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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DELTAMETHRIN

SUMMARY REPORT (1)

1. Deltamethrin, (S)-α-cyano-3-phenoxybenzyl, (1R)-cis-3-(2,2-dibromovinyl)-2,2-dimethyl cyclopropanecarboxylate, is a synthetic type II pyrethroid insecticide and acaricide. Deltamethrin (98% cis isomer) is used topically (dip, spray or pour-on) for the control of ectoparasites in cattle, sheep and poultry. In cattle, recommended treatment schedules range from 0.25 mg/kg bw to 1.5 mg/kg bw as a single application or as repeated applications depending on parasitic pressure (repeated every 3 to 6 weeks). In sheep, the recommended doses range from 0.94 mg/kg bw to 4.5 mg/kg bw as a single treatment, repeated 10 or 21 days later when necessary. In chicken, the recommended dose is 0.08 mg/kg bw.

   Deltamethrin is also widely used as a pesticide on crops.

2. Deltamethrin changes the permeability of sodium channels of nerve membranes leading to prolonged depolarisation and hyperexcitability, which tends to be reversible. Deltamethrin administered intravenously at single doses greater than or equal to 0.1 mg/kg bw to dogs affects cardiovascular and respiratory functions and alters electroencephalogram patterns (convulsions); higher doses lengthen barbiturate sleeping time in mice. Deltamethrin increases the spontaneous catecholamine secretion by bovine chromaffin cells *in vitro*.

3. Pharmacokinetic studies were performed in rats and in mice.

   In male rats treated with oral doses of 0.64 to 1.6 mg/kg bw ^{14}C-labelled deltamethrin (at 3 different sites of the molecule), deltamethrin is degraded to a large number of metabolites derived from its acid (6 compounds) and alcohol moieties (8 substances) and from the cyano group (3 metabolites). Within 8 days 79% of the total radioactivity were recovered, 36% in faeces and 43% in urine. Deltamethrin and hydroxydeltamethrin derivatives were also found. The principal mechanisms of metabolism are ester cleavage and oxidation of the 4'-position of the alcohol moiety, conjugation as both phenoxy-hydroxyl and carboxylic acid, glucuronidation. The acid moiety is rapidly excreted as the glucuronide, with smaller amounts excreted as the free molecule and as glycine conjugate. Cleavage of the deltamethrin ester group leads to release of cyanide which is converted mainly to thiocyanate and to 2-iminothiazolidine-4-carboxylic acid. Metabolites do not contain the intact pyrethrin structure.

   Female rats received 2.4 mg ^{14}C-labelled deltamethrin/kg bw by intravenous route. Within 24 hours 64.9% of the administered dose were excreted, 74.27% via urine and 25.73% via faeces. Then the remaining radioactivity was excreted, so that within 120 hours, 86.6% of the radioactivity administered was recovered, the major fraction being recovered urine (in toto 63.28%).

   Only low concentrations of radioactivity could be measured in the brain: 96, 9, and 2 µg/kg at 4, 24 and 120 hours post injection. At 24 hours post injection, the concentrations of radioactivity were 34 µg/kg in muscle, 1665 µg/kg in fat, 272 µg/kg in liver and 211 µg/kg in kidney, they then declined to 5, 1395, 39 and 29 µg/kg in muscle, fat, liver and kidney respectively, 120 hours post injection.

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After oral administration of 1.7 to 4.4 mg/kg bw ^{14}C- labelled deltamethrin (in 3 different sites of the molecule) to male mice, nearly all the radioactivity was excreted within 8 days after administration. The metabolic pathway is similar to that described in rats, but the relative percentage of the metabolites found in urine and faeces is slightly different.

4. The following LD_{50} values were found when deltamethrin was administered orally in peanut oil as lipophilic vehicle: 30 to 50 mg/kg bw in the adult rat and 20 to 30 mg/kg bw in the mouse, using peanut oil as vehicle.

   Dermal toxicity of deltamethrin administered to rats in xylene vehicle is negligible: no toxic signs were elicited by 800 mg/kg bw, possibly due to poor absorption.

5. Long term repeated toxicity studies were carried out in rats and dogs.

   In a pre-GLP 90-day repeated oral toxicity study in rats, deltamethrin (as a solution in polyethylene glycol 200) was given at doses of 0, 0.1, 1 and 2.5 and 10 mg/kg bw/day. The treatment was followed by one week recovery period. At the two highest doses, only a significant decrease in body weight and in liver weight of females were reported. The dose of 1 mg/kg bw/day was retained as NOEL

   In a pre-GLP 90-day dog study followed by a 20-week recovery period, deltamethrin was given orally in polyethylene glycol 200 at doses of 0, 0.1, 1.0, 2.5 and 10 mg/kg bw/day. At the two high doses, liquid faeces were reported. Depression or alteration of limb reflexes were reported: 1 out of 6 in the lowest and control groups, 3 out of 10, 5 out of 10 and 2 out of 10 in 1.0, 2.5 and 10 mg dose groups. After the recovery period, these findings could only be observed in the 2.5 and 1 mg/kg dose groups. A NOEL of 0.1 mg/kg bw/day was retained for this study.

