



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

FENVALERATE

SUMMARY REPORT (1)

1. Fenvalerate (α cyano-3-phenoxybenzyl α -(4-chlorophenyl)isovalerate, CAS N° 51630-58-1) is a synthetic type II pyrethroid insecticide presenting two chiral centres giving four optical isomers : 22% of [2S, α S] isomer ((S)- α -cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-isovalerate); 28% of [2S, α R] isomer; 22% of [2R, α R] isomer; and 28% of [2R, α S] isomer. The diastereoisomer ratio is 44/56 minimum, expressed on the ratio of the sum (S-S) plus (R-R) enantiomers to the sum of (S-R) plus (R-S) enantiomers. The SS enantiomer provided nearly all the insecticidal activity. It is an acaricide intended for external use against ectoparasites in cattle including dairy cows. Fenvalerate is intended to be used as spray or bath at a recommended dosage of 1 mg/kg bw.

Fenvalerate has also been widely used as pesticide for the protection of crops.

2. Fenvalerate may be considered as a type II pyrethroid by virtue of the presence of the α -cyano group although no description of the spectrum of behavioural effects characteristic of type II pyrethroids has been provided. Similarly, although the information has not been provided in the dossier it may be assumed that fenvalerate, in common with other members of this class of compounds, exerts its toxic effects in insects and mammals by changes in the permeability of sodium channels of nerve membranes, leading to prolonged depolarisation and activation, followed by block of the nerve action potential.
3. The pharmacokinetics and metabolism of fenvalerate and its isomers were widely studied in rodents and dogs.

In vitro, rat liver microsomes metabolise ^{14}C -fenvalerate into 9 metabolites, the structural formula of five of these have been identified.

In female rats given a single intravenous dose of 4.8 mg/kg bw of ^{14}C -fenvalerate, more than 84% of the administered radioactivity was recovered within 5 days, the urinary excretion accounting for at least 57%. The highest residue concentrations were measured in fat (2976 and 2482 μg equivalents/kg at 24 and 120 hours post dose, respectively). In muscle, liver and kidney, the concentrations were 57, 530 and 381 μg equivalents/kg respectively, 24 hours after administration. These concentrations declined to 11, 106 and 67 μg equivalents/kg in muscle, liver and kidney at 120 hours post-dose.

In rats given a single oral dose of 8.4 mg/kg bw of ¹⁴C-fenvalerate in corn oil, more than 95% of the administered radioactivity was eliminated within 5 days, the faecal excretion accounting for at least 60%. In urine, the parent compound was not detected. 2-(4-chlorophenyl)-3-isovaleryl acid [CPIA], 2-(dihydroxy)- 2-(4-chlorophenyl)-3-isovaleryl acid and the α and β diastereoisomers of 2-hydroxy-2-(4-chlorophenyl)-3-isovaleryl acid were the major urinary compounds accounting for 7, 3, 4 and 2% of the administered dose respectively. There were also 7-8 minor unidentified metabolites each accounting for less than 1% of the administered dose. In faeces, the parent compound represented about 40% of the administered dose. Two other metabolites were also identified: 4-hydroxyfenvalerate and 2-(4-chlorophenyl)-3-isovaleryl acid accounting for about 3 and 4% of the administered dose respectively. About 14 to 30% of the faecal radioactivity could not be identified or was unextractable.

In pregnant rats, oral doses of ¹⁴C-fenvalerate or ¹⁴C-S-fenvalerate administered once or for five consecutive days at doses of 10 and 2.5 mg/kg bw resulted in only a small proportion of the administered dose (0.07%) being dispositioned into foetuses.

There were no significant qualitative or quantitative differences in metabolites found in male and female mice after oral doses of 25 or 100 mg/kg bw of ¹⁴C-fenvalerate for 28 days.

