



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

15 February 2017  
EMA/CVMP/567262/2016  
Committee for Medicinal Products for Veterinary Use

## European public MRL assessment report (EPMAR) Fluralaner (poultry)

On 6 February 2017 the European Commission adopted a Regulation<sup>1</sup> establishing maximum residue limits for fluralaner in poultry, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Fluralaner is used in veterinary medicine as an ectoparasiticide in companion animals. In chickens, fluralaner is intended to be used for the treatment and control of red poultry mite infestations.

Intervet International B.V. submitted to the European Medicines Agency an application for the establishment of maximum residue limits, on 21 December 2015.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 6 October 2016 the establishment of maximum residue limits for fluralaner in poultry.

Subsequently the Commission recommended on 16 December 2016 that maximum residue limits in poultry are established. This recommendation was confirmed on 6 January 2017 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 6 February 2017.

---

<sup>1</sup> Commission Implementing Regulation (EU) No 2017/201, O.J. L 32, of 07 February 2017



# Summary of the scientific discussion for the establishment of MRLs

Substance name:	Fluralaner
Therapeutic class:	Antiparasitic agents / Agents against ectoparasites
Procedure number:	EMA/V/MRL/004380/FULL/0001
Applicant:	Intervet International B.V.
Target species requested:	Chicken
Intended therapeutic indication:	Treatment and control of red poultry mite infestations
Route(s) of administration:	Oral

## 1. Introduction

Fluralaner (carbamoyl benzamide phenyl isoxazoline) is an ectoparasiticide of the isoxazoline class which acts as an antagonist on ligand-gated chloride channels (gamma-aminobutyric acid (GABA) receptor and glutamate receptor). Fluralaner is a racemate, with an enantiomer ratio of 1.

Currently fluralaner is used in veterinary medicine as an ectoparasiticide in companion animals.

In chickens, fluralaner is intended to be used for the treatment and control of red poultry mite infestations. The substance is to be administered by two oral doses of 0.5 mg/kg bw via drinking water, seven days apart.

Fluralaner is not used in human medicine.

## 2. Scientific risk assessment

### 2.1. Safety assessment

#### 2.1.1. Overview of pharmacological properties

##### Pharmacodynamic properties including mode of action

Fluralaner is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA receptor and glutamate receptor), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes resulting in uncontrolled activity of the central nervous system and death. This mode of action is known from well-established animal ectoparasiticides.

##### Pharmacokinetic properties (mostly in laboratory animals)

In rat and dogs plasma kinetics were studied in the repeated dose oral toxicity studies; the  $C_{max}$  was reached within 2-8 hours in rats (when dosed up to 40 mg/kg bw), in dogs the  $C_{max}$  could not be determined due to the study design and it appeared that fluralaner levels were still increasing after 24 hours.

Fluralaner is highly bound to plasma proteins as observed in cats and dogs (as well as in calves, sheep and broiler chickens), i.e. approximately 100%. Liver and fat are the target tissues for fluralaner in dogs and rats (as well as in laying hens), directly followed by kidney.

Fluralaner is metabolised to many metabolites as confirmed in rats and dogs (and chickens). It is postulated that metabolism of fluralaner proceeds by hydroxylation of the dichlorophenyl ring, the dihydroisoxazole ring and/or the side chain to yield mono- and dihydroxylated metabolites. Subsequent

conjugation reactions result in the monohydroxy and dihydroxy sulphates. The metabolism also proceeds by N-dealkylation to the corresponding amide or by amide hydrolysis of the side chain to the corresponding carboxylic acid.

