EGGVP
European Group for Generic Veterinary Products

Position Paper

Brussels, 26 April 2013

EGGVP Position on Residues of Tetracyclines

On 11 March 2013, DG SANCO informed EGGVP that, for substances belonging to the tetracycline group, the theoretical maximum daily intake exceeds the ADI.
Different possibilities appear on the table to address the issue; DG SANCO has requested EGGVP to share its views on what would be the most appropriate approach to solve this situation.

Description of the issue

The CVMP elaborated MRLs for tetracycline, chlortetracycline and oxytetracycline based on reviews by the 36th and 45th Joint WHO/FAO Expert Committee on Food Additives (JECFA). A microbiological ADI was established based on a study with human volunteers, in which induction of resistance to Enterobacteriaceae was determined following treatment with oxytetracycline. No induction of resistance was seen following a dose of 2 mg per person per day. Using this no-effect level and applying a safety factor of 10 an ADI of 0–3 µg/kg bodyweight (or 180 µg/day) was established.

The following MRLs (Annex I) were elaborated in 1995:

Pharmacologically active substance	Marker Residue	Animal Species	MRLs	Target Tissues	Other Provisions
Tetracycline Oxytetracycline Chlortetracycline	Sum of parent drug and its 4-epimers	All food-producing species	600 µg/kg 300 µg/kg 100 µg/kg 100 µg/kg 200 µg/kg	Kidney Liver Muscle Milk Eggs	

Based on these MRLs and the standard food-basket the theoretical maximum daily intake is:

Matrix	Consumption (kg)	MRL (µg/kg)	Intake (µg)
Liver	0.1	300	30
Kidney	0.05	600	30
Muscle	0.3	100	30
Fat	0.05	NA	NA
Milk	1.5	100	150
Eggs	0.1	200	20
Total Intake:			260

The current potential intake of **260 µg/day** represents 144% of the current ADI.

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EGGVP opinion

Background

The current EMA/CVMP ADI for tetracyclines at 3 µg/kg (180 µg/day) was established by the CVMP in 1995 based on a JECFA assessment from 1993, on the basis of studies in humans where the dose of tetracycline 2 mg/day did not result in the presence of resistant *Enterobacteriaceae* in the feces. Furthermore, a 10-fold safety factor was applied.

In 1998, at their 50th meeting, the JECFA re-evaluated the ADI for tetracyclines based on the submission of new microbiological safety data. This new data on the effects of tetracycline on human gastrointestinal bacterial flora showed the selection of resistant *Enterobacteriaceae* is a very sensitive end-point for evaluating the microbiological effect of tetracyclines on human intestinal microflora and that individuals show little variation with respect to this effect. The original NOEL of 2 mg/day from a human study remained appropriate. It was concluded that the 10-fold safety factor was no longer necessary.

As a result, an increase of the ADI to 0 – 30 µg/kg was adopted by JECFA. However CVMP did not follow JECFA, and ADI value for tetracyclines in Europe has remained 10x below JECFA value since then.

Recommendation

It is the opinion of EGGVP that the current EMA/CVMP ADI should be reviewed in light of the further studies presented and evaluated at the 50th JECFA meeting and the conclusion of this meeting that a higher ADI could be safely established.

According to the stated the above, the safety factor of 10 applied by JECFA in 1993 and later on adopted by CVMP appears to be very conservative (and has subsequently been considered unnecessary by JECFA). Given the JECFA opinion, there appears to be scope to reduce this large safety factor whilst still maintaining consumer safety.

EGGVP proposes applying a **safety data factor of 5**, instead of 10; the resulting ADI would then be **360 µg/day**. This proposal takes into consideration JEFCA's position of no safety margin, but is based on a more cautious approach regarding any possible effects on consumer safety; at the same time it would eliminate the potential for maximum residue daily intake (260 µg/day) which is exceeding the current ADI.

This proposal would also allow anticipation in the case there is a need to establish MRLs for honey in the future. At present, there are neither authorized tetracyclines in the EU for bees nor MRLs established for this product in honey. But should this be the case in future (tetracyclines are widely used in bees in other geographic areas), according to EGGVP's proposal there would still be a margin of 100 µg/day remaining for the establishment of MRLs in honey without surpassing the proposed ADI of 360 µg/day.

EGGVP **does not consider it necessary to lower the present MRLs**. There appear not to be substantiated reasons for doing so. The toxicological evaluation of oxytetracycline,

tetracycline, and chlortetracycline made by JEFCA in 1998 confirmed that these drugs have a low degree of toxicity. Also the fact that the current MRLs for tetracyclines have been in place for almost 15 years without creating any issue on human health is an indication of their validity and guarantees that they are safe for the consumer. And the fact that the current MRL values for tetracyclines in the EU are already equal to or lower than those established in other areas globally (like US, Canada, New Zealand, Australia) should not simply be ignored.
One must also take into account that not lowering the current MRLs would also allow keeping residue surveillance programs as they are now, without a need to adapt them to new established MRLs.

The last point for consideration is that lowering MRLs would result in considerable research effort, investment and sacrifice of experimental animals being required by many companies for developing the safety and residue dossiers and establish new withdrawal periods (with no evidence of this being necessary to protect consumer safety). By this way, many products will most likely disappear since investment in such 'old' products will not be cost effective