   In a 90-day dog study, followed by a 4-week recovery period, deltamethrin (inserted as powder in gelatine capsules) was administered at doses of 0, 2, 10 or 50 mg/kg bw. At 50 mg/kg bw systemic toxicity (significant reduction in body weight gain and food consumption, vomiting and salivation) and neurological clinical signs (including unsteady gait and trembling) were reported. Such findings were not reported at 2 and 10 mg/kg bw/day. A NOEL of 10 mg/kg bw/day was retained for this study.

   In a 1-year study dogs (4 animals per sex and per group) received deltamethrin (in gelatine capsules) at doses of 0, 1, 10 or 50 mg/kg bw/day. At 10 and 50 mg/kg bw, clinical neurological signs including unsteady gait, tremors, splaying of limbs were observed in both sexes. Significantly reduced erythrocyte packed cell volume and total haemoglobin were also recorded. A dose-related statistically significant reduction in body weight gain was observed for all treated males over the dosing period. Having considered that the weight gain of the control group was higher than expected by comparison with historical data and that the weights of the animals of the two lowest doses were within the biological range for this strain, source and age, a NOEL of 1 mg/kg bw/day was retained.

   In a 2-year repeated dose toxicity study in dogs, groups of 16 animals (8 per sex) received in their diet deltamethrin at levels of 0, 1, 10 and 40 mg/kg feed (approximately equivalent to 0, 0.025, 0.265 and 1 mg/kg bw/day). Neurological exams were conducted at approximately one year and before sacrifice. No differences between control group and treated groups were reported following neurological examinations (cranial nerves, segmental reflexes, postural reactions. No compound-related gross or microscopic changes were observed. The relative weight of spleen was higher in the highest dose group than in controls, but this observation was not related to histological findings. Therefore, 1 mg/kg bw/day was retained as NOEL.

6. In a pre-GLP 3-generation study in rats, deltamethrin was administered in the diet at 0, 2, 20 and 50 mg/kg feed corresponding to doses equivalent to 0.1, 1.1 and 3 mg/kg bw. At the highest dose, only significant decreases in mean food consumption and in the body weight were reported. No effects on fertility, gestation, lactation, litter size and pups were recorded. The NOEL for maternotoxicity was 1.1 mg/kg bw/day. No foetotoxicity was reported up to 3 mg/kg bw/day.

   In a 2-generation study in rats, deltamethrin was given in the diet at dose levels of 0, 5, 20, 80 or 320 mg/kg feed, equivalent to 0,0.25 to 0.8, 1.05 to 3.10, 4.2 to 12.4 mg/kg bw, 18.3 to 43.8 mg/kg bw. At the highest dose, toxicity was reported for parents and pups (reduced body weight gain and food consumption for parents, reduction of reproductive organ weight, mortality in pups the first week post-weaning, clinical signs of neurological impairment). Both pre-weaning weight gain and post-weaning weight gain as well as food consumption were significantly reduced in the F_1-generation at 80 mg/kg feed, equivalent to 4.2 to 12.4 mg/kg bw/day. No effects on fertility were observed. No effects on adult or peri-/postnatal toxicity were reported at 20 mg/kg feed, equivalent to 1.05 to 3.10 mg/kg bw.

7. Teratogenicity studies were carried out in rat, mice and rabbits.

   In pre-GLP teratogenicity study in mice, the animals received 0.1, 1 and 10 mg deltamethrin/kg bw of by gavage(vehicle not indicated). The number of implantation sites, of foetal losses and of viable foetuses was not affected by the treatment. At 1 and 10 mg/kg bw, the mean weight of the foetuses was significantly lower than of controls (1.26 and 1.24 g *versus* 1.35 g). A delayed ossification was reported at all doses. Due to the poor quality of the study no NOEL could be retained.

   Deltamethrin dissolved in corn oil was administered to mice by gavage at doses of 0, 3, 6 and 12 mg/kg bw/day during days 7 to 16 of gestation. A dose-related reduction in maternal weight gain during pregnancy and in the number of pregnant animal was reported. A significant increase in the occurrence of supernumerary ribs was reported for all doses (23.4%, 47.1% and 28.2% in the low, middle and high dose group *versus* 13.3% in the control group). No NOEL could be retained for this study (lower than 3 mg/kg bw/day).

   In a pre-GLP teratogenicity study in rats, the animals received 0.1, 1 and 10 mg deltamethrin/kg by gavage (vehicle not indicated). Although the number of implantation sites, of foetal losses and of viable foetuses was not affected by the treatment, due to the poor quality of the study no NOEL was retained.

   Deltamethrin dissolved in corn oil was administered to rats by gavage at doses of 0, 1.25, 2.5 and 5 mg/kg bw/day during days 7 to 16 of gestation. A dose-related reduction in maternal weight gain during pregnancy was reported (44.4, 43.9, 36.5 g in the low, middle and high dose group *versus* 45.6 g) in the control group. At the two high doses, a significant depression in pup growth was reported on day 15 and day 22 but not at day 36 post-partum. As maternotoxicity was reported at all doses and in absence of information on pup growth at 1.25 mg/kg bw/day, no NOELs were retained for this study.

