CEFUROXIME SODIUM

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ADDENDUM

to the monograph prepared by the 58th meeting of the Committee and published in

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INTRODUCTION

Cefuroxime is a cephalosporin with activity against a wide range of Gram-positive and Gram-negative bacteria. It is used in veterinary medicine by intramammary administration (as sodium salt) for the treatment of mastitis. In human medicine it is also used as the 1-(acetoxy)ethyl ester of the drug (cefuroxime axetil) for the treatment of different bacterial infections.

Cefuroxime sodium is available for veterinary use as Spectrazol™ Dry Cow (12,5% cefuroxime sodium) and Spectrazol™ Wet Cow (9,22% cefuroxime sodium). Spectrazol™ Dry Cow is a long-acting formulation intended for treatment of subclinical mastitis in dry cows and for prevention of new infections during the dry period. It is used as a single dose syringe (375 mg of cefuroxime) for intramammary administration, for a total dose of 1.5 g per animal. Spectrazol™ Wet Cow is used in the treatment of clinical mastitis and is supplied as a syringe (250 mg cefuroxime sodium) for intramammary administration, for a total dose of 1 g per animal, per day.

For the first time cefuroxime was evaluated by the 58th meeting of JECFA in 2002. The Committee established a temporary microbiological ADI of 0-30 µg per kg of body weight and recommended a temporary MRL of 50 µg/kg for cefuroxime parent compound in milk from cattle. The available data were not sufficient to permit the establishment of MRLs for other edible tissues (JECFA, 2002).

The Committee requested the following information to be provided by 2004:

1. Data to clarify whether the residues other than parent compound found in bovine milk are due primarily to metabolism or to non-metabolic decomposition of parent cefuroxime in milk;
2. Identification of the non-parent residues found in bovine milk, including an assessment of their potential toxicity.

None of the requested information was provided to the 62nd meeting of the Committee. The Sponsor argued that the information requested by the 58th JECFA could be provided on the basis of additional interpretations of previously submitted data and without the conduct of further studies. The Sponsor re-submitted the key reports included in the previous dossier. In addition, scientific articles published in the open literature on: (1) pharmacokinetics of cefuroxime in humans, (2) stability of cefuroxime in liquid environment, and (3) HPLC analytical methods for cefuroxime determination in blood plasma, were made available by the Sponsor, in response to a request of the drafting expert of the Committee.

Since no new information had been provided to the Committee and the additional interpretations offered by the Sponsor did not adequately address the problems identified by the 58th JECFA, further questions for clarification were raised by the experts of the Committee and written responses were received from the Sponsor. It was re-emphasized by the Committee that in the report of the pivotal study of Ferguson and Batten (1996) there were still serious unexplained discrepancies in the sets of analytical data obtained with direct samples of individual milkings and with pools of individual milkings, respectively. Some of these discrepancies occurred although the same validated method had been used (HPLC-MS). In other cases different methods were used which should produce essentially equivalent results (HPLC-radioanalysis vs. HPLC-MS). The discrepancies could not be resolved on the basis of the submissions to the 58th and 62nd JECFA. They could be resolved if one would assume that a major part of the residues representing parent drug had gradually decomposed during storage and treatment of the samples. The Sponsor accepted that there was an unexplained discrepancy in the results of the analysis of milk obtained at the critical fifth milking after the last infusion. Furthermore the responses of the Sponsor revealed that certain critical samples underwent several freezing-thawing cycles during storage and further processing. In fact, on the basis of the responses of the Sponsor the Committee could no longer exclude that degradation of residues occurred post-sampling, possibly during thawing/freezing cycles to an extent that the results obtained and reported for the residue composition of stored milk are not representative of the residue composition of fresh milk taken directly from the cow. The additional information contained in the responses of the Sponsor partly invalidate the pivotal study of Ferguson and Batten. Only the results of measurements of radioactivity in samples of milk appear to be fully reliable in this study. This conclusion should be kept in mind when reading the following part of this document.

