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# Separation of Chiral Pyrethroid Pesticides and Application in Pharmacokinetics Research and Human Exposure Assessment

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## 1. Introduction

The pesticides are originally used to kill insects, fungi and other organisms hazarding crops to improve agricultural production. With the development of technology, people have been gradually aware of the impact of pesticides to the environment and food safety. More than 25% of over 650 existing commercial pesticides are characterized by chirality (Zheng, 2001; Williams, 1996). Of the commercial pesticides, the pyrethroid insecticides account for 25% of the sales of pesticides in the world, and most of them have chiral isomers(You et al., 2001). The chiral enantiomers of pesticides were usually not distinguished in previous studies, and as a result, the risk assessment of pyrethroid pesticides was incomplete.

With the development of stereochemistry, the chirality of compounds has aroused wide concern. The researches on medicine and pesticides have penetrated into the field of molecular stereochemistry. Especially in the field of medicine, there have been more researches on and application of the single enantiomers of chiral drugs, and the natures of the enantiomers have been well studied. However, the researches on chiral pesticides relatively lag behind. The researches of various natures of pyrethroid pesticides are usually carried out by using racemic mixture, so there are few detailed data and related researches of single chiral enantiomers. Despite the same chemical and physical properties of the enantiomers of chiral pesticides, they may have entirely different biological activities, toxicities, toxicologies and metabolic pathways in the biological systems. For instance, usually only one out of the four chiral monomers of permethrin is provided with high insecticide efficiency, and the remaining three are low efficient or even ineffective in terms of insecticidal effect. And of the eight chiral enantiomers of cypermethrin, only two monomers of cis- cypermethrin and two monomers of trans- cypermethrin have high insecticidal effect. And as a result, not only the cypermethrin with 8 chiral monomers but the beta-cypermethrin with 4 highly effective monomers has been commericially producted.

The overwhelming number of widely used pyrethroid pesticides are almost sold and used in the form of racemic mixtures. The use of low efficient or ineffective isomers of the racemic mixtures not only cannot effectively control insect pests, resulting in the waste of manpower

and material resources, but will pollute the environment, reduce the quality of agricultural products, and may lead to toxic side effects or drug induced sufferings, and thus cause serious impact on human health. It is therefore of great significance to evaluate the possible hazards and the influence of the single chiral monomers of pesticides on environment and human health by using the separation technology of chiral enantiomers.

## 2. Introduction of pyrethroid pesticides

The pyrethroid pesticides are primarily used in agriculture, such as controlling the cotton, vegetables and fruit-eating and leaf-eating pests, and the total sales in this area account for 95% (Katsuda, 1999). In addition, pyrethroid pesticides are also widely used as household insecticides to control mosquitoes, cockroaches and parasites in farm animals.

### 2.1 Production history of pyrethroid pesticides

Pyrethroid pesticides are efficient, broad-spectrum and quick neurotoxic pesticides developed on the base of the researches on the chemical structure of the natural pyrethrins. They can be divided into type Ⅰ pyrethroids without cyano-group (CN) and type Ⅱ pyrethroids containing CN by the presence of CN in the molecules. The chemical structures of common pyrethroid pesticides are shown in Figure 1.

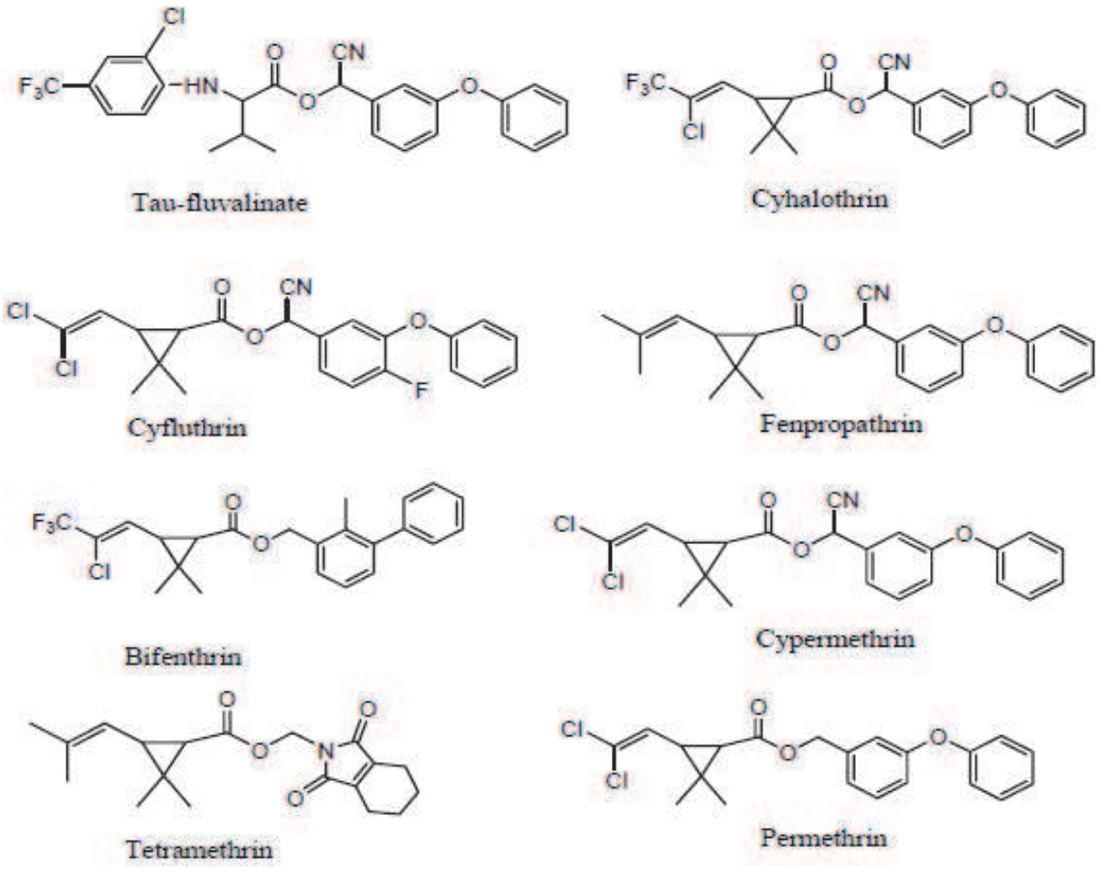


Fig. 1. Structures of pyrethroid pesticides

The researches on synthesis of pyrethroids have been carried out since the 1940s when the chemical structure of the active ingredients contained in an insecticidal plant called pyrethrum was studied and determined (Cox, 2002). In 1949, Schechter and his colleagues from the United States synthesized the first commercial pyrethrin analogues: propylene permethrin. In the 1950s to 1960s, a number of similar compounds, which were known as synthetic pyrethroids, were successfully developed. In the early 1970s, permethrin, the first pyrethroids, with light stability which can be applied to pests control in agriculture and forestry was synthesized by a team led by M. Elliottm in UK, and then popularized and applied in agriculture. Thereafter the pyrethroid pesticides have become booming. There are more than 70 pyrethroid pesticides varieties in the world including more than 20 leading ones. They have been considered the fourth largest pesticides, currently accounting for 19% of the sales of the insecticides in the world (Liu et al., 2004).

In recent years, the chiral pesticides, as a new research field, have attracted extensive attention. The commercial chiral pesticides, however, are few in number and with the majority of pyrethroid pesticides, including *beta*-cyfluthrin, *alpha*-cypermethrin (*cis*-cypermethrin), *theta*-cypermethrin (*trans*-cypermethrin), *beta*-cypermethrin, S-fenvalerate, deltamethrin, *d-trans*-allethrin, etc.. The cypermethrin series account for 26.5% of the pyrethroid pesticides. The production of single enantiomer of deltamethrin (*1R-cis-3R*) has been currently achieved commercially.

