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Enantioselective Behaviors of Chiral Pesticides and Enantiomeric Signatures in Foods and the Environment

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ABSTRACT: Unreasonable application of pesticides may result in residues in the environment and foods. Chiral pesticides consist of two or more enantiomers, which may exhibit different behaviors. This Review intends to provide progress on the enantioselective residues of chiral pesticides in foods. Among the main chiral analytical methods, high performance liquid chromatography (HPLC) is the most frequently utilized. Most chiral pesticides are utilized as racemates; however, due to enantioselective dissipation, bioaccumulation, biodegradation, and chiral conversion, enantiospecific residues have been found in the environment and foods. Some chiral pesticides exhibit strong enantioselectivity, highlighting the importance of evaluation on an enantiomeric level. However, the occurrence characteristics of chiral pesticides in foods and specific enzymes or transport proteins involved in enantioselectivity needs to be further investigated. This Review could help the production of some chiral pesticides to single-enantiomer formulations, thereby reducing pesticide consumption as well as increasing food production and finally reducing human health risks.

KEYWORDS: *chiral analysis, enantiomer, stereoselectivity, bioaccumulation, biodegradation, chiral conversion*

■ INTRODUCTION

Pesticides are designed to control and prevent pests, weeds, and plant diseases in the fields and pastures, thereby improving productivity and food quality. The consumption of pesticides kept increasing as a consequence of the growing requirement for food production induced by the expanding global population. However, unreasonable application of pesticides may result in pesticide residues in the environment and in foods, making them a potential threat to public health. For instance, higher consumption of fruits and vegetables containing high pesticide residues had an association with lower chance of pregnancy and live birth after infertility treatment with assisted reproductive technology.[1]

The pesticide maximum residue limit (MRL) is the maximum residue concentration of a pesticide that is legally permitted or acceptable in agricultural commodity, food, or feed. The MRLs can differ significantly across countries that are not globally harmonized. For instance, China, US Environmental Protection Agency (EPA), European Union, Canada, New Zealand, and Japan all set respective MRLs for regulating the use of pesticides. A report published by European Food Safety Authority (EFSA) suggested about 5.1% of the foods on the European market in 2020 contained pesticide residues above European Union MRL when considering the measurement uncertainty.[2] A nationwide survey in China which investigated 733 pesticides in 134 types of fruits and vegetables from 2012 to 2017 showed that the over-standard (MRL Chinese national standards) frequency of pesticides is 2.9%.[3] A report provided by US Food and Drug Administration (FDA) demonstrated the frequency of pesticides exceeding MRL federal standards in domestic and import human foods from 2009 to 2017, which were 2.0% and 9.1%, respectively.[4] However, a study reviewed pesticide residues in fruits and vegetables in Middle East, and found the exceedance rate ranged from 1% to 61%.[5] Owing to the large population involved, it is extremely important to determine pesticide residues in foods.

Chirality is a phenomenon permeated in the natural world which arises from asymmetric arrangements, such as atoms, molecules, and larger structures. Chiral molecules could exist as two identical chemical structures, known as enantiomers, which are mirror images, but cannot be overlapped with each other. For instance, when a carbon atom is attached to four different substituents (atoms or functional groups), two absolute configurations which are mirror images of each other are possible (Figure S1A). When a chemical structure contains two asymmetric atoms, two pairs of enantiomers are possible (Figure S1B). Generally, enantiomers can be specified as *R*-form or *S*-form according to the Cahn−Ingold−Prelog standard sequence rule after determining the absolute configuration by the combination of experimental and calculated electronic circular dichroism spectra.[6] Enantiomers with unknown absolute configurations were commonly defined as (+)- or (−)-forms depending on the direction of rotation of plane-polarized light by solution.

The enantiomers have identical physical and chemical properties except for the rotation of plane-polarized light and exhibit similar behaviors in an abiotic environment. However, due to different spatial structures, enantiomers may exert

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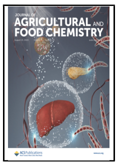

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Table 1. Chiral Analysis Methods of Pesticides in Foods from 2013 to 2022

Methods	Pesticides	Columns[a]	Matrixes	LODs	LOQs	Reference
HPLC-UV	Cyflumetofen	Chiralpak AD-H column	Cucumber, tomato and apple	0.1−0.15 mg·kg^{-1}	0.33−0.5 mg·kg^{-1}	27
HPLC-UV	Etoxazole	Lux Cellulose-1, Chiralpak IC, and Chiralpak AD columns	Cucumber, cabbage and tomato	0.015 mg·kg^{-1}	0.5 mg·kg^{-1}	13
HPLC-UV	Flufiprole	Lux Cellulose-2 column	Cabbage, cucumber, tomato, apple and grape	0.007−0.008 mg·kg^{-1}	0.021−0.025 mg·kg^{-1}	28
HPLC-UV	Flutriafol	Lux Cellulose-2 column	Cucumber, tomato, grape, pear and wheat	<0.015 mg·kg^{-1}	0.003−0.05 mg·kg^{-1}	29
HPLC-UV	Isofenphos-methyl	Lux Cellulose-3 column	Spinach, pak choi, cucumber, tomato and pear	0.008−0.011 mg·kg^{-1}	0.027−0.037 mg·kg^{-1}	30
HPLC-UV	Metconazole	Enantiopak OD column	Flour	0.69−0.90 mg·kg^{-1}	1.64−1.73 mg·kg^{-1}	31
HPLC-UV	Sulfoxaflor	ChromegaChiral CCA column	Brown rice, cucumber and apple	0.05−0.07 mg·kg^{-1}	<0.22 mg·kg^{-1}	32
HPLC-UV	Triticonazole	Lux Cellulose-2 column	Cucumber, tomato, pear, cabbage and apple	0.0012−0.0031 mg·kg^{-1}	0.0036−0.0091 mg·kg^{-1}	16
HPLC-MS/MS	Benalaxyl, Bromuconazole, Diniconazole, Epoxiconazole, Fenamiphos, Fenarimol, Fenbuconazole, Hexaconazole, Isocarbophos, Mandipropamid, Metconazole, Napropamide, Paclobutrazol, Penconazole, Profenofos, Prothioconazole, Tebuconazole, Tetraconazole, Triticonazole, Uniconazole	Chiralpak IG column	Cucumber, tomato, cabbage, grape, mulberry, apple and pear		0.33−1.50 ng·g^{-1}	24
HPLC-MS/MS	Carfentrazone-ethyl	Superchiral S-AD-RH chiral column	Brown rice, Rice husk, wheat and Corn	0.7−6.0 μg·kg^{-1}	2.5−20 μg·kg^{-1}	33
HPLC-MS/MS	Cloquintocet-mexyl	Homemade MDCPC chiral column [stationary phase: 3, −5-dichloro-phenylcarbamated mono-6-ethylenediamine-β-cyclodextrin]	Millet, enoki mushroom, oilseed rape, and watermelon	0.06−0.15 μg·kg^{-1}	0.2−0.5 μg·kg^{-1}	34
HPLC-MS/MS	Cyflumetofen	Trefoil AMY1	Apple	2.8−4.7 μg·L^{-1}	10 μg·L^{-1}	35
HPLC-MS/MS	Difenoconazole	Superchiral S-OX column	Citrus	0.0002−0.0004 mg·kg^{-1}	0.0044−0.011 mg·kg^{-1}	36
HPLC-MS/MS	Hexaconazole, tebuconazole, triticonazole, flutriafol, diniconazole, paclobutrazol	Self-made BCDP column [stationary phase: stilbene diamido-bridged bis(β-cyclodextrin)-bonded]	Apple, strawberry, banana, cucumber, tomato and *brassica campestris*	0.05−0.10 μg·kg^{-1}	0.20−0.30 μg·kg^{-1}	37
HPLC-MS/MS	Isocarbophos	Chiralpak AD-3R column	Orange pulp, peel and kumquat	0.2−0.5 μg·kg^{-1}		38
HPLC-MS/MS	Malathion	Chiralpak IC column	Chinese cabbage, apple and grape	1 μg·kg^{-1}	3−5 μg·kg^{-1}	39
HPLC-MS/MS	Mandipropamid	Lux Cellulose-2 column	Potato, pepper, grape and watermelon	0.2 μg·kg^{-1}	1 μg·kg^{-1}	40
HPLC-MS/MS	Mefentrifluconazole and ipfentrifluconazole	Chiral MX(2)-RH column	Orange, grape, cucumber, potato, wheat and soybean		5 μg·kg^{-1}	41
HPLC-MS/MS	Paclobutrazol, myclobutanil, diniconazole, and epoxiconazole	Chiralcel OD-RH column	Honey	0.005−0.028 ng·g^{-1}	0.017−0.093 ng·g^{-1}	42
HPLC-MS/MS	Penconazole	Lux Cellulose-2 chiral column	Cucumber, tomato, head cab-	0.5 μg·kg^{-1}	2.5 μg·kg^{-1}	43

