysis of environmental matrices (e.g., wastewater, surface water, soil, sediment) are the trace concentrations of the target compounds present in an extremely complex medium with an enormous diversity of non-target analytes [54,55]. This struggle highlights the significance of an efficient clean-up during the sample preparation in order to eliminate interferences and therefore reduce the matrix effects that negatively affect selectivity and limits of quantification [56]. Matrix effect can be caused by endogenous compounds (e.g., humic or fluvic acids, lipids, among others) or exogenous compounds resulting from the analytical method (e.g., as salts or other reagents added to the matrix), that can originate enhancement or more frequently suppression of the analytical signal (e.g., GC-MS or LC-MS). The effect of matrix composition on the electrospray ion source in LC-MS methods interferes with the ionization ability of the substances and their signal [57]. This phenomenon influences both qualitative and quantitative analysis. For example, cleanup during sample preparation is very important to avoid large amounts of co-extracted matrix constituents [58]. In the case of environmental matrices, they are complex and present high variability, and even the same type of matrix collected in different locations and/or time, may have different composition [56]. Chiral analysis encompasses an additional challenge because different matrix effect may arise for a pair of enantiomers. The possible chiral environment of the matrix (e.g., wastewater effluents contain a high variety of microorganisms, which is not expected in pharmaceuticals streams) can lead to differences in matrix effect for a pair of enantiomers. Additionally, as matrix effect results from different components which decrease or increase the analytical signal, it is expected to be more pronounced with increasing complexity of the matrix [59]. Therefore, matrix effect has to be estimated for each enantiomer in the matrices to be analyzed. The most common methods for matrix effect assessment are: post-column infusion method, post-extraction addition method and calibration graph slopes comparison, where two calibration graphs (one in the solvent and the other in the post-extraction spiked samples) are drawn and compared [56].

Enantioselective studies on environmental matrices frequently employ solid phase extraction (SPE) [60,61]. Solvent extraction coupled to ultrasonic baths [9] was already reported and only a few works reported the use of liquid–liquid extraction (LLE) [11,62] and dispersive liquid–liquid microextraction (DLLME) [63,64]. One recent work described the use of supramolecular solvent (SUPRAS) microextraction [65] and another one microwave assisted extraction for sludge [66]. Since 2009, SPE has been generally used as sample preparation procedure in enantioselective environmental analysis [13,57,61,62,64,66–95]. Two on-line methods were also reported, using RAM-BSA columns in a 2D LC-MS/MS system coupled to polysaccharide-based CSPs under reversed elution mode [54,55].

Until the last decade, enantioselective studies for analysis of chiral compounds in the environment employed CD-based CSPs [61,85,96–99] or indirect methods using enantiomerically-pure derivatizing reagents [9,60], which have been used until today [67,70,80,83,89]. Since 2010, a trend is being verified for the use of three types of CSPs: protein-based [68,69,74–77,81,82,100,101], polysaccharide-based [54,55,78,79,102] and macrocyclic antibiotic-based CSPs [13,26,27,63,64,71–73,76,78,88,91,103]. The first reports describing the use of macrocyclic antibiotic-based CSPs for environmental analysis were published in 2006–2007 [84,104], but its application was later intensely reported from 2010 [13,26,27,57,71–73,76,78,86,87,90,93,94,103,105]. Other works were published using normal elution mode, namely for the study of beta-blockers in surface waters [78,79] and for the monitoring of enantioselective biodegradation of warfarin in soils [11]. The majority of enantioselective analysis for environmental applications have been employing the reversed elution

mode [54,55,57,62,68,69,72,74–77,81,82,86,100,103–105]. The polar ionic elution mode is nowadays used frequently with macrocyclic antibiotic-based CSPs, being reported either in biodegradation studies and environmental monitoring of pharmaceuticals and some illicit drugs [13,26,27,66,71,76,87].

Both enantioselective GC [106] and LC [107] methods can be implemented by direct method with CSPs, even though there are few CSPs available for GC [108–110]. Enantioselective GC methods have advantages as fast analysis and high sensitivity, reproducibility and selectivity, with no need of using solvents and additives that are often toxic [111]. Nevertheless, enantioselective GC analytical methods are often limited to the analysis of high thermally stable and volatile compounds [111]. In the case of non-volatile analytes, derivatization using a chiral derivatization reagent is needed for chiral separation, enhancement of thermal stability and volatility of the analytes [111]. GC methods have been used widely for the enantioselective analysis of various environmental pollutants [111], such as agrochemical pesticides, using electron capture detector (ECD) and mass spectrometry (MS) detection. GC-MS/MS was employed in the first works reporting enantioselective environmental analysis by indirect methods using enantiomerically-pure derivatizing reagents [9,60], or by direct methods using CSPs [61,85]. Despite indirect [70,83] and direct methods [67,80,89] remaining in some studies, LC-MS/MS has been the analytical technique of election for illicit drugs and pharmaceutical while GC-MS and GC-ECD have been the most used for pesticides [13,54,55,57,62,64–69,71–77,80–82,84,87,88,90–92,95,100–105]. Although much less used, LC-DAD, LC-UV and LC-FD detection have been used in some of the studies [11,26,27,54,63,78,79,86]. On the other hand, most pesticides are transparent towards UV radiation and therefore, ECD and MS have been the most used detection techniques [12,97,112–115].

#### 4. Chiral Bioactive Compounds of Environmental Concern

This section describes the reports on occurrence of illicit drugs and pharmaceuticals, pesticides, PCBs and PCMs in aquatic environmental matrices. In environmental analysis, two main descriptors are used to describe chiral signatures, the Enantiomeric Fraction (*EF*) and the Enantiomeric Ratio (*ER*) [116]. However, two other terms for the quantitation of a mixture of stereoisomers can be found in the literature, Enantiomeric Excess (*ee*) and Enantiomeric Composition (*ec*) [116]. The *ee* represents the excess of one enantiomer over the other:

$$ee = \frac{(E1 - E2)}{(E1 + E2)} \times 100$$

while *ec* is the mole fraction of one enantiomer in a mixture:

$$ec = \frac{E1 \text{ (or } E2)}{(E1 + E2)}$$

and can be simply quoted as % *E1*, or alternatively % *E2*. This term was recently replaced by *EF*, which is given by:

$$EF1 \text{ (or } EF2) = \frac{E1 \text{ (or } E2)}{(E1 + E2)}$$

*ER* is described as the ratio between the one enantiomer over the other, being 1 the *ER* of racemic mixtures and infinite for pure enantiomers:

$$ER = \frac{E1}{E2}$$

##### 4.1. Illicit Drugs and Pharmaceuticals

Only a few illicit drugs and some therapeutic classes of pharmaceuticals such as beta-blockers, antidepressants and its metabolites, antifungals, and NSAIDs have been enantioselectively analyzed in environmental matrices (Table 1) [9,11,13,26,27,54,55,57,60–64,67–93,95,100–105,117].

The first study on enantioselective occurrence of pharmaceuticals in the environment reported ibuprofen and its metabolites in WWTP influents (Switzerland), with an enrichment of the (*S*)-ibuprofen and a ee decrease from raw wastewater to effluent [60]. However, in the same study, surface waters were also generally enriched with the (*S*)-form, showing that although this enantiomer is mostly excreted by humans, it is also degraded at a higher extent in the WWTPs and in surface water [60]. The NSAIDs ibuprofen, naproxen, and ketoprofen were studied by Hashim et al. (2011) and were found at concentrations levels of ng/L and EFs frequently superior than 0.5 in WWTP effluents in Australia [80]. In another study, these authors reported a decreasing of these compounds concentrations from influent ( $\mu\text{g/L}$  levels) to effluent (ng/L levels) [67]. In that work, EF varied considerably between influents and effluents, mainly for ibuprofen and naproxen. Another study showed that the (*S*)-enantiomers of naproxen and ibuprofen were predominant in influent wastewaters, however EF decreased in WWTP effluents, suggesting that enantiomerization of profens may occur during processes occurring at WWTPs [89].

The proton pump inhibitors omeprazole, lansoprazol and pantoprazol were studied in environmental matrices, being omeprazol enantiomers detected in an influent sample of a WWTP (Brazil) and in an estuarine water sample (Douro River, Portugal) [54,55]. In another study [64], EFs of lansoprazole, pantoprazole, and rabeprazole were close to 0.5 in influents, effluents and river water, however omeprazole was found enriched with (*S*)-enantiomer. Its EF decreased significantly during wastewater treatment, from 0.70 in the influent to 0.53 in the effluent, indicating its stereoselective degradation. In the same study, the EF values of the four proton pump inhibitors in river water were similar to those determined in the effluent.

Another therapeutic class frequently studied is beta-blockers. Metoprolol was determined in influents and effluents of some WWTPs in France [90], being detected in all samples with mean concentrations ranging between 97 and 687 ng/L in influents (close to racemic) and from 18.6 to 157 ng/L in effluents, where EF varied from 0.57 up to 0.70, except in one WWTP effluent (EF = 0.5). The results of that work indicated a (*S*)-metoprolol enrichment during wastewater treatment in most cases, which extent was dependent on the WWTP [90].

The antidepressant fluoxetine has been enantioselectively analyzed in some works. For example, it was found enriched in its (*S*)-form in a study dealing with analysis of both raw wastewater and treated effluent, with an EF between 0.68 and 0.71 [81,100].