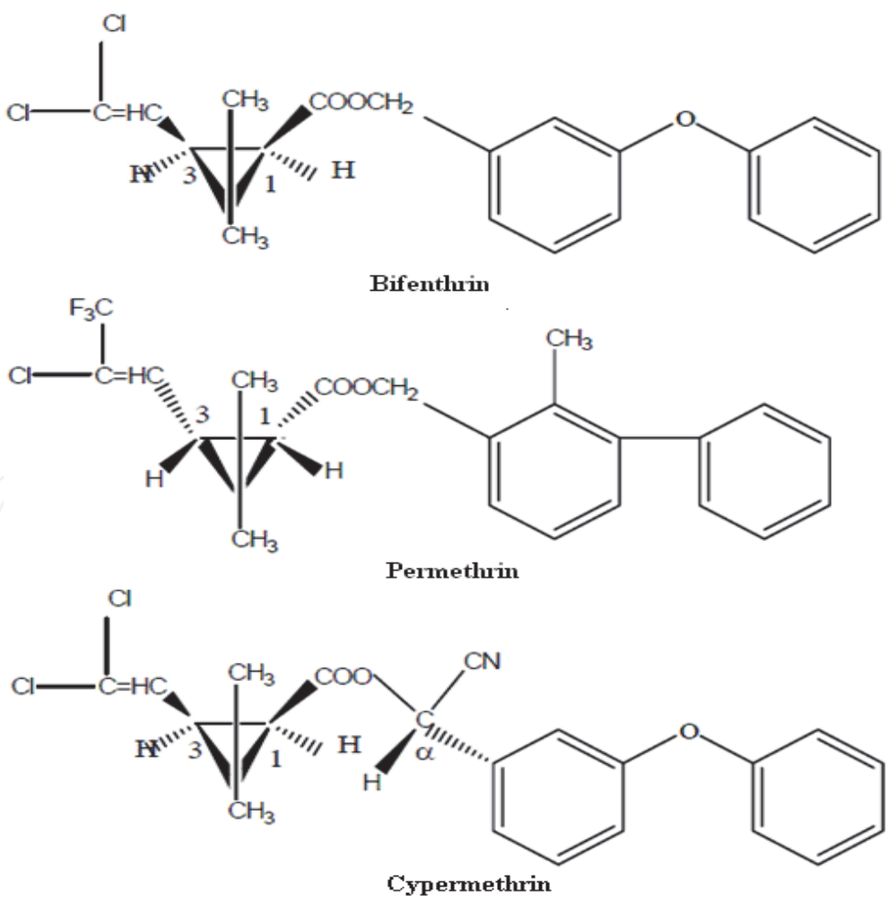


Fig. 2. Stereo-structures of bifenthrin, permethrin and cypermethrin

### 2.2 Chirality of pyrethroid pesticides

Chirality, a property of molecules having a non-superposable mirror image, is a term used to express the asymmetry of the molecular structure of compounds. And chirality is one of the essential attributes of the nature (Schulgasser et al., 2004). A chiral molecule is a type of molecule that lacks an internal plane of symmetry and thus has a non-superposable mirror image. The feature that is most often the cause of chirality in molecules is the presence of an asymmetric carbon atom. With the growing worldwide attention to the chirality of compounds, many countries have carried out compulsory registration of chiral pesticides, and meanwhile the data of the biological activities and degradation of the enantiomers must be declared. The pyrethroid pesticides enjoy 30% market share of pesticides in the world, most of which contain one or more chiral centers. The chirality of pyrethroid pesticides deriveds from the two chiral carbons in the traillylantimonite structure of the acid part and the α carbon atom of the alcohol part. Therefore, there may be up to 3 chiral carbon atoms in pyrethroid pesticides, and there may be 2, 4 or 8 chiral isomers (Table 2) and all the enantiomer are greatly different in their biological activities (Owen, 1975). The representative stereo-structures of pyrethroids are shown in Figure 2. The pollution of racemic mixtures has been long regarded as a single compound during the evaluation of the environmental behavior, ecological effects, potential toxicity and toxicology of the pyrethroid pesticides. And the racemic mixture of the pesticides containing two or more enantiomers have been treated as a compound without taking the feature of configuration transformation or prior metabolism of the enantiomers into account, which result in the unreliable risk assessment of pyrethroid pesticides.

### 2.3 Toxicological mechanism of pyrethroid pesticides

The pyrethroid pesticides, as neurotoxic pesticides, are provided with high lipophilicity, poor water-solubility, long residues and slow metabolic rate in the environment. The toxicity is mainly characterized by (i) the severe toxicity. The insecticidal activity of pyrethroids mainly resides in their action on voltage-sensitive sodium channels in the nervous system, extremely enlarging the sodium channels and leading to the hyperexcitability of the nervous system; (ii) the negative temperature dependence. The pyrethroid pesticides are of better insecticidal effect at low temperature than in high temperature; (iii) the selective toxicity. In virtue of the important role of neural sodium channels in the selective toxicity, the pyrethroid pesticides are much more toxic to insects than mammals; (iv) the varied targets. A variety of receptors, channels and enzymes are likely to be the targets of pyrethroids.

Despite the high toxicity of pyrethroid pesticides to insects, fishes, etc and low or moderate toxicity to human or mammalian, they will lead to some neurotoxic symptoms such as convulsions, tremor, ataxia, paralysis, etc. by affecting the sodium channel of human body (Albert & Pombo-Willar., 1997). Long-term exposure to pyrethroids may cause injury to the lymph nodes and spleen and the risk of canceration, and it has been found that the currently used pyrethroid pesticides, such as bifenthrin, cypermethrin, fenvalerate, etc. which have immune toxicity, will affect the function of human's immunity system. People chronically exposed to these pesticides will suffer from chronic intoxication characterized by headaches, dizziness, nausea, skin itching and other symptoms. The pyrethroid pesticides with halogen hydrocarbons and phenyl ether radical, which are provided with anti-androgen and thyroxine interferent, are considered one of chemical pesticides with environmental hormones (Hill, 1985).

| pyrethroids | Number of chiral centre | Number of chiral monomers |
|---|---|---|
| empenthrin | 3 | 8 |
| fenfluthrin | 2 | 4 |
| fenpirithrin | 3 | 8 |
| furethrin | 3 | 8 |
| imiprothrin | 2 | 4 |
| prallethrin | 3 | 8 |
| pyresmethrin | 2 | 4 |
| resmethrin | 2 | 4 |
| tefluthrin | 2 | 4 |
| tetramethrin | 2 | 4 |
| transfluthrin | 2 | 4 |
| kadethrin | 1 | 2 |
| fenpropathrin | 1 | 2 |
| fenvalerate | 2 | 4 |
| terallethrin | 1 | 4 |
| protifenbute | 1 | 2 |
| flucythrinate | 2 | 4 |
| fluvalinate | 2 | 4 |
| brofluthrinate | 2 | 4 |
| flufenprox | 1 | 2 |
| cycloprothrin | 2 | 4 |

Table 1. pyrethroids and the number of stereoisomers

### 2.4 Organism's resistance to pyrethroid pesticides

Although the pyrethroid pesticides have been widely used for only thirty years, the reports show that the resistance to them has covered all categories of insects. Compared with organophosphorus pesticides and carbamate pesticides, pyrethroid pesticides are much more likely to cause pests' resistance (Mahmoud et al., 1988). The domestic and foreign practices, surveys and studies have shown that, the pests in high selective environment where the pyrethroid pesticides applied in successive years or repeatedly applied in one year will be quickly provided with tolerance with high ratio and the cross-resistance in different categories. The resistance are in two main mechanisms: one is target resistance, that is, with the changes in the action target under the sequential action of pesticides, the pesticides cannot be combined themselves with targets; the other is metabolic resistance, that is, the pesticides are degraded and prevented to act on targets through the increased detoxification enzyme activity by the increase in gene expression or gene mutations. A large number of literature and reports suggest that the resistance to pyrethroid pesticides is the result from, on one hand, the changes in two amino acids found in the sodium channel gene in the resistant strains, which might be one of the main mechanisms leading to the highly resistance of housefly to the pyrethroid pesticides (Brewer &Tremble, 1994), on the other hand, the increase in the detoxification capacity of the detoxification enzymes related to the

metabolism, such as the high expression of chymotrypsin gene or the increased activity of esterase and mixed-function oxidases, which is also one of the main mechanisms of insects' resistance to pyrethroids (Josi & Reutter, 1989; Hu et al, 2008).

## 3. Separation of chiral monomers of pyrethroid pesticides

### 3.1 Detection methods of pyrethroid pesticides

The total amount of mixed modification pesticides should be determined prior to the separation of chiral monomers of pyrethroid pesticides. Currently, mainly two kinds of methods are applied to detection of pyrethroid pesticides. One is the chromatographic detection technology based on instrument method, and the other is the immunoassay technology based on the specific immune response of the antigen and antibody. The latter, including radioimmunoassay (RIA) and enzyme-linked immunoassay (EIA), is fast and sensitive. By virtue of its high specificity, it can handle a large number of samples in one application. However, due to the antibodies used in immunoassay technology are generally with high specificity and thus have poor ability of identifying other analogues, it is generally not suitable to the multi-residue detection. And furthermore, additional analytical methods such as gas/liquid chromatography coupled with mass spectrometry must be applied to the accurate quantification and confirmation after the detection by immunoassay methods.

However, the immunoaffinity chromatography (IAC), which developed from the immunological technique, provides a good solution for the purification of pyrethroid pesticides under detection in the complex sample matrix. It is a major research trend in the field of detection of pyrethroid pesticide residues by using equipment detection ( Húsková et al., 2009).