Comparative metabolism studies administering [<sup>14</sup>C]-fluralaner to rats, dogs and chickens demonstrate the similarity in metabolic profiles between dogs, rats and chickens. Parent compound fluralaner was the major component in all tissues in all species. All metabolites produced in target species chicken, including major metabolite, fluralaner carboxylic acid, were also found in dog tissues and confirm that the dog is an appropriate species for toxicological testing. All metabolites were also produced in rat, though the major metabolite fluralaner carboxylic acid was only detected in plasma. It is concluded that the toxicity studies performed in the rat are suitable for the evaluation of the safety of fluralaner-related tissue residues. Fluralaner accumulates and steady state of fluralaner plasma concentrations were reached after approximately 30 days in rats and about 90 days in dogs indicating a long half-life; due to the study design no actual half-lives could be calculated. It appears that fluralaner undergoes enterohepatic recirculation.

The main excretion route is faecal: up to 49% in rats and 17% in dogs over 148 hours (4 hours after the last administration when administered for 7 consecutive days). Urinary elimination was limited: up to 3.7% in rats as well as in dogs.

### **2.1.2. Calculation of pharmacological ADI, if relevant**

Mammalian GABA receptors are significantly less sensitive than arthropod GABA receptors. In addition, no evidence of neurotoxic potential has been observed in the repeated dose toxicity studies. Consequently derivation of a pharmacological ADI is not considered necessary.

### **2.1.3. Overview of toxicology**

#### *Single-dose toxicity*

An acute oral toxicity study in rats, using the test item formulated in 0.5% carboxy methylcellulose (w/v) aqueous solution containing 0.1% polysorbate 80 (v/v) revealed that fluralaner is of low acute oral toxicity (LD<sub>50</sub> higher than 2000 mg/kg bw; limit dose). No adverse effects were observed, except for slightly ruffled fur in all animals.

#### *Repeated dose toxicity*

Repeated dose oral toxicity was extensively studied in rats (including studies with durations of 28 and 90 days) and dogs (28, 90 days and 52 weeks).

In a 90-day oral toxicity study rats were given fluralaner by gavage at doses of 0, 20, 40 or 400 mg/kg bw/day. Liver effects were observed at all doses in this study (e.g. decreased phospholipid concentrations in males, decreased globulin concentrations in females, hepatocellular fatty changes in both sexes). In addition to liver effects, effects on thymus (decreased weight in males and females, atrophy) and adrenals (increased weight in females) and microscopic changes in lung (alveolar histiocytosis) and thymus (atrophy) were observed at the dose of 400 mg/kg bw/day. No NOEL could be established from this study, though the effects were considered mild at the lower doses.

In a second 90-day oral toxicity study rats were given fluralaner by gavage at doses of 0, 2, 4 or 8 mg/kg bw/day. No effects were observed in this study. A NOEL of 8 mg/kg bw/day was derived from this study.

The 28-day oral toxicity study in rat, with fluralaner administered at doses of 0, 30, 60 and 600 mg/kg bw, confirmed the effects on liver, thymus and adrenals. Hepatocellular fatty change was observed at all

doses, though considered mild at the lower doses. Decreased thymus and increased adrenal weights were observed at the highest dose.

In a 90-day oral toxicity study dogs were given fluralaner by capsule at doses of 0, 2, 4 and 8 mg/kg bw/day. Reductions in cholesterol and phospholipids were observed at 4 and 8 mg/kg bw/day in both males and females. In addition, reduction of triglyceride concentrations were observed at 4 and 8 mg/kg bw/day in males. The NOEL was established at 2 mg/kg bw/day.

As dogs were considered the most sensitive species based on the repeated dose toxicity studies, a 52-week oral toxicity (by capsule) study was performed in dogs, administering fluralaner at a dose of 0, 1, 2, or 4 mg/kg bw/day. Reductions in cholesterol and phospholipids were observed in males at 2 and 4 mg/kg bw/day, and in females at 4 mg/kg bw/day. Reduction of triglyceride concentrations was observed at 2 mg/kg bw/day in males and in females at 4 mg/kg bw/day. The NOEL was established at 1 mg/kg bw/day.

