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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.

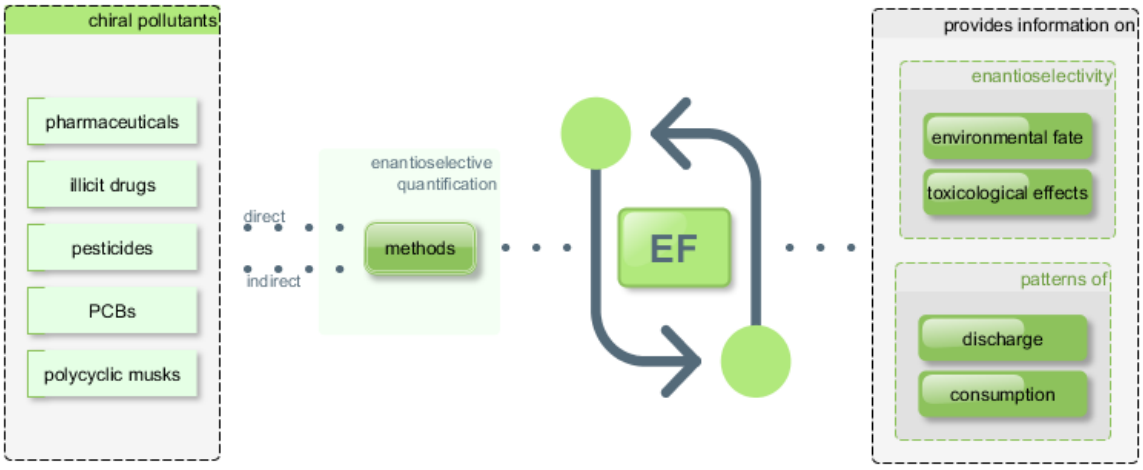

Figure 1. Schematic representation of the importance of determination of enantiomeric fraction (EF) in environmental analysis of chiral pollutants.

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:

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

and can be simply quoted as % *E*1, or alternatively % *E*2. This term was recently replaced by *EF*, which is given by:

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

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 (µg/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 temazepan [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_2O-2-propanol (90:10, *v*/*v*), 1 mM ammonium acetate, pH 5.0.	***United Kingdom*** 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_2O-2-propanol (90:10, *v*/*v*), 1 mM ammonium acetate, pH 5.0.	***England*** Influent (IWW) and effluent (EWW) wastewater River water (RW): 6 locations near the WWTP discharge zone	17.4–3112.5 ng L^{-1} (IWW); 4.3–145.2 ng L^{-1} (EWW); 0.3–4.3 ng L^{-1} (SW); 0.6–70.3 ng L^{-1} (IWW); 0.4–1.3 ng L^{-1} (EWW); 0.3–0.4 ng L^{-1} (SW); 7.2–32.4 ng L^{-1} (IWW); 6.3–24.5 ng L^{-1} (EWW); 0.9–1.9 ng L^{-1} (SW); 0.7–455.4 ng L^{-1} (IWW); 0.6–177.7 ng L^{-1} (EWW); 0.5–24.8 ng L^{-1} (SW); 1.4 ng L^{-1} (IWW); n.d. (EWW); n.d. (SW); 8.7–1979.5 ng L^{-1} (IWW); 5.3–265 ng L^{-1} (EWW); 6.3–28.9 ng L^{-1} (SW); 15–99.9 ng L^{-1} (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_2O-2-propanol (90:10, *v*/*v*), 1 mM ammonium acetate, pH 5.0.	***England*** Wastewater influent and effluent	EF = 0.52–0.84; EF $\geq$ 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_2O-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)	***Not referred*** 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.
MDMA	*UPLC-MS/MS;* Chiral-CBH column (100 mm × 2 mm i.d., 5 µm); H_2O-2-propanol (85:15, *v*/*v*) (1 mM ammonium acetate) Chirobiotic V column, (100 × 2.1 mm, i.d. 5 µm); Methanol (4 mM ammonium acetate, 0.005% formic acid)	***Not referred*** Effluent wastewater.	EF showed temporal changes (0.24–0.38);	[95]
Atenolol			EF did not show temporal changes;	
Citalopram			EF did not show temporal changes;	
Desmethylcitalopram			EF did not show temporal changes;	
Fluoxetine			EF did not show temporal changes;	
Mirtazapine			EF did not show temporal changes;	
Metoprolol			EF did not show temporal changes;	
Propranolol			EF did not show temporal changes.	
Amphetamine	*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_2O-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)	***Not referred*** Influent (IWW) and effluent (EWW) wastewater; Sludge (Sl.).	IWW: EF = 0.64; EWW: EF = 0.42;	[93]
Methamphetamine			IWW: EF = 0.89; EWW: EF = 0.63;	
MDMA			IWW: EF = 0.36; EWW: EF = 0.22;	
MDA			IWW: EF = 0.59; EWW: EF = 0.42;	
Alprenolol			IWW: EF = 0.51; EWW: EF = 0.48;	
Atenolol			IWW: EF = 0.50; EWW: EF = 0.54;	
Citalopram			IWW: EF = 1.0; EWW: EF = 1.0;	
Desmethylcitalopram			IWW: EF = 0.26; EWW: EF = 0.10;	
Desmethylvenlafaxine			IWW: EF = 0.57; EWW: EF = 0.52;	
Fluoxetine			IWW: EF = 0.69; EWW: EF = 0.62;	
Mirtazapine			IWW: EF = 0.25; EWW: EF = 0.19;	
Metoprolol			IWW: EF = 0.33; EWW: EF = n.d.;	
Propranolol			IWW: EF = 0.46; EWW: EF = 0.41;	
Salbutamol			IWW: EF = 0.65; EWW: EF = 0.57;	
Sotalol			IWW: EF = 0.50; EWW: EF = 0.50.	
Venlafaxine			Venlafaxine	
Ibuprofen	*LC-MS/MS* Chiral-AGP (100 × 2 mm, i.d. 5 µm) column with a Chiral-AGP (10 × 2.0 mm, i.d. 5 µm) guard column; Aqueous solution of 10 mM ammonium acetate with 1% of acetonitrile, pH 6.7	***United Kingdom*** Effluent wastewater; River water (South West England).	EF = 0.65	[101]
Naproxen			EF = 0.92	
Fexofenadine			EF = 0.55	
Tetramisole			EF = 0.50	
Ketoprofen			-	
Aminorex			-	
Chloramphenicol			-	
3-N-Dechloroethylifosfamide			-	
10,11-dihydro-10-hydroxycarbamazepine			-	
Dihydroketoprofen			-	
Ifosfamide			-	
Praziquantel			-	

Table 1. *Cont.*

Chiral Compounds	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
Aminorex	*LC-MS/MS* Polysaccharide amylose tris-3,5-dimethylphenylcarbamate column and a cellulose tris-(3-chloro-4-methylphenylcarbamate column (150 × 2.1 mm, i.d. 2.5 µm); CO_2-methanol/acetonitrile/2-propanol, 1:1:1, *v*/*v* with 10 mM ammonium acetate and 0.1% ammonium hydroxide under a gradient program (in positive ionization); Polysaccharide amylose tris-3,5-dimethylphenylcarbamate column (150 × 2.1 mm, i.d. 2.5 µm); CO_2-methanol with 0.1% ammonium hydroxide under a gradient program (in negative ionization).	***Northern and Western Europe*** Influent and effluent wastewater.	EF = 0.4 (IWW)	[102]
2-hydroxyibuprofen			EF = 0.2 (IWW)	
Ibuprofen			EF = 1.0 (IWW)	
Imazalil			EF = 0 (IWW)	
Naproxen			EF = 1.0 (IWW and EWW)	
Ofloxacin			EF = 0 (IWW)	
Tetramisole			EF = 0.6 (IWW and EWW)	
Carprofen			-	
Chloramphenicol			-	
3-N-dechloroethylifosfamide			-	
Flurbiprofen			-	
Ifosfamide			-	
Omeprazole			-	
Praziquantel			-	
Indoprofen			-	
Carboxyibuprofen	Chirobiotic T column (250 × 2.1 mm, i.d. 5 µm); Methanol-10 mM ammonium acetate (30/70, *v*/*v*), pH 4.2.	***United Kingdom*** Influent and effluent wastewater; River water (South West England).	EF = 0.83 (IWW)	[105]
Chloramphenicol			-	
2-hydroxyibuprofen			EF = 0.79 (IWW)	
Ibuprofen			EF = 1.0 (IWW)	
Ifosfamide			-	
Indoprofen			-	
Ketoprofen			-	
Naproxen			EF = 1.0 (IWW)	
Praziquantel			-	
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_2O-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).	IWW: <LOQ—455 ng L^{-1}; EF = 0.68; EWW: <LOQ—115 ng L^{-1}; EF = 0.78.	[77]
MDA			IWW: 11.8—45.8 ng L^{-1}; EF = 0.26–0.47; EWW: 12.3—19.0 ng L^{-1}; EF = 0.4–0.58.	
Amphetamine			IWW: <LOQ—3112.5 ng L^{-1}; EF = 0.59–0.84; EWW: <LOQ—19.7 ng L^{-1}; EF = 0.68–1.0.	
Methamphetamine			IWW: <LOQ—1.8 ng L^{-1}; EF = 0.22–0.53; EWW: <LOQ; EF = 0.70–1.0.	
Ephedrine			IWW: <LOQ—15171 ng L^{-1}; EF = 0.81–1.0; EWW: <LOQ—84.1 ng L^{-1}; EF = 0.72–1.0.	
Venlafaxine			IWW: 28.8–325.5 ng L^{-1}; EF = 0.35–0.65; EWW: 25–222 ng L^{-1}; EF = 0.46–0.69.	
Atenolol			IWW: 4288–19160 ng L^{-1}; EF = 0.30–0.47; EWW: 1480–18831 ng L^{-1}; EF = 0.40–0.61.	