Table 1. continued

Methods	Pesticides	Columns[a]	Matrixes	LODs	LOQs	Reference
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HPLC-MS/MS	Penthiopyrad	Superchiral S-IC column	Apple, cucumber, soybean, wheat, corn, potato, citrus, and grape	0.0015 mg·kg^{-1}	0.01 mg·kg^{-1}	44
HPLC-MS/MS	Permethrin	LiChroCART 250–4 ChiraDex column	Apple, orange, melon, green pepper, tomato, green bean and cabbage	0.2–0.3 μg·kg^{-1}	1.0–1.2 μg·kg^{-1}	45
HPLC-MS/MS-Qtrap	Triazolone, triadimenol, paclobutrazol, isocarbophos, indoxacarb	Chiralpak AD-RH column	Tea	0.2–1 μg·kg^{-1}	0.5–5 μg·kg^{-1}	46
HPLC-HRMS/MS	Indoxacarb	Superchiral S-OD column	Brown rice and Rice hulls	0.07–0.8 mg·kg^{-1}	6.25–25.0 mg·kg^{-1}	47
GC-MS/MS	Acephate, methamidophos	BGB-176 SE column	Cabbage, pakchoi	0.005–0.008 mg·kg^{-1}		48
GC-MS/MS	*cis*-bifenthrin *cis*-cyhalothrin Cypermethrin Cyfluthrin Permethrin Tetramethrin	BGB-172 column	Wild bird eggs	0.03–0.46 ng·g^{-1} lipid	0.10–1.54 ng·g^{-1} lipid	49
GC-MS/MS	Cyfluthrin, cypermethrin	β-Dex 325 column	Chicken, beef, fish, eggs, milk	0.002–6.43 ng·g^{-1} lipid	0.006–21.4 ng·g^{-1} lipid	50
GC-MS/MS	Fenpropidin, Fenpropimorph, and Spiroxamine	BGB-172 column	Grapes, Sugar Beets, and Wheat		0.001–0.02 mg·kg^{-1}	15
SFC-UV	Fenpropathrin	Chiralpak AD-3 chiral column	Apple puree, strawberry puree, and tomato puree		0.2 mg·kg^{-1}	51
SFC-UV	Triadimenol	Trefoil AMY1 column	Pumpkin puree, apple puree, and tomato puree		0.05 mg·kg^{-1}	52
SFC-UV	Triticonazole	EnantioPak OD column	Cucumbers and tomatoes	1.50–2.50 mg·kg^{-1}	2.50–4.50 mg·kg^{-1}	53
SFC-MS	Tebuconazole, myclobutanil, penconazole, metalaxyl, benalaxyl	Lux amylose-1 and Lux cellulose-5	Wine		0.5–2.5 ng·mL^{-1}	54
SFC-MS/MS	lambda-Cyhalothrin and metalaxyl	Lux Cellulose-1 and Lux Amylose-3 columns	Tomato, orange, leek and cayenne	<5 μg·kg^{-1}	<5 μg·kg^{-1}	19
SFC-MS/MS	Diniconazole	ChromegaChiral CCA column	Tea, grapes and apples	0.001 mg·L^{-1}	0.005–0.01 mg·kg^{-1}	55
SFC-MS/MS	Dinotefuran	Trefoil AMY1 3.0 column	Honey	0.5–2.5 μg·kg^{-1}	2.5–12.5 μg·kg^{-1}	17
SFC-MS/MS	Fenbuconazole	Trefoil AMY 1 column	Tomatoes, cucumbers, apples, peaches, rice and wheat	0.04–0.99 μg·kg^{-1}	0.13–3.31 μg·kg^{-1}	18
SFC-MS/MS	Flutriafol	Chiralpak IA-3 column	Tomato, cucumber, apple, grape	0.12–0.25 μg·kg^{-1}	0.41–0.83 μg·kg^{-1}	56
SFC-MS/MS	Isofenphos-methyl	Chiralpak IA-3 column	Wheat, corn, peanut	0.02–0.15 μg·kg^{-1}	0.06–0.50 μg·kg^{-1}	57
SFC-MS/MS	Metalaxyl	Trefoil CEL1 chiral column	Tobacco	0.006–0.007 mg·kg^{-1}	0.019–0.020 mg·kg^{-1}	58
SFC-MS/MS	Metalaxyl, benalaxyl and dimethenamid	ChromegaChiral CCA column	Four varieties of *Cannabis sativa*	0.04–0.41 μg·kg^{-1}	0.12–1.38 μg·kg^{-1}	59
SFC-MS/MS	Mevinphos	Trefoil AMY1 column	Tobacco	3.0–11.2 μg·L^{-1}	11–35 μg·L^{-1}	60

Table 1. continued

Methods	Pesticides	Columns[a]	Matrixes	LODs	LOQs	Reference
SFC-MS/MS	Penconazole, tebuconazole, triadimefon, myclobutanil, and triadimenol	Trefoil AMY 1 column	Tobacco	0.26−3.24 $\mu g\cdot kg^{-1}$	0.79−10.36 $\mu g\cdot kg^{-1}$	61
SFC-MS/MS	Propiconazole	Chiralpak AD-3 column	Wheat straw, wheat grain, grape	0.17−0.58 $\mu g\cdot kg^{-1}$	0.56−1.94 $\mu g\cdot kg^{-1}$	62
SFC-MS/MS	Pyrisoxazole	Chiralpak IA-3 column	Cucumber, tomato	0.03−0.15 $\mu g\cdot kg^{-1}$	0.09−0.48 $\mu g\cdot kg^{-1}$	63
SFC-MS/MS	Sulfoxaflor	Chiralpak IA-3 column	Cucumber, tomato		1.3−1.8 $\mu g\cdot kg^{-1}$	64
SFC-Q-TOF/MS	Diniconazole	ChromegaChiral CCA column	Tea, apple and grape	0.001 $mg\cdot L^{-1}$	0.005−0.01 $mg\cdot kg^{-1}$	55

[a] Stationary phase of the commercial columns. Chiralpak AD/Chiralpak AD-H/Chiralpak AD-RH/Chiralpak AD-3/Chiralpak AD-3R/Superchiral S-AD-RH/Lux amylose-1/ChromegaChiral CCA/Trefoil AMY1 column: amylose tris(3,5-dimethylphenylcarbamate) coated on silica gel. Lux amylose-3 column: amylose tris(3-chloro-5-methylphenylcarbamate) coated on silica gel. Chiralpak IA-3 column: amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel. Chiralcel OD-RH/Enantiopak OD/Superchiral S-OD/Lux Cellulose-1/Trefoil CEL1 column: cellulose tris(3,5-dimethylphenylcarbamate) coated on silica gel. Lux Cellulose-2/Superchiral S-OX column: cellulose tris(3-chloro-4-methylphenylcarbamate) coated on silica gel. Chiral MX(2)-RH column: cellulose tris(4-chloro-3-methylphenylcarbamate) coated on silica gel. Lux cellulose-3 column: cellulose tris(4-methylbenzoate) coated on silica gel. Lux cellulose-5 column: cellulose (3,5-dichlorophenyl carbamate) coated on silica gel. Chiralpak IC/Superchiral S-IC column: cellulose tris(3,5-dichlorophenylcarbamate) immobilized on silica gel. Chiralpak IG column: cellulose tris(3-chloro-5-methylphenylcarbamate) immobilized on silica gel. LiChroCART 250-4 ChiraDex column: covalently bonded β-cyclodextrin. CP-Chiralsil-Dex CB column: heptakis(2,3,6-tri-*O*-metil)-β-cyclodextrin directly bonded to dimethylpolysiloxane. BGB-176 SE column: coated with 20% 2,3-dimethyl-6-(*tert*-butyldimethylsilyl)-β-cyclodextrin dissolved in SE-52 (5% phenyl-, 95% methylpolysiloxane). BGB-172 column: coated with 20% (*tert*-butyldimethylsilyl)-β-cyclodextrin dissolved in BGB-15 (15% phenyl-, 85% methylpolysiloxane). β-Dex 325 column: (nonbonded) 25% 2,3-di-*O*-methyl-6-*O*-(*tert*-butyldimethylsilyl)-β-cyclodextrin.

different affinities for particular proteins, such as receptors, transporters, and enzymes. Therefore, enantiomers have greatly different behaviors in a biotic environment (i.e., enantioselectivity). A prominent example is thalidomide. *R*-(+)-Thalidomide displayed good therapeutic effects in the treatment of erythema nodosum leprosum, whereas *S*-(−)-thalidomide proved to be a potent human teratogen, which caused birth defects. Due to racemization in vivo, infants delivered from mothers who had taken thalidomide during their pregnancy had severe teratogenic congenital disabilities. Previous researchers found some chiral pesticides showed enantioselective activity, toxicity, accumulation, and metabolism rates. For instance, *R*-(−)-tebuconazole exerted 16.8−68.4-fold higher activity than *S*-(+)-tebuconazole against three common pathogens in apple grooves (*Botryosphaeria berengeriana*, *Colletotrichum gloeosporioides*, and *Alternaria alternate*).[7] The toxicity of *S*-dinotefuran on two species of honeybees (*Apis mellifera* and *Apis cerana*) was 20−114 times greater than that of *R*-dinotefuran.[8] The accumulation and metabolism rates of *S*-lactofen in *Lemna minor* were significantly higher than those of *R*-lactofen.[9] Therefore, enantioselectivity should be taken into consideration in the risk assessment and application of chiral chemicals. However, because enantioselectivity is not addressed in pesticide legislation, the majority of chiral pesticides are still manufactured and utilized as a racemic mixture.

