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CHIRALITY IN SYNTHETIC AGROCHEMICALS: BIOACTIVITY AND SAFETY CONSIDERATION

(Technical Report)

Prepared for publication by

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Pesticides report 37: Chirality in synthetic agrochemicals: Bioactivity and safety consideration (Technical Report)

Abstract: Most synthetic agrochemicals with chiral structures are marketed as racemates even though the desired biological activity may be derived from only one enantiopure isomer. However some synthetic agrochemicals such as pyrethroid insecticides, aryloxypropanoate herbicides and triazole fungicides are marketed as the most biologically active enantiopure isomer. Numerous reports describing the relative biological actitivites, preparations and analyses of enantiopure agrochemicals are available. Some examples of how different enantiomers in racemates are selectively metabolized have also been reported. When agrochemicals have chiral structures, efforts should be made to define the mode of action, elucidate metabolic pathways and to define the human and environmental toxicity of each enantiopure isomer. If there are large differences in the biological activities of individual enantiomers in racemates, it is desirable to develop and use only the enantiopure isomer with the highest sought-after biological activities.

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1. INTRODUCTION

Chirality is an important concept in various fields of chemistry, and its significance has long been recognized in relation to the relative biological activity of the individual enantiopure isomers of natural compounds and synthetic drugs. Because all organisms constitute a chiral environment and most enzymatic pathways are stereoselective, it is not surprising that there is a great deal of enantiomeric and enantiotopic selectivity when chiral and prochiral compounds, including many drugs and synthetic agrochemicals, are introduced into biological systems. For example, only L-amino acids are of nutritional value for animals, L-glutamate is used as a food flavor enhancer, whereas the D-isomer does not have any such properties. Many

insecticides that are derived from natural products (e.g. pyrethroids) have chiral structures, the insecticidal activity being associated with one or more of the individual enantiomers. In the case of insecticidally active pyrethroids, this enantiomeric selectivity arises from the chiral nature of the site of action in the insect nervous system. Herbicidal 2-aryloxypropanoates exhibit their activity by inhibiting an acetyl-CoA carboxylase. The enantiomeric selectivity of these herbicides is thus understandable through the chiral nature of the enzyme molecule.

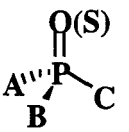
On the laboratory synthesis of new synthetic chiral agrochemicals, racemates are usually produced. Many chiral agrochemicals are synthesized and supplied as racemates, although the desired biological activity may be limited to individual enantiopure isomers; the other isomers being much less effective or even completely inactive. In some cases, the unwanted stereoisomers may cause "adverse" effects on the target and/or non-target organisms.

If there is a big difference in a certain desired biological activity between enantiomers, it is preferable to use only the isomer with the desired biological activity in order to reduce the environmental impact of the chemical even when the other isomers do not exhibit any significant adverse effects. However, the resolution of the racemates or enantioselective synthesis is often a technically difficult and an expensive process. It is therefore necessary to carefully evaluate the relative benefit of developing the enantiopure isomer instead of a racemate as an agrochemical.

Several monographs and reviews on the stereochemistry of agrochemicals and pharmaceuticals have been recently published (Ref.1 - 4). Therefore the objective of the present paper is not to present an extensive review of chiral agrochemicals, but (a) to briefly review the current state of knowledge relating to chirality in agrochemicals, and (b) to define where the specific consideration of chirality is advisable. It will afford a scientific basis for regulatory decisions regarding the chirality of a certain agrochemical. We will also suggest areas of high priority research with chiral agrochemicals.

2. ORGANOPHOSPHORUS COMPOUNDS

Organophosphorus compounds are widely used as insecticides and fungicides, and to some extent as herbicides. Most of these compounds have a P=S or P=O bond as well as three other substituents on the pentavalent phosphorus to produce compounds with the tetrahedral structure illustrated below.



Thus, when the substituents A,B and C are different from each other, the "P-atom" is a chiral center resulting in one enantiomeric pair. Numerous studies on the preparation of enantiopure isomers of O-P compounds, chromatographic separation, and differential biological activities (toxicities, enzyme-inhibition activities, and biodegradabilities) have been published (see ref. in Table 1; (1/5) - (5/5)). Some studies have determined the absolute configuration of isomers with the P-atom as a chiral center. However there are still many isolated enantiopure isomers of unknown absolute configuration. In this section, we will briefly describe differing biological activities of enantiomers and also the synthesis, resolution, and analysis. A monograph containing discussions relevant to this section has been published.(Ref. 5)

2.1 Biological activity

Studies on the relative toxicities, enzyme inhibition activities, and biodegradabilities of enantiopure isomers of various organophosphorus compounds are summarized in Table 1. *In vitro* activity toward the site of action, e.g. acetylcholine esterase (AChE), may be different between enantiomers, but metabolic detoxication/toxication of one or more enantiopure isomers may also be a major factor which determines overall differences in insecticidal or fungicidal activities, as has been described (Ref. 44). Some examples of enantiotopically selective metabolic transformations of prochiral insecticides have been reported (Ref. 45, 46, 47 and 48), although these transformations did not relate to the different activity between enantiomers. Generally insecticidal activity can be correlated with mouse toxicity: usually (*R*)-isomers have greater activity than (*S*)-isomers. There are however some cases (e.g. EPN) in which the isomers have similar toxicity to mice. The reverse order of toxic effects exhibited by EPN and leptophos isomers in the

Table 1 Chiral organophosphorus agrochemicals; structure, biological activity and biotransformation. (In case of unknown absolute configurations, the sign of optical rotation is indicated. Toxicity:acute, AChE:acetylcholinesterase, mfo:mixed function oxidase.)