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_2O-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 (−) Pseudophedrine 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_2O-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^{-1}; (*R*)-form 39.5–212.9 ng L^{-1}; 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^{-1}; E2 < MQL—13.9 ng L^{-1}; EF = 0.53–0.72; EWW: E1 n.d.–4.0 ng L^{-1}; E2 < MQL—10.0 ng L^{-1}; EF = 0.71 IWW: 14.3–72.3 ng L^{-1}; EWW: <MQL—14.8 ng L^{-1}; IWW: 51.0–329.7 ng L^{-1}; EWW: <MQL—27.7 ng L^{-1}; n.d. IWW: E1 57.2–286.5 ng L^{-1}; E2 56.7–343.8 ng L^{-1}; EF = 0.45–0.50; EWW: E1 80.2–178.2 ng L^{-1}; E2 123.7–248.3 ng L^{-1}; 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*).	***Spain*** 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.	**Portugal** Effluent wastewater from 3 WWTPs.	EF = 0.54–0.55 - - - - - -	[57]
Salbutamol	*LC-MS/MS*; Chirobiotic V column (250 mm x 2.1 mm i.d., 5 µm); Methanol(4 mM ammonium acetate)-formic acid (99.95:0.005, *v*/*v*).	***Italy*** 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 Temazepan	*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 temazepan; Methanol-20 mM ammonium acetate aqueous solution (90:10, *v*/*v*), 0.1% formic acid (pH 4).	***Canada*** 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).	***Canada*** Raw and treated wastewater from a tertiary WWTP (Alberta).	IWW: 971 ± 30 ng L^{-1}; EWW: 664 ± 22 ng L^{-1}; IWW: 307 ± 18 ng L^{-1}; EWW: 207 ± 11 ng L^{-1}; IWW: 18 ± 2 ng L^{-1}; EWW: 14 ± 0.1 ng L^{-1}; IWW: 411 ± 15 ng L^{-1}; EWW: 375 ± 24 ng L^{-1}; IWW: 51 ± 2 ng L^{-1}; EWW: 20 ± 0.5 ng L^{-1}; IWW: <MQL; EWW: <MQL; IWW: 10 ± 1 ng L^{-1}; EWW: 45 ± 1 ng L^{-1}; IWW: 20 ± 3 ng L^{-1}; EWW: 17 ± 1 ng L^{-1}; IWW: 529 ± 10 ng L^{-1}; EWW: 466 ± 24 ng L^{-1}.	[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).	***Canada*** Influents and effluents wastewaters from 1 rural aerated lagoon and 2 urban tertiary WWTP (Alberta).	160–1100 ng L^{-1}; EF ≈ 0.5 (both influent and effluent). 170–520 ng L^{-1}; EF = 0.5 (influent) EF ≠ 0.50 (effluent). 20–92 ng L^{-1}; 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 α-methoxy-α-(trifluoromethyl)phenylacetic acid*; MDN-5S column (30-m, 0.25-mm i.d., 0.25-μm 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^{-1}; EF = 0.42–0.53. 13–250 ng L^{-1}; EF = 0.50 ± 0.02. 3–160 ng L^{-1}; EF ≤ 0.42.	[61].
Metoprolol	*GC-MS after diastereomer formation with the chiral derivatizing reagent (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid);* MDN-5S column (30-m, 0.25-mm i.d., 0.25-μm film thickness), carrier gas helium.	***USA*** River water (Trinity River, Dallas, TX); Effluent wastewater.	10–571 ng L^{-1}; EF = 0.31–0.44. <1–2269 ng L^{-1}; EF = 0.50 ± 0.03.	[85].
Metoprolol	*LC-MS/MS*; Reprosil AGP column (100 × 2 mm i.d., 5 μm); H_2O-acetonitrile (98:2, *v*/*v*), containing 10 mM ammonium acetate.	***Germany*** River water (stretch of river Gründlach, Northern Bavaria).	42–440 ng L^{-1}; EF = 0.43–0.49.	[75]
Metoprolol and two of its metabolites: α-Hydroxymetoprolol (α-OH-metoprolol) Deaminated metoprolol (COOH-metoprolol)	*LC-MS/MS*; enantiomers of metoprolol and four stereoisomers of α-OH-metoprolol: in-line high-pressure filter (4 mm, 0.5 μm) and a Chiral-CBH column (100 × 2.0 mm i.d., 5 μm) 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 α-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 μm) and a Chiral AGP column (100 mm × 2.0 mm, 5 μm) with a Chiral-AGP guard column (10 × 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: α-Hydroxymetoprolol Metoprolol acid O-desmethylmetoprolol	*LC-MS/MS*; CHIROBIOT V (250 mm × 4.6 mm i.d., 5 μm); Mobile phase not referred. H_2O-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 × 4.6 mm i.d., 5 μm); 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 (±0.07) ng L^{-1}; (*R*)-propranolol: 1.35 (±0.07) ng L^{-1}.	[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*)	***Spain*** 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)-â-cyclodextrin; 1:1 diluted with OV1701) fused silica column (16 m, i.d. 0.25 mm)	***Switzerland*** Lake, rivers and sea water (North Sea) Influents wastewaters Effluent wastewaters after secondary treatment.	n.d.—7.8 ng L^{-1}; ER = 0.7–4.2. 990–3300 ng L^{-1}; ER = 5.8–8.0. 2–81 ng L^{-1}; 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-b-cyclodextrin as CSP, carrier gas helium.	***Spain*** 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*).	***Spain*** Influents and effluents 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.	***Australia*** 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.	***Australia*** Effluent wastewater from a tertiary wastewater treatment plant (Sydney)	4.6–120 ng L^{-1}; EF = 0.49–0.62; 3.1–207 ng L^{-1}; EF = 0.54–0.66; 1.6–178.9 ng L^{-1}; 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.	***Australia*** 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*).	***Japan*** 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_2O (35:65, *v*/*v*).	***Brazil*** Influent and effluent wastewater; River water (Monjolinho River; São Carlos, SP).	Lansoprazole: n.d.; Pantoprazole: 0.15–0.18 µgL^{-1} in treated effluents; 0.013 µgL^{-1} 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_2O (35:65, *v*/*v*).	***Brazil*** Influent and effluent wastewater; River water (Monjolinho River; São Carlos, SP). ***Portugal*** 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*)	***China*** 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*).	***France*** 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)	***Israel*** 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 µm) and a Chiral AGP column (100 mm × 2.0 mm, 5 µm) with a Chiral-AGP guard column (10 mm × 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 × 4.6 mm i.d., 5 µm); 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 × 4.6 mm i.d., 5 µm). 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*; α1-acid glycoprotein column (100 mm × 4.0 mm i.d., 5 µm); 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 × 2 mm i.d., 5.0 µm) with a HSA guard column (10 mm × 2 mm i.d.); Acetonitrile-H_2O (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^{-1}; EF = 0.48; EWW: <MQL—12.4 ng L^{-1}; EF = 0.48; Sludge: 230.9–231.9 ng g^{-1} (dw); EF = 0.49–0.50.	[74]
Econazole Miconazole Tebuconazole Propiconazole	*LC-MS/MS;* AGP column (100 mm × 4 mm i.d., 5.0 µm) with an AGP guard column (10 mm × 4 mm i.d.); Gradient of H_2O containing 10 mM ammonium acetate (pH 7.0) and acetonitrile.		IWW: 1–1.2 ng L^{-1}; EF not determined; EWW: 0.29–0.51 ng L^{-1}; EF not determined; Sludge: 8.3–120.8 ng g^{-1} (dw); EF = 0.50–0.51; IWW: 6.0–11.3 ng L^{-1}; EF = 0.50; EWW: 0.25–0.87 ng L^{-1}; EF = 0.47; Sludge: 87.9–1258.0 ng g^{-1} (dw); EF = 0.49–0.50.	
			n.d.; n.d.	

