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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CYHALOTHRIN

SUMMARY REPORT

1. Cyhalothrin is a type II pyrethroid insecticide and acaricide. Technical-grade cyhalothrin is approximately 96% pyrethroids with cyhalothrin representing 95%. The main non-pyrethroid impurity is 3-phenoxybenzaldehyde (up to 0.5%).

   The cyhalothrin molecule contains three asymmetric carbons and a centre for geometric isomerism; this gives a total of 16 possible isomers, comprising 8 pairs of enantiomers. Cyhalothrin contains 2 pairs of enantiomers, A and B, both pairs of *cis*-isomers, in a ratio of 60:40, whereas lambdacyhalothrin (used as pesticide only) is just the B pair of enantiomers.

   Cyhalothrin is intended for external use against ectoparasites in cattle, pigs and sheep, including dairy animals. Application may be either pour-on (0.2 mg of cyhalothrin per treatment in cattle and 0.1 mg cyhalothrin per treatment in sheep and pigs), spraying (up to 250 mg per animal and treatment) or dip tanks (up to 50 g cyhalothrin per 1000 litres of water).

2. The mechanism of action of pyrethroids is by changing the permeability of sodium channels of nerve membranes leading to prolonged depolarisation and hyperexcitability, which tends to be reversible. Apart from the effects on neuromuscular function, no information on the pharmacodynamics of cyhalothrin is available.

3. The pharmacokinetics of cyhalothrin do not show significant interspecies differences between rats, dogs and cattle.

   The oral bioavailability is 50% or higher; following absorption, cyhalothrin is rapidly metabolised in the liver and is excreted in both urine and faeces (20 to 50% and 40 to 65% of the dose, respectively). Approximately 0.8% of the total administered dose is present in cow's milk.

   The main metabolic products, cyclopropanecarboxylic acid and 3-cyanophenoxybenzoic acid, are produced from the hydrolysis of the ester linkage. Metabolites do not contain the intact pyrethrin structure and are excreted mainly as conjugates.

   Cyhalothrin is highly lipophilic. Following topical administration the highest tissue concentrations are found in the body fat, followed by bone marrow and liver. A limited fraction of unaltered cyhalothrin (less than 5% in the rat, approximately 10 to 15% in the dog) persists in the body fat.

   In male rats administered orally with 1 mg/kg bw ^{14}C-labelled cyhalothrin in corn oil for 119 days, the radioactivity levels in blood were equivalent to 0.2 mg/kg for the whole duration of treatment; levels in liver and kidney reached a plateau of 2.5 mg/kg and 1.2 mg/kg, respectively, after 70 days of treatment, while maximum levels in fat were 10 mg/kg at the end of treatment. After the end of the administration, radioactivity levels dropped rapidly in blood, liver and kidney; however the half-life in fat was 30 days.

4. Acute toxicity upon oral administration is high, especially using suitable i.e. lipophilic vehicles. The oral LD_{50} values of cyhalothrin administered in corn oil are 51 to 65 mg/kg bw and 37 to 62 mg/kg bw in the rat and mouse, respectively.

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5. A set of adequate repeated-dose toxicity feeding trials on rats and mice are available, including a one 90-day and four 28-day and rat studies, and one 28-day mouse study.

   Neurological signs characteristic of pyrethroid compounds (e.g. muscular trembling, unsteadiness) were observed in some, but not all, studies. The NOEL for apparent neurotoxicity in the rat was 5 mg/kg bw/day. Adaptive liver changes (including increased relative organ weight and proliferation of smooth endoplasmic reticulum) were observed at lower dose levels than those inducing neurotoxicity: the NOEL in the rat was 0.45 mg/kg bw/day. In the rat a dose-related reduction of weight gain was seen both in a 28-day study (NOEL 0.25 mg/kg bw/day) and in the 90-day study (NOEL unidentified) down to a dietary exposure level of 10 mg/kg feed (approximately to 0.5 mg/kg bw/day). In the 90-day study, sporadic reduced mean corpuscular volume was observed even at the 10 mg/kg feed exposure level.

6. In two studies performed under GLP, cyhalothrin was administered in corn oil by gelatine capsules to Beagle dogs for 26 or 52 weeks. The NOEL for neurological signs (muscular trembling, unsteadiness, vomiting) was 2.5 mg/kg bw/day in the 26 week study and 0.5 mg/kg bw in the 52-week study. A dose-related increased incidence of liquid faeces was observed in both studies at all dose levels, but this effect is considered as not of toxicological significance.