Table 1 (1/5)

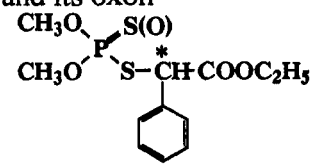
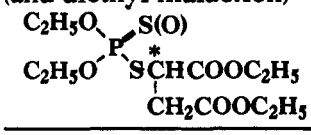
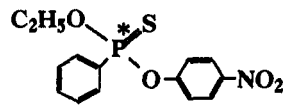
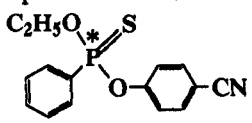
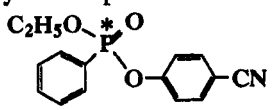
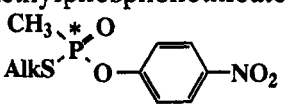
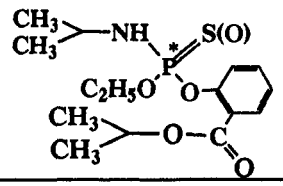
Compound	*In vivo*	*In vitro*
Phenthoate (Papthion) and its oxon 	Insecticidal activities [Mosquito, army worm etc. (+) > (-)] [Housefly (-) > (+)] Mouse toxicity (+) > (-) (Ref. 6)	AChE inhibition (+) > (-) (Ref. 6)
Diethyl malathion (and diethyl malaoxon) 	Insecticidal activity (Housefly) (+) > (x 2) (-) Mouse toxicity (+) > (x 2) (-) (Ref. 7 and 8)	AChE inhibition (+) > (-) Carboxyesterase inhibition (+) > (-) (Ref. 7)
Malaoxon	----------	AChE inhib. (*R*)>(x 8.6)(*S*)(Ref.9)
Isomalathion	----------	AChE inhibition (*R*) > (x 3-13) (*S*) Brain AChE inh. (*R*) > (x 4-9) (*S*) Electric eel AChE inh.(*S*) > (*R*) (Ref. 9)
EPN 	Insecticid.activity; hen toxicity (*R*)-(+)>(*S*)-(-) (Also for oxon) Hen paralysis (*S*)-(-)>(*R*)-(+) Mouse toxicity (*R*)-(+)=(*S*)-(-) (Ref.10 & 11)	
Cyanofenphos (*O*-4-Cyanophenyl *O*-ethyl phenylphosphonothioate) 	Insecticidal activities (*R*)-(+) > (x 20) (*S*)-(-) Mouse toxicity (*R*)-(+) = (*S*)-(-) (Ref. 12)	
Cyanofenphos oxon 	Insecticidal activities : (*R*)-(+) >/= (x 53) (*S*)-(-) (Ref. 12 and 13)	Metabolism rate (*S*)-(-) > (*R*)-(+) (Ref. 12)
S-Alkyl *O*-4-nitrophenyl methylphosphonothioate 	Insecticidal activities (-)>(+) (Ref. 14)	Hydrolysis rate (-) > (+) (AChE and Acetyl esterase) (Ref. 14)
Isofenfos and its oxon 	Insecticidal activities (+)>>(-) (also oxon) (Ref. 15)	AChE inhibition of oxon, and mfo dependent metabolism of oxon (+) >> (-) Production of oxon (-) > (x 4) (+) (Ref. 16 and 17)

Table 1 (2/5)

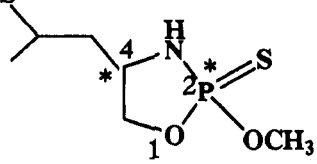
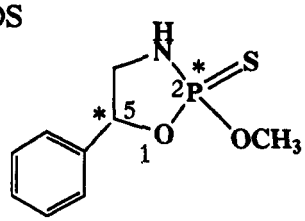
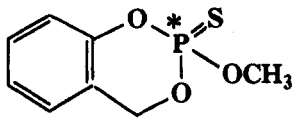
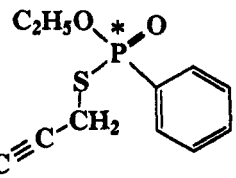
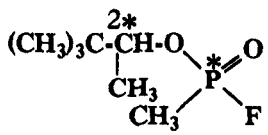
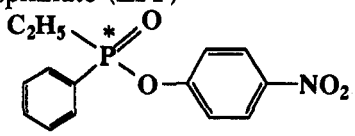
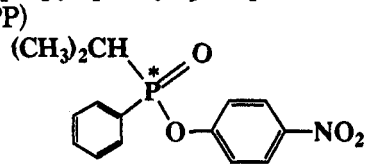
Compound	*In vivo*	*In vitro*
*i*BMOS 	Insecticidal activities cis (2*R*,4*S*) > (2*S*,4*R*) trans (2*S*,4*S*) > (2*R*,4*R*) (Ref. 18)	
5-PMOS 	Insecticidal activities cis (2*R*,5*R*) > (2*S*,5*S*) (x 6.5 - 27) trans (2*S*,5*R*) > (2*R*,5*S*) (x 1.5 - 3) (Ref. 18)	
Dioxabenzofos (Salithion) 	Insecticidal activities (*S*)-(-) > (x ca.2) (*R*)-(+) (Ref. 18 and 19)	AChE inihibition of oxon (*S*)-(-) > (*R*)-(+) (Ref. 18 and 19)
O-Ethyl *S*-(propyn-3-yl) phenylphosphonothioate (EPPP) 	Insecticidal activities (*R*) > (x ca.2) (*S*) (Ref. 18)	
O-Pinacolyl methylphosphonofluoridate (soman) 	Mouse acute toxicity: 2(-), P(-) > 2(+), P(-) (>> 2(+), P(+) & 2(-), P(+)) (Ref. 20)	AChE inhibition : 2(+), P(-) ≈2(-), P(-) (>> 2(+), P(+) & 2(-), P(+)) (Ref. 20)
O-4-Nitrophenyl ethyl(phenyl)-phosphinate (EPP) 		AChE inhibition:(+) > (-) Bovine pancreatic α-chymotrypsin inhibition: (-) > (+) (Ref. 21)
O-4-Nitrophenyl isopropyl(phenyl)phosphinate (IPP) 		AChE inhibition: (+) > (-) Bovine pancreatic α-chymotrypsin inhibition: (-) > (+) (Ref. 21)

Table 1 (3/5)

