COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FLUMETHRIN

SUMMARY REPORT (1)

1. Flumethrin is a synthetic pyrethroid ectoparasiticide. In veterinary medicine it is applied topically to sheep, cattle and goats, as a 1% w/v pour-on (in approximately 75% liquid paraffin, 10% 2-octyldodecanol and 0.5% Solvesso 150) or as a plunge dip (6% w/v flumethrin in approximately 73% Solvesso 200, 3% Solvesso 150 and emulsifiers), for the control of ticks, lice and mites. The pour-on is applied at a rate of 2 mg/kg bw. The plunge dip is diluted at a rate of 1 litre product in 900 litres water. For control of scab, the sheep must be dipped for one minute. Plastic strips impregnated with 3.6 mg flumethrin are hung in beehives for the diagnosis and treatment of varroatosis in honeybees. Four strips per hive are used for mature colonies and 2 per hive for immature colonies.

2. Flumethrin has 4 centres of isomerism. Post 1982/83, the material used in safety studies and in all formulated products consisted of the trans-Z isomer (trans-Z1:trans-Z2 in the ratio 45-60 : 33-48. The trans-E isomers (maximum 1%) and cis-Z isomers (maximum 2%) appeared only as by-products.

3. Flumethrin is a type II synthetic pyrethroid and causes a long-lasting prolongation of the normally transient increase in sodium permeability of the nerve membrane during excitation, resulting in long-lasting trains of repetitive firing. The α-cyano group on the phenoxy-fluorobenzyl alcohol moiety is considered to be responsible for the long-lasting prolongation of sodium permeability. The type II pyrethroids produce a distinct poisoning syndrome which is characterised by choreoathetosis (sinuous writhing of the whole body) and salivation.

4. When groups of rats were given a 1 mg/kg bw oral dose of $^{14}$C[Cl]-flumethrin (in 5% aqueous Cremophor vehicle), 68% of the radioactivity was eliminated in the faeces during the first 24 hours and approximately 2% in the urine. Conversely, following oral administration of 1 mg/kg bw $^{14}$C[F]-flumethrin, 45% of the radioactivity was eliminated in urine and the rest in the faeces. Females appeared to absorb a considerably higher percentage of the flumethrin dose after oral administration than males. The plasma elimination half lives of $^{14}$C[Cl]- and $^{14}$C[F]-flumethrin in orally dosed rats were approximately 160 hours and 8 hours respectively. No information on the nature of the metabolites derived from the acid moiety (chlorophenyl-ring labelled) which remain in the blood of treated rats for prolonged periods are available. Repeated daily oral dosing of 1 mg/kg bw $^{14}$C[Cl]-flumethrin to 8 male rats resulted in an accumulation of plasma radioactivity. After oral administration of 1 mg/kg bw $^{14}$C-flumethrin to rats of both sexes, residue concentrations were highest in plasma ($V_{ss}$ approximately 0.4 l/kg), and most of the radioactivity remained in the stomach for up to 312 hours after administration.

5. In the rat, flumethrin was shown to be metabolised by hydrolysis of its central ester bond to form permethrin acid and 3-phenoxy-4-fluorobenzyl alcohol. In groups of male rats (n = 3) given an oral dose of 10 mg/kg bw $^{13}$C[F]-flumethrin, four 3-phenoxy-4-fluorobenzyl alcohol -derived metabolites (3-phenoxy-4-fluorobenzyl alcohol, 3-(hydroxyphenoxy)-4-fluorobenzoic acid and their respective glycine conjugates were detected.
6. The acute toxicity of flumethrin was very variable and depended on the solvent vehicle. The acute oral LD<sub>50</sub> values ranged from 41 mg/kg bw (female Wistar rats using 2% Cremophor EL as the solvent vehicle) to 3849 mg/kg bw (male Wistar rats using Miglyol as the solvent vehicle). The trans-Z2 isomer was more acutely toxic than the trans-Z1 isomer. In male Wistar rats, no mortalities occurred following oral dosing with 5000 mg/kg bw of the trans-Z1 isomer (in aqueous Cremophor) but 4 out of 5 rats died following oral dosing with 50 mg/kg bw of the trans-Z2 isomer.

