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Review

Chiral Analysis of Pesticides and Drugs of Environmental Concern: Biodegradation and Enantiomeric Fraction

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Abstract: The importance of stereochemistry for medicinal chemistry and pharmacology is well recognized and the dissimilar behavior of enantiomers is fully documented. Regarding the environment, the significance is equivalent since enantiomers of chiral organic pollutants can also differ in biodegradation processes and fate, as well as in ecotoxicity. This review comprises designed biodegradation studies of several chiral drugs and pesticides followed by enantioselective analytical methodologies to accurately measure the enantiomeric fraction (EF). The enantioselective monitoring of microcosms and laboratory-scale experiments with different environmental matrices is herein reported. Thus, this review focuses on the importance of evaluating the EF variation during biodegradation studies of chiral pharmaceuticals, drugs of abuse, and agrochemicals and has implications for the understanding of the environmental fate of chiral pollutants.

Keywords: enantiomeric fraction (EF); enantioselectivity; chiral analysis; biodegradation; pesticides; pharmaceuticals

1. Introduction

Chiral organic pollutants are a major trend in environmental science research and include compounds with different physical chemical properties and applications, such as pesticides, herbicides, pharmaceuticals, flame retardants, and synthetic polycyclic musk [1]. In general, agrochemicals are commercialized as racemic mixtures [2], although the bioactivity of these compounds is primarily associated with only one stereoisomer [3,4]. However, a few examples of pesticides are marketed as single enantiomeric formulations, namely some pyrethroid insecticides, aryloxypropanoate herbicides, and triazole fungicides [4]. Currently, in the pharmaceutical industry, chiral drugs are often developed and employed as single enantiomers and more enantiopure pharmaceutical preparations are being approved each year [5].

Despite the well-known importance of enantioselectivity on pharmacokinetic, pharmacodynamics, and toxicology in biological processes [3,6,7], stereochemistry is often neglected in environmental

research considering enantiomers as a unique molecular entity. However, when a racemate reaches the environment, enantiomers of the compound can differ significantly in their environmental fate as well as in their toxicological impacts; the evaluation of the enantiomeric fraction (EF) is of critical importance to assess the environmental risk of each enantiomer. Enantioselective analysis of chiral organic compounds is also important to evaluate their susceptibility to biodegradation, which can give useful insight into the biodegradative treatment to apply, as firstly proposed by Buser et al. [8]. The use of EF as an appropriate parameter for quantification of enantiomers in environmental analysis has been addressed [9]. Enantioselective studies on biodegradation, ecotoxicity, and environmental fate are crucial to provide an accurate risk assessment of chiral organic compounds [10–15]. Concerning the enantioselectivity of degradation processes, biotic mediums assume further relevance since biodegradation is expected to be enantioselective while abiotic degradation rates in an achiral environment are usually non-enantioselective [16–18]. Although less common, enantioselective abiotic degradation, namely in adsorption processes to sludge and soils, has been reported [19,20]. The EF of a chiral compound can suffer variations due to enantioselective degradation processes, and different events may contribute to these deviations: enantiomerization, racemization, or one enantiomer being preferentially degraded, leading to the enrichment of one enantiomeric form and thus accumulating in the medium [21]. The first studies on the stereoselectivity of chiral pollutants date from 1988 [22], with the first reports on the enantioselective degradation of pesticides regarding the herbicides diclofop-methyl and fenoxaprop-ethyl in soil [23], and 1999 with one of the initial studies concerning the anti-inflammatory ibuprofen in aqueous environmental matrices [8].

The most recent reviews on chiral pollutants emphasize the occurrence and toxicity of chiral pesticides and/or drugs [5,7,18,24–26] and explore the importance of chirality in the environment. The purpose of this review is to focus on enantioselective biodegradation studies using environmental matrices and on the importance of chiral analysis throughout EF as an indicator of enantioselectivity during the degradation processes. Two types of chiral organic compounds are considered: pesticides and drugs (pharmaceuticals and drugs of abuse).

2. Chiral Organic Pollutants in the Environment

Pharmaceuticals are an important group of pseudo-persistent compounds that have been detected at concentrations ranging from ng L^{-1} to μg L^{-1} in aquatic environments, causing great concern about non-target populations and, directly or indirectly, about human health via drinking water and foodborne exposure [27,28]. In 2013, the European Commission launched a Directive regulating several priority substances [29] and, more recently, a watch list of substances of environmental concern was published, including five pharmacologically active compounds (PACs): one anti-inflammatory (diclofenac), one synthetic hormone (17*alpha*-ethinylestradiol), and three antibiotics belonging to the macrolide class (azithromycin, clarithromycin, and erythromycin) [30].

PACs reach the environment by three main ways: the disposal of pharmaceuticals from manufacturing, hospitals, and other healthcare services; the elimination of unused pharmaceuticals through wastewater treatment plants (WWTPs) or solid waste facilities; and the excretion route after human and/or veterinary use [27]. The potential contamination of the main environmental compartments, such as surface water, ground water, and soils, which are constantly interconnected, may result in pharmaceuticals ending up in drinking water [31].

Concerning veterinary pharmaceuticals, they reach ecosystems by other pathways including treatment carried out on pets, in aquacultures, and in livestock production, with the spread of pharmaceuticals occurring directly via run-off or leaching to the ground water, or indirectly via manure use as fertilizer on agricultural soils [32,33]. In human or animal organisms, pharmaceuticals undergo metabolism, which includes chemical reactions (e.g., oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization) that transform them into more hydrophilic compounds, allowing for easier excretion in urine and feces [33]. Usually, a fraction of the administered PACs is

excreted unchanged. As such, pharmaceuticals can be excreted in the parent form, as one or several metabolites, or in both forms in varying proportions [34].

Most of the PACs and/or their metabolites resulting from human excretion reach domestic sewage, which is collected for treatment at municipal WWTPs. Since WWTPs are not designed to eliminate completely organic compounds at low concentrations [12], the WWTPs' effluents are considered the main source of human PACs in the environment and represent a critical contribution to the increasing loading of pharmaceuticals in the environment [35,36]. The main transformation processes of human PACs occurring within the WWTPs are sorption and biodegradation, with the latter suggested as the most important elimination process in wastewater treatment [37]. The non-biodegradable fraction and transformation products represent the "pharmaceutical bulk" of the effluent load in surface waters. For a complete understanding of the distribution and removal of each pharmaceutical in WWTPs, it is important to consider and compare both influent and effluent liquid and solid phases (i.e., sewage sludge and suspended solids) [38–40].

Additional concerns arise with chiral PACs, which represent more than half of the drugs currently in use [41]. Chiral PACs are administrated as racemates or as enantiomerically pure forms [42]. Each enantiomer can suffer metabolism, leading to other stereoisomeric compounds, or can be excreted unchanged. The study of chiral PACs in the different environmental compartments may provide valuable insight about the transport and fate of these chemicals in the environment. Although chiral PACs reach different compartments in the environment through the same pathways described for PACs in general, they have been detected in the environment with different values of EF, due to the enantioselectivity in the metabolism and/or in the biodegradation in WWTPs [43–45], as represented in Figure 1.