RESPONSE OF THE SPONSOR TO THE REQUEST FOR

INFORMATION BY THE 58TH MEETING OF JECFA

1. Clarification whether the residues other than parent compound found in milk are primarily due to metabolism or to non-metabolic decomposition of parent cefuroxime in milk environment

The response of the Sponsor was submitted in the form of an expert report. This report stated that the main objective of the study in which [^{14}C]-cefuroxime had been intramammary infused to lactating cattle (Ferguson and Batten, 1996), was to determine the concentrations of antibacterially active residues, including the parent compound and to establish relationships between the concentrations of parent compound, other antibacterially active residues, and total radioactive residues of cefuroxime. The need to characterize or identify components that were devoid of antibacterial activity was not perceived as being important, given the emphasis being placed on antibacterially active residues (Parker, 2003). However, the Sponsor could also not provide information on the microbiological activity of potential metabolites or breakdown products.

From the analysis of milk obtained at different time points after administration of ^{14}C-cefuroxime it was found that cefuroxime was transformed into other compounds. The parent compound was a significant component of the antibacterially active residues up to the 3rd milking after the last administration of cefuroxime, however marked differences between results obtained by the HPLC methods and a microbiological assay have not been explained by the Sponsor. Samples of the milk of all eight cows used in the experiment were taken at the 5th milking after the last cefuroxime infusion to prepare a pool. The concentrations of cefuroxime in six samples were above the limit of quantification of the analytical method (HPLC-MS), with a mean of 0.143 µg/g and a range from 0.011 to 0.328 µg/g. Contrary to expectations the concentration in the pool was below 0.01 µg/g (Ferguson and Batten, 1996) meaning that more than 90% of the parent drug had disappeared during the time period between the analysis of the individual samples and the analysis of the pool.

Liquid chromatographic analysis of milk samples taken up to the 5th milking indicated that – at the time of analysis - more than 80% of the radiolabelled residues were unidentified substances**.** When samples of subsequent milkings were analyzed, the parent compound was almost not detected, while more cefuroxime transformation products were present. According to the expert report identification of the radioactive components in milk other than unchanged parent compound was not performed and samples have been destroyed (Parker, 2003).

Concerning the possibility of non metabolic degradation of cefuroxime in milk environment, the submission claimed that the published scientific evidence is equivocal (Parker, 2003). Okumura *at al.* (1979) incubated cefuroxime with rat plasma or with homogenates of rat liver, kidney, spleen or lung in phosphate buffered saline at pH 7.2 and 37 ^{o}C for up to 90 minutes and recovered 90% or more of the parent compound. The Merck Index (1989) notes that aqueous solutions of sodium cefuroxime are stable at room temperature for 13 hours, and that less than 10% decomposition occurs in 48 hours at 25 ^{o}C. However, repeated measurement of cefuroxime in milk samples from the study of Ferguson and Batten indicated that concentrations decreased significantly over a storage period of two weeks. This finding was attributed to differences in batch recoveries of the HPLC-MS method by the authors of the study (Ferguson and Batten, 1996). However, according to the expert report, these decreases were probably too great to be fully accounted for in this way, and it is also possible that the cefuroxime was lost either during freezer storage or during freeze-thawing or due to bacterial metabolism in the non-sterile samples (Parker, 2003).

According to the expert report transformation of cefuroxime in the udder is too great to be accounted for solely, or even predominantly, by a non-enzymatic mechanism. Even if cefuroxime is unstable to some extent in the environment of the mammary gland, there are no reasons for supposing that it would not be similarly unstable in other biological matrices. It is unlikely that the fluids in the udder possess any qualities that result in more rapid non-enzymatic degradation of cefuroxime than would be seen, for example, in blood (Parker, 2003).

Results of pharmacokinetic studies in rats, dogs and humans show that cefuroxime is rapidly and almost completely (80-95% of the dose) excreted unchanged (> 95%) in urine during 24-72 hours (Foord, 1976; Gower and Dash, 1977; Nanbo *et al.*, 1979), while it is extensively metabolized and slowly eliminated with milk after being infused into the udders of lactating cows (Ferguson and Batten, 1996). According to the expert report, the differences are not due to the animal species, but to the route of administration, and it is probable that in rats, dogs and humans the drug is rapidly excreted before there is an opportunity for significant metabolism to take place. The nominal 12 hours between milkings in cows is a long time for a drug that is normally eliminated with a short half-life, and it is very likely that metabolism could occur that would not have taken place if the drug had been administered by a route that allowed rapid excretion (Parker, 2003). Furthermore, results of pharmacokinetic studies in cattle show that cefuroxime is rapidly eliminated after being administered by intravenous or intramuscular injection with a half-life ($t_{1/2\beta}$) of 1.15-1.47 hours (Silley and Rudd, 1986; Soback *et al.*, 1989; Chaudhary *et al.*, 2001). The routes by which cefuroxime is metabolized within mammary gland are not unique and are similar to metabolic pathways available for transformation of cefuroxime in rats, dogs and humans after its non-intramammary administration. Cefuroxime is not resistant to metabolism, but most of the dose escapes transformation because it is cleared from the body before metabolism can occur, however, it can not be ruled out that some of the metabolites in milk are unique to cattle dosed by intramammary infusion (Parker, 2003).