A study focused in the enantioselective determination of azole antifungals showed that these pharmaceuticals were racemic or almost racemic in the raw wastewater (EFs = 0.45–0.53) and a weak enantioselectivity was observed during treatment at WWTP [88]. The EFs of the dissolved antifungals differed from those of the sorbed fraction in the suspended particulate matter, proposing different behaviors for these enantiomers in the two distinct phases of the wastewater.

Recently, a new method was proposed to distinguish metabolic excretion from industrial discharge through the EF analysis [87]. In this work, the authors reported EF values of salbutamol in wastewater effluents differing significantly from commercial preparations, which were expected due to the known stereoselective metabolism. However, one-day peaks of this pharmaceutical were observed and the EFs were similar to commercial preparations, indicating a possible industrial disposal [87].

### Multi-Class Enantioselective Analysis

The challenge in environmental analysis is the development of multi-residue analytical methods. Concerning achiral methods, this is well established, e.g., for pharmaceuticals from various therapeutic classes [118]. However, enantioselective analytical methods are normally limited to pharmaceuticals belonging to one or few therapeutic classes, due to the difficult simultaneous enantioselective separation of different therapeutic classes/chemical natures using the same chromatographic conditions. MacLeod et al. (2007) were the pioneers of multi-class enantioselective analysis of pharmaceuticals in environmental samples, using LC-MS/MS and a Chirobiotic V™ in reversed elution mode to analyze beta-blockers (atenolol, metoprolol, nadolol, pindolol, propranolol, and sotalol),

selective serotonin re-uptake inhibitors (citalopram, fluoxetine) and a beta2-agonist (salbutamol) in wastewaters [104]. The same chromatographic conditions were applied by MacLeod and Wong (2010) to analyze in the same matrix, beta-blockers (atenolol, metoprolol, propranolol, sotalol), selective serotonin re-uptake inhibitors (citalopram and paroxetine), the NSAID naproxen and the benzodiazepine temazepam [103]. More recently, López-Serna (2013) used LC-MS/MS and a vancomycin-based CSP under polar ionic elution mode to analyze 16 pharmaceuticals (analgesics, antibiotics, beta-agonists, psychiatric and cardiovascular drugs) and 2 metabolites in WWTP influents and effluents, and river water (Spain) [71]. Enantioselective determination of multiclass pharmaceuticals and drugs of abuse was first reported in 2010, using LC-MS/MS and a protein-based CSP under reversed elution mode [82]. The same research group used LC-MS/MS and a system of two CSPs, a protein-based CSP under reversed elution mode and a vancomycin-based CSP under polar ionic elution mode, to quantify in wastewater effluents and river water (United Kingdom), amphetamine-like drugs of abuse (amphetamine, methamphetamine, MDA (3,4-methylenedioxyamphetamine), MDMA (3,4-methylenedioxy-methamphetamine)), beta-blockers (propranolol, atenolol, metoprolol), and antidepressants (fluoxetine and venlafaxine) [76].

Two studies focused on the enantioselective determination of 11 chiral veterinary and human pharmaceuticals in environmental water samples [101] and another including 15 pharmaceuticals [102] showed respectively, an EF of 0.5 and 0.6 for an anti-helminthic tetramisole, which is administrated in the (S)-form as veterinary drug, suggesting its enantiomerization or its use as adulterant in illicit cocaine production. Kasprzyk-Hordern and co-workers published recently a multi-residue method for enantioselective separation of chiral pharmaceuticals using teicoplanin as chiral selector for the simultaneous enantioresolution of carboxyibuprofen, chloramphenicol, 2-hydroxyibuprofen, ibuprofen, ifosfamide, indoprofen, ketoprofen, naproxen and praziquantel. An eco-friendly analytical method was developed for the first time for multi-residue enantioselective determination of selective serotonin reuptake inhibitors and a metabolite, beta-blockers and one beta2-adrenergic agonist, with venlafaxine being determined in WWTP effluents with EF values between 0.54 and 0.55 [57]. Evans et al. published the first method for enantioselective determination of chiral drugs in solid and liquid environmental matrices, highlighting the importance of studying the solid fraction to avoid overestimation of the removal rates occurring at WWTPs [66]. The diurnal variation on EF was also addressed recently, since it can be related to direct disposal of unused medicines, but no diurnal variability in the enantiomeric distribution of the target chiral analytes was observed [95].

**Table 1.** Environmental chiral analysis of pharmaceuticals and drugs of abuse.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Amphetamine Methamphetamine MDMA MDA	UPLC-MS/MS; Chiral-CBH column (100 mm × 2 mm i.d., 5 µm) with a Chiral-CBH guard column (10 mm × 2.0 mm i.d.); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 5.0.	<i>United Kingdom</i> Influent (IWW) and effluent (EWW) wastewater; River water.	IWW: EF = 0.6; EWW: EF = 0.4; IWW: EF > 0.5; EWW: EF > 0.5; IWW: EF < 0.5; EWW: EF < 0.5; IWW: EF > 0.5; EWW: EF < 0.5.	[92]
Amphetamine Methamphetamine MDMA MDA MDEA Ephedrine Norephedrine	UPLC-MS/MS; Chiral-CBH column (100 mm × 2 mm i.d., 5 µm) with a Chiral-CBH guard column (10 mm × 2.0 mm i.d.); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 5.0.	<i>England</i> Influent (IWW) and effluent (EWW) wastewater River water (RW): 6 locations near the WWTP discharge zone	17.4–3112.5 ng L <sup>-1</sup> (IWW); 4.3–145.2 ng L <sup>-1</sup> (EWW); 0.3–4.3 ng L <sup>-1</sup> (SW); 0.6–70.3 ng L <sup>-1</sup> (IWW); 0.4–1.3 ng L <sup>-1</sup> (EWW); 0.3–0.4 ng L <sup>-1</sup> (SW); 7.2–32.4 ng L <sup>-1</sup> (IWW); 6.3–24.5 ng L <sup>-1</sup> (EWW); 0.9–1.9 ng L <sup>-1</sup> (SW); 0.7–455.4 ng L <sup>-1</sup> (IWW); 0.6–177.7 ng L <sup>-1</sup> (EWW); 0.5–24.8 ng L <sup>-1</sup> (SW); 1.4 ng L <sup>-1</sup> (IWW); n.d. (EWW); n.d. (SW); 8.7–1979.5 ng L <sup>-1</sup> (IWW); 5.3–265 ng L <sup>-1</sup> (EWW); 6.3–28.9 ng L <sup>-1</sup> (SW); 15–99.9 ng L <sup>-1</sup> (IWW); n.d. (EWW); n.d. (SW).	[68]
Amphetamine Methamphetamine MDMA MDA Ephedrine Pseudoephedrine	UPLC-MS/MS; Chiral-CBH column (100 mm × 2 mm i.d., 5 µm) with a Chiral-CBH guard column (10 mm × 2.0 mm i.d.); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 5.0.	<i>England</i> Wastewater influent and effluent	EF = 0.52–0.84; EF ≥ 0.5; EF = 0.68 (mean); EF > 0.5; EF = 0.81–0.96; -	[69]
Amphetamine Methamphetamine MDMA MDA Ephedrine Pseudoephedrine Norephedrine Alprenolol Atenolol Citalopram Desmethylcitalopram Desmethylvenlafaxine Fluoxetine Mirtazapine Metoprolol Propranolol Salbutamol Sotalol Tramadol Venlafaxine	UPLC-MS/MS; Chiral-CBH column (100 mm × 2 mm i.d., 5 µm) with a Chiral-CBH guard column (10 mm × 2.0 mm i.d.); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 5.0. Chirobiotic V column, (250 × 2.1 mm, i.d. 5 µm) with a Chirobiotic V guard column (20 × 1.0 mm, i.d. 5 µm); Methanol (4 mM ammonium acetate, 0.005% formic acid)	<i>Not referred</i> Influent (IWW) and effluent (EWW) wastewater; Sludge (Sl.).	IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = 0.7; IWW: EF = 0.6; EWW: EF = 0.5; Sl.: EF = 0.5; IWW: EF = 0.7; EWW: EF = 0.9; Sl.: EF = 0.4; IWW: EF = 0.6; EWW: EF = 0.5; Sl.: EF = 0.3; IWW: EF = 0; EWW: EF = 0; Sl.: EF = n.d.; IWW: EF = 1; EWW: EF = 0.2; Sl.: EF = n.d.; IWW: EF = 0; EWW: EF = 0.3; Sl.: EF = 0.1; IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = 0.7; IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = 0.4; IWW: EF = 0.6; EWW: EF = 0.7; Sl.: EF = 0.6; IWW: EF = 1; EWW: EF = n.d.; Sl.: EF = 0.6; IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = 0.5; IWW: EF = 0.7; EWW: EF = 0.7; Sl.: EF = 0.7; IWW: EF = 0.3; EWW: EF = 0.2; Sl.: EF = 0.5; IWW: EF = 0.3; EWW: EF = n.d.; Sl.: EF = 0.4; IWW: EF = 0.4; EWW: EF = 0.4; Sl.: EF = 0.5; IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = n.d.; IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = 0.5; IWW: EF = 0.7; EWW: EF = 0.7; Sl.: EF = 0.7; IWW: EF = 0.5; EWW: EF = 0.5; Sl.: EF = 0.5;	[66]





Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Aminorex	LC-MS/MS	Northern and Western Europe Influent and effluent wastewater.	EF = 0.4 (IWW)	[102]
2-hydroxyibuprofen	Polysaccharide amylose		EF = 0.2 (IWW)	
Ibuprofen	tris-3,5-dimethylphenylcarbamate column and a cellulose		EF = 1.0 (IWW)	
Imazalil	tris-(3-chloro-4-methylphenylcarbamate column		EF = 0 (IWW)	
Naproxen	(150 × 2.1 mm, i.d. 2.5 µm);		EF = 1.0 (IWW and EWW)	
Ofloxacin	CO <sub>2</sub> -methanol/acetonitrile/2-propanol, 1:1:1, v/v with		EF = 0 (IWW)	
Tetramisole	10 mM ammonium acetate and 0.1% ammonium		EF = 0.6 (IWW and EWW)	
Carprofen	hydroxide under a gradient program		-	
Chloramphenicol	(in positive ionization);		-	
3-N-dechloroethylfosfamide	Polysaccharide amylose		-	
Flurbiprofen	tris-3,5-dimethylphenylcarbamate column (150 × 2.1 mm,		-	
Ifosfamide	i.d. 2.5 µm);		-	
Omeprazole	CO <sub>2</sub> -methanol with 0.1% ammonium hydroxide under		-	
Praziquantel	a gradient program (in negative ionization).		-	
Indoprofen		-		
Carboxyibuprofen		EF = 0.83 (IWW)	[105]	
Chloramphenicol		-		
2-hydroxyibuprofen		EF = 0.79 (IWW)		
Ibuprofen	Chirobiotic T column (250 × 2.1 mm, i.d. 5 µm);	EF = 1.0 (IWW)		
Ifosfamide	Methanol-10 mM ammonium acetate (30/70, v/v), pH 4.2.	-		
Indoprofen		-		
Ketoprofen		-		
Naproxen		EF = 1.0 (IWW)		
Praziquantel		-		
			IWW: <LOQ—455 ng L <sup>-1</sup> ; EF = 0.68; EWW: <LOQ—115 ng L <sup>-1</sup> ; EF = 0.78. IWW: 11.8—45.8 ng L <sup>-1</sup> ; EF = 0.26–0.47; EWW: 12.3—19.0 ng L <sup>-1</sup> ; EF = 0.4–0.58. IWW: <LOQ—3112.5 ng L <sup>-1</sup> ; EF = 0.59–0.84; EWW: <LOQ—19.7 ng L <sup>-1</sup> ; EF = 0.68–1.0. IWW: <LOQ—1.8 ng L <sup>-1</sup> ; EF = 0.22–0.53; EWW: <LOQ; EF = 0.70–1.0. IWW: <LOQ—15171 ng L <sup>-1</sup> ; EF = 0.81–1.0; EWW: <LOQ—84.1 ng L <sup>-1</sup> ; EF = 0.72–1.0. IWW: 28.8–325.5 ng L <sup>-1</sup> ; EF = 0.35–0.65; EWW: 25–222 ng L <sup>-1</sup> ; EF = 0.46–0.69. IWW: 4288–19160 ng L <sup>-1</sup> ; EF = 0.30–0.47; EWW: 1480–18831 ng L <sup>-1</sup> ; EF = 0.40–0.61.	[77]
MDMA	LC-MS/MS; Chiral-CBH column (100 mm × 2 mm, 5 µm) with a Chiral-CBH guard column (10 mm × 2.0 mm); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 5.0.	Location n.a.; River water; Influent and effluent wastewater (7 WWTPs using mainly activated sludge and trickling filters technologies).		
MDA				
Amphetamine				
Methamphetamine				
Ephedrine				
Venlafaxine				
Atenolol				

Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Amphetamine Methamphetamine MDA MDMA Propranolol Atenolol Metoprolol Fluoxetine Venlafaxine	LC-MS/MS; Chiral-CBH column (100 × 2 mm, i.d. 5 µm) with a Chiral-CBH µm guard column (10 × 2.0 mm i.d., 5 µm); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 7.0.	United Kingdom River water (River Avon, Salford, Somerset).	<MQL; <MQL; <MQL; <MQL; <MQL; <MQL; <MQL; <MQL; <MQL.	[76]
Amphetamine Methamphetamine MDA MDMA Propranolol Atenolol Metoprolol Fluoxetine Venlafaxine	LC-MS/MS; Chirobiotic V column, (250 × 4.6 mm, i.d. 5 µm) with a Chirobiotic V guard column (20 × 4.0 mm, i.d. 5 µm); Methanol containing 4 mM ammonium acetate and 0.005% formic acid.	United Kingdom River water (River Avon, Salford, Somerset); Effluent wastewater	EWW: <MQL; RW: <MQL; EWW: <MQL; RW: <MQL; EWW: <MQL; RW: n.d.; EWW: <MQL; RW: <MQL; EWW: EF = 0.43; RW: EF = 0.45; EWW: EF = 0.55; RW: EF = 0.47; EWW: EF = 0.54; RW: <MQL; EWW: EF = 0.43; RW: EF = 0.58; EWW: <MQL; RW: <MQL.	
Amphetamine Methamphetamine MDA MDEA MDMA Ephedrine 1R,2S (-) Pseudoephedrine 1S,2S (+) Norephedrine Venlafaxine	LC-MS/MS; Chiral-CBH column (100 mm × 2 mm, 5 µm) with a Chiral-CBH guard column (10 mm × 2.0 mm); H <sub>2</sub> O-2-propanol (90:10, v/v), 1 mM ammonium acetate, pH 5.0.	Location n.a. Wastewater influent and effluent (4 WWTPs).	IWW: (S)-form 24.2–155.2 ng L <sup>-1</sup> ; (R)-form 39.5–212.9 ng L <sup>-1</sup> ; EF = 0.54–0.62; EWW: n.d.; IWW: (S)- and (R)-forms n.d.; EWW: (S)-form n.d. - <MQL; (R)-form n.d.; n.d.; IWW: n.d. - <MQL; EWW: n.d.; IWW: E1 <MQL—5.5 ng L <sup>-1</sup> ; E2 <MQL—13.9 ng L <sup>-1</sup> ; EF = 0.53–0.72; EWW: E1 n.d.—4.0 ng L <sup>-1</sup> ; E2 <MQL—10.0 ng L <sup>-1</sup> ; EF = 0.71 IWW: 14.3–72.3 ng L <sup>-1</sup> ; EWW: <MQL—14.8 ng L <sup>-1</sup> ; IWW: 51.0–329.7 ng L <sup>-1</sup> ; EWW: <MQL—27.7 ng L <sup>-1</sup> ; n.d. IWW: E1 57.2–286.5 ng L <sup>-1</sup> ; E2 56.7–343.8 ng L <sup>-1</sup> ; EF = 0.45–0.50; EWW: E1 80.2–178.2 ng L <sup>-1</sup> ; E2 123.7–248.3 ng L <sup>-1</sup> ; EF = 0.37–0.48.	[82]
Metoprolol Propranolol Atenolol Fluoxetine Venlafaxine Ibuprofen Flurbiprofen Naproxen	LC-MS/MS; Chirobiotic V column, (250 × 4.6 mm, i.d. 5 µm) with a Chirobiotic V guard column (20 × 4.0 mm, i.d. 5 µm); Chiralpak AD-RH column, (150 × 4.6 mm, i.d. 5 µm).	China Surface water (Dongting Lake).	0.48–0.64 0.44–0.56 n.d. - 0.46–0.51 - n.d. -	[94]

Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
16 pharmaceuticals (analgesics, antibiotics, beta-agonists, psychiatric and cardiovascular drugs) and two metabolites	LC-MS/MS; Chirobiotic V (250 × 2.1 mm i.d., 5 µm) with a Chirobiotic V guard column (20 mm × 1.0 mm i.d., 5 µm); Methanol(4 mM ammonium acetate)-formic acid (99.95:0.005, v/v).	<b>Spain</b> Influent and effluent wastewaters; River water (24 sampling locations; Guadalquivir River basin).		[71]
Venlafaxine Fluoxetine Norfluoxetine Alprenolol Bisoprolol Metoprolol Propranolol Salbutamol	LC-MS/MS; Chirobiotic V column (150 mm × 2.1 mm i.d., 5 µm); Ethanol-10 mM ammonium acetate aqueous solution (92.5:7.5, v/v), pH 6.8.	<b>Portugal</b> Effluent wastewater from 3 WWTPs.	EF = 0.54–0.55 - - - - -	[57]
Salbutamol	LC-MS/MS; Chirobiotic V column (250 mm × 2.1 mm i.d., 5 µm); Methanol(4 mM ammonium acetate)-formic acid (99.95:0.005, v/v).	<b>Italy</b> 24-h raw wastewater composite samples from 2 WWTPs (Nosedo and San Rocco, Milan).	EF one-day peaks = 0.484 ± 0.019 EF regular = 0.452 ± 0.018.	[87]
Atenolol Metoprolol Propranolol Sotalol Citalopram Paroxetine Naproxen Temazepam	LC-MS/MS; Chirobiotic V column (250 mm × 4.6 mm i.d., 5 µm) and Chiralpak AD-RH column (150 mm × 4.6 mm i.d., 5 µm) for temazepam; Methanol-20 mM ammonium acetate aqueous solution (90:10, v/v), 0.1% formic acid (pH 4).	<b>Canada</b> Wastewater effluents from 1 rural aerated lagoon and 2 urban tertiary WWTP (Alberta).	EF = 0.40–0.52; EF = 0.39–0.52; - EF = 0.34–0.41; EF = 0.44–0.62; - EF = 0.39–0.49.	[103]
Atenolol Citalopram Fluoxetine Metoprolol Nadolol Pindolol Propranolol Salbutamol Sotalol	LC-MS/MS; Inline filter and a Chirobiotic V (250 mm × 4.6 mm i.d., 5 µm) with a nitrile guard cartridge (10 mm × 3 mm i.d.); Methanol-20 mM ammonium acetate aqueous solution (90:10, v/v), 0.1% formic acid (pH 4).	<b>Canada</b> Raw and treated wastewater from a tertiary WWTP (Alberta).	IWW: 971 ± 30 ng L <sup>-1</sup> ; EWW: 664 ± 22 ng L <sup>-1</sup> ; IWW: 307 ± 18 ng L <sup>-1</sup> ; EWW: 207 ± 11 ng L <sup>-1</sup> ; IWW: 18 ± 2 ng L <sup>-1</sup> ; EWW: 14 ± 0.1 ng L <sup>-1</sup> ; IWW: 411 ± 15 ng L <sup>-1</sup> ; EWW: 375 ± 24 ng L <sup>-1</sup> ; IWW: 51 ± 2 ng L <sup>-1</sup> ; EWW: 20 ± 0.5 ng L <sup>-1</sup> ; IWW: <MQL; EWW: <MQL; IWW: 10 ± 1 ng L <sup>-1</sup> ; EWW: 45 ± 1 ng L <sup>-1</sup> ; IWW: 20 ± 3 ng L <sup>-1</sup> ; EWW: 17 ± 1 ng L <sup>-1</sup> ; IWW: 529 ± 10 ng L <sup>-1</sup> ; EWW: 466 ± 24 ng L <sup>-1</sup> .	[104]
Atenolol Metoprolol Propranolol	LC-MS/MS; In-line filter Chirobiotic V (250 mm × 4.6 mm i.d., 5 µm) with a nitrile guard cartridge (10 mm × 3 mm i.d.); Methanol-0.1% TEAA in water (90:10, v/v), acetic acid (pH 4).	<b>Canada</b> Influents and effluents wastewaters from 1 rural aerated lagoon and 2 urban tertiary WWTP (Alberta).	160–1100 ng L <sup>-1</sup> ; EF ≈ 0.5 (both influent and effluent). 170–520 ng L <sup>-1</sup> ; EF = 0.5 (influent) EF ≠ 0.50 (effluent). 20–92 ng L <sup>-1</sup> ; EF ≈ 0.5 (both influent and effluent).	[84]

Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Propranolol	GC-MS after diastereomer formation with the chiral derivatizing reagent $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid; MDN-5S column (30-m, 0.25-mm i.d., 0.25- $\mu$ m film thickness), carrier gas helium.	USA Surface water Wastewater influent Wastewater effluent after secondary treatment (7 WWTPs in California and New York).	<0.1–32 ng L <sup>-1</sup> ; EF = 0.42–0.53. 13–250 ng L <sup>-1</sup> ; EF = 0.50 $\pm$ 0.02. 3–160 ng L <sup>-1</sup> ; EF $\leq$ 0.42.	[61].
Metoprolol	GC-MS after diastereomer formation with the chiral derivatizing reagent (-)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid); MDN-5S column (30-m, 0.25-mm i.d., 0.25- $\mu$ m film thickness), carrier gas helium.	USA River water (Trinity River, Dallas, TX); Effluent wastewater.	10–571 ng L <sup>-1</sup> ; EF = 0.31–0.44. <1–2269 ng L <sup>-1</sup> ; EF = 0.50 $\pm$ 0.03.	[85].
Metoprolol	LC-MS/MS; Reprosil AGP column (100 $\times$ 2 mm i.d., 5 $\mu$ m); H <sub>2</sub> O-acetonitrile (98:2, v/v), containing 10 mM ammonium acetate.	Germany River water (stretch of river Gründlach, Northern Bavaria).	42–440 ng L <sup>-1</sup> ; EF = 0.43–0.49.	[75]
Metoprolol and two of its metabolites: $\alpha$ -Hydroxymetoprolol ( $\alpha$ -OH-metoprolol) Deaminated metoprolol (COOH-metoprolol)	LC-MS/MS; enantiomers of metoprolol and four stereoisomers of $\alpha$ -OH-metoprolol: in-line high-pressure filter (4 mm, 0.5 $\mu$ m) and a Chiral-CBH column (100 $\times$ 2.0 mm i.d., 5 $\mu$ m) with a Chiral-CBH guard column; 2% (v/v) methanol in hydroxylamine (5.0 mM)-acetic acid (0.65 mM) buffer at pH 7.0.	Sweden Treated wastewater samples from a municipal WWTP, Uppsala).	(S)-metoprolol: 1140–1860 pM; (R)-metoprolol: 939–1770 pM; EF metoprolol = 0.51–0.55; EF $\alpha$ -OH-metoprolol = 0.13–0.48.	[62]
	LC-MS/MS; enantiomers of COOH-metoprolol: in-line high-pressure filter with a replaceable cap frit (4 mm, 0.5 $\mu$ m) and a Chiral AGP column (100 mm $\times$ 2.0 mm, 5 $\mu$ m) with a Chiral-AGP guard column (10 $\times$ 2.0 mm); Methanol-10 mM ammonium acetate buffer at pH 5.0 (5:95, v/v)		n.d.	
Metoprolol and three of its metabolites: $\alpha$ -Hydroxymetoprolol Metoprolol acid O-desmethylmetoprolol	LC-MS/MS; CHIROBIOT V (250 mm $\times$ 4.6 mm i.d., 5 $\mu$ m); Mobile phase not referred. H <sub>2</sub> O-30 mM ammonium acetate in methanol at pH 6.0 (10:90, v/v).	France Influent and effluent wastewater.	IWW: 0.49–0.52; EWW: 0.57–0.70.	[90]
Atenolol Metoprolol Pindolol Propranolol	LC-UV; Chiralpak AD-H, Lux Cellulose-1, Sumichiral OA-4900 and Chirobiotic T, (250 $\times$ 4.6 mm i.d., 5 $\mu$ m); n-hexane-ethanol-DEA (70:30:0.3, v/v/v)	Spain River water (Cega River, Segovia).	Not determined; Not determined; Not determined; (S)-propranolol: 1.22 ( $\pm$ 0.07) ng L <sup>-1</sup> ; (R)-propranolol: 1.35 ( $\pm$ 0.07) ng L <sup>-1</sup> .	[78]

Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Atenolol Metoprolol Pindolol Propranolol	LC-UV; Lux Cellulose-1 (250 × 4.6 mm i.d., 5 µm); Gradient elution mobile phase polarity from n-hexane-Ethanol-DEA (90:10:0.5, v/v/v) to (60:40:0.5, v/v/v)	<i>Spain</i> River water (Cega River, Segovia).	<LOQ; <LOQ; <LOQ; <LOQ.	[79]
Ibuprofen, and its main metabolites	GC-MS; Homemade OV1701-DMPen (DMPen ) heptakis(2,6-O-dimethyl-3-O-n-pentyl)- $\beta$ -cyclodextrin; 1:1 diluted with OV1701) fused silica column (16 m, i.d. 0.25 mm)	<i>Switzerland</i> Lake, rivers and sea water (North Sea) Influent wastewaters Effluent wastewaters after secondary treatment.	n.d.—7.8 ng L <sup>-1</sup> ; ER = 0.7–4.2. 990–3300 ng L <sup>-1</sup> ; ER = 5.8–8.0. 2–81 ng L <sup>-1</sup> ; ER 0.9–2.	[60]
Ibuprofen Naproxen	GC-MS; Astec ChiralDex chiral column (20-m, 0.25-mm i.d., 0.12-µm film thickness) coated with dimethyl- $\beta$ -cyclodextrin as CSP, carrier gas helium.	<i>Spain</i> Influent and effluent wastewaters from a conventional WWTP from León (Castilla y León, Spain).	IWW EF = 0.73–0.90, EWW EF = 0.60–0.76; IWW EF = 0.88–0.90, EWW EF = 0.71–0.86.	[83]
Ibuprofen Ketoprofen Naproxen	LC-MS/MS Sumichiral OA-2500 (stationary phase:(R)-1-naphthylglycine and 3,5-dinitrobenzoic acid (250 mm × 46 mm i.d., 5 µm); Tetrahydrofuran-50 mM ammonium acetate in methanol (90:10, v/v).	<i>Spain</i> Influent and effluent wastewaters from 2 WWTPs (Córdoba)	EF IWW: 0.79–0.86; EF EWW: 0.63–0.68; EF IWW: 0.54–0.68; EF EWW: 0.61–0.68; EF IWW: 0.99; EF EWW: 0.93–0.96.	[65]
Ibuprofen Naproxen	GC-MS after diastereomer formation with the chiral derivatizing reagent (R)-1-phenylethylamine; HP5-MS fused silica capillary column (30 m, 0.25 mm i.d., 0.25 µm film thickness), carrier gas helium.	<i>Australia</i> Influent and effluent wastewater from 3 WWTPs	EF IWW: 0.6–0.8; EF EWW: 0.5. EF IWW: 1.0; EF EWW: 0.7–0.9.	[89]
Ibuprofen Ketoprofen Naproxen	GC-MS after diastereomer formation with the chiral derivatizing reagent (R)-1-phenylethylamine; HP5-MS fused silica capillary column (30 m, 0.25 mm i.d., 0.25 µm film thickness), carrier gas helium.	<i>Australia</i> Effluent wastewater from a tertiary wastewater treatment plant (Sydney)	4.6–120 ng L <sup>-1</sup> ; EF = 0.49–0.62; 3.1–207 ng L <sup>-1</sup> ; EF = 0.54–0.66; 1.6–178.9 ng L <sup>-1</sup> ; EF = 0.66–0.86.	[80]
Ibuprofen Ketoprofen Naproxen	GC-MS after diastereomer formation with the chiral derivatizing reagent (R)-1-phenylethylamine; HP5-MS fused silica capillary column (30 m, 0.25 mm i.d., 0.25 µm film thickness), carrier gas helium.	<i>Australia</i> Effluent wastewater from MBR of a WWTP (Bega Valley)	EF IWW: 0.88–0.94 EF EWW: 0.38–0.40; EF IWW: 0.56–0.60 EF EWW: 0.54–0.68; EF IWW: 0.99 EF EWW: 0.86–0.94.	[67]

Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Naproxen 6-O-desmethyl desmethyl-naproxen	LC-MS/MS; Chiralpak AD-RH (150 mm × 4.6 mm i.d.); Acetonitrile-0.1% formic acid (50:50, v/v).	<b>Japan</b> Influent and effluent wastewaters (Tokyo); River water (Tama River basin, Tokyo).	EF IWW: 1.0; EF EWW: 0.88–0.91; RW: 0.84–0.98.	[91]
Lansoprazole Pantoprazole	LC-MS/MS; Amylose tris-(3,5-dimethoxyphenylcarbamate) (150 mm × 4.6 mm i.d.) coated onto APS-Nucleosil (500 Å, 7 µm, 20%, w/w); Acetonitrile-H <sub>2</sub> O (35:65, v/v).	<b>Brazil</b> Influent and effluent wastewater; River water (Monjolinho River; São Carlos, SP).	Lansoprazole: n.d.; Pantoprazole: 0.15–0.18 µgL <sup>-1</sup> in treated effluents; 0.013 µgL <sup>-1</sup> in river water.	[55]
Omeprazole	LC-MS/MS; LC-UV; Amylose tris-(3,5-dimethylphenylcarbamate) (150 mm × 4.6 mm i.d.) coated onto APS-Nucleosil (500 Å, 7 µm, 20%, w/w); Acetonitrile-H <sub>2</sub> O (35:65, v/v).	<b>Brazil</b> Influent and effluent wastewater; River water (Monjolinho River; São Carlos, SP). <b>Portugal</b> Estuarine water samples (Douro River).	Both enantiomers were detected in one influent sample (not quantified); Both enantiomers were detected in one estuarine water sample (not quantified).	[54]
Omeprazole Lnsoprazole Pantoprazole Rabeprazole	LC-MS/MS; LC-UV; Chiralpak IC (250 mm × 4.6 mm i.d., 5 µm) Cellulose tris (3,5-dichlorophenylcarbamate) immobilized on silica; Acetonitrile-5 mM ammonium acetate in water (40:60, v/v)	<b>China</b> Influent and effluent wastewater from a municipal WWTP (Shenyang); River water (riverbank from the South Canal of Shenyang).	IWW: 0.70; EWW: 0.53; RW: 0.54. IWW: 0.51; EWW: 0.52; RW: 0.52. IWW: 0.54; EWW: 0.51; RW: 0.53. IWW: 0.52; EWW: <MQL; RW: 0.51.	[64]
Venlafaxine	LC-MS/MS; Chirobiotic V column (250 mm × 2.1 mm i.d., 5 µm) with a Chirobiotic guard column (10 mm × 2 mm i.d.); Tetrahydrofuran-8.7 mM ammonium acetate aqueous solution at pH 6.0 (10:90, v/v).	<b>France</b> Wastewater effluent River water	EF = 0.46–0.74.	[72]
Venlafaxine and its metabolites O-desmethylvenlafaxine, N-desmethylvenlafaxine, O,N- didesmethylvenlafaxine, N,N- didesmethylvenlafaxine and tridesmethylvenlafaxine	LC-MS/MS; CHIROBIOT V (250 mm × 4.6 mm i.d., 5 µm); LC-MS/MS α1-acid glycoprotein column (100 mm × 4.0 mm i.d., 5 µm)	<b>Israel</b> Six wastewater treatment plants (WWTPs) operating under different conditions.		[73]

Table 1. Cont.

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Fluoxetine and norfluoxetine	LC-MS/MS; In-line high-pressure filter with a replaceable cap frit (4 mm, 0.5 $\mu\text{m}$ ) and a Chiral AGP column (100 mm $\times$ 2.0 mm, 5 $\mu\text{m}$ ) with a Chiral-AGP guard column (10 mm $\times$ 2.0 mm); Acetonitrile-10 mM ammonium acetate buffer, pH 4.4 (3:97, v/v).	Sweden Influent and effluent wastewater from a municipal WWTP (Uppsala).	IWW: (S)-fluoxetine: 52 pM; (R)-fluoxetine: 21 pM; EF = 0.71; EWW: (S)-fluoxetine: 48 pM; (R)-fluoxetine: 19 pM; EF = 0.71; IWW: (S)-norfluoxetine: 27 pM; (R)-norfluoxetine: 12 pM; EF = 0.69; EWW: (S)-norfluoxetine: 9 pM; (R)-norfluoxetine: 4 pM; EF = 0.68.	[81,100]
Fluoxetine and norfluoxetine	LC-FD; Chirobiotic V column (150 mm $\times$ 4.6 mm i.d., 5 $\mu\text{m}$ ); Ethanol-10 mM ammonium acetate buffer (87.5:12.5, v/v), pH 6.8.	Portugal Effluent wastewater from a municipal WWTP.	n.d.	[86]
Hexaconazole Triadimefon Tebuconazole Penconazole	LC-DAD Chiralpak IC column 250 mm $\times$ 4.6 mm i.d., 5 $\mu\text{m}$ . with the CSPs [cellulose tris-(3,5-dichlorophenylcarbamate)] polymer immobilized on silica; n-hexane/2-propanol (90:10, v/v).	Ground water River water	n.d.	[63]
Econazole Miconazole Tebuconazole Ketoconazole	LC-MS/MS; $\alpha$ 1-acid glycoprotein column (100 mm $\times$ 4.0 mm i.d., 5 $\mu\text{m}$ ); Mobile phase not referred.	China Wastewater (dissolved and suspended particulate matter) sludge and river water (Pearl River Delta)	EF (dissolved phase) = 0.47–0.53; EF (suspended particulate matter) = 0.45–0.53; EF (sludge) 0.47–0.53; EF (river water) = 0.47–0.61.	[88]
Ketoconazole	LC-MS/MS; HSA column (100 mm $\times$ 2 mm i.d., 5.0 $\mu\text{m}$ ) with a HSA guard column (10 mm $\times$ 2 mm i.d.); Acetonitrile-H <sub>2</sub> O (10:90, v/v) containing 10 mM ammonium acetate (pH 7.0).	China Influent and effluent wastewater and sludge from a sewage treatment plant (Guangzhou, South China).	IWW: <MQL—91.6 ng L <sup>-1</sup> ; EF = 0.48; EWW: <MQL—12.4 ng L <sup>-1</sup> ; EF = 0.48; Sludge: 230.9–231.9 ng g <sup>-1</sup> (dw); EF = 0.49–0.50.	
Econazole Miconazole Tebuconazole Propiconazole	LC-MS/MS; AGP column (100 mm $\times$ 4 mm i.d., 5.0 $\mu\text{m}$ ) with an AGP guard column (10 mm $\times$ 4 mm i.d.); Gradient of H <sub>2</sub> O containing 10 mM ammonium acetate (pH 7.0) and acetonitrile.		IWW: 1–1.2 ng L <sup>-1</sup> ; EF not determined; EWW: 0.29–0.51 ng L <sup>-1</sup> ; EF not determined; Sludge: 8.3–120.8 ng g <sup>-1</sup> (dw); EF = 0.50–0.51; IWW: 6.0–11.3 ng L <sup>-1</sup> ; EF = 0.50; EWW: 0.25–0.87 ng L <sup>-1</sup> ; EF = 0.47; Sludge: 87.9–1258.0 ng g <sup>-1</sup> (dw); EF = 0.49–0.50. n.d.; n.d.	[74]

IWW: influent of WWTP; EWW: effluent of WWTP; EF: Enantiomeric fraction; ER: Enantiomeric ratio; MDA: 3,4-methylenedioxyamphetamine; MDMA: 3,4-methylenedioxy-methamphetamine).



#### 4.2. Environmental Chiral Analysis of Pesticides, PCBs and PCMs

Besides pharmaceuticals and illicit or abuse drugs, many other relevant environmental pollutants (e.g., pesticides, organohalogenated compounds, polycyclic aromatic hydrocarbons, among others) are chiral compounds and are used as racemic mixtures or as enantiomerically pure forms. Pesticides are the most well studied class of environmental pollutants concerning enantiomeric composition. Several reports have demonstrated their occurrence, distribution and biodegradation in various matrices including biota. Besides pesticides, to the best of our knowledge, only PCBs and PCMs were reported in aquatic environmental samples (surface waters, sediments, rain water and wastewaters).

