Pyrethroids

Insecticides

Background Information

Pyrethroids were first synthesized in 1949 but were not commercialized until after the development of photostable pyrethroids, such as permethrin and fenvalerate, in the mid-1970s[1]. Today pyrethroids account for more than one-third of the insecticides currently marketed in the world, and have generally supplanted the more toxic organophosphates as the insecticides of choice[2].

Pyrethroids are a class of synthetic insecticides that are structurally similar to pyrethrins - a refined pyrethrum extract derived from chrysanthemum flowers that possess insecticidal properties - and act in a similar manner, but have been modified to increase their environmental stability and their insecticidal properties[3].

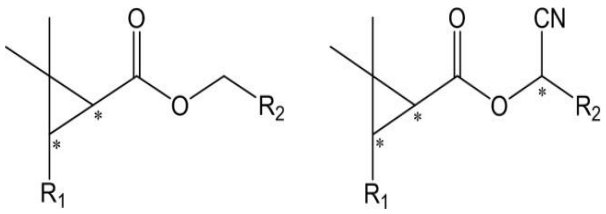

Figure 1. Basic pyrethroid structure

The first pyrethroids to be synthesized, e.g. allethrin and tetramethrin, consisted of a basic cyclopropane carboxylic ester structure and are known as type I pyrethroids (Figure 1). The insecticidal activity of newer pyrethroids was enhanced further by the addition of a cyano group at the alpha-carbon and these compounds are referred to as type II pyrethroids, e.g. cyfluthrin and cypermethrin[4]. Fenvalerate and esfenvalerate are also considered type II synthetic pyrethroids although they lack the cyclopropane ring.

Pyrethroids act as neurotoxins and target insect's central nervous system. There they interact with sodium channels and affect the electrical impulse transmission resulting in total paralysis of the insect. Pyrethroids are much less toxic to mammals than organophosphates and carbamate compounds but present a high toxicity to honey bees and a wide range of aquatic organisms[5].

The majority of pyrethroid formulations also include piperonyl butoxide as a synergist, which is added to significantly increase the potency of each pesticide[6].

The CORESTA Guide No. 1 sets the Guidance Residue Levels (GRLs) for bifenthrin, cyfluthrin (sum), cyhalothrin (sum) including λ-cyhalothrin, cypermethrin (sum), deltamethrin, fenvalerate (sum) including esfenvalerate, permethrin (sum), tefluthrin and tralomethrin[8].

Properties [7]

Compound	CAS RN (see note 1)	Mass	Formula	Solubility (at 20-25 °C)
Bifenthrin	82657-04-3	422.9	$C_{23}H_{22}ClF_3O_2$	Water < 1 µg/L; soluble in acetone, dichloromethane and toluene; slightly soluble in methanol
Cyfluthrin	68359-37-5	434.3	$C_{22}H_{18}Cl_2FNO_3$	Water 2-4 µg/L; dichloromethane > 200 g/L; n-hexane 1-20 g/L; toluene > 100 g/L
Cyhalothrin	68085-85-8	449.9	$C_{23}H_{19}ClF_3NO_3$	Water 0.0042 mg/L; acetone, dichloromethane, ethyl acetate, hexane, methanol and toluene, all > 500 g/L
λ-Cyhalothrin	91465-08-6	449.9	$C_{23}H_{19}ClF_3NO_3$	Water 0.005 mg/L; acetone, dichloromethane, ethyl acetate, hexane, methanol and toluene, all > 500 g/L
Cypermethrin	52315-07-8	416.3	$C_{22}H_{19}Cl_2NO_3$	Water 0.004 mg/L; acetone, ethyl acetate, methanol and toluene, all > 250 g/L; dichloromethane 252 g/L; n-hexane 59.8 g/L
Deltamethrin	52918-63-5	505.2	$C_{22}H_{19}Br_2NO_3$	Water 0.27 µg/L; acetone 500 g/L; cyclohexanone 750 g/L; dichloromethane 700 g/L; ethanol 15 g/L; ethyl acetate 267 g/L; methanol 6.8 g/L
Esfenvalerate	66230-04-4	419.9	$C_{25}H_{22}ClNO_3$	Water 0.002 mg/L; acetone, ethanol and methanol, all > 450 g/L; hexane 77 g/L
Fenvalerate	51630-58-1	419.9	$C_{25}H_{22}ClNO_3$	Water < 10 µg/L; n-hexane 53 g/L; methanol 84 g/L
Permethrin	52645-53-1	391.3	$C_{21}H_{20}Cl_2O_3$	Water < 0.006 mg/L; hexane > 650 g/L; methanol 204 g/L
Tefluthrin	79538-32-2	418.7	$C_{17}H_{14}ClF_7O_2$	Water 0.02 mg/L; acetone, dichloromethane, ethyl acetate, hexane and toluene, all > 500 g/L; methanol 262 g/L
Tralomethrin	66841-25-6	665.0	$C_{22}H_{19}Br_4NO_3$	Water 80 µg/L; acetone, dichloromethane and toluene, all > 1000 g/L; ethanol > 180 g/L

Note 1 *- Unstated stereochemistry for majority of pyrethroids*

Structures

Pyrethroids exist as a complex mixture of isomers rather than a single compound. Depending on their structure, pyrethroids possess two or three chiral centers represented by four or eight stereoisomers, respectively[5,9]. For example, cypermethrin has three chiral centers and is a mixture of eight isomers (1R*cis*αR, 1R*cis*αS, 1S*cis*αR, 1S*cis*αS, 1R*trans*αR, 1R*trans*αS, 1S*trans*αR, 1S*trans*αS)[10]. The stereochemistry of each pyrethroid isomer affects not only its insecticidal activity but also its toxicity against non-target organisms.