Food intake is closely related to organisms and human health. Pesticide enantiomers remaining in foods may interact with enzymes or proteins in the organism's internal environment in different ways, resulting in dramatic different behaviors and health risks. The aim of this Review is to provide a comprehensive overview of the enantioselective behaviors and enantiomeric signatures of chiral pesticides in foods and the environment. First, we summarized the information on chiral analysis methods, which are necessary to achieve enantioseparation and further quantification. Second, the enantiomer-specific residues and enantioselective dissipation of chiral pesticides in the environment were elucidated. Next, we elaborated the enantiomer-specific occurrence, enantioselective bioaccumulation, and biodegradation behaviors of chiral pesticides in foods. Furthermore, the chiral interconversions of pesticides in the biotic environment were discussed. This Review highlighted the importance of exploring the enantioselectivity of chiral pesticides in the environment and foods, which is of great significance to the health risk assessment of chiral pesticides and the production of optically pure pesticides.

■ CHIRAL ANALYTICAL METHODS

Analysis of chiral pesticides on an enantiomeric level relies on techniques for enantioseparation, in which high performance liquid chromatography (HPLC), gas chromatography (GC), and supercritical fluid chromatography (SFC) are most heavily employed. The analytical technique most suitable for a specific pesticide is highly dependent on its physicochemical properties. Table 1 presents the chiral analysis methods of pesticides in foods from 2013 to 2022.

■ HPLC

To date, HPLC is the most preferred analytical technique for a majority of chiral chemicals, especially for thermally unstable substances. It features several advantages, such as a great variety of chiral column types, many operation modes in separation, and good compatibility with different detectors, but consumes more organic solvents. Among commercially available chiral columns, polysaccharide-based columns are the most popular due to their excellent enantiomer resolutions capability, such as amylose tris(3,5-dimethylphenylcarbamate) and cellulose tris(3,5-dimethylphenylcarbamate) (Table 1). For instance, simultaneous separation and determination of nine pairs of chiral pesticide (indoxacarb, benalaxyl, carfentrazone-ethyl, quizalofop-ethyl, isocarbophos, fenamiphos, simeconazole, napropamide, paclobutrazol) enantiomers were realized using a Chiralpak AD-RH column coated with amylose-tris(3,5-dimethylphenylcarbamate).[10] Due to the possible modifications of stereospecific conformation during immobilization, immobilized polysaccharide-based chiral columns have lower chiral recognition potential than columns coated with polysaccharides.[11] The molecular mechanisms of chiral recognition employing chiral stationary phase in HPLC has been comprehensively reviewed.[12] HPLC separations can be performed under three modes, reverse-phase, normal-phase, and polar organic mobile-phase modes. The reverse-phase HPLC is the most frequently utilized due to its compatibility with mass spectrometry detectors. Commonly, higher enantiomeric separation resolution was obtained in normal-phase conditions than in reverse-phase conditions. For instance, etoxazole enantiomers can be baseline separated under normal-phase and reverse-phase HPLC, and better resolution was observed under normal-phase HPLC.[13] However, the mobile phase under normal-phase conditions is incompatible with mass spectrometry detectors, thus hampering its application in trace analysis. Due to the great solubility of analyte in the mobile phase, polar organic mobile-phase HPLC can achieve fast analysis, which has become increasingly popular in chiral analysis. Merino et al. developed an enantioseparation method for 17 pesticides on immobilized amylose tris(3-chloro-5-methylphenyl-carbamate) column under polar-organic conditions.[14]

■ GC

GC is the best choice for the analysis of volatile and thermally stable pesticides, such as organochlorine, organophosphorus, and pyrethroids pesticides. GC presents advantages of high efficiency, easy coupling with MS and no consumption of organic solvents. However, the limited types of chiral columns have restricted its application in chiral analysis. Besides, the high temperature used in GC may trigger the chiral inversion of the thermally unstable enantiomer. Some nonvolatile chiral pesticides may also be analyzed after derivatization with an achiral reagent prior to the GC measurement. However, the derivatization process significantly increased the pretreatment time and may bring about racemization of the pesticide enantiomers. Among commercially available chiral columns, cyclodextrin derivative-based columns are the most frequently employed (Table 1). The enantiomeric separation of amorolfine, fenpropidin, fenpropimorph, and *cis*- and *trans*-spiroxamine was achieved on a BGB-172 column, which is coated with 20% (*tert*-butyldimethylsilyl)-β-cyclodextrin in 15% phenyl- and 85% methylpolysiloxane.[15]

■ SFC

Despite the short history, SFC has gained more popularity in chiral analysis, not only due to its high-resolution capacity and shorter analysis times and equilibration times but also due to the reduced usage of organic solvents. Rapid and highly efficient separations of chiral compounds with various polarities can be achieved in SFC. The enantioseparation of triticonazole, dinotefuran, and fenbuconazole can be achieved in 3 or 4 min using SFC.[16−18] The chiral columns used in SFC are similar to that in HPLC, and polysaccharide-based columns are also the most commonly utilized (Table 1). Efficient SFC separation of 21 chiral pesticides was realized in 18 min using coated with cellulose tris(3,5-dimethylphenylcarbamate) as the chiral stationary phase.[19]

Two-dimensional chromatography may achieve simultaneous separation of various chemicals with greatly different polarities and provide remarkably higher separation efficiency and peak capacity than one-dimensional chromatography, which has attracted increasing attention. Two-dimensional chromatography can also be applied to the enantiomeric analysis of chiral pesticides. For instance, chiral × achiral comprehensive two-dimensional liquid chromatography (LC × LC) technique was developed and successfully separated 17 chiral pesticides, in which a chiral column was applied as the first-dimension column to separate the pesticide enantiomers and an achiral column was applied in the second dimension to separate different pesticides.[20] Chiral × achiral two-dimensional high-resolution GC technique (GC × GC) successfully separated 17 chiral congeners of pesticide toxaphene in laying hens and eggs.[21] However, the long analysis time has limited its application in enantiomeric determination.

Among various detectors, ultraviolet (UV), tandem mass spectrometry (MS/MS) and high-resolution mass spectrometry (HRMS) detectors are the most often employed in chiral analysis. UV is a nondestructive technique; however, it could only analyze chemicals having UV absorption. Due to the significant enhancement of analytical sensitivity, detectors based on MS could analyze trace pesticide enantiomers in foods, which has become the most prominent tool to measure pollutants in foods.

It is possible to achieve multipesticide residue analysis using HPLC-MS/MS or GC-MS/MS equipped with achiral columns, but scarce studies have faced on multipesticide enantiomeric analysis using chiral columns. This may be because of the difficulty in simultaneously chiral separation of multiple pesticides on one chiral column. For instance, Zhang et al. used 11 chiral columns to analyze enantiomeric concentrations of 17 chiral pesticides in the environment.[22] Two chiral columns (α1-acid glycoprotein column and human serum albumin column) were used to investigate the enantiomeric compositions of four chiral pesticides (econazole, ketoconazole, miconazole, and tebuconazole).[23] The use of two or more columns would greatly increase the analysis time. Some research found that certain chiral columns exerted greater enantiomeric separation potential for chiral pesticides. Simultaneous chiral analysis of 22 pesticides can be realized using the Chiralpak IG column.[24,25] Simultaneous separation for enantiomers of four chiral pesticides (metalaxyl, napropamide, triticonazole, and metconazole) was achieved on the Lux 3u Cellulose-4 column.[26] Enantioseparation of 17 chiral pesticides was achieved, in which the Chiralpak IG column showed greater separation ability than Lux Cellulose-2 and Lux Cellulose-4.[20]

■ ENANTIOSELECTIVE DISSIPATION IN THE ENVIRONMENT

The enantiomer fraction (EF) value, which generally defined as the concentration of *R*-enantiomer compared to the total concentration of *R*- and *S*-enantiomer (or the concentration of (−)-enantiomer compared to the total concentration of (−)- and (+)-enantiomer), is considered a good indicator to describe the enantioselectivity of chiral compounds. Generally, EF values ranged from 0 to 1. EF < 0.5 means an enrichment of *S*-enantiomer (or (+)-enantiomer), while EF > 0.5 means an excess of *R*-enantiomer (or (−)-enantiomer), and EF $= 0.5$ means equal amounts of individual enantiomers (i.e., racemate or racemic mixture).

