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

EMEA/CVMP/512/01-FINAL

ANNEX I

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

Recommendations of the CVMP in preparation of Community Comments on Codex Alimentarius MRLs for Veterinary Drugs

Follow-up of 12th CCRVDF meeting: Objections of the European Community to proposed CCRVDF/JECFA MRLs

At the 12th CCRVDF meeting the European Community objected to the draft CCRVDF MRLs for cyfluthrin, deltamethrin, eprinomectin and flumequine. The meeting requested the European Community to provide further scientific justification. Below are the conclusions of the CVMP following the re-consideration of these substances.

1. CYFLUTHRIN

1.1 Background

Comparison EU (CVMP)/draft CCRVDF (JECFA/JMPR) MRLs:

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	3 µg/kg bw	Cyfluthrin	Bovine	10 µg/kg	50 µg/kg	10 µg/kg	10 µg/kg	20 µg/kg
Draft CCRVDF (JECFA/ JMPR)	20 µg/kg bw	Cyfluthrin	Bovine	20 µg/kg	200µg/kg	20µg/kg	20 µg/kg	40 µg/kg

1.2 Consideration by the CVMP

Comments on assessments of CVMP and JECFA/JMPR:
An ADI of 3 µg/kg bw was established by the **CVMP** based on the NOEL of 0.3 mg/kg bw for the prolongation of barbiturate sleeping time in mice and a safety factor of 100. The marker residue has been set as the sum of the 4-cyfluthrin diasteromers. Tissue distribution of cyfluthrin has been taken into account with fat being the major target tissue.

The proposed Codex MRLs are based on the ADI established by the **JMPR** for the pesticidal use of the substance. The ADI of 20 µg/kg bw is based on the NOEL of 2 mg/kg bw/day derived from a 2-year oral toxicity study in rats using a safety factor of 100.

CVMP position:
The CVMP has concerns regarding the ADI and the MRLs proposed. It is recommended that JECFA/JMPR should review the ADI and proposed MRLs in the light of the comments below.

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The study chosen as pivotal study for the determination of the ADI does not appear appropriate:

- The NOEL derived from the rat study cannot be recognised. In this study rats were exposed to 0, 50, 150 and 450 mg cyfluthrin/kg feed (equal to 0, 2, 8 and 25 mg/kg bw in females and 0, 2, 6, 19 mg/kg bw in males). Data show that the 2 high dose levels resulted in dose-dependent weight gain retardation, but at all dose levels various haematological parameters were changed (e.g. serum glucose levels and haemoglobin concentrations).
- There is evidence from pharmacological data and recent acute neurotoxicity investigations that specific effects of cyfluthrin or ß-cyfluthrin may occur at lower doses, especially when vehicles mimicking fat/water emulsions are used. Thus, the pharmacodynamic effects of cyfluthrin (2% cremophor) include prolongation of barbiturate sleeping time in mice (0.1/0.3/1.0 mg/kg bw) at a dose of 1 mg/kg bw (NOEL 0.3 mg/kg bw. Neurotoxicity investigations revealed effects on locomotor activity at single doses via gavage and cremophor (LOEL of 0.5 mg/kg bw).

However, considering that cyfluthrin is currently at step 4, it is proposed that at this time point the European Community does not oppose the advancing of proposed Codex MRLs. Instead, it is proposed that the concerns would be presented to Codex, and that JECFA/JMPR be asked to review their evaluation, and to comment on the concerns expressed and questions raised. It is proposed that the EU should state that they would object to the advancing of the proposed Codex MRLs to step 8, unless their comments would have been considered and satisfactorily addressed.

2. DELTAMETHRIN

2.1 Background

Comparison EU (CVMP)/Draft CCRVDF(JECFA/JMPR) MRLs:

	ADI	TARGET SPECIES	MARKER RESIDUE	MRLs (µg/kg)					
				Muscle	Fat	Liver	Kidney	Milk	Eggs
EU (CVMP)	10 µg/kg bw	Bovine	Deltamethrin	10*	50*	10*	10*	20*	N/A
		Ovine	"	10*	50*	10*	10*	none	N/A
		Chicken	"	10*	50*	10*	10*	N/A	50*
		Fin fish	"	10*					
Draft CCRVDF (JECFA/ JMPR)	10 µg/kg bw	Bovine	Deltamethrin	30#	500	50	50	30#	N/A
		Ovine	"	30#	500	50	50	none	N/A
		Chicken	"	30#	500	50	50	N/A	30#
		Salmon	"	30#					

* Provisional MRLs due to questions on the analytical method.