##### 4.2.1. Pesticides

The extensive and intensive use of pesticides has led to a broad distribution and high levels of pesticides in all environmental compartments. Some pesticides are lipophilic and tend to accumulate not only in soil and sediments, but also in the food web, persisting for more time than expected and causing adverse effects [6,98,119]. In fact, pesticides already banned for many years as  $\alpha$ -hexachlorocyclohexane (lindane,  $\alpha$ -HCH), chlordane and DDT are still found in aquatic animals and in different regions of the globe [120,121]. Besides their persistence and toxicity, various pesticides are chiral and used as racemic mixtures or enantiomerically pure. Data about enantioselective occurrence, distribution, degradation and toxicological effects is imperative for an accurate environmental risk assessment [98]. Selective degradation or accumulation of single enantiomers may have toxicological implications. Indeed, some studies demonstrated that pesticides enantiomers selectively interact with biological systems and may behave as completely different substances [120]. For instance, the (-) enantiomer of *o,p'*-DDT has a higher estrogenic activity than (+) *o,p'*-DDT [122]. Song et al. reported the enantioselective estrogenic activities of seven chiral pesticides and thyroid hormone antagonistic effects of two chiral pesticides [6].

Enantiomers of  $\alpha$ -HCH and chlordane, among others, were found in aquatic animals from the Baltic Sea (fish and seals), Arctic (seals) and Antarctic Seas (penguins) with changed isomeric and EF [98,120,121]. Table 2 shows the concentration and enantiomeric composition (ER or EF) of  $\alpha$ -HCH, *cis* and *trans*-chlordane, octachlorochlordane, heptachlor-*exo*-epoxide, oxychlordane, dichlorprop (DCPP), mecoprop (MCPP), pentachloro-cyclohexene and bromocyclin in environmental samples, namely surface waters (e.g., river, sea and lake), sediments, rain water and wastewaters (Table 2). The ER of  $\alpha$ -HCH enantiomers was evaluated for the first time in a study developed by Faller et al. in 1991 [97] in North Sea regions. In this study, concentrations of the isomers  $\alpha$ -HCH and  $\gamma$ -HCH were up to 2.89 and 2.72 ng L<sup>-1</sup> respectively [97]. The authors found that the ER of (+/-)  $\alpha$ -HCH varied among the different regions of the North Sea. The relation (+/-)  $\alpha$ -HCH was lower than 1 in an area of the North Sea where concentrations of  $\gamma$ -HCH were higher than  $\alpha$ -HCH. This result suggested a possible transformation of (-)- $\alpha$ -HCH from  $\gamma$ -HCH. In contrast, in another North Sea area, the ER of (+/-)  $\alpha$ -HCH was higher than 1 suggesting a different microbiological process in this region. In this case, (-)- $\alpha$ -HCH was degraded preferably than (+)- $\alpha$ -HCH. The authors showed that different microbiological process influenced the degradation of  $\alpha$ -HCH isomers and suggested a correlation between the ER of (+/-)  $\alpha$ -HCH and the concentrations of isomers  $\alpha$ -HCH and  $\gamma$ -HCH. Another study developed by Padma et al. 2003 investigated the variation in ER of  $\alpha$ -HCH enantiomers in the York river estuary due to the microbiological activity (Table 2) [114]. Surprising, the  $\alpha$ -HCH ER values were close to 1 in the freshwater region of the estuary, i.e., in the head of the river, where the bacterial activity was high. In contrast, at the mouth of the river, where salinity of the estuary was higher and bacterial activity was lower, the ER values were non-racemic (ER  $\neq$  1) and  $\alpha$ -HCH concentrations were significantly higher. A degradation study of the fungicide metalaxyl showed that soil pH and redox conditions are important factors affecting the enantioselectivity of metalaxyl degradation [123]. These studies demonstrated that ERs can provide important information, nevertheless these data must be carefully interpreted in the context of other information. The chiral separation of other pesticides as DCPP and MCPP were reported in various matrices from Switzerland

(e.g., rain water, lake and rivers) [115,124]. Buser et al. reported the occurrence of various pesticides and the enantioselective analysis of DCP and MCP [124]. Results showed that both enantiomers (*R* and *S*) of MCP were found though only the (*R*)-enantiomer was registered and used as an herbicide in Switzerland. The pesticide DCP was hardly present. Authors suggested enantioselective degradation of MCP and DCP in soil leading to residues enriched in (*R*)-enantiomers. A biodegradation study of MCP conducted by the same group, showed compositions of (*R*)-form higher than (*S*)-enantiomer, as expected from the soil degradation data. However, in other lakes, unexpectedly, a “reversed” composition of  $S > R$  was found. This suggested the occurrence of additional biotic processes in the aquatic environment and/or contamination with racemic MCP from another source. Laboratory incubation of MCP and DCP in lake and river water confirmed significant racemization [124]. The racemization was biologically mediated and led to residues of MCP and DCP in these waters, which were enriched in the (*S*)-enantiomers. Gerecke et al. also reported ER of MCP [125]. MCP is used in a racemic ratio (*R/S*-MCP) in urban areas for protection and conservation of materials, whereas only (*R*)-MCP is used in all other applications as agriculture. Thus, the authors showed that ER could be employed to distinguish between these sources and potential contaminations. Bethan et al. reported the enantioselective analysis of bromocyclen in water and muscle tissues of trout and beam from the river Stor, Germany and WWTPs. The authors found non-racemic ERs of (+/-) bromocyclen in surface water and a higher degradation of (+)-bromocyclen in the fish muscle tissue of breams [126]. They also suggested a possible correlation between ER and pesticide concentration. Jantune et al. investigated the spatial distribution of various chiral organochloride pesticides in Arctic surface waters [121]. In this study, again, different spatial enantioselective degradation was found for  $\alpha$ -HCH. Enrichment of (+) heptachlor-*exo*-epoxide (a metabolite of heptachlor) was found in all regions, while *trans*- and *cis*-chlordane were nearly racemic.

#### 4.2.2. Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are ubiquitous contaminants of great environmental concern. Due to their persistence, toxicity, and bioaccumulation [127], these compounds were included in the list of Priority Substances of the Water Frame Directive and Stockholm Convention [128,129]. PCBs and their metabolites methylsulfonyl-PCBs have been found in various species as in blubber from Baltic grey seals, fish, birds and mammalian species including humans [130–135]. High contaminant levels were found in grey seals from the Baltic Sea and PCBs and their metabolites methylsulfonyl-PCBs were reported as the third most abundant class of anthropogenic substances, present at levels at 10–20% of the total PCBs [136]. Surprisingly, few works reported the occurrence of these compounds in aquatic matrices. Wong et al. reported the occurrence of PCB 91 in non-racemic levels with ER of 0.56 in sediments from lake Hartwell [10]. Also, Benická et al. reported non-racemic occurrence of PCB 95 in sediments from Hudson River, USA [137]. In contrast, Glausch et al. reported racemic levels of PCBs 95, 132, and 149 in Elsenz River sediment in southern Germany [138]. Wong et al. also found non-racemic ERs for PCBs 91, 95, 132, 136, 149, 174, and 176 in sediment cores from Lake Hartwell [10] and in bed-sediment samples from the Hudson and Housatonic Rivers indicating that some of the PCB biotransformation processes identified at these sites were enantioselective [10]. Similar to pesticides, the enantioselectivity of PCB 91 was reversed between the Hudson and Housatonic River sites, which suggested that the two sites would have different PCB biotransformation processes with different enantiomer preferences.

#### 4.2.3. Polycyclic Musks (PCMs)

To the best of our knowledge there are only three reports about the occurrence of chiral polycyclic musks (PCMs) in environmental samples as surface waters and WWTPs [139,140]. These substances are fragrances used in personal care products. Due to their lipophilicity these compounds might adsorb in suspended matter during wastewater treatment and contribute for their occurrence in influents and effluents from WWTPs, surface waters and aquatic organisms. Concern about these compounds is

growing due to their potential harmful effects on aquatic organisms and human health [141]. Berset et al reported the enantioseparation of various PCMs [140]. Though the ER were not determined for all compounds due to their low resolution, HHCB, AHTN, AHDI and ATII showed non-racemic ER suggesting a enantioselective biodegradation during wastewater treatment [140]. Lee et al. reported the occurrence of five PCMs enantiomers in river and WWTPs samples [139]. Isomers *cis* and *trans* from HHCB were found and their enantiomeric composition was nearly racemic river and in influent samples. In contrast, significant non-racemic ER for HHCB was observed in the effluent of one of the WWTPs. Nevertheless, other WWTPs investigated did not show enantioselective biotransformation. The authors suggested that not only biotransformation may occur but also sorption on sludge may contribute to the removal of PCMs from wastewater and difference in the enantiomeric composition.