2. Identification of the non-parent residues found in milk, including an assessment of their potential toxicity

In humans and different animal species cefuroxime, when administered orally as the axetil derivative or parenterally as the sodium salt, is rapidly and almost completely excreted in urine during 24-72 hours. According to the Sponsor's expert report, cefuroxime metabolism occurs in all species, but the rate of this process is generally slower than the rate of excretion. However, if excretion is "blocked" by trapping the cefuroxime in the udder, than the results of metabolism become more evident. Whether these metabolites are exactly the same in different animal species and in humans, as those found in bovine milk after intramammary administration, cannot be known because there are no results from comparative metabolism studies. If some of the metabolites of cefuroxime are different, than this creates concerns about their toxicity (Parker, 2003).

Results of the study with radiolabelled cefuroxime in cattle suggest that the concentrations of parent compound in milk decrease faster than the total radioactive residues. The expert report assumes that a concentration of parent compound in milk equivalent to the temporary MRL of 50 μg/kg corresponds to a "total residue" concentration of approximately 3 mg equivalents/kg (Parker, 2003). Assuming human consumption of 1.5 kg of milk per day, this total milk residue equates to a daily intake of 4.5 mg equivalents, which is less than 1.9% of the temporary toxicological ADI of 240 mg per 60 kg person established by the 58th meeting of the JECFA. Even if the metabolites of cefuroxime were 50 times more toxic than the mixture of parent compound and metabolites to which laboratory animals were exposed in toxicity studies, they would not pose a risk to human health. However, there are no reasons to believe that the non-parent residues of cefuroxime in milk would be more toxic than unchanged cefuroxime (Parker, 2003).

According to the expert report tissue residues of cefuroxime also need to be combined with the ADI. Due to limited absorption from the udder (< 20% of the dose), tissue residues are low, however, actual data on concentrations of "total residue" are not available for the period shortly after infusion of cefuroxime. Considering the data from the radiolabelled study (Ferguson and Batten, 1996), 24 hours after first infusion of cefuroxime about 4% of the dose had been excreted in urine and faeces, and at least 78% of the dose had been excreted either in milk or was located within mammary gland. Thus, less than 18% (540 mg) of the total dose of cefuroxime may have been absorbed from the udder into the blood, but not yet excreted. Assuming that all of absorbed dose was concentrated in the kidneys and that the two kidneys of a mature cow weight together 1.6 kg, than the concentration of total cefuroxime-derived residue in kidneys would have been estimated as 338 mg equivalents/kg. Assuming a daily intake of 50 g of kidney per day, the intake of residues by a 60 kg consumer would be 17 mg equivalents, which amounts to only 7% of the temporary toxicological ADI established by the 58th meeting of the JECFA. This assumption is clearly an exaggeration and takes no account of residues located in non-edible tissues, organs or body fluids, so in reality, it is unlikely that the edible tissues residues use up more than 1% of the temporary toxicological ADI. It is also unlikely that a cow will be slaughtered so soon after treatment, except in emergency. Furthermore, results of the study with radio-labeled cefuroxime in cows show that tissue residues are very low 7 days after treatment with cefuroxime (Table 1). Assuming daily consumption of 100 g of liver, 50 g of kidney, 300 g of muscle and 50 g of fat, these total residues account for only 0.007% of the temporary toxicological ADI or only 1% of the temporary microbiological ADI. Based on available information, it could be concluded that 50 μg/kg of cefuroxime would be a suitable concentration for a permanent MRL for bovine milk and it was not necessary to set MRL values for edible tissues in cattle (Parker, 2003).

Table 1. Mean total cefuroxime-derived residues in tissues of eight cows 7 days after the last of three successive intramammary doses of 1,000 mg [14C]-cefuroxime (Ferguson and Batten, 1996).

