European Community Comments for the

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Washington, D.C., 28 - 31 March 2000

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Consideration of maximum residue limits at steps 6 (7)

This document compares the residue evaluations of JECFA and the European Community, if possible. Shading highlights differences. If necessary comments are made on the substance or the reasoning for the differences in the evaluation. Finally, the position of The European Community on the substance is summarised.

The following abbreviations are used:

EC	=	European Community
CVMP	=	Scientific Committee for Veterinary Medicinal Products of the EU
JECFA	=	Joint FAO/WHO Expert Committee on Food Additives
ADI	=	acceptable daily intake
MRL	=	maximum residue limit
bw	=	body weight
LOQ	=	Limit of quantification
VICH	=	Veterinary International Committee for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals

General Remark:

It has to be emphasised that yet again final report of the proceeding JECFA Meeting (51st session) is again not available before comments on the MRL adopted in this session are to be made. This fact alone should prevent consideration of the proposed MRLs at this time. Consequently only if the results of the EU evaluation and the JECFA evaluation are somewhat similar, it would be considered that the evaluation is based on similar data.

Comments on individual substances

The comments on the individual substances below presents a comparison of the European Community MRLs with the Codex/JECFA MRLs (differences are highlighted with shadows in the tables) and the European Community position on the Codex proposal.

1. Chlortetracycline, oxytetracycline and tetracycline

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs (muscle)
EC	3 µg/kg bw	Sum of parent drug and its 4-epimer	All food producing species	100 µg/kg
Codex	0-30 µg/kg bw	Parent drugs, singly or in combination	Fish	200 µg/kg[1,2]

[1] applies to oxytetracycline only
[2] Penaeus monodon

CVMP and JECFA established microbiological ADIs based on the same NOEL (2mg/kg bw) for selection of resistant *Enterobacteriaceae* in humans *in vivo.*

EUROPEAN COMMUNITY
The ADI was established by applying a safety factor of 10 to the NOEL. This safety factor is considered necessary as microbiological *in vivo* studies, particularly in humans, are still in a development stage and generally not validated.
This approach was also previously followed by JECFA.

The marker residue defined in the European Community includes the 4-epimer of the tetracyclines. This epimer is formed in varying amounts during sample treatment. The epimer is microbiologically active, probably by re-conversion to the respective tetracycline. Therefore, residue analysis lacking consideration of the epimer fail to lack to measure the true tetracycline concentration in tissues.

Codex
JECFA re-evaluated oxytetracycline, tetracycline and chlortetracycline and established an ADI of 0-30 µg/kg bw without applying a safety factor. JECFA considered the selection of resistant Enterobacteriaceae as a very sensitive endpoint for evaluation the microbiological effect of tetracyclines on the human intestinal microflora and individuals would show little variation with respect to this effect. As a consequence JECFA proposed higher MRLs.

POSITION:

The establishment of the ADI without applying a safety factor cannot be supported on the reasons given above.

The European Community does not support the JECFA/Codex MRLs.

2. Cyfluthrin

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EC	1 µg/kg bw	Cyfluthrin	Bovine	10 µg/kg	50 µg/kg	10 µg/kg	10 µg/kg	20 µg/kg
Codex	0-20 µg/kg bw	Cyfluthrin	Bovine	20 µg/kg	200µg/kg	20µg/kg	20 µg/kg	40 µg/kg

Cyfluthrin is used both as veterinary medicinal product and as pesticide.

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A provisional ADI of 1µg/kg (0.001 mg/kg bw, i.e. 0.06 mg/person) was established by CVMP, based on the NOEL of 0.01 mg/kg bw of the inclined plane test in rats using a safety factor of 10. The safety factor of 10 was considered sufficient, as the NOEL is based on the most sensitive pharmacological endpoint available in a vehicle (cremophor), which may enhance the toxicity of cyfluthrin above expected levels for humans.