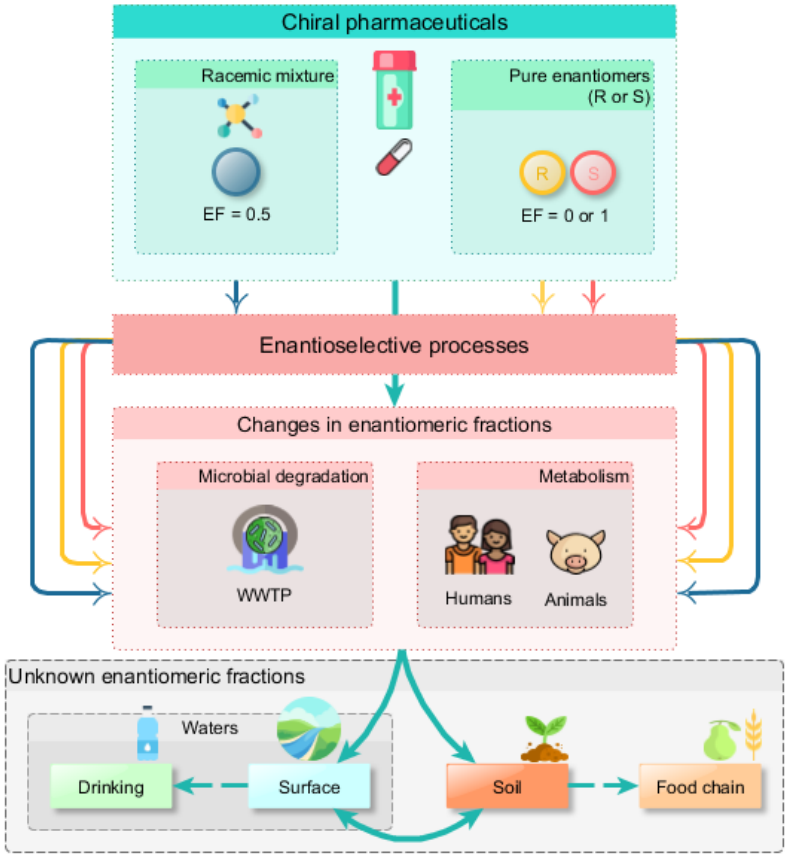

Figure 1. Representative pathways of chiral PACs in the environment. Adapted from [46].

Enantioselectivity has also been demonstrated in several ecotoxicological studies, regarding the survival and sublethal effects of highly ecologically relevant end points, such as growth, reproduction, and feeding rate [47,48]. Nevertheless, only a few therapeutic classes of chiral PACs have been reported in environmental matrices, concerning the quantification of their enantiomers [43–45,49–55]. Additionally, the biodegradation in biotic mediums, as occurs in secondary treatment of WWTPs, adds complexity to this issue since it is also expected to be enantioselective [8,56,57]. Recently, some authors have reported enantioselectivity occurring during biodegradation and a need to quantify the enantiomers in this circumstance (this point will be further discussed in Section 3).

Regarding agrochemicals, pesticides are the group of compounds that covers the largest number of substances, and can be grouped into several classes: insecticides, herbicides, fungicides, rodenticides, molluscicides, insect repellents, nematicides, and plant growth regulators [58,59]. Application of pesticides is a worldwide and of utmost importance for current agricultural productivity standards and the control of vectors and pests of public health relevance [60]. The dissipation rate of a pesticide into the environment is the primary indicator to its environmental fate [61]; these concepts are further explained in a recent review work [62]. Applied pesticides in agricultural fields affect the surrounding environmental compartments at four major levels: (i) air, through volatilization and wind action; (ii) soil, through direct application and run-off; (iii) surface waters, through run-off and via drainage systems; and (iv) ground water, via leaching and preferred water flow [62–64]. The dissipation of an applied pesticide is the predominant removal pathway and is influenced not only by its chemical characteristics but also by several environmental aspects, such as photodegradation, temperature, surface wash-off, spatial variability, humidity, and soil properties [62]. The reports on pesticides' occurrence in the environment are extensive and regard several matrices, namely soil, sediment, surface water, and ground water [65–68]. In the European Directive 2013/39/EC, the extended list of 45 priority substances included 19 pesticides [29].

Almost one-third of marketed pesticides are chiral and most of them are used as racemates even though the desirable activity is generally dependent on one unique enantiomer, while the other(s) may produce toxic or harmful effects on non-target organisms [2,25,69,70]. Enantioselectivity has been demonstrated in environmental fate [71], field experiments [72], toxicological studies [73], and biodegradation [74], regarding some of the most common pesticides. Works reporting enantioselective biodegradation of chiral pesticides will be further discussed in Section 4.

3. Biodegradation Studies of Chiral Drugs

In the last two decades studies on biodegradation of organic pollutants have become very popular and the number of publications in this area has grown substantially. Enantioselectivity is not always considered in the studies of biodegradation of chiral compounds and most of the published works addressing it date from the year 2000 onward, as observed using specific search keywords. Since 2000 ScienceDirect® offers 193 papers related with "pharmaceuticals + enantioselective + biodegradation" out of the 269 papers related to the same keywords when no time frame was selected. In this review, studies on enantioselective biodegradation of chiral compounds will be discussed, reporting the most representative examples. EF assessment during biodegradation experiments is crucial to understanding the stereoselectivity, concerning degradative routes and elimination and/or enrichment of the target enantiomers. Biodegradation studies with pharmaceuticals and drugs of abuse are usually designed for laboratory batch incubation experiments [75–78] or laboratory-scale bioreactors [79–82]. Enantioselective studies with constructed wetlands have also been reported [83]. Table 1 shows enantioselective biodegradation studies of chiral drugs in different environmental matrices and the chiral analytical techniques used to assess the EF during degradation, published between 1999 and 2017. In the original papers [8,10,75–93], 22 different compounds from nine different drug classes are mentioned, including anti-inflammatory agents, antidepressants, and beta-blockers as the three most represented classes (Figure 2).

Table 1. Chiral drugs discussed in this review and the chiral analytical techniques used to quantify enantiomers in biodegradation studies.

Title	Chiral Drugs	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
antibiotics	ofloxacin, levofloxacin	minimal salts medium inoculated with activated sludge	laboratory-scale microcosms, under aerobic conditions, with and without an extra carbon source	HPLC-FD; LC-MS/MS	enantioselective biodegradation of ofloxacin observed; (*S*)-ofloxacin degraded at higher extents; biodegradation of levofloxacin ((*S*)-enantiomer) led to (*R*)-enantiomer formation	[77]
anticoagulants	warfarin	sterile and nonsterile turfgrass and groundcover soil	aerobic and ambient temperature incubation	HPLC-FD	fast degradation of warfarin in the nonsterile soils while no degradation was observed in the sterile conditions; slightly enantioselective biodegradation with (*R*)-warfarin being preferentially degraded	[10]
antidepressants	fluoxetine	minimal salts medium inoculated with a single microbial strain	batch experiment incubations with an additional carbon source under aerobic conditions, protected from light	HPLC-FD	enantioselective biodegradation of fluoxetine was observed; (*R*)-fluoxetine preferentially degraded	[89]
	fluoxetine	synthetic wastewater	laboratory-scale aerobic granular sludge sequencing batch reactor	HPLC-FD	fluoxetine degraded at low extents and following a non-enantioselective pattern	[80]
	fluoxetine, norfluoxetine	WWTP effluents	microcosms tests at laboratory scale under aerobic conditions, protected from light	HPLC-FD	fluoxetine degradation followed a non-enantioselective pattern; no formation of the metabolite norfluoxetine was observed	[90]
	venlafaxine	river water	laboratory-scale experiments to assess photolysis, sorption and biodegradation	LC-MS/MS	venlafaxine sorption and biotranformation processes were non-enantioselective; venlafaxine biodegradation was enantioselective and formed (*O*)-desmethylvenlafaxine	[76]
	venlafaxine, metabolites	WWTP effluents charged with activated sludge	laboratory-scale incubation of effluents with activated sludge under anaerobic and aerobic conditions	LC-MS/MS	venlafaxine degradation presented slight enantioselectivity; (*O*)-desmethylvenlafaxine showed (*S*) to (*R*)-enantiomer enrichment exclusively under aerobic conditions	[75]