\# Guidance values at twice the limit of quantification; no residues were measured.

2.2 Consideration by the CVMP

Comments on assessments CVMP and JECFA/JMPR:

While both the **CVMP** and the **JECFA** adopted an ADI of 10 µg/kg bw based on a NOEL of 1 mg/kg bw from long term studies in rats, mice and dogs, the two committees came to different conclusions on setting MRLs for deltamethrin. These appear to have been complicated in both cases by the requirement of both to take into account pre-existing determinations by their respective counterparts involved in assessment of plant protection products, rather than fundamental scientific arguments.

In 1990 the **JMPR** established MRLs for deltamethrin as a pesticide, taking into account use as a veterinary drug: 500 µg/kg in meat (fat), 50 µg/kg in offal and 20 µg/kg in milk. The target species were not specified. The **JECFA** took account of these MRLs and recommended the same MRLs for liver, kidney and fat. The JECFA noted that the concentrations of residues in muscle, milk and eggs were less than twice the limit of quantification of the analytical methods used and therefore recommended MRLs based on the sensitivity of the methods. These 'guidance MRLs' were 30 µg/kg for muscle in cattle, sheep, chickens and salmon and for cows' milk and chickens' eggs, expressed as parent drug. These "guidance MRLs" should not be used in determining the TMDI.

In 1999 the **CVMP** established MRLs for deltamethrin in animal tissues taking into account those already fixed for pesticidal use by Council Directive 98/82/EC of 50 µg/kg for fat and eggs (the lower limit of determination). Provisional MRLs of 10 µg/kg muscle, liver and kidney, and 20 µg/kg for bovine milk were determined based on the current LOQ of 5 µg/kg.

The CVMP MRL values represent a TMDI of about 8% of the ADI, compared to 72% from pesticidal use.

As stated above, the principal problem in the differences between the MRLs set by JECFA and CVMP result from the procedural requirement of both to take into account previous pesticidal assessments.

One point of confusion noted was that the JMPR MRLs were based on the sum of 3 isomers, cis-deltamethrin, trans-deltamethrin and alpha-3-deltamethrin as the marker residue. This approach was also originally adopted by the JECFA but was not followed by the CVMP, as deltamethrin (cis-deltamethrin) is the only substance present in edible tissues. The JECFA subsequently decided to use deltamethrin as marker residue, but do not appear to have altered the MRLs to take this change into account.

Based on the CVMP estimate for intake from pesticidal use, and marker: total residue data from JMPR, the TMDI of deltamethrin equivalents using the MRLs for liver, kidney and fat will amount to 80% using the EU MRLs and 114% using the JECFA values (see table below).

Tissue	**Intake (kg)**	**Marker: Total Ratio**	**CVMP**		**JECFA**	
			MRL	**Residue**	**MRL**	**Residue**
Liver	0.1	0.04	10	25	50	125
Fat	0.05	0.6	50	4.2	500	42
Kidney	0.05	0.03	10	17	50	83
Total Veterinary Intake				46.2		250
Pesticide Intake (72% ADI)				432		432
TMDI (% ADI)				478.2 (80%)		682 (114%)

CVMP position:

The CVMP has concerns regarding the estimated daily intake of deltamethrin residues, which would result in the ADI be exceeded. However, considering that deltamethrin is currently at step 4, it is proposed that at this time point the EU does not oppose the advancing of proposed Codex MRLs. Instead, it is proposed that the concerns would be presented to Codex, and that JECFA/JMPR be asked to review their evaluation, and to comment on the concerns expressed and questions raised. It is proposed that the European Community should state that they would object to the advancing of the proposed Codex MRLs to step 8, unless their comments would have been considered and satisfactorily addressed.

3. EPRINOMECTIN

3.1 Background

Comparison EU (CVMP)/draft CCRVDF (JECFA) MRLs :

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	5 µg/kg bw	Eprinomectin B1a	Bovine	50 µg/kg	250 µg/kg	1500 µg/kg	300 µg/kg	20 µg/kg
Draft CCRVDF (JECFA)	10 µg/kg bw	Eprinomectin B1a	Bovine	100 µg/kg	250 µg/kg	2000µg/kg	300 µg/kg	20 µg/kg

CVMP position:
Having re-considered the assessemnt of the JECFA, it can be concluded that the draft CCRVDF (JECFA) MRLs do virtually provide the same degree of consumer safety as the EU/CVMP MRLs. Therefore, the CVMP recommends to support the draft CCRVDF MRLs.