   Pregnant dams received 0, 1, 3.3, 7 and 11 mg deltamethrin/kg bw/day (in corn oil). In the two dose groups, maternal toxicity (1 and 14 of 25 animals died at 7 mg/kg bw/day and 11 mg/kg bw/day) and neurological clinical findings including convulsions, increased salivation were reported. No adverse effects were reported for foetuses. The NOEL for maternotoxicity was 3.3 mg/kg bw/day and deltamethrin was not teratogenic up to 11 mg/kg bw/day.

   In teratogenicity study in rabbits, the animals received 1, 4 and 16 mg deltamethrin/kg bw (vehicle not indicated) by gavage. The number of foetal losses was significantly higher in all dosed groups without clear dose relationship. Due to the poor quality of the study no NOEL was retained.

   Deltamethrin (in carboxymethylcellulose) was given by gavage to pregnant dams at 0, 10, 25 and 100 mg/kg bw/day. In the highest dose group, maternal toxicity was reported (one animal died).

Litter resorptions were reported for all doses but was without toxicological significance as the variations where within the biological range of the strain. An increase in the number of foetuses with 27 presacral vertebrae was reported (28, 18 and 31 foetuses in the 10, 25 and 100 mg/kg bw groups *versus* 6 in the control group. Several developmental variations (wrist flexure, unossified hyoïd body, unossified pubic and tail bones) occurred among the high-dose group on a litter basis, compared to the control group 16, 15 and 51 cases in the 10, 25 and 100 mg/kg bw groups *versus* 2 in the control group. In absence of a dose-response pattern, no conclusion on the significance of these findings can be reached. A NOEL for maternotoxicity and developmental toxicity of 25 mg/kg bw/day was retained.

8. Deltamethrrin was tested in a series of *in vitro* tests [Salmonella microsomal assay (3 studies), V79 Chinese Hamster cells tests (3 studies), unscheduled DNA synthesis test]. The first three ones were not carried out according to the current requirements. All these tests gave negative results. It should be reported that in one Chinese hamster ovary (CHO) cell tests where cremophor was used as solvent a positive result was reported at concentrations equivalent to 1 mmol and higher, with metabolic activation. This finding, not observed with dimethyl-sulphoxide, may have resulted from a subtoxic effect of the solvent itself (Cremophor 2%).

   In published literature it was reported that *in vivo* deltamethrin induced clastogenicity in mouse bone marrow following intraperitoneal treatment with high doses (162.5 mg/kg bw) and *in vitro* in human cultured blood cells at concentration of at least 100 µg/ml. An increase of sister chromatid exchange in bone marrow was reported following a single oral dose of 20 mg deltamethrin/kg bw (in peanut oil), but not at doses of 13.2 mg/kg and lower.

   In a series of 3 adequately performed *in vivo* tests in mice, deltamethrin given orally in oily vehicle did not show any genotoxic potential, including the micronucleus and dominant-lethal assays *in vivo*, the highest dose levels tested being 20 mg/kg bw.

   Overall it can be concluded that residues of deltamethrin do not present a genotoxic risk to the consumer.

9. Three carcinogenicity studies and one combined long term toxicity/carcinogenicity study were carried in rats and mice.

   In carcinogenicity study in CD rat, the animals received in their diet deltamethrin at dose levels of 0, 2, 20, 50 mg deltamethrin/kg feed), equivalent to doses of 0, 0.09, 0.8, 2.1 mg/kg bw/day in males and 0, 0.11, 1.1, 2.8 mg/kg bw/day in females. In males an increase of Leydig cell adenomas was reported at the highest dosage: 6 out of 38 *versus* control group number 1, 0 out of 37 and control group number 2, 4 out 35; at the low-dose group 1 out 38 and at the mid-group 1 out 30). The significance of this finding can be questionable as the number of tumours in the high dose group is not significantly higher than in the second control group.

   In a combined long term toxicity/carcinogenicity study in rats, deltamethrin was given in the diet at dose levels of 25, 125, 500 and 800 mg/kg feed equivalent to 1.1, 5.4, 22.2 and 35.9 mg/kg bw/day for males and 1.5, 7.3, 29.5 and 47 mg/kg bw/day for females. At termination the only finding was a significant increased incidence of eosinophilic hepatocytes at the two highest dosages with ballooned cells in males at 35.9 and 22.2 mg/kg bw. Some minor hepatoxicity was observed at 5.4 mg/kg bw/day in males. A NOEL of 1 mg/kg bw/day was retained for this study.

In two carcinogenicity studies in mice, deltamethrin was given in the diet at dose levels of 0, 1,5, 25 and 100 mg/kg feed equivalent to 0, 0.12, 0.61, 3.1, 12 mg/kg bw/day in males and 0, 0.15, 0.76, 3.8 and 15 mg/kg bw/day in females for 2 years in a first study and of 0, 10, 100, 1000 and 2000 mg/kg feed equivalent to 1.5, 15.7, 155.4 and 314.8 mg/kg bw/day for males and 2.0, 19.6, 189.3 and 395.1 mg/kg bw/day for females for 97 weeks in a second study. No carcinogenic potential of deltamethrin in mice could be seen up to 314.8 mg/kg bw/day for males and 395.1 mg/kg bw/day for females.

Deltamethrin did not present a carcinogenic potential up to the highest dose tested (314.8 mg/kg bw/day and 395.1 mg/kg bw/day in male and female mice respectively and 35.9 and 47 mg/kg bw/day in male and female rats, respectively.