**Table 2.** Environmental chiral analysis of pesticides, PCBs and PCMs.

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.	
Pesticides	$\alpha$ -HCH	<i>GC-ECD</i> heptakis (3- <i>O</i> -butyryl-2,6-di- <i>O</i> -pentyl)- $\beta$ -CD (60 m), carrier gas hydrogen	<i>North Sea regions</i>	$\alpha$ -HCH: 0.54–2.86 ng L <sup>-1</sup> ER (+/-, $\alpha$ -HCH) = 0.88–1.19 $\gamma$ -HCH: 0.31–2.72 ng L <sup>-1</sup>	[97]
	$\alpha$ -HCH	<i>GC-ECD</i> $\beta$ -dex 120 chiral column	<i>USA</i> York river estuary	(+) $\alpha$ -HCH: 11.6–79.3 pg L <sup>-1</sup> (-) $\alpha$ -HCH: 20.6–103.0 pg L <sup>-1</sup> ER (+/-, $\alpha$ -HCH) = 0.71–1.06	[114]
	$\alpha$ -HCH	<i>GC-ECD</i> $\gamma$ -DEX 120 column (20% $\gamma$ -CD, 20 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas hydrogen	<i>Island</i> Water rivers and lakes	$\alpha$ -HCH: 1.2–5.8 ng L <sup>-1</sup> $\gamma$ -HCH: 0.23–0.65 ng L <sup>-1</sup> ER ( $\alpha/\gamma$ , HCH) = 3.5–13.8	[142]
	$\alpha$ -HCH	<i>GC-ECD</i> column A: heptakis (3- <i>O</i> -butyryl-2,6-di- <i>O</i> -pentyl)- $\beta$ -CD (25 m, i.d. 0.25 mm); column B: 50% heptakis (2,3,6-tri- <i>O</i> -n-pentyl)- $\beta$ -CD and 50% OV1701(25 m, i.d. 0.25 mm), carrier gas helium	<i>North sea and Baltic sea</i>	$\gamma$ -HCH: 2.0–7.7 ng L <sup>-1</sup> $\alpha$ -HCH: 0.2–5.8 ng L <sup>-1</sup> ER ( $\gamma/\alpha$ , HCH) = 0.67–10.0 ER (+/-, $\alpha$ -HCH) = 0.81–0.92	[99]
	$\alpha$ -HCH	<i>GC-MS</i> 30% tert-butyl dimethylsilylated- $\beta$ -CD in PS-086 (20 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness)	<i>Arctic regions</i> water from Bering and Chukchi Seas	$\alpha$ -HCH: 0.05–5.32 ng L <sup>-1</sup> $\gamma$ -HCH: 0.10–1.33 ng L <sup>-1</sup> ER ( $\alpha/\gamma$ , HCH) = 0.35–12.40	[121]
	$\alpha$ -HCH	<i>GC-MS</i> Beta-DEX (20% permethylated- $\beta$ -CD in polydimethylsiloxane, (30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness) and BGB-172 (20% tert-butyl dimethylsilylated- $\beta$ -CD in OV-1701, (30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	<i>Arctic Ocean</i> Surface water	ER (+/-, $\alpha$ -HCH) = 0.68–1.09	[143]
	$\alpha$ -HCH	<i>GC-MS</i> Betadex-120 (20% permethylated $\beta$ -CD in methyl phenylpolysiloxane (30 m, i.d. 0.25 mm)	<i>Canada</i> Lake Ontario and Niagara River Rain water	ER (+/-, $\alpha$ -HCH) = 0.86 ER (+/-, $\alpha$ -HCH) = 0.99	[112]
	$\alpha$ -HCH	<i>Not described</i>	<i>Scotland</i> Kintyre Peninsula Air	EF ( $\alpha$ -HCH) = 0.480	[144]
$\alpha$ -HCH	<i>GC-MS</i> 20% tert-butyl dimethylsilylated $\beta$ -cyclodextrin in OV-1701	<i>China</i> Pearl River Delta	EF( $\alpha$ -HCH) = 0.104–0.910	[12]	

Table 2. Cont.

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
$\alpha$ -HCH	GC-MS BGB (20% tert-butyldimethylsilylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	USA Alabama Agricultural soil Cemeteries	EF( $\alpha$ -HCH) = 0.48–0.53 EF( $\alpha$ -HCH) = 0.50	[113]
PCCH	GC-ECD column A: heptakis (3- <i>O</i> -butyryl-2,6-di- <i>O</i> -pentyl)- $\beta$ -CD (25 m, i.d. 0.25 mm); column B: 50% heptakis (2,3,6-tri- <i>O</i> -n-pentyl)- $\beta$ -CD and 50% OV1701(25 m, i.d. 0.25 mm), carrier gas helium	North sea and Baltic sea	ER ( $\gamma_1/\gamma_2$ ) PCCH = 1.12–1.17 ER ( $\beta_1/\beta_2$ ) PCCH = 0.97	[99]
bromocyclin	GC-ECD 50% heptakis(6- <i>O</i> -tert-butyl-dimethylsilyl-2,3-di- <i>O</i> -methyt)- $\beta$ -CD and 50% OV-1701 ~w/w (25 m, i.d. 0.25 mm, 0.125 $\mu$ m film thickness) carrier gas hydrogen	Germany River Stör WWTPs	n.d.–261 pg L <sup>-1</sup> ; ER (-/+ ) = 1.01–1.0 760–11,500 pg L <sup>-1</sup>	[126]
MCPP	GC-MS FS 71 PS-086 + 20% Me- $\beta$ -CD, (15 m, 0.25 mm i.d., 0.13 $\mu$ m film thickness)	Switzerland Rain water	R-MCPP: up to 50 ng L <sup>-1</sup> S-MCPP: up to 19 ng L <sup>-1</sup>	[115]
MCPP	GC-MS OV1701-TBDM (TBDM, heptakis-(6- <i>O</i> -tert-butyldimethylsilyl-2,3-di- <i>O</i> -methyl)- $\beta$ -CD) fused silica (20 m, i.d. 0.25 mm) column with 35% of the chiral selector (amount relative to OV1701)	Switzerland Lake and rivers	R-MCPP: <0.2 to 25 ng L <sup>-1</sup> S-MCPP: <0.2 to 121 ng L <sup>-1</sup> ER (R/S) = 0.21–4.36	[124]
MCPP	GC-MS Not described	Switzerland WWTPs and Lake Greifensee	ER (R/S) = ~1 to 2	[125]
DCPP	GC-MS FS 71 PS-086 + 20% Me- $\beta$ -CD, (15 m, 0.25 mm i.d., 0.13 $\mu$ m film thickness)	Switzerland Rain water	R-dichlorprop: up to 106 ng L <sup>-1</sup> S-dichlorprop: up to 11 ng L <sup>-1</sup>	[115]
DCPP	GC-MS OV1701-TBDM (TBDM, heptakis-(6- <i>O</i> -tert-butyldimethylsilyl-2,3-di- <i>O</i> -methyl)- $\beta$ -CD) fused silica (20 m, i.d. 0.25 mm) column with 35% of the chiral selector (amount relative to OV1701)	Switzerland Lake and rivers	R-DCPP: <0.2 to 2.7 ng L <sup>-1</sup> S-DCPP: <0.2 to 2.7 ng L <sup>-1</sup>	[124]

Table 2. Cont.

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
TC	GC-MS BGB-172 (20% tert-butyltrimethylsilylated- $\beta$ -CD in OV-1701, (30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium)	Arctic Ocean Surface water	ER (+/- TC): 0.97–1.03	[143]
TC	Not described	Scotland Kintyre Peninsula Air	EF (TC) = 0.476	[144]
TC	GC-MS 20% tert-butyltrimethylsilylated $\beta$ -cyclodextrin in OV-1701	China Pearl River Delta	EF (TC) = 0.112–0.734	[12]
TC	GC-MS Betadex (20% permethylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	USA Alabama Agricultural soil Cemeteries	EF (TC) = 0.47–0.49 EF (TC) = 0.40–0.50	[113]
CC	GC-MS BGB-172 (20% tert-butyltrimethylsilylated- $\beta$ -CD in OV-1701, (30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium)	Arctic Ocean Surface water	ER (+/- CC) = 0.94–1.06	[143]
CC	Not described	Scotland Kintyre Peninsula Air	EF (CC) = 0.511	[144]
CC	GC-MS 20% tert-butyltrimethylsilylated $\beta$ -cyclodextrin in OV-1701	China Pearl River Delta	EF (CC) = 0.043–0.813	[12]
CC	GC-MS Betadex (20% permethylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	USA Alabama Agricultural soil Cemeteries	EF (CC) = 0.50–0.56 EF (CC) = 0.48–0.53	[113]
OXY	GC-MS BGB (20% tert-butyltrimethylsilylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	USA Alabama Agricultural soil Cemeteries	EF (OXY) = 0.55–0.60 EF (OXY) = 0.550	[113]
HEPX	GC-MS BGB (20% tert-butyltrimethylsilylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	USA Alabama Agricultural soil Cemeteries	EF (HEPX) = 0.69–0.73 EF (HEPX) = 0.50–0.76	[113]

Table 2. Cont.