#### 3.1.1 Chromatographic detection technology

Due to the generally higher boiling point (between 130-200 ℃) and good thermal stability and weaker polarity, the gas chromatography is used as a main analytical technology. Meanwhile, the electronegative elements (halogens) in the chemical structure of pyrethroid pesticides can better respond to some selective detectors, such as electron capture detector (ECD) or negative chemical ionization (NCI) mass spectrometry detector (Wu et al., 2010). Húsková et al ( Húsková et al., 2009) detected 23 endocrine interferon pesticides, including pyrethroid pesticides, in apple by using GC-MS. By comparing EI mode and NCI mode, the results showed that the NCI mode has a higher linear correlation coefficient, sensitivity and better selectivity. Wu et al(Wu et al., 2010) determined 11 pyrethroid pesticides by using liquid-liquid extraction and GC-ECD detection, and the detection limits were between 0.29 ng / L ~ 2.29 ng/L. Francesc et al(Francesc et al., 2005)determined kinds of pyrethroid pesticides in vegetable oil by gas chromatography-tandem mass spectrometry (GC-MS/MS) coupled with solid-phase extraction, and the detection limit were up to 0.3 ~ 1.4 ng/g.

However, due to the trace amount of the pesticide residues in the samples, how to minimize the loss in extraction is of great importance to the sensitivity and accuracy of the detection method. As a result, the purification technology jn the process of the sample pretreatment is crucial for the sensitivity of the detection method. Because of complex of the matrix of plant and animal tissues and the feature of pyrethroid pesticides' easily accumulating in fat tissue pose great challenges to the sample pretreatment. So the solid phase extraction (SPE), liquid-liquid extraction (LLE), gel permeation chromatography (GPC) and other complex sample

pretreatment methods are generally applied(Khay et al., 2008). Massive toxic organic solvents used in this process leads to high costs of detection and disadvantages to the environmental protection. Therefore, the IAC integrating the functions of separation, purification and concentration of sample and with high selectivity can highly purify and concentrate the specific ingredients in complex samples. So that IAC can greatly simplify the sample pretreatment process, improve the efficiency of extraction, avoid the repeated extraction and concentration, while avoiding the use of massive organic solvents and reducing costs. Therefore, as an environment friendly product, IAC is one of the major research trends in the field of sample purification.

### 3.1.2 Immunoassay technology

The immunoassay (IA), in spite of its specificity, sensitivity and large analysis capacity, is limited in the field of determination of pyrethroid pestices due to the difficulty in development of antibody and its limited application to single compound or compounds with similar structures. However, compared to traditional instrumental analysis methods, IA with the advantage of specificity, convenience, large analysis capacity, low costs, is becoming a hotspot in the field of rapid detection of pesticide residues. The preparation of antibodies of pyrethroids has begun in the late 1970s. Hammock et al (Keith et al., 1978) from the EPA-NERL/Human exposure research laboratory of the University of California acted as pioneer in preparing polyclonal antibody of bioallethrin in 1978. Thereafter, polyclonal antibodies of fenpropathrin, S-fenvalerate, permethrin, deltamethrin, cypermethrin and other of pyrethroid pesticides, and the class selective antibody for type Ⅰ pyrethroid pesticides and type Ⅱ pyrethroid pesticides were prepared by the team. And the corresponding ELISA methods were established (Keith et al., 1978; Shan et al., 2001; Mak et al.,2005). Skeritt et al (Skerritt et al., 1992) prepared the monoclonal antibody of phenothrin and permethrin respectively, and analyzed the residues of corresponding pyrethroids in the grain samples; the Corbel Laboratory of France prepared the monoclonal antibody which can identify deltamethrin (Queffelec et al., 1998).

Many research teams in China have also carried out the exploratory studies on the immunological analysis of pyrethroid pesticides. Zhejiang University applied for the patent by the title of *"Fenvalerate artificial antigen, antibody and its application"* in 2005 (ZL03114897.2). Yangzhou University prepared the polyclonal antibody of fenvalerate (Zhu et al., 2004). Gao Hongbin from China Agricultural University prepared the polyclonal antibody of cyhalothrin and developed the ELISA detection method (Gao et al., 2006). Li Bo et al from Nanjing Agricultural University (Li, 2007) prepared the polyclonal antibody which can identify bifenthrin and cypermethrin. Luo Ailan et al (Luo, 2004) prepared the polyclonal antibody which can identify permethrin, cypermethrin, fenpropathrin, deltamethrin and cyhalothrin in Yangzhou University and established ELISA detection technologies for the 5 pyrethroid pesticides.

Currently, the immunoaffinity chromatography (IAC), which is based on the specific combination of antigen with antibody, is promising in the analysis of pyrethroid pesticide residue as a SPE technology using the feature of antigen-antibody specific reversible binding. In virtue of its low cost and high sensitivity, more and more researchers have begun to develop the IAC technology applying in the determination of pyrethroid pesticides. And the multi-immunoaffinity of multiple antibody and class selective antibody can separate and purify multi-residue components in one application and thus provide the

immunoassay with the ability to handle determination of multi-residue, which is the development trend of affinity chromatography technology in the area of residue determination.

The author's laboratory successfully prepared polyclonal antibody and IAC column which can identify 6 pyrethroids including tau-fluvalinate, cyhalothrin, cyfluthrin, fenpropathrin, cypermethrin and deltamethrin, and the IAC columns were applied to the purification of biological samples such as pork samples (Kuang et al., 2009; Kuang et al., 2009). Based on the above researches, an Indirect competitive Enzyme-Linked Immunosorbent Assay based on monoclonal antibody for the detection of Pyrethroids' metabolite PBA was developed in our lab, and the ELISA method was successfully applied to the determination of 3-PBA in pig urine.

### 3.2 Methods of chiral separation of pyrethroid pesticides

The method used to obtain a single enantiomer of chiral compound can be roughly divided into synthesis and racemic mixture separation method. The synthesis method can be divided into chiral synthesis and asymmetric synthesis. Despite the ability to obtain the active single enantiomer, synthesis method is not widely applied due to its tedious synthesis process, high cost and low optical purity. The racemic mixture separation method is widely used due to its easy implementation, relatively simple operation and low cost. Over 65% of non-natural chiral pesticides are obtained by the racemic mixture separation or intermediate products. The racemic mixture separation method include crystal separation, chemical separation, biological separation, extraction separation, chiral membrane separation and chromatographic separation, in which the chromatographic separation is the most widely used one.

#### 3.2.1 Method of chiral liquid chromatographic separation of pyrethroid pesticides

High performance liquid chromatography (HPLC), a method widely used in the separation and analysis of pesticides, can not only apply to analysis but preparation of chiral monomers of pyrethroid pesticides. The working principle of HPLC in the field of chiral separation of pyrethroid pesticides is to show the difference of physical and chemical specificity of the optical active enantiomers by the introduction of asymmetric atoms or creation of chiral environment. With this theoretical basis, the method of chiral separation of enantiomer molecules by HPLC can be divided into two categories: direct method and indirect method. The direct method falls into two methods: the method of mobile phase additives and the method of chiral stationary phase. The method of mobile phase additives is to add chiral selector into mobile phase and the chiral selector was combined with the chiral enantiomers, and then the chiral enantiomers are separated by the functions of stereo-selective attraction or repulsion of the non-chiral stationary phase. The principle of the method of chiral stationary phase separation is that the temporary compounds with different stability produced by the combination of the two enantiomers with chiral stationary phase, and the ones with poor stability will be eluted earlier when the mobile phase passes through and thereby the purpose of the separation of enantiomers is achieved.The indirect method falls into two methods as well: one is to separate the enantiomers by the derivatization of enantiomer by chiral derivatization reagent and then separate the derivative products by non-chiral stationary phase; the other is to separate the enantiomers by the derivatization of enantiomer by non-chiral derivatization reagent and then separate enantiomers by chiral stationary phase (Huhnerfuss & Shah, 2009).

Owing to the reaction of chiral derivatization, the indirect method is usually cumbersome and needing more complex aftertreatment. The method of chiral mobile phase additives is tedious as well. Furthermore, for chiral separation of pyrethroids, the molecular structure of pyrethroids lacks the functional groups which are needed for the reaction with chiral selectors, So it is frequently necessary to hydrolyze pyrethroids into acid, while, for pyrethroid pesticides containing CN, the chirality of the compound will be lost or changed with the loss of CN in the hydrolysis process. And as a result, the method of chiral mobile phase additives is not applicable to chiral separation of pyrethroids. The chiral stationary phase method is the one most widely used method in the field of chiral separation of pyrethroid pesticides by HPLC (Haginaka, 2002).