Table 1. *Cont.*

Title	Chiral Drugs	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
antifungals	climbazole	WWTP effluents charged with activated sludge	biotic and sterile batch anoxic degradation experiments, under dark and light conditions	LC-MS/MS	enantioselective degradation of climbazole observed under biotic conditions; faster degradation of E1-climbazole	[92]
anti-hyperlipidemic agents	metoprolol, ibuprofen, naproxen, gemfibrozil	river water	microcosm experiments to assess photolysis and biotransformation	GC-MS/MS	no degradation observed in the dark; metoprolol EF remained unchanged in the microcosms; metoprolol EF decrease along the river flow suggested biological mediated-degradation	[86]
anti-hyperlipidemic and anti-inflammatory agents	Ibuprofen clofibric acid	river water	incubation with a river biofilm reactor	GC-MS	ibuprofen and two metabolites were degraded in the biofilm reactor; (*R*)-ibuprofen, pharmacologically inactive, degraded faster	[84]
anti-inflammatory agents	ibuprofen, naproxen, ketoprofen	synthetic wastewater	laboratory-scale membrane bioreactor	GC-MS/MS	ibuprofen EF decreased during biodegradation and (*S*)-ibuprofen was preferentially degraded; (*R*)-ketoprofen degraded at a greater extent with minor increase in EF; (*S*)-naproxen EF significantly decreased during biodegradation, and (*R*)-naproxen concentration increased, suggesting enantiomeric inversion	[81]
	ibuprofen	surface waters; WWTP influents and effluents	incubation of fortified lake water; incubation with activated sludge under aerobic conditions	GC-MS/MS	rapid degradation of ibuprofen in the incubation experiments; (*S*)-ibuprofen exhibited faster degradation rates	[8]
	ibuprofen	urban wastewater; synthetic wastewater	aerated batch reactors inoculated with microalgae	GC-MS	enantioselective biodegradation of (*S*)-ibuprofen observed; EF decreased over degradation time	[91]
	ibuprofen, naproxen	synthetic wastewater; real wastewater	removal efficiency in WWTP, pilot and microcosm-scale constructed wetlands	GC-MS	(*S*)-ibuprofen degraded faster under aerobic conditions; under anaerobic conditions ibuprofen degradation was non-enantioselective; naproxen presented an enantioselective degradation profile both under aerobic and anaerobic conditions	[83]
antidepressants and beta-blockers	atenolol, metoprolol, fluoxetine	minimal salts medium inoculated with activated sludge	batch experiment incubations with and without an extra carbon source under aerobic conditions	HPLC-FD	metoprolol enantioselective biodegradation was observed; (*S*)-metoprolol degraded at higher extents; atenolol and fluoxetine biodegradation processes were non-enantioselective	[88]

Table 1. *Cont.*

Title	Chiral Drugs	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
beta-blockers	propranolol	WWTP secondary effluents; river water	microcosm experiments to simulate biotransformation in WWTP (activated sludge) and in surface water	GC-MS/MS	EF varied in the incubation with activated sludge but not in the non-inoculated conditions; EF remained unchanged in the surface water experiments	[85]
	alprenolol, propranolol	minimal salts medium inoculated with activated sludge	batch experiment incubations with and without an extra carbon source under aerobic conditions	HPLC-FD	enantioselective biodegradation of both drugs was observed; (*S*)-alprenolol and (*S*)-propranolol slightly higher degraded; enantioselective degradation pattern sustained in the presence of the extra carbon source	[87]
antidepressants, beta-blockers, and bronchodilators	alprenolol, bisoprolol, metoprolol, propranolol, venlafaxine, salbutamol, fluoxetine, norfluoxetine	synthetic wastewater	aerobic granular sludge-sequencing batch reactor	LC-MS/MS	enantioselective biodegradation of norfluoxetine observed; (*R*)-norfluoxetine preferentially degraded; non-enantioselective removal of the other target compounds	[93]
antidepressants, beta-blockers, bronchodilators, and synthetic psychoactive agents	MDMA (3,4-methylenedioxy-methamphetamine), MDA (3,4-methylenedioxyamphetamine), ampethamine, methamphetamine, venlafaxine, fluoxetine, O-desmethylvenlafaxine, atenolol, metoprolol, propranolol, alprenolol, sotalol, salbutamol, mirtazapine, citalopram, desmethylcitalopram	receiving waters (mixture of river water and WWTP effluent); activated sludge	receiving surface waters and activated sludge simulating microcosms systems under light, dark, biotic and abiotic conditions	LC-MS/MS	enantioselective degradation of amphetamines, beta-blockers and antidepressants observed; (*S*)-forms preferentially degraded for amphetamines and antidepressants and (*R*)-forms for beta-blockers; metabolites tested showed higher enantioselective degradation rates than parent compounds	[82]
synthetic psychoactive agents	amphetamine, methamphetamine	river water	microcosm bioreactors in the light (microbial degradation) and in the dark (photochemical processes)	LC-MS/MS	EF variations observed exclusively under biotic conditions; non-racemic by-products formation during the biodegradation	[79]
	amphetamine, methamphetamine, MDMA, MDA	WWTP effluents; river water	receiving surface waters and activated sludge simulating microcosms systems	LC-MS/MS	enantioselective biodegradation of all compounds observed in activated sludge simulating microcosms with the (*S*)-enantiomers being preferentially degraded; (*R*)-enantiomers limited or non-degraded; racemic MDMA enantioselective biodegradation resulted in (*R*)-enantiomer enrichment and formed (*S*)-MDA; MDMA slight enantioselective degradation observed in river water	[78]

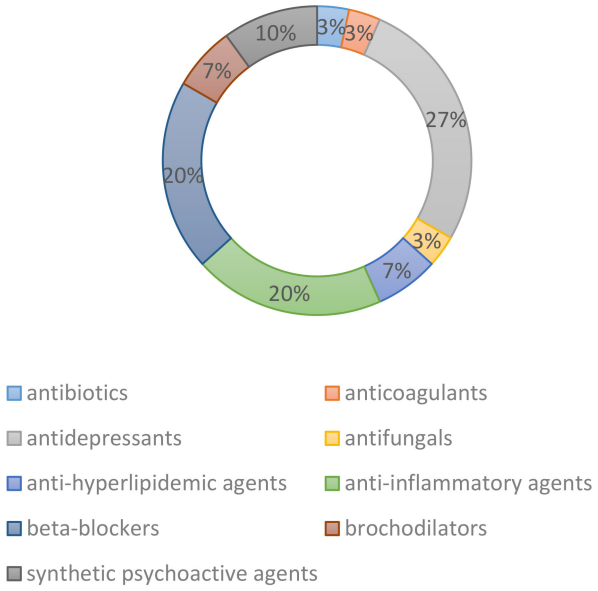

Figure 2. Relative percentages of each PAC classes mentioned in the reviewed enantioselective biodegradation studies.