10. Deltamethrin was not a skin sensitiser when tested in guinea pigs by the Magnusson and Kligman test.

    Balb/c mice treated with a single intraperitoneal dose as low as 6 mg/kg bw showed a significant reduction in thymus weight in the absence of any effect on bodyweight. Further *in vivo* studies on mice treated intraperitoneally with 25 mg/kg bw as well as *in vitro* experiments, showed that deltamethrin increases the rate of apoptotic death of thymocytes.

    F344 male rats orally received deltamethrin in soybean oil for 28 days at doses of 1, 5 and 10 mg/kg bw. At dose levels of 5 and 10 mg/kg bw/day increased relative weight of mesenteric lymph nodes and decreased relative weight of thymus and adrenal glands were observed. Specific tests were performed on a satellite group of SRBC-immunised rats, suggesting an immunostimulating activity (increased number of antibody-forming cells in spleen, enhanced natural killer cell activity). No clinical signs were observed at any dose level, except for significantly reduced weight gain at 10 mg/kg bw. The NOEL for immunological effects was 1 mg/kg bw.

11. A number of specific neurotoxicity studies was performed in rats.

    In an inclined plane test, rats treated orally with 25 mg/kg bw deltamethrin in corn oil for two consecutive days showed systemic toxicity, including mortality in 2 of the 5 males. Although no alterations of performance were observed, no conclusions can be drawn from this study as it was too poorly reported.

    In an acute neurotoxicity study, male adult Sprague-Dawley rats were treated orally with single doses of 0 (vehicle), 5, 15 or 50 mg/kg bw deltamethrin in corn oil. The animals were submitted to a full neurotoxicity screening battery 3 hours, 7 days and 14 days after treatment. Systemic toxicity, including mortality in males, and marked neurotoxicity with a broad range of neurological and locomotion alterations were observed at 50 mg/kg bw up to 7 days post-dosing. At 15 mg/kg bw slight effects (salivation, impaired open field mobility) were observed 3 hours post-dosing. No histopathological changes were detected at termination on day 15. As no neurotoxicity was apparent at 5 mg/kg bw, this dosage was retained as NOEL.

    In a 13-week neurotoxicity study, Sprague-Dawley rats received deltamethrin in the diet at concentrations of 0 (basal diet), 50, 200 or 800 mg/kg feed, equivalent to approximately 0, 4, 14, 54 mg/kg bw/day for males and 0, 4, 16, 58 m/kg bw/day for females. The animals were submitted to a full neurotoxicity screening battery at weeks 3, 7 and 12 of treatment. Systemic toxicity, including mortality, neurological signs (unsteady gait, hypersensitivity to noise) and markedly impaired performance in the neurotoxicity assays was observed in the high dose group throughout the study and a slight increase of retinal degeneration in females of the high dose group. Neuropathological examination was performed by means of haematoxylin-eosin stain. The NOEL for neurotoxicity was 200 mg/kg feed, equivalent to 15 mg/kg bw/day.

12. Transient irritation of skin, of ocular and of nasal mucosa as well as face itching was observed upon occupational cutaneous exposure to deltamethrin; the concurrent presence of solvents in the formulation could have been a contributing factor.

    Cases of severe systemic poisoning have been recorded upon occupational exposure of crop sprayers, including fatal outcomes. Such cases resulted from combined inhalation, cutaneous (and possibly even oral) absorption. Neurotoxic signs in surviving people lasted for several weeks: the lowest dose associated with severe signs of toxicity is 100 mg/person and day (approximately 1.5 mg/kg bw).

    No signs of intolerance were elicited in human male volunteers given a single dose of 3 mg ^{14}C-deltamethrin orally in polyethylene glycol (approximately 0.04 to 0.05 mg/kg bw). Plasma radioactivity peaked within 2 hours and remained above the detection limit (0.2 Kbq/l) for 48 hours. Consistent half-lives were observed for plasma elimination and urinary excretion, namely 10 to 11.5 hours and 10 to 13.5 hours, respectively. The total elimination was 64 to 77% of the dose after 96 hours, faecal excretion accounting for 10 to 26%, only.

13. Deltamethrin was evaluated by the Joint FAO/WHO Meeting on Pesticides Residues (JMPR) in 1982. An ADI of 0.01 mg/kg bw was established on the basis of long-term studies in mice, rats and dogs.

    Deltamethrin was also assessed in 1998 by the experts of the Swedish National Chemicals Inspectorate in the frame of an EU review programme on active substances in plant protection products. In view of the quality, extent and consistency of the data, an ADI of 0.01 mg/kg/bw was established.

14. From the set of toxicological studies provided, an overall NOEL of 1 mg/kg bw/day was retained for rats, mice and dogs. By applying a safety factor of 100 to the toxicological NOEL of 1 mg/kg bw/day retained from chronic and long term toxicity studies, an ADI of 10 µg/kg bw, i.e. 600 µg/person was established.

15. Several metabolism and depletion studies on deltamethrin in edible tissues of laying hens, lactating cows, sheep and horses were carried out following different administration routes. Most of the radiometric studies were carried out using the test substance labelled separately with ^{14}C on both sides of its central ester linkage: benzyl ^{14}C label or the gem-dimethyl-^{14}C. As both labels did not lead to significant differences in results, no reference to the position of the label will be made in the following paragraphs.