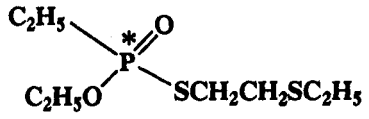
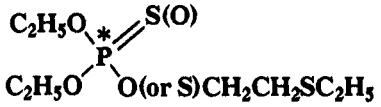
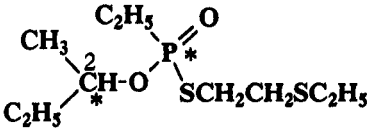
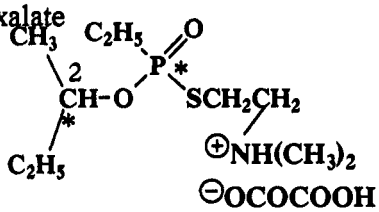
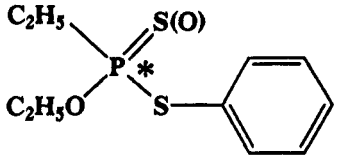
Compound	*In vivo*	*In vitro*
O-Ethyl *S*-(2-ethylsulfanylethyl) ethylphosphonothioate 	Insecticidal activities (-) > (+) (6:1 - 10:1) (Ref. 22)	AChE inhibition (fly head) (-) > (+) (11:1) (Ref. 22)
Demethon (& Demethon analog): 		AChE inhibition(electric eel, human erythrocytes, bovine) and ChE inhibition (horse erythrocytes) (-) > (x 10-20) (+) (Ref. 23)
O-Butan-2-yl *S*-(2-ethylsulfanyl-ethyl) ethylphosphonothioate 	Insecticidal activities P(-) > P(+) (Ref. 24)	AChE inhibition P(-) >> P(+) 2(-) = 2(+) (Ref. 24)
O-Butan-2-yl *S*-[2-(dimethyl-ammonium)-ethyl] ethyl-phosphonothioate hydrogen oxalate 		ChE's inhibition (P*S*)>>(x 40~1630) (P*R*) (Ref. 25)
Fonofos (Dyfonate) and its oxon 	Insecticidal activities (*R*)>(*S*) Mouse toxicity (*R*)>(*S*) (Ref. 26 - 28) (Oxon: Insecticidal activities (*S*) > (*R*) Mouse toxicity (*S*) > (*R*)) *In vivo* metabolism Fonofos and fonofos oxon: (*S*) > (*R*) (Ref. 26 - 28) Plant root absorption:(*S*)>(*R*) Plant metabolism : (*R*)>(*S*) (Ref. 29)	AChE, ChE's, Chymotrypsin, Trypsin, Esterases } (*S*) oxon >> (*R*) oxon (x 4~6) (Ref. 26 - 28) Metabolism (mouse liver mfo) Fonofos to oxon: [(*R*) to (*S*) oxon] (rapid) > (x ca. 2 of) [(*S*) to (*R*) oxon] (P=S to P=O : retention)

Table 1 (4/5)

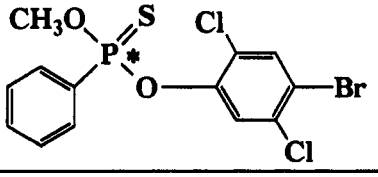
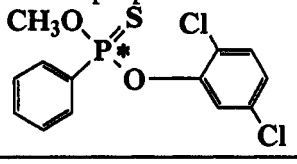
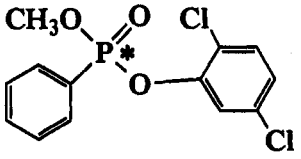
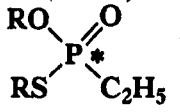
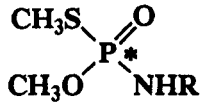
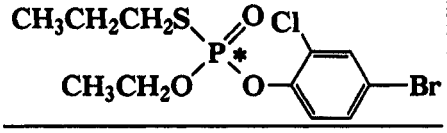
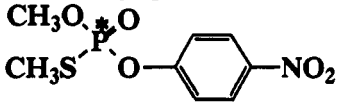
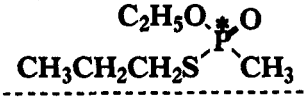
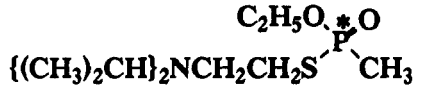
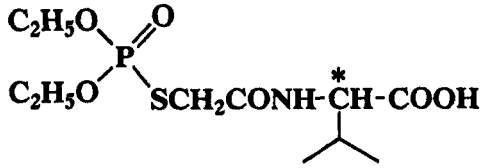
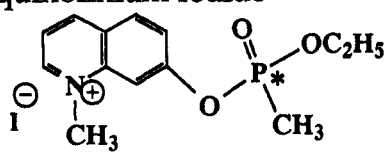
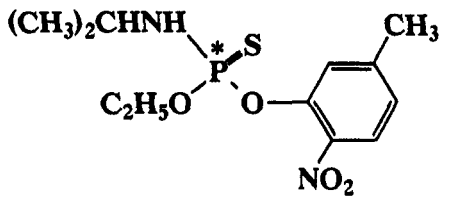
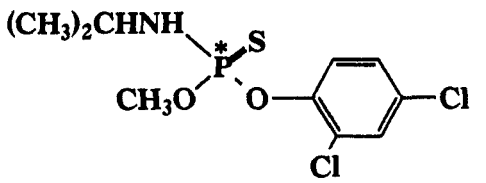
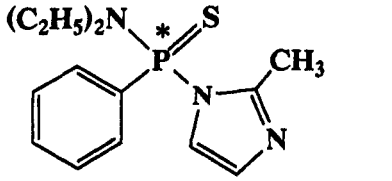
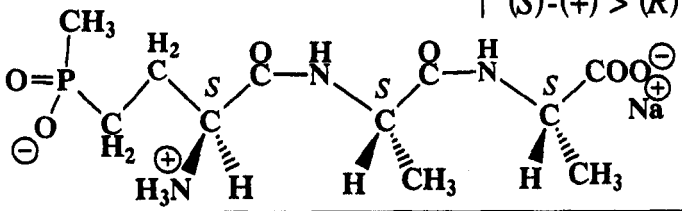
Compound	*In vivo*	*In vitro*
Leptophos(*O*-3-Bromo-2,5-dichlorophenyl *O*-methyl phenylphosphonothioate) 	Leptophos (and its oxon) Toxicity housefly (*R*)-(+)>(*S*)-(-) mouse (*R*)-(+)>or=(*S*)-(-) Delayed neurotoxicity hen (ip) (*S*)-(-)>(*R*)-(+) (Ref.30, 31)	
Debromoleptophos 	Toxicity housefly (*R*)-(+) > (*S*)-(-) mouse (*R*)-(+)> or =(*S*)-(-) (Ref.30, 31)	
Debromoleptophos oxon 	Toxicity housefly (*R*)-(+) > (*S*)-(-) mouse (*R*)-(+) > (*S*)-(-) (Ref. 30)	AChE inhibition: bovine erythrocyte & housefly head (*R*)-(+) > (*S*)-(-) Brain neurotoxic esterase inhibition : (hen) (*S*)-(-) > (*R*)-(+) (Ref.31)
O,S-Dimethyl ethylphosphonothioate (and *O,S*-Diethyl analog)  R=Me or Et	Acute toxicities (*S*)-(-) > (*R*)-(+) (Ref.32)	AChE inhibition (*S*)-(-) > (*R*)-(+) (Ref.32)
Methamidophos and Acephate  R=H or Ac	Insecticidal activities housefly (*R*)-(+) > (*S*)-(-) *Bl.germanica* (*R*)-(+) > (*S*)-(-) (Ref.32)	
Profenofos 	Insecticidal activity (*R*)- (-) > (*S*)-(+) Acute mouse toxicity (*R*)-(-) > (*S*)-(+) (Ref.34)	AChE and ChE's (*S*)-(+) > (*R*)-(-) (Ref.34)
Isomer of methyl parathion 	Acute toxicity : rat (-) > (+) (Ref.35)	
Methyl phosphonothiolates 	Acute toxicity : rat (*R*)-(+) > (x5) (*S*)-(-) (Ref.36)	
	Acute toxicity : rat (*S*)-(-) > (x6) (*R*)-(+) (Ref.36)	

