

RESIDUES OF VETERINARY DRUGS

CEFUROXIME (addendum)

First draft prepared by

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1. EXPLANATION

Cefuroxime is a cephalosporin antibacterial agent that is active against a range of Gram-positive and Gram-negative bacteria. Intramammary infusions of cefuroxime are used in veterinary medicine for the treatment of clinical mastitis in lactating cattle and for dry-cow therapy. Cefuroxime is also used in human medicine.

At its fifty-eighth meeting (Annex 1, reference 157), the Committee established a temporary acceptable daily intake (ADI) for cefuroxime of 0–30 µg/kgbw on the basis of the MIC₅₀ for *Bifidobacterium* spp. The Committee also noted that a toxicological ADI of 0–4 mg/kgbw could be established on the basis of a no-observed-effect level (NOEL) for cefuroxime of 400 mg/kgbw per day for haematological changes identified in a 27-week study of toxicity in dogs treated orally, and applying a safety factor of 100.

The evaluation of cefuroxime residues performed by the Committee at its fifty-eighth meeting showed that a large percentage of the total radiolabelled residue in milk had not been identified. In pooled milk collected from eight cows, for example, >80% of the total radiolabelled residue was not identified in samples from the first, second, third and fifth milkings, corresponding to 12, 24, 36 and 60h after the last treatment. The mean concentrations of total radiolabelled cefuroxime equivalents in these pooled samples were 270, 38, 16 and 2 mg/kg, respectively. The concentrations of total radiolabelled cefuroxime equivalents were <1 mg/kg at the sixth and subsequent milkings and <0.1 mg/kg at the tenth and subsequent milkings.

The Committee at its previous meetings has discounted the significance of unidentified residues that comprise ≤10% of the total residue, by considering them as equally potent as the parent compound. In the case of cefuroxime, the unidentified residues represented >80% of the total, thus justifying the need for a more complete identification of the toxicological significance of these residues.

Therefore, the Committee at its fifty-eighth meeting in 2002 requested that the following information be provided for evaluation in 2004: the results of studies to (1) identify the residues in milk and clarify whether the residues other than parent compound are due primarily to metabolism or to non-metabolic decomposition of cefuroxime; and (2) characterize the toxicological significance of non-parent radiolabelled residues in milk.

2. *BIOLOGICAL DATA*

No new data were supplied for review by the present Committee. Instead, the sponsor provided an expert report that included a re-evaluation of previously submitted data. To address the questions posed by the Committee at its fifty-eighth meeting, the report explained that:

- Given the emphasis of the Committee on the antimicrobial activity of cefuroxime residues, the characterization of residues devoid of antimicrobial activity was perceived as not important. Therefore, no attempt had been made to characterize the toxicological importance of unidentified residues.
- Identification of the unidentified fraction of the total radiolabelled residue might have been feasible in milk collected up to the third milking after the last treatment, when concentrations of all residues were at their highest levels, but this was not done and the samples had since been destroyed.
- After the fifth milking, when the concentration of cefuroxime would be in compliance with the maximum residue limit (MRL), the identification of transformation products would have been impossible, owing to the small amount of radiolabelled residue present at this time and the poor resolution of components by radio-analysis and high-performance liquid chromatography (HPLC).
- The appearance of unidentified cefuroxime residues was not caused by species differences in metabolism but by the route of administration. Metabolites may not have been detected in studies of pharmacokinetics in healthy animals or humans, owing to the rapid clearance of cefuroxime from plasma. Therefore, it was reasoned that cefuroxime infused into the udder could be metabolized during the 12h between milkings. However, it could not be determined with any degree of certainty whether the unidentified residue fraction consisted of the products of metabolism or of non-metabolic degradation.
- The toxicological profile of the unidentified residue remains unknown.

3. *COMMENTS*

The Committee noted that the sponsor's expert report also drew attention to the observation that cefuroxime is poorly absorbed from the udder and therefore consumer exposure to tissue residues would be minimal. This was supported by the conclusions of the Committee at its fifty-eighth meeting after review of a residue study in dairy cows treated with cefuroxime by intramammary infusion. Seven days after administration of cefuroxime, total concentrations of radiolabelled residues in

tissues had declined to near or below the limits of detection. The present Committee also noted that unidentified radiolabelled residues were also detected in kidney tissue.

The Committee re-evaluated the residue depletion study submitted by the sponsor and noted that when milk samples were re-analysed by high-performance liquid chromatography–mass spectrometry (HPLC–MS), 14 days after the first analysis, significantly lower concentrations of cefuroxime were measured in all samples. The Committee posed additional technical questions to the manufacturer in relation to milk sample collection, storage, and cefuroxime stability in milk samples that had been frozen and thawed before analysis. On the basis of the answers provided, the Committee concluded that it was unable to confirm the ratio of cefuroxime to cefuroxime-related residues identified at the fifty-eighth meeting. The Committee further concluded that data from this study could not be further considered for the purpose of establishing an MRL for cefuroxime in cows' milk.

The Committee at its present meeting also considered the results of studies reported in the published literature, which show that cefuroxime is unstable in aqueous solutions, including biological matrices, at temperatures $>30^{\circ}\text{C}$. Descarbamoyl cefuroxime, a degradation product of the hydrolysis of cefuroxime, and other products of hydrolysis have been identified in various studies.

On the basis of this information, the Committee concluded that it was likely that cefuroxime is unstable in the udder environment and also in milk samples subjected to repeated freeze–thaw cycles. It could not be determined from the currently available information whether unidentified cefuroxime residues in milk are products of metabolism or of simple degradation.

The Committee reviewed published studies on the pharmacokinetics of cefuroxime in human patients with renal insufficiency and thus decreased clearance of cefuroxime from plasma. Metabolism of cefuroxime was not observed in these patients. Therefore, the Committee concluded that the data did not support the sponsor's suggestion that increased metabolism of cefuroxime may occur after longer periods of systemic exposure.

4. EVALUATION

After consideration of all available data, including additional residue information provided to the Committee and considering that:

- No new information had been provided in response to requests for data on the identification and toxicity of the unidentified residues of cefuroxime in milk;
- The Committee was unable to adequately evaluate the metabolism or degradation of cefuroxime in milk; and
- The radiolabelled-residue depletion study in cows could no longer be used to determine the relationship between residues of parent compound, other antimicrobial active residues and total residues of cefuroxime.

The present Committee concluded that it could not extend the temporary ADI or MRLs established at its fifty-eighth meeting. Therefore, the temporary ADI and MRLs for cefuroxime in milk were not extended and were therefore withdrawn.

5. REFERENCE

Parker, R.C. (2003) Cefuroxime MRLs. Expert report responding to questions raised by the 58th JECFA.