16. In laying hens, the information provided previously was completed by new studies.

    In metabolism studies, laying hens received, by oral route, 7.5 mg ^{14}C deltamethrin/hen/day for 3 consecutive days (approximately estimated at 5 mg/kg bw/day). About 83% of the administered ^{14}C was eliminated during the first 24 hours. Within 120 hours after a single intravenous administration of 0.4 mg^{14}C-deltamethrin/kg bw approximately 66.1% of the administered dose was recovered, the major amount (54%) being excreted within 48 hours.

    Four groups of 6 laying hens received ^{14}C deltamethrin at daily doses of 0.15 mg/kg bw for 3 days either by oral route or dermal applications. Within 23 hours following the last oral administration, 84.1 to 94.7% of the administered radioactivity was recovered in excreta. Within 23 hours after the last dermal application only 1.5 to 1.9% of the applied dose was recovered in excreta, the major proportion (61.3%) remaining at the application site (skin, dressings, swabs and feathers).

    After dermal applications of deltamethrin at daily doses of 0.15 mg/kg bw for three days, the major metabolites identified in excreta were polar substances and deltamethrin, accounting for approximately 30% of the radioactivity.

    After oral administrations of 7.5 mg ^{14}C deltamethrin/hen/day for three consecutive days

(approximately estimated at 5 mg/kg bw/day), fourteen metabolites were isolated and identified by a combination of thin layer chromotography, gas chromotography, gas chromotography-mass spectrometry and high-resolution mass spectometry techniques. Deltamethrin was metabolised through cleavage of the ester bound followed by hydroxylation of one or both of the gem-dimethyl groups and hydroxylation of the 2'-,4'-, 5- or 6-positions of the phenoxybenzyl moiety. Extensive hydroxylation and oxidation led to a variety of products which were excreted free or as glucuronides. Deltamethrin was the major residue identified in egg yolk (19 to 47% of the total radioactivity). In liver and kidney, deltamethrin accounted for 23 to 51% and 24.8 to 28% of the total radioactivity. However, only a small fraction of the total radioactivity could be extracted for liver and egg yolk (25 to 66%) whereas more than 80% could be extracted in kidney. The nature of the metabolites found in edible tissues including eggs could not be fully clarified since the amounts of these residues were too small.

Twenty-three hours after the last repeated dermal application of ^{14}C-deltamethrin at daily doses of 0.15 mg/kg bw for 3 days, the mean concentrations of radioactivity (12 animals) in tissues were approximately 1, 5 and 6.50 µg equivalents deltamethrin/kg in muscle, skin+fat and liver. In pooled liver samples, the majority of the radioactivity was associated with unidentified polar metabolites (5.4 to 12.8% of the total tissue radioactivity) and deltamethrin (5.3 to 10.9% of the total tissue radioactivity). 42.9 to 68.5% of the radioactivity could not be extracted. No information on the percentage of deltamethrin with regard to the total radioactivity was available for fat, kidney and muscle of chickens.

In a residue depletion study carried out with unlabelled, laying hens were sprayed by a formulation of deltamethrin diluted at 25 mg/l or 50 mg/l (dose in mg/kg bw/day non stated). Groups of 5 animals were slaughtered 1, 2, 3, 4 and 8 days after the application. At any time, the concentrations of deltamethrin in kidney ranged from 10 to 7 µg/kg (limit of detection). In liver, deltamethrin could be measured up to 8 days after treatment, the mean concentrations being 20.6 and 29.3 µg/kg at 3 and 8 days post treatment. In muscle and in fat, the concentrations were below 12 µg/kg.

17. Several depletion studies were also carried in hens following intravenous or oral administrations.

In hens, one hour after intravenous administration 0.4 mg/kg of ^{14}C-deltamethrin, the mean concentrations of radioactivity (groups of 3 animals) were 113, 153, 102, 1103 and 963 µg equivalents deltamethrin/kg in muscle, fat, skin, liver and kidney respectively. Then, they declined to 6, 116, 35, 122 and 43µg equivalents deltamethrin/kg in muscle, fat, skin , liver and kidney respectively, 24 hours post dose. Significant amounts could still be measured, at 120 hours post injection: 31 equivalents deltamethrin/kg in liver, 90 µg equivalents/kg in fat, 18 µg equivalents/kg in skin and 13 µg equivalents/kg in kidney.

In another study at 24 hours after the last oral administration of ^{14}C-deltamethrin at daily doses of 0.15 mg/kg bw for 3 days, the mean concentrations of radioactivity (12 animals) in muscle, liver and skin+fat were below 4 µg equivalents deltamethrin/kg. In pooled liver samples, polar metabolites represented 5.7 to 18.5% of the total tissue radioactivity and deltamethrin, 1.6 to 3.1% of the total tissue radioactivity. In addition, 53.7 to 80% of the radioactivity could not be extracted. No information was available for the other edible tissues.

Groups of 10 chickens received 0.6 mg/kg bw of deltamethrin in their feed for 10 weeks. They were slaughtered 3, 7, 14 and 21 days after the end of the treatment. Residues of deltamethrin were assayed by a HPLC method and the limits of quantification and detection were 2 and 1 µg/kg respectively. At any slaughtering point the concentrations of deltamethrin were equal or below 5 µg/kg in skin, 2 to 3 µg/kg in fat and below the limit of detection in muscle and liver.