The design and development of the highly selective chiral stationary phase (SCP) are crucial for the successful chiral separation of pyrethroid pesticides by HPLC. The CSP used in chiral HPLC include CSP of cyclodextrins, proteins, crown ethers, polysaccharides, polyacrylamides, polymeric chiral surfactants, macrocyclic antibiotics and some low-molecular-weight molecules such as Pirkle type compounds. The pirkle-type CSP (also known as Pirkle type 1A), which was the pioneer CSP used in the chiral separation of pyrethroid pesticides, was first developed by Pirkle et al (Pirkle et al, 1981) in 1980. Chapman (Chapman, 1983) firstly separated the four chiral enantiomers of fenpropathrin and fenvalerate respectively by using benzeneacetic and a-[(3,5-dinitrobenzoyl amino] as CSP. Cayley et al (Cayleya & Simpson, 1986)made a systematic study in chiral separation of enantiomers of pyrethroids by using ionic bonded Pirkle type 1A CSP. The experiment results show that ionic bonded CSP is more efficient than covalent bonded CSP. Edwards et al (Edwards et al., 1987) separated 3 pair out of the 4 pair enantiomers of the cypermethrin by using cellulose derivative chiral stationary phase with hexane and isopropanol used as the mobile phase, and the two enantiomers of the alpha-cypermethrin were also well separated. Schurig et al. (Schurig et al., 1996) partly separated the two enantiomers of alpha-cypermethrin on cyclodextrins chiral stationary phase by using methanol / water as mobile phase. Yang Guosheng (Yang & Dai, 1998) separated the chiral isomers in fenpropathrin and methothrin in the mobile phase system of hexane and isopropanol by using Pirkle CSP. Wang Peng et al (Wang, 2006) made chiral separation of the enantiomers of alpha-cypermethrin and theta-cypermethrin under normal phase HPLC on the homemade chiral stationary phase by coating cellulose-tris 3, 5-dimethylphenyl carbamate (CDMPC) onto aminopropyl silica gel, and baseline separation can be achieved. Sánchez (Sánchez et al., 1998) separated bifenthrin and fenpropathrin by using Chiralspher chiral column, and he separated the enantiomers of tau-fluvalinate and permethrin on the Chiralcel OJ chiral column with hexane/ethanol as the mobile phase. This method has achieved baseline separation and was applied to the detection of residues of these pesticides in water. Faraoni (Faraoni et al., 2005) completely separated the enantiomers of fenvalerate and cyfluthrin by using non-chiral liquid phase chromatographic column coupled with chiral liquid chromatographic column (stationary phase of polysaccharide derivative and "Pirkle" column) , and this method was applied in the researches on the selective degradation of the chiral monomers of fenvalerate in soil under laboratory conditions. Bicker (Bicker et al., 2004) separated the chiral isomers of various pyrethroids by using quinine as chiral stationary phase. Li, et al. (Li et al., 2003) carried out chiral liquid chromatographic separation of fenpropathrin, beta-cypermethrin, beta-cyfluthrin and S-fenvalerate by using Chiralcel OD and Chirex 3020 chiral liquid chromatographic columns. Liu et al (Liu et al,

2005) achieved a complete separation of the enantiomers of cis-bifenthrin and permethrin on the non-chiral column coupled with Sumichiral OA-2500-I chiral analytical columns. Liu, et al. (Liu et al., 2005) separated 8 enantiomers of cyfluthrin and cypermethrin by using Chirex 00G-3019-DO chiral column respectively. The author's laboratory successfully separated isomers of cypermethrin, allethrin and cyfluthrin, and as Fig. 4 showed, 8 isomers of cypermethrin and cyfluthrin were separated, and the separation method was used to analysis the isomers of cypermethrin in pork samples (Kuang et al., 2010) The following Table 2 is made for the summary.

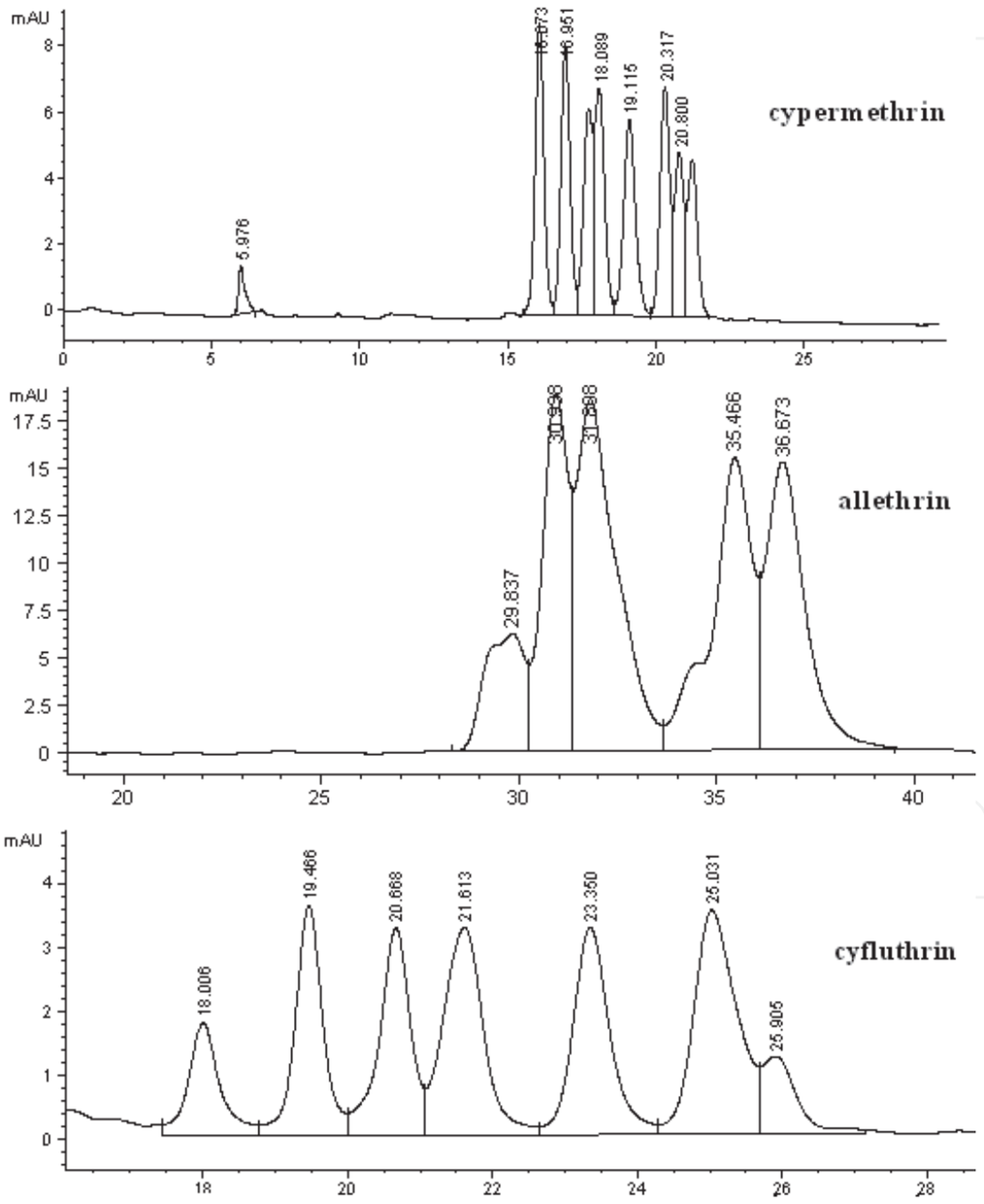


Fig. 4. Chiral separation of cypermethrin, allethrin and cyfluthrin on the CD-ph LC column

| pyrethroids | Type of LC stationary phase | Separation | References |
|---|---|---|---|
| deltamethrin | N-(3,5-Dinitrobenzoyl)-(R)-(-)--phenylglycine | 8 peaks | (Maguire, 1990) |
| cypermethrin | Daicel chiracel OD | 6 peaks | (Edwards et al., 1997) |
| cypermethrin | Glycine Derivative I~II | 8 peaks | (Naobumi et al., 1990 ) |
| phenothrin | 10% QF-1 Sumipax OA-2000 | 6peaks | (Doi et al., 1985) |
| deltamethrin | RP-8/Lichrosorb Si-60 | 1 peaks | (Mourot et al., 1979) |
| cypermethrin | Pirkle type Amino column | 5 peaks | (Chapman, 1983) |
| cyfluthrin | Dupont zorbax | 5 peaks | (Tephem et al., 1990) |
| cypermethrin | Sumichiral OA-2500-I, Chirex DOG-3019-DO | 4 peaks | (Liu et al., 2005) |
| cis-permethrin, trans-permethrin | Sumichiral OA-2500-I | each 2 peaks | (Liu et al., 2005) |
| fenvalerate | Pirkle I-A | 4peaks | (Cayley & Simpson, 1986) |
| fenvalerate | Brush-type chiral stationary phase | 4peaks | (Lee et al., 1987) |
| permethrin | Brush-type ligand exchange chiral stationary phase | 4peaks | (Dondi et al., 1999) |
| tetramethrin | OA-4700 pirkle column and β-cyclodextrin | 4peaks | (Deng, 2004) |
| prallethrin, Bioallethrin, prallethrin, cyphenothrin | Cellulose | each 2peaks | (Xu, 2003) |
| cis-bifenthrin (BF)，permethrin (PM) | Sumichiral OA-2500-I | BF-2peaks, PM-2peaks | (Liu et al., 2005) |
| cypermethrin、cyfluthrin | Chirex 00G-3019-OD column | 8 peaks | (Mancini et al., 2004) |
| bifenthrin | OJ Daice chiral column | 8 peaks | |
| cis-bifenthrin, trans-bifenthrin | Pirkle type Chiralcel OJ | each 4peaks | |
| fenvalerate | Chiralcel CD | fenvalerate 4peaks | (Li et al., 2006) |
| fenpropathrin，beta-cypermethrin | Chiralcel CD | each 2 peaks | |
| S, R-bioallethrin | β-cyclodextrin as chiral additive, C8 column | 2 peaks | (Li et al., 2006) |
| cis-cypermethrin ，trans-cypermethrin | Cellulose-tris(3,5-dimethylphenylcarbamate) | each 2peaks | (Wang, 2006) |
| cypermethrin | Supelcosil LC-CN column coupled with Chiralcel OD-H | 7 peaks | (Ta et al., 2006) |
| cis-cypermethrin | Chiralcel CD column | 2 peaks | (Edwards et al., 1987 ) |
| bifenthrin and fenpropathrin | Lichrospher Si-60 column，Chriraspher column | each 2peaks | (García et al., 1996) |