7. Groups of 15/sex/dose Wistar rats were fed diets containing 0, 10, 50 or 250/150 mg/kg feed for 13 weeks. The test substance was a 50% premix with colloidal SiO<sub>2</sub> carrier. Due to severe weight loss the dose level of 250 mg/kg feed was reduced to 150 mg/kg feed during week 3. Body weight gain was significantly reduced in the rats given 150 mg/kg feed compared with the controls. Skin lesions, described as ulcerative dermatitis, were observed in the 50 and 150 mg/kg feed groups and were dose-related in severity. The NOEL was 10 mg/kg feed, equivalent to 0.7/0.8 mg/kg bw per day. The study was not well reported and because of this it was difficult to draw conclusions about some aspects. No information concerning the bioavailability of flumethrin added in the SiO<sub>2</sub> carrier has been provided but the similarity of the results obtained in the two feeding studies with and without the carrier indicate that any effect of the carrier must have been minor.

8. In GLP repeated-dose toxicity study, groups of 20/sex/dose Wistar rats were fed diets containing 0, 10, 40 or 160 mg/kg feed flumethrin for up to 15 weeks. During mixing of the diets, 1% peanut oil was added to minimise dust formation. At 160 mg/kg feed, body weight gain was significantly reduced. Sever skin lesions were observed in the 160 mg/kg feed group. Some mild skin lesions were also observed in the 40 mg/kg feed group. Decreased red cell values and increased leucocyte counts in the 160 mg/kg feed group were probably associated with the skin lesions. At termination, histopathological examination revealed ulcerative skin lesions in all rats given 160 mg/kg feed and some rats from the 40 mg/kg feed group. Increased extramedullary haematopoiesis and reduced haemosiderin storage in the spleen were also observed in the 160 mg/kg feed group. The NOEL was 10 mg/kg feed, equivalent to 0.7/0.8 mg/kg bw per day in males/females respectively.

9. Groups of 4/sex/dose Beagle dogs were fed diets containing 0, 50, 100 or 200 mg/kg feed flumethrin for 13 weeks. The test substance was a 45.3% premix with colloidal SiO<sub>2</sub> carrier. Skin lesions and emesis were observed in the groups receiving 50 mg/kg feed and above and were dose-related in incidence and severity. Over the 13 weeks, the mean body weight of males given 200 mg/kg feed was decreased and females in this group gained less weight than the controls. During the first 9 to 10 weeks of the study, food intake of the dogs given 200 mg/kg feed was lower than that of the controls. Blood urea nitrogen (BUN) concentrations were significantly increased in dogs given 200 mg/kg feed and slightly increased in dogs given 100 mg/kg feed. At termination, treatment-related skin lesions were observed in all treated groups; the epithelial layer of the epidermis was thickened and covered with hyperkeratotic material in places. In 2 dogs given 200 mg/kg feed, the epidermis was ulcerated. No NOEL was established in this study.

10. A supplementary study was carried out in order to establish a NOEL in the dog. Groups of 4/sex/dose Beagle dogs were fed diets containing 0 or 25 mg/kg feed flumethrin for 13 weeks. The test substance was a 41.2% premix with colloidal SiO<sub>2</sub> carrier. There were no signs of toxicity and the dogs given 25 mg/kg feed had the same shiny, well-groomed coats as the untreated dogs. There were no substance-related effects on body weight gain, food consumption, body temperature, heart rate, ophthalmoscopy, haematology, clinical chemistry or urinalysis values. At termination, there were no substance-related gross pathological changes. Because of the absence of gross changes, a histopathological examination was not carried out. The NOEL was 25 mg/kg feed, equivalent to 0.88 mg/kg bw per day.