18. In hens treated with ^{14}C-deltamethrin at daily doses of 0.15 mg/kg bw for 3 days administered by oral route or dermal application, it was shown that the concentrations of radioactivity in eggs were below the limits of detection of the analytical method (3.8 to 4.6 µg and 1 µg equivalents deltamethrin/kg after oral administration and dermal application, respectively).

    After spraying of laying hens with a formulation of deltamethrin diluted at 25 mg/l or 50 mg/l (dose in mg/kg bw/day non stated), the concentrations of deltamethrin in eggs (10 eggs per point) were below the limit of detection (5 µg/kg).

19. Having considered the available information, it was concluded that deltamethrin was extensively metabolised in laying hens and only low concentrations of total radioactivity could be measured in edible tissues after dermal application. Considering the depletion of deltamethrin in laying hens following dermal application at higher doses (0.15 mg/kg bw) than the ones recommended for treatment (0.08 mg/kg bw), it was concluded that the most suitable marker will be the parent compound deltamethrin and the MRLs should be set at values within a range of 5 to 10 µg/kg.

20. Depletion data were provided for sheep.

    Four groups of 3 sheep received 4 mg deltamethrin/kg bw applied as a pour-on solution. Animals were slaughtered at 3, 7, 14 and 28 days after application. The concentrations of deltamethrin in edible tissues were assayed by gas chromatography with electron capture detection. In muscle, liver and kidney, the concentrations were below 10 µg/kg at any time. Mean concentrations of 40 and 20 µg deltamethrin/kg were measured in perirenal fat at 3 and 7 days post treatment. At later sampling times, the concentrations were close to the limit of detection (10 µg/kg).

    In another study in sheep, deltamethrin (in 1% miglyol) was applied topically to the mid-point of the shoulder of each animal, the fleece being parted to ensure skin contact. Groups of 3 animals were slaughtered at 3, 7 and 14 days. In the perirenal and omental fat, the mean concentrations were equal to or below the limit of quantification (10 µg/kg).

    Several other depletion studies were carried out in sheep, which were dipped in a solution containing 15 or 10 mg deltamethrin/l (doses in mg/kg bw not stated). The residues were assayed by gas chromatography with electron capture detection. It was shown that residues in fat were the highest at 3 days post dose (means of 19 and 13 µg/kg in omental and renal fat). From 7 days onwards residues in fat did not exceed 5 µg/kg. Residues in muscle, liver and kidney did not exceed 5 µg/kg with an exception of 32 µg/kg found in a 7-day muscle sample.

21. Studies in sheep indicated that fat is the target tissue where the concentrations of deltamethrin are the highest whereas in other edible tissues the concentrations were equal or less than 5 µg/kg.

22. In bovine, the information provided previously was completed by recently carried out studies.

    The metabolism of deltamethrin by cow liver was studied in *in vitro* incubation in presence of various enzyme fractions e.g. soluble and normal microsomes and microsomes plus NADPH in presence of deltamethrin labelled in ^{14}C-labelled with the acid and benzyl moieties. The main metabolic pathway was due to the cleavage of the ester bond to yield compounds which were oxidised and reduced. The same metabolites as the chickens ones were identified in this study, however, their amounts were very small.

    In a radiometric study in two lactating cows, ^{14}C-deltamethrin pour-on was applied for 3 consecutive days at a dose rate of 1.5 mg/kg bw/day, the highest recommended dose. Within 24 hours after the last application, only a low fraction of radioactivity (less than 1.5%) was recovered in excreta, the major fraction of the radioactivity (approximately 72%) being located at the site of application. The blood levels of radioactivity remained low (1 to 4 µg equivalents deltamethrin/kg at 1 hour post-dosing and less than 1 µg/kg at 12 hours post-dosing).

After dermal application of ^{14}C-deltamethrin at 2 mg/kg bw, the percentage of deltamethrin with regard to the total radioactivity was approximately 58% in muscle, 90% in fat. In liver the percentage could not be estimated as most of the radioactivity was not extractable. In kidney, large variations occurred according to the slaughtering point (7 to 60%).

After administration of ^{14}C-deltamethrin pour-on for 3 consecutive days at a dose rate of 1.5 mg/kg bw/day to two lactating cows, approximately 63.7 and 30.5 to 33.9% of the radioactivity in liver and kidney could not be extracted, whereas in fat and skin, nearly all the radioactivity was extractable (less than 1.5%). However, in liver and in kidney, after acid hydrolysis in presence of 3 molar hydrochloride acid, the majority of the residual radioactivity was released. Only 4.8 to 6% of the total radioactivity were not extracted from the matrices.

^{14}C-Deltamethrin was the primary radioactive component in renal fat and milk fat, accounting for about 54% of the total radioactive residue. Deltamethrin was extensively biotransformed in liver and kidney to *m*-phenoxybenzyl-glutamate and Br_2C-acid, as well as five unknown metabolites, their number and percentages when expressed with regard to the total radioactivity varying according to the site of the label. In one animal, deltamethrin represented 3.9, 3.1, 59.4 and 95.8% of the total radioactivity in liver, kidney, fat and skin whereas no deltamethrin could be found in the other animal.