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 α-hexachlorocyclohexane (lindane, α-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 α-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 α-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 α-HCH enantiomers was evaluated for the first time in a study developed by Faller et at in 1991 [97] in North Sea regions. In this study, concentrations of the isomers α-HCH and γ-HCH were up to 2.89 and 2.72 ng L^{-1} respectively [97]. The authors found that the ER of (+/-) α-HCH varied among the different regions of the North Sea. The relation (+/-) α-HCH was lower than 1 in an area of the North Sea where concentrations of γ-HCH were higher than α-HCH. This result suggested a possible transformation of (-)-α-HCH from γ-HCH. In contrast, in another North Sea area, the ER of (+/-) α-HCH was higher than 1 suggesting a different microbiological process in this region. In this case, (-)-α-HCH was degraded preferably than (+)-α-HCH. The authors showed that different microbiological process influenced the degradation of α-HCH isomers and suggested a correlation between the ER of (+/-) α-HCH and the concentrations of isomers α-HCH and γ-HCH. Another study developed by Padma et al. 2003 investigated the variation in ER of α-HCH enantiomers in the York river estuary due to the microbiological activity (Table 2) [114]. Surprising, the α-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 α-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 DCPP and MCPP [124]. Results showed that both enantiomers (*R* and *S*) of MCPP were found though only the (*R*)-enantiomer was registered and used as an herbicide in Switzerland. The pesticide DCPP was hardly present. Authors suggested enantioselective degradation of MCPP and DCPP in soil leading to residues enriched in (*R*)-enantiomers. A biodegradation study of MCPP 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 MCPP from another source. Laboratory incubation of MCPP and DCPP in lake and river water confirmed significant racemization [124]. The racemization was biologically mediated and led to residues of MCPP and DCPP in these waters, which were enriched in the (*S*)-enantiomers. Gerecke et al. also reported ER of MCPP [125]. MCPP is used in a racemic ratio (*R*/*S*-MCPP) in urban areas for protection and conservation of materials, whereas only (*R*)-MCPP 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 α-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 suspend 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	α-HCH	*GC-ECD* heptakis (3-*O*-butyryl-2,6-di-*O*-pentyl)-β-CD (60 m), carrier gas hydrogen	***North Sea regions***	α-HCH: 0.54–2.86 ng L^{-1} ER (+/-, α-HCH)= 0.88–1.19 γ-HCH: 0.31–2.72 ng L^{-1}	[97]
	α-HCH	*GC-ECD* β-dex 120 chiral column	***USA*** York river estuary	(+) α-HCH: 11.6–79.3 pg L^{-1} (-) α-HCH: 20.6–103.0 pg L^{-1} ER (+/-, α-HCH) = 0.71–1.06	[114]
	α-HCH	*GC-ECD* γ-DEX 120 column (20%-γ-CD, 20 m, i.d. 0.25 mm, 0.25 μm film thickness), carrier gas hydrogen	***Island*** Water rivers and lakes	α-HCH: 1.2–5.8 ng L^{-1} γ-HCH: 0.23–0.65 ng L^{-1} ER (α/γ, HCH) = 3.5–13.8	[142]
	α-HCH	*GC-ECD* column A: heptakis (3-*O*-butyryl-2,6-di-*O*-pentyl)-β-CD (25 m, i.d. 0.25 mm); column B: 50% heptakis (2,3,6-tri-*O*-n-pentyl)-β-CD and 50% OV1701(25 m, i.d. 0.25 mm), carrier gas helium	***North sea and Baltic sea***	γ-HCH: 2.0–7.7 ng L^{-1} α-HCH: 0.2–5.8 ng L^{-1} ER (γ/α, HCH) = 0.67–10.0 ER (+/-, α-HCH) = 0.81–0.92	[99]
	α-HCH	*GC-MS* 30% tert-butyldimethylsilylated-β-CD in PS-086 (20 m, i.d. 0.25 mm, 0.25 μm film thickness)	***Arctic regions*** water from Bering and Chukchi Seas	α-HCH: 0.05–5.32 ng L^{-1} γ-HCH: 0.10–1.33 ng L^{-1} ER (α/γ, HCH) = 0.35–12.40	[121]
	α-HCH	*GC-MS* Beta-DEX (20% permethylated-β-CD in polydimethylsiloxane, (30 m, i.d. 0.25 mm, 0.25 μm film thickness) and BGB-172 (20% tert-butyldimethylsilylated-β-CD in OV-1701, (30 m, i.d. 0.25 mm, 0.25 μm film thickness), carrier gas helium	***Arctic Ocean*** Surface water	ER (+/-,α-HCH) = 0.68–1.09	[143]
	α-HCH	*GC-MS* Betadex-120 (20% permethylated β-CD in methyl phenylpolysiloxane (30 m, i.d. 0.25 mm)	***Canada*** Lake Ontario and Niagara River Rain water	ER (+/-, α-HCH) = 0.86 ER (+/-, α-HCH) = 0.99	[112]
	α-HCH	*Not described*	***Scotland*** Kintyre Peninsula Air	EF (α-HCH) = 0.480	[144]
	α-HCH	*GC-MS* 20% tert-butyldimethylsilylated β-cyclodextrin in OV-1701	***China*** Pearl River Delta	EF(α-HCH) = 0.104–0.910	[12]

Table 2. *Cont.*

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
α-HCH	*GC-MS* BGB (20% tert-butyldimethylsilylated β-CD, 30 m, i.d. 0.25 mm, 0.25 μm film thickness), carrier gas helium	***USA*** Alabama Agricultural soil Cemeteries	EF(α-HCH) = 0.48–0.53 EF(α-HCH) = 0.50	[113]
PCCH	*GC-ECD* column A: heptakis (3-*O*-butyryl-2,6-di-*O*-pentyl)-β-CD (25 m, i.d. 0.25 mm); column B: 50% heptakis (2,3,6-tri-O-n-pentyl)-β-CD and 50% OV1701(25 m, i.d. 0.25 mm), carrier gas helium	***North sea and Baltic sea***	ER (γ_1/γ_2) PCCH = 1.12–1.17 ER (β_1/β_2) PCCH = 0.97	[99]
bromocyclin	*GC-ECD* 50% heptakis(6-*O*-tert-butyl-dimethylsilyl-2,3-di-*O*-methyt)-β-CD and 50% OV-I7O1 ~*w*/*w* (25 m, i.d. 0.25 mm, 0.125 μm film thickness) carrier gas hydrogen	***Germany*** River Stör WWTPs	n.d.–261 pg L^{-1}; ER (-/+) = 1.01–1.0 760–11,500 pg L^{-1}	[126]
MCPP	*GC-MS* FS 71 PS-086 + 20% Me-β-CD, (15 m, 0.25 mm i.d., 0.13 μm film thickness)	***Switzerland*** Rain water	R-MCPP: up to 50 ng L^{-1} S-MCPP: up to 19 ng L^{-1}	[115]
MCPP	*GC-MS* OV1701-TBDM (TBDM, heptakis-(6-*O*-tert-butyldimethylsilyl-2,3-di-*O*-methyl)-β-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^{-1} S-MCPP: <0.2 to 121 ng L^{-1} 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-β-CD, (15 m, 0.25 mm i.d., 0.13 μm film thickness)	***Switzerland*** Rain water	R-dichlorprop: up to 106 ng L^{-1} S-dichlorprop: up to 11 ng L^{-1}	[115]
DCPP	*GC-MS* OV1701-TBDM (TBDM, heptakis-(6-*O*-tert-butyldimethylsilyl-2,3-di-*O*-methyl)-β-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^{-1} S-DCPP: <0.2 to 2.7 ng L^{-1}	[124]