In mice and rats the pharmacokinetics of radiolabelled fenvalerate and esfenvalerate were comparable with the exception of 2-(4-chlorophenyl)-3-isovaleryl acid-cholesterol ester, which was detected only in mice treated with fenvalerate. *In vivo*, fenvalerate is extensively metabolised. Hydrolysis of the ester linkage is the primary metabolic pathway. The acid and the alcohol portions of fenvalerate undergo hydroxylation and oxidation respectively. The acidic metabolites resulting from ester cleavage may undergo conjugation to glycine or glucuronic acid. There were no apparent differences in the nature and amount of metabolites and in the patterns of ¹⁴C excretion and tissue residues between fenvalerate and the (S) isomer in rats and mice.

In dogs given single oral doses of 1.7 mg/kg of ¹⁴C-fenvalerate, 79.1 to 87.1% of the administered dose was eliminated within 3 days. Fenvalerate was metabolised mainly by oxidation at the 4'-phenoxy position of the alcohol moiety and at the C-2 and C-3 positions of the acid moiety, cleavage of the ester linkage and conjugation of the resultant carboxylic acids, phenols and alcohols with glucuronic acid, sulphate and/or amino acids. There were some species differences between dogs and rodents.

4. The acute toxicity of fenvalerate has been studied in the hamster, rat, mouse, rabbit, domestic fowl, pheasant, partridge and trout, following oral, intravenous and dermal application. The oral toxicity was dependent on the vehicle used and the LD₅₀ in rat ranged from 310 to more than 3200 mg/kg bw depending on the vehicle used. Precise comparisons are not possible because of the different vehicles used, but oral toxicities in the hamster and mouse were of the same order as in the rat. Fenvalerate was more toxic by the intravenous route (LD₅₀ in mouse 65 mg/kg bw) and less toxic when applied dermally (LD₅₀ more than 5000 mg/kg bw in rat and mouse and more than 2500 mg/kg bw in rabbit). No information was provided on acute toxicity of fenvalerate administered orally in a suitable lipophilic vehicle (e.g. corn oil).
5. Repeated dose oral toxicity studies were carried out in rats, hamsters, mice and dogs.

Due to the inadequacies of the studies conducted in mice and hamsters, no NOEL could be retained.

Three-month oral toxicity studies were conducted in rats and in dogs:

Carworth Farm E rats, 6 animals per sex per group, received fenvalerate at dietary levels of 125, 500, 1000, and 2000 mg/kg feed for 90 days, equivalent to 10, 41.4, 77.8 and 161.4 mg/kg bw for males, and 11.3, 45.6, 90.4 and 187.7 mg/kg bw for females. In the highest dosage group, 85% of the animals died during the test. A dose-dependent decrease in body weight gain and various changes in biochemical and haematological parameters were observed in both sexes. However, the variation of kidney weight reported in the females at the lowest dosage can be considered to have no toxicological significance and a LOEL of 125 mg/kg feed (10 mg/kg bw/day) can be retained.

In dogs, fenvalerate was administered at doses of 0.05, 1.25 and 12.5 mg/kg bw/day in their diet, for 90 days. No adverse effects were observed in dogs fed fenvalerate up to 12.5 mg/kg bw/day.

In another study, groups of 12 Beagle dogs received in their diet oral doses of 250, 500 and 1000 mg fenvalerate/kg diet, approximately equivalent to oral doses of 8, 16 and 32 mg/kg bw/day. Dose-related neurotoxic signs and changes in serum total cholesterol were reported even at the lowest dosage. An increased incidence and severity of hepatic multifocal microgranulomas were recorded in all treated animals (8, 11, and 12 out of 12 in the 250, 500 and 1000 mg fenvalerate/kg diet groups versus 4 out of 12 in the control group). Histiocytic cell infiltrates in the mesenteric lymph nodes were also reported in 2 out of 12 in the mid-dose group and 6 out of 12 in the high dose group. No NOEL could be retained in this study.

6. The toxicity of the different enantiomers of fenvalerate in mice was reported. Mice were fed diets containing each of the isomers of fenvalerate for up to 52 weeks at doses ranging from 125 to 2000 mg/kg feed approximately equivalent to 19 to 300 mg/kg bw/day.