Table 2. Summary of LC chiral analysis of pyrethroids

### 3.2.2 Gas chromatographic chiral separation of pyrethroid pesticides

Gas chromatography (GC) has been widely used in the separation of various enantiomers of pyrethroid pesticides due to its advantages of lower detection limit compared with other techniques(Eljarrat et al,2008; Hassan & Imran, 2004). The separation principle is mainly based on the hydrogen action, mating action and inclusion action of the chiral stationary phase. The commonly used chiral stationary phase of GC columns can be divided into three types: amino acid derivatives, chiral metal complexes and chiral cyclodextrins derivatives (CD) (Wang, 2006). In the Currentlly commercialed gas chiral chromatographic columns, the vast majority are produced by using derivatized cyclodextrins as the chiral stationary phase. The shortcomings of GC chiral separation are high cost and much time consumption. Liu, et al. (Liu et al., 2004; Liu et al., 2005) made chiral separation of bifenthrin, permethrin, cypermethrin and cyfluthrin by using the BGB-172 gas capillary chromatographic collum with 20% tert-butyldimethylsilyl-β-CD dissolved in 15% diphenyl and 85% dimethylpolysiloxane used as stationary phase. It was the first time to analyze the pyrethroid pesticides, cypermethrin and cyfluthrin in biological matrix by combining solid phase micro extraction (SPME) with gas chromatographic electron capture detection (ECD). And 6 peaks of the 8 chiral monomers of cypermethrin were separated on the column, and the two peaks of cis-bifenthrin reached completely baseline separation, and 3 of the 4 chiral enantiomers of permethrin can be separated. We have achieved good chiral separation of bifenthrin, permethrin and cypermethrin by using BGB-172 column based on the research work of Liu, and the chromatographyic picture of chiral separation are shown in Figure 3, and six separated peaks of theoretic eight peaks of cypermethrin were obtained from the column and baseline separation of *cis*-bifenthrin was realized. The detection of eantionmer fraction (EF) of bifenthrin or cypermethrin in tea samples was carried out and the results showed that EF value of some enantiomer of cypermethrin changed depending on the fermentation degree of tea (Kuang et al., 2010). Kutter and Class (Kutter & Class, 1992) made chiral separation of allethrin and cypermethrin by using non-chiral column DB-1701 column coupled to CDX-B chiral column with permethylated-β-cyclodextrins as stationary phase, and cis- isomers were well separated, but the trans-isomers were not well separated. Nie et al. (Nie et al., 2000) separated some enantiomers of pyrethroids containing ester by using different chiral stationary phases. Compared with single derivatized cyclodextrins CSPs, the mixed derivatized cyclodextrins CSPs are more effective in the separation of chiral enantiomers of pyrethroids. Studies have shown that some pyrethroids with thermal instability tend to be degraded during gas chromatographic analysis and lead to the transformations between enantiomers. The transformations between enantiomers of some pyrethroids even happen in organic solvents. Qin and Gan (Qin & Gan, 2007) discovered that permethrin is stable in all organic solvents, but the transformations between enantiomers of cypermethrin appear in acetone and methylene dichloride when they carried out chiral separation using gas chromatography. The transformations between enantiomers are affected by the temperature and they are affected by the water as a latent solvent when the pesticides are applied. Therefore, exposure to water or some solvent may lead to spurious results of chiral separation. In addition, for the pyrethroids with many chiral isomers, the transformations between the enantiomers may cause that of enantiomers with high biological activity into the inactive ones and lead to the product failure.

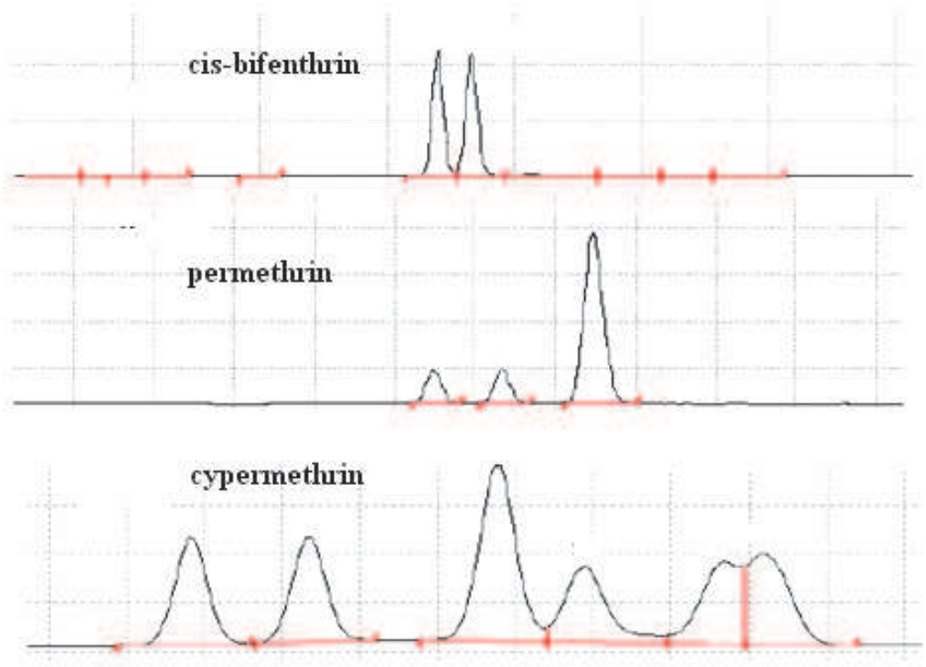


Fig. 3. Chiral GC separation of bifenthrin, permethrin and cypermethrin on BGB-172 column

| Pyrethroid | Type of GC stationary phase | Detection method | Separation | References |
|---|---|---|---|---|
| cyfluthrin | achiral column | GC/MS | 4 peaks | (Leicht et al., 1996) |
| phenothrin | 4% DEGS | GC | 4 peaks | (Doi et al., 1985) |
| cypermethrin(CP） | BGB-172 | GC/ECD | CP-6 peaks | (Liu et al., 2004; Liu et al., 2005) |
| bifenthrin(BF) | BGB-172 | GC/ECD | BF-2 peaks | |
| permethrin( PM), | BGB-172 | GC/ECD | PM-3 peaks | |
| chrysanthemic acid | brush-type chiral stationary phase | GC-FID | 2 peaks, badly separated | (Naobumi et al., 1983) |
| cypermethrin | permethylated-β-cyclodextrins | GC | 3 peaks | (Chen, 2002) |
| cypermethrin | B-DEX225 | GC/MS | 7 peaks | (Yu, 2000) |
| pyrethroic acid methyl esters | cyclodextrin derivatives | GC | 4 peaks | (Shi et al., 2002) |

Table 3. Summary of GC chiral analysis of pyrethroids

### 3.2.3 Capillary electrophoresis chiral separation of pyrethroid pesticides

The capillary electrophoresis is a novel technology used in the separation of chiral pyrethroids. The commonly used chiral selectors include cyclodextrins and their derivatives, macrocyclic antibiotics, amino acid - metal complexes, chiral crown ethers, etc. 85% of the capillary electrophoresis chiral separation are currently carried out on cyclodextrins filler(Wang, 2006). Ševcík, et al. ( Ševcík et al., 1997) separated cypermethrin, permethrin and fenpropathrin by using the micellar electrokinetic chromatography (MEKC). Odium dodecyl sulfatse (SDS) and cetyltrimethyl ammonium bromide (CTAB) were used as

surfactant. β-cyclodextrins, hydroxypropyl-β-cyclodextrins, dimethyl-β-cyclodextrins, γ-cyclodextrins and other chiral stationary phases were tried as chiral stationary phase. The results show that, by using γ-cyclodextrins and SDS, the two enantiomers of fenpropathrin were well separated, and 7 of 8 enantiomers of cypermethrin can be separated, and 4 enantiomers of permethrin can be separated, but the separation of the first 3 peaks is not obvious. Karcher et al. (Karcher & Rassi, 1997) taking OG (n-octyl-β-dglucoside) and OM (n-octyl-β-O-maltopyranoside) as chiral surfactants, set up the method to separate the hydrolysis products such as permethrin, cypermethrin, fenpropathrin and fenvalerate by using micellar electrokinetic capillary chromatography (MEKC). With the presence of carboxylic acid in the hydrolysis products, the separation of enantiomers will be simpler with the reduced enantiomers caused by the decreased chiral centers.