11. Flumethrin was well tolerated in the target species when administered topically at the indicated dose rate. Treatment of cattle at double the recommended rate caused transient erythema at the application site and diarrhoea in some animals. Treatment of sheep and goats at 10 times the recommended rate caused signs of toxicity and treatment at 20 times the recommended dose caused 50% mortality in sheep. However, the toxic effects of the vehicle alone, appeared to play a considerable role.
12. In a 2-generation reproduction study in rats with 2 litters per generation, flumethrin was administered in the diet at concentrations of 0, 1, 5 or 50 mg/kg feed. The test substance was a 45.6% premix with colloidal SiO\textsubscript{2} carrier. Food consumption and body weight gain were reduced in parental animals of the P and F\textsubscript{1} generations. There were no effects on mating, fertility or gestation length. In the 50 mg/kg feed group, pup viability on days 1 to 4 post-partum and pup body weights were depressed and signs of pyrethroid-poisoning were observed in the pups of the F\textsubscript{1a} and F\textsubscript{1b} litters. The NOEL was 5 mg/kg feed, equivalent to 0.36 and 0.40 mg/kg bw per day, in males and females respectively. No developmental landmarks or behavioural parameters were investigated in the offspring. Although concern had been expressed that exposure to relatively low doses of pyrethroids during a critical post-natal period could result in behavioural and neurochemical abnormalities, a new study in which NMRI mice were given oral doses of bioallethrin (0.7 and 3.5 mg/kg bw per day) or deltamethrin (0.7 mg/kg bw per day) indicated that this concern was unfounded.

13. Groups of 28 mated female rats received doses of 0, 0.5, 1.0 or 2.0 mg/kg bw per day orally by gavage from days 6 to 15 of gestation. The test substance was administered in a vehicle of 2% aqueous Emulphor. Signs of toxicity (hypoactivity, ptosis, ataxia and salivation) were observed in the dams given 1.0 and 2.0 mg/kg bw. Body weight and food consumption were significantly reduced in the 2.0 mg/kg bw group. Placental weight and the weight of viable foetuses were significantly reduced in the 2.0 mg/kg bw group. The incidence of foetal delayed ossification was significantly increased in the 2.0 mg/kg bw group. There was no evidence of teratogenicity at any dose level. The NOELs were 0.5 mg/kg bw per day for maternal toxicity and 1.0 mg/kg bw per day for foetotoxicity.

14. Groups of 17 inseminated female rabbits were given daily oral doses of 0, 0.5, 1.7 or 6.0 mg/kg bw per day flumethrin from days 7 to 19 of gestation. The test substance was administered as a solution in aqueous Emulphor. Body weight gain and food consumption were significantly reduced at 6.0 mg/kg bw. Foetal weights were slightly reduced in the group given 6.0 mg/kg bw. There was no evidence of teratogenicity at any dose level. The NOEL for both maternal toxicity and foetotoxicity was 1.7 mg/kg bw per day.

15. Flumethrin was assayed for mutagenic potential in several in vitro assays for gene mutation in *Salmonella typhimurium*, in an in vitro assay for gene mutation in *Saccharomyces cerevisae* D7, in two in vitro assays for gene mutation in mammalian cells (a mouse lymphoma assay and a V79-HPRT assay) in two cytogenetics assays in mammalian cells (human lymphocyte cultures and Chinese hamster V79 cells), in an in vitro unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes and in 2 in vivo micronucleus assays. Positive results were obtained in one in vitro assay for gene mutation with strain TA98 of *Salmonella typhimurium*. However negative results were obtained in subsequent assays with this strain. All the other tests gave negative results. Although flumethrin gave positive results in mouse bone marrow by chromosomal analysis and micronucleus test in a published study, the experiment was carried out using a product containing 60% flumethrin and 40% unidentified ingredients; consequently no reliance could be placed on these results. The Committee concluded that flumethrin was not genotoxic.

16. In a combined chronic toxicity and carcinogenicity study, groups of Wistar rats were fed diets containing 0, 2, 10, 50 or 250 mg/kg feed of the test substance for up to 24 months. At termination, 2 males and 3 females given 250 mg/kg feed had skin ulcers associated with crusting, dermal fibrosis, phlegmon and peripheral acanthosis. The incidence and severity of liver bile duct proliferation were significantly increased in males given 50 and 250 mg/kg feed. There was no evidence of carcinogenicity. The NOEL was 10 mg/kg feed, equivalent to 0.47/0.60 mg/kg bw per day in males/females respectively. The isomer ratio of the test material used in this study was trans-Z + trans-E in a ratio ranging from 50:50 to 30:70 whereas the commercial product is almost entirely the trans-Z isomer. Nevertheless, taking into account the lack of pre-neoplastic lesions in the repeated-dose toxicity studies and the negative mutagenicity results, which had been obtained with test material typical of the commercial product, and also the lack of carcinogenic potential of pyrethroids such as cyfluthrin which had a similar chemical structure, the Committee concluded that flumethrin did not have carcinogenic potential.
17. Two batches of flumethrin gave negative results in the guinea pig maximisation test of Magnussen and Kligman.