Table 1 (5/5)

Compound	*In vivo*	*In vitro*
Monothiophosphate derivatives of (*R*)- and (*S*)-valine 		Rat liver Carboxyesterase inhibition (*R*) >/= (*S*) (Ref.37)
7-(Methylethoxyphosphinyloxy) 1-methyl-quinolinium iodide (MEPQ) 		ChE inhibition (*R*) and (*S*): similar rate (Ref.38)
O-Ethyl *O*-2-nitro-5-methylphenyl *N*-isopropylphosphoramidothioate 	Herbicidal activities (-) > (x 3-5) (+) (Ref.39) Degradation rate (+) > (-) (Ref.40)	AChE inhibition (Bovine erythrocytes) (-)oxon>(+)oxon (Ref.40)
DMPA 	PGR (Fescue) (-) > (x 24) (+) (Ref.41)	
N,N-Diethyl 2-methylimidazol-1-yl phenylphosphinamidothioate 	Fungicidal activities (+) = (-) Mouse toxicity (-) > (x 2) (+) (Ref.42 and 43)	
Bilanafos 	Herbicidal activities (*S*)-(+) > (*R*)-(-)	

chicken ((*S*) > (*R*)) is also a notable exception. Bialaphos, sodium salt of L-2-amino-[(hydroxy)(methylphosphoryl)]butyryl-L-alanyl-L-alanine, was first isolated from an actinomycete. In this instance, having the carbon chiral centers, the (*S*)-(+)-isomer is more herbicidally active than the (*R*)-(-)-isomer. The differences in activity between the enantiomers are sometimes very large (e.g. cyanofenphos and its oxon), while there are cases that the differences are small (e.g. salithion).

2.2 Preparation (Optical resolution and chiral (asymmetric) synthesis)

Seiber and Tolkmith (Ref. 49) prepared both chiral isomers of *O*-methyl *O*-2,4-dichlorophenyl isopropylphosphoramidothioate (DMPA) and compared their plant growth regulating activity. Optically active bioxabenzofos (salithion) was synthesized by condensing saligenin with an optically active thiophosphoryl chloride (Ref. 50). Yoshitake et al. (Ref. 51) used brucine to resolve isomers of *O*-ethyl *O*-phenyl phenylphosphonothioate in the course of preparation of ^{14}C-labeled compounds for use in a metabolism study. Miyazaki et al (Ref. 33) used similar methods to isolate enantiopure isomers of methamidophos and acephate. Armstrong and Fukuto (Ref. 32) reported on methods to synthesize enantiopure isomers of *O,S*-dimethyl (and -diethyl) ethylphosphonothioate. Both enantiomers of profenofos were prepared by separating its diastereoisomeric *S*-proline esters. (Ref. 52). Phosphinothricin, the important component of bialaphos, was prepared by asymmetric synthesis using an optically active Schiff base and its Michael addition to methyl methylvinylphosphinate (Ref. 53). However in spite of these methodologies for preparation, there are no commercially available organophosphorus pesticides consisting of enantiopure isomer with P-atom at the chiral center, where the most active isomer has been resolved.

2.3 Analysis

The majority of the published procedures for separating enantiomers of organophosphorus compounds have involved the use of chiral HPLC columns. For example, enantiopure isomers of isofenphos and oxon were resolved on a Chiralcel OC column (Ref. 16), and methamidophos and acephate were resolved on a Chiralcel OA column (Ref. 33). Methamidophos, acephate and ethyl *p*-nitrophenyl phosphoramidate were resolved by HPLC using Chiralcel OD and micro LC columns (Ref. 54). *O*-Aryl *O*-ethyl *S*-propyl phosphorothioate was derivatized with *O*-aryl *N*-[(2*S*)-2-(carboxyethyl)pyrrolidinyl] *S*-propyl phosphorothioamidate and the resulting diastereoisomers were separated on a μPorasil column (Ref. 34).

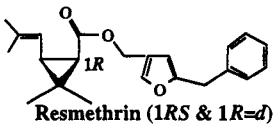
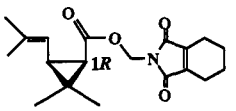
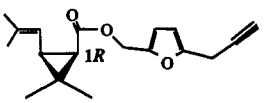
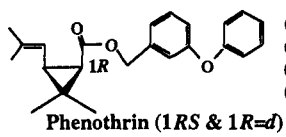
3. PYRETHROIDS

Pyrethroids, derived from natural products of plant origin and having several chiral centers, have been used as optically active insecticides. Earlier synthetic pyrethroids were usually prepared from a natural product such as chrysanthemic acid, pyrethrolone etc. Thus, they are based on specific configurations of the natural products. More recently novel kinds of synthetic pyrethroids have been prepared without using natural product precursors but were nevertheless enantiopure. Some of the enantiopure isomer(s) derived from these processes have been developed as commercial pesticides. In this section, we will briefly survey the synthetic chiral pyrethroids. The configurations and mode of action of pyrethroids have been recently reviewed (Ref. 55).