Table 2. *Cont.*

Chiral Compound	Analytical Method	Location/Matrix	Concentration/ER, EF	Ref.
TC	*GC-MS* BGB-172 (20% tert-butyldimethylsilylated-β-CD in OV-1701, (30 m, i.d. 0.25 mm, 0.25 μm 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-butyldimethylsilylated β-cyclodextrin in OV-1701	***China*** Pearl River Delta	EF (TC) = 0.112–0.734	[12]
TC	*GC-MS* Betadex (20% permethylated β-CD, 30 m, i.d. 0.25 mm, 0.25 μm 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-butyldimethylsilylated-β-CD in OV-1701, (30 m, i.d. 0.25 mm, 0.25 μm 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-butyldimethylsilylated β-cyclodextrin in OV-1701	***China*** Pearl River Delta	EF (CC) = 0.043–0.813	[12]
CC	*GC-MS* Betadex (20% permethylated β-CD, 30 m, i.d. 0.25 mm, 0.25 μm 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-butyldimethylsilylated β-CD, 30 m, i.d. 0.25 mm, 0.25 μm 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-butyldimethylsilylated β-CD, 30 m, i.d. 0.25 mm, 0.25 μm 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 β-CD, 30 m, i.d. 0.25 mm, 0.25 μm film thickness), carrier gas helium	***USA*** Alabama Agricultural soil Cemeteries	EF (MC5) = 0.25–0.46 EF (MC5) = 0.41–0.47	[113]
	DDT	*GC-MS* 20% tert-butyldimethylsilylated β-cyclodextrin in OV-1701	***China*** Pearl River Delta	EF (o,p′-DDT) = 0.102–0.801	[12]
	DDT	*GC-MS* BGB (20% tert-butyldimethylsilylated β-CD, 30 m, i.d. 0.25 mm, 0.25 μm film thickness), carrier gas helium	***USA*** Alabama Agricultural soil Cemeteries	EF (o,p′-DDT) = 0.41–0.55 EF (o,p′-DDT) = 0.50–0.57	[113]
PBs	PCB 91	*GC-ECD and GC-MS* Chirasil-Dex	***USA*** Lake Hartwell sediment	ER (first/second enantiomer) = 0.56	[110]
	PCBs 95, 132, and 149	*GC-ECD* Chirasil-Dex (10 m, i.d. 0.25 mm, 0.2 μm film thickness), carrier gas hydrogen	***Germany*** River Elsenz	ER (PCBs 95, 132, and 149) ~1	[138]
	PCB 95	*GC-ECD* Chirasil-Dex CB (25 m, i.d. 0.25 mm 0.25 μm film thickness), carrier gas hydrogen	***USA*** 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	***USA*** 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-β-CD (25 m × 0.25 mm × 0.25 μm film thickness)	***U.K*** 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-butyldimethylsilyl-β-CD in DV-1701 (25 m, i.d.0.25 mm, 0.25 μm film thickness), carrier gas helium	***Korea*** Nakdong River WWTPs Influent Effluent	<18.0–342.0 ng L^{-1}; ER (trans-HHCB) = 0.86–1.09 ER (cis-HHCB) = 0.95–1.10 <785.0–3491 ng L^{-1}; ER (trans-HHCB) = 0.91–1.01 ER (cis-HHCB) = 1.03–1.14 <284.0–576.0 ng L^{-1}; 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 μm film thickness) OV 1701 capillary column, carrier gas helium	***Switzerland*** 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)-a-cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	1679 ng L^{-1}; EF = 0.25/0.25/0.26; 28.1 ng L^{-1}; 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 μm film thickness) OV 1701 capillary column, carrier gas helium	***Switzerland*** 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)-a-cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	31.2 ng L^{-1}; EF = 0.50; 4.6 ng L^{-1}; EF = 0.50;	[70]
	AHDI	*GC-MS/MS* Cyclosil-B: heptakis (2,3-di-*O*-methyl-6-*O*-tert-butyldimethylsilyl-β-CD in DV-1701 (25 m, i.d.0.25 mm, 0.25 μm film thickness), carrier gas helium	***Korea*** Nakdong River WWTPs Influent Effluent	<69.0 ng L^{-1} <69.0 ng L^{-1}	[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	***Switzerland*** WWTPs Influent Effluent Sewage sludge Aerobic Anaerobic	 ER = 0.97 ER = 1.19 ER = 1.16 ER = 0.95	[140]
ATII	*GC-MS/MS* Cyclosil-B: heptakis (2,3-di-*O*-methyl-6-*O*-tert-butyldimethylsilyl-β-CD in DV-1701 (25 m, i.d.0.25 mm, 0.25 µm film thickness), carrier gas helium	***Korea*** Nakdong River WWTPs Influent Effluent	 <107.0 ng L^{-1} <107.0 ng L^{-1}	[139]
ATII	*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	***Switzerland*** WWTPs Influent Effluent Sewage sludge Aerobic Anaerobic	 ER = 0.86 ER = 2.94 ER = 0.92 ER = 0.79	[140]
ATII	*GC-MS*; Chiral heptakis (2,3-di-*O*-methyl-6-*O*-t-butyl dimethylsilyl)-a-cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	5.0 ng L^{-1}; EF = 0.55; n.d.	[70]
DPMI	*GC-MS/MS* Cyclosil-B: heptakis (2,3-di-O-methyl-6-O-tert-butyldimethylsilyl-β-CD in DV-1701 (25 m, i.d.0.25 mm, 0.25 µm film thickness), carrier gas helium	***Korea*** Nakdong River WWTPs Influent Effluent	 <79.0 ng L^{-1} <79.0 ng L^{-1}	[139]
DPMI	*GC-MS*; Chiral heptakis (2,3-di-*O*-methyl-6-*O*-t-butyl dimethylsilyl)-a-cyclodextrin column combined with a (non-chiral) HP-5MS column.	Effluent wastewater biologically treated; Advanced treated recycled water.	66.6 ng L^{-1}; EF = 0.48. 2.2 ng L^{-1}; 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; ATII: 5-acetyl-1,1,2,6-tetramethyl-3-isopropyl-indane; CC: cis-chlordane; CD: cyclodextrin; DCPP: 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-l,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; MCPP: 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-l-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 (µg/L—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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References

1. Murray, K.E.; Thomas, S.M.; Bodour, A.A. Prioritizing research for trace pollutants and emerging contaminants in the freshwater environment. *Environ. Pollut.* **2010**, *158*, 3462–3471. [CrossRef] [PubMed]
2. Han, D.; Currell, M.J. Persistent organic pollutants in China's surface water systems. *Sci. Total Environ.* **2017**, *580*, 602–625. [CrossRef] [PubMed]
3. Ribeiro, C.; Ribeiro, A.R.; Tiritan, M.E. Priority substances and emerging organic pollutants in portuguese aquatic environment: A Review. *Rev. Environ. Contam. Toxicol.* **2015**, *238*, 1–44.
4. Barbosa, M.O.; Moreira, N.F.F.; Ribeiro, A.R.; Pereira, M.F.R.; Silva, A.M.T. Occurrence and removal of organic micropollutants: An overview of the watch list of EU decision 2015/495. *Water Res.* **2016**, *94*, 257–279. [CrossRef] [PubMed]
5. Ribeiro, A.R.; Castro, P.M.L.; Tiritan, M.E. Environmental fate of chiral pharmaceuticals: Determination, degradation and toxicity. In *Environmental Chemistry for a Sustainable World*; Lichtfouse, E., Schwarzbauer, J., Robert, D., Eds.; Springer: Dordrecht, The Netherlands, 2012; Volume 2, pp. 3–45.
6. Song, Q.; Zhang, Y.; Yan, L.; Wang, J.; Lu, C.; Zhang, Q.; Zhao, M. Risk assessment of the endocrine-disrupting effects of nine chiral pesticides. *J. Hazard. Mater.* **2017**, *338*, 57–65. [CrossRef] [PubMed]
7. Albuquerque, N.C.P.; Carrão, D.B.; Habenschus, M.D.; Oliveira, A.R.M. Metabolism studies of chiral pesticides: A critical review. *J. Pharm. Biomed. Anal.* **2017**, in press. [CrossRef] [PubMed]
8. Ye, J.; Zhao, M.; Liu, J.; Liu, W. Enantioselectivity in environmental risk assessment of modern chiral pesticides. *Environ. Pollut.* **2010**, *158*, 2371–2383. [CrossRef] [PubMed]

9. Winkler, M.; Lawrence, J.R.; Neu, T.R. Selective degradation of ibuprofen and clofibric acid in two model river biofilm systems. *Water Res.* **2001**, *35*, 3197–3205. [CrossRef]
10. Wong, C.S.; Garrison, A.W.; Foreman, W.T. Enantiomeric composition of chiral polychlorinated biphenyl atropisomers in aquatic bed sediment. *Environ. Sci. Technol.* **2001**, *35*, 33–39. [CrossRef] [PubMed]
11. Lao, W.; Gan, J. Enantioselective degradation of warfarin in soils. *Chirality* **2012**, *24*, 54–59. [CrossRef] [PubMed]
12. Li, J.; Zhang, G.; Qi, S.; Li, X.; Peng, X. Concentrations, enantiomeric compositions, and sources of HCH, DDT and chlordane in soils from the Pearl River Delta, South China. *Sci. Total Environ.* **2006**, *372*, 215–224. [CrossRef] [PubMed]
13. Bagnall, J.; Malia, L.; Lubben, A.; Kasprzyk-Hordern, B. Stereoselective biodegradation of amphetamine and methamphetamine in river microcosms. *Water Res.* **2013**, *47*, 5708–5718. [CrossRef] [PubMed]
14. Maia, A.S.; Ribeiro, A.R.; Castro, P.M.L.; Tiritan, M.E. Chiral Analysis of Pesticides and Drugs of Environmental Concern: Biodegradation and Enantiomeric Fraction. *Symmetry* **2017**, *9*, 196. [CrossRef]
15. IUPAC. Basic terminology of stereochemistry. *Pure Appl. Chem.* **1996**, *68*, 2193–2222.
16. Testa, B.; Caldwell, J.; Kisakürek, M.V. *Organic Stereochemistry: Guiding Principles and Biomedicinal Relevance*; Wiley-VCH: Berlin, Germany, 2014.
17. Solomons, T.W.G. *Organic Chemistry*, 10th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2011.
18. Allenmark, S. *Chromatographic Enantioseparation: Methods and Applications*, 2nd ed.; Ellis Horwood Ltd.: London, UK, 1991.
19. Eliel, E.L.; Wilen, S.H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, NY, USA, 1994; p. 1267.
20. Tiritan, M.E.; Ribeiro, A.R.; Fernandes, C.; Pinto, M.M.M. Chiral Pharmaceuticals. In *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons, Inc.: New York, NY, USA, 2016.
21. Mannschreck, A.; Kiesswetter, R.; von Angerer, E. Unequal activities of enantiomers via biological receptors: Examples of chiral drug, pesticide, and fragrance molecules. *J. Chem. Educ.* **2007**, *84*, 2012–2018. [CrossRef]
22. Lima, V.L.E. Drugs and chirality: A brief overview. *Quim. Nova* **1997**, *20*, 657–663. [CrossRef]
23. Nunez, M.C.; Garcia-Rubino, M.E.; Conejo-Garcia, A.; Cruz-Lopez, O.; Kimatrai, M.; Gallo, M.A.; Espinosa, A.; Campos, J.M. Homochiral drugs: A demanding tendency of the pharmaceutical industry. *Curr. Med. Chem.* **2009**, *16*, 2064–2074. [CrossRef] [PubMed]
24. Wainer, I.W.; Drayer, D.E. *Drug Stereochemistry: Analytical Methods and Pharmacology (Clinical Pharmacology, No 18)*, 2nd ed.; Marcel Dekker: New York, NY, USA, 1993; p. 432.
25. Gal, J. Chiral drugs from a historical point of view. In *Chirality in Drug Research*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2006; pp. 1–26.
26. Ribeiro, A.R.; Afonso, C.M.; Castro, P.M.L.; Tiritan, M.E. Enantioselective biodegradation of pharmaceuticals, alprenolol and propranolol, by an activated sludge inoculum. *Ecotoxicol. Environ. Saf.* **2013**, *87*, 108–114. [CrossRef] [PubMed]
27. Ribeiro, A.R.; Afonso, C.M.; Castro, P.M.L.; Tiritan, M.E. Enantioselective HPLC analysis and biodegradation of atenolol, metoprolol and fluoxetine. *Environ. Chem. Lett.* **2013**, *11*, 83–90. [CrossRef]
28. Maia, A.S.; Castro, P.M.L.; Tiritan, M.E. Integrated liquid chromatography method in enantioselective studies: Biodegradation of ofloxacin by an activated sludge consortium. *J. Chromatogr. B* **2016**, *1029–1030*, 174–183. [CrossRef] [PubMed]
29. Moreira, I.S.; Amorim, C.L.; Ribeiro, A.R.; Mesquita, R.B.R.; Rangel, A.O.S.S.; van Loosdrecht, M.C.M.; Tiritan, M.E.; Castro, P.M.L. Removal of fluoxetine and its effects in the performance of an aerobic granular sludge sequential batch reactor. *J. Hazard. Mater.* **2015**, *287*, 93–101. [CrossRef] [PubMed]
30. Amorim, C.L.; Moreira, I.S.; Ribeiro, A.R.; Santos, L.H.M.L.M.; Delerue-Matos, C.; Tiritan, M.E.; Castro, P.M.L. Treatment of a simulated wastewater amended with a chiral pharmaceuticals mixture by an aerobic granular sludge sequencing batch reactor. *Int. Biodeterior. Biodegrad.* **2016**, *115*, 277–285. [CrossRef]
31. Buerge, I.J.; Poiger, T.; Müller, M.D.; Buser, H.-R. Influence of pH on the stereoselective degradation of the fungicides epoxiconazole and cyproconazole in soils. *Environ. Sci. Technol.* **2006**, *40*, 5443–5450. [CrossRef] [PubMed]
32. Liang, C.; Huang, J.; Zhang, X. Effects of engineered nanoparticles on the enantioselective transformation of metalaxyl agent and commercial metalaxyl in agricultural soils. *J. Agric. Food Chem.* **2016**, *64*, 7688–7695. [CrossRef] [PubMed]