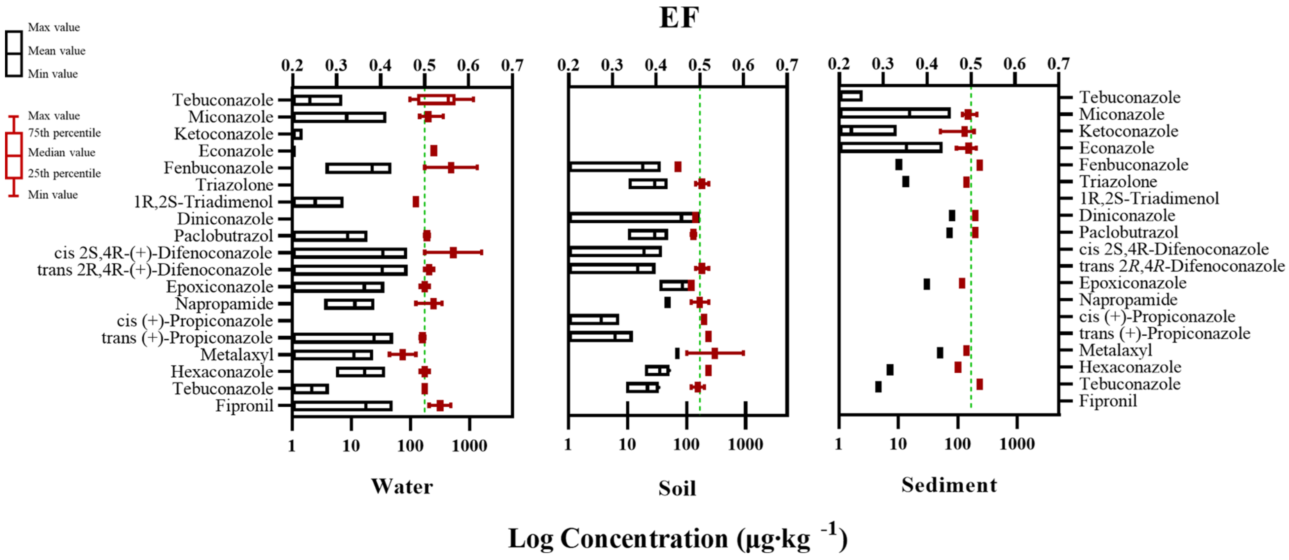

Figure 1. Concentrations (black floating bar) and EFs (red box and whisker plots) of chiral pesticides detected in environmental water, soil, and sediment. Data from refs 23 and 25.

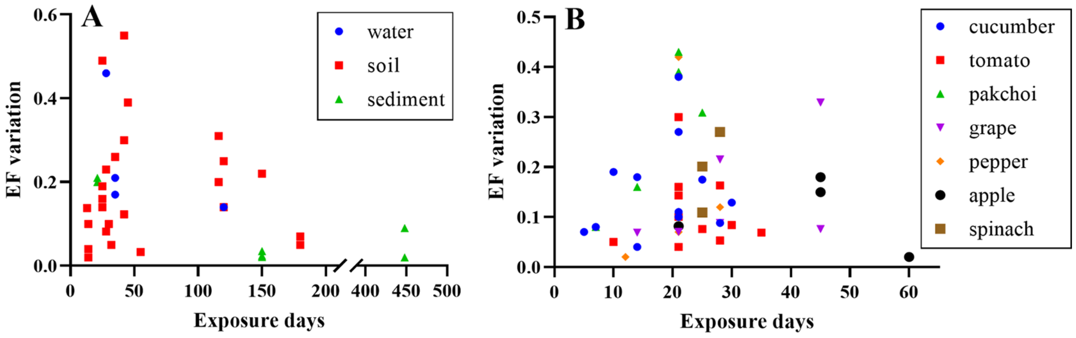

Figure 2. EF variation of chiral pesticides (A) in the environmental matrixes and (B) in foods during cultivation process with exposure time (data from Table S1 and Table S2).

■ ENANTIOMER-SPECIFIC RESIDUES

Generally, chiral pesticides were introduced into the environment as racemate; however, enantiomers may exhibit enantioselective dissipation in the environment, thereby leading to enantiomer-specific residues in the environment. Figure 1 presented enantiomeric profiling of some chiral pesticides in environmental water, soil, and sediment. The concentrations of chiral pesticides in environmental water, soil, and sediment were generally below 100 $\mu g \cdot L^{-1}$ or $\mu g \cdot kg^{-1}$, and the EF values were commonly in the range 0.4−0.6. However, some chiral pesticides may exert strong enantiospecific residues in the environment. An investigation across China found the residues of *R*-enantiomers of metalaxyl and triticonazole in agricultural soils were significantly greater than residues of the corresponding *S*-enantiomers.[26] Strong enantiomer-specific residues of ethiprole and difenoconazole were found in sediments in peri-urban areas near Yangtze River, with EF values in the range 0.04−0.20 and 0.50−0.88, respectively.[22] Currently, the occurrence characteristics of chiral pesticides in the environment have remained poorly documented. Most studies on pesticide residues in the environment only determined the total amount of chiral pesticides rather than the contents of the enantiomers.[65]

■ ENANTIOSELECTIVE DISSIPATION PROCESS

The enantiomer-specific residues in the environment were mainly due to the pesticide enantiomer dissipating in the environmental matrixes (soil, sediment, and water) at different rates. Generally, the dissipation of pesticides followed first-order kinetics, and the half-life is a key parameter to describe the kinetics of pesticides, which is the time required for half of the pesticides to be dissipated. The dissipation half-life can be calculated by $T_{1/2} = 0.693/k$, where k is the dissipation rate constant. Short half-life means pesticides dissipated quickly, and long half-life means pesticides dissipated slowly. Table S1 shows the enantioselective dissipation of chiral pesticides in the environmental matrix. The dissipation of *R*-(+)- and *S*-(−)-ethiprole in soil under field conditions after application was investigated, and the results demonstrated EF values of ethiprole increased from 0.494 to 0.884 during the 45-day experiment, suggesting relative enrichment of the *S*-(−)-ethiprole in soil. This was owing to the fact that the dissipation of *R*-(+)-ethiprole was faster than that of *S*-(−)-ethiprole, with the half-lives of 11.6 and 34.7 days, respectively.[66] Field and laboratory experiment proved the preferential dissipation of (−)-*cis*-bifenthrin and (−)-*cis*-permethrin in sediment.[67] The enantioselectivities in various environmental matrixes may be the same or different. *S*,*R*-(−)-Epoxiconazole degraded faster than *R*,*S*-(+)-epoxiconazole in soil, river sediment and water.[68]

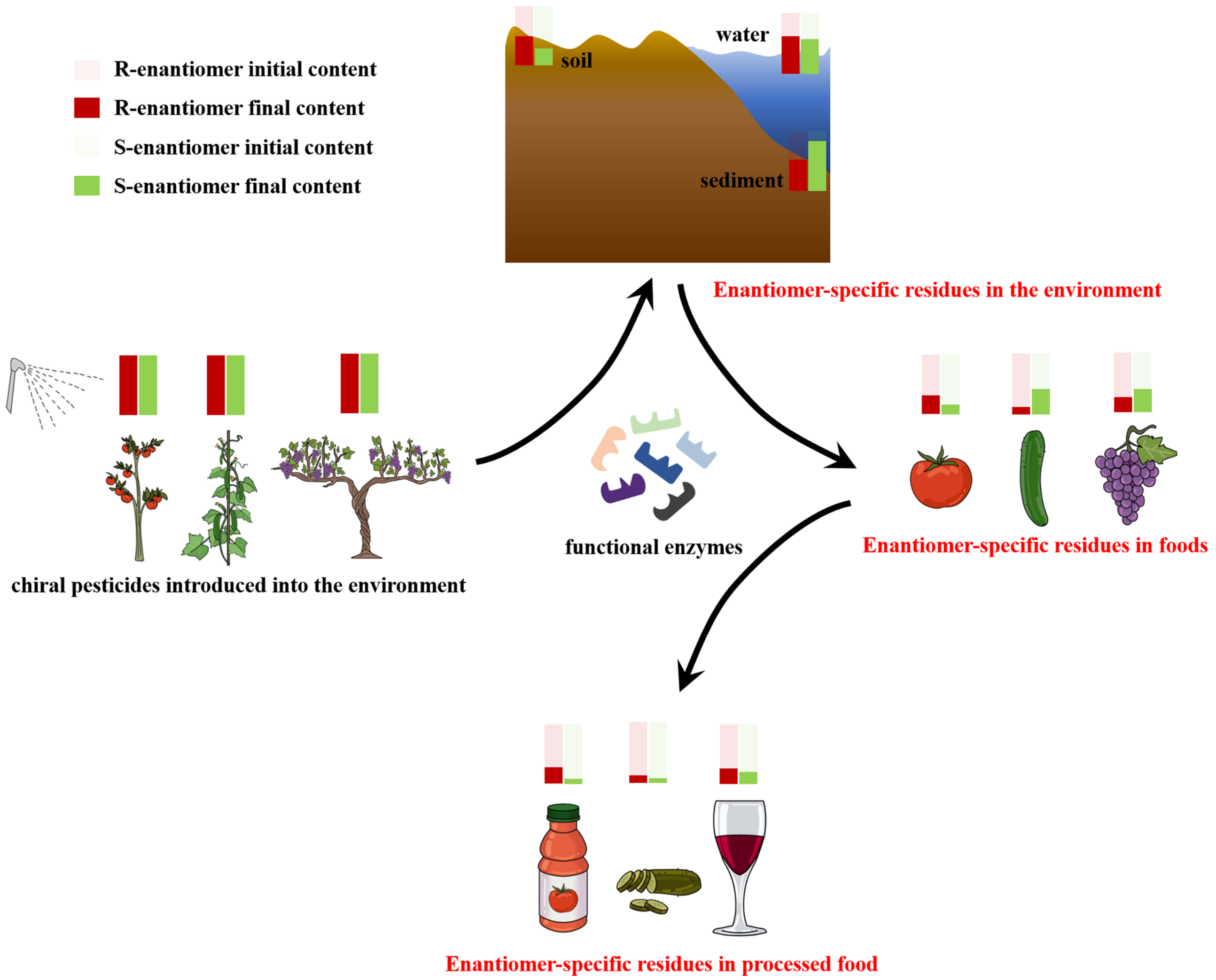

Figure 3. Schematic diagram of enantiomer-specific residues in foods of chiral pesticides mediated by functional enzymes in the biotic environment.