7. No data are available with regard to the tolerance in target species following dermal exposure.

   Dermal toxicity of cyhalothrin in polyethylene glycol vehicles is low in both rats and rabbits. The NOEL in the rabbit following a 3-week exposure was 100 mg/kg bw. Other vehicles have not been tested and, as in veterinary products cyhalothrin is suspended in oily formulations, the bioavailability and hence the toxicity, might be higher.

8. In a 3-generation feeding study on the rat no specific impairment of the reproductive functions were observed. The NOEL for toxic effects on adults and pups (reduced weight gain in adults, reduced litter size and birth weights in the F2 and F3-generations) was 10 mg/kg feed (0.5 to 0.7 mg/kg bw/day).

9. Cyhalothrin did not elicit specific effects on prenatal development in 2 gavage developmental toxicity (segment-II studies) in the rat and rabbit, corn oil being used as vehicle. Maternal toxicity, (including neurological signs in the rat) was observed at the higher dose levels (15 and 30 mg/kg bw/day in the rat and rabbit, respectively). The NOEL for maternal toxicity was 10 mg/kg bw/day in both species. No effects on embryonic or foetal development were seen even at the highest dose levels.

10. Cyhalothrin was not mutagenic when tested on 5 *Salmonella typhimurium* strains with and without metabolic activation; it did not induce cell transformation on Syrian Hamster kidney cells in presence of metabolic activation, whereas equivocal results (i.e. modest, not clearly dose-related increase of transformed colonies) were obtained in absence of metabolic activation. Negative results were obtained in two *in vivo* oral studies, i.e. bone marrow micronucleus in the rat (high dose level: 15 mg/kg bw for 1 or 5 days) and dominant lethal in the mouse (high dose level: 10 mg/kg bw for 5 days); corn oil was used as vehicle in both studies. From these studies it can be concluded that cyhalothrin is not mutagenic.

11. A 2-year feeding study was performed on Alpk/AP rats at dose levels up to 250 mg/kg feed (approximately 12.5 mg/kg bw/day). At the time of terminal sacrifice there was no statistically significant increase in the incidence of any tumours type when compared with control values.

    In an adequate 2-year feeding study on ChrL CD-1 mice a significant, but not clearly dose-related, increase of mammary adenocarcinomas was observed in females at 100 and 500 mg/kg feed (approximately 10 and 50 mg/kg bw/day): however, the increase remained within the control range. No such increase was observed at 20 mg/kg feed (approximately 2 mg/kg bw). The incidence was 2% in controls, 0% at 20 mg/kg feed, 14% at 100 mg/kg feed and 12% at 500 mg/kg feed , respectively. Historical control data from 17 studies conducted with the same strain of mouse (CD-1) over the period of 1980 to 1982, showed this type of tumor to be highly variable with incidences of between 2 and 12%. Thus the number of tumours seen on the 2-year feeding study in mice are not greatly out of line with those noted in other studies.

12. The inclined plane test was initially used to evaluate the effects of cyhalothrin on neuromuscular function. Cyhalothrin was administered in corn oil to fasted groups of 2 male or 2 female Crl:CD.BR rats at dose levels of 50, 100 and 200 mg/kg bw (males) or 25, 40 or 75 mg/kg bw (females) by oral gavage. A control group received corn oil only. Subsequent groups were dosed with 15, 30 and 60 mg/kg bw cyhalothrin in a similar manner. One hour prior to and then at intervals (30 minutes, 2, 5, 7 and 24 hours) after dosing the rats were placed on a smooth plane whose angle of inclination was gradually increased until the rat could no longer remain in place at its starting position. Each rat was given 3 replicate attempts on the plane and the angle at which it lost its position was recorded at each occasion. Clinical signs at doses of 50, 60 or 75 mg/kg bw consisted of emprosthotonus, lethargy, ataxia, writhing, snout staining, salivation, splayed gait, hunched posture, hypothermia, sunken flanks, vocalisation, high stepping gait, increased activity and irritability with most signs occurring 4 to 6 hours after dosing. Animals given 200 mg/kg bw were sacrificed on day 3 after the inclined plane phase had been completed. Only minimal clinical signs were noted in animals given 30 mg/kg bw while at 15 mg/kg bw soft faeces in females was the only adverse clinical finding. No conclusions can be made about the inclined plane phase of this study. The group sizes were too small. The doses used were too high, causing severe clinical signs at most of the dose levels. The inclined plane test is a sensitive test of subtle effects on motor co-ordination at doses, which do not cause obvious clinical neurotoxic responses.