In addition to the 90-day dog studies, two 4-week toxicity studies in dogs were provided with respective oral dose (by capsule) levels of 0, 100, 250, 750 mg/kg bw/day and 0, 20, 40, 100 mg/kg bw/day. The 4-week toxicity studies were considered supportive of the pivotal 90-day and 52-week studies. In both studies reductions in cholesterol and phospholipid levels were observed. In addition, vacuolation in the adrenal cortex and changes in organ weights of the thymus, prostate and liver were observed. Also interstitial inflammation in lungs was observed (4 out of 8 animals when dosed 750 mg/kg bw/day). No NOELs could be derived from these studies due to effects observed at all dose levels.

#### *Reproductive toxicity, including developmental toxicity*

Reproductive toxicity, including developmental toxicity has been studied in a one-generation toxicity study in rat, a two-generation toxicity study in rat and three developmental toxicity studies, one in rat and two in rabbit.

In the one-generation study rats were given fluralaner at dose levels of 0, 50, 100 or 500 mg/kg bw/day. Liver, thymus, lung and adrenals were affected in parents at the lowest dose of 50 mg/kg bw/day, resulting in a LOAEL of 50 mg/kg bw/day. The effects are consistent with the adverse effects observed in the repeated dose studies. The reproduction toxicity NOEL can be set at 100 mg/kg bw/day, based on reduced litter size due to reduced implantation rate and increased post-implantation loss at the higher dose of 500 mg/kg bw/day. No NOAEL for effects on pups could be determined from the data. Statistically significant reductions in thymus weight, and lymphoid atrophy in the thymus were observed in pups at all doses (including at the lowest dose of 50 mg/kg bw/day), showing a clear dose response.

In the two-generation study rats were given fluralaner at dose levels of 0, 8, 50 or 500 mg/kg bw/day. In the P and/or F1 generation, peribronchial inflammatory lesions in the lungs and increased hypertrophy of the adrenal cortex and atrophy/involution of the thymus were observed at all dose levels, resulting in a LOAEL of 8 mg/kg bw/day for parental toxicity, though the effects are considered marginal at the lowest dose. The reproduction toxicity NOEL was set at 50 mg/kg bw/day, based on post-implantation, post-natal and breeding loss at the higher dose of 500 mg/kg bw/day. The NOEL for effects on pups was set at 50 mg/kg bw per day based on reduced body weight, clinical signs, pathological findings, and delayed physical and sexual development at 500 mg/kg bw per day.

Developmental toxicity was studied in the rat at fluralaner doses (oral gavage) of 0, 100, 300 or 1000 mg/kg bw/day. Food consumption was significantly reduced in the two higher dose groups; in the highest dose group, body weight and body weight gain were also reduced. In the foetuses of rats in the two highest dose groups, a higher incidence of dilated renal pelvis/ureter and supernumerary ribs were observed at both foetus and litter level. The NOEL for maternal and foetal toxicity was 100 mg/kg bw/day.

Developmental toxicity was studied in rabbit at fluralaner doses (oral gavage) of 0, 50, 250 or 1000 mg/kg bw/day. The NOAEL for maternal toxicity was 50 mg/kg bw/day, based on reduction in food consumption at 250 mg/kg bw/day. No NOAEL for foetal toxicity could be established. The LOAEL was 50 mg/kg bw per day based on embryo-foetal developmental effects observed at the lowest dose of 50 mg/kg bw/day. An additional prenatal developmental toxicity using lower oral doses of 10, 25 and 250 mg/kg bw/day was therefore conducted. Fatty changes of the liver and the related changes in blood biochemistry were observed at all doses in dams, although were considered mild at the lowest dose level. A developmental toxicity NOAEL was set to 10 mg/kg bw/day based on the increase in fusions in cervical vertebra 2 at 25 mg/kg bw/day.