23. Three heifers were treated with a xylene based pour-on formulation containing ^{14}C-deltamethrin at a dose of 2 mg/kg bw. In the animal slaughtered after 3 days, the radioactivity concentrations were 9 µg equivalents deltamethrin/kg in muscle, 94 µg equivalents/kg in perirenal/omental fat, 214 µg equivalents/kg in liver and 81 µg equivalents/kg in kidney. In the 7-day slaughtered animal the radioactivity concentrations were 7.5 µg equivalents deltamethrin/kg in muscle, 171 µg equivalents/kg in perirenal/omental fat, 323 µg equivalents/kg in liver and 79 µg equivalents/kg in kidney , In the 14-day slaughtered animal, the radioactivity concentrations were 8 µg equivalents deltamethrin/kg in muscle, 157 µg equivalents/kg in perirenal/omental fat, 309 µg equivalents/kg in liver and 48 µg equivalents/kg in kidney.

    In another study, 24 hours after the end of the repeated pour-on application of ^{14}C-deltamethrin for 3 consecutive days at a dose of 1.5 mg/kg bw/day to two lactating cows, the radioactive residues were in the magnitude of 1 to 2 µg equivalents deltamethrin kg in muscle, 9 to 11 µg equivalents/kg in renal fat, 4 to 8 µg equivalents/kg in omental, 9 to 13 µg equivalents/kg in liver and 10 µg equivalents/kg in kidney.

24. In an previously available depletion study, groups of 6 cattle (3 males and 3 females) were treated at 1 mg/kg bw by spraying. Animals were slaughtered 0.5, 1, 3 and 5 days post application. Significant amounts of deltamethrin were measured only in fat: 60.5, 73, 150 and 68 µg/kg at 0.5, 1, 3 and 5 days post-dose, respectively. In the other edible tissues, deltamethrin the concentrations were below the 2.5 µg/kg for liver and below 5 µg/kg in kidney and muscle inn most of the samples. In another after application by pour-on to 4 groups of 6 animals at the recommended dosage of 0.75 mg/kg bw, the deltamethrin concentrations in muscle and liver were too low to be quantified (less than 1.5 to less than 3 µg/kg for muscle and less than 2.5 µg/kg for liver). In kidney, mean concentrations of 10.2 and 15 µg/kg could be measured at 3 and 5 days after treatment. In fat, the concentrations were the highest with 27.9, 109 and 105 µg/kg, 1, 3 and 5 days post dosing. After topical application of 1 mg deltamethrin/kg bw (in miglyol 812) to 3 groups of 3 calves, approximately 88, 49 and 31 µg of deltamethrin/kg were measured in perirenal fat 3, 7 and 14 days post application, respectively. In omental fat, 61, 44, 41 µg/kg were measured 3, 7 and 14 days post dose respectively.

    In a study using non-radiolabelled compound, 6 Holstein cows were dermally dosed at 0.4 mg deltamethrin/kg bw applied twice (on days 1 and 8), the lowest recommended dose. The animals were slaughtered 1 and 7 days after the end of the treatment. The residues of cis-, trans- and alpha-R-deltamethrin were determined by a gas chromatography. In all samples of subcutaneous and

omental and renal fat, the concentrations of each compound was below 5 µg/kg. No determination of residues in other edible tissues was carried out.

In another study using non-radiolabelled compound, 12 lactating cows were dermally dosed at 1.6 mg deltamethrin/kg bw applied twice (on days 1 and 8), the highest therapeutic dose. The animals were slaughtered 1, 3, 7 and 14 days after the end of the treatment. The residues of deltamethrin, trans-deltamethrin and alpha-R-deltamethrin were determined by gas chromatography. In liver, kidney and muscle, the concentrations of deltamethrin and of trans-deltamethrin and alpha-R-deltamethrin were below 5 µg/kg at any time. In the omental and renal fat, no residues of trans-deltamethrin could be detected and only traces of alpha-R-deltamethrin (below the limit of quantification of 5 µg/kg) were seen. In the omental and renal fat, the mean concentrations of deltamethrin were 60.2, 69.3, 58.3 and 62.5 µg/kg at 1, 3, 7 and 14 days post-dose respectively.

25. In a study in two lactating cows, after ^{14}C-deltamethrin pour-on administration for 3 consecutive days at a dose of 1.5 mg/kg bw/day, less than 0.01% of the radioactivity was found in milk. Concentrations of radioactivity in whole milk ranged from 1 to 2 µg/kg during the treatment and 24 hours after the end of the treatment.

    In a residue depletion study using non-labelled deltamethrin the residues of deltamethrin in milk ranged from 5.3 to 2.5 µg/kg during the 5 days post treatment by percutaneous application to 6 lactating dairy cows (1 mg/kg bw). In another study, after percutaneous administration of deltamethrin at 1 mg/kg bw in 6 animals, the concentrations of deltamethrin in whole milk ranged from 4 to 1.8 µg/kg during the 5 days post dosing. Several studies on the depletion of deltamethrin in milk carried out after topical application of doses ranging from 0.66 mg/kg bw to 1 mg/kg bw confirmed that the concentrations of deltamethrin in whole milk did not exceed 10 µg/kg.