However, 1*R*-*cis*-α*S*-cypermethrin showed a faster degradation rate than 1*S*-*cis*-α*R*-cypermethrin in soil and sediment. The preferential dissipation of *S*-*cis*-permethrin in soil was found, while the reverse preference was found in sediment.[69] Enantioselective dissipation of fluazifop-butyl in soils was found which was not observed in water with different pHs (4.0, 7.4, and 9.0).[70]

A relatively large number of studies have evaluated the enantioselective dissipation of chiral pesticides in the environment. As displayed in Figure 2A, most experiments were conducted in soil. The findings demonstrated that the enantioselective dissipation may be dramatically different in various soils. For instance, different dissipation preferences were found in different types of Chinese soils. *S*-Pyraclofos was preferentially degraded in soil from Nanchang, an opposite preference was found in soil from Hangzhou, and no enantioselectivity was observed in soil from Zhengzhou.[6] The dissipation rate of *R*-(+)-quizalofop-ethyl was greater than that of *S*-(−)-quizalofop-ethyl in soils from Xinxiang and Dazhou, whereas the enantioselectivity was reversed in soil from Nanchang.[71] The preferential degradation of *R*-fluazifop-butyl was found in soil from Beijing; however, *S*-fluazifop-butyl dissipated faster in soil from Anhui.[70] Generally, the enantioselective behavior of pesticides can be affected by the physicochemical properties of soil, such as pH, organic matter, moisture, temperature and soil texture.[72] A previous study investigated the enantioselective dissipation of metalaxyl in 20 different soils covering a broad range of properties and found the enantioselectivity in aerobic soils was correlated with pH. *S*-Metalaxyl degraded preferentially in soils with pH < 4, whereas reversed preference was found in soils with pH > 5. *R*- and *S*-metalaxyl exerted similar dissipation rates in soils with pH 4−5.[73] Similarly, preferential dissipation of (+)-imazamox was found in neutral soils, and an opposite enantioselectivity was observed in strongly acidic soils, while no enantioselectivity occurred in slightly acidic soils.[74] Soil enrichment with organic nutrient could shift the enantioselectivity of dichlorprop toward the preferential dissipation of the *S*-dichlorprop.[75] *R*-(−)-Mandipropamid degraded more rapidly than *S*-(+)-mandipropamid in four types of soils, resulting in relative enrichment of the *S*-(+)-mandipropamid. The dissipation rates of enantiomers may be affected by the temperature to a different extent. The half-lives of the *R*-(−)- and *S*-(+)-mandipropamid in soil decreased 1.07−1.95 and 1.08−1.79 times with each 10 °C increase in incubation temperature, respectively. Moisture contents showed similar effects on the dissipation rate of enantiomers.[76] There were significant positive correlations between enantioselectivity of myclobutanil and soil texture (including clay, silt and sand contents).[77]

The coexisting pollutants might also affect the chiral selective dissipation of pesticides in the environment. The EF value of α-cypermethrin in soil ranged from 0.42 to 0.44 during the 90-day experiment, indicating the (+)-(1*R*,*cis*,α*S*) enantiomer dissipated preferentially. However, the EF of α-cypermethrin was nearly 0.5 when soil was contaminated with 10−50 mg/kg Pb^{2+} or Cd^{2+}, indicating no enantioselectivity of α-cypermethrin happened in the presence of 10−50 mg/kg Pb^{2+} or Cd^{2+}.[78] Preferential enrichment of *R*-quizalofop-ethyl in soil amended with biosolids was found; however, no enantioselectivity occurred when soil was amended with biosolids containing ZnO.[79] Similarly, the presence of ZnO or TiO_2 nanoparticles inhibited the enantioselective dissipation of metalaxyl in soil.[80] However, the coexistence of oxytetracycline had very limited influence on the enantioselective degradation of beta-cypermethrin in soil.[81] The presence of norfloxacin had no effect on the enantioselectivity of acetochlor in sediment.[82]

MECHANISM OF ENANTIOSELECTIVE DISSIPATION

As a matter of fact, microorganisms play a pivotal role in the enantioselective degradation process of pesticides in the environment, leading to enantioselective enrichment of chiral pesticides in soil, sediment, and water (Figure 3). After cultivation for 60 days, the EF values of imazethapyr in unsterilized soils were 0.530−0.581, which were significantly higher (0.502−0.506) than those in sterilized soils.[83] The preferential dissipation of (−)-hexaconazole, (−)-flutriafol, and (−)-tebuconazole was found in native sediment, whereas no enantioselectivity took place in sterilized sediment.[84] In periurban areas near Yangtze River, different enantioselectivities of tebuconazole were found in different sites of sediment, which was closely associated with the genus *Arenimonas*.[22] These results indicated that enantioselectivity occurred under the effect of active microorganisms, especially specific functional microorganisms. A bacterial strain *Sphingopyxis* sp. DBS4 isolated from contaminated soil preferentially removed *S*-dichlorprop as compared to *R*-dichlorprop.[85] Preferential dissipation of *R*-mandipropamid in soil was observed, which mainly relied on six bacterial genera (*Burkholderia, Paraburkholderia, Hyphomicrobium, Methylobacterium, Caballeronia,* and *Ralstonia*) in soil. And three bacterial genera (*Haliangium, Sorangium,* and *Sandaracinus*) were responsible for the dissipation of the *S*-mandipropamid.[86] A study isolated 50 microorganisms from agricultural soils and found a strain of *Brevibacillus brevis* was responsible for the enantioselective dissipation of fungicides metalaxyl and furalaxyl.[87] Zhai et al. investigated the dissipation of prothioconazole in five soils, and found the enantioselectivity may be caused by *Proteobacteria, Fusobacteria, Firmicutes, Thaumarchaeota, Saccharibacteria, Chloroflexi, Chlorobi, Actinobacteria* and *Nitrospirae*.[72] *Cupriavidus nantongensis* $X1^T$ isolated from contaminated soil was responsible for the enantioselective dissipation of isocarbophos, isofenphos-methyl, and profenofos.[88,89]

The enantioselective degradation of chiral pesticides by functional microorganisms may proceed via three routes: (1) microorganisms express two functional enzymes, and each of them only transforms a single enantiomer. (2) Microorganisms express a single functional enzyme for exclusively converting a single enantiomer. (3) Microorganisms express a single functional enzyme which could metabolize enantiomers at different rates.[90] A study investigated the relationship between functional microorganisms in soil and enantioselectivity, and the results showed that the enantioselectivity dominantly managed by the activation of metabolically quiescent microorganisms or the induction of enantiomer-specific enzymes.[75] The environmental conditions (pH, organic matter, moisture, temperature, and soil texture) and the coexisting pollutants may alter the enantioselectivity by influencing the activity of the soil microorganisms or enzymes in the charge of degrading enantiomers. Due to different groups of related microbial genotypes being activated, enantioselective preference can be reversed in different environmental conditions.[75] Significant environmental changes, such as tropical deforestation and global warming, may considerably change the enantioselectivity of chiral chemicals by altering the microbial community composition.[75] Currently, the specific mechanisms for the enantioselective degradation of each pesticide are still not fully understood, owing to the difficulty in identifying the complicated microbial communities involved in enantioselective degradation.

Moreover, extracellular enzymatic activity also contributes to the enantioselective dissipation of pesticides in the environment. Preferential dissipation of *R*-metalaxyl was found in soil without active microorganisms but remaining extracellular enzymatic activity, suggesting the role of extracellular enzymatic activity in the enantioselective dissipation processes.[91] Besides, due to the chiral structures in soil and sediments, such as minerals and organic matters, the sorption process of metalaxyl on soil proved to be enantioselective, leading to enrichment of *R*-metalaxyl in soil.[92]

ENANTIOSELECTIVE BIOACCUMULATION IN FOODS

Plants and animals can absorb pesticides from an ambient environmental medium and accumulate them in their tissues. The net process by which a pollutant is taken up by an organism as a result of uptake through all possible routes of exposure, such as air, soil, water, sediment, and foods, is called bioaccumulation. Bioaccumulation factor (BAF), the concentration ratio between an organism and the surrounding medium, can be used to describe the accumulation capacity. Both field and laboratory results proved that the bioaccumulation process of chiral pesticides is enantioselective.