33. Sunsandee, N.; Ramakul, P.; Hronec, M.; Pancharoen, U.; Leepipatpiboon, N. Mathematical model and experimental validation of the synergistic effect of selective enantioseparation of (S)-amlodipine from pharmaceutical wastewater using a HFSLM. *J. Ind. Eng. Chem.* **2014**, *20*, 1612–1622. [CrossRef]
34. Székely, G.; Csordás, B.; Farkas, V.; Kupai, J.; Pogány, P.; Sánta, Z.; Szakács, Z.; Tóth, T.; Hollósi, M.; Nyitrai, J.; et al. Synthesis and Preliminary Structural and Binding Characterization of New Enantiopure Crown Ethers Containing an Alkyl Diarylphosphinate or a Proton-Ionizable Diarylphosphinic Acid Unit. *Eur. J. Org. Chem.* **2012**, *2012*, 3396–3407.
35. Hauser, A.W.; Mardirossian, N.; Panetier, J.A.; Head-Gordon, M.; Bell, A.T.; Schwerdtfeger, P. Functionalized graphene as a gatekeeper for chiral molecules: An alternative concept for chiral separation. *Angew. Chem. Int. Ed.* **2014**, *53*, 9957–9960. [CrossRef] [PubMed]
36. Kupai, J.; Rojik, E.; Huszthy, P.; Szekely, G. Role of Chirality and macroring in imprinted polymers with enantiodiscriminative power. *ACS Appl. Mater. Interfaces* **2015**, *7*, 9516–9525.
37. Ghazali, N.F.; Ferreira, F.C.; White, A.J.P.; Livingston, A.G. Enantiomer separation by enantioselective inclusion complexation–organic solvent nanofiltration. *Tetrahedron Asymmetry* **2006**, *17*, 1846–1852. [CrossRef]
38. Rukhlenko, I.D.; Tepliakov, N.V.; Baimuratov, A.S.; Andronaki, S.A.; Gun'ko, Y.K.; Baranov, A.V.; Fedorov, A.V. Completely chiral optical force for enantioseparation. *Sci. Rep.* **2016**, *6*, 36884. [CrossRef] [PubMed]
39. Reich, S.; Schurig, V. Stopped-flow multidimensional gas chromatography: A new method for the determination of enantiomerization barriers. *J. Microcolumn Sep.* **1999**, *11*, 475–479. [CrossRef]
40. Reich, S.; Trapp, O.; Schurig, V. Enantioselective stopped-flow multidimensional gas chromatography: Determination of the inversion barrier of 1-chloro-2,2-dimethylaziridine. *J. Chromatogr. A* **2000**, *892*, 487–498. [CrossRef]
41. Schurig, V.; Reich, S. Determination of the rotational barriers of atropisomeric polychlorinated biphenyls (PCBs) by a novel stopped-flow multidimensional gas chromatographic technique. *Chirality* **1998**, *10*, 316–320. [CrossRef]
42. Welch, C.J. Evolution of chiral stationary phase design in the Pirkle laboratories. *J. Chromatogr. A* **1994**, *666*, 3–26. [CrossRef]
43. Vetter, W. Gas Chromatographic Enantiomer Separation of Polychlorinated Biphenyls (PCBs): Methods, Metabolisms, Enantiomeric Composition in Environmental Samples and their Interpretation. *Isr. J. Chem.* **2016**, *56*, 940–957. [CrossRef]
44. Vetter, W.; Bester, K. Gas chromatographic enantioseparation of chiral pollutants-techniques and results. *Chiral Anal.* **2006**, 131–213. [CrossRef]
45. Ward, T.J.; Ward, K.D. Chiral separations: A review of current topics and trends. *Anal. Chem.* **2012**, *84*, 626–635. [CrossRef] [PubMed]
46. Zhang, Y.; Wu, D.R.; Wang-Iverson, D.B.; Tymiak, A.A. Enantioselective chromatography in drug discovery. *Drug Discov. Today* **2005**, *10*, 571–577. [CrossRef]
47. Ward, T.J.; Ward, K.D. Chiral Separations: Fundamental Review 2010. *Anal. Chem.* **2010**, *82*, 4712–4722. [CrossRef] [PubMed]
48. Taylor, D.R.; Maher, K. Chiral separations by high-performance liquid chromatography. *J. Chromatogr. Sci.* **1992**, *30*, 67. [CrossRef]
49. Haginaka, J. Pharmaceutical and biomedical applications of enantioseparations using liquid chromatographic techniques. *J. Pharm. Biomed. Anal.* **2002**, *27*, 357–372. [CrossRef]
50. Lämmerhofer, M. Chiral recognition by enantioselective liquid chromatography: Mechanisms and modern chiral stationary phases. *J. Chromatogr. A* **2010**, *1217*, 814–856. [CrossRef] [PubMed]
51. Ribeiro, A.R.; Maia, A.S.; Cass, Q.B.; Tiritan, M.E. Enantioseparation of chiral pharmaceuticals in biomedical and environmental analyses by liquid chromatography: An overview. *J. Chromatogr. B* **2014**, *968*, 8–21. [CrossRef] [PubMed]
52. Fernandes, C.; Tiritan, M.E.; Pinto, M. Small molecules as chromatographic tools for HPLC enantiomeric resolution: Pirkle-Type chiral stationary phases evolution. *Chromatographia* **2013**, *76*, 871–897. [CrossRef]
53. Haginaka, J. Recent progresses in protein-based chiral stationary phases for enantioseparations in liquid chromatography. *J. Chromatogr. B* **2008**, *875*, 12–19. [CrossRef] [PubMed]