    The acoustic startle response test was used as an alternative to the inclined plane test. The suitability of the use of this test for assessing a type II pyrethroid is questionable, as many substances can elicit a complex dose-response relationship. In some cases high doses can cause a decreased response (in contrast to type I pyrethroids which give an increase response) and an increased response at lower doses. Group of 10 male and 10 female Alpk:AP_fSD rats were treated using single oral gavage doses of 0, 5, 15 or 75 mg/kg bw cyhalothrin in corn oil. Clinical signs of neurotoxicity were present on day 2, that is 24 hours after administration, in some males and females given 75 mg/kg bw cyhalothrin. All animals had recovered by day 3 or 4. These signs included ataxia, high stepping gait, increased response to touch, salivation, subdued behaviour, tip toe gait. There were no treatment-related signs seen in animals given 5 or 15 mg cyhalothrin/kg bw. There was no effect on time to maximum amplitude for either sex on days 1 or 8 in any group. At 75 mg/kg bw cyhalothrin, there was an apparent reduction in the mean response amplitude in males and females; this had fully recovered by day 8. There were slight increases in mean response amplitude on day 1 in females given 5 and 15 mg/kg bw but these were not dose related and appeared to be due, in the view of the conducting laboratory, to larger control values. It was not considered to be compound related. It was concluded that no adverse effects were reported up to 15 mg/kg bw in this study. This test is not considered as a suitable test to study the neurological effects. The inclined plane tests have been usually used for the other pyrethroids (utilising lower doses of the test substance).

    In the repeated-dose toxicity trials neurological effects were addressed by means of cage-side observations and NOELs of 0.5 mg/kg bw/day in oral repeated toxicity studies in dogs and rats were retained.

13. No specific studies on the influence of cyhalothrin on the immune system were provided. In repeated dose toxicity studies decreased white blood cell counts were observed in male mice following dietary exposure for 28 days to 100 mg cyhalothrin/kg feed (approximately 10 mg/kg bw/day) and higher. The repeated dose toxicity studies in other species did not show alterations of white blood cells or organs potentially related to immunity (thymus, lymph nodes, spleen, and bone marrow).

    Cyhalothrin is a skin sensitiser in guinea pig when tested by the Magnusson and Kligman test.

14. The available human data on cyhalothrin concern the occurrence of acute, but transient facial and/or ocular paraesthesia upon occupational cutaneous exposure. Such effects have been reported for many other pyrethroids as well. No cases of systemic poisoning have been recorded.

    No clinical or haematological effects were observed in six human volunteers dosed 5 mg lambdacyhalothrin (B pairs of enantiomers only) in corn oil (approximately 0.05 to 0.07 mg/kg bw).

15. Cyhalothrin was evaluated by Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1984 and 1986. An ADI of 0.02 mg/kg bw was established on the basis of the long-term studies in rats and mice and of the reproduction study in the rat.

16. An ADI of 0.005 mg/kg bw (i.e. 0.3 mg/person) was calculated by the CVMP by applying a safety factor of 100 to the NOEL of 0.5 mg/kg bw, for clinical signs of neurotoxicity in a 52-week study in dogs. The safety factor of 100 was considered justified as the toxicity study in the dog was conducted with a suitable lipophilic vehicle.

17. According to studies using radiolabelled cyhalothrin and oral administration in cattle, the total absorbed dose undergoes extensive cleavage giving rise to the cyclopropane carboxylic acid and phenoxy-benzoic acid and their derivative metabolites. Approximately 50% and 27% of the radioactivity was excreted in faeces and urine within 16 hours after the last administration. In faeces, the radioactivity was mainly due to the unchanged compound but only small amounts of the parent compound were detected in bile.

    Two lactating Friesian cows were orally dosed twice daily for 7 consecutive days with ^{14}C-cyhalothrin (2 different label sites, 1 animal per label) at a daily dose of 1 mg/kg. The cows were killed 16 hours after the last dose. Radioactivity levels measured by liquid scintillation counting in edible tissues were 165 µg equivalents cyhalothrin/kg in muscle, 2700 µg/kg in perirenal fat, 1500 µg/kg in subcutaneous fat, 1300 µg/kg in liver and 600 µg/kg in kidney. The parent compound was found in all matrices; it accounted for 2 to 3% of total residues in liver, 15% of total residues in kidney. The residue in fat was due almost entirely to unchanged cyhalothrin. Radioactive residues in muscle were not further analysed as their concentration was too low.