Detailed scientific explanations can be provided, if requested

4. FLUMEQUINE

4.1 Background

Comparison EU (CVMP)/draft CCRVDF (JECFA) MRLs:

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EU (CVMP)	8.25 µg/kg bw (microbiological)	Flumequine	Bovine	200 µg/kg	300 µg/kg	500 µg/kg	1500 µg/kg	50 µg/kg
			Ovine, porcine,	200 µg/kg	300 µg/kg	500 µg/kg	1500 µg/kg	None, N/A
			Chicken	400 µg/kg	250 µg/kg	800 µg/kg	1000 µg/kg	N/A
			Turkey	400 µg/kg	250 µg/kg	800 µg/kg	1000 µg/kg	N/A
			Trout	600µg/kg[1]				N/A
Draft CCRVDF (JECFA)	0-30 µg/kg bw (toxicological)	Flumequine	Bovine, ovine, porcine, chicken	500µg/kg	1000µg/kg	500µg/kg	3000µg/kg	None
			Trout	500µg/kg[1]				N/A

[1]muscle/skin in natural proportions

4.2 Consideration by the CVMP

Comments on assessments of CVMP and JECFA:

ADI:

The **CVMP** established a microbiological ADI of 8.25 µg/kg bw based on the lowest MIC_{50} (0.33 µg/ml) for the most sensitive predominant micro-organism (*E. coli*). This microbiological ADI, being lower than the toxicological one, was adopted for the calculation of MRLs.

The **JECFA** established a higher microbiological ADI for flumequine based on the MIC_{50} of the most predominant species in human gut flora, i.e. *Fusobacterium*. In this case the toxicological ADI (rounded up to 30 µg/kg bw) led to a lower ADI and was therefore adopted by the JECFA for the calculation of MRLs. It is also noted that JECFA MRLs do not follow the residue distribution.

Further information intended to substantiate the concerns by the European Community:

The ADI proposed as basis for the establishment of CCRVDF MRLs is a toxicological ADI, based on the NOEL of 25 mg/kg bw/day for hepatotoxicity in a 3-month study in mice and a safety factor of 1000. This high safety factor was chosen to reflect the short duration of the study and the lack of histo-chemical characterisation of the foci of altered hepatocytes.. However, for this compound the most sensitive parameter to be considered should be the microbiological effects. Using the lowest MIC_{50} (0.33 µg/ml) for the most sensitive predominant micro-organism (*E. coli*) a microbiological ADI of 8.25 µg/kg bw can be calculated. This ADI is lower than the toxicological one proposed and should, therefore, be retained as the basis for the establishment of the MRLs. The difference reported for the microbiological ADI established by the CVMP and the JECFA is due to a different MIC_{50} and to the value given to the daily faecal bolus (150 ml versus 220 ml) (see paragraph 13, CVMP Summary Report, EMEA/MRL/624/99-FINAL, July 1999).

Taking into account the ratio of marker to total residues, which differs in the different animal species, and the residues in milk, the microbiological ADI would be exceeded by different amounts in different species which cannot be accepted. This comment does not apply for the MRL for trout.

Furthermore, it should be noted that the approach to establish microbiological ADIs is currently under review in the EU, which is likely to influence the assessment in another review of the substance in the future. In addition the ongoing harmonisation activities, particularly within the VICH process, will influence the assessment of microbiological safety.

CVMP position:
The differences between CVMP MRLs and JECFA MRLs are mainly due to the difference in the ADI established, particularly being the difference in the assessment of the microbiological effects. The use of JECFA MRLs would mean that 96% of the ADI of 8.25 µg/kg bw is used in the case of cattle and chicken and it is not possible to establish an MRL for cow's milk anymore. Furthermore, the use of JECFA MRLs for pigs would lead to exceeding the microbiological ADI with 24%.

Therefore, the CVMP recommended continuing not to support the draft CCRVDF (JECFA) MRLs, with the exception of the MRL for trout. The draft CCRVDF MRL for trout is considered acceptable.