3.1 Biological activity

A comparison of the biological activities of stereoisomers of synthetic pyrethroids retaining the chrysanthemic acid moiety are shown in Table 2. Among the esters constructed from the isomeric chrysanthemic acids, those containing the (1*R*)-(+)-acid moiety show higher insecticidal activity than the corresponding (*S*)-(-)-acid ester (Ref. 56). The (1*R*)-isomer of chrysanthemic acid is a part of pyrethrin (natural origin) itself, and therefore it is not surprising that commercial products have been developed retaining the (1*R*)-chrysanthemic acid structure. Although the (*R*)-isomer confers a greater insecticidal action, there are smaller differences in the mammalian toxicity between (1*R*)- and (1*S*)-(and *trans* and *cis*)-isomers, as shown in Table 2 (Ref. 57).

Table 2 Structures and biological activities of some chrysanthemic acid esters(- means not measured).

Structure : The (1*R*)-*cis*-isomer is shown.		H.Fly KT_{50}* (s)	G.cockroach LD_{50} (μg/insect)	Mouse acute LD_{50} (oral) (mg/kg)
 Resmethrin (1*RS* & 1*R*=*d*)	(1*R*)-(+)*trans*	280	0.55	590
	(1*R*)-(+)*cis*	170	0.21	152
	(1*S*)-(-)*trans*	-	>30	500
	(1*S*)-(-)*cis*	-	>30	3700
 Tetramethrin (1*RS*)	(1*R*)-(+)*trans*	84	2.43	930
	(1*R*)-(+)*cis*	120	<30	>1000
	(1*S*)-(-)*trans*	-	-	-
	(1*S*)-(-)*cis*	-	-	-
 Furamethrin (1*RS*)	(1*R*)-(+)*trans*	96	2.88	1700
	(1*R*)-(+)*cis*	143	26	-
	(1*S*)-(-)*trans*	-	-	-
	(1*S*)-(-)*cis*	-	-	-
 Phenothrin (1*RS* & 1*R*=*d*)	(1*R*)-(+)*trans*	-	0.78	>5000
	(1*R*)-(+)*cis*	-	1.10	>2500
	(1*S*)-(-)*trans*	-	>30	>5000
	(1*S*)-(-)*cis*	-	>30	>5000

(* : Time of 50% knockdown)

When the acid moiety of synthetic pyrethroids is modified to various cyclopropane or non-cyclopropane derivatives, the synthetic acid moiety still has one or more chiral carbons in many cases. In particular, various C3-modified chrysanthemic acid analogs retain the (1*R*)- configuration as shown below (Table 3) and have highly insecticidal activities with low mammalian toxicities (Ref. 58 and 59)

Phenylalkanoic acids were developed as an effective acid moiety in synthetic pyrethroids. These acids have the chiral a-carbon to which, in many cases, an isopropyl group is connected.

Fenvalerate (Ref. 60 and 61) and flucynthrinate are examples of compounds containing this moiety (see Table 4 for the structures). Fluvalinate (D-valine derivative) (Ref. 62) is also closely related to this class of compounds.

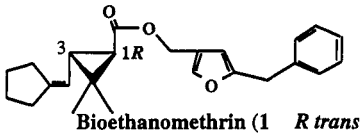
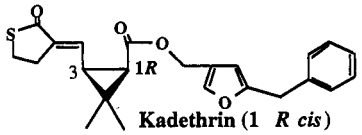
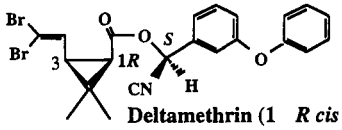
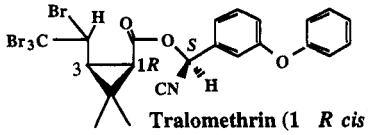
The most insecticidally-active isomer of the respective compound in this group has the absolute configuration that corresponds to the (1*R*)-configuration of chrysanthemic acid. Although the designation of the α-carbon in these active 3-methylbutanoic acid derivatives is (*S*), the close similarity of the stereochemical environment of these derivatives to that of (1*R*)-chrysanthemate is obvious (Ref. 63) (Table 4). Fencyclate (Ref. 64) is also chiral at the α-position, but detailed data on the biological activities of these isomers are not available.

Very detailed studies on the biological activities of fenvalerate demonstrated granuloma formation in mice after long-term administration of a high dose of this pyrethroid as its stereoisomeric mixture (though no indication of tumorigenicity/carcinogenicity). It was subsequently shown that the granuloma formation was caused by only one isomer (Bα: 2*R*, α*S*) and that this isomer has essentially no insecticidal activity. One of its metabolites, a cholesteryl ester, is the cause of the granuloma. Subsequently the most insecticidally active enantiopure isomer Aα (2*S*, α*S*) was purified and marketed as "esfenvalerate" a product completely devoid of granuloma induction. (Ref. 65 and 66).

3.2 Preparation

Various methods for the preparation of enantiopure chrysanthemic acid and several cyclopropane/non-cyclopropane-analogs have been reported. Some of those methods include optical resolution of a synthetic

Table 3 Structures and biological activities of C3-modified chrysanthemic acid esters

	H. Fly LD_{50} (ng/insect) topical	Rat acute LD_{50} (mg/kg) oral	iv
 **Bioethanomethrin (1 *R trans*)**	140	100	5 - 10
 **Kadethrin (1 *R cis*)**	34	140-1300	0.5
 **Deltamethrin (1 *R cis*)**	*	25-130	2.5
 **Tralomethrin (1 *R cis*)**		99-3000	

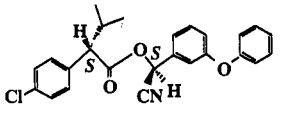
(* Relative toxicity: 1150 x Pyrethrin I)

intermediate which is used to synthesize the desired product [e.g. selective crystallization of dihydrochrysanthemolactone, salt formation with enantiopure 1-phenyl-2-(4-methylphenyl)ethylamine for 3-methylbutanoic acid derivatives etc]. (Ref. 67 and 68). Enantiopure naturally occurring products are sometimes very convenient starting materials for the synthesis. For example a monoterpene, (+)-car-3-ene, was utilized for the preparation of enantiopure chrysanthemic acid isomers (Ref. 69), whilst D-valine is derivatized to produce fluvalinate (Ref. 62).