18. Neurotoxicity was evaluated in the inclined plane test with flumethrin administered as a single dose in Cremophor:water (2%) or corn oil/milk emulsions. The NOELs were 0.3 mg/kg bw and 1.0 mg/kg bw for the Cremophor and milk formulations respectively. Statistically significant effects were found following dosing with 5 mg/kg bw in either vehicle. No positive control group was included and the sensitivity of the study is uncertain.

19. The metabolite permethrin acid was not mutagenic in an *in vitro* assay for gene mutation using only strain TA98 of *Salmonella typhimurium*. It was of moderate acute oral toxicity when tested using water with 0.5% Tylose as the solvent vehicle; the acute oral LD_{50} values were 935 and 620 mg/kg bw in male and female Wistar rats respectively. In a 4-week repeated-dose toxicity study in Wistar rats, the substance was less toxic than flumethrin; there were no signs of toxicity; the NOELs were 26.7 and 28.2 mg/kg bw in males/females respectively. The toxicity of permethrin acid was also less than that of flumethrin in the inclined plane test.

20. Flumethrin was evaluated by the Joint FAO/WHO Meeting on Pesticide Residues in 1996. An ADI of 0 - 0.004 mg/kg bw per day was calculated by applying a safety factor of 100 to the NOEL of 0.36 mg/kg bw per day which was established in the multigeneration study. Due to uncertainties over the bioavailability of the flumethrin administered, the CVMP was unable to adopt this ADI. Instead, an ADI of 1.8 µg/kg bw (108 µg/person) was calculated by applying a safety factor of 200 to the NOEL of 0.36 mg/kg bw per day which was established in the 2-generation study. The NOEL in this 2-generation study was similar to that established for reversible effects observed in the inclined plane test following oral administration of the cremophor formulation (0.3 mg/kg bw) and lower than the NOEL (1.0 mg/kg bw) in the inclined plane test for the milk formulation. The NOEL provides an adequate safety margin to allow for possible imprecision in the NOEL in the inclined plane test.

21. In cattle, the ratio of permethrin acid to flumethrin concentration in the tissues was approximately 55:40. Residues of flumethrin were detected in the milk of cattle treated topically with 2 mg/kg bw flumethrin but negligible (below 5 µg/l; limit of quantification of the method) concentrations of permethrin acid were detected.

22. A lactating cow and a steer were intravenously dosed with 1 mg/kg bw 14C[Cl]-flumethrin. Eight hours after treatment, the highest tissue concentrations of flumethrin were detected in the liver, these were 12.9 and 3.36 equivalents mg/kg flumethrin (21.13% and 4.42% of dose administered) respectively. Forty-eight hours after topical administration of 14C[F]-flumethrin (approximately 1.8 mg/kg bw) to a lactating cow, 71.7% of the administered dose remained in the fat/skin of the application site. The residue concentration in milk never exceeded 3 µg/l, with respect to flumethrin concentrations other samples assayed could be ranked as follows: urine (281 µg/l), bile (70 µg/l), kidneys (10 µg/kg), liver (9 µg/kg). The ratio of residues of flumethrin to total residues in liver, kidney, muscle and fat were 87%, 35%, 29% and 24% for the cow and 29%, 15%, 36% and 28% for the steer. Flumethrin represented 68% of the residues in milk.