Tissue	Mean residue ± SD (mg equivalents/kg)
Liver	0.035 ± 0.011
Kidneys	0.101 ± 0.046
Muscles	< 0.020
Fat	< 0.060

Assessment of the Sponsors response to Question 1

Results of studies in which [^{14}C]-cefuroxime was intramammary infused in cows show that antibacterially active residues (including the parent compound) are eliminated with milk, however, concentrations below the temporary MRL for the parent compound of 50 μg/kg are not reached before the 5th milking. Moreover, based on HPLC analysis, more than 80% of the radiolabelled residues present in milk samples taken before the 5th milking were unidentified metabolites or degradation products of cefuroxime and in subsequent milkings amounts of cefuroxime transformation products were even higher (Ferguson and Batten, 1996).

Whether these metabolites or non-metabolic degradation products are exactly the same in different animal species and in humans cannot be known, because there are no results from comparative studies. If some of them are different, than this creates concerns about their toxicity.

The main arguments of the Sponsor concerning non-metabolic decomposition of cefuroxime in milky/liquid environment are the following. There is a deficit in specific experimental evidence for such a theory. Furthermore, existing results (Okumura *et al.*, 1979; The Merck Index, 1989; Ferguson and Batten, 1996) regarding cefuroxime stability are equivocal, and even if

cefuroxime is unstable to some extent in the milky environment of the udder there are no reasons for supposing that it would not be similarly unstable in other biological matrices (Parker, 2003).

Unfortunately, the Sponsor did not perform tests of the stability of cefuroxime in bovine milk. However, results of tests of the stability of ceftiofur (a third-generation cephalosporin) in milk and blood plasma indicate marked differences in long-term stability in these biological matrices (Erskine *et al.*, 1995). Ceftiofur lost 86.8% of bioactivity within 30 minutes following the addition to serum at 20 ^{o}C. Ceftiofur in serum stored at -20 ^{o}C continued to lose bioactivity, so that by 3 weeks of storage, only 1.2% of the original activity was detected. However, ceftiofur activity in milk, immediately after mixing and after 3 weeks of storage at -20 ^{o}C, did not differ from activity before storage (Erskine *et al.*, 1995).

In the study of Okumura *et al.* (1979) only about 90% of the drug was recovered after 90 minutes of incubation at 37 °C. In the study of Ferguson and Batten (1996) HPLC-MS measurements of cefuroxime in milk samples taken at the 5th milking following the last infusion of the drug were repeated within 14 days**.** The results of the second analysis were significantly lower in all samples ranging clearly above the LOQ of the method upon first analysis. The Sponsor confirmed these discrepancies (Parker 2004), but gave no satisfactory explanation for these findings which could be indicative for cefuroxime decomposition during storage.

Time dependent instability of cefuroxime at 4 ^{o}C was shown in long-term studies in 5% dextrose. After 11, 21 and 30 days of incubation, cefuroxime recoveries were 93.0, 89.6 and 78.3%, respectively (Galanti *et al.*, 1996). Schlesser *et al.* (2001) defined the time of cefuroxime stability in 5% dextrose solution as the time during which the lower confidence limits of the residual value remained superior to 90% of the initial concentration by regression analysis. The stability of cefuroxime solution was estimated at 13 days when stored at 4 ^{o}C (Schlesser *et al.*, 2001). In another study in 5% dextrose or in 0.9% NaCl injectable solution cefuroxime sodium was stable (96% recovery) at 5 ^{o}C during 30 days, however, at 25 ^{o}C recoveries amounted to only < 94, < 87 and < 75% after 1, 2 or 4 days, respectively. Stability test performed at -10 ^{o}C showed almost complete (> 99%) stability of cefuroxime (Das Gupta and Stewart, 1986). Similar results on stability of cefuroxime in aqueous solutions were obtained by Wang and Notari (1994). Maximum stability was observed in the pH range from 4 to 7, where the time during which cefuroxime concentration exceeded 90% of its initial concentration at 25 ^{o}C was 1.2 days. The predicted shelf-life for aqueous cefuroxime solutions in the pH range 4-7 as a function of temperature shows values of < 1 (30 ^{o}C), 2.5 (20 ^{o}C), 12.5 (10 ^{o}C) and 45 days (2.5 ^{o}C). In the same study descarbamoyl cefuroxime was identified as a degradation product of cefuroxime hydrolysis, which still possesses a ß-lactam ring (Wang and Notari, 1994). Barnes (1990) reported that at 25 ^{o}C in solutions for intravenous administration cefuroxime degraded by first-order kinetics with a rate constant of 7.04 x 10^{-2}/day and a t_{90} (time to reach 90% of the original concentration) of 36 hours. At 4 ^{o}C the rate constant was 5.23 x 10^{-3}/day with a t_{90} of 20 days. However, over the time-scale studied, the kinetics approximated to zero-order at this temperature. Jorgensen *et al.* (1988) provided stability data for cefuroxime in different media. Several examples are given in Table 2.