54. Barreiro, J.C.; Vanzolini, K.L.; Madureira, T.V.; Tiritan, M.E.; Cass, Q.B. A column-switching method for quantification of the enantiomers of omeprazole in native matrices of waste and estuarine water samples. *Talanta* **2010**, *82*, 384–391. [CrossRef] [PubMed]
55. Barreiro, J.C.; Vanzolini, K.L.; Cass, Q.B. Direct injection of native aqueous matrices by achiral–chiral chromatography ion trap mass spectrometry for simultaneous quantification of pantoprazole and lansoprazole enantiomers fractions. *J. Chromatogr. A* **2011**, *1218*, 2865–2870. [CrossRef] [PubMed]
56. Kruve, A.; Rebane, R.; Kipper, K.; Oldekop, M.-L.; Evard, H.; Herodes, K.; Ravio, P.; Leito, I. Tutorial review on validation of liquid chromatography–mass spectrometry methods: Part II. *Anal. Chim. Acta* **2015**, *870*, 8–28. [CrossRef] [PubMed]
57. Ribeiro, A.R.; Santos, L.H.M.L.M.; Maia, A.S.; Delerue-Matos, C.; Castro, P.M.L.; Tiritan, M.E. Enantiomeric fraction evaluation of pharmaceuticals in environmental matrices by liquid chromatography-tandem mass spectrometry. *J. Chromatogr. A* **2014**, *1363*, 226–235. [CrossRef] [PubMed]
58. Tian, M.; Zhang, Q.; Shi, H.; Gao, B.; Hua, X.; Wang, M. Simultaneous determination of chiral pesticide flufiprole enantiomers in vegetables, fruits, and soil by high-performance liquid chromatography. *Anal. Bioanal. Chem.* **2015**, *407*, 3499–3507. [CrossRef] [PubMed]
59. Silva, V.P.A.; Paz, M.S.O.; Cavalcante, R.M.; Nascimento, R.F. Strategy for correction of matrix effect on the determination of pesticides in water bodies using SPME-GC-FID. *J. Braz. Chem. Soc.* **2017**, *28*, 1081–1090. [CrossRef]
60. Buser, H.-R.; Poiger, T.; Müller, M.D. Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. *Environ. Sci. Technol.* **1999**, *33*, 2529–2535. [CrossRef]
61. Fono, L.J.; Sedlak, D.L. Use of the chiral pharmaceutical propranolol to identify sewage discharges into surface waters. *Environ. Sci. Technol.* **2005**, *39*, 9244–9252. [CrossRef] [PubMed]
62. Barclay, V.K.H.; Tyrefors, N.L.; Johansson, I.M.; Pettersson, C.E. Chiral analysis of metoprolol and two of its metabolites, α-hydroxymetoprolol and deaminated metoprolol, in wastewater using liquid chromatography–tandem mass spectrometry. *J. Chromatogr. A* **2012**, *1269*, 208–217. [CrossRef] [PubMed]
63. Luo, M.; Liu, D.; Zhou, Z.; Wang, P. A new chiral residue analysis method for triazole fungicides in water using dispersive liquid-liquid microextraction (DLLME). *Chirality* **2013**, *25*, 567–574. [CrossRef] [PubMed]
64. Zhao, P.; Deng, M.; Huang, P.; Yu, J.; Guo, X.; Zhao, L. Solid-phase extraction combined with dispersive liquid-liquid microextraction and chiral liquid chromatography-tandem mass spectrometry for the simultaneous enantioselective determination of representative proton-pump inhibitors in water samples. *Anal. Bioanal. Chem.* **2016**, *408*, 6381–6392. [CrossRef] [PubMed]
65. Caballo, C.; Sicilia, M.D.; Rubio, S. Enantioselective determination of representative profens in wastewater by a single-step sample treatment and chiral liquid chromatography-tandem mass spectrometry. *Talanta* **2015**, *134*, 325–332. [CrossRef] [PubMed]
66. Evans, S.E.; Davies, P.; Lubben, A.; Kasprzyk-Hordern, B. Determination of chiral pharmaceuticals and illicit drugs in wastewater and sludge using microwave assisted extraction, solid-phase extraction and chiral liquid chromatography coupled with tandem mass spectrometry. *Anal. Chim. Acta* **2015**, *882*, 112–126. [CrossRef] [PubMed]
67. Hashim, N.H.; Stuetz, R.M.; Khan, S.J. Enantiomeric fraction determination of 2-arylpropionic acids in a package plant membrane bioreactor. *Chirality* **2013**, *25*, 301–307. [CrossRef] [PubMed]
68. Baker, D.R.; Kasprzyk-Hordern, B. Spatial and temporal occurrence of pharmaceuticals and illicit drugs in the aqueous environment and during wastewater treatment: New developments. *Sci. Total Environ.* **2013**, *454–455*, 442–456. [CrossRef] [PubMed]
69. Kasprzyk-Hordern, B.; Baker, D.R. Estimation of community-wide drugs use via stereoselective profiling of sewage. *Sci. Total Environ.* **2012**, *423*, 142–150. [CrossRef] [PubMed]
70. Wang, L.; McDonald, J.A.; Khan, S.J. Enantiomeric analysis of polycyclic musks in water by chiral gas chromatography–tandem mass spectrometry. *J. Chromatogr. A* **2013**, *1303*, 66–75. [CrossRef] [PubMed]
71. López-Serna, R.; Kasprzyk-Hordern, B.; Petrović, M.; Barceló, D. Multi-residue enantiomeric analysis of pharmaceuticals and their active metabolites in the Guadalquivir River basin (South Spain) by chiral liquid chromatography coupled with tandem mass spectrometry. *Anal. Bioanal. Chem.* **2013**, *405*, 5859–5873. [CrossRef] [PubMed]
72. Li, Z.; Gomez, E.; Fenet, H.; Chiron, S. Chiral signature of venlafaxine as a marker of biological attenuation processes. *Chemosphere* **2013**, *90*, 1933–1938. [CrossRef] [PubMed]

73. Gasser, G.; Pankratov, I.; Elhanany, S.; Werner, P.; Gun, J.; Gelman, F.; Lev, O. Field and laboratory studies of the fate and enantiomeric enrichment of venlafaxine and O-desmethylvenlafaxine under aerobic and anaerobic conditions. *Chemosphere* **2012**, *88*, 98–105. [CrossRef] [PubMed]
74. Huang, Q.; Zhang, K.; Wang, Z.; Wang, C.; Peng, X. Enantiomeric determination of azole antifungals in wastewater and sludge by liquid chromatography–tandem mass spectrometry. *Anal. Bioanal. Chem.* **2012**, *403*, 1751–1760. [CrossRef] [PubMed]
75. Kunkel, U.; Radke, M. Fate of pharmaceuticals in rivers: Deriving a benchmark dataset at favorable attenuation conditions. *Water Res.* **2012**, *46*, 5551–5565. [CrossRef] [PubMed]
76. Bagnall, J.P.; Evans, S.E.; Wort, M.T.; Lubben, A.T.; Kasprzyk-Hordern, B. Using chiral liquid chromatography quadrupole time-of-flight mass spectrometry for the analysis of pharmaceuticals and illicit drugs in surface and wastewater at the enantiomeric level. *J. Chromatogr. A* **2012**, *1249*, 115–129. [CrossRef] [PubMed]
77. Kasprzyk-Hordern, B.; Baker, D.R. Enantiomeric profiling of chiral drugs in wastewater and receiving waters. *Environ. Sci. Technol.* **2012**, *46*, 1681–1691. [CrossRef] [PubMed]
78. Morante-Zarcero, S.; Sierra, I. Comparative HPLC methods for β-blockers separation using different types of chiral stationary phases in normal phase and polar organic phase elution modes. Analysis of propranolol enantiomers in natural waters. *J. Pharm. Biomed. Anal.* **2012**, *62*, 33–41. [CrossRef] [PubMed]
79. Morante-Zarcero, S.; Sierra, I. Simultaneous enantiomeric determination of propranolol, metoprolol, pindolol, and atenolol in natural waters by HPLC on new polysaccharide-based stationary phase using a highly selective molecularly imprinted polymer extraction. *Chirality* **2012**, *24*, 860–866. [CrossRef] [PubMed]
80. Hashim, N.H.; Khan, S.J. Enantioselective analysis of ibuprofen, ketoprofen and naproxen in wastewater and environmental water samples. *J. Chromatogr. A* **2011**, *1218*, 4746–4754. [CrossRef] [PubMed]
81. Barclay, V.K.H.; Tyrefors, N.L.; Johansson, I.M.; Pettersson, C.E. Trace analysis of fluoxetine and its metabolite norfluoxetine. Part I: Development of a chiral liquid chromatography–tandem mass spectrometry method for wastewater samples. *J. Chromatogr. A* **2011**, *1218*, 5587–5596. [CrossRef] [PubMed]
82. Kasprzyk-Hordern, B.; Kondakal, V.V.R.; Baker, D.R. Enantiomeric analysis of drugs of abuse in wastewater by chiral liquid chromatography coupled with tandem mass spectrometry. *J. Chromatogr. A* **2010**, *1217*, 4575–4586. [CrossRef] [PubMed]
83. Matamoros, V.; Hijosa, M.; Bayona, J.M. Assessment of the pharmaceutical active compounds removal in wastewater treatment systems at enantiomeric level. Ibuprofen and naproxen. *Chemosphere* **2009**, *75*, 200–205. [CrossRef] [PubMed]
84. Nikolai, L.N.; McClure, E.L.; MacLeod, S.L.; Wong, C.S. Stereoisomer quantification of the -blocker drugs atenolol, metoprolol, and propranolol in wastewaters by chiral high-performance liquid chromatography-tandem mass spectrometry. *J. Chromatogr. A* **2006**, *1131*, 103–109. [CrossRef] [PubMed]
85. Fono, L.J.; Kolodziej, E.P.; Sedlak, D.L. Attenuation of Wastewater-Derived Contaminants in an Effluent-Dominated River. *Environ. Sci. Technol.* **2006**, *40*, 7257–7262. [CrossRef] [PubMed]
86. Ribeiro, A.R.; Maia, A.S.; Moreira, I.S.; Afonso, C.M.; Castro, P.M.L.; Tiritan, M.E. Enantioselective quantification of fluoxetine and norfluoxetine by HPLC in wastewater effluents. *Chemosphere* **2014**, *95*, 589–596. [CrossRef] [PubMed]
87. Depaolini, A.R.; Fattore, E.; Cappelli, F.; Pellegrino, R.; Castiglioni, S.; Zuccato, E.; Fanelli, R.; Davoli, E. Source discrimination of drug residues in wastewater: The case of salbutamol. *J. Chromatogr. B* **2016**, *1023–1024*, 62–67. [CrossRef] [PubMed]
88. Huang, Q.; Wang, Z.; Wang, C.; Peng, X. Chiral profiling of azole antifungals in municipal wastewater and recipient rivers of the Pearl River Delta, China. *Environ. Sci. Pollut. R.* **2013**, *20*, 8890–8899. [CrossRef] [PubMed]
89. Khan, S.J.; Wang, L.; Hashim, N.H.; McDonald, J.A. Distinct enantiomeric signals of ibuprofen and naproxen in treated wastewater and sewer overflow. *Chirality* **2014**, *26*, 739–746. [CrossRef] [PubMed]
90. Souchier, M.; Benali-Raclot, D.; Casellas, C.; Ingrand, V.; Chiron, S. Enantiomeric fractionation as a tool for quantitative assessment of biodegradation: The case of metoprolol. *Water Res.* **2016**, *95*, 19–26. [CrossRef] [PubMed]
91. Suzuki, T.; Kosugi, Y.; Hosaka, M.; Nishimura, T.; Nakae, D. Occurrence and behavior of the chiral anti-inflammatory drug naproxen in an aquatic environment. *Environ. Toxicol. Chem.* **2014**, *33*, 2671–2678. [CrossRef] [PubMed]