23. No radiolabelled studies were carried out with labelling in both the fluorophenyl group and the para-chlorophenyl group. In a special study, the isomeric composition of flumethrin residues in serum, milk and tissues of cattle was investigated following intravenous application of a 5% flumethrin solution in N-methylpyrrolidone. This formulation was used to maximise the residue concentrations. The cows were killed 4 or 8 hours after dosing. Under the HPLC chromatographic conditions employed, the trans-Z1 and trans-Z2 isomers were separable. Only liver appeared to show a shift towards a higher proportion of the more toxic Z2 isomer.
24. Six groups of cattle (n = 2) were topically treated twice with a 1% flumethrin preparation (2 mg/kg bw) with a 14 day interval between treatments and groups sacrificed at several timepoints between 1 and 28 days after the last treatment. Residues of flumethrin persisted longest in the fat tissues, maintaining a steady concentration of approximately 60 µg/kg from 1 to 28 days after treatment. Residues in the liver, muscle and kidney could not be detected 7 days after treatment (below 10 µg/kg).

25. Groups of 3 cattle were topically dosed 1 to 4 mg/kg bw flumethrin and sacrificed 24 or 72 hours after treatment. Cattle were also dosed by plunge dipping in 67 mg flumethrin per litre water. One day after both these treatments, the muscle, liver, kidney and fat tissues of cattle contained flumethrin concentrations below 20 µg/kg (mostly below 5 µg/kg). Groups of cattle were overdosed with flumethrin as follows: spray treated 3 times 1.2 mg/kg bw with 14 days between doses and 3 day withdrawal, topically treated with 5 times 1.2 mg/kg bw with 7 days between doses and 12 hour withdrawal, and sprayed with 5 times 1.5 mg/kg bw treatment over 56 days.

All these treatments resulted in tissue flumethrin concentrations below 50 µg/kg.

26. One day after therapeutic topical administration of 2 mg/kg bw flumethrin, permethrin acid concentrations (expressed as equivalents of 14C-flumethrin) in the liver, kidney, fat and muscle tissues were 25.8, 18.7, 14.3 and 8.7 µg/kg respectively. Permethrin acid concentrations in all tissues had depleted to below 10 µg/kg by 21 days after treatment.

27. Groups of 3 lactating cows in early (high) and late (low) stages of lactation were twice topically treated (backline from withers to tail) with 1% flumethrin at 2 mg/kg bw, with a 14 day interval between each dose. Milk were collected after the second treatment at 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 hour timepoints. The milk of high yielding cows contained mean flumethrin concentrations of: below 1.0, 10.2, 19.3, 13.7, 19.7, 15.0, 22.0, 10.7, 10.0 and 9.0 µg/l respectively. The milk of low yielding cows contained flumethrin at: 28.0, 13.3, 38.7, 53.3, 35.3, 40.5, 13.3, 8.7 and 20.0 µg/l respectively. The concentration of permethrin acid in these milk samples were below 5 µg/l (the analytical limit of detection). The concentrations of flumethrin detected were more than halved when administration of a therapeutic dose was limited to the area of the backline between the hip and tail. In two further studies, dairy cows were given 2 topical treatments with a 1% pour-on formulation at doses of 2 mg/kg bw flumethrin. Milk samples were collected at intervals before and after treatment and assayed using an HPLC assay with a limit of quantification of 5 µg/l. The maximum flumethrin concentration found was 135 µg/l in the milk from one cow taken 2 days after the last treatment. Neither study complied with the requirements of Volume VI of The Rules Governing Medicinal Products in the European Community in terms of the numbers of animals.

28. Tissues from groups of sheep therapeutically treated with flumethrin by topical application of pour-on or dipping formulations tended to contain residue concentrations below the analytical limit of quantification (10 µg/kg). One fat sample from a sheep taken 120 hours after topical treatment with 1 mg/kg bw flumethrin contained flumethrin at 33 µg/kg, all other were below the limit of quantification. The muscle tissues of sheep dipped in 60 mg/kg feed flumethrin contained flumethrin concentrations of approximately 20 µg/kg at 24 and 72 hour timepoints after treatment.

29. A group of 3 goats were topically treated with 6 mg/kg bw flumethrin and pooled milk samples collected pre-treatment and 12 and 24 hours after treatment. These samples were found to contain flumethrin at below 10, 11.6 and 16.7 µg/l respectively.