Neurotoxic signs (hyperexcitability, tremors) and mortality were only observed in the groups treated with 1000 mg of [2S, α S] isomer per kg feed and with 2000 mg of [2S, α R] isomer per kg of feed but not in mice treated with either the [2R, α R] or [2R, α S] isomers.

Microgranulomatous changes in liver, spleen and lymph nodes (mandibular and mesenteric) were observed in mice treated with the [2R, α S]-isomer at 125 and 1000 mg/kg feed for 1, 2 or 3 months. The histological changes were identical to those in racemic fenvalerate. These changes did not occur in mice treated with the other isomers. It was shown that 2-(4-chlorophenyl)-3-isovaleryl acid-cholesterol ester may be the causative agent of microgranulomatous changes in liver.

7. A 3-generation reproduction study was conducted in rats given fenvalerate in their diet at doses of 0, 1, 5, 25 and 250 mg/kg feed, (equivalent to 0, 0.1, 0.5, 2.5, 25 in mg/kg bw/day respectively) for 2 successive generations. Only a significant decrease in bodyweight gain of the F2b parents was reported at 250 mg/kg feed. No adverse effect on fertility was noted at the tested doses. A NOEL of 25 mg/kg feed approximately equivalent to 1.25 mg/kg bw/day for reproductive toxicity was retained.

8. Embryotoxicity/teratogenicity studies were carried out in mice and rabbits.

In mice, fenvalerate dissolved in corn oil, was given orally in gelatine capsules to pregnant animals at doses of 0, 5, 15 and 50 mg/kg bw/day from day 6 to day 15 of gestation. Neurotoxicity and/or increased mortality were reported in the dams at the two highest doses. Five mg/kg bw/day was the NOEL for maternotoxicity. However, fenvalerate was neither teratogenic nor embryotoxic at the doses tested.

In rabbits, fenvalerate was given orally in corn oil to pregnant animals at doses of 0, 12.5, 25 and 50 mg/kg bw/day from day 6 to day 18 of gestation. Decreased bodyweight gain was observed in the dams at the highest dose. No teratogenic or embryotoxic effects of fenvalerate were observed at any dose levels tested. Twenty five mg/kg bw/day was considered as the NOEL for maternotoxicity.

9. Fenvalerate was devoid of mutagenic activity in an Ames test, in host mediated assays in mice (with *Salmonella typhimurium* and *Saccharomyces cerevisiae* as indicators), in a dominant lethal assay in male mice, and in a bone marrow micronucleus test in Chinese hamsters (after oral administration of fenvalerate).

In vitro induction of chromosomal aberrations (20 to 50 μ g/ml) and sister chromatid exchanges (2 to 50 μ g/ml) were observed in cultured human lymphocytes. The ability of fenvalerate to induce chromosome damage and sister chromatid exchange was not correlated with concentration.

In one *in vivo* study, it was shown that the intraperitoneal administration of fenvalerate to mice at high doses (150 and 200 mg/kg bw) induced chromosomal aberrations. Intraperitoneal administration of fenvalerate at doses of 150 and 200 mg/kg bw/day for two days induced micronuclei in bone marrow. Such effect was not observed after two administrations of 100 mg/kg bw of fenvalerate. However, as this study was not conducted according to the current guidelines and due to the inadequacy of the experimental design, this result should be interpreted with caution.

The evidence indicates that fenvalerate does not cause gene mutations. Despite the fact that the data on the clastogenic potential of fenvalerate are equivocal after intraperitoneal administration, it was concluded that oral ingestion of residues of fenvalerate is unlikely to have mutagenic potential.

10. Combined chronic/carcinogenicity studies in rats (two studies) and in mice (four studies) were provided.

In rats, fenvalerate was administered in the diet at doses from 1 to 1000 mg/kg feed for 24 months. An increase in the incidence of mammary tumours was noted in the treated group but without dose relationship (51%, 57%, 70%, 65% and 55% at terminal sacrifice in the 1, 5, 25, 250 and 1000 mg/kg feed groups versus 43% for the control group).