The location of the various chiral centers of each pyrethroid are indicated by * in Figure 1. The presence of two chiral centers in the cyclopropane ring results in two pairs of diastereoisomers (Figure 2), which are designated *cis* and *trans* based on the orientation of the C-1 and C-3 substituents in relation to the plane of the cyclopropane ring[11,12].

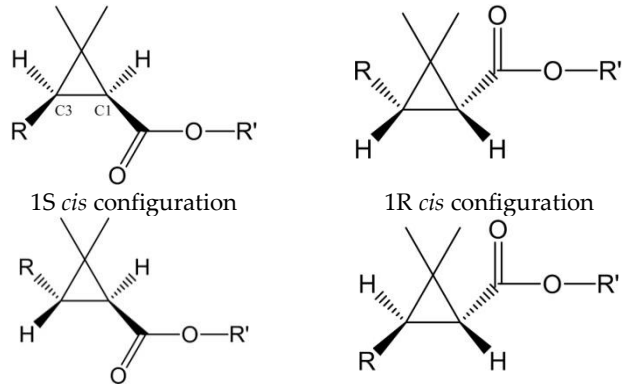

Figure 2. Four possible enantiomers of Type I pyrethroids[11-13]

The 1R conformations about the cyclopropane ring are considerably more toxic than the 1S isomers[14]. All type II pyrethroids possess an additional chiral center at the alpha-carbon with the αS conformation considerably more toxic towards insects when compared to the αR conformation[3,14,15].

Compound	Chiral Centers	Stereoisomers
Bifenthrin	2	4
Cyfluthrin	3	8
Cyhalothrin	3	8
λ-Cyhalothrin	3	2 [*λ-cyhalothrin consists of a pair of isomers of cyhalothrin*]
Cypermethrin	3	8
Deltamethrin	3	1 [*Only one isomer is synthesized and sold commercially – 1RcisαS*]
Esfenvalerate	2	1 [*Esfenvalerate is the 2SαS-isomer of fenvalerate*]
Fenvalerate	2	4
Permethrin	2	4
Tefluthrin	2	4
Tralomethrin	3	1

The production of pyrethroids with differing isomeric ratios is one reason for the wide variation in reported toxicity of these compounds. Some pyrethroids are sold commercially as optically pure stereoisomer (e.g. deltamethrin and esfenvalerate), an optically rich mixture (e.g. λ-cyhalothrin) or as a mixture of all stereoisomers (e.g. cypermethrin and permethrin). Pyrethroid structures are shown in Figure 3.