#### *Genotoxicity*

The potential mutagenic effects of fluralaner have been investigated in three *in vitro* tests (Ames-test, mouse lymphoma thymidine kinase locus assay, chromosomal aberration test in human lymphocytes *in vitro*) and one *in vivo* test (micronucleus assay in bone marrow cells of the mouse) of genotoxicity. The results of all four tests were negative. Based on these data it was concluded that fluralaner does not have mutagenic potential.

#### *Carcinogenicity*

Carcinogenicity studies were not conducted. This is justified by the negative results in all genotoxicity tests and the absence of pre-neoplastic lesions in the oral (sub-)chronic repeated dose toxicity studies. There is no evidence for a carcinogenic potential of fluralaner.

#### *Studies of other effects including immunotoxicity and neurotoxicity*

Thymus atrophy was observed in several studies, but was mostly associated with high doses and/or not accompanied by significant or consistent adverse effects on other organs of the immune system or haematology. The repeated dose toxicity studies were considered sufficient to cover potential effects on the immune system. No effects on the nervous system have been reported in the provided toxicity tests. Absence of additional neurotoxicity studies is therefore justified.

### **2.1.4. Calculation of the toxicological ADI or alternative limit**

Using the overall NOAEL of 1 mg/kg bw/day, based on effects in the 52-week study in dogs (reductions in cholesterol, phospholipids and triglycerides observed at 2 mg/kg bw/day), and applying an uncertainty factor of 100, an ADI of 10 µg/kg bw was established, equivalent to 600 µg/person.

### **2.1.5. Overview of microbiological properties of residues**

Antibacterial activity of fluralaner has been tested against 100 bacterial strains representing the normal human gut flora. Fluralaner did not exert clear antimicrobial activity against the gut flora.

### **2.1.6. Calculation of microbiological ADI**

The establishment of a microbiological ADI is not considered necessary as the substance has no antimicrobial activity.

### **2.1.7. Observations in humans**

No data on effects of fluralaner in humans were available for review.

### 2.1.8. Findings of EU or international scientific bodies

No relevant evaluations by EU or international scientific bodies were identified.

### 2.1.9. Overall conclusions on the ADI

Neither a pharmacological or a microbiological ADI are considered necessary for fluralaner. The toxicological ADI of 10 µg/kg bw is established as the overall ADI.

## 2.2. Residues assessment

### 2.2.1. Pharmacokinetics in target species

Fluralaner is well absorbed in laying hens, with an oral bioavailability of 91% (after oral gavage). When fluralaner was administered via the drinking water at a dose rate of 0.5 mg/kg bw to laying hens, repeated after 7 days, the  $C_{max}$  was 323.7 ng/ml (at  $t_{max}$  36 hours) and 355.1 ng/ml (at  $t_{max}$  12 hours) respectively after first and second administration. The AUC was calculated to be 1297 ng.day/ml after the first administration (from time 0 to day 7) and 2388 ng.day/ml after the second administration (from day 7 to infinity), indicating accumulation of fluralaner. When administered at a single oral dose of 0.25, 0.5 and 1 mg fluralaner/kg bw, it was demonstrated that the  $C_{max}$  (respectively 326.2, 599.7 and 1301.6 ng/ml) and  $AUC_{inf}$  (1317.5, 2249.9 and 4581.7 ng.day/ml) were proportional to the applied dose. R- and S-enantiomers of fluralaner were shown to display similar pharmacokinetic profiles. The plasma half-life of fluralaner in chickens, determined after intravenous administration was about 5 days.

A radiolabelled residue study administering [ $^{14}C$ ]-fluralaner at two single doses of 0.5 mg fluralaner/kg bw, 7 days apart by oral gavage demonstrated that a large portion of the total dose is excreted via eggs, i.e. a mean of 28.8% of total dose. Excreta were not collected, though fluralaner and/or metabolites were measured at high concentrations in bile (mean of 15140 - 4690.30 µg equivalents/kg at 24 - 168 hours after administration).