92. Evans, S.E.; Bagnall, J.; Kasprzyk-Hordern, B. Enantioselective degradation of amphetamine-like environmental micropollutants (amphetamine, methamphetamine, MDMA and MDA) in urban water. *Environ. Pollut.* **2016**, *215*, 154–163. [CrossRef] [PubMed]
93. Evans, S.; Bagnall, J.; Kasprzyk-Hordern, B. Enantiomeric profiling of a chemically diverse mixture of chiral pharmaceuticals in urban water. *Environ. Pollut.* **2017**, *230*, 368–377. [CrossRef] [PubMed]
94. Ma, R.; Wang, B.; Lu, S.; Zhang, Y.; Yin, L.; Huang, J.; Deng, S.; Wang, Y.; Yu, G. Characterization of pharmaceutically active compounds in Dongting Lake, China: Occurrence, chiral profiling and environmental risk. *Sci. Total Environ.* **2016**, *557–558*, 268–275. [CrossRef] [PubMed]
95. Petrie, B.; Proctor, K.; Youdan, J.; Barden, R.; Kasprzyk-Hordern, B. Critical evaluation of monitoring strategy for the multi-residue determination of 90 chiral and achiral micropollutants in effluent wastewater. *Sci. Total Environ.* **2017**, *579*, 569–578. [CrossRef] [PubMed]
96. Aboul-Enein, H.Y.; Ali, I. Analysis of the chiral pollutants by chromatography. *Toxicol. Environ. Chem.* **2004**, *86*, 1–22. [CrossRef]
97. Faller, J.; Huhnerfuss, H.; König, W.A.; Ludwig, P. Gas chromatographic separation of the enantiomers of marine organic pollutants distribution of -HCH enantiomers in the North Sea. *Mar. Pollut. Bull.* **1991**, *22*, 82–86. [CrossRef]
98. Hühnerfuss, H.; Faller, J.; Kallenborn, R.; König, W.A.; Ludwig, P.; Pfaffenberger, B.; Oehme, M.; Rimkus, G. Enantioselective and nonenantioselective degradation of organic pollutants in the marine ecosystem. *Chirality* **1993**, *5*, 393–399.
99. Hühnerfuss, H.; Faller, J.; König, W.A.; Ludwig, P. Gas chromatographic separation of the enantiomers of marine pollutants. 4. Fate of hexachlorocyclohexane isomers in the Baltic and North Sea. *Environ. Sci. Technol.* **1992**, *26*, 2127–2133.
100. Barclay, V.K.H.; Tyrefors, N.L.; Johansson, I.M.; Pettersson, C.E. Trace analysis of fluoxetine and its metabolite norfluoxetine. Part II: Enantioselective quantification and studies of matrix effects in raw and treated wastewater by solid phase extraction and liquid chromatography–tandem mass spectrometry. *J. Chromatogr. A* **2012**, *1227*, 105–114. [CrossRef] [PubMed]
101. Camacho-Muñoz, D.; Kasprzyk-Hordern, B. Multi-residue enantiomeric analysis of human and veterinary pharmaceuticals and their metabolites in environmental samples by chiral liquid chromatography coupled with tandem mass spectrometry detection. *Anal. Bioanal. Chem.* **2015**, *407*, 9085–9104. [CrossRef] [PubMed]
102. Camacho-Muñoz, D.; Kasprzyk-Hordern, B.; Thomas, K.V. Enantioselective simultaneous analysis of selected pharmaceuticals in environmental samples by ultrahigh performance supercritical fluid based chromatography tandem mass spectrometry. *Anal. Chim. Acta* **2016**, *934*, 239–251. [CrossRef] [PubMed]
103. MacLeod, S.L.; Wong, C.S. Loadings, trends, comparisons, and fate of achiral and chiral pharmaceuticals in wastewaters from urban tertiary and rural aerated lagoon treatments. *Water Res.* **2010**, *44*, 533–544. [CrossRef] [PubMed]
104. MacLeod, S.L.; Sudhir, P.; Wong, C.S. Stereoisomer analysis of wastewater-derived b-blockers, selective serotonin re-uptake inhibitors, and salbutamol by high-performance liquid chromatography-tandem mass spectrometry. *J. Chromatogr. A* **2007**, *1170*, 23–33. [CrossRef] [PubMed]
105. Camacho-Muñoz, D.; Kasprzyk-Hordern, B. Simultaneous enantiomeric analysis of pharmacologically active compounds in environmental samples by chiral LC–MS/MS with a macrocyclic antibiotic stationary phase. *J. Mass Spectrom.* **2017**, *52*, 94–108. [CrossRef] [PubMed]
106. Schurig, V.; Juza, M. Analytical separation of enantiomers by gas chromatography on chiral stationary phases. *Adv. Chromatogr.* **2015**, *52*, 117–168.
107. Hegade, R.S.; De Beer, M.; Lynen, F. Chiral stationary phase optimized selectivity liquid chromatography: A strategy for the separation of chiral isomers. *J. Chromatogr. A* **2017**, *1515*, 109–117. [CrossRef] [PubMed]
108. Eljarrat, E.; Guerra, P.; Barceló, D. Enantiomeric determination of chiral persistent organic pollutants and their metabolites. *TrAC Trends Anal. Chem.* **2008**, *27*, 847–861. [CrossRef]
109. Rykowska, I.; Wasiak, W. Recent advances in gas chromatography for solid and liquid stationary phases containing metal ions. *J. Chromatogr. A* **2009**, *1216*, 1713–1722. [CrossRef] [PubMed]
110. Wong, C.S.; Garrison, A.W. Enantiomer separation of polychlorinated biphenyl atropisomers and polychlorinated biphenyl retention behavior on modified cyclodextrin capillary gas chromatography columns. *J. Chromatogr. A* **2000**, *866*, 213–220. [CrossRef]