FIELD STUDY

Previous field study largely focused on the enantioselective bioaccumulation of organochlorine pesticides in edible plants and animals, such as zucchini, pumpkin, cucumber, lettuce, spinach, pepper, tomato,[93] salmon,[94] Arctic cod,[95] and lake fish.[96] Recent field research has started to explore the enantioselective bioaccumulation of other pesticides. Corcellas et al. investigated the levels and enantiomer signatures of four pyrethroids (permethrin, cyhalothrin, cyfluthrin, and cypermethrin) in edible river fish in Iberian river basins in Spain.[97] The concentration of pyrethroids ranged from 12 to 4938 ng·g^{-1}, and enantioselective bioaccumulation was found, which depended on the studied species. For instance, the EFs of *cis*-permethrin 1 in barbels and trouts were 0.27−0.47 and 0.41−0.45; however, EF was 0.58−0.76 in gudgeons, revealing preferential enrichments of different enantiomers.[97] Currently, except for organochlorine pesticides, the field study of the

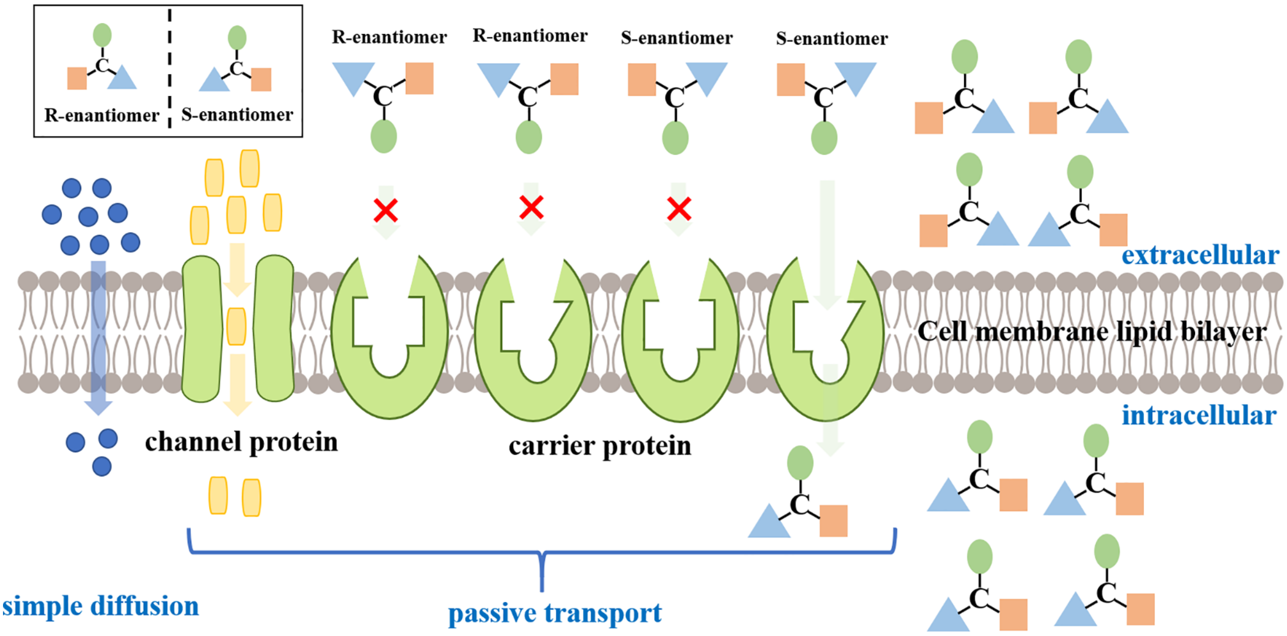

Figure 4. Schematic diagram of enantiomer-specific enrichment of chiral pesticides in organisms.

enantioselective bioaccumulation of pesticides is quite limited and still needs to be further investigated.

LABORATORY STUDY

The uptake of metalaxyl by lettuce from soils was enantioselective, with the preferential accumulation of *R*-metalaxyl.[98] Loaches were exposed in water spiked with racemic flufiprole to investigate the bioaccumulation charactersstics, and the BAF values for *R*- and *S*-flufiprole in loach (*Misgurnus anguillicaudatus*) were 14.8 and 47.7 after 22 days of exposure, respectively, indicating *S*-flufiprole was preferentially bioaccumulated in loach.[99] Similarly, enantioenrichment of (+)-α-HCH was found in loaches after exposed to rac-α-HCH.[100] The bioaccumulation of cypermethrin on the freshwater mussel *Unio gibbus* was enantioselective, with the preference of 1*R*-3*R*-α*R*-cypermethrin and 1*S*-3*S*-α*R*-cypermethrin.[101] Laying hens were fed with processed animal feed contaminated with organochlorine pesticides for 30 days, and preferential enrichment of (−)-*cis*-chlordane in muscle and egg yolk of laying hens was observed.[102] However, the laboratory research on enantioselective bioaccumulation mainly concentrated on model organisms, such as rats, earthworms, and zebrafish. In order to comprehensively evaluate the risks of chiral pesticides, more studies on enantioselective bioaccumulation of chiral pesticides in foods, especially edible fish, is required.

MECHANISM OF ENANTIOSELECTIVE BIOACCUMULATION

Cell membranes serve as robust biological barriers to retard the entrance of xenobiotics. Most pesticides were absorbed across cell membranes via carrier-mediated processes, and the accumulation in organism cells is energy-dependent.[103,104] Enantioselectivity may occur during carrier-mediated processes due to some carrier proteins exhibiting enantioselective substrate recognition (Figure 4), leading to enantioselective bioaccumulation of pesticides in organisms, such as P-glycoprotein, organic anion transporters, organic cation transporters and peptide transport proteins.[105] Enantioselective transport of cetirizine across Caco-2 cell monolayers was observed, in which P-glycoprotein and multidrug resistance-associated protein involved in the relevant process.[106,107] Organic anion transporter peptides mediated the enantioselective absorption of fexofenadine by Caco-2 cells.[108] Bioaccumulation may favor only one enantiomer, or the two enantiomers showed different bioaccumulation properties. For instance, the absorption rate of *R*-esmolol by Caco-2 cells was higher than that of *S*-esmolol due to different transporters participating in their transport.[109] The preference of stereoselectivity and the enantioselective bioaccumulation properties proved to be species-specific, tissue-specific, concentration-dependent, and transporter-dependent.[105] Therefore, though quite a few studies have investigated the enantioselective bioaccumulation of chiral pesticides in model organisms, it is still hard to predict the enantioselective bioaccumulation behavior of pesticides in foods, which still needs further study.

ENANTIOSELECTIVE BIODEGRADATION IN FOODS

Except for some persistent pesticides, such as organochlorine pesticides, most pesticides in foods can be gradually degraded under the function of intrinsic enzymes or additional enzymes, in which the process usually occurs in cultivation and processing. Previous research indicated that the degradation rates of pesticide enantiomers in foods may be significantly different; i.e., the degradation process can be enantioselective.

CULTIVATION PROCESS

Studies on enantioselective degradation during cultivation process were mainly conducted on crops, vegetables, and fruits in the field (Table S2). The half-lives of *R*-(−)- and *S*-(+)-triticonazole in pear were 5.02 and 2.01 days, respectively, indicating the preferential degradation of *S*-(+)-triticonazole and the relative enrichment of *R*-(−)-triticonazole in pear.[110] The degradation rate of *S*-(−)-novaluron in tomatoes was greater than that of *R*-(+)-novaluron, leading to relative

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enrichment of *R*-(+)-novaluron in tomatoes.[111] Enantioselective degradation of oxathiapiprolin in tomato and pepper was found, with *R*-(−)-oxathiapiprolin preferentially degraded.[112] *S*-(−)-Tetraconazole showed a higher degradation rate in rice than its enantiomer.[113] (+)-Indoxacarb was preferentially degraded in fresh tea leaves.[114] Degradation of the *R*-isocarbophos in rice was faster than that of the *S*-isocarbophos.[115] The final residue of (−)-tebuconazole in wheat was higher than the residue of its enantiomer.[116] Similarly, an enantioselective residue of dinotefuran in rice was observed.[117] After pesticide application, the EF variations of chiral pesticides remaining in agricultural products were commonly below 0.3 (Figure 2B). The residues of (+)-*S*-tebuconazole decreased more rapidly than those of (−)-*R*-tebuconazole in cucumber, with the EF values decreasing from 0.500 to 0.310 after 10 days, resulting in relative enrichment of the (−)-*R*-tebuconazole in cucumber.[118] The degradation of *S*-(+)-penthiopyrad in cucumber and tomato was faster than that of *R*-(−)-penthiopyrad under greenhouse and open field conditions, with the EF ranging from 0.50 to 0.80 during a 21-day experiment.[119] However, some chiral pesticides exhibit strong enantioselectivity. The EF values of acephate in pakchoi increased from 0.533 to 0.963 after 21 days, indicating *S*-acephate was preferentially degraded and *R*-acephate was enriched in pakchoi.[120] The EF values of dufulin decreased from 0.499 to 0.082 after 14 days, suggesting *R*-dufulin degraded significantly faster than the corresponding *S*-enantiomer in watermelon.[121] Preferential degradation of (+)-hexaconazole was found in head cabbage, with the EF values changing from 0.5 to 0.0 after 21 days.[122] Enantioselectivities can occur in various agricultural products, which may be the same or different. *S*-Diniconazole showed faster degradation than *R*-diniconazole in four kinds of fruits (apple, pear, jujube, and peach).[123] (−)-*R*-zoxamide was preferentially degraded in tomato, an opposite preference was found in pepper and grape, and no enantioselectivity was observed in cucumber.[124] *S*-(+)-Mandipropamid degraded more rapidly than the *R*-(−)-mandipropamid in tomato and Chinese cabbage, whereas reversed preference was found in cucumber and cowpea.[125] In addition, the enantioselectivity can also be influenced by pesticide application modes. Stronger enantioselectivity of myclobutanil in cucumber was found under root douche treatment in comparison with foliar spraying treatment.[126] However, the degradation process of dinotefuran in tomato by foliage treatment exhibited stronger enantioselectivity than that by root treatment.[127]