Highest concentrations of total radioactive residues (TRR) in tissues were observed in liver followed by skin and fat, kidneys and muscle. Mean TRR levels in liver were 1479 µg equivalents/kg at 12 hours after the last administration decreasing to 337 µg equivalents/kg at 168 hours after the last administration. Mean TRR levels in kidney were 1091 µg equivalents/kg at 12 hours after the last administration decreasing to 248 µg equivalents/kg at 168 hours after the last administration. Mean TRR levels in muscle were 211 µg equivalents/kg decreasing to 48 µg equivalents/kg at 168 hours after the last administration. Mean TRR levels in skin and fat were 1118 µg equivalents/kg at 12 hours after the last administration decreasing to 319 µg equivalents/kg at 168 hours after the last administration. The major component detected in all tissues was fluralaner. Fluralaner concentrations were additionally measured by LC-MS/MS in this study.

In eggs, the TRR concentrations increased following the first dose administration, reaching a maximum (average) of 737.31 µg fluralaner equivalents/kg on day 7. The TRR concentrations then decreased before increasing to a (average) maximum of 939.80 µg fluralaner equivalents/kg on day 13. From day 13, TRR concentrations decreased down to a minimum of 200.52 µg fluralaner equivalents/kg on day 22. The major component detected in whole eggs was fluralaner. Fluralaner concentrations were additionally measured by LC-MS/MS.

Only one major metabolite was identified in chicken, i.e. carboxylic acid of fluralaner, being present in kidney at a level of 10.7% and 10.2% TRR (corresponding to 74 and 25 µg equivalents/kg respectively) at the slaughter time points of 48 hours and 168 hours.

The radiolabelled study in laying hens was adequately performed. Tissues were combusted to  $^{14}\text{CO}_2$ , absorbed in Carbosorb and analysed by Liquid Scintillation Counting. Combustion efficiency was within the range 97-103%.

### **2.2.2. Residue depletion studies**

A residue depletion study was performed in laying hens with the test item administered at the recommended dose (two single doses of 0.5 mg fluralaner/kg bw, 7 days apart) and by the recommended administration route (orally, in drinking water). The study demonstrated that egg fluralaner concentration increased over 7 days, reaching a maximum mean level of 610.3 µg/kg on day 7 (144-168 hours after the first administration). Then levels decreased slightly before increasing again to a maximum mean egg fluralaner concentration of 828.4 µg/kg on day 14 (144-168 hours after the second administration). Thirteen days after the last treatment fluralaner concentrations were below the lower limit of quantification in all collected eggs. This observation period after the last treatment covered the complete egg yolk development period.

In a residue depletion study in laying hens the test item was administered at the recommended dose (two single doses of 0.5 mg fluralaner/kg bw, 7 days apart) and by the recommended administration route (orally, in drinking water). Animals were slaughtered and tissues collected at 2, 4, 7 and 10 days following the second administration. The highest concentrations of fluralaner were observed 1 day after the last administration of the product with highest mean residue levels observed in liver (1301.1 µg/kg) and skin and fat (1275.8 µg/kg), followed by kidney (841.2 µg/kg). Lower amounts were found in muscle (108.2 µg/kg). The residues depleted in all tissues at a comparable rate.

#### **Selection of marker residue and ratio of marker to total residues**

In the radiolabelled residue study described above the parent compound, fluralaner, was the major residue present in all tissues and eggs. Therefore, fluralaner is considered to be an appropriate marker residue.

In tissues, the ratios of marker to total residues were rather constant over the different withdrawal periods (day 1, 2, 4 and 7). Average ratios of marker to total residue of 76.5% for muscle, 71.2% for liver, 65.9% for kidney and 78.5% for skin and fat were calculated. In eggs, the mean ratios of marker to total residues at different time points (day 3 up to day 17 after first administration) were within the same range: 74.6 to 86.8% (for time points from day 3 up to and including day 17); an average marker to total residues ratio of 80% was calculated for eggs.

### **2.2.3. Monitoring or exposure data**

No monitoring or exposure data were available.