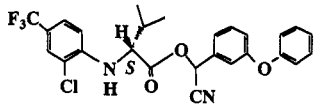
Asymmetric induction has also been used for the synthesis of an enantiopure cyclopropane derivative, e.g. dichlorovinyl analog of chrysanthemic acid (Ref. 70).

Several synthetic pyrethroids contain an optically active α-cyanobenzyl alcohol derivative as the alcohol moiety. Such compounds can sometimes conveniently be prepared by the ester formation of a racemic α-cyano-alcohol with an appropriate enantiopure acid followed by recrystallization of the resulting diastereomeric esters. Deltamethrin (Ref. 71) and esfenvalerate (Ref. 72) can be prepared by this procedure.

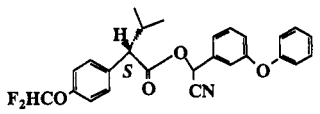
Table 4 α-Substituted 3-methylbutanoic acid esters and related pyrethroids



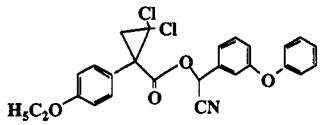
Fenvalerate [Esfenvalerate (2*S*,α*S*)]
(*RS,RS* : rat oral acute LD_{50}: 360-370 mg/kg)



Fluvalinate (2*S*)
(rat oral acute LD_{50}: 260-280 mg/kg)



Flucythrinate (2*S*)
(rat oral acute LD_{50}: 70-80 mg/kg)



Fencyclate

3.3 Analysis

The analytical method using enantiomers of octan-2-ol to esterify the stereoisomers of chrysanthemic acid followed by gas chromatographic separation was developed (Ref. 73). The method was applied to the analysis of phenothrin stereoisomers. (Ref. 74). Separation of enantiopure isomers of phenothrin was also achieved by HPLC using a Sumipax OA-2000 chiral column (Ref. 74). Allethrolone isomers were also separated by GC using an OA-300 chiral column after esterification with *N*-isopropyl carbamate (Ref. 75).

4. TRIAZOLES

Several chiral *N*-substituted azoles are used as broad spectrum fungicides, some of which also show plant growth regulating activities (Table 5).

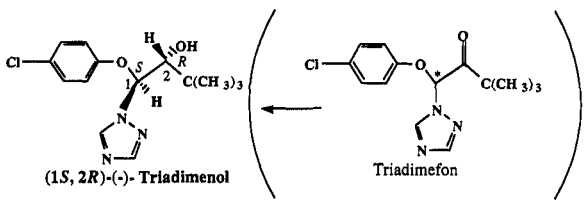
4.1 Biological activity

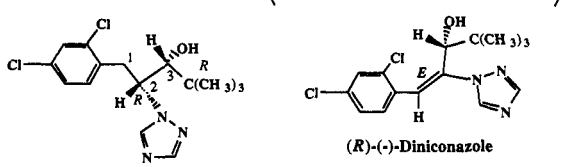
Triadimefon [(+)-(*S*)-configuration by X-ray diffraction] has one chiral carbon; however there does not seem to be any significant difference in the biological activities of its enantiomeric forms. Triadimenol produced by reduction of triadimefon yields four stereoisomers. The (1*S*, 2*R*)-isomer has the highest fungicidal activity (Ref. 77).

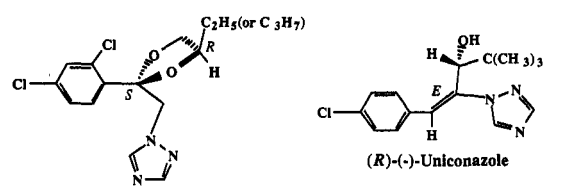
Among the 4 isomers of diclobutrazol, the (1*R*, 2*R*)-isomer has the highest fungicidal and sterol-biosynthesis inhibiting activities (Ref. 78). A related dehydro-compound, diniconazole, has 4 isomers due to a double bond (*E* and *Z*) and a chiral carbon (*R* and *S*). The (*E*)-isomers are more active than the (*Z*)-isomer, and the fungicidal activity of the (*R*)-(-)-isomer is much greater than the (*S*)-(+)-isomer. Interestingly, the (*S*)-(+)-isomer has much greater plant growth regulating activities than the (*R*)-(-)-isomer. The phenomenon is more prominent in the monochloro-analog uniconazole (Ref. 79). Etaconazole also has 4 stereoisomers, among which the (2*S*, 4*R*)-isomer had the highest fungicidal activity (Ref. 80).

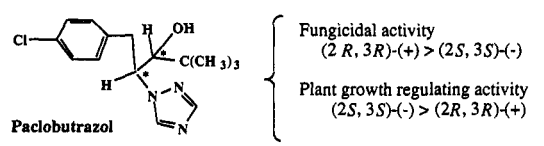
Table 5 Triazoles as fungicides

(Unless otherwise noted, the most fungicidally active isomers are shown.)









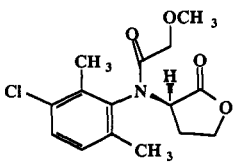
4.2 Preparation and analysis

Triadimefon was optically resolved to its enantiopure isomers via salt formation with camphor sulfonic acid followed by recrystallization. Diastereomers of triadimenol were resolved by HPLC. Diniconazole isomers were prepared by recrystallization of a diastereomers following derivatization with an enantiopure reagent and also by asymmetric reduction. Etaconazole was prepared by use of an enantiopure butane-1,2-diol derivative to yield a diastereomeric mixture; the isomers were resolved by HPLC (Ref. 80). The HPLC separation can be used in analytical procedures.