    In the study with non-radiolabelled deltamethrin, milk from the experimental animals dermally treated with 0.4 to 1.6 mg deltamethrin/kg bw (6 animals per dose), applied twice (on days 1 and 8) milk was collected during treatment until their sacrifice. Deltamethrin and 2 other compounds, trans-deltamethrin and alpha-R-deltamethrin were assayed and could be quantified in two samples (25 µg/kg in toto). At any time, the concentrations of each compound were below the limit of quantification (5 µg/kg).

26. Having considered the available information, it was concluded that deltamethrin was extensively metabolised in cattle and only low concentrations of total radioactivity could be measured in edible tissue after dermal application. Considering the depletion of deltamethrin in cattle including lactating cows after dermal application at higher doses, it was concluded that the most suitable marker residue will be the parent compound (deltamethrin).

27. In a radiometric study in horses, ^{14}C-deltamethrin was administered dermally to 2 animals, once a day for 3 consecutive days at nominal dose level of 1 mg/kg bw. The position of the ^{14}C was either benzyl or the gem-dimethyl site. Both animals were sacrificed approximately 24 hours after the last application. Approximately 5.2% of the administered dose was recovered in excreta, the major fraction being excreted via faeces (approximately 90% of the retrieved radioactivity). A significant percentage of the administered dose (approximately 50%) remained at the application site.

    Radioactivity in plasma could only be detected in one of the two treated animals and the concentrations ranged from 990 to 2580 µg/kg during the treatment. No information was available after the last application.

    The mean concentrations of the radioactivity were 3.5 µg equivalents deltamethrin/kg in muscle, 21 µg equivalents/kg in fat, 13 µg equivalents/kg in liver and 14 µg equivalents/kg in kidney.

28. A routine analytical method based on a gas chromatography with electron capture detection was presented in the ISO 78/2 format. In this method, the combined residue levels of tralometrin (only used as pesticide), deltamethrin, trans-deltamethrin and alpha-R-deltamethrin in meat, milk and eggs were detected. The limit of quantification for each compound was 15 µg/kg for bovine and chicken fat and 5 µg/kg for the other edible tissues of bovine and chicken including eggs and milk. This method was not validated according to the requirements of volume VI of the Rules Governing Medicinal Products in the European Union.

    For sheep, analytical methods based on gas chromatography with electron capture are available for monitoring residues of deltamethrin in the edible tissues but not validated according to the requirements of Volume VI.

29. MRLs in animal tissues and products were set at 50 µg/kg for fat, meat and for eggs by Council Directive 98/82/EC concerning the use of deltamethrin as pesticide. This level was indicated as the lower limit of analytical determination.

30. The Joint FAO/WHO Expert Committee on Food Additives also assessed deltamethrin in 1999 and allocated the following MRLs for cattle, sheep, chicken and salmons: 30 µg/kg for muscle, 50 µg/kg for liver, 50 µg/kg for kidney, 500 µg/kg for fat or fat+skin, 30 µg/kg for milk and 30 µg/kg for eggs, based on the ADI established by FAO/WHO Meeting on Pesticides Residues (JMPR).

Conclusions and recommendation

Having considered that:

- an ADI of 10 µg/ kg bw i.e. 600 µg/person has been established,
- since deltamethrin is also widely employed as pesticide on plants used for human consumption, the portion of the ADI to be allocated to products of animal origin is 40%, i.e. 240 µg/day,
- the parent compound was retained as the marker residue,
- deltamethrin is so extensively metabolised that a ratio of deltamethrin towards total residues could not be established,
- taking into account the MRLs in animal tissues from use of deltamethrin as pesticide, fixed by Council Directive 98/82/EC, the same MRLs (50 µg/kg) are established for fat and eggs, and consequently, 10 µg/kg for the other edible tissues (liver, muscle and kidney),
- in absence of data for ovine milk and in absence of routine analytical method, no MRLs for ovine milk could be set,
- routine analytical methods to determine residues of deltamethrin in edible tissues of bovine species including milk and chickens including eggs and of ovine species are available but not fully validated;

the Committee recommended the inclusion of deltamethrin into 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
Deltamethrin	Deltamethrin	Bovine	10 µg/kg 50 µg/kg 10 µg/kg 10 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	Provisional MRLs expire on 1.7.2001
		Ovine	10 µg/kg 50 µg/kg 10 µg/kg 10 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.7.2001 Not for use in animals from which milk is produced for human consumption
		Chicken	10 µg/kg 50 µg/kg 10 µg/kg 10 µg/kg 50 µg/kg	Muscle Skin + Fat Liver Kidney Eggs	Provisional MRLs expire on 1.7.2001

Based on these MRL values, the daily intake will represent about 8% of the ADI; this margin allows for total residue correction and is compatible with the Estimated Maximum Daily Intake (EMDI) and with the Theoretical Maximum Daily Intake (TDMI) of residues of deltamethrin from the pesticide use, which amount to 16% and 72%, respectively.

LIST OF QUESTIONS

1. The applicant should provide routine analytical method for all edible tissues of the target species including milk and eggs validated in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community and presented in a standard, internationally recognised format (e.g. ISO 78/2).