The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CLOSANTEL

SUMMARY REPORT

At its 36th Session, JECFA (Joint FAO/WHO Expert Committee on Food Additives) had proposed the following MRLs for closantel, expressed as mg/kg closantel :

Target tissue	*Bovine*	*Ovine*
Muscle	0.5	1.5
Liver	1.0	1.5
Kidney	2.0	1.5
Fat	ND	1.5

JECFA had adopted provisional MRLs for the bovine species because metabolism studies were missing which would have permitted to characterise the total residues and the relationship, in the course of time, between closantel, selected as marker residue, and these total residues. Also missing was the residue study, carried out at the dose recommended by the laboratory.

With respect to the ovine species, results of studies of residues kinetics allowed to envisage, for the sake of simplicity, a single MRL for all the various food commodities.

At its 40th Session, JECFA undertook to re-evaluate, on the basis of additional scientific information, the MRLs which had been established in 1990.

*With regard to the **bovine species***

Metabolic studies provided according to the JECFA request. have shown that closantel was poorly metabolised in the majority of the tissues, except liver. It represented at least 70% of total residues in fat, 80% in kidnen and 100% in muscle. On the other hand it represented only 10% in liver. Kinetic studies using radio-labelled elements have shown that the radioactivity concentration ratio between plasma and tissues did not vary with time for the bovine nor for the ovine species. As a result the provisional MRLs proposed in 1990 were modified as follows :

- 1 mg/kg for muscle which corresponds to approximately 1 mg/kg total residues in as much as one can estimate that closantel is not significantly metabolised in this tissue;
- 1 mg/kg for liver which corresponds to approximately 10 mg/kg total residues in as much as closantel represents 10% of the amount of total residues in this tissue;
- 3 mg/kg for kidney which corresponds to approximately 3.75 mg/kg total residues in as much as closantel represents 80% of the amount of total residues in this tissue;
- 3 mg/kg for fat which corresponds to approximately 4.29 mg/kg total residues in as much as closantel represents 70% of the amount of total residues in this tissue.

On the basis of these new MRLs and of the standard food package, the amount of total residues that may be daily absorbed by the consumer is 1.7 mg which is lower than the ADI established at 1.8 mg. Whereas withdrawal times to be respected are lower than 14 days after oral administration (10 mg/kg), they remain much longer (42 days) after parenteral administration (5 mg/kg).

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*With regard to the **ovine species***

New information on closantel kinetics have shown that, due to biological variations, closantel residue levels in kidney could, from time to time, exceed the MRL established at 1.5 mg/kg. Since the amount of residues daily absorbed of 0.85 mg was much lower than the established ADI of 1.8 mg, JECFA has reconsidered the MRLs established in 1990 in order to include a safety margin which could account for the biological variation.

The new MRLs proposed for the ovine species are as follows :

1.5 mg/kg for muscle and liver, 2 mg/kg for fat and 5 mg/kg for kidney.

On the basis of these new MRLs, the amount of residues that may be daily absorbed is 1.05 mg, which is lower than the ADI established at 1.8 mg.

In summary, MRLs adopted for closantel by the 40th JECFA read as follows :

Target tissue	*Bovine*	*Ovine*
Muscle	1 mg/kg	1.5 mg/kg
Liver	1 mg/kg	1.5 mg/kg
Kidney	3 mg/kg	5 mg/kg
Fat	3 mg/kg	2 mg/kg

The Working Party on the Safety of Residues of the Committee for Veterinary Medicinal Products agreed to follow these JECFA recommendations.