The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FLUMETHRIN
(Extension to sheep)

SUMMARY REPORT (2)

1. Flumethrin is a synthetic pyrethroid ectoparasiticide. Since 1982/83, the flumethrin used in safety studies and in proprietary products has consisted of the *trans*-Z isomer (*trans*-Z1:*trans*-Z2 in the ratio 45 to 60 : 33 to 48), with other isomers present only as impurities. Flumethrin is applied topically to cattle, as a pour-on, for the control of ticks, lice and mites, at a dose rate of 2 mg/kg bw. There are also plastic strips impregnated with flumethrin which are hung in beehives, for the diagnosis and treatment of varroa in honey bees. Flumethrin is not used for crop protection purposes.

   The Committee for Veterinary Medicinal Products (CVMP) previously retained an ADI of 1.8 µg/kg bw (108 µg/person) for flumethrin, by applying a safety factor of 200 to the NOEL of 0.36 mg/kg bw/day which was established in a 2-generation reproduction study.

   Flumethrin is currently in Annex I 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
Flumethrin	Flumethrin (sum of *trans*-Z-isomers)	Bovine	10 µg/kg 150 µg/kg 20 µg/kg 10 µg/kg 30 µg/kg	Muscle Fat Liver Kidney Milk	

   and in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Flumethrin	Honey bees	

2. An application has now been received for the extension of the MRLs to sheep. Flumethrin is proposed for topical administration by plunge dipping, or by pour-on, for the control of ectoparasites such as ticks, lice, keds and psoroptic, chorioptic and sarcoptic mites. For the treatment of sheep scab by plunge dipping, the dip concentrate would be diluted with water to a concentration of 67 mg flumethrin per litre of dip wash. The sheep would be immersed for one minute and the head submerged twice during that period. The dose used in dipping corresponds to approximately 1.8 mg/kg bw.

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3. The backs of 2 male sheep were shaved and the sheep were then treated topically at a target dose of 3.3 mg/kg bw flumethrin, ^{14}C-labelled in the chlorophenyl ring. The dose was left in contact with the skin for 1 hour and the sheep were killed 24 or 72 hours after dosing. Absorption was very low and was estimated to be 1.7% and 3% in the sheep killed 24 and 72 hours after dosing respectively. The highest plasma concentrations of radioactivity (9 µg equivalents/kg) were found at slaughter in the sheep killed 72 hours after dosing. For this sheep, 0.4% and 1.6% of the administered dose were recovered from the urine and faeces respectively. At 24 and 72 hours after dosing, 28.3% and 16.3% of the administered dose, were recovered from the skin taken from the application site. Residues in other tissue tissues were very low. 24 and 72 hours after dosing, were 18 and 44 µg equivalents/kg in fat, 9 and 25 µg equivalents/kg in kidney and 22 and 23 µg equivalents/kg in liver. Only trace amounts were found in liver.

4. Two male and 2 female sheep were given a single intravenous injection of 1 mg/kg bw flumethrin, ^{14}C-labelled in the chlorophenyl ring. Urine and faeces were collected and 1 male and 1 female were killed 24 hours after dosing. The 2 other sheep were killed 72 hours after dosing. The male sheep, scheduled for the 24 hours slaughter, was incorrectly dosed and so the measurements for this animal were excluded from the results. Approximately 44% and 30% of the administered dose were recovered from the faeces and urine collected up to 72 hours after dosing. In the female killed 24 hours after dosing, total radioactive residues in liver, kidney, plasma, fat and muscle were 1321, 392, 302, 172 and 61 µg equivalents/kg respectively. The pattern of residues distribution was very similar in both animals killed 72 hours after dosing; the mean total residues in liver, kidney, plasma, fat and muscle were 239, 91, 86, 217 and 41 µg equivalents/kg respectively.

5. Samples of urine and tissues from the previous study were analysed by 2 HPLC methods. In urine 7 different metabolites but no flumethrin were found. The major component in urine was flumethrin acid which accounted for 3.5 to 14.2% of the administered dose when analysed by the first method and 4.5 to 16.3% by the second. Samples of liver and fat from the previous study were extracted prior to analysis. In liver 87% of the total residues 24 hours after dosing were extractable using acetonitrile:water. However 72 hours after dosing, the extraction efficiency had declined to 50%. Flumethrin acid was the main component of the residues in liver, corresponding to approximately 63% and 29% of the total residues in liver at 24 and 72 hours after dosing, respectively. Expressed as mean results of the 2 HPLC methods, residues of flumethrin in liver were 95 µg/kg and 20 µg/kg, 24 hours and 72 hours after dosing, corresponding to 7.2% and 8.2% of the total radioactive residues in liver. Approximately 83% of the total residues in fat were extractable. Flumethrin was the major component of the residues in fat. The mean residues of flumethrin were 76 µg/kg and 137 µg/kg, corresponding to 43.9% and 62.9% of the total residues in fat, 24 and 72 hours after dosing respectively. Small amounts of flumethrin acid (accounting for up to around 3% of the total residues) were found in some fat samples. Residues in kidney and muscle were too low for the determination of the ratio of residues of flumethrin to total residues in these tissues.