Oldham and Andrews (1996) described the preparation of a simple, unpreserved aqueous solution of cefuroxime sodium (equivalent to 5% cefuroxime) from Zinacef® injection and sterile water for injections. The eye drops were chemically stable for 24 hours at room temperature and for 21 days at 2 ^{o}C during simulated patient use. The authors concluded that solutions may be frozen at -30 ^{o}C for up to 12 months with negligible loss of antibacterial potency, and on thawing at room temperature the stability is maintained for 21 days at 2 ^{o}C or for 14 days at 8 ^{o}C.

From stability studies of 14 different cephalosporins (including cefuroxime) it was seen that within 4 hours after dissolving in water at room temperature (25 ^{o}C) their degradation (hydrolysis) is generally not higher than 20%. After 260 hours however, only < 2% of the original amount of the drug e.g. cefuroxime, was still present. Moreover, formation of four unknown hydrolysis products of cefuroxime (named as D_1-D_4) has also been observed. The D_1 degradation product showed almost total instability and disappeared together with the parent compound after 150 hours of incubation, while D_2, D_3 and D_4 degradation products started to form about 50 hours after dissolution in water (Gáspár *et al.*, 2002).

Table 2. Stability of cefuroxime in human body fluids and bacteriological media at three temperatures (Jorgensen et al., 1988).

Diluent	% of starting concentration at*:		
	-20 °C for 7 days	35 °C for 8 hours	35 °C for 18 hours
Pooled human serum**	-	84.0	-
Pooled human urine**	-	95.0	-
Distilled water	95.6	79.3	-
Mueller-Hinton brothsupplemented withCa and Mg cations	94.7	86.6	79.7
Trypticase soy broth	94.0	82.8	81.0
Thioglycolate 135 °C medium	91.0	87.0	68.2

* - Mean of duplicate determinations of two concentrations (20 and 80 µg/ml) of drug

** - pH of pools adjusted to 7.4

Coomber *et al.* (1982) developed an HPLC assay for cefuroxime. In operating instructions they suggest to "store the standard and sample solutions in a refrigerator until they are required for injection; under these conditions cefuroxime sodium decomposes at a rate of approximately 0.05% per hour". Lecaillon *et al.* (1982) reported the maximum storage time, which produced less than 5% degradation, as 14 days at 5 ^{o}C for standard solutions and > 5 hours at room temperature in the autosampler for treated plasma and urine samples.

All these results indicate temperature and time dependent instability of cefuroxime sodium in aqueous solutions (including biological matrices) with rapid degradation rates in temperatures above 30 ^{o}C.

Results of pharmacokinetic studies in rats, dogs and humans show that cefuroxime is rapidly and almost completely excreted in urine in unchanged form during 24-72 hours (Foord, 1976; Gower and Dash, 1977; Nanbo *et al.*, 1979), while it is extensively metabolised and slowly eliminated with milk after being infused into the udders of lactating cows (Ferguson and Batten, 1996). In the opinion of the Sponsor the difference is predominantly a result of the route of administration and it is probable that laboratory animals and humans excrete cefuroxime so rapidly, because there is no opportunity (sufficient persistence time) for significant metabolism to take place, and most of the dose escapes transformation (Parker, 2003).

No evidence to support this hypothesis was presented. However, studies of the pharmacokinetics of cefuroxime in human patients with severe renal insufficiency could probably clarify whether metabolism can occur if the rate of excretion is reduced.