Concerning the analytical methods used to quantify the enantiomers during biodegradation, a clear trend is observed. The first works used gas chromatography coupled with mass spectrometry (GC-MS) and were predominantly aimed at the enantioselective analysis of anti-inflammatory agents [8,81,83–86]. This pattern changed after 2012, when almost all works began to use liquid chromatography (LC), mostly coupled with mass spectrometry (MS) using CSP [75–79,92], a tendency that continues nowadays, with the single exception of a work published in 2009 in which GC-MS was used [91]. Regarding GC analysis, both direct and indirect methods for chiral determinations are reported. Indirect methods include a derivatization step to convert the target enantiomers in diastereomers so they can be separated through an achiral method [81,85,86]. Direct methods using CSP described the usage of a homemade modified beta-cyclodextrin column [8] and methyl-derivatized beta-cyclodextrin columns [83,91].

Degradation of chiral anti-inflammatory agents, specifically nonsteroidal anti-inflammatory drugs (NSAIDs), were the starting point of enantioselective biodegradation studies with pharmaceutical compounds [8,84]. Ibuprofen, ketoprofen, and naproxen biodegradation was reported in different environmental matrices as surface waters [8,84,86], WWTPs influents and effluents [8,83,91], and synthetic wastewater, the latter to operate a laboratory-scale bioreactor and constructed wetlands [81,83]. All the works with NSAIDs reported the use of GC-MS to perform the chiral analysis, although different methodologies are reported [8,83–86,91]. Generally enantioselective biodegradation was observed for the NSAIDs in all matrices. (*S*)-ibuprofen degraded faster and/or at higher extents in almost all matrices and studies [8,81,83,91], except for one work with a river biofilm reactor where the pharmacologically inactive (*R*)-ibuprofen was preferentially degraded [84]. Although it has been claimed that degrading microorganisms prefer the use of the (*R*)-enantiomer, as verified by Winkler et al. [84], the majority of reports on enantioselective biodegradation of ibuprofen achieved disagreeing results, describing preferential degradation of (*S*)-ibuprofen. Accordingly, the influence of specific experimental settings (such as aerobic/anaerobic conditions) has been stated as preponderant in the enantioselective degradation of (S)-ibuprofen by other authors [83,94]. Naproxen presented enantioselective degradation profiles as well, with the EF decreasing under both aerobic and anaerobic conditions in WWTP treatments [83] and potential occurrence of enantiomeric inversion during a membrane bioreactor operation, where the (*S*)-form EF decreased over time and the (*R*)-form

concentration increased [81]. Biodegradation of ketoprofen showed a slight preference towards the (*R*)-ketoprofen, and a slight increase of EF was observed [81].

Biodegradation assays of beta-blockers and antidepressants are herein discussed. The biodegradation of the beta-blockers alprenolol, atenolol, propranolol, and metoprolol and the antidepressant fluoxetine by an activated sludge inoculum collected from a WWTP was recently reported by our group [87,88]. Briefly, biodegradation studies of alprenolol, propranolol, and metoprolol were monitored using HPLC-FD with a vancomycin-based CSP. Biodegradation occurred in the same stereoselective pattern, with the (*S*)-form being degraded to a slightly higher extent. The presence of another growth substrate maintained such behavior and enhanced the biodegradation up to 14%. Atenolol and fluoxetine biodegraded in a non-enantioselective way [88]. The assays were performed by supplementing the compounds into a mineral growth medium inoculated with the activated sludge inoculum, in the absence and in the presence of acetate, a ready source of carbon and energy.

As an example, chromatograms of samples supplemented with 1 μg mL^{-1} of alprenolol at different times are presented in Figure 3 to illustrate the degradation behavior obtained from the single supplementation.

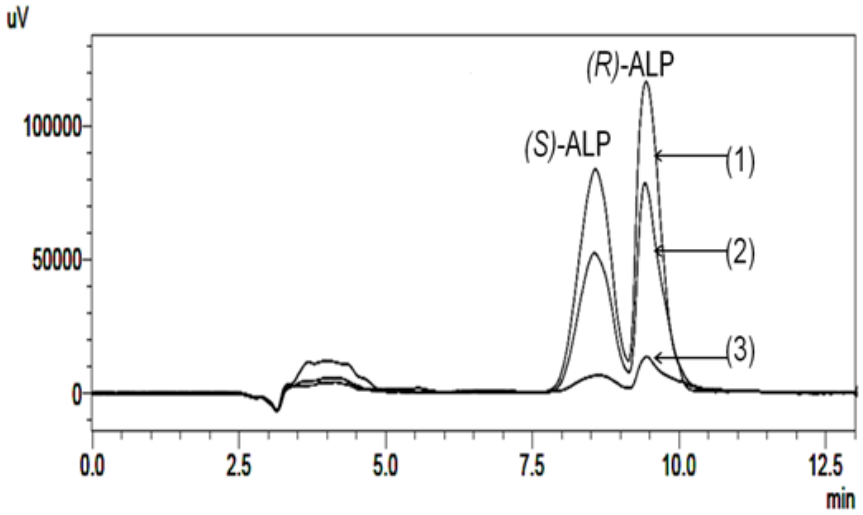

Figure 3. Representative chromatograms illustrating the loss of (*R*)- and (*S*)-enantiomers of alprenolol (ALP) during biodegradation assays of 1 μg mL^{-1} solutions of a mineral growth medium containing activated sludge supplemented with acetate. The numbers represent: (1) initial time; (2) 8th day; (3) 15th day. Reproduction with permission of Elsevier (Figure 3 from Ribeiro et al. [87]).

Acetate slightly increased the biodegradation extent of all enantiomers of all beta-blockers, which may be due to a higher metabolic activity of the cells in the presence of a readily available growth substrate. For all compounds, the enantioselectivity of the degradation process in the presence of acetate was the same as that observed without this additional energy source. Activated sludge could remove both enantiomers of fluoxetine. The removal percentage was approximately 80% at an initial concentration of 1 μg mL^{-1} in the presence and absence of the extra carbon source. The half-life of both enantiomers was similar and biodegradation seemed to be non-enantioselective.

The biodegradation of pharmaceuticals in mixtures can be different from individual supplementation [34,51]; however, the monitoring analytical methods required separation of all enantiomers of the pool of compounds. Alprenolol and propranolol were supplemented as a mixture at two different initial concentrations (0.5 and 5 μg mL^{-1}), and degradation was monitored for 15 days using a validated HPLC-FD method with a vancomycin-based CSP for the simultaneous separations of the enantiomers of both compounds. Also, a mixture of metoprolol, atenolol, and fluoxetine was

assessed in the exact same chromatographic conditions (mobile phase, column oven temperature, and flow rate). In this report, despite the similar order of magnitude of the biodegradation rate in the single and mixed supplementation, the degradation rates of the mixtures were different to that occurring during single supplementation. All enantiomers had their degradation rate diminished. It is important to assess the mixture effect, since pharmaceuticals can affect the metabolism of each other [34,51]. These phenomena may be explained by competition for the same enzyme and can affect biodegradation in a real environment.

The degradation of racemic-fluoxetine and its enantiomers in wastewater effluents, as well as their enantioselective degradation by *L. portucalensis* F11 [89], a microbial strain with the capacity to degrade a range of fluorinated aromatic compounds, was also studied and monitored with a HPLC-FD method with a vancomycin-based CSP under reversed mode of elution. This strain was used as a model organism to study the influence of stereochemistry on the biodegradation of enantiomers of fluoxetine [89]. Non-enantioselective degradation and no formation of enantiomers of the metabolite norfluoxetine were observed in the spiked wastewater samples. However, fluoxetine was degraded in an enantioselective manner by *L. portucalensis* F11, in assays performed with the single bacteria strain, with preferential degradation of the (*R*)-enantiomer, both at racemic and single enantiomeric supplementation [89]. The single enantiomer supplementation showed the total removal of (*R*)-fluoxetine with a slower degradation rate compared to the racemic supplementation. In the case of (*S*)-fluoxetine, almost total removal was observed with a faster degradation rate compared to the racemic supplementation. No racemization was observed [89]. This is in accordance with previous publications that enforce the dependency of the degradation pattern and the enantioselectivity on the microorganism phylogenies.