### **2.2.4. Analytical method for monitoring of residues**

Two analytical LC-MS/MS methods have been developed and validated for the determination of fluralaner, one for chicken tissues and one for eggs. The methods are presented in an internationally recognized format and have been validated in line with the current requirements of Volume 8 of The Rules Governing Medicinal Products in the European Union.

Residues are detected using mass spectrometry which is specific with regard to possible interferences of tissue matrix or interferences of other commonly used veterinary drugs.

The data showed that the methods are acceptable for the determination of fluralaner in chicken tissues in the range of 20 – 160 µg/kg (kidney), 30 – 280 µg/kg (liver), 5 – 40 µg/kg (muscle), 40 – 360 µg/kg (skin

and fat) and in chicken eggs in the range of 400 – 2400 µg/kg. Dilution of samples by up to 4 fold is acceptable for muscle, skin and fat and egg samples; for liver and kidney samples dilution by up to 8 fold is acceptable.

Practicability and applicability under normal laboratory conditions was adequately demonstrated. It was noted that the routine analytical method includes an in-house internal standard (D4-fluralaner), which is available upon request.

The relevant European Reference laboratory has reviewed the proposed analytical methods and pointed out that for tissues the validation was not performed over a concentration range around the proposed MRL levels. However the CVMP considered that with the inclusion of the dilution step the relevant range is adequately covered.

### 2.2.5. Findings of EU or international scientific bodies

No relevant evaluations by EU or international scientific bodies were identified.

## 3. Risk management considerations

### 3.1. Potential effects on the microorganisms used for industrial food processing

The substance is not intended for use in animals producing milk for human consumption and therefore potential effects in dairy products were not investigated.

### 3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No relevant factors were identified for consideration of the risk management recommendations.

### 3.3. Elaboration of MRLs

Based on the tissue distribution of the marker residue fluralaner, and the ratios of marker to total residues, the following MRLs have been calculated:

Muscle:	65 µg/kg
Skin and fat:	650 µg/kg
Liver:	650 µg/kg
Kidney:	420 µg/kg
Eggs:	1300 µg/kg

#### Detailed calculation of theoretical daily intake of residues

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Muscle	0.30	65	0.765	25.5
Fat #	0.09	650	0.785	74.5



Edible tissue or products	Daily consumption (kg)	MRL proposal ( $\mu\text{g}/\text{kg}$ )	Ratio of the marker/total residue	Amount per edible tissue or product ( $\mu\text{g}$ )
Liver	0.10	650	0.712	91.3
Kidney	0.01	420	0.659	6.4
Eggs	0.10	1300	0.800	162.5

# skin and fat in natural proportions

Maximum theoretical daily intake: 360.2 $\mu\text{g}$

Based on the acceptable daily intake (ADI) of 600  $\mu\text{g}$  fluralaner/person/day and the MRL values proposed, the total theoretical daily intake represents 60% of the ADI.

This leaves part of the ADI available for other food commodities such as milk.

Fluralaner is not used in plant protection products nor in biocide products and consequently no consideration of intake of residues from these sources is necessary.

### 3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009, the CVMP considered the possibility of extrapolating the maximum residue limits recommended for fluralaner on the basis of residue data in chickens to other food producing species. Taking into account the current scientific knowledge, the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	Extrapolation possible (Yes/No)	Justification
Poultry species other than chickens (including eggs)	Yes	As the marker residue is the parent compound in chicken tissues and eggs, it is probable that it would also be present in tissues and eggs from other poultry species.  Although it was not specifically demonstrated, the analytical method for monitoring of residues in chicken tissues and eggs is expected to be basically applicable for monitoring of residues in tissues and eggs of other poultry species.
Cattle (including milk)	No	No pharmacokinetic or residue depletion data were available for cattle. As cattle meat and milk is consumed on a regular basis and in large quantities across the EU, and as metabolism can be significantly different in cattle compared to chicken species specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues.  No analytical method for monitoring of residues in cattle tissues and milk was available for evaluation.
Sheep (including milk)	No	No pharmacokinetic or residue depletion data were available for sheep. As sheep meat is consumed on a regular basis and in large quantities across the EU, and as metabolism can be significantly different in sheep compared to chicken, species specific data are considered necessary in order to quantify the possible impact on