Currently, the enantioselective degradation of chiral pesticides in foods of animal origin is still frequently overlooked. Loaches were exposed to racemic flufiprole until an accumulation equilibrium was reached. After transfer into clean water, the EF of flufiprole in loach *Misgurnus anguillicaudatus* increased from 0.50 to 0.73, suggesting *S*-flufiprole was preferentially degraded.[99] Enantioselective degradation of tebuconazole was found in rabbit muscle after intravenous administration of racemate, with *S*-(+)-tebuconazole being preferentially degraded.[128] The residue of *R*-flutriafol was significantly higher than that of *S*-flutriafol in rabbit meat after intravenous administration of racemate.[129] Similarly, the level of (−)-fluoroxypyr methylheptyl ester was higher than that of its corresponding enantiomer in rabbit muscle after administration of racemate.[130]

■ PROCESSING PROCESS

The agricultural products can be processed by different techniques into various popular food products after harvest. Common food process techniques include washing, peeling, drying, fermentation, cooking, roasting, frying, boiling, freezing, infusion, and juicing. An investigation by EFSA found the exceedance rates of pesticide residues in unprocessed and processed foods from European market in 2018 were 4.7% and 3.6%, respectively.[131] This may be due to the fact that the majority of process techniques could reduce pesticide residues, which was affected by the physicochemical properties of pesticides, the type of techniques and foods.[132,133] However, few studies have been published to discuss the influence of processing on the enantioselectivity of chiral pesticides.

Previous research reported that enantioselectivity may occur during food processing process, especially fermentation process. Wine is a popular alcoholic beverage consumed for thousands of years, which is made by fermentation of rice, sorghum, grape, and other cereal and fruits. Famoxadone residue in apple cider and grape wine was reduced during the wine-making process. The half-life of *R*-(−)-famoxadone was lower than that of *S*-(+)-famoxadone, with the half-lives being 231.0 and 346.5 h, respectively, indicating the preferential dissipation of *R*-(−)-famoxadone.[134] Similarly, triadimefon dissipated during barley storage and beer brewing. *S*-Triadimefon was preferentially degraded, resulting in relative enrichment of *R*-triadimefon in beer.[135] The dissipation rate of *R*-metamifop in the fermentation of rice wine was greater than that of its enantiomer.[136]

Enantioselective degradation of mandipropamid was found during wine-making process, with *R*-mandipropamid preferentially degrading, resulting in the enrichment of *S*-mandipropamid in grape wine.[137] (+)-Cyflumetofen was degraded in preference to (−)-cyflumetofen during apple wine and apple vinegar fermentation.[138] Zoxamide was selectively degraded during wine-making process, with *R*-zoxamide degrading faster in red and white wine.[139] Diclofop-methyl enantiomers exerted the different degradation rates in alcohol fermentation of grape must and sucrose solution with dry yeast, with the preferential degradation of *S*-(−)-diclofop-methyl in both alcohol fermentation.[140] Enantioselective dissipation of tetraconazole during strawberry wine-making process was found, with (−)-tetraconazole degrading faster.[141]

Tea is one of the most popular beverages in the world, which is generally produced from the leaves of tea plant, such as *Camellia sinensis*. Enantioselective residues of indoxacarb in commercial green tea and black tea products were found, with the EF values ranging from 0.274 to 0.475.[114] During Puer tea processing, 1*R*,2*S*-cycloxaprid dissipated faster than 1*S*,2*R*-cycloxaprid in raw tea or ripen tea processing, indicating the preferential degradation of 1*R*,2*S*-cycloxaprid.[142] Pickle is a type of fermented food with a long history, which is made by preserving raw vegetables in brine solution under the action of microorganisms for a certain period of time. Enantioselective degradation of diclofop-methyl was found during the cabbage pickling process. The half-life of *R*-(+)-diclofop-methyl (4.95 days) in pickled cabbage was significantly higher than that of *S*-(−)-diclofop-methyl (less than 12 h), resulting in the enrichment of *R*-(+)-diclofop-methyl in both pickled cucumber and brine solution.[143] Similarly, the residue of *S*-paclobutrazol in brine was greater than that of *R*-paclobutrazol, which maybe the consequence of the enantioselective degradation of paclobutrazol in Chinese cabbage during pickling process.[144]

MECHANISM OF ENANTIOSELECTIVE BIODEGRADATION

After entering plants and animals, pesticides may undergo biodegradation via a combination of phase I and II metabolism, which are generally enzyme mediated. The cytochrome P450 (CYP450) monooxygenase family is the main enzyme system involved in phase I metabolism. The enantioselective degradation of chiral chemicals may be attributed to the following reasons: (1) The enantiomers were degraded by different enzymes. For instance, the hydroxylation rate of (+)-risperidone by CYP450 enzymes was significantly higher than that of (−)-risperidone, with CYP2D6 and CYP3A participating their hydroxylation process, respectively.[145] (2) The enantiomers were degraded by the same enzyme but at different rates. CYP2D6 could catalyze the hydroxylation of two enantiomers of bupropion, and the hydroxylation rate of *S*-bupropion was faster.[146] (3) The enantiomers were degraded by the same enzyme, which preferentially degraded one enantiomer and only finally degraded the other. CYP3A4 preferably metabolized *cis*-RS metconazole over the its enantiomer.[147] (4) Only one enantiomer can be degraded by the enzyme, and the other enantiomer can be degraded after isomerization. Human CYP450 enzymes could only metabolize *S*-(+)-myclobutanil from racemic mixtures.[148] The species-specific enantioselective trend and degradation may result from the species-specific enzyme.[149] Species-specific enantioselective residues of metalaxyl were observed in human hepatoma HepG2, rat hepatic H4IIE, chicken hepatic LMH and grass carp hepatic L8824 cells.[150]

Pesticides can be applied via foliar spray, soil, or seed priming to control pest, plant pathogens, and weeds problems for plants. After soil application or seed dressing, pesticides were first taken up by the plants until reaching equilibrium and then degraded by plants. After foliar spray application, plants were capable of absorbing and metabolizing pesticides remaining on plant. The different enantioselectivities of specific pesticides after root treatment and foliar treatment was probably attribute to the enantioselective dissipation by soil microorganism and/or the enantioselective absorption from soil to plant by root membrane.[126] Therefore, after spraying application of indoxacarb on rice paddy, the residues of *R*- and *S*-indoxacarb in brown rice at 14 days were 0.039−0.052 and 0.055−0.075 mg·kg^{-1}, which was probably due to the enantioselective degradation of indoxacarb in the rice plants.[151]

During the food fermentation process, the enantioselective dissipation degradation of pesticides was probably attributed to the fact that specific microorganisms involved in fermentation could also contribute to the enantioselective degradation of pesticides. For instance, soy sauce is a kind of traditional fermented seasoning used in Asian countries, which is produced by fermentation of a mixture of soybean, wheat, and salt by certain strains of koji mold. During soy sauce brewing processes, the degradation of *S*-(−)-diclofop-methyl was faster than *R*-(+)-diclofop-methyl by *Saccharomyces rouxii*, while no stereoselectivity was observed by *Aspergillus oryzae*.[152] Currently, the effects of microorganisms or enzymes isolated from agricultural products or processed foods on the enantioselective degradation of chiral pesticides need further research.