Fluoxetine is used in large amounts; however, there are only few studies concerning its biodegradation and reports on enantioselective biodegradation are rare [89,90]. A reversed-phase enantioselective LC-MS/MS method using a Chirobiotic™ V CSP was used to study the occurrence of fluoxetine in WTTP samples and revealed that the influent was more enriched in (*R*)-enantiomer than the effluent, suggesting the preferential degradation of this enantiomer in the treatment processes [95]. However, it is necessary to consider that influent and effluent samples do not necessarily represent the same plug of water and that the EF in the influent does not necessarily remain constant. This study confirmed the enantioselective biodegradation of fluoxetine by the single bacterium previously observed in our group [89], in which the (*S*)-enantiomer dissipation was slower than the (*R*)-enantiomer, and also reassured us that racemization phenomena were not occurring. Fluoxetine biotransformation to the metabolite norfluoxetine, which is known from human metabolism, was not detected in biodegradation by *L. portucalensis* F11 [89]. These results are in accordance with the abovementioned study performed in our laboratory concerning biodegradation of racemic-fluoxetine at a higher concentration of 10 μg mL^{-1} by activated sludge collected from a WWTP [88].

The removal of fluoxetine in a non-enantioselective manner was also recently reported in an aerobic granular sludge sequential batch reactor, suggesting adsorption of the compound to the aerobic granules [80]. This finding confirms the importance of studying not only the aqueous compartments but also the solids, such as sludge, soils, and river sediments, as reported by many authors [45,96,97]. A different study referred to an aerobic granular sludge-sequencing batch reactor (AGS-SBR) operated with simulated wastewater containing a mixture of chiral PACs, namely alprenolol, bisoprolol, metoprolol, propranolol, venlafaxine, salbutamol, fluoxetine, and norfluoxetine [93]. The AGS-SBR exhibited the highest removal efficiency for norfluoxetine, with preferential removal of the (*R*)-enantiomer indicating that enantioselective biologically mediated processes occurred. Removal was non-enantioselective for the other chiral PACs, and occurred through biosorption onto AGS. This study was monitored by LC-MS/MS using a Chirobiotic™ V CSP under the reverse-phase elution mode and the same analytical method developed and reported in a previous work [93]. Different works have reported the utilization of batch reactors in enantioselective biodegradation experiments with different drugs such as amphetamine, methamphetamine [79], and NSAIDs [81,84,91]. Considering

existing reports on biodegradation experiments using batch reactors, the main strengths highlighted are the robustness of reactors' functionality, the ability to survive pollutant shock loads, and high biomass density (compared to batch incubations with bacterial consortia or activated sludge inoculum) [80,93]. Conversion of lab-scale operating reactors to full-scale reactors applied to real scenarios has been accomplished, and Portugal, the Netherlands, South Africa, and China have full-scale batch reactors currently in operation [98]. Advances in this type of technology will benefit the diffusion of its application in the future [99].

Concerning antibiotics, there are many reports regarding biodegradation [100,101], but very few citations about enantioselectivity in degradation studies. In our recent work, concerning biodegradation of racemic-ofloxacin and (*S*)-ofloxacin (levofloxacin) by an activated sludge consortium, enantioselective degradation was observed with the (*S*)-enantiomer from the racemic mixture being degraded at higher extents and the degradation of the enantiopure (*S*)-ofloxacin leading to enrichment of the *R*-form [77]. Similar behavior was observed for the same antibiotics using the single bacterial strains *L. portucalensis* F11 and *Rhodococcus* sp. FP1, under aerobic conditions (manuscript submitted for publication). Both works were followed by LC-FD and LC-MS/MS with a Chirobiotic™ R CSP under reverse-phase mode and isocratic elution, using 0.45% triethylamine aqueous solution (pH 3.6) and ethanol (80/20, *v/v*) and ammonium formate in water (concentration 20 mM, pH 4.25) and ethanol (80/20, *v/v*) as mobile phases, respectively. Reports on the enantioselective biodegradation of chiral drugs are still scarce, although there are other studies including warfarin, venlafaxine, climbazole, and synthetic psychoactive agents (amphetamine, methamphetamine, and related compounds). Macrocyclic antibiotics-based CSP, mainly Chirobiotic™ columns, are most often used in enantioselective biodegradation studies of chiral PACs [75–77,79,80,82,87–90,93], but other chiral selectors such as cyclodextrin-based [91], polysaccharide-based [92], protein-based [78,82], and Pirkle-type [10] CSP have been reported. For more information, please refer to the literature [10,11,75,76,78,79,82,92].

Different studies have considered metabolites originating during the biodegradation of chiral compounds [75,82,84,91,93]. Matamoros et al. followed the formation of the two major human metabolites of ibuprofen during experiments with microalgae reactors (carboxy-ibuprofen and hydroxy-ibuprofen) [91]. These metabolites, described as the most abundant originating during biodegradation, were already present at the beginning of experiments with wastewater, agreeing with occurrence data for these compounds usually found in this type of matrix [102]. Carboxy-ibuprofen and hydroxy-ibuprofen followed the degradation pattern of the parent compound, which, according to the authors, established biodegradation as the key process for their removal [91]. The formation of these metabolites was not enantioselectively monitored and analyzed. A different study with ibuprofen [84] described the detection and identification of the same two metabolites during experiments with a river biofilm reactor, as well as their degradation. The authors suggested that the degradation pathway of ibuprofen in river systems and the metabolites originated differ from those observed in human metabolism. Hydroxy-ibuprofen appears first and carboxy–ibuprofen shows more persistence in human metabolism; the opposite has been verified for the environment [84]. Amorim et al. observed enantioselective removal of norfluoxetine (metabolite of fluoxetine) in an AGS-SBR experiment and variations of the compound EF throughout the different operational phases of the reactor. Enantioselective degradation of metabolites of venlafaxine, citalopram, and MDMA was reported in two recent studies [75,82]. Degradation of the metabolite O-desmethylvenlafaxine exhibited notable enantiomeric enrichment under aerobic conditions and none under anaerobic conditions, contrary to the results obtained for the parent compound, which involved only slight stereoisomeric selectivity [75]. Evans et al. reported higher degradation extents of desmethyl metabolites of venlafaxine, citalopram, and MDMA both for stereoselective metabolic and non-stereoselective photochemical processes [82].

A recent study described beta-blockers' enantiomer adsorption by sludge using batch experiments, and reported the abiotic enantioselectivity of the processes [19]. The authors observed that the enantioselectivity of adsorption phenomena increased with the hydrophilicity of the compounds

through variation of the EF of the beta-blockers sorbed on sludge. This work presents a new vision of the enantioselective behavior of chiral compounds in the environment, suggesting that it may not be solely associated with biologically mediated processes.