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
MC5	GC-MS Betadex (20% permethylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	<b>USA</b> Alabama Agricultural soil Cemeteries	EF (MC5) = 0.25–0.46 EF (MC5) = 0.41–0.47	[113]
DDT	GC-MS 20% tert-butyldimethylsilylated $\beta$ -cyclodextrin in OV-1701	<b>China</b> Pearl River Delta	EF (o,p'-DDT) = 0.102–0.801	[12]
DDT	GC-MS BGB (20% tert-butyldimethylsilylated $\beta$ -CD, 30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium	<b>USA</b> Alabama Agricultural soil Cemeteries	EF (o,p'-DDT) = 0.41–0.55 EF (o,p'-DDT) = 0.50–0.57	[113]
PBs	PCB 91	<b>USA</b> Lake Hartwell sediment	ER (first/second enantiomer) = 0.56	[110]
	PCBs 95, 132, and 149	<b>Germany</b> River Elsenz	ER (PCBs 95, 132, and 149) $\sim$ 1	[138]
	PCB 95	<b>USA</b> Sediments Hudson River in New York State	ER = 0.5–0.6	[137]
PCBs 91, 95, 132, 136, 149, 174, and 176	GC-MS Chirasil-Dex Cyclosil-B	<b>USA</b> Sediments Hudson and Housatonic Rivers	ER (E1/E2, PCB 91) = 0.56–1.28 ER (E1/E2, PCB 95) = 0.67–1.02 ER (+/-, PCB 132) = n.d.–1.32 ER (+/-, PCB 136) = n.d.–5.33 ER (+/-, PCB 149) = 0.91–2.31 ER (+/-, PCB 174) = n.d.–3.71 ER (+/-, PCB 176) = n.d.–1.02 ER (+/-, PCB 183) = n.d.–1.04	[10]
PCBs 95, 136, 149	GC-MS Chirasil-Dex (10% permethylated 2,3,6-tri-O-methyl- $\beta$ -CD (25 m $\times$ 0.25 mm $\times$ 0.25 $\mu$ m film thickness))	<b>UK</b> West Midlands Air Soil	EF (95) = 0.488–0.499 EF (136) = 0.495–0.503 EF (149) = 0.495–0.500 EF (95) = 0.444–0.496 EF (136) = 0.472–0.522 EF (149) = 0.490–0.544	[145]

Table 2. Cont.

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.	
Polycyclic musk	HHCB	GC-MS/MS Cyclosil-B: heptakis (2,3-di-O-methyl-6-O-tert-butyl dimethylsilyl- $\beta$ -CD in DV-1701 (25 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium)	<i>Korea</i> Nakdong River WWTPs Influent Effluent	<18.0–342.0 ng L <sup>-1</sup> ; ER (trans-HHCB) = 0.86–1.09 ER (cis-HHCB) = 0.95–1.10 <785.0–3491 ng L <sup>-1</sup> ; ER (trans-HHCB) = 0.91–1.01 ER (cis-HHCB) = 1.03–1.14 <284.0–576.0 ng L <sup>-1</sup> ; ER (trans-HHCB) = 0.74–1.04 ER (cis-HHCB) = 0.69–1.25	[139]
	HHCB	GC-MS/MS 14% cyanopropylphenyl/86% dimethyl polysiloxane) doped with proprietary amounts of cyclodextrin material (30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness) OV 1701 capillary column, carrier gas helium	<i>Switzerland</i> WWTPs Influent Effluent Sewage sludge Aerobic Anaerobic	ER (trans-HHCB) = 1.0 ER (cis-HHCB) = 0.97 ER (trans-HHCB) = 0.81 ER (cis-HHCB) = 1.00 ER (trans-HHCB) = 0.93 ER (cis-HHCB) = 0.98	[140]
	HHCB	GC-MS; Chiral heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)- $\alpha$ -cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	1679 ng L <sup>-1</sup> ; EF = 0.25/0.25/0.26; 28.1 ng L <sup>-1</sup> ; EF = 0.24/0.24/0.25;	[70]
	AHTN	GC-MS/MS 14% cyanopropylphenyl/86% dimethyl polysiloxane) doped with proprietary amounts of cyclodextrin material (30 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness) OV 1701 capillary column, carrier gas helium	<i>Switzerland</i> WWTPs Influent Effluent Sewage sludge Aerobic Anaerobic	ER = 0.94 ER = 0.96 ER = 1.17 ER = 0.99	[140]
	AHTN	GC-MS; Chiral heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)- $\alpha$ -cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	31.2 ng L <sup>-1</sup> ; EF = 0.50; 4.6 ng L <sup>-1</sup> ; EF = 0.50;	[70]
	AHDI	GC-MS/MS Cyclosil-B: heptakis (2,3-di-O-methyl-6-O-tert-butyl dimethylsilyl- $\beta$ -CD in DV-1701 (25 m, i.d. 0.25 mm, 0.25 $\mu$ m film thickness), carrier gas helium)	<i>Korea</i> Nakdong River WWTPs Influent Effluent	<69.0 ng L <sup>-1</sup> <69.0 ng L <sup>-1</sup>	[139]



Table 2. Cont.

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
AHDI	GC-MS/MS 14% cyanopropylphenyl/86% dimethyl polysiloxane) doped with proprietary amounts of CD material (30 m, i.d. 0.25 mm, 0.25 µm film thickness) OV 1701 capillary column, carrier gas helium	<i>Switzerland</i> WWTPs	ER = 0.97	[140]
		Influent Effluent Sewage sludge Aerobic Anaerobic	ER = 1.19 ER = 1.16 ER = 0.95	
ATI	GC-MS/MS Cyclosil-B: heptakis (2,3-di-O-methyl-6-O-tert-butyl dimethylsilyl-β-CD in DV-1701 (25 m, i.d.0.25 mm, 0.25 µm film thickness), carrier gas helium	<i>Korea</i> Nakdong River WWTPs Influent Effluent	<107.0 ng L <sup>-1</sup> <107.0 ng L <sup>-1</sup>	[139]
ATI	GC-MS/MS 14% cyanopropylphenyl/86% dimethyl polysiloxane) doped with proprietary amounts of CD material (30 m, i.d. 0.25 mm, 0.25 µm film) OV 1701 capillary column, carrier gas helium	<i>Switzerland</i> WWTPs Influent Effluent Sewage sludge Aerobic Anaerobic	ER = 0.86 ER = 2.94 ER = 0.92 ER = 0.79	[140]
ATI	GC-MS; Chiral heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)-α-cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	5.0 ng L <sup>-1</sup> ; EF = 0.55; n.d.	[70]
DPMI	GC-MS/MS Cyclosil-B: heptakis (2,3-di-O-methyl-6-O-tert-butyl dimethylsilyl-β-CD in DV-1701 (25 m, i.d.0.25 mm, 0.25 µm film thickness), carrier gas helium	<i>Korea</i> Nakdong River WWTPs Influent Effluent	<79.0 ng L <sup>-1</sup> <79.0 ng L <sup>-1</sup>	[139]
DPMI	GC-MS; Chiral heptakis (2,3-di-O-methyl-6-O-t-butyl dimethylsilyl)-α-cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	66.6 ng L <sup>-1</sup> ; EF = 0.48. 2.2 ng L <sup>-1</sup> ; EF = 0.51.	[70]

AHDI: 6-acetyl-1,1,2,3,3,5-hexamethyl-indane; AHTN: 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetra-hydronaphthalene; ATI: 5-acetyl-1,1,2,6-tetramethyl-3-isopropyl-indane; CC: cis-chlordane; CD: cyclodextrin; DCP: 2-(2,4-dichlorophenoxy)-propionic acid, (dichlorprop); DDT: dichlorodiphenyltrichloroethane; DPMI: 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone; EF: Enantiomeric fraction; ER: Enantiomeric ratio; GC-ECD: gas chromatography electron-capture detection; GC-MS gas chromatography mass spectrometry detection; α HCH: α-1,2,3,4,5,6-hexachlorocyclohexane (lindane); HEPX: heptachlor-*exo*-epoxide; HHCB: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclo-penta-2-benzopyrane; MC5: octachlorochlordane; MCP: 2-(4-chloro-2-methylphenoxy)propionic acid, (mecoprop); n.d.: not detected; OXY: oxychlordane; PCB 95: 2,2',3,5',6-pentachlorobiphenyl; PCB 91: 2,2',3,4',6-pentachlorinated biphenyls; PCB 132: 2,2',3,3',4,6'-hexachlorobiphenyl; PCB 136: 2,2',3,3',6,6'-Hexachlorobiphenyl; PCB 149: 2,2',3,4',5',6-hexachlorobiphenyl; PCB 174: 2,2',3,3',4,5,6'-Heptachlorobiphenyl; PCB 176: 2,2',3,3',4,6,6'-Heptachlorobiphenyl; PCB 183: 2,2',3,4,4',5',6-Heptachlorobiphenyl; PCCH: β-1,3,4,5,6-pentachloro-1-cyclohexene; TC: trans-chlordane.

## 5. Conclusions

The reports about the occurrence of chiral bioactivity show the variation in the enantiomeric composition in aquatic matrices. In this sense, various studies have been demonstrating not only a selective microbial degradation of the enantiomers in field applications and laboratory microcosms, but also a possible correlation to other factors as physicochemical parameters or concentration of compounds. Also, various studies demonstrated the occurrence of enantiomers of bioactive compounds, nevertheless ecotoxicological studies concerning enantiomerically pure forms on non-target organisms at the environment level are scarce but of highly important in order to understand and evaluate the environmental risk and the possible enantioselectivity in ecotoxicity. In fact, the detection limits (few ng/L) provided by the modern analytical techniques are well below those usually tested in toxicological effects ( $\mu\text{g/L}$ – $\text{mg/L}$ ). Considering pharmaceuticals and PCBs, there is an urgent need for more studies about the occurrence, environmental fate and biodegradation studies and their metabolites to evaluate the ecotoxicological effects of these compounds. Regarding PCMs, few studies reported their enantiomeric composition. Also, factors that affect enantiomeric composition are still not understood.

Future studies must be done to elucidate the exact mechanisms responsible for the differences in EF or ER values in some environmental samples. These findings also show the importance to develop chiral analytical methods for the quantification of these compounds in environmental samples.

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