## 4. Selective biological toxicity of chiral monomers of pyrethroid pesticides

The chiral enantiomers of pyrethroid pesticides are characterized by certain degree of chiral selective biological toxicity. Different chiral isomer may be coupled with the same or different targets of organisms at the same or different positions in different degrees, resulting in the same or opposite efficacy or toxicity, and thus the activities of various enantiomers are quite different (Owen, 1975). In 1974, Elliottt discovered that the *cis* isomer of natural permethrin C-1 has insecticidal toxicity, and the *trans* isomer is inactive in terms of insecticidal activity (Elliott et al., 1974). At present, most attention has been focused on the pesticide of *cis*-bifenthrin (*cis*-BF) which has two enantiomers with the structures of 1S-cis-BF and 1R-cis-BF. 1R-cis-BF is more effective than 1S-cis-BF on the target organisms, while on endocrine toxicity, the estrogenic effects of 1S-cis-BF is significantly higher than 1R-cis-BF. Therefore, R-type is better than S-type in terms of insecticidal activity and otherwise in terms of toxicity. The *2S-aS* isomers of fenvalerate and cyfluthrin are more toxic to insects, while their *2R-aR* isomers have little insecticidal activity. Cypermethrin has enantiomer selective toxicity to the aquatic organism C.dubia, and 2 out of its 8 enantiomers (*1R-cis-aR* and *1R-trans-aR*) have strong toxicity to C.dubia (Liu & Gan, 2004). The insecticidal activity of deltamethrin is only associated to the dextral cis-isomers (synthesized from1*R, 3R* permethrin and *S-a*-cyanohydrin) and the other 6 stereo-isomers have been demonstrated to be inactive (Domine, 1982). The *1R-trans-aS* isomer of prallethrin has high insecticidal activity, and its enantiomer (1S-trans-αR) has only 1/200 of its activity. *S, S*-fenvalerate is the one with the highest activity in the 4 isomers of fenvalerate. According to the OECD standards, Wang Jiajia (Wang, 2008) studied the effect of beta-cypermethrin and its 4 chiral isomers on the development of zebrafish embryonic. The results showed that beta-cypermethrin has the strongest toxicity to the zebrafish embryonic at 48h. The isomer of *1R-cis-aS* is the most toxic one in the 4 chiral isomers, and then followed by *1R-trans-aS*, and the isomers of *1S-cis-aR* and *1S-trans-aR* have no teratogenic effect. In terms of cytotoxicity to SHSY5Y, the isomer of 1R-cis-αS is most toxic one.

The pyrethroid pesticides also show stereoisomeric selectivity in terms of acute toxicity to mammals. The studies show that the acute neurotoxicity of pyrethroids to mammals is associated to the three-dimensional chemical configuration of C-1 chiral center of pyrethroid pesticides. In general, the isomer with acute neurotoxicity to mammals is the same as that with insecticidal activity to the target organisms. The three-dimensional structure of the C-3 chiral centers of some pyrethroid pesticides, such as resmethrin and permanone, directly affects the acute neurotoxicity to mammals (Kolaczinski & Curtis, 2004). In a research of the

neurotoxicity of the isomers of deltamethrin to the central nervous system of rodents, it was found that the isomer of 1*R* has obvious neurotoxicity to mammals, and *1S* isomer showed no neurological toxicity even at high concentrations (Ray & Fry, 2006).
Therefore, different chiral isomers of pyrethroids have different biological activities and neurotoxicities, and thereby the residues and metabolisms in the environment and biological organisms also vary greatly. The selectivity of chiral enantiomers on neurotoxicity may be caused by the inherent structural differences of enantiomers of pyrethroids or the different metabolic rates of enantiomers in organisms. Anyway, the detailed molecular mechanism is not precisely known.

## 5. Pollution of pyrethroid pesticides and the degradation difference of chiral monomer in the environment

### 5.1 Pollution of pyrethroid pesticides in the environment

The wide application of pyrethroid pesticides in agriculture and pest control in urban areas causes their residues in the environment. According to statistics of Denmark in 2008, 89% of environmental pollution caused by the pesticides ascribed to the application of pyrethroid pesticides spray (Danish EPA, 2009). In 2009-2010, the detection results of contamination of pyrethroid pesticides in water and sediment in Spain Ebro Delta showed that 22 detected water samples contained cypermethrin residues with the maximum concentration of 57.2 ng/L, including 3 water samples containing deltamethrin residues with the maximum of 58.8 ng/L. Only the cypermethrin residues were detected in all sediment samples, and the amount was up to 71.9 ng/g. The results show that cypermethrin pollution in the water and sediment in Mingaibuluo Delta was in a serious situation (Feo et al., 2010).
More than 58,000 kg of the pyrethroid pesticides have been applied to the pest control of corn, cotton, soybean, rice, wheat and other crops in the United States since 1991 to 2000, and more than 117,000 kg active pyrethroid pesticides were applied in 2002 alone, causing a profound influence on the water quality in the United States. According to the statistics of International Emergency Economic Powers Act (IEEPA) in 2007, more than 1300 kinds of aquatic organisms were influenced by the water polluted by pesticides (Moore et al., 2009). University of California carried out a one-year follow-up detection during 2007-2008 on the water and sediment in the small streams flowing through the city of Sacramento and California, and the results showed that the detected samples had been polluted by pyrethroid pesticides in different levels, in which the residues of bifenthrin was 73ng / L in the water, and up to 1211ng / g in the sediments. Bifenthrin was given primary attentionin in the pyrethroid pesticides contamination in this region, followed by cypermethrin and cyfluthrin containing minor pollution (Weston et al., 2009). Environmental Protection Agency of the United States (USEPA) studied the situation of pyrethroid pesticides contamination in the air in the living environment in North Carolina and Ohio, and the results showed that pyrethroid pesticide pollution was detected in 69 of the 85 detected air samples, and the average content of pyrethroid pesticides in air dust was 100 ng / g (James et al., 2008).
Studies have reported that, in natural water systems in China, there is generally no pyrethroid pesticide residues in well water and tap water, but cypermethrin can be detected in the river water (Yu, 2008), and in urban sewage, residues of bifenthrin, cypermethrin, fenvalerate and deltamethrin and other pyrethroids at the contamination level of 0.04 ~ 1.3μg / L were detected (Chen et al., 2005; Chen et al., 2007). The residues of pyrethroid

pesticides in the water are mainly adsorbed onto the surface of suspended particles, and then accumulated in sediments. The amount in the sediment is often hundreds or even thousands of times of that in the water (Yue, 2009). Analyzing the residue of pyrethroid pesticides in the sediment samples is an effective quantitative method to evaluate the contamination situation of pyrethroid pesticides (Weston et al., 2004). Li et al(Li et al., 2010)detected several pyrethroid pesticides in the contaminated sediments in the streams in Guangzhou by microwave extraction and gas chromatography mass spectrometry, of which the amount of beta-cypermethrin was 4.5 ng/g dry weight, permethrin 12.2 ng/g dry weight, cypermethrin 27.9 ng/g dry weight and cis-fenvalerate 2.27ng/g dry weight.
The pyrethroid pesticides in the environment can bring harm to human and food producing animals via the accumulation in plants and acqutics. As a result, in addition to the researches on the degradation of pyrethroid pesticides in animal and human, those in the environment have been also a focus at home and abroad.