4. Biodegradation Studies of Chiral Pesticides

The earliest enantioselective studies on pesticides' biodegradation date back to the 1970s [103], but it was only in the 1990s that the subject began to be widely explored [13,104–115]. A research on ScienceDirect® under the keywords "pesticides + enantioselective + biodegradation" provides 267 results. This review will not cover all the works on the topic and therefore was limited to papers published after 2006, the year when a comprehensive review on environmental fate and biochemical transformations of chiral pollutants was published [1]. As previously stated regarding chiral drugs, the EF calculation during biodegradation experiments is one of the most useful tools to understand the enantioselectivity of the processes. Studies on the degradation of pesticides involving incubation tests are mostly performed in laboratory-scale batch experiments [21,116–153], with rare exceptions where the treatment performance of constructed wetlands was investigated [154].

Table 2 shows enantioselective biodegradation studies of chiral pesticides in different environmental matrices and the chiral analytical techniques used to assess the EF during degradation, published between 2006 and 2017. In the original papers [21,116–155] 41 different compounds from 14 different pesticide classes are mentioned, with triazole fungicides and phenoxy herbicides being the two most represented classes (Figure 4). Dissipation studies and field-only experiments with no incubation experiments considered were left out [72,149,156–167].

Table 2. Chiral pesticides discussed in this review (works published between 2006 and 2017) and the chiral analytical techniques used to quantify enantiomers in biodegradation studies.

Chiral Pesticide	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
amides	-	-	-	-	-
beflubutamid	soil	laboratory incubation experiments under aerobic conditions with acidic and alkaline matrices	GC-MS	enantioselective degradation of beflubutamid observed in alkaline soil; (-)-beflubutamid degraded slower in alkaline soil; both enantiomers degraded similarly in acidic soil; highly enantioselective degradation of the metabolite phenoxybutanamide observed	[116]
aminophosphonic acid derivatives	-	-	-	-	-
dufulin	soil	laboratory incubation experiments under sterile and non-sterile conditions with racemic mixture and individual enantiomers	HPLC-DAD	faster degradation of enantiopure (*S*)-dufulin compared to its antipode; enantiomerization not observed during incubation of individual enantiomers	[117]
chloroacetanilides	-	-	-	-	-
metolachlor	soil	laboratory incubation experiments under sterile and non-sterile conditions	GC-ECD	enantioselectivity observed during degradation; (*S*)-metolachlor degraded faster than the racemic mixture	[118]
metolachlor	runoff waters	laboratory scale wetlands; column wetlands	GC-MS	enantioselective degradation of metolachlor observed; EF variations detected along the wetland distinct zones	[154]
diphenyl ethers	-	-	-	-	-
lactofen and metabolites	sediment	laboratory incubation experiments with racemic mixture and individual enantiomers	HPLC-VWD	enantioselective degradation observed with (*S*)-lactofen and (*S*)-desethyl lactofen being preferentially degraded and enrichment of the (*R*)-forms.	[119]
imidazolinones	-	-	-	-	-
imazethapyr	soil	laboratory incubation experiments under aerobic, sterile and non-sterile conditions with variable pH, humidity and temperature settings	HPLC-UV-CD	(*R*)-imazethapyr preferentially degraded in all samples; average (*R*)-imazethapyr half-lives significantly shorter than its antipode; EF values significantly higher in less acidic soil	[120]
neonicotinoids	-	-	-	-	-
cycloxaprid	soil	laboratory incubation experiments under anoxic and flooded conditions with racemic mixture and individual enantiomers	HPLC-LSC; LC-MS/MS	enantioselective abiotic and biotic cycloxaprid degradation not observed; non-enantioselective transformation could be related to the absence of oxabridged ring in the transformation products	[121]

Table 2. *Cont.*

Chiral Pesticide	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
cycloxaprid	soil	laboratory incubation experiments under aerobic conditions	HPLC-DAD	non-enantioselective degradation of racemic-cycloxaprid and its (1*S*2*R*)- and (1*R*2*S*)-enantiomers observed in the soil samples tested	[122]
paichongding	soil	laboratory incubation experiments under anaerobic conditions	HPLC-DAD; LC-MS/MS	enantioselective degradation of paichongding observed; types of soil influenced enantiomers degradation rates; degradation process originated three achiral transformation products	[123]
organochlorines	-	-	-	-	-
α-HCH, *cis*- and *trans*-chlordane, *o*,*p*'-DDT	woodland and grassland background soil	laboratory incubation experiments under aerobic conditions	GC-ECNI-MS	enantioselectivity degradation observed in field and laboratory experiments	[124]
organophoshorus	-	-	-	-	-
malathion	soil, environmental waters	laboratory incubation experiments	HPLC-VWD	(*S*)-malathion degraded faster than the active (*R*)-malathion in all environmental samples; biodegradation of pure enantiomers of malathion showed enantiomeric inversion in soil and water samples	[125]
oxadiazines	-	-	-	-	-
indoxacarb	soil	laboratory incubation experiments under sterile and non-sterile conditions with acidic and alkaline matrices	HPLC-DAD	enantioselective degradation of indoxacarb observed under non-sterile conditions; (*R*)-indoxacarb degraded faster in acidic soil; (*S*)-indoxacarb preferentially degraded in alkaline soil; enantiomerization observed in both acidic and alkaline soils	[126]
phenoxies	-	-	-	-	-
diclofop-methyl, diclofop	algae cultures	laboratory incubation experiments	HPLC-FD	enantioselective degradation of diclofop and diclofop-methyl observed and influenced by temperature	[127]
diclofop-methyl	agricultural soil, Chinese cabbage	laboratory incubation experiments; field experiments in spiked plants	HPLC-DAD	enantioselective degradation of diclofop-methyl observed in two of the tested soil samples, where (-)-enantiomer degraded faster; (+)-enantiomer preferentially degraded in cabbage	[128]
dichlorprop-methyl	sediment	laboratory incubation experiments with bacterial strain isolated from activated sludge	HPLC-UV-CD; GC-ECD	(*R*)-dichlorprop-methyl preferentially degraded at different pH values; enantioselectivity more evident at neutral pH conditions	[129]

Table 2. *Cont.*

Chiral Pesticide	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
fluazifop-butyl	soil, water	laboratory incubation experiments under different pH conditions (water) with racemic mixture and individual enantiomers	LC-MS/MS	enantioselective degradation of fluazifop-butyl observed in two soil samples but not on water; enantiomeric form preferentially degraded varied within soil samples	[130]
mecoprop	soil sampled at different depths	laboratory incubation experiments under aerobic and anaerobic conditions	LC-MS/MS	(*R*)-mecoprop preferentially degraded under aerobic conditions in soils from 3 and 6 m depth when using nM mecoprop concentrations; (*S*)-mecoprop preferentially degraded in all samples when using higher mecoprop concentrations (µM)	[131]
quizalofop-ethyl, quizalofop-acid (metabolite)	soil	laboratory incubation experiments with racemic mixture and individual enantiomers	HPLC-UV	enantioselective degradation of quizalofop-ethyl observed; (*S*)-quizalofop-ethyl degraded faster both in acidic and alkaline soils; quizalofop-acid degraded faster in acidic soil; quizalofop-acid enantiomerization observed with enrichment of the (*R*)-enantiomer	[132]
spiroxamine	soil	laboratory incubation experiments under anaerobic conditions	LC-MS; GC-MS	non-enantioselective degradation of spiroxamine observed	[133]
phenylamides	-	-	-	-	-
benalaxyl	agricultural soil, cucumber plant	laboratory incubation experiments in the dark	HPLC-DAD	enantioselective degradation of benalaxyl observed; (*S*)-benalaxyl degraded faster in plants and (*R*)-benalaxyl degraded faster in soils	[134]
benalaxyl	soil, vegetables	laboratory incubation experiments with soil; growth of plants in controlled environment with fungicide application	HPLC-DAD	enantioselective degradation observed in soil where (*R*)-benalaxyl dissipated faster; (*S*)-benalaxyl preferentially degraded in all vegetables with resulting enrichment of (*R*)-benalaxyl.	[135]
benalaxyl	freshwater algae cultures	laboratory incubation experiments	HPLC-UV	enantioselective degradation of benalaxyl observed; (*S*)-benalaxyl half-life slightly smaller and relative enrichment of the (*R*)-enantiomer occurred	[136]
furalaxyl, metalaxyl	microbial liquid cultures	laboratory incubation experiments with the individual compounds and its mixture	HPLC-MS	enantioselective degradation of furalaxyl and metalaxyl observed with one of the isolated microorganisms; (*R*)-enantiomers of both compounds preferentially degraded	[137]

