

## CYPERMETHRIN

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### ADDENDUM

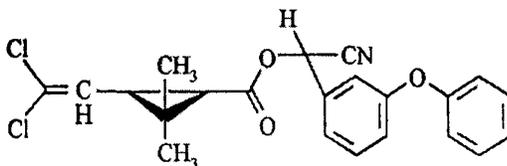
to the cypermethrin residue monograph prepared by the 47<sup>th</sup> meeting of the Committee  
and published in FAO Food and Nutrition Paper 41/9, Rome, 1997

#### IDENTITY

**Chemical Structure:** (RS)- $\alpha$ -cyano-3-phenoxybenzyl-(1RS, 3RS, 1RS, 3RS)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylate (IUPAC name)  
(RS)-cyano-(3-phenoxyphenyl)methyl(1RS)-*cis-trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate (Chemical Abstracts name); CAS No. 52315-07-8

Cypermethrin is a mixture of all eight possible chiral isomers.

#### Structural Formula:



**Molecular Formula:** C<sub>22</sub>H<sub>19</sub>Cl<sub>2</sub>NO<sub>3</sub>  
**Molecular Weight:** 416.3

Cypermethrin was first reviewed by the Joint Meeting on Pesticide Residues (JMPR) in 1979 and subsequently in 1981, 1986, 1988 and 1990. MRLs have been recommended for a wide range of crops, meat and milk products and feed commodities. Whereas cypermethrin has been used on horses, deer, goats and sheep, it was evaluated for use on cattle, sheep and poultry by the 47<sup>th</sup> meeting of the Committee. Temporary MRLs were recommended for cattle, sheep and poultry in muscle, liver, kidney and fat. The Committee required the following information to further elaborate MRLs:

1. Radiodepletion studies that extend beyond the recommended withdrawal times and using the drug in its topical formulation. The study should determine the depletion of the total residues and the parent drug.
2. Evidence to verify the limited information concerning no-interconversion of isomeric forms during metabolism in the target species.
3. Further information on the validation of the analytical methods, particularly data on how the LOD and LOQ were derived.

The Committee will need to ascertain the contribution of ingested pesticide residues from non-food animal sources and subtract this from the ADI to calculate the permitted theoretical maximum daily intake for cypermethrin from food animals when it is used as a veterinary drug.

#### PHARMACOKINETICS

One male and one female sheep were dosed orally with a mixture of 80% *cis* and 20% *trans* <sup>14</sup>C-cypermethrin isomers at 1mg/kg BW. Blood and excreta were collected over a seven-day period. Maximum plasma concentrations were observed at 8h for males (140  $\mu$ g/kg) and 12h for females (144  $\mu$ g/kg). The depletion half-life was 37h and 42h for the

male and female sheep, respectively. By 144h post-dosing, more than 95.8% of the radioactivity was cleared from the plasma. In males, 44% of the dose was cleared into the urine and most of the clearance was in the first 48h; in females, the corresponding value was 35%. In males, 30% of the dose was excreted into the faeces; in females, 35% of the dose was in the faeces.

#### Radiodepletion study in sheep

A new study was submitted investigating the radiodepletion of  $^{14}\text{C}$ -cypermethrin administered orally to adult sheep, not topically as requested. Three groups of five sheep comprising at least two of each sex per group were dosed orally with 1mg/kg BW  $^{14}\text{C}$ -cypermethrin. The ratio of the *cis* and *trans* isomers in the preparation was 4:1. The groups were slaughtered at 1, 3 and 5 days after dosing. Muscle, liver, kidney and fat samples were collected and the total residues were determined by combustion and liquid-scintillation counting. (see table 1).