The MRLs set in the European Community are provisional and will be reviewed further to the receipt of additional studies.
Furthermore, the European Community MRLs for the veterinary product are linked to the European Community MRLs previously established in 1994 for the use of the substance as pesticide. Therefore on reasons of surveillance the same MRLs for the use as veterinary medicinal products as for the pesticidal use have to be set.

Codex
The proposed Codex MRLs are based on ADI established by JMPR for the pesticidal use of the substance. The ADI of 20 µg/kg bw (0.02 mg/kg bw i.e. 1.2 mg/person) 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.

POSITION:

The European Community does not support the JECFA/Codex MRLs.

Cyfluthrin should be referred to the CCPR/CCRVDF WP on dual use substances.

3. Danofloxacin

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EC	0-24 µg/kg bw	Danofloxacin	Bovine, chicken	200µg/kg	100µg/kg[1]	400µg/kg	400µg/kg	30µg/kg
			Porcine	100µg/kg	50µg/kg	200µg/kg	200µg/kg	
Codex	0-20 µg/kg bw	Danofloxacin	Bovine, chicken	200µg/kg	100µg/kg[1]	400µg/kg	400µg/kg	--
			Porcine	100µg/kg	100µg/kg	50µg/kg	200µg/kg	

[1]fat+skin for chicken

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The toxicological ADI set by the CVMP is based on the NOEL of 2.4 mg/kg bw/day for arthropathy observed in a 3-month repeated-dose study in immature dogs and applying a safety factor of 100.

The European Community MRLs for bovine and chicken are identical to the ones set by JECFA. The European Community MRLs proposed for pigs differ from those proposed by JECFA, due to the difference in the consideration of tissue residue distribution.

Codex

The toxicological ADI established by JECFA was based on the same NOEL and applying the same safety factor, but it was rounded down to 20 µg/kg bw.

The MRLs for pigs do not reflect the tissue residue distribution.

POSITION:

The differences in the ADI are not significant and the differences in the porcine MRLs are not major considering that only 30% of the ADI is used.
The European Community may support the JECFA/Codex MRLs for bovine, chicken and pigs.

4. Eprinomectin

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EC	5 µg/kg bw	Eprinomectin B1a	Bovine	50 µg/kg	250 µg/kg	1500 µg/kg	300 µg/kg	20 µg/kg
Codex	0-10 µg/kg bw	Eprinomectin B1a	Bovine	100 µg/kg	250 µg/kg	2000µg/kg	300 µg/kg	20 µg/kg

EUROPEAN COMMUNITY
The toxicological ADI of 5 µg/kg bw was established based on the NOEL of 1 mg/kg bw/day from the 53-week toxicity study in dogs and applying a safety factor of 200. This safety factor is being used by CVMP in the establishment of ADIs for avermectins where toxicity data in CF-1 mice are absent.

The MRLs set were based on the tissue distribution at 10 days (non radiolabelled study) taking into account the ratio of parent compound towards total residues: 75% for muscle, 100% for fat, 80% for liver, 78% for kidney and 80-85% for milk.

Codex
JECFA used the same NOEL to establish the toxicological ADI using however a safety factor of 100 resulting in an ADI of 10 µg/kg bw.

CVMP Position:
The MRLs proposed by JECFA in muscle and liver, which are 2-fold higher than the European Community MRLs, would exceed the ADI established by the CVMP, which is defended by the CVMP.

Therefore, the CVMP cannot support the proposed Codex MRLs.

POSITION:

The MRLs proposed by JECFA in muscle and liver, which are 2-fold higher than the European Community MRLs, would exceed the ADI established in the European Community.

The European Community do not support the JECFA/Codex MRLs.