In another study, rats received fenvalerate in their diet at levels of 50, 150, 500 and 1500 mg/kg feed for 24 to 28 months. No neoplastic lesions occurred, when compared to controls. Microgranulomatous changes in the lymph nodes, liver and spleen were reported for the two highest doses. The NOEL for these changes was 150 mg/kg feed (7.5 mg/kg bw/day).

In mice given oral dosages of 10 to 3000 mg/kg feed for 12 to 24 months, no neoplastic lesions occurred, when compared to controls. Most findings consisted of microgranulomatous changes in the lymph nodes, liver and spleen. The NOEL for these changes was 30 mg/kg feed, i.e. 3.48 and 4.29 mg/kg bw/day for males and females respectively.

An initiation/promotion model was investigated in Sprague-Dawley rats. Fenvalerate induced an enhancement of gamma-glutamyl transpeptidase-positive foci in liver at a dose of 75 mg/kg bw.

In a metabolite-cooperation assay in the Chinese hamster lung fibroblast, fenvalerate and its metabolite 2-(4-chlorophenyl)isovaleric inhibited the intercellular exchanges. Fenvalerate could be considered as a potential tumour promoter although it showed no carcinogenic potential in rats and mice after oral administration.

11. Fenvalerate induced no sign of skin allergy in guinea-pigs when tested by Magnusson-Kligman or Landsteiner-Draize methods. Fenvalerate was mildly irritating to skin and eyes of rabbits. Only summaries of these studies were provided.

12. In rats and mice given a single oral administration of fenvalerate at doses of 32 to 1000 mg/kg bw, clinical neurotoxic signs were recorded for doses equal to or higher than 200 mg/kg bw and histopathological lesions (swelling of axons, vacuolation and phagocytosis of myelin) were described for doses equal to or higher than 56 mg/kg bw for mice and 100 mg/kg bw for rats. No adverse effects were noted at doses of 32 mg/kg bw for mice and 50 mg/kg bw for rats.

In rats given repeated oral doses of fenvalerate at levels of 50 to 400 mg fenvalerate/kg bw/day for 7 days, a small increase in both β -glucosidase and β -galactosidase enzyme activities indicative of limited axonal degeneration was found. The changes in β -galactosidase were only reported at the highest dose level. The changes in the β -glucosidase activity were noted at all doses but without a dose relationship. A LOEL of 100 mg/kg bw/day could be retained for biochemical indicators of axonal degeneration and a NOEL of 50 mg/kg bw/day retained for acute, reversible functional deficits based on the results from the inclined plane and slip angle tests.

In hens, oral administrations of 1 g fenvalerate/kg bw/day for two 5-day treatment periods induced no neurotoxic signs.

In light of the results of studies conducted with deltamethrin and cypermethrin, two α -cyanopyrethroids with chemical structures similar to fenvalerate, further testing on the potential neurobehavioral effects of early post-natal exposure to fenvalerate was not considered necessary for the assessment of its potential risk to humans.

13. In humans, transient irritative symptoms in skin and respiratory tract were reported after single or repetitive topical contacts, with 0.13 mg/cm² or 0.081 mg/kg or inhalation. After acute oral poisoning of 2 g to 100 g fenvalerate, digestive symptoms (nausea, vomiting) were described.
14. The *Codex Alimentarius* adopted an ADI of 0.02 mg/kg bw in 1986. Since then, a considerable amount of new information has become available but has not been presented. It was not possible to identify the study on which the ADI of 0.02 mg/kg bw was elaborated by the Joint Meeting on Pesticide Residues (JMPR) and what safety factor the JMPR used.
15. An ADI of 12.5 μ g/kg bw (i.e. 750 μ g/person), can be established for fenvalerate by applying a safety factor of 100 to the NOEL of 1.25 mg/kg bw/day retained from the 3-generation reproduction study in rats.
16. Limited information on plasma pharmacokinetics of fenvalerate in the target species are available.