		<p>consumer safety of exposure to residues.</p> <p>No analytical method for monitoring of residues in sheep tissues and milk was available for evaluation.</p>
Goats (including milk)	No	<p>No pharmacokinetic or residue depletion data were available for goats. Metabolism can be significantly different in goats compared to chicken. Consequently species specific metabolism and residue data are needed in order to draw conclusions on safe MRL levels.</p> <p>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in goats tissues or milk.</p>
Pigs	No	<p>No pharmacokinetic or residue depletion data were available for pigs. As pigs meat is consumed on a regular basis and in large quantities across the EU, and as metabolism can be significantly different in pigs compared to chicken, specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues.</p> <p>No analytical method for monitoring of residues in pig tissues was available for evaluation.</p>
Horses (including milk)	No	<p>No pharmacokinetic or residue depletion data were available for horses. Metabolism can be significantly different in horses compared to in chicken. Consequently, species specific metabolism and residue data are needed in order to draw conclusions on safe MRL levels.</p> <p>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in horses tissues.</p>
Rabbits	No	<p>No pharmacokinetic or residue depletion data were available for rabbits. Metabolism can be significantly different in rabbits compared to in chicken. Consequently, species specific metabolism and residue data are needed in order to draw conclusions on safe MRL levels.</p> <p>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in rabbits tissues.</p>
Fin fish	No	<p>Metabolism in fin fish is generally less complicated than in chickens. Consequently, since the parent compound is the marker residue in chicken it can be assumed that the parent compound would also be the suitable marker residue in fish meat. However, no analytical method for monitoring of residues in fin fish was available for evaluation.</p>
Honey	No	<p>Residue depletion in honey does not occur through metabolism and therefore conclusions drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in</p>

		honey. No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in honey.
--	--	---

### 3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- a toxicological ADI of 10 µg/kg bw (i.e. 600 µg/person) was derived,
- fluralaner was retained as the marker residue in tissues as well as eggs,
- the ratios of marker to total residues were relatively constant over the time period of residue depletion and were determined to be 76.5% in muscle, 78.5% in skin and fat, 71.2% in liver, 65.9% in kidney and 80.0% in eggs,
- highest residue levels were observed in liver and skin and fat, followed by kidney. Lower amounts were found in muscle,
- extrapolation of the maximum residue limits recommended for chickens to poultry is considered appropriate,
- a validated analytical method for the monitoring of residues of fluralaner in edible chicken tissues (liver, kidney, muscle, and skin and fat) and eggs is available,
- although it was not specifically demonstrated, the analytical method for monitoring of residues in chicken tissues is expected to be basically applicable for monitoring of residues in poultry tissues;

the Committee recommends the establishment of maximum residue limits for fluralaner in chicken tissue and eggs. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, the conclusions can be extrapolated to other poultry species, in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Fluralaner	Fluralaner	Poultry	65 µg/kg 650 µg/kg  650 µg/kg 420 µg/kg 1300 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney Eggs	NO ENTRY	Antiparasitic agents / Agents against ectoparasites

Based on the acceptable daily intake (ADI) of 600 µg fluralaner/person/day and the MRL values, the total theoretical daily intake represents 60% of the ADI.

## 4. Background information on the procedure

Submission of the dossier:

21 December 2015

Steps taken for assessment of the substance

Application validated:	20 January 2016
Clock started:	21 January 2016
List of questions adopted:	19 May 2016
Consolidated response to list of questions submitted:	8 July 2016
Clock restarted:	11 July 2016
CVMP opinion adopted:	6 October 2016