



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OXYTETRACYCLINE, TETRACYCLINE, CHLORTETRACYCLINE

SUMMARY REPORT (3)

1. The CVMP evaluated oxytetracycline in the past and established an ADI of 0-0.003 mg/kg bw, based on effects on the human gut flora. Based on this ADI and taking into account the typical residue distribution of oxytetracycline in tissues, the following MRLs established by the 36th JECFA were adopted: kidney 600 µg/kg, liver 300 µg/kg, eggs 200 µg/kg, muscle 100 µg/kg, milk 100 µg/kg.
2. It was decided to apply these MRLs on a provisional basis not only to oxytetracycline but also to tetracycline and chlortetracycline (expiry date 1-1-1996). In order to establish final MRLs for these compounds the following information was required:
 - a validated routine analytical method for the determination of these compounds in edible products of the target animals;
 - information regarding the microbiological activity in human and gut flora of tetracycline and chlortetracycline in comparison with that of oxytetracycline.

The additional data requested have now been provided by various companies.

3. Recently, tetracycline and chlortetracycline were evaluated by the 45th JECFA. It was concluded that both tetracycline and chlortetracycline are of low toxicity: LD₅₀ values in mice and rats vary between 2150 and >5000 mg/kg bw, there is no evidence of reproductive or developmental toxicity and there is no evidence of carcinogenic effects or of a genotoxic potential. The lowest overall NOELs are 100 and 250 mg/kg bw/day for chlortetracycline and tetracycline, respectively. Antimicrobial data provided the most appropriate endpoint for the evaluation of tetracycline and chlortetracycline. Although the data package was more limited for chlortetracycline than for tetracycline, it was concluded that the antimicrobial potency of chlortetracycline and tetracycline is comparable to that of oxytetracycline. In view of this similarity, the JECFA established a group ADI of 0-3 µg/kg bw for oxytetracycline, tetracycline and chlortetracycline alone or in combination.
4. The microbiological activity of tetracycline and chlortetracycline compared to that of oxytetracycline was determined in in vitro MIC-studies with human enteric isolates. From these data it can be concluded that, despite minor differences, the spectrum of antimicrobial activity is comparable for tetracycline, chlortetracycline and oxytetracycline.
5. The oxytetracycline, tetracycline and chlortetracycline are rapidly but moderately absorbed from the gastrointestinal tract, with lowest absorption being for chlortetracycline. Following absorption through various routes of administration, these 3 tetracycline compounds are widely distributed in the body with highest levels in kidney and liver, and in bone and dentine. The oxytetracycline, tetracycline and chlortetracycline undergo minimal or no metabolism and they are excreted in urine and faeces either unchanged or in a microbiologically inactive form. Although there are differences between oxytetracycline, tetracycline and chlortetracycline in percentage urinary and faecal excretion, these differences are not substantial. Given the polarity of these substances, they are not detectable in fat to any great extent.

6. From residue data it can be concluded that the residue distribution for oxytetracycline, tetracycline and chlortetracycline in food-producing animals is comparable.
7. For the complete recovery of the compounds, the 4-epimers of oxytetracycline, tetracycline and chlortetracycline have to be determined. The 4-epimers of the compounds occur in samples and are formed during sample preparation. The 4-epimers are in equilibrium with the parent compound. Therefore, the marker residue is the sum of the parent drug and its 4-epimers.
8. Suitable and well validated HPLC methods are available which can be used in the surveillance of residues of tetracycline, oxytetracycline and chlortetracycline in tissues of cattle, sheep, pig, turkey, trout, carp, and in milk and eggs. This method takes into account the 4-epimers of oxytetracycline, tetracycline and chlortetracycline.
9. In view of the similarity in antimicrobial activity of oxytetracycline, tetracycline, chlortetracycline the JECFA group ADI of 0-3 µg/kg bw for these tetracycline compounds, can be adopted.
10. In addition, having evaluated the risk for the consumer, the Committee did not follow the JECFA proposal to have as well MRLs for combination of residues of these substances.

Conclusions and recommendation

Since the spectrum of antimicrobial activity is comparable for tetracycline, chlortetracycline and oxytetracycline, leading to the same ADI;

Since the pharmacokinetics profiles of these 3 substances are similar;

Since there are validated HPLC-methods for the monitoring of residues of tetracycline, oxytetracycline and chlortetracycline in edible products from target animals, and the residue distribution for these tetracycline compounds in food-producing animals is comparable;

Since the JECFA agreed on the same MRLs for the 3 substances;

The previously allocated MRLs can be considered as final for oxytetracycline, tetracycline and chlortetracycline and the Committee recommends the inclusion into Annex I of Council Regulation (EEC) No 2377/90 of these compounds for all food producing species in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Tetracycline	Sum of parent drug and its 4-epimer	All food producing species	600 µg/kg	Kidney	
Oxytetracycline			300 µg/kg	Liver	
Chlortetracycline			100 µg/kg	Muscle	
			100 µg/kg	Milk	
			200 µg/kg	Eggs	

In addition the Committee recommends that muscle should be the target tissue for fish.