CHIRAL CONVERSION IN THE BIOTIC ENVIRONMENT

Some chiral pesticides are configurationally unstable and may be reversibly transformed from one enantiomer to the other. Chiral conversion of pesticide enantiomers may occur in the environment, during the cultivation of plants and animals as well as the food processing process. Some specific enantiomers can transform into their opposite pair. For instance, *R*-fipronil underwent significant enantiomeric transformation to *S*-fipronil in freshwater mussel *Anodonta woodiana*.[153] High concentration of (−)-cyflumetofen was readily converted to (+)-cyflumetofen in acidic soil.[154] Significant conversion of *R*-indoxacarb to *S*-indoxacarb took place during the growth of fresh tea leaves and the processing of green tea, resulting in enrichment of *S*-indoxacarb in green tea.[155] Some pesticide enantiomers may be interconverted with each other at different rates. During the cucumber pickling process, mutual transformation existed between paclobutrazol enantiomers, and *R*-paclobutrazol showed a significantly higher inversion tendency than *S*-paclobutrazol.[156] Conversion phenomena between the sulfoxaflor enantiomers were observed during Pu-erh tea and Black tea processing, with 2*S*,3*S*-sulfoxaflor exerting a 2.5 times higher inversion rate than 2*R*,3*R*-sulfoxaflor.[157] Significant enantiomerization of indoxacarb in acidic and alkaline occurred, and the rate of *S*-(+)-indoxacarb convert to *R*-(−)-indoxacarb was greater than that of reverse process.[158]

The conversion of inactive *S*-haloxyfop into active *R*-haloxyfop was observed in soils, while no inversion was observed in sterilized soil.[159] Significant racemization of enantiopure mecoprop and dichlorprop occurred in soil, indicating inversion from one enantiomer to another, which was not found in sterilized soil.[160] These consequences suggested the involvement of microorganisms in enantiomer conversion. As a matter of fact, enantiomerization may undergo via two mechanisms, enzymatic and nonenzymatic routes. Enzyme-catalyzed enantiomerization is commonly mediated by epimerases and racemases, which operate at stereogenic centers adjacent to an electron withdrawing carbonyl functionality and are able to break and then re-form a bond, usually a C−H bond. Nonenzymatic interconversion was generally temperature-dependent or pH-dependent. For instance, racemization of malathion, phenthoate, fenpropathrin, and triadimefon in water and soil was found, which was pH-dependent.[161−163] Both enzymatical and nonenzymatical mediated enantiomerization can achieve mutual conversion between two enantiomers, while the directional conversion from one enantiomer to the other was generally enzymatical mediated.

Currently, few studies are available on the chiral conversion of pesticides in a biotic environment. As a matter of fact, the study of chiral transformation requires the utilization of individual enantiomers to perform the experiment. However, the majority of research was conducted by racemate, which was unable to evaluate the chiral transformation. This may be due to the difficulty in the preparation of individual enantiomers, which hampered the investigation of chiral conversion in the biotic environment.

■ IMPLICATION

Increasing pressure on food production has led to the continued development and use of pesticides. However, abuse and misuse of pesticides may lead to pesticide residues in the environment and in human foods, which has received increasing concern due to their potential hazardous impacts. Chiral pesticides have one or more chiral centers, resulting in two or more enantiomers. Currently, chiral pesticides account for 28% of commercial pesticides; however, only about 7% of chiral pesticides were sold as pure active enantiomers.[164] The majority of chiral pesticides are usually manufactured and utilized as racemic mixtures owing to the fact that enantioselectivity is not addressed in pesticide legislation. The existing MRLs for chiral pesticides employed by most nations were generally set based on the racemate residue data from field trials, which may differ from the residue of individual enantiomer. Besides, the potential biological effects of racemate and the individual enantiomers, such as toxicity, carcinogenicity, and endocrine disrupter activity, are generally different. For instance, *R*-dichlorprop is an active herbicide, while *S*-dichlorprop is nonherbicidal active. *R*-Metalaxyl is the fungicidally active and *S*-metalaxyl is the fungicidally less active.[73] Only *S*-metolachlor is the active compound. The activity of *R*-triticonazole against *Fusarium graminearum* was 4.28-fold greater than that of *S*-triticonazole owing to stronger bound with fungal CYP51B.[165] *R*-(−)-Oxathiapiprolin exerted 2.49−13.30-fold higher bioactivity than that of *S*-(+)-oxathiapiprolin against six kinds of oomycetes due to the better glide score with the binding site.[112] After entering into the environment, chiral pesticides may exert enantioselective adverse impacts on organisms, such as microorganisms, plants, and animals. For instance, *S*-paclobutrazol could stimulate the growth and development of beneficial bacteria, whereas *R*-paclobutrazol was able to inhibit phytopathogenic bacteria.[166] Triticonazole showed significant enantioselectivity in toxicity to wheat, with *S*-triticonazole having greater inhibition effects on the germination of wheat seeds.[167] *R*-Dichlorprop exhibited higher phytotoxicity to maize than *S*-dichlorprop.[168] (−)-Enantiomers of fonofos and profenofos exerted greater toxicity toward freshwater invertebrates *Ceriodaphnia dubia* and *Daphnia magna* than its antipodes.[67] Enantioselective toxicity of flufiprole was found, with *R*-flufiprole being more toxic to loach *Misgurnus anguillicaudatus* than *S*-flufiprole.[169] Moreover, pesticide enantiomers may adversely impact food components and quality. *R*-Tebuconazole had greater effects on the flavor and appearance of grape wines.[170] Therefore, risk assessment of chiral pesticides using residues and the toxicity of racemates may lead to underestimation.

On the other hand, microorganisms, plants, and animals have the ability to accumulate and metabolize pesticides, in which the process may be enantioselective. Generally, chiral pesticides entered into the environment as racemate; however, amounts of enantiomers finally remaining on foods may be different. For instance, the EF values of tebuconazole in commercial strawberry and cucumber were 0.63 and 0.43, respectively. The EF value of flutriafol in tomato was 0.57.[37] Enantiospecific residues of pesticides in foods may originate from several reasons: (1) enantioselective dissipation of pesticide in the environment. Chiral pesticides may be enantioselectively dissipated in the environment (such as soil, sediment, and water), resulting in enrichment of specific enantiomer in the environment. After being taken up by plants or animals, enantiospecific residue occurred in the foods of plant and animal origin. (2) Enantioselective bioaccumulation of pesticide in plants and animals. Pesticide enantiomers in the environment may be taken up by plants or animals at different rates, leading to enrichment of specific enantiomers in foods. (3) Enantioselective biodegradation of pesticide in plants or animals during cultivation and processing processes. The biodegradation of pesticide enantiomers in plants or animals may be via different pathways or occur at different rates, causing enantiomer-specific residues. (4) Chiral conversion of pesticide enantiomers in the environment, plants, or animals. One enantiomer of pesticides may irreversibly convert into the other in the environment or foods, resulting in differentiate amounts of enantiomers in foods. (5) The combined effects of enantioselective dissipation, bioaccumulation, biodegradation, and chiral conversion. Owing to the fact that the accumulation and degradation of enantiomers depends on environmental conditions, species, and tissues, it is difficult to predict which enantiomer is preferentially enriched and degraded. The occurrence of chiral conversion processes makes the interpretation of the data more complex. However, if the enantioselective enrichment and degradation characteristics of pesticides in the specific environment, animals, and plants are known, chiral signatures in foods can be regarded as a powerful tool to trace the origin of pesticides. Previous research found the enantioselective signature of chiral o,p′-DDT can be used to track the fate and sources of DDT in the environment.[171]

Generally, chiral pesticides are produced and utilized as racemates. However, owing to enantioselective dissipation, bioaccumulation, biodegradation, and chiral conversion, the enantiomer fraction finally remaining in agricultural products and foods may be different from that of the racemate, posing unknown risks to organisms and human. It is important to comprehensively consider the activity, toxicity, bioaccumulation, and metabolism of pesticide enantiomers and to produce optically pure pesticides with high efficiency, fast degradation, low toxicity, and low bioaccumulation, which could not only improve food production but also reduce pesticide application, finally reducing organism and human health risks. This Review highlights the importance of investigating chiral pesticides at the enantiomeric level and the needs to consider the following when investigating the chiral pesticides:

i. The reverse-phase HPLC is the most frequently utilized chiral analysis methods, and SFC has gained increasing popularity. Simultaneous analysis of multiple chiral pesticides can be realized on one chiral chromatographic column, such as the Chiralpak IG column.

ii. Due to the enantioselective dissipation of pesticides mediated by microorganisms or functional enzymes, some chiral pesticides exhibited strong enantiospecific residues in soil, sediment and water. However, the enantiomeric profiling of chiral pesticides in environmental water, soil, and sediment remained poorly documented because most studies on pesticide residues in the environment only determined the total amount of chiral pesticides rather than their enantiomers.

iii. The bioaccumulation of chiral pesticides may be enantioselective due to some transport proteins exhibiting enantioselective substrate recognition. Similarly, owing to the substrate selectivity of enzyme, the biodegradation of chiral pesticides could also be enantioselective. The preference of stereoselectivity and the enantioselective bioaccumulation/biodegradation properties was related to species. However, the study on enantioselective bioaccumulation and biodegradation of chiral pesticides in edible fish is still frequently overlooked.

iv. Some chiral pesticides may be reversibly transformed from one enantiomer to the other in the biotic environment. However, few studies are available on the chiral conversion of pesticides, which may be hampered by the difficulty in preparation of pesticide enantiomers.

v. Though microorganisms, protein, and enzymes played pivotal roles in the enantioselective process of pesticides in the environment and organisms, the specific mechanisms for the enantioselectivity of each pesticide were still not fully understood, owing to the difficulty in identifying the complicated microbial communities, proteins or enzymes involving in enantioselectivity. Therefore, it is still challenging to predict the enantioselectivity of chiral pesticides in the environment and organisms.

vi. Enantioselective dissipation in the environment could alter the enantiomeric compositions of pesticides. Therefore, chiral signatures of pesticides in foods have potential to be used as indicators to trace the origin of chiral pesticides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jafc.3c02564.

Diagram of enantiomers; detailed enantioselectivity information on chiral pesticides in the environmental matrix and foods (PDF)

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