6. In a GLP-compliant study, 20 cross-bred ewes were treated with a commercial dip formulation according to the proposed dose regimen. No details of the wool length were provided. The dip bath was prepared at a nominal concentration of 70 mg flumethrin per litre of dip wash. The sheep were killed (4 per time-point) at 12 hours, 24 hours, 48 hours, 4 days or 7 days after dipping and residues in tissues were determined using the proposed routine analytical method based on HPLC. In this assay, the limits of quantification and detection were 20 µg/kg and 10 µg/kg, respectively. Residues of flumethrin in all samples of kidney, muscle and omental fat were below the limit of detection. In liver, detectable residues were found in 1 sample at 24 hours (20 µg/kg) and one sample at 4 days (20 µg/kg). In subcutaneous fat, detectable residues were found in single samples taken at 12 hours (30 µg/kg), 24 hours (10 µg/kg) and 4 days (20 µg/kg).

7. The low absorption of flumethrin was confirmed in an older, non-GLP study carried out in Merino ewes, 3 weeks before shearing. Two different dip formulations were used at 2 different concentrations; 60 mg/litre and 90 mg/litre. Two sheep from each treatment group were slaughtered 24 and 72 hours after dosing and residues of flumethrin in tissues were determined using an HPLC method with a limit of detection of 5 μg/kg. Detectable residues (up to 40 μg/kg) were found only in fat samples.

8. Two residue depletion studies were carried out using pour-on formulations. In the first study, female and castrated male sheep, with wool 3 to 3.5 cm long, were treated at a dose rate of 2 mg/kg bw and were slaughtered (3 per time point) at 12, 14, 24, 48 or 72 hours after treatment. Residues of flumethrin in tissues were determined using HPLC. Residues of 60 μg/kg were found in 1 fat sample taken from a sheep killed 14 hours after dosing. Residues in all other tissues were below the limit of detection (stated to be 50 μg/kg). In a later study, sheep were treated at a dose of 1 mg/kg bw and slaughtered (2 per time point) at 1, 3, 5, 7 or 10 days after dosing. No details of the sex, breed or wool length was provided. Residues of flumethrin in tissues were determined using HPLC. Residues in all kidney samples were below the limit of quantification (stated to be 2 μg/kg). The highest residues were found in the samples taken 5 and 7 days after dosing and were in the range 2.9 to 54.4 μg/kg in fat, 2.0 – 9.4 μg/kg in muscle and from below the limit of quantification to 10.1 μg/kg in liver.

9. The proposed routine analytical method was based on HPLC with UV detection and was described in the ISO 78/2 format. The method was the same as that previously adopted for bovine tissues and was satisfactorily validated for ovine tissues. The limit of quantification was 10 μg/kg for ovine liver, muscle, kidney and fat.

Conclusions and recommendation

Having considered that:

- an ADI of 1.8 μg/kg bw per day (108 μg/person per day) was established for flumethrin,
- flumethrin was identified as the marker residue and accounted for 63% and 8% of the total residues in ovine fat and liver, respectively, 72 hours after treatment,
- the residues in ovine muscle and kidney were too low for the ratio of marker to total residues to be determined; in both cases the ratio was assumed to be 1,
- the distribution of residues in ovine tissues was similar to that observed in bovine tissues and it would be appropriate for the MRLs to have the same numerical values,
- flumethrin is not used in crop protection and there is no consumer intake from agricultural use,
- a validated analytical method was available for the determination of residues of flumethrin (sum of *trans*-Z isomers) in the edible tissues of ovine,
- for sheep milk the minor species policy of the CVMP as laid down in document EMEA/CVMP/153a/97-FINAL, Note for Guidance on the Establishment of Maximum Residue Limits for Minor Animal Species, could not be applied, due to the absence of required validation data for the analytical method;

the Committee for Veterinary Medicinal Products recommends the inclusion of MRLs for flumethrin in ovine tissues in Annex I 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
Flumethrin	Flumethrin (sum of *trans*-Z isomers)	Ovine	10 μg/kg 150 μg/kg 20 μg/kg 10 μg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.

Based on these MRLs values, the daily intake derived from sheep meat and cow's milk would represent 96.4% of the ADI.