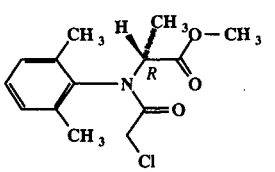
5. ACYLANILIDES

Clozylacon, an acylanilide fungicide, is used for soil application. Its (*R*)-form is prepared from (*S*)- malic acid via its lactonated form, or by the process including Rh(or Ru)-catalyzed asymmetric hydrogenation of a double bond in the five-membered ring intermediate. Another example of acylanilides, CGA 29212 having the (*R*)-configuration, is highly fungicidal. The substitution of

chlorine in this acylanilide with methoxyl group produces metalaxyl, the racemic form of which is fungicidally more active than CGA 29212. The significance of chirality of fungicides for agricultural use is described in detail in a recently published review (Ref. 81).



Clozylacon



CGA 29212 (*R*)

6. ARYLOXYPROPANOATES AND SOME OTHER HERBICIDES

A wide variety of 2-aryloxypropanoic acids and their esters have been developed as commercial herbicides and plant growth regulators. They inhibit acetyl-CoA carboxylase in chloroplasts thus exhibiting herbicidal activities. The 2-position of propanoates is the chiral center because it is substituted with an aryloxy group. There are many reports indicating that, usually, the (*R*)- isomer has a higher herbicidal activity than the (*S*)-isomer. Structurally related anilino-propanamide derivatives are also herbicidally active, and some reports are available that describe the different activities of their enantiomers (Ref. 82-86).

6.1 Biological activity

Studies have demonstrated that (+)-enantiomers of 2-aryloxypropanoates [e.g. 2-(2,4-dichlorophenoxy)propanoic acid] were active in alfalfa embryo induction whereas the (-)-forms were inactive (Ref. 82).

Strathmann and collaborators (Ref. 83) advocated the use of only the biologically active isomers of phenoxy-herbicides, including fluoroglycofen-Et, dichloroprop P and mecoprop P and thereby the reduction of the total amount of the chemical applied under field condition. A similar view was expressed by Morvan and collaborators (Ref. 84) who applied a mixture of fluoroglycofen-ethyl and dichlorprop-P for early postemergence control of dicotyledons in cereals. Fluazifop-P-butyl ((*R*)-form) has been used as a selective grass herbicide for rape and other broad-leaved crops (Ref. 85). Dichlorprop-P ((*R*)-form: Duplosan PP, BASF) and mecoprop-P ((*R*)-form: Duplosan KV, BASF) are marketed. Both enantiomers of diclofop-methyl showed similar pre-emergence herbicidal activity in controlling weeds in the rice field. But in post-emergence application, the (*R*)-(+)-isomer had higher activities against millets and oats. The (*R*)-forms of quinofop-ethyl, trifop-methyl and napropamide (an aryloxyalkanamide), also have higher herbicidal activities. Fenoprop and related compounds also show the similar stereoisomeric selectivity.

Fenoxaprop-ethyl (HOE 046360, the biologically active enantiopure isomer of HOE 33171) showed the same spectrum of biological activity as racemates and there were no significant differences in toxicological

and ecological behaviors; thus the use of this isomer would reduce the amount of technical active ingredient in the applied field (Ref. 86). The post-emergence herbicidal activity of 2-[(pyridyloxy)phenoxy]propanoates resides exclusively in the (*R*)-isomer; however, the (*R*)- and (*S*)-isomer had equivalent pre-emergence activity (Ref. 87). Microbial conversion of the (*S*)-isomer to (*R*)-isomer in soil was observed which may explain why the response to the two isomers was the same in the pre-emergence activity.

The herbicidal activities of some other 2-[(aryloxy)phenoxy]propanoic acids and their derivatives are reported, and are shown in Table 6 along with the above described aryloxypropanoates.

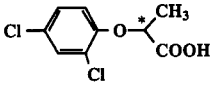
Anilinopropanamide derivatives are herbicides structurally related to aryloxypropanoates. The (*R*)-isomer of WL-19511 is more biologically active than the (*S*)-isomer; in contrast the (*S*)-isomers of flamprop-M-isopropyl, metolachlor, and CGA-29212 have higher herbicidal activities than the other enantiomers (Ref. 88).

The (*R*)-isomers of imidazole-5-carboxylic acid esters show higher herbicidal activity than the (*S*)-isomers (Table 6). Imidazolinone herbicides such as imazamethabenz, imazapyr, imazaquin and imazethapyr all have chiral structures, but information on the relative biological activities of individual enantiomers is not yet available.

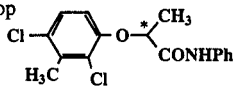
Table 6 Structure of aryloxypropanoic acids and related herbicides

[Aryloxypropanoic acids and related herbicides]

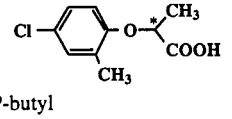
Dichlorprop



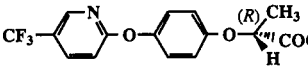
Clomeprop



Mecoprop

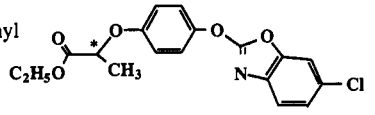


Fluazifop-P-butyl

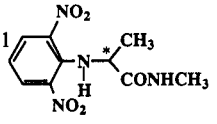


Herbicidal activity (*R*) > (*S*) [(*S*)-acid is transformed to (*R*)-acid in fresh soil.(Ref. 89)]

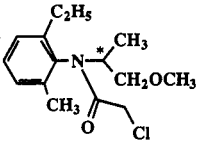
Fenoxaprop-ethyl



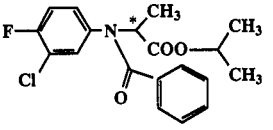
WL-19511



Metolachlor

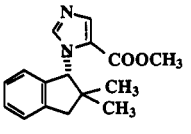


Flamprop-M-isopropyl

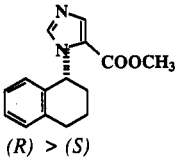


[Other types of chiral herbicides]

(Imidazole-5-carboxylic acid esters Relative herbicidal activity shown)



(R) >> (S) ≈ 0

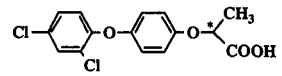


(R) > (S)

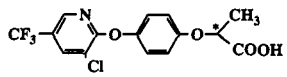
Table 6 (continued)