Results of pharmacokinetic studies in healthy humans (in most cases creatinine clearance > 100 ml/min./1.73 m^2) or in patients with severe renal impairment (creatinine clearance < 20 ml/min./1.73 m^2) are presented in Table 3. Analysis of these results generally indicates a good comparability of the results obtained by different authors. In healthy humans cefuroxime is quickly eliminated from the blood plasma with a half-life of about 1.4 hour and almost all (93-100%) of parenterally administered dose is excreted in urine in unchanged form during 24 hours. Furthermore, results obtained by HPLC assay indicate that cefuroxime has almost total metabolic stability in the body and the only metabolite observed in human urine (1.3% of the dose during 8 hours) is Δ2-cefuroxime, a hydrolysis product of the cefuroxime axetil (Ishibiki *et al.*, 1990).

In patients with severe renal insufficiency however, elimination from the blood plasma and urinary excretion of cefuroxime are markedly reduced. Reported values for cefuroxime half-life in renal impairment are about 10-times higher (in individuals with tubular necrosis even up to 28.3 hours) than in normal patients (van Dalen, *et al.*, 1983), what is a result of almost proportional decrease of the total body clearance (Table 3). Proportional 10-times increase of the AUC values for unchanged cefuroxime in blood plasma has also been observed in renal failure, and 24-hour urinary excretion was reduced even below 20% of the administered dose (Table 3). Moreover, microbiological disc diffusion assay and HPLC assay for cefuroxime yielded statistically identical results for blood plasma, as well as for urine (Bundtzen *et al.*, 1981; Massias *et al.*, 1998).

It is interesting, however, that in patients with end-stage of renal failure the half-life of elimination is not infinitely high and never exceed 30 hours (Vree and Hekster, 1990). The elimination must therefore proceed by mechanism other than renal excretion (van Dalen *et al.*, 1979). The mechanism by which this non-renal elimination takes place is still unknown. Analysis of linear correlations between the renal and total body clearances of cefuroxime and creatinine clearance shows that in patients with severe renal failure extrarenal clearance remained almost constant and it amounted only 8.24 ml/min. (Walstad *et al.*, 1983).

All the above results on pharmacokinetics of cefuroxime in humans indicate that this compound has almost total metabolic stability in healthy humans as well as in patients with severe or even end-stage renal failure. It cannot be excluded however, that during long persistence in the body cefuroxime undergoes some biotransformation.

Therefore, the Sponsor statements that (1) "it is possible that in humans the drug is rapidly excreted before there is an opportunity for significant metabolism to take place" and (2) "most of the dose escapes transformation because it is cleared from the body before metabolism can occur" appear unjustified.

It is very likely that the difference in cefuroxime metabolism between e.g. humans and cattle are related to a route of administration and specific transformation processes (bacteria dependent metabolism?) within the udder during lactation. However, this cannot be explained based on examples of cefuroxime pharmacokinetics after non-mammary administration (even in severe renal failure), simply because the drug is a strong acid and do not penetrate easily from the blood into acidic environment of milk. Moreover, it has small volume of distribution (V_d) – below 0.3 l/kg b.w. (Bundtzen *et al.*, 1981; Chaudhary *et al.*, 2001). Results from human studies also show that cefuroxime concentrations in milk ranged from 0.09 to 0.59 μg/ml at 30 to 90 minutes after oral administration of 500 mg of cefuroxime axetil (Nakamura *et al.*, 1987).

This means that they were about 10-times lower than corresponding concentrations observed in blood plasma (Ishibiki *et al.*, 1990; Konishi *et al.*, 1993; Nix *et al.*, 1997). Unfortunately, Nakamura *et al.* (1987) used bioassay technique for cefuroxime determination in milk samples which makes impossible assessment in scale of potential metabolites separation.

Table 3. Pharmacokinetic parameters of cefuroxime in healthy humans or in patients with renal insufficiency.