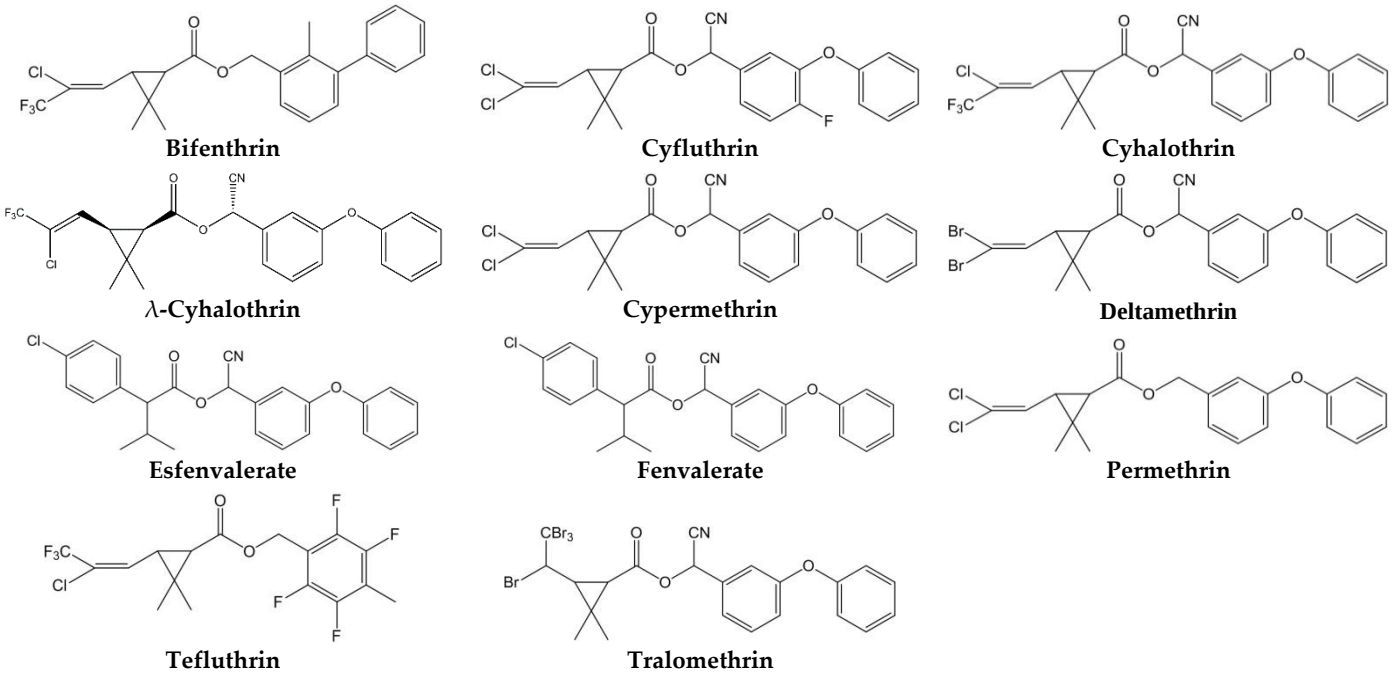

Figure 3. Pyrethroid structures[7]

Sample Preparation *(extraction and clean-up)*

Although all pyrethroids are virtually insoluble in water their extraction efficiency from tobacco is improved with the addition of water which allows the cell structure to hydrate prior to the addition of an organic solvent. The solvents of choice are primarily acetone, ethyl acetate or acetonitrile[16]. Acetonitrile is becoming more popular due to its compatibility with LC-based applications and acetone, which is the U.S. FDA's most common solvent due to the number of extensive validations performed with it[16]. However, acetone is the least selective solvent.

Due to the complex tobacco matrix, clean-up procedures such as liquid-liquid extraction or solid-liquid partitioning must be used to remove potential interferences[17,18]. Alternative clean-up procedures include solid-phase extraction (SPE), which utilizes cartridges, such as florisil, alumina, carbon black, and C18. The addition of salts, such as sodium sulfate or magnesium sulfate, should also be considered during the clean-up step to assist the migration of pyrethroids into the organic solvent layer[16]. Dispersive–SPE is another clean-up step closely identified with the QuEChERS methodology, which is applicable to the extraction of pyrethroids[16,19,20].

Analysis *(chromatography and quantitation)*

Due to their poor water solubility, gas chromatography is the instrumental technique generally used for routine pyrethroid analysis[21-24], coupled to either a mass spectrometer (GC-MS) or micro-electron capture detector (GC-μECD). GC-MS employing negative chemical ionization (nCI) is an effective way to improve detection limits for pyrethroids containing Cl, F or Br atoms compared with electron-impact ionization (EI). The pyrethroids of current interest[7] all possess one or more halogenated atoms in their structure, which makes the μECD both a selective and sensitive technique to use. Nowadays GC-MS/MS becomes more and more popular due to its increased sensitivity and selectivity improving the confirmation of identity.

The number of chiral isomers of each synthetic pyrethroid complicates the analysis with multiple peaks per compound being observed (Figure 4). Care must be exercised with the instrument conditions used as inter-conversion of pyrethroids is possible, for example tralomethrin degrades to deltamethrin in the GC inlet[25].

Where pyrethroid diastereoisomer and enantiomer separation into individual stereoisomers is of interest, liquid chromatography utilizing a chiral analytical column and appropriate detection, often UV, is typically employed[12]. The use of liquid chromatography tandem mass-spectrometry (LC-MS/MS) utilizing atmospheric pressure chemical ionization (APCI) is also becoming more common in the analysis of pyrethroids. One advantage of using LC-MS/MS is its ability to distinguish tralomethrin from deltamethrin.

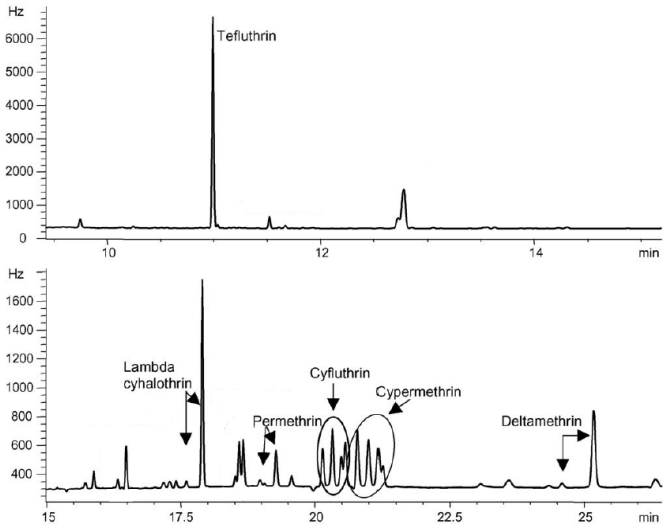

Figure 4. Examples of GC-μECD chromatograms of selected pyrethroids[18]

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