111. Sanganyado, E.; Lu, Z.; Fu, Q.; Schlenk, D.; Gan, J. Chiral pharmaceuticals: A review on their environmental occurrence and fate processes. *Water Res.* **2017**, *124*, 527–542. [CrossRef] [PubMed]
112. Ridal, J.J.; Bidleman, T.F.; Kerman, B.; Fox, M.E.; Strachan, W.M. Enantiomers of alfa-Hexachlorocyclohexane as Tracers of Air-Water Gas Exchange in Lake Ontario. *Environ. Sci. Technol.* **1997**, *31*, 1940–1945. [CrossRef]
113. Wiberg, K.; Harner, T.; Wideman, J.L.; Bidleman, T.F. Chiral analysis of organochlorine pesticides in Alabama soils. *Chemosphere* **2001**, *45*, 843–848. [CrossRef]
114. Padma, T.V.; Dickhut, R.M.; Ducklow, H. Variations in α-hexachlorocyclohexane enantiomer ratios in relation to microbial activity in a temperate estuary. *Environ. Toxicol. Chem.* **2003**, *22*, 1421–1427. [CrossRef] [PubMed]
115. Bucheli, T.D.; Müller, S.R.; Heberle, S.; Schwarzenbach, R.P. Occurrence and Behavior of Pesticides in Rainwater, Roof Runoff, and Artificial Stormwater Infiltration. *Environ. Sci. Technol.* **1998**, *32*, 3457–3464. [CrossRef]
116. Schurig, V. Terms for the quantitation of a mixture of stereoisomers. *Top. Curr. Chem.* **2013**, *340*, 21–40. [PubMed]
117. Caballo, C.; Sicilia, M.D.; Rubio, S. Fast, simple and efficient supramolecular solvent-based microextraction of mecoprop and dichlorprop in soils prior to their enantioselective determination by liquid chromatography-tandem mass spectrometry. *Talanta* **2014**, *119*, 46–52. [CrossRef] [PubMed]
118. Madureira, T.V.; Barreiro, J.C.; Rocha, M.J.; Cass, Q.B.; Tiritan, M.E. Pharmaceutical trace analysis in aqueous environmental matrices by liquid chromatography–ion trap tandem mass spectrometry. *J. Chromatogr. A* **2009**, *1216*, 7033–7042. [CrossRef] [PubMed]
119. Verbruggen, E.M.J.; Van den Brink, P.J. *Review of Recent Literature Concerning Mixture Toxicity of Pesticides to Aquatic Organisms*; RIVM Report 601400001/2010; National Institute for Public Health and the Environment: Utrecht, The Netherlands, 2010.
120. Carlsson, P.; Warner, N.A.; Hallanger, I.G.; Herzke, D.; Kallenborn, R. Spatial and temporal distribution of chiral pesticides in Calanus spp. from three Arctic fjords. *Environ. Pollut.* **2014**, *192*, 154–161. [CrossRef] [PubMed]
121. Jantunen, L.M.; Bidleman, T. Air-water gas exchange of hexachlorocyclohexanes (HCHs) and the enantiomers of c-HCH in arctic regions. *J. Geophys. Res.* **1996**, *101*, 28837–28846. [CrossRef]
122. McBlain, W.A.; Lewin, V.; Wolfe, F.H. Differing estrogenic activities for the enantiomers of o,p′-DDT in immature female rats. *Can. J. Physiol. Pharmacol.* **1976**, *54*, 629–632. [CrossRef] [PubMed]
123. Buerge, I.J.; Poiger, T.; Müller, M.D.; Buser, H.-R. Enantioselective degradation of metalaxyl in soils: Chiral preference changes with soil pH. *Environ. Sci. Technol.* **2003**, *37*, 2668–2674. [CrossRef] [PubMed]
124. Buser, H.-R.; Müller, M.D. Occurrence and transformation reactions of chiral and achiral phenoxyalkanoic acid herbicides in lakes and rivers in switzerland. *Environ. Sci. Technol.* **1998**, *32*, 626–633. [CrossRef]
125. Gerecke, A.C.; Schärer, M.; Singer, H.P.; Müller, S.R.; Schwarzenbach, R.P.; Sägesser, M.; Ochsenbein, U.; Popow, G. Sources of pesticides in surface waters in Switzerland: pesticide load through waste water treatment plants—current situation and reduction potential. *Chemosphere* **2002**, *48*, 307–315. [CrossRef]
126. Bethan, B.; Bester, K.; Huhnerfuss, H.; Rimkus, G. Bromocyclen contamination of surface water, waste water and fish from northern germany, and gas chromatographic chiral separation. *Chemosphere* **1997**, *34*, 2271–2280. [CrossRef]
127. Harju, M.; Bergman, A.; Olsson, M.; Roos, A.; Haglund, P. Determination of atropisomeric and planar polychlorinated biphenyls, their enantiomeric fractions and tissue distribution in grey seals using comprehensive 2D gas chromatography. *J. Chromatogr. A* **2003**, *1019*, 127–142. [CrossRef] [PubMed]
128. UNEP, U.n.e.p.C. TREATIES-4. Stockholm convention on persistent organic pollutants. Adoption of amendments to Annexes A, B and C by decisions SC-4/10, 4/11, 4/12, 4/13, 4/14, 4/15, 4/16, 4/17 and 4/18. In Proceedings of the Conference of Plenipotentiaries, Stockholm, Sweden, 22 May 2001.
129. EU-Directive. Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. *Off. J. Eur. Union* **2013**, *L.226*, 1–17.
130. Wiberg, K.; Letcher, R.; Sandau, C.; Duffe, J.; Norstrom, R.; Haglund, P.; Bidleman, T. Enantioselective gas chromatography/mass spectrometry of methylsulfonyl PCBs with application to arctic marine mammals. *Anal. Chem.* **1998**, *70*, 3845–3852. [CrossRef] [PubMed]

131. Grimm, F.A.; Hu, D.; Kania-Korwel, I.; Lehmler, H.J.; Ludewig, G.; Hornbuckle, K.C.; Duffel, M.W.; Bergman, A.; Robertson, L.W. Metabolism and metabolites of polychlorinated biphenyls (PCBs). *Crit. Rev. Toxicol.* **2015**, *45*, 245–272. [CrossRef] [PubMed]
132. Mamontova, E.A.; Tarasova, E.N.; Mamontov, A.A. PCBs and OCPs in human milk in Eastern Siberia, Russia: Levels, temporal trends and infant exposure assessment. *Chemosphere* **2017**, *178*, 239–248. [CrossRef] [PubMed]
133. Norström, K.; Czub, G.; McLachlan, M.S.; Hu, D.; Thorne, P.S.; Hornbuckle, K.C. External exposure and bioaccumulation of PCBs in humans living in a contaminated urban environment. *Environ. Int.* **2010**, *36*, 855–861. [CrossRef] [PubMed]
134. Reich, S.; Jimenez, B.; Marsili, L.; Hernández, L.M.; Schurig, V.; González, M.J. Congener specific determination and enantiomeric ratios of chiral polychlorinated biphenyls in striped dolphins (stenella coeruleoalba) from the mediterranean sea. *Environ. Sci. Technol.* **1999**, *33*, 1787–1793. [CrossRef]
135. Wiberg, K.; Bergman, A.; Olsson, M.; Roos, A.; Blomkvist, G.; Haglund, P. Concentrations and enantiomer fractions of organochlorine compounds in baltic species hit by reproductive impairment. *Environ. Toxicol. Chem.* **2002**, *21*, 2542–2551. [CrossRef] [PubMed]
136. Chu, S.; Covaci, A.; Van de Vijver, K.; De Coen, W.; Blust, R.; Schepens, P. Enantiomeric signatures of chiral polychlorinated biphenyl atropisomers in livers of harbour porpoises (Phocoena phocoena) from the southern North Sea. *J. Environ. Monit.* **2003**, *5*, 521–526. [CrossRef] [PubMed]
137. Benická, E.; Novakovsky, R.; Hrouzek, J.; Krupcík, J.; Sandra, P.; Zeeuw, J.D. Multidimensional gas chromatographic separation of selected PCB atropisomers in technical formulations and sediments. *J. High Resolut. Chromatogr.* **1996**, *19*, 95–98. [CrossRef]
138. Glausch, A.; Blanch, G.P.; Schurig, V. Enantioselective analysis of chiral polychlorinated biphenyls in sediment samples by multidimensional gas chromatography-electron-capture detection after steam distillation-solvent extraction and sulfur removal. *J. Chromatogr. A* **1996**, *723*, 399–404. [CrossRef]
139. Lee, I.; Gopalan, A.I.; Lee, K.P. Enantioselective determination of polycyclic musks in river and wastewater by GC/MS/MS. *Int. J. Env. Res. Public Health* **2016**, *13*. [CrossRef] [PubMed]
140. Berset, J.D.; Kupper, T.; Etter, R.; Tarradellas, J. Considerations about the enantioselective transformation of polycyclic musks in wastewater, treated wastewater and sewage sludge and analysis of their fate in a sequencing batch reactor plant. *Chemosphere* **2004**, *57*, 987–996. [CrossRef] [PubMed]
141. Brausch, J.M.; Rand, G.M. A review of personal care products in the aquatic environment: Environmental concentrations and toxicity. *Chemosphere* **2011**, *82*, 1518–1532. [CrossRef] [PubMed]
142. Falconer, R.L.; Bidleman, T.F.; Gregorb, D.J. Air-water gas exchange and evidence for metabolism of hexachlorocyclohexanes in Resolute Bay, N.W.T. *Sci. Total Environ.* **1995**, *160–161*, 65–74. [CrossRef]
143. Jantunen, L.M.M.; Bidleman, T.F. Organochlorine pesticides and enantiomers of chiral pesticides in arctic ocean water. *Arch. Environ. Contam. Toxicol.* **1998**, *35*, 218–228. [CrossRef] [PubMed]
144. Kurt-Karakus, P.B.; Stroud, J.L.; Bidleman, T.; Semple, K.T.; Jantunen, L.M.M.; Jones, K.C. Enantioselective degradation of organochlorine pesticides in background soils: Variability in field and laboratory studies. *Environ. Sci. Technol.* **2007**, *41*, 4965–4971. [CrossRef] [PubMed]
145. Jamshidi, A.; Hunter, S.; Hazrati, S.; Harrad, S. Concentrations and chiral signatures of polychlorinated biphenyls in outdoor and indoor air and soil in a major U.K. conurbation. *Environ. Sci. Technol.* **2007**, *41*, 2153–2158. [CrossRef] [PubMed]