5. Flumequine

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs			
				Muscle	Fat	Liver	Kidney
EC	8.25 µg/kg bw (microbiological)	Flumequine	Bovine, ovine, porcine,	200 µg/kg	300 µg/kg	500 µg/kg	1500 µg/kg
			Chicken	400 µg/kg	250 µg/kg	800 µg/kg	1000 µg/kg
			Trout	600µg/kg[1]			
Codex	0-30 µg/kg bw (toxicological)	Flumequine	Bovine, ovine, porcine, chicken	500µg/kg	1000µg/kg	1000µg/kg	3000µg/kg
			Trout	500µg/kg[1]			

[1]muscle/skin in natural proportions

Both JECFA and CVMP established a toxicological ADI based on the NOEL of 25 mg/kg bw for hepatotoxicity in a 90-day mouse study applying a safety factor of 1000 to account for the short duration of the study. The microbiological ADIs derived were however different in both approach and result.

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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.

Codex

JECFA established a higher microbiological ADI for flumequine based on the MIC_{50} of the most predominant species in human gut flora for *Fusobacterium* and *Clostridium*. 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.

JECFA MRLs have been established without information on the ratio of marker residue towards total residues and the values do not follow the residue distribution.

POSITION:

The differences between European Community MRLs and Codex MRLs are mainly due to the difference in the ADI established, particularly being the difference in the assessment of the microbiological effects.

The European Community do not support the JECFA/Codex MRLs.

The European Community instead proposes that the decision be deferred to await the ongoing harmonisation activities, particularly within VICH, on the assessment of antimicrobial effects.

6. Imidocarb

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs				
				Muscle	Fat	Liver	Kidney	Milk
EC	10 µg/kg bw	Imidocarb	Bovine, Ovine	300 µg/kg	50 µg/kg	2000 µg/kg	1500 µg/kg	50 µg/kg
Codex	0-10 µg/kg bw	Imidocarb	Bovine	300 µg/kg	50 µg/kg	2000 µg/kg	1500 µg/kg	50 µg/kg

POSITION:

The European Community may support the JECFA/Codex MRLs.

7. Sarafloxacin

	ADI	MARKER RESIDUE	TARGET SPECIES	MRLs			
				Muscle	Fat	Liver	Kidney
EC	0.4 µg/kg	Sarafloxacin	Chicken	-	10 µg/kg[1]	100 µg/kg	-
			Turkey	-	-	-	-
Codex	0-0.3 µg/kg	Sarafloxacin	Chicken	10 µg/kg	20 µg/kg[1]	80 µg/kg	80 µg/kg
			Turkey	10 µg/kg	20 µg/kg[1]	80 µg/kg	80 µg/kg

[1]fat/skin

The approach followed by both expert committees to establish the microbiological ADI differs leading however to similar magnitude for the value of the ADI.

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A microbiological ADI of 0.4 µg/kg was calculated by CVMP based on the geometric mean MIC_{50} (0.031 µg/ml) selected in 10 micro-organisms including *E. Coli*, corrected for differences in *in vitro* and *in vivo* conditions and a bioavailability factor of 0.9.

The MRLs were established at 6 hours after withdrawal of the drug, 89% and 86% of the total residues in the liver were in the form of parent compound. At one day of drug withdrawal, the residues were only measurable in liver and skin. Tissue distribution was applied at 18 hours withdrawal period. The LOQs of the analytical method were 10 µg/kg for liver, skin, fat and muscle, and 50 µg/kg for kidney.

As the depletion of residues showed that the total residues in edible tissues other than in liver were relatively low, MRLs were allocated only for fat (LOQ) and liver but not for the other edible tissues.

Codex

The JECFA microbiological ADI (0-0.3 µg/kg) was established based on the mean MIC_{50} (0.125 µg/ml) for 3 strains of human clinical isolates of *Peptostreptococcus* spp., which was the most sensitive strain, using a bioavailability of 0.7 and a correction factor of 2 for the limited MIC data available.

The MRLs do not follow the tissue distribution. MRLs were set for muscle, fat/skin, liver and kidney. The MRL values for broilers are equally applied to turkeys. The LOQ of the analytical method was 5 µg/kg.

POSITION:

The differences of the ADIs are not significant and the theoretical maximum daily intakes calculated on the basis of the CVMP vs JECFA MRLs are similar

The European Community may support the JECFA/Codex MRLs.