    In another radiometric study, 4 cows were topically treated once daily for 3 consecutive days with ^{14}C-lambdacyhalothrin at a dose of 0.4 mg/kg bw (2 different label sites, 2 animals per label). Twenty-four hours after the last treatment, the radioactivity levels were 102, 112, 225, 114 and 22 µg equivalent lamdacyhalothrin/kg in perirenal fat, subcutaneous fat, liver, kidney and muscle respectively. Lamdacyhalothrin was the major component of the muscle and fat residue accounting for 92% and 100% of the total radioactivity. In kidney and liver, it represents approximately 30% and 7% respectively.

    No radiolabelled studies in sheep and pigs were provided

    No pharmacokinetic studies using topical treatment are available for the target species.

18. Unlabelled residue studies have been carried out in cattle, pigs and sheep to determine the amount of parent compound cyhalothrin in meat and milk after topical administration in oily solutions (0.05% w/v pure cyhalothrin). The main tissue residues of unchanged cyhalothrin were found in the peri-renal fat, followed by subcutaneous fat with differences depending on the target species as well as on the route and frequency of treatment.

    In a first study, 24 heifers were treated with 4 pour-on applications of 30 ml of 2% cyhalothrin in maize oil at weekly intervals (approximately 2 mg/kg bw per treatment). Seven hours after the last treatment the mean residues were 911 and 674µg/kg in perirenal and subcutaneous fat respectively. Then they declined to 873 and 611 µg/kg after 3 days and to 670 and 354 µg/kg at 14 days. Residues in liver were always below the detection limit (100 µg/kg). No data were provided for kidney and muscle.

    In a second study, groups of 5 animals were sprayed on 7 occasions at 14-day intervals at a dose of 275 mg per animal. In addition, each animal was fitted with ear tag-tape containing 1 g of cyhalothrin. Six hours after the last treatment, the cyhalothrin concentrations were below the limit of quantification (10 µg/kg) in muscle and in liver, 10 µg/kg in kidney, 319 µg/kg in perirenal fat and 262 µg/kg in subcutaneous fat. The concentrations of cyhalothrin declined very slowly to 172 and 146 µg/kg at 3 days and to 157 and 124 µg/kg at 14 days respectively.

    In a third study, groups of 5 animals were sprayed with 15 ml of a 1% lambdacyhalothrin formulation on 4 occasions at 14 day interval at a dose of 0.5 mg/kg bw. Six hours after the last treatment, the cyhalothrin concentrations were below the limit of quantification (10 µg/kg) in muscle and in liver, 20 µg/kg in kidney, 350 µg/kg in perirenal fat and 170 µg/kg in subcutaneous

fat. Then the concentrations of cyhalothrin in perirenal fat ranged from 140 to 230 µg/kg between day 3 and 14 and declined to 80 µg/kg at 28 days post dosing.

19. Twelve pigs were treated once with a pour-on application of 5 ml of 2% cyhalothrin in maize oil. Mean residues in abdominal fat were 84 µg/kg after 3 days, 53 µg/kg after 7 days and 35 µg/kg after 14 days. Mean residues in subcutaneous fat: 75 µg/kg (3 days), 35 µg/kg (7 days) and less than 10 µg/kg (14 days). Residues were not detectable in liver, kidney, and muscle. Skin at the site of application showed the following mean residues: 820 µg/kg after 3 days, 353 µg/kg after 7 days and 331 µg/kg after 14 days. In flank skin the mean residues were 229 µg/kg (3 days), 145 µg/kg (7 days) and 88 µg/kg (14 days).

20. Twelve sheep were treated with 3 pour-on applications of 5 ml of 2% cyhalothrin in maize oil at fortnightly intervals. Residues in perirenal fat and in subcutaneous fat were below 100 µg/kg even at the first sampling time, i.e. 16 hours after treatment. Residues were not detectable in liver, kidney, and muscle.

21. Two lactating Friesian cows were orally dosed twice daily for 7 consecutive days with ^{14}C-cyhalothrin (2 different labelling sites, 1 animal per label) at a daily dose of 1 mg/kg. During treatment, the concentrations of radioactivity ranged from 300 to 440 µg equivalents cyhalothrin/kg between days 3 and 7 of dosing. All the radioactive material was associated with the milk fat and consisting to 90% of cyhalothrin.