Table 2. *Cont.*

Chiral Pesticide	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
metalaxyl	sewage sludge	laboratory incubation experiments under anaerobic conditions	HPLC-UV-CD	(*S*)-metalaxyl from the racemic mixture degraded faster, presenting a $T_{1/2}$ much lower than the (*R*)-metalaxyl; racemic mixture $T_{1/2}$ lower than the (*R*)-enantiomer	[138]
phenylpyrazoles	-	-	-	-	
fipronil	sediment	laboratory incubation experiments under anaerobic conditions	GC-MS	enantioselective degradation of fipronil observed; fipronil EF varied during incubation period in sulfidogenic sediments and the (*S*)-enantiomer was preferentially degraded	[139]
fipronil	soil	laboratory incubation experiments under aerobic and anaerobic conditions	HPLC-DAD	almost non-enantioselective degradation of racemic fipronil observed; (*S*)-fipronil preferentially degraded under anaerobic conditions with flooded soil; no enantiomerization of fipronil observed	[140]
fipronil	algae cultures	laboratory incubation experiments with racemic mixture and individual enantiomers	HPLC-UV	enantioselective degradation of fipronil observed; EF varied from 0.5 to 0.65 in 17 days; longer half-life values observed for (*S*)-fipronil	[141]
pyrethroids	-	-	-	-	-
alpha-cypermethrin	soil	laboratory incubation experiments	HPLC-VWD; GC-ECD	enantioselective degradation of α-cypermethrin observed; EF varied from 0.55 to 0.61 in 42 days; (+)-(1*R*,cis,α*S*)-cypermethrin preferentially degraded	[142]
beta-cypermethrin	soil	laboratory incubation experiments under sterile and non-sterile conditions	HPLC-VWD	enantioselective degradation of *beta*-cypermethrin observed; different degradation rates observed for the four *beta*-cypermethrin isomers; EF variation noticed during the degradation process	[143]
beta-cypermethrin-	soil	laboratory incubation experiments under sterile and non-sterile conditions with acidic and alkaline matrices, and with racemic mixture and individual enantiomers	HPLC-UV	enantioselective degradation of racemic-*beta*-cypermethrin observed only in non-sterile soils; different degradation rates and half-lives observed for the four *beta*-cypermethrin isomers; no enantiomeric enrichment observed during degradation of individual enantiomers	[144]

Table 2. *Cont.*

Chiral Pesticide	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
(Z)-*cis*-bifenthrin, *cis*-permethrin, cyfluthrin, cypermethrin	soil, sediment	laboratory incubation experiments under aerobic and anaerobic conditions	GC-ECD	enantioselective degradation of *cis*-bifemthrin, pemethrin and cyfluthrin observed	[145]
fenpropathrin, fenvalerate	soil	laboratory incubation experiments with acidic and alkaline matrices	HPLC-UV	slightly enantioselective degradation of fenpropathrin and fenvalerate in alkaline samples where (*S*)-fenpropathrin and (α*S*,2*R*)-fenvalerate were degraded faster; racemization observed in alkaline samples but not on acidic soils	[146]
triazoles	-	-	-	-	-
epoxiconazole, cyproconazole	soil	laboratory incubation experiments under different pH conditions	GC-MS	soil pH affected degradation enantioselectivity; enantioselective degradation of epoxiconazole observed at higher pH values	[147]
enilconazole	soil	laboratory incubation experiments under different conditions of light and UV irradiation	CE	enantioselective degradation of enilconazole not observed in alkaline soil	[148]
fenbuconazole, RH-9129 (metabolite), RH-9130 (metabolite)	soil	laboratory incubation experiments under aerobic and anaerobic conditions	LC-MS/MS	enantioselective degradation of fenbuconazole observed under aerobic and anaerobic conditions; (-)-fenbuconazole preferentially degraded; enantioselective degradation of the metabolites differed with aeration and pH conditions	[21]
flutriafol, hexaconazole, tebuconazole	sediment	laboratory incubation experiments under sterile and non-sterile conditions	HPLC-UV	enantioselective degradation of the three triazole fungicides observed; (-)-enantiomers preferentially degraded in native conditions; no significant enantioselective degradation observed under sterilized conditions	[155]
triadimefon	soil	laboratory incubation experiments in sterile and non-sterile conditions	HPLC-UV	(*R*)-triadimefon preferentially degraded in acidic and alkaline soils; racemization observed in the abiotic degradation of enantiopure triadimefon enantiomers	[150]

Table 2. *Cont.*

Chiral Pesticide	Matrix	Biodegradation Experiment	Analytical Method	EF/Observations	Reference
triadimenol	soil	laboratory incubation experiments in sterile and non-sterile conditions	HPLC-UV	relative enantioselective degradation of triadimenol observed; epimerization observed in incubations with enantiopure triadimenol enantiomers	[151]
tebuconazole	agricultural soil, vegetables	laboratory incubation experiments in sterile and non-sterile conditions	HPLC-DAD, LC-MS/MS	tebuconazole EF varied slightly during biodegradation in soil samples; (*R*)-tebuconazole degraded faster than the (*S*)-enantiomer in tested soils	[152]
tebuconazole, myclobutanil	soil	laboratory incubation experiments under aerobic and anaerobic conditions with racemic mixture and individual enantiomers	LC-MS/MS	enantioselective degradation of tebuconazole observed in aerobic and anaerobic soils; (*S*)-tebuconazole preferentially degraded; enantioselectivity correlated with the soils organic carbon content; (+)-myclobutanil preferentially degraded in aerobic soils; similar degradation rates of myclobutanil enantiomers in anaerobic soils	[153]

Notes: CE, capillary electrophoresis; CD, circular dichroism; ECD, electron capture detector; ECNI, electron capture negative ion; LSC, liquid scintillation counter; VWD, variable wavelength detector.

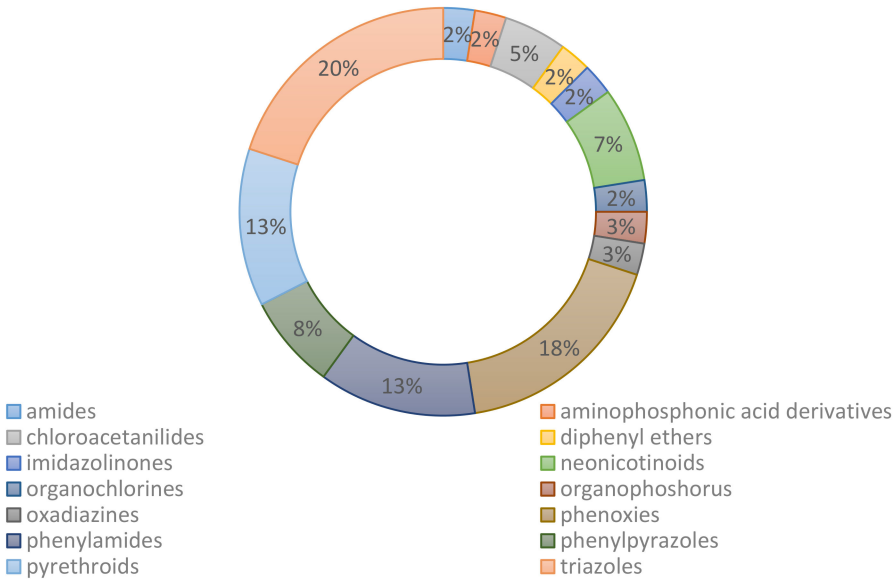

Figure 4. Relative percentages of each pesticide classes mentioned in the reviewed enantioselective biodegradation studies.