### 5.2 Difference in degradation of chiral monomers of pyrethroid pesticides in the environment

The varied metabolism rates of chiral pesticides in the environment may mainly be caused by the differences in selective metabolisms of the bacteria in the soil. Megharaj et al. (Megharaj et al., 1989) screened $10^3$ strains from the soil which can selectively degrade cypermethrin and fenvalerate and they can degrade different chiral isomers in different rates. Sakata et al. (Sakata et al., 1992) screened $10^3$ strains from the soil which can selectively degrade cypermethrin and fenvalerate. Under the action of these bacteria, the iscomers of *1R-trans-aS*, *1S-cis-aS* and *1S-trans-aS* in the 8 isomers of the cypermethrin were degraded with great speed, and the remaining 5 isomers were hardly degraded; and the degradation rate of the *2R-aS* iscomer of the fenvalerate was significantly greater than the other three. The further study showed that the selectivity is caused by the interaction of the enzymes with different degradation mechanism in the degrading of bacteria, which indicated the presence of the degrading enzymes with high selectivity in the soil. Liu, et al. (Liu et al., 2005) via their researches on the environmental behavior of bifenthrin and cypermethrin, discovered that the enantiomers (-) of cis-bifenthrinand alpha-cypermethrin in the field sediments were preferentially degraded, leading to the increased proportion of their enantiomers (+), and the same degradation was observed when the sediments were cultured under the laboratory conditions.

## 6. Metabolism of pyrethroid pesticides in animals

### 6.1. Metabolism of pyrethroid pesticides in animals

Scientists have carried out more researches on the metabolism of pyrethroid pesticides in animal to further understand the potential metabolic processes of such pesticides in human body and thus find out effective ways to solve human pesticide poisoning. For example, due to the similar hydrolysis rate of pyrethroids in rat and human liver microsomes, we can speculate the potential metabolic pathway of the pesticides in human body by the researches on the rodents (Ross et al,. 2005). Mandal et al. ( Mandal et al.,1992) reported that the fenvalerate could be rapidly absorbed and metabolized in goats, and the half-life of fenvalerate was close to 2h in the case of intragastric administration. Orinak (Orinak, 1993) discovered that the alpha-cypermethrin reached the peak concentration in the blood in sheep body after about 24 h. JECFA has carried out intragastric administration of $^{14}C$

marked alpha-cypermethrin on rat with the dose of 2 mg/kg, and it reached the peak concentration in the blood after 3 ~ 4h, and then was rapidly metabolized in the body, and mainly excreted from the urine except for small accumulation in fat and skin tissue. In the case of the same oral dose, urinary metabolites and metabolic pathways of mice and rats and other animals were similar to those of human volunteers. The studies showed that, the main metabolic pathways of pyrethroids in mammals include cleavage and hydrolysis of ester bond followed by the hydroxylation and conjugation of cyclopropyl and phenoxyl in molecules. Due to large amounts of esterase and oxidase existing in the liver, the metabolism of pyrethroids mainly occurs in the liver of mammals and the detoxication could be reached through hydrolysis and oxidation. The biological half-life of many pyrethroids including permethrin, cypermethrin, deltamethrin, fenvalerate was 8 to 12 h (Leng et al., 1997). The bondage of 3 - phenoxybenzyl ester in the structure of pyrethroids could be hydrolyzed in the body into the same metabolites of 3-phenoxybenzoic acid (3 - PBA) which was excreted in the form of urine. In addition, *cis* and *trans*-2, 2 - (dichlorovinyl) -2,2-dimethylcyclopropane carboxylic acids (*cis*-DCCA and *trans*-DCCA) and 4-fluoro-3-phenoxybenzoic acid (4-F-3-PBA) were also the primary metabolites of pyrethroid pesticides, and can serve as the biomarkers of the assessment of human exposure to pyrethroids (Li et al., 2010). Degradation processes of some pesticides are shown in Figure 4.

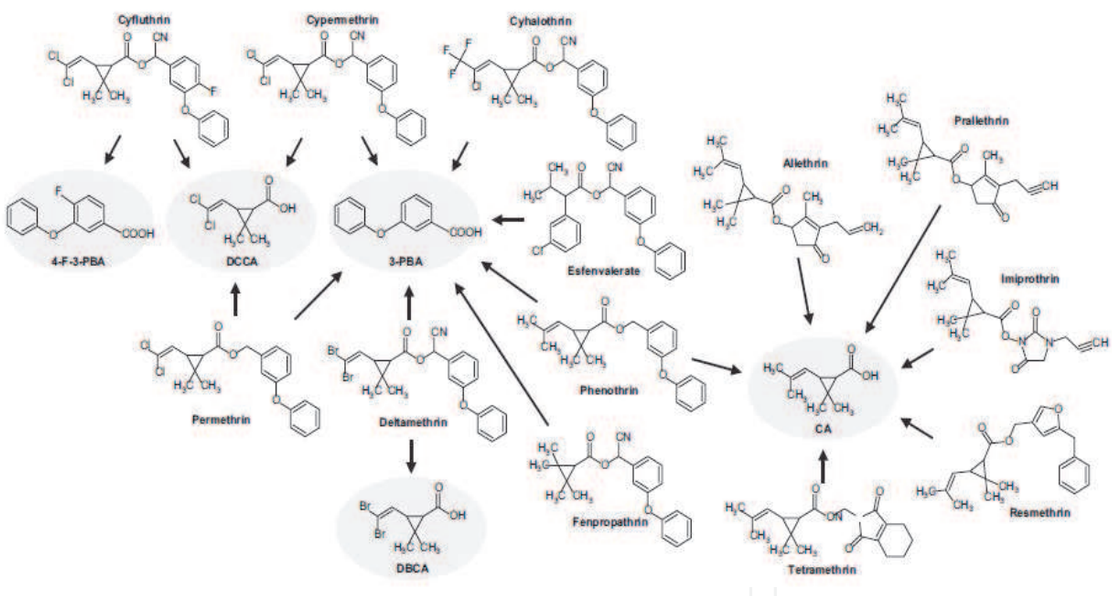


Fig. 4. Metabolic structure chart of some pyrethroids

Various carboxylesterases (CEs) contained in animal and human body, which can degrade pyrethroids, play a key role in the pesticide metabolism and detoxification. The CEs, primarily including hCE-1 and hCE-2, are of the highest activity in the liver (Testa et al., 2003). In addition to the liver, other tissues and organs are of equal importance to the metabolism of pyrethroids because of the presence of CEs in lung, small intestine, plasma and lymphocytes(James et al., 2008; Nishi et al., 2005). The human body also contains a variety of oxidative enzymes which participate in the metabolism of pyrethroids, such as dehydrogenase and cytochromes P450. The alcohol dehydrogenase and aldehyde,

dehydrogenase may participate in the oxidation processes of the phenoxybenzyl alcohol, the intermediate metabolite of permethrin, and thus the detoxication is achieved (Crow et al., 2007). But pyrethroids themselves will dampen the number and activity of the degrading enzymes. For instance, flumethrin can reduce 36% of cytochromes oxidase P450 in number in mouse liver microsomes(Nakamura et al., 2007). Eraslan et al. (Eraslan et al., 2007)treated mice with cypermethrin alone and discovered that the activity of superoxide dismutase in red blood cells was reduced in certain stages of the treatment process and the activity of catalase was significantly reduced in the whole process.

### 6.2 Metabolism of chiral monomers of pyrethroid pesticides in animals

The researches on the selective metabolism of pyrethroid pesticides in animals are the more in-depth section in the researches of the selective behaviors of the chiral compounds. Two factors, on one hand, the many unknown fields in the degradation process of exogenous chiral pollutants due to the complex physiological and biochemical responses in animals, on the other hand, the great concern of human on the security and the sustainable development of human body and the ecological environment, have attracted researchers to explore the activities and provide a scientifically theoretical and practical foundation for the biological safety.

In animal body, pyrethroids are metabolized by different cytochromes P450, and so different enantiomers of pyrethroids and their metabolites always show different pharmacological and metabolism features. However, owing to the complex stereostructure of the pyrethroids, which always include several chiral centers and *cis* and *trans* isomers, and the limited separation means of chiral monomers, there are few researches on the selectivity of the optical isomers of such compounds in animal body, and most of which are merely based on the selectivity of the *cis* and *trans* isomers. Takamatsu et al (Takamatsu et al., 1987), carried out oral administration on rats by marking the 4 optical isomers of fenvalerate with $^{14}$C, and applied the $^{14}$C monomers to the suspension of organ microsomes for cultivation in vitro as well. The results showed that the optical isomers had selectivity in different organs and the selectivity is different for the 4 optical isomers. The results of cultivation in vitro in liver microsomes were consistent with the results in vivo, suggesting that the liver was the main place of degradation. Compared with α-chiral carbon atoms, the chiral structure of 2-chiral carbon atom of fenvalerate made greater contribution to the selectivity in rats. Nishi et al. (Nishi et al., 2005)studied the hydrolysis made by carboxylesterase hCE-1 and hCE-2 to pyrethroids in human liver, and the results showed that the 2 kinds of enzymatic hydrolysis of *trans*-permethrin and *trans*-cypermethrin were faster than the corresponding *ci*- isomers. Crow et al (Crow et al, 2007) also reported that *trans*-isomers' degradation rate of pyrethroid pesticides in rat liver cells was significantly faster than *cis*-isomers. The trans-isomers had strong stereoselectivity during the hydrolysis of pyrethroids. For instance, the *trans*-isomers of permethrin were hydrolyzed faster than *cis*-isomers. The hCE-2 could hydrolyze *trans*-permethrin, but could not hydrolyze deltamethrin or resmethrin. Miyamoto et al. (Miyamoto et al., 1986) discovered that pyrethroid pesticides had no significant stereoselectivity in mouse plasma. Wang et al (Wang et al,, 2006) conducted a metabolism experiment of a pair of enantiomer of *theta (trans)*-cypermethrin in rats. The results showed that the dextro- enantiomer were degraded faster in the plasma, heart, liver and kidney. After the intravenous injection of single enantiomer in rats, the laevo-enantiomers were transformed into dextro- enantiomer.

