The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CYPERMETHRIN
(Extension to *Salmonidae*)

SUMMARY REPORT (2)

1. Cypermethrin is a synthetic pyrethroid insecticide, which is applied topically to cattle, sheep, goats, pigs and chickens for the control of ectoparasites such as lice, fleas, ticks and blowflies. It consists of a mixture of 4 *cis*- and 4 *trans*- isomers.

   This summary report refers to an application for the extension of the MRLs for cypermethrin (isomer ratio 40:60) to *Salmonidae*. Cypermethrin is intended for the treatment and control of parasites such as sea lice in *Salmonidae*. The fish would be treated by addition of cypermethrin to the sea water cage at a dose of 5.0 µg cypermethrin per litre of seawater for a period of 1 hour.

   An ADI of 15 µg/kg bw per day (900 µg/person/day) was established for alphacypermethrin, which comprised the 2 most toxic of the *cis*- isomers. Because the ratio of *cis*- : *trans*- isomers in commercial cypermethrin products was very variable and depended on the manufacturing source, it was agreed that the ADI which had been established for alphacypermethrin should be used in elaborating MRLs for cypermethrin.

   Currently, cypermethrin is included in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Cypermethrin	Cypermethrin (sum of isomers)	Bovine, ovine, caprine	20 µg/kg 200 µg/kg 20 µg/kg 20 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.1.2002
		Bovine, ovine, caprine	20 µg/kg	Milk	Provisional MRLs expire on 1.1.2002 Further provisions in Council Directive 93/57/EC are to be observed

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Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Cypermethrin	Cypermethrin (sum of isomers)	Porcine	20 µg/kg 200 µg/kg 20 µg/kg 20 µg/kg	Muscle Skin + fat Liver Kidney	Provisional MRLs expire on 1.1.2002
		Chicken	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg	Muscle Skin + fat Liver Kidney Eggs	
Cypermethrin	Cypermethrin (sum of isomers)	*Salmonidae*	50 µg/kg	Muscle and skin in natural proportions	

Additional data on the routine analytical method were provided in response to the list of questions further to the recommendation of provisional MRLs for cypermethrin in *Salmonidae*.

2. Target species tolerance studies were carried out using cypermethrin of cis/trans isomer ratio 40:60. These data showed that salmon can tolerate twice the recommended dose rate for twice the indicated treatment period with no evidence of adverse effects. Treatment at 4 times the recommended dose rate for twice the indicated treatment period resulted in toxic signs but there were no mortalities. Recovery from the toxic effects was complete, 24 hours later.

3. Published papers referring to studies in trout using cypermethrin ^{14}C-labelled in the cyclopropyl moiety or in the benzyl moiety, indicated that ester cleavage, the major metabolic pathway of cypermethrin in mammals, was of minor importance in trout. In trout, metabolism was mainly by 4'-hydroxylation and conjugation. *In vitro* studies using trout liver preparations indicated that the overall rate of biotransformation of cypermethrin was significantly slower in fish than in mammals or birds. Trout liver microsomes metabolised both *cis*- and *trans*- isomers of cypermethrin at comparable rates.

4. Rainbow trout were exposed to ^{14}C-cypermethrin in water at a temperature of 14 ± 1°C for 22 days after which the fish were kept in untreated water. The fish were sampled at intervals and analysed (whole fish) for total radioactivity and for unmetabolised cypermethrin using GLC. The proportion of residues of cypermethrin : total residues was fairly constant at a mean of 67%, from days 13 to 22 of treatment.

5. In a residues depletion study, salmon were treated at a nominal dose of 5 µg cypermethrin *(cis:trans* ratio *40:60)* per litre of seawater for a period of 1 hour. Analysis of the water samples showed that the actual dose was 7.88 µg/litre. The water temperature was in the range 5.7 to 6.0°C. Groups of 10 fish were killed one hour, and 20, 27 and 48 hours after the end of treatment and the residues of cypermethrin in muscle, skin and liver were determined using GLC. The limits of quantification were 23 µg/kg for muscle and liver and 27 µg/kg for skin. Residues in all samples of muscle and skin were below the limit of quantification at all time points. Residues in liver were in the range of 32 to 98 µg/kg one hour after the end of treatment but depleted to below the limit of detection (11.4 µg/kg) 20 hours after the end of treatment.

6. In a second residues depletion study, salmon were treated at a nominal dose of 10 µg cypermethrin *(cis:trans* ratio *40:60)* per litre of seawater for a period of 1 hour. Analysis of the water samples showed that the actual dose was 11.1 µg/litre. The water temperature was in the range 10.0 to 11.9°C. Groups of 10 fish were killed 1, 20, 27, 48 and 72 hours after the end of treatment. The residues of cypermethrin in muscle, skin and liver were determined using GLC. The limits of quantification were 23 µg/kg for muscle and liver and 27 µg/kg for skin. Residues in all samples of muscle and skin were below the limit of quantification. Residues in liver were in the range below the limit of detection up to 68 µg/kg one hour after the end of treatment but depleted to below the limit of detection (11.4 µg/kg for liver) 20 hours after the end of treatment. Although there were no residue depletion data for muscle and skin in natural proportions, this was justified by the very low residues found.

7. The proposed routine analytical method was based on HPLC with ultra violet detection. The limit of quantification of the method was 25 µg/kg for salmon muscle and skin in natural proportions. However the chromatograms showed that the isomers in fish tissue were detected as a single composite chromatographic peak and interference from other pyrethroids had not been investigated. Interference from bronopol and amoxicillin had been investigated but unequivocal evidence of the absence of interference from these substances had not been provided. Specificity and repeatability had not been adequately demonstrated.

Conclusions and recommendation

Having considered that:

- an ADI of 15 µg/kg bw (900 µg/person) was established for cypermethrin,
- cypermethrin (sum of isomers) was identified as the marker residue,
- the percentage of marker to total residues in *Salmonidae* was 67%,
- an analytical method for monitoring residues of cypermethrin in *Salmonidae* was available, but was not satisfactorily validated,
- the Applicant has committed to address the outstanding issues;

the Committee recommends, in accordance with Article 4 of Council Regulation (EEC) No 2377/90 as amended, a 18 months extension of the provisional MRLs for cypermethrin in *Salmonidae*, in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Cypermethrin	Cypermethrin (sum of isomers)	*Salmonidae*	50 µg/kg	Muscle and skin in natural proportions	Provisional MRLs expire on 1.7.2003

Based on the above MRL, the daily intake of total residues, from the consumption of 300 g fish per day, will represent about 2.5% of the ADI.

Before the Committee for Veterinary Medicinal Products can consider the inclusion of cypermethrin for *Salmonidae* in Annex I of Council Regulation (EEC) No 2377/90, the points included in the list of questions should be addressed.

LIST OF QUESTIONS

1. The Applicant should provide a routine analytical method, fully validated in accordance with Volume VI of the Rules Governing Medicinal Products in the European Union. In particular, specificity and repeatability should be adequately demonstrated.