In cattle (i.e. 3 steers), after a single intravenous administration of 2 mg/kg bw of fenvalerate, the half life of the secondary phase of the plasma residue depletion ($T_{1/2\beta}$) was 1005 minutes, the mean residence time (MRT) was 172 minutes, the systemic clearance was 10.4 ml/min/kg and the Volume at steady state was 1800 ml/kg. The relatively high ratio between $T_{1/2\beta}$ and MRT suggests that a significant portion of the dose was eliminated from plasma, possibly by metabolism, prior to emergence of a terminal elimination phase.

In cattle (i.e. 3 cows), repeated oral administration of fenvalerate in the diet at 0.11 mg ¹⁴C-fenvalerate/kg of feed equivalent to a daily dose of 2 mg/cow/day for 21 days, the plasma concentrations of ¹⁴C-fenvalerate ranged from 16 to 24 μ g equivalents/l.

After a single topical application of 1 mg/kg bw of fenvalerate in five male calves, plasma fenvalerate concentrations were determined by a GC/electron capture detection (ECD) method with a limit of quantification of 2.5 μ g/kg. The fenvalerate levels in plasma samples collected up to 7 days after the application were below the limit of quantification. It was concluded that following pour on administration of a preparation containing fenvalerate to cattle at a dose of 1 mg/kg, the cutaneous penetration of fenvalerate is extremely low.

17. Several studies were carried out using radiolabelled fenvalerate in order to study its distribution profile in tissues and milk and its metabolism after oral administration to cattle.

In bovine given repeated oral administrations of ¹⁴C-fenvalerate at doses of 0.11 to 0.15 mg/kg feed for 21 days (2 mg/cow/day), about 60 % of the daily dose was eliminated daily.

Following oral treatment with ¹⁴C-fenvalerate at doses of 5 mg/kg feed for 4 days, the total excretion of fenvalerate in milk accounted for 0.44 and 0.64% of the total dose for the cows fed 5 and 15 mg/kg feed, respectively.

In cattle, 24 hours after the end of repeated oral administrations of ¹⁴C-fenvalerate at doses of 0.11 to 0.15 mg/kg feed for 21 days, the radioactivity levels in all edible tissues were lower or equal to 10 μ g equivalents/kg. Low concentrations of radioactivity were measured in milk: 1 to 2 μ g equivalents/kg.

Twenty four hours after the end of repeated oral administrations of ¹⁴C-fenvalerate at doses of 11 mg/kg feed for 28 days, the concentrations of total radioactivity in muscle, fat, liver, kidney were: less than 40 to 60, 680 to 790, 340 and 180 μ g equivalents/kg respectively. Concentrations of radioactivity ranging from 20 to 90 μ g equivalents/kg were measured in milk.

Twenty four hours after the end of repeated oral administrations of ^{14}C -fenvalerate at a dose of 79 mg/kg feed (2 animals), the ^{14}C residues in muscle, liver, kidney and fat were 300, 2200, 1600 and 2600 μg equivalents/kg, respectively. ^{14}C -Fenvalerate residues in milk quickly reached a plateau after 3 to 7 days of treatment with a mean concentration in the magnitude of 500 μg equivalents/kg respectively. After the end of the treatment, they declined to reach 310, 120 and 60 $\mu\text{g}/\text{kg}$ at 1, 2 and 3 days.

An attempt was made to identify the composition of the metabolites in edible tissues. Eighty three percent of the ^{14}C -residues in liver were extractable. Tissue-bound residues represented 17% of the total ^{14}C -residues. In the extractable fraction (combined organic and water soluble fractions), 50% of the total ^{14}C - residue was 2-(4-chlorophenyl)-3-isovaleryl acid, 1 % fenvalerate and 16% Phosphate Buffer Acid.