30. Groups of sheep were treated with 2 mg/kg bw flumethrin topically by pour-on (6% solution) or drenching (dose applied in 2 litres), the flumethrin concentration in milk samples were independently assessed (within two months) and found to be below 10 µg/l the analytical limit of detection.
31. When bee colonies were exposed to strips impregnated with flumethrin in the spring, pre-winter, and during the nectar flow period the flumethrin content of wax from proximal combs were 30, 40 and 90 µg/kg respectively. The highest concentration of flumethrin detected in beeswax was 130 µg/kg, found in a sample from a hive treated during the nectar flow period. In all of these studies where honey samples were assessed, the concentration of flumethrin in honey was found to be below the analytical limit of detection (1 to 2 µg/kg). Transfer of flumethrin from beeswax to honey was negligible but residues in beeswax may accumulate if the wax is re-used over several years. Residues of up to 61 µg/kg flumethrin were found in wax from hives which had been treated annually for approximately 10 years. In a residue surveillance study, no residues of flumethrin were detected in honey samples from several different European countries but residues of up to 3000 µg/kg were found in beeswax. The CVMP noted that the regulation of allowable concentrations of flumethrin in beeswax was a matter for individual Member States.

32. The proposed routine analytical method was based on liquid-liquid extraction followed by quantification by HPLC with UV (266 nm) detection. The limits of quantification were 10 µg/kg for bovine and ovine liver, muscle, kidney and fat, 5 µg/kg for bovine milk and 3 µg/kg for honey. The method used dichloromethane, which may be unacceptable in some laboratories. The limits of detection had been demonstrated using a lower number of blank samples than were recommended and were 5 µg/kg for bovine and ovine liver, 4 and 3 µg/kg for bovine and ovine kidney, 2 and 3 µg/kg for bovine and ovine muscle, 3 and 2 µg/kg for bovine and ovine fat and 1 µg/kg for bovine milk. The method was validated in accordance with Volume VI of The Rules Governing Medicinal Products in the European Community for both species.

33. It was noted that flumethrin had been evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) during 1996 and MRLs had been elaborated for bovine fat and milk and for honey. The JMPR considered that there was insufficient information to elaborate MRLs for ovines. The CVMP was unable to adopt the JMPR MRLs for bovine fat and milk because these were based on a higher ADI. Flumethrin is not used in crop protection and there is no consumer intake from agricultural use.

34. No information regarding the ratio of marker to total residue in sheep was available, therefore no MRLs could be recommended for this species. Because the analytical method had not been validated for goats no MRLs could be recommended for this species.
Conclusions and recommendation

Having considered that:

- an ADI of 1.8 µg/kg bw per day (108 µg/person per day) had been established for flumethrin,
- 8 hours after intravenous dosing, approximately 30% of the residues present in the liver, muscle, kidney and fat of bovines consisted of flumethrin,
- approximately 70% of the residues in bovine milk consisted of flumethrin,
- residues in honey were usually below the limit of quantification of the analytical method and so it was not necessary to establish MRLs for flumethrin in honey,
- a validated analytical method for the determination of residues of flumethrin (sum of trans-Z isomers) in the edible tissues and milk of bovines is available;

the Committee recommends the inclusion of flumethrin into Annex I of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

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<th>Pharmacologically active substance(s)</th>
<th>Marker residue</th>
<th>Animal species</th>
<th>MRLs</th>
<th>Target tissues</th>
<th>Other provisions</th>
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</thead>
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<tr>
<td>Flumethrin</td>
<td>Flumethrin (sum of trans-Z isomers)</td>
<td>Bovine</td>
<td>10 µg/kg</td>
<td>Muscle</td>
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<td></td>
<td></td>
<td></td>
<td>150 µg/kg</td>
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<td></td>
<td>30 µg/kg</td>
<td>Milk</td>
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</table>

Based on the above MRLs, the theoretical maximum daily intake of residues was estimated to be 108 µg/day, i.e. 100% of the ADI.

The Committee also recommends the inclusion of flumethrin into Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

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<th>Other provisions</th>
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<td>Flumethrin</td>
<td>Honey bees</td>
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