[Aryloxyphenoxypropanoic acids and derivatives]

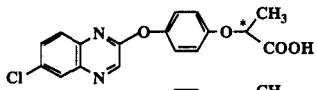
Diclofop



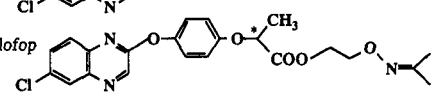
Haloxyfop



Quizalofop



Propaquizalofop



Isoxapyrifop

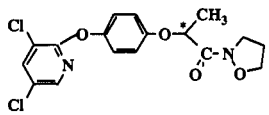
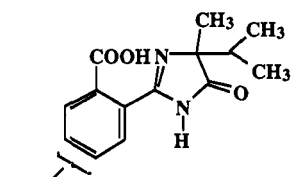
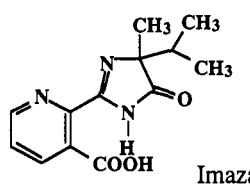


Table 6 Continued



Imazamethabenz

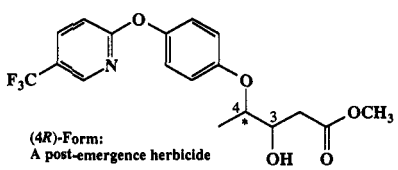


Imazapyr

6.2 Preparation

In general, only one of the diastereomers of 2-aryloxypropanoic acid esters is herbicidally active, and many reports (including abundant patents) are now available for the selective preparations of the desired enantiopure isomers. Sih and collaborators (Ref. 90) utilized lipase to hydrolyze 2-(chlorophenoxy)-propanoate to obtain enantiopure aryloxypropanoic acids. In their work, several new heterocyclic amines were found to be enantioselectively effective inhibitors in the *Candida* lipase system. Fukui and collaborators (Ref. 91) reported the enantioselective esterification of 2-(4-chlorophenoxy)propanoic acid with celite-adsorbed lipase OF 360 from *Candida cyclindracea* ; this system was used for the long-term continuous production of enantiopure herbicide ingredients.

Methyl 3-hydroxy-4-{4-[(5-trifluoromethyl-2-pyridyl)oxy]phenoxy}pentanoate isomers were prepared and their (*R*)-form (at the position C-4) was highly active as a post-emergence herbicide. The C-3



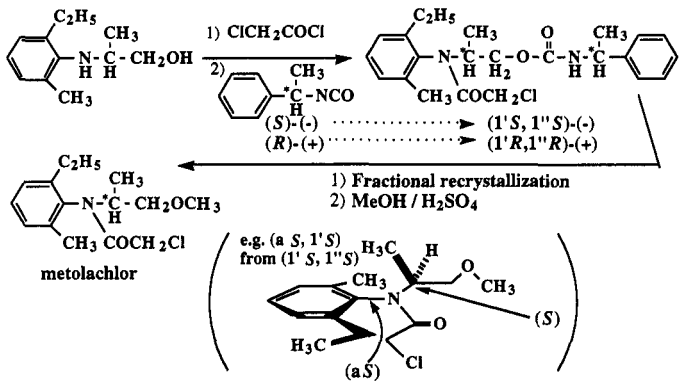
(4*R*)-Form:
A post-emergence herbicide

stereochemistry had no effect on the biological activities.

An enantiopure isomer of metolachlor was prepared by fractional recrystallizations of a diastereomeric carbamate mixture derived by coupling an intermediate alcohol with an enantiopure reagent (Ref. 92).

6.3 Analysis

Gas chromatographic separation of enantiomers is now possible using various chiral stationary phases. Per-*O*-pentylated cyclodextrin columns were reported to be effective in separating enantiomers of mecoprop,



dichlorprop and fenoprop; these isomers were resolved using a capillary column with 1:1 mixture of per-*O*-pentylated β-cyclodextrin and per-*O*-methylated β-cyclodextrin as the stationary phase (Ref. 93). HPLC separation of enantiomers using chiral stationary phases (e.g. ionically bound D-phenylglycine), was reported, (e.g. Ref. 94). Determination of enantiomeric purity of fluazifop-P-butyl using a diode-laser based polarimetric HPLC detector was reported (Ref. 95). In a recent review, Skidmore described various examples of derivatizations of carboxylic acids followed by HPLC and GC analyses to provide resolution of enantiomers (Ref. 96).

7. CONCLUSIONS

1. A large number of examples of differences in biological activities between enantiomers of chiral agrochemicals have been observed.

2. Differences in biological activities between the enantiomeric forms of a chiral agrochemical may result either from the difference in intrinsic activities at the site of action or from the difference in rates of metabolic detoxication as well as other processes which reduce the concentration of the active isomer at the target site.

3. Although some individual stereoisomers and enantiopure isomers of synthetic agrochemicals are now being marketed (e.g. pyrethroid insecticides, aryloxypropanoate herbicides, and triazole fungicides), no single enantiopure isomer of chiral organophosphorus insecticides is commercially available.

4. The separation of an enantiomeric pair or chiral synthesis is often a technically difficult and/or laborious and expensive process. However, techniques for asymmetric syntheses and separations of enantiomers with chiral HPLC and GC columns have been developed for several agrochemicals. Further improvements in methods for preparation of pure enantiopure isomers can be expected.

5. In one instance (esfenvalerate) where an undesirable toxic response to a non-target organism was shown to result from a less biologically active single enantiopure isomer in a stereoisomeric mixture, the toxic isomer was removed and the more active isomer was marketed; thus reducing adverse effects.

8. RECOMMENDATIONS

1. Studies are needed to better define the mechanisms of toxicity and metabolism of individual enantiopure isomers of chiral and prochiral agrochemicals in target and non-target organisms.

2. Where one or more enantiopure isomers in a mixture pose significant environmental or human health risks, then the isomer should be removed even where it contributes to the desired biological activity.

3. Where an enantiopure isomer does not have the desired biological activity, it is preferable to remove the isomer when economically feasible, even if it does not pose a significant risk. The use of only the stereoisomer with the desired biological activity will reduce the total amount of chemicals introduced into the environment, and therefore it merits careful consideration.

4. Better methods for production of enantiopure isomers (biotechnology, asymmetric synthesis and/or separation) are needed.

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