The author's research group, by using chiral liquid chromatography, successfully separated and prepared two chiral enantiomers (*1R-3R-áS* and *1S-3S-áR*) of *alpha(cis)*-cypermethrin , and carried out animal experiment of pharmacokinetics and tissue distribution in Wu Zhishan Inbred's miniature pig by using the two enantiomers. The chiral separation was carried out in the collected blood and tissue samples. In the case of feeding single monomer to the miniature pig, all the tissues of the pig at 12h showed significant transformation among isomers of cypermethrin, and no obvious transformation was found in the two monomers in the blood sample within 2h, which is consistent with the research of Miyamoto et al. (Miyamoto et al., 1986). With the exception of the *1R-3R-áS* conformation in fat mainly transforming to its enantiomer *1S-3S-áR*, in other tissues *1R-3R-áS* transformed into the configurations of *1R-3R-áR*, *1R-3S-áS* and *1S-3R-áR*. 23.9% of *1R-3R-áS* conformation transformed into *1R-3R-áR* configuration in the liver. 1S-3S-áR configuration transformed into 1R-3S-áS or 1S-3R-áR configurations in other tissues except for in the fat, and the transformation rate was up to 35.7% at 12 h. No transformation of 1S-3S-áR configuration into its enantiomer 1R-3R-áS conformation was observed in all the tissues. On the whole, the transformations of monomers in the tissues were not so identical. The highest degree of transformation of enantiomers was observed in the liver, and it may be caused by the large amount of enzymes in the liver. The lowest degree of transformation of enantiomers was found in the fat.

The development of the researches on different metabolisms of pyrethroids in animal will provide a foundation to further understand its toxicity and residual rules, which will represent more truthfully the effects of the pollution of related pesticides on human health. All of these researches can also offer a basis to the pollution control, the guidance of rational pesticide use and the development of relevant analytical methods and maximum residue limit standards, and ultimately minimize the toxic side effects of pesticides to human health.

## 7. Human exposure to chiral pyrethroid pesticides and risk assessment

### 7.1 Introduction Total Diet Study in China

The World Health Organization (WHO), the lead of United Nations agency for health, supports total diet studies as the one of the most cost-effective means for assuring that people are not exposed to unsafe levels of toxic chemicals through food. A total diet study (TDS) enables the estimation and monitoring of dietary exposures to chemical residues, contaminants and nutrient elements. A TDS involves purchasing at the retail level foods commonly consumed by the population, preparing them as for normal consumption, homogenizing and compositing them, and finally, analyzing the foods for the chemicals of interest. Beginning 1990 the Chinese TDS has become an important tool for monitoring dietary exposures to chemicals and their associated risk to public health and such studies have been undertaken five times in China at irregular intervals.

The study design and experimental methods of the 4th Chinese TDS were similar to those used to carry out the TDS in 1990 (Chen & Gao, 1993). The food composite approach was used to study the total diet in four regions representing the average dietary patterns of different geographical areas on the mainland and covering about 50% of the Chinese population (Zhao et al., 2003). Each region comprised three provinces: North 1(N1) comprised Heilongjiang, Liaoning and Hebei; North 2 (N2) comprised Henan, Shanxi and Ningxia; South 1 (S1) comprised Jiangxi, Fujian and Shanghai; South 2 (S2) comprised Hubei, Sichuan and Guangxi. Average food consumption of a “standard” A Chinese man

(18-45 years old with average body weight of 60kg) from 90 households (30 household per survey site) was used as the standard food consumption model for the province and the value of three provincial pooled composite was used as the food basket consumption pattern for each region. All food consumed by the standard man was aggregated into 13 food groups, namely cereals and products, Legumes, nuts, and products, potatoes and products, vegetables and products, fruits and products, meats and products, eggs and products, milk and products, aquatic foods and products, sugars, beverages and water, alcohol beverages, condiments and cooking oil. The samples were collected from local markets，grocery stores and rural households, then cooked and prepared according to local food habits of each province. The prepared foods were then blended to form the respective group composites with weights proportional to the average daily consumption for the province. These provincial composites were shipped to the National Institute of Nutrition and Food Safety in Beijing, where the composites were further mixed to form four regional basket composites according to their corresponding weight proportion in food consumption. The samples were then frozen at -30° until analysis.

### 7.2 Exposure and characteristics of chiral residues of pyrethroid insecticides in Chinese diet

The detection results of the composite samples in the fourth Chinese total diet study in 2007 showed that despite a certain level of contamination of pyrethroid pesticides in different parts of China, China was generally in a situation of low level of pollution. For instance, the positive rate of cypermethrin, which is of the highest frequency of detectable pyrethroid pesticides, was 27.5%, and the highest content in meat composites from Fujian Province was 95.65 μg/kg. The contribution rates of different food varied by regions in dietary exposure, the intake of meats and aquatic products were important sources of pyrethroid pesticides exposure through dietary intake. On the whole, Chinese residents' dietary exposure to pyrethroid pesticides was in a low level and far below the acceptable daily intake (ADI) recommended by JECFA. According to the exposure assessment combining with dietary consumption, the upper limit of dietary exposure in Fujian was only 1.59% of the ADI value recommended by JECFA. However, multi-residue of pyrethroid pesticides in the same composite sample was found in some areas (fox example, Hubei). Whether different pyrethroid pesticides have cooperativity is still under study, and the potential health risk caused by the diet exposure of multi-residues of pyrethroid pesticides are worthy of attention.

The results of the chiral separation of the cypermethrin positive composite samples in the total diet study showed that some chiral isomers of cypermethrin disappeared in the samples of legumes from Hubei, fruits from Henan, fruits from Guangxi, and vegetable from Heilongjiang, which may caused by the application of cypermethrin pesticide with fewer chiral monomers such as *alpha(cis)*-cypermethrin, *theta(trans)*-cypermethrin. In addition, the samples of the total diet study were cooked instant samples, while the high temperatures during cooking may be one of the causes leading to the disappearance of some isomers. Significantly enriched isomers ( *1R-3S-aS* and *1S-3R-aR)* were found in animal food samples including aquatic foods from Hebei and meats from Jiangxi, and no remarkable change in the enantiomeric fraction in the meats sample from Liaoning was found. The specific reasons remains to be further studied.

The next work of our research team is to achieve information of other chiral pyrethroid pesticides in TDS samples, such as *cis*-bifenthrin, cyfluthrin, permethrin, etc.. Currently, the

5th Chinese TDS is underway, and we will apply our established method to the determination of chiral isomers in all of those TDS samples. With the combined two sets of results, more information will be acquired to assess the risk of chiral isomers on human body exposure.

## 8. Conclusions

The chiral separation of synthetic pyrethroids has been mainly achieved by HPLC or GC techniques. Different types of chiral columns based on cyclodextrins have been used for this purpose. Different chiral isomers of pyrethroids have different biological activities and toxicities, and thereby the residues and metabolisms in the environment and biological organisms also vary greatly.

About the different pyrethroids studied, it is necessary to bring out that only few of them have been studied in the field of chiral separation, chiral metabolism and chiral activity and toxicity perhaps due to the difficulties in the obtain of pure standards and single isomers. There is a wide range of synthetic pyrethroids yet to be studied for separating their enantiomers. With the development of technology of chiral isomers separation and preparation, the researches on the selective metabolism, residual behavior in organisms and environment will eventually get rid of the mist on the chiral isomers, and further guide the production, use and setup of regulations of chiral pesticides, and finally achieve the purpose of protect human health and environment.

## 9. Acknowledgments

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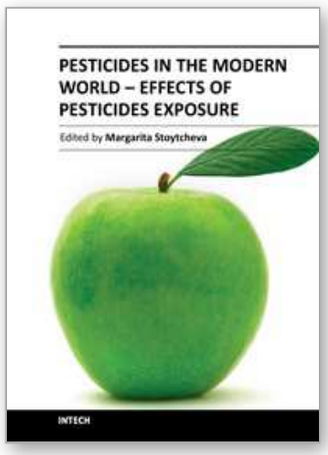


**Pesticides in the Modern World - Effects of Pesticides Exposure**

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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950â€™s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestockâ€™s yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising worldâ€™s population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

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