The majority of the ^{14}C -residues in kidney were recovered in the tissue homogenate (92% of the total ^{14}C residues). Tissue-bound residues represented 8% of the total ^{14}C residues. In the kidney extractable fraction (combined organic and water soluble fractions), 26% of the total ^{14}C - residue was 2-(4-chlorophenyl)-3-isovaleryl acid, 17% fenvalerate and 10% Phosphate Buffer Acid.

^{14}C -Fenvalerate accounted for more than 90% of the total ^{14}C residues in muscle and fat.

18. Several studies on the depletion of fenvalerate in edible tissues after topical applications were provided.

In a first study, lactating cows were sprayed 3 times, at weekly intervals, at the estimated rate of 50 mg per square foot (e.g. 2 g per animal per dose in total), the highest concentrations of fenvalerate were found in the renal fat as follows: 420 $\mu\text{g}/\text{kg}$, 110 $\mu\text{g}/\text{kg}$, 120 $\mu\text{g}/\text{kg}$ at 7, 28 and 58 days respectively. In all the other edible tissues (liver, kidney and muscle), the fenvalerate concentrations were lower than or equal to the limit of detection (10 $\mu\text{g}/\text{kg}$).

In a second study, 3 Holstein cows were sprayed, 3 times, at weekly intervals at the estimated rate of 50 mg per square foot (e.g. 2 g per animal in total) with fenvalerate formulated in xylene. The concentrations of fenvalerate found in the renal fat were 60, 120 and 120 $\mu\text{g}/\text{kg}$, at 1, 3 and 7 days after the last application. In all the other edible tissues (liver, kidney and muscle), the fenvalerate concentrations were lower than or equal to the limit of detection (10 $\mu\text{g}/\text{kg}$).

Ninety and 120 days after a single dermal application of fenvalerate at a dose of 0.5 g of fenvalerate/animal, fenvalerate concentrations could be still detected by an HPLC method (limit of detection of 1 $\mu\text{g}/\text{kg}$). All fenvalerate concentrations were below 5 $\mu\text{g}/\text{kg}$ except in two samples (8.97 $\mu\text{g}/\text{kg}$ in a 90 day liver sample and 8.06 $\mu\text{g}/\text{kg}$ in a 90-day muscle sample).

19. Several studies on the depletion of fenvalerate in milk after topical applications were provided

After repeated topical administration of fenvalerate (in xylene formulation) per spray, 3 times at weekly intervals, at the estimated rate of 50 mg per square foot (e.g. 2 g per animal in total) in lactating cows, the highest concentration of fenvalerate found in the milk cream was 230 $\mu\text{g}/\text{kg}$, 3 days after the last application. In whole milk the highest fenvalerate levels was 40 $\mu\text{g}/\text{kg}$. In another study carried out according to the same treatment regimen, fenvalerate was not detected in milk (limit of detection of the analytical method was 10 $\mu\text{g}/\text{kg}$).

Three days after each of 6 consecutive topical applications of 0.1 g fenvalerate at intervals of 3 or 4 days, (2 cows), the concentrations of fenvalerate residues expressed as the sum of the 2 diastereoisomers (X and Y) ranged from less than 0.20 to 1.140 $\mu\text{g}/\text{kg}$ in whole milk. Then, they declined to be in the magnitude of 0.20 $\mu\text{g}/\text{kg}$ or less 4 days after the fifth treatment. In the same experiment, 2 Holstein cows were also treated with 0.5 g of fenvalerate in 3 consecutive topical applications at intervals of 14 days. Residues in whole milk were at a maximum 6 hours after treatment (1.02 to 2.43 $\mu\text{g}/\text{kg}$) and declined to less than 0.2 $\mu\text{g}/\text{kg}$ over 21 days after the last treatment.