Regarding the analytical methods used to quantify pesticides' enantiomers during biodegradation, the trend is clear and high-performance liquid chromatography with a diode array detector (HPLC-DAD) [117,122,123,126,128,134,135,140,152] and an ultraviolet detector (UV) [120,129,132,136,138,141,144,146,150,151,155], as well as liquid chromatography tandem-mass spectrometry (LC-MS/MS) [21,121,123,130,131,152,153], are the predominant quantification approaches employed. Other analytical methods have been reported, such as GC [116,118,124,133,139,145,147,154] and capillary electrophoresis [148]. Chromatographic stopped-flow techniques have been used to monitor enantiomerization studies [168]. All the works with GC described direct enantioselective methods using cyclodextrin-based CSP, the CSP most often applied in enantioselective analysis of organochlorine compounds [169,170]. Enantioselective LC-MS/MS methods performed direct chiral analysis, mostly using polysaccharide-based CSP [21,123,130,152,153], although the utilization of a cyclodextrin-based CSP was also described [131]. Soil is the major matrix used in pesticides' biodegradation studies, accounting for more than 70% of the works considered in this review, probably because it is the primary environmental compartment with which they are in contact. This matrix choice propensity in biodegradation studies with pesticides is clearly different to that observed for pharmaceuticals and drugs of abuse, where environmental waters are the main matrix used.

Triazole fungicides are the class with a higher number of compounds employed in biodegradation studies. Enantioselectivity was observed for all triazole compounds considered, although at different degrees depending on experimental conditions such as aeration and pH range [21,147,148,150,153]. A comprehensive study with fenbuconazole conducted with soil in laboratory incubation experiments monitored not only the biodegradation of the target fungicide but also the formation and biodegradation of two chiral metabolites [21]. Results demonstrated enantioselectivity during the biodegradation of fenbuconazole and during the biodegradation of the two chiral metabolites monitored, in which the (+)-enantiomer of the parent compound was preferentially degraded—the opposite of the pattern observed for the metabolites with (-)-enantiomers, which degraded faster and to a larger extent. Epoxiconazole biodegradation in soil exhibited greater enantioselectivity at higher pH levels [147]. Conversely, the biodegradation of enilconazole in soil samples at alkaline pH was not enantioselective [148]. Triadimefon-enantioselective biodegradation was observed at acidic and alkaline pH levels in a similar matrix, and in both conditions the

(*R*)-enantiomer was preferentially degraded [150]. pH's impact on biodegradation has been correlated with enzymatic reactions and microbiological activity and can, consequently, affect the enantioselectivity of the degradative course [148,171]. These results suggest that, as well as for the matrix chemical characteristics, the specific individual structure of a compound has a great impact on its enantioselective behavior during degradative processes, and different outcomes regarding the enantioselectivity may be obtained for compounds that are chemically related.

Phenoxy herbicides are another pesticide class frequently used to assess enantioselectivity during biodegradation. Generally, all the studies reported enantioselective biodegradation to some extent in the various matrices considered (for instance, algae cultures, agricultural soil, sediment, water, and vegetables) [127–130]. Diclofop-methyl exhibited diverse enantioselective behaviors in different biodegradation matrices, with its (-)-enantiomer being degraded faster in soil samples and more slowly in Chinese cabbage samples [128]. The same multiplicity of enantioselective behaviors was observed for fluazifop-butyl, which was enantioselectively biodegraded in soil, though the enantiomer preferentially degraded varied within samples, while its degradation on water samples was non-enantioselective [130].

Fipronil is a phenylpyrazole broad-spectrum insecticide broadly used on house pets as well as in pest control on agricultural fields [139]. Different works reported the biodegradation of fipronil in several matrices (sediment, soil, and algae cultures) [139–141]. Fipronil biodegradation was enantioselective, although with different contours: in sediment samples the (*S*)-enantiomer was preferentially degraded and variations in the EF were observed during the degradation period [139]; in algae cultures the EF of racemic fipronil also varied during the degradation period but the (*S*)-enantiomer had longer half-life values, persisting longer in the medium [141]; and in soil samples the racemic fipronil biodegradation was almost non-enantioselective, even though the (*S*)-enantiomer was slightly more degraded under anaerobic conditions [140].

Benalaxyl is a phenylamide fungicide widely used in tomato, grape, potato, tobacco, and soybean crops; its biodegradation has been reported as enantioselective in different matrices as soil, plants and vegetables [134,135], and freshwater algae cultures [136]. Biodegradation in plants and vegetables showed faster degradation of (*S*)-benalaxyl in diverse experimental conditions, while experiments in soil reported preferential degradation of (*R*)-benalaxyl [134,135]. (*S*)-benalaxyl exhibited somewhat smaller half-life values in freshwater algae cultures and in the same study enrichment of the (*R*)-enantiomer was also reported [136]. Degradation in vegetables also resulted in (*R*)-benalaxyl enrichment [135].

Beta-cypermethrin is a pyrethroid insecticide with four isomers and is one of the most used worldwide, notwithstanding its well-known toxic effects against different organisms and environmental compartments [1,25,172]. Two different studies on soils reported the enantioselective biodegradation of *beta*-cypermethrin [143,144] and in both works different degradation rates and extents were observed for the four isomers. Additionally, no enantiomeric enrichment was detected when enantiopure isomers were employed in biodegradation experiments [144].

All the works discussed here reinforce the importance of developing enantioselective methods to determine the EF of chiral organic pollutants in the environment and to encourage more concern about the stereochemistry in this field. Concerning enantioselective biodegradation studies, samples tend to be cleaner and with higher concentration than in soils, effluents, and surface water samples, allowing for easier sample preparation process and feasibility in EF quantification [173,174].

5. Conclusions and Future Perspectives

Overall regardless of the great importance given to chiral organic pollutants, the stereochemistry involved in biodegradation is still frequently overlooked. Although enantioselective methods and biodegradation experiments have evolved in recent years, namely regarding pesticide compounds, studies with chiral pharmaceuticals and drugs of abuse are nonetheless only a minor part of the research work in this field. The study of enantioselective processes associated with the formation

and degradation of chiral metabolites of chiral compounds is practically non-existent. In addition to the occurrence and environmental fate of the metabolites and products of transformation of chiral pollutants, it is of great importance to evaluate the inherent enantioselectivity given their potential consequences for the environment.

The understanding of the impact of stereoselectivity on the degradation and transformation of chiral organic compounds in environmental matrices and non-target organisms is key for an improved environmental risk assessment of these pollutants, since these developments can represent unexpected ecotoxicological effects. Further knowledge of enantioselective environmental processes could help the agrochemical industry to redirect production of broadly applied chiral compounds to enriched- or single-enantiomer formulations, thus reducing the pollutant load of racemic mixtures into the environment.

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