Health status: H: Healthy RI: Renal insufficiency **Cl_{CR}:** Creatinine clearance **Dose and route**	**Cmax** **(µg/ml)**	**Tmax** **(min.)**	**T1/2** **(h)**	**Vd** **(l/1.73 m2)**	**ClB** **(ml/min/ 1.73 m2)**	**ClR** **(ml/min/1.73 m2)**	**AUC** **(µg/ml/h)**	**24 h urinary excretion** **(% of dose)**	**Reference**
H 500 mg i.v.	C0 = 82.7	T0 = 0	1.1	11.09		136	50.4	95.1	Foord, 1976
H 1000 mg i.v.	C0 = 181.4	T0 = 0	1.1	12.83		169.6	90.8	99.1	
H 500 mg i.m.	26.9	29	1.2	13.45		128.9	59.2	96.5	
H 750 mg i.m.	34.9	31	1.4	15.81		137.9	88.6	101.9	
H 1000 mg i.m.	40.4	45	1.1	15.05		146.3	101.3	103.4	
H 500 mg i.v.	42.0	15	1.1	11.7	148		53.1	93.1	Gower and Dash, 1977
H 750 mg i.v.	52.6	15	1.1	12.5	152		74.0	94.8	
H Cl_{CR} >115 ml/min. 1000 mg i.v.			1.6-2.1 (1.9)*		124-506 ml/min. (374 ml/min.)*	115-261 ml/min. (188 ml/min.)*		89.5-100 (95.6)*	van Dalen et al., 1979
RI ClCR<40 ml/min. 1000-1500 mg i.v.			4.4-17.4 (10.5)*		13-154 ml/min. (46 ml/min)*	3.5-138 ml/min. (34 ml/min.)*		13-88.7 (49.7)*	
H Cl_{CR}>60-120 ml/min./1.73 m^2 750 mg *i.v.*	72.0	5	1.7	0.19 l/kg	123	128	109	96	Bundtzen *et al.*, 1981
RI Cl_{CR}<20 ml/min./1.73 m^2 750 mg *i.v.*	66.0	5	17.6	0.27 l/kg	13	5.5	1070	45	

Health status: H: Healthy RI: Renal insufficiency **Cl_{CR}:** Creatinine clearance **Dose and route**	**Cmax** **(µg/ml)**	**Tmax** **(min.)**	**T1/2** **(h)**	**Vd** **(l/1.73 m2)**	**ClB** **(ml/min/ 1.73 m2)**	**ClR** **(ml/min/1.73 m2)**	**AUC** **(µg/ml/h)**	**24 h urinary excretion** **(% of dose)**	**Reference**
RI Cl_{CR}<20 ml/min. 750 mg *i.v.*	52.2-125		6.5-22.3 (12.4)*	11.9-29.6 l (18.1 l)*	15.3-22.9 ml/min (18 ml/min.)*	3.5-13.8 ml/min. (9 ml/min.)*		25-63 (46)*	Walstad *et al.*, 1983
H 500 mg *p.o.*	6.7	121	1.4	33.5 l			27.3	54.5 (during 8 hours)	Ishibiki *et al.*, 1990
RI Cl_{CR}<30 ml/min. 500 mg *i.v.*	48.7		12.6	22.8 l	22.3 ml/min.				Davies *et al.*, 1991
H Cl_{CR}>85 ml/min./1.73 m^2 500 mg *p.o.*	4.4	180	1.4				21.6	41.9	Konishi *et al.*, 1993
RI Cl_{CR}<15 ml/min./1.73 m^2 500 mg *p.o.*	9.2	240	16.8				258	17.5	
H 500 mg *p.o.*	5.2	147	1.3				19.9		Nix *et al.*, 1997
H 750 mg *p.o.*	6.5		1.5				52.4		Massias *et al.*, 1998

H - this also means that Cl_{CR} values were usually > 100 ml/min./1.73 m^2 or Cl_{CR} values were not specified

* - recalculated mean values

Assessment of the Sponsor response to Question 2

Assessment of the Sponsor response to Question 1 indicates that it is not possible to determine the identity of the products of the transformation of cefuroxime in bovine milk without specific experimental data.

The central point in the assessment of the toxicity of the residues of cefuroxime is whether the residues (metabolites) found in milk are the same compounds which are formed in animal species used for toxicity testing and in exposed humans, as those found in bovine milk. In the present case, however, the nature of metabolites and degradation products is not known and the data requested by the 58th JECFA have not been provided by the Sponsor. The additional interpretations in the newly submitted expert report are not suited to replace the required experimental data.

CONCLUSIONS AND RECOMMENDATION

Considering that:

- the information requested by the 58th JECFA has not been provided by the Sponsor;
- the nature of the products of the transformation of cefuroxime in bovine milk remains unknown;
- it is not possible to assess the toxicological significance of unknown cefuroxime residues in bovine milk;

the Committee decided not to extend the temporary ADI for cefuroxime and the temporary MRL for cefuroxim in bovine milk.

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