This is provisional English translation of an excerpt from the original full report.

Risk Assessment Report
Cefalonium (veterinary medicines)

Food Safety Commission of Japan (FSCJ)
March 2011

Executive summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of cefalonium (CAS No. 5575-21-3), a cephalosporin antibiotic. The risk assessment was carried out using two reports of the European Medicines Evaluation Agency (EMEA)[1] and other three documents including data available on: pharmacokinetic tests (rats, dogs, and pigs); residue tests (cows); acute toxicity tests (mice and rats); subacute toxicity tests (rats and dogs); reproductive and developmental toxicity tests (rats); genotoxicity tests; and microbiological effect tests.

It was confirmed that no genotoxicity was attributed to cefalonium in the living body based on various genotoxicity tests. No preneoplastic changes were observed in a repeated dose toxicity test. Neither chronic toxicity nor carcinogenicity test was conducted on this substance. The cefalonium molecule does not contain any structural alerts. Hence, cefalonium was not considered to be a genotoxic carcinogen, thus it was decided that an acceptable daily intake (ADI) could be determined accordingly.

Reduced serum globulin was an effect reportedly observed at the lowest dose in a 13-week subacute toxicity test in rats, based on which the no observed adverse effect level (NOAEL) was set at 4 mg/kg body weight/day in the EMEA reports.

Unlike the EMEA's calculation, FSCJ calculated a toxicological ADI to be 0.004 mg/kg body weight/day by applying a different safety factor of 1,000 which was composed of 10 for species difference, 10 for individual difference, and 10 for additional safety factor to the use of NOAEL. The additional safety factor of 10 above was introduced considering the fact that neither chronic toxicity nor carcinogenicity test was conducted.

The microbiological ADI was calculated to be 0.0016 mg/kg body weight/day according to a current internationally recognized formula established by International Cooperation on Harmonization of Technical Requirements for Registration of Vererinary Medicinal Products (VICH).

This microbiological ADI of 0.0016 mg/kg body weight/day is smaller than the toxicological ADI of 0.004 mg/kg body weight/day, thereby ensuring toxicological safety.

In conclusion, the ADI of cefalonium was determined to be 0.0016 mg/kg body weight/day.

[1] EMEA, COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS,CEFALONIUM SUMMARY REPORT (1), 1999 and EMEA, COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS, CEFALONIUM SUMMARY REPORT (2), 2002

Risk assessment (extracted from Part III of the original risk assessment report)

1. EMEA evaluation

In the EMEA evaluation reports, taking into account the insufficient quality of toxicity dataset, the toxicological ADI of cefalonium is set at 0.02 mg/kg body weight/day (1.2 mg/human/day) by applying a safety factor of 200 to the NOAEL of 4 mg/kg body weight/day which was derived from a 13-week subacute toxicity test in rats.

The microbiological ADI is determined based on the *in vitro* geometric mean minimum inhibitory concentration at 50% growth inhibition (MIC_{50}) of 0.0046 mg/ml. The microbiological ADI is calculated by applying 150 ml of feces, 1 fraction of exposed intestinal flora, and 60 kg of human body weight to the following formula established by theCommittee for Medicinal Products for Veterinary Use (CVMP):

$$ADI = \frac{\frac{0.0046 \times 4^{*2}}{3^{*1}} \times 150^{*3}}{1^{*4} \times 60}$$

= 0.0153 mg/kg body weight/day

*1: It is set at 3 to give allowance for the possible transmission of a cephalosporin resistant factor through chromosomes and plasmids.
*2: It is set at 4 as the product of 2 considering the effects of bacterial flora concentration and 2 considering the effects of β-lactamase-producing bacteria.
*3: 150 mL (amount of daily feces)
*4: It is conservatively set at 1 for fraction of exposed intestinal flora.

The microbiological ADI of 0.0153 mg/kg body weight/day is slightly lower than the toxicological ADI of 0.02 mg/kg body weight/day. Thus, it was concluded in the EMEA's reports that the microbiological ADI should be used as an ADI of cefalonium.

2. Toxicological ADI

FSCJ noted that mutagenic potential for cefalonium was tested in various *in vitro* and *in vivo* tests. *In vitro*, cefalonium induced increase in structural chromosomal aberrations, however, cefalonium was negative in three in vitro tests (i.e. mutagenicity tests, the gene conversion test and the gene mutation test) and in two *in vivo* tests (i.e. micronucleus tests and unscheduled DNA synthesis test. Based on the test results above, FSCJ confirmed that no genotoxicity was attribuable to cefalonium in the living body. No preneoplastic changes were observed in a repeated dose toxicity test. Neither chronic toxicity nor carcinogenicity test was conducted on this substance. The cefalonium molecule does not contain any structural alerts. Hence, cefalonium was not considered to be a genotoxic carcinogen; thus an acceptable daily intake (ADI) could be determined accordingly.

Reduced serum globulin was an effect reportedly observed at the lowest dose in a 13-week subacute toxicity test in rats, based on which the no observed adverse effect level (NOAEL) is set at 4 mg/kg body weight/day as in the EMEA reports.

FSCJ considered that application of a safety factor of 1,000, which was composed of 10 for species difference, 10 for individual difference, and 10 for additional safety factor was practical for setting the toxicological ADI of 0.004mg/kg body weight/day. The additional safety factor of 10 above was introduced considering the fact that neither chronic toxicity nor carcinogenicity test was conducted.

Thus, the toxicological ADI of cefalonium should be set at 0.004 mg/kg body weight/day.

3. Microbiological ADI

In this risk assessment, FSCJ decided to use detailed findings obtained from a comprehensive FSCJ food safety survey conducted in 2006 on microbiological effects of veterinary antibacterial agents. The findings were sufficient for estimation of microbiological ADI according to VICH guidelines. A MIC_{calc} was calculated, consequently to establish a microbiological ADI, according to the internationally recognized formula available in the VICH Guidelines[2].

The microbiological ADI was calculated by applying 0.000427 mg/mL (the calculated MIC [MIC_{calc}] of cefalonium), 220 g of colon content, 1 fraction of exposed bacteria, and 60 kg of human body weight to the following VICH formula:

$$ADI = \frac{0.000427^{*1}}{1^{*3}} \times \frac{220^{*2}}{60} = 0.00157$$

$$= 0.0016 \text{ (mg/kg body weight/day)}$$

*1: Calculated from the lower limit of the 90% confidence limit of the mean MIC_{50} (active against test agents) of the relevant bacterial genera.
*2: Colon contents
*3: Factor for fraction of exposed intestinal flora is set at 1, because no observation was obtained for absorption rate in oral cefalonium administration.

It was considered appropriate to set the microbiological ADI at 0.0016 mg/kg body weight/day which was calculated from a current internationally recognized VICH formula.

4. ADI determination

The microbiological ADI of 0.0016 mg/kg body weight/day was smaller than the toxicological ADI of 0.004 mg/kg body weight/day, thereby ensuring toxicological safety, thus, the ADI of cefalonium should be set at 0.0016 mg/kg body weight/day.

5. Conclusion

The following value should be used as an ADI for cefalonium:

0.0016 mg/kg body weight/day.

Ministry of Health Labour Welfare will estimate the amount of human exposure to rifaximin and elaborate new or revised maximum residue limits (MRLs) for cefalonium in food concerned, not to exceed the ADI above. The proposed MRLs will be reviewed by the FSCJ for any advice, where necessary.

[2] VICH GL36 (SAFETY), namely "Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI", have been adopted in Japan since March 2006.