    Seven Friesian cows in early to mid lactation were treated once with a 10 ml pour-on application of 2% cyhalothrin. Residues reached a mean maximum level of 39 µg/kg at the 4th milking after treatment. Cyhalothrin concentrations declined to 20 and 16 µg/kg at the 7th and 9th milkings.

    In a second study, 4 lactating cows were treated with 4 pour-on applications of 30 ml of 2% cyhalothrin in maize oil at weekly intervals (approximately 2 mg/kg bw per treatment). All animals had highest residues following the first treatment on the 5th milking after treatment with levels between 50 and 310 µg/kg. In all cases, the residues had depleted to below 50 µg/kg by the 7th milking.

    Two cows were similarly treated on 4 occasions, with 90 ml on the first occasion and 60 ml of formulation on the remaining occasions. Selected samples of collected milk were analysed by gas chromatography with electron capture detection (limit of detection 0.001 mg/kg). Maximum residues of up to 470 µg/kg following the 90 treatment or 250 µg/kg following a 60 ml treatment were reached at 3 or 5 milkings after treatment. Residues remained higher than 50 µg/kg until the 16th milking after treatment.

22. No residue depletion studies are available with regard to ewe's milk.

23. Cyhalothrin was identified as marker residue in cattle. From the results of the different radiometric studies, it was estimated that cyhalothrin represents 100% of the total residues in muscle and fat, 20% in kidney and 90% in milk.

    In absence of radiolabelled studies in sheep and pigs no marker residue could be identified for these animal species.

24. Lambdacyhalothrin, which differs from cyhalothrin by the number of isomers only, but not cyhalothrin itself, is marketed in the EU as a pesticide for crops. Maximum levels in animal tissues and products were fixed at 500 µg/kg for meat[1], preparations of meat, offals and animal fats and 50 µg/kg for milk by Council Directive 94/29/EC, the marker residue being expressed as lambda-cyhalothrin including other mixed isomeric constituents (sum of isomers).

[1] In the case of foodstuffs with a fat content of 10% or less by weight, the residue is related to the total body weight of the boned foodstuff. In such cases, the maximum level is one-tenth of the value related to the fat content, but must be no less than 10 µg/kg.

25. Routine analytical methods validated in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community and presented in ISO 78/2 format are available. They are based on gas chromatography with mass-specific detection (GC-MS). The methods are designed to monitor residues of cyhalothrin in bovine and ovine tissues and bovine milk. The limits of quantification (determined by addition of the 2 peak areas for the 2 pairs of enantiomers (A and B) of cyhalothrin) are 25 µg/kg for bovine and ovine liver, kidney and muscle, 250 µg/kg for bovine and ovine fat and 10 µg/kg for bovine milk.

    The possible analytical interference with other pyrethroids likely to be analysed in food monitoring programmes was studied, namely with deltamethrin, alphacypermethrin, permethrin, and fenvalerate. No significant interference was found.

    No method was available for monitoring residues of cyhalothrin in the sheep milk and pig tissues.

Conclusions and recommendation

Having considered that:

- an ADI of 0.0050 mg/kg bw per day (i.e. 0.30 mg/person) has been established,
- no marker residue can be established for sheep and pigs,
- taking into account the MRLs in animal tissues from use as pesticide of lambdacyhalothrin, a compound closely related to cyhalothrin, fixed by Council Directive 94/29/EC, the same MRLs of 500 µg/kg are established for meat and offal and of 50 µg/kg for milk,
- however, in cattle, residue concentrations in liver, kidney and muscle are very low and nearly always 10 µg/kg, therefore only an MRL for kidney is proposed for surveillance purposes,
- cyhalothrin is the marker residue in cattle and accounts for 100% of total residues in fat, 20% in kidney and 90% in milk,
- validated analytical methods for the determination of residues of cyhalothrin in edible bovine tissues and milk are available,

the Committee recommends the inclusion of cyhalothrin 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
Cyhalothrin	Cyhalothrin (sum of isomers)	Bovine	500 µg/kg 50 µg/kg 50 µg/kg	Fat Kidney Milk	

Based on these MRLs values, the daily intake will represent about 40% of the ADI. This allows about 60% of the ADI for potential intake of the B pair of enantiomers from residues in crops treated with lambdacyhalothrin.