After a single application of 2 g of fenvalerate per animal (e.g. 2.90 and 3.67 mg/kg bw), significant amounts of residues could be quantified by GLC with a limit of quantification of 10 µg/l. The highest concentration detected 3 to days after the application was 1000 µg/kg. Then they declined to 230, 60 and 10 µg/kg, at 7, 14 and 24 days post dosing. Only 2 animals were used in this study.

In another study, twelve lactating dairy Normande cows were each sprayed once with 0.5 g of fenvalerate. Fenvalerate concentrations in milk were determined by HPLC with a limit of detection of 10 µg/kg. At the first milking, the average fenvalerate concentration was 345 µg/kg (range 200 to 550 µg/kg). They increased up to 653 µg/kg (range 250 to 900 µg/kg) at the 5th milking and then declined to 42 (range 20 to 60) and 15 µg/kg (range less than 10 to 40 µg/kg), at the 12th and 16th milkings respectively. This study was not conducted in accordance with Good Laboratory Practice and the analytical method was not properly validated. Therefore, the results of this study must be interpreted with caution as they are entirely different from those obtained in other studies.

The depletion studies of fenvalerate in tissues or in milk were made using dosages much higher than the recommended one.

20. For the pesticidal use of fenvalerate and esfenvalerate, maximum residue limits have been established in the EU (Commission Directive 2000/42/EC of 22 June 2000). These MRLs are for the sum of RR and SS isomers 20 µg/kg for chicken meat and 200 µg/kg for other meat products and for the sum of RS and SR isomers 20 µg/kg for chicken meat and 50 µg/kg for other meat products expressed in terms of fat content. These values correspond to MRLs of 25 µg/kg (expressed as the sum of the 4 isomers) for tissues with a fat content of less than 10% (muscle, liver and kidney). For cows milk MRLs have been established by the same Commission Directive, as the sum of RR and SS isomers at 20 µg/kg for cow milk and for the sum of RS and SR isomers as 20 µg/kg for cow milk. These values correspond to MRLs of 40 µg/kg (expressed as the sum of the 4 isomers) . The marker residue was defined as being the sum of the fenvalerate isomers.

The ratio of marker residue to total residues after topical treatment of cattle with fenvalerate had not been established, but in view of the small portion of the ADI and the minimal metabolism following oral administration of fenvalerate the sum of the 4 isomers were considered as an appropriate marker residue.

21. An analytical method for monitoring residues based on gas chromatography with electron capture detection is available but not validated in accordance with Volume 8 of the Rules Governing Medicinal Products in the European Union, particularly with respect to the specificity, accuracy, precision and limit of detection. The raw data concerning the validation were not available and the method has not been presented conforming to an internationally recognised format (e.g. ISO 78/2).

Conclusions and recommendation

Having considered that:

- a toxicological ADI of 12.5 µg/kg/day (i.e. 750 µg/person) was established,
- the sum of isomers of fenvalerate was identified as marker residue,
- for fenvalerate and esfenvalerate MRLs were previously established for the pesticidal use in the EU by Commission Directive 2000/42/EC,
- an analytical method for monitoring residues of fenvalerate in bovine was available, but was not validated;

The Committee for Veterinary Medicinal Products recommends the inclusion of fenvalerate in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Fenvalerate	Fenvalerate (sum of RR, SS, RS and SR isomers)	Bovine	25 µg/kg 250 µg/kg 25 µg/kg 25 µg/kg 40 µg/kg	Muscle Fat Liver Kidney Milk	Provisional MRLs expire on 1.7.2004

Based on these MRLs, it was calculated that the consumer intake of total residues from the consumption of bovine tissues would account for approximately 11,2% of the ADI mentioned above. This would allow for total residues correction and the pesticidal use.

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

LIST OF QUESTIONS

1. The applicant should provide a validated routine analytical method for monitoring purposes in accordance with the Volume 8 of the Rules Governing Medicinal Products in the European Union specially with respect to the specificity, accuracy, precision and limit of detection. Raw data of the validation should also be made available. The analytical method should be described in an internationally recognised format (e.g. ISO 78/2).