**Table 1. Total residues of cypermethrin in  $\mu\text{g equiv./kg}$  in sheep tissues after oral administration of 1mg/kg BW  $^{14}\text{C}$ -cypermethrin.**

<i>Muscle</i>	Individual values	Mean $\pm$ SD
Day 1	12, 10, 12, 17, 14	13 $\pm$ 2.7
Day 3	9, 8, 0, 10, 9	7.2 $\pm$ 4.1
Day 5	0, 0, 0, 0, 0	0 $\pm$ 0
<i>Liver</i>		
Day 1	348, 295, 331, 348, 349	334 $\pm$ 23
Day 3	99, 148, 145, 132, 151	135 $\pm$ 21
Day 5	59, 57, 69, 66, 77	66 $\pm$ 8
<i>Kidney</i>		
Day 1	425, 327, 416, 302, 569	408 $\pm$ 105
Day 3	56, 52, 87, 48, 57	60 $\pm$ 16
Day 5	18, 14, 18, 18, 18	17 $\pm$ 2
<i>Fat</i>		
Day 1	39, 40, 53, 70, 47	50 $\pm$ 13
Day 3	75, 90, 48, 75, 79	73 $\pm$ 15
Day 5	60, 46, 46, 49, 60	52 $\pm$ 7

The tissues collected from the five sheep slaughtered on day 1 post dosing were analysed for their content of both the *cis* and *trans* cypermethrin by radio-TLC. The ratio of marker residue to total residues in the edible tissues gave similar values to the results submitted for the 47<sup>th</sup> meeting by Crawford and Hutson (1977). The results are shown in table 2. No residues of the *trans* isomer were detected. This supports the observation in rats that the *trans* isomers are much more rapidly metabolised than the *cis* isomers (Casida et al., 1976).

**Table 2. The total residues and marker residue content of sheep tissues 1 day after oral treatment with  $^{14}\text{C}$ -cypermethrin at 1mg/kg BW.**

Tissue.	Total Residues ( $\mu\text{g equiv. /kg}$ )	% TR extracted	<i>cis</i> -CYP ( $\mu\text{g/kg}$ )	<i>trans</i> -CYP ( $\mu\text{g/kg}$ )	Ratio CYP: TR	CYP: TR <sup>1</sup> (1980 data)
Muscle	13 $\pm$ 3	99.5 $\pm$ 24.5	3 $\pm$ 2	0	0.21	nm.
Liver	334 $\pm$ 23	71.7 $\pm$ 7.5	13 $\pm$ 5	0	0.04	<0.01
Kidney	408 $\pm$ 105	96 $\pm$ 2.7	5 $\pm$ 1	0	0.12	0.08
Fat	50 $\pm$ 13	107 $\pm$ 17	43 $\pm$ 16	0	0.86	0.65

Footnote: Data submitted to 47<sup>th</sup> meeting of the Committee.

## APPRAISAL

No information has been submitted to answers requests 1 and 2 and there was no indication that the sponsors would provide this information in the near future.

A study in sheep treated orally with a radiolabelled 80:20 *cis:trans* isomer ratio was made available to the Committee. This study did not address the topical administration of cypermethrin, and the isomer ratio was different from that of the isomer mixture of 45:55 *cis:trans* cypermethrin which had been evaluated at the forty seventh meeting.

In answer to request 3, a suitable analytical method for measuring residues of the 80:20 *cis:trans* cypermethrin was submitted to the Committee. The method allows measurement of the Cypermethrin as the sum of all eight isomers. As the isomers were coeluted in the GC, the method could be used to measure the sum of the isomers in mixtures of Cypermethrin containing isomers at different ratios.

## MRL

Since the Committee did not receive answers to its requests for further information, and there is no viable prospect that relevant information will be provided in the future, it is recommended that the temporary MRLs recommended for all animal tissues and milk are not extended. The Committee also noted that no information was made available for the toxicological evaluation of the 80:20 *cis:trans* cypermethrin.

## REFERENCES

**Beyerbach, A. (1999).** <sup>14</sup>C-Cypermethrin : Absorption, distribution, metabolism and excretion in sheep. Draft report, Covance Laboratories for Vericore Ltd, Report No. 1412/021-D1141.

**Casida, J. E., Ueda, K., Gaughan, L. C., Jao, L.T. and Sutherland, D.M. (1976),** Structure-biodegradability relationships in pyrethroid insecticides. Arch. Environ. Contam. Tox., 3, 491-500.

**Crawford, M. J. and Hutson, D. H. (1977).** TLGR.0098.77 The elimination and retention of WL 43467 when administered dermally or orally to sheep.