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

Risk Assessment Report
Fosfomycin (veterinary medicines)

Food Safety Commission of Japan (FSCJ)
April 2010

Executive summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of Fosfomycin (CAS No. 23155-02-4), using a set of data submitted from the Ministry of Health, Labour and Welfare (MHLW).

Fosfomycin is an antimicrobial of phosphonic acid family used as a veterinary medicine to treat coliform-caused diarrhea and salmonellosis in cows and pseudotuberculosis of Perciformes in Japan. Fosfomycin calcium is used as an additive in feed or drinking water, and fosfomycin sodium is used as an injection.

The data used for the risk assessment include pharmacokinetic tests of fosfomycin calcium in rats, rabbits, dogs, cows, and yellowtails; residue tests of fosfomycin calcium in cows and yellowtails, and of fosfomycin sodium in cows; acute toxicity tests of fosfomycin calcium and fosfomycin sodium in mice and rats; subacute toxicity tests in rats, rabbits, and dogs; reproductive and developmental toxicity tests in rats and rabbits; genotoxicity tests and microbiological effect tests. Becuause fosfomycin was suggested to be no genotoxic to be considered for human health, though chronic toxicity and carcinogenicity tests were not conducted, FSCJ decided that the acceptable daily intake (ADI) could be established by using a safety factor that includes an additional factor.

The lowest value among the no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) identified in various toxicity tests was the LOAEL of 175 mg (titer)/kg bw per day obtained from a 35-day subacute toxicity test in rats.

The toxicological ADI was calculated to be 0.175 mg/kg bw by applying a safety factor of 1,000 that consists of species difference of 10, individual difference of 10, and an additional factor of 10, to the LOAEL of 175 mg (titer)/kg bw per day, thus obtained. The additional factor of 10 was set because of the facts that the LOAEL in the 35-day subacute toxicity test in rats should be converted into the NOAEL, that fosfomycin was administered for 6 but not 7 days a week, and that neither chronic toxicity nor carcinogenicity tests were conducted.

On the other hand, the microbiological ADI was calculated to be 0.019 mg/kg bw per day according to the internationally recognized formula available in the International Cooperation on Harmonisation of Technical Requirements for Resistration of Veterinary Medicinal Products (VICH) Guidelines. This microbiological ADI is much smaller than the toxicological ADI, thereby ensuring toxicological safety.

Thus, FSCJ concluded that the ADI should be set at 0.019 mg/kg bw per day in the risk assessment of fosfomycin.

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

1. Toxicological effects

Subacute toxicity tests

FSCJ evaluated the submitted data o 35- or 182-day tests in rats, a 35-day test in rabbits, and a 182-day test in dogs, to examine the subacute toxicity. Toxic effects that were observed at the lowest dose include diarrhea, autopsy findings such as erosion, hyperplasia, and exfoliation of glandular stomach mucosa, and histopathological findings such as erosion of the stomach and ileum mucosa in the 35-day subacute toxicity test in rats. The LOAEL in these tests was 175 mg (titer)/kg bw per day.

Reproductive and developmental toxicity tests

Despite lack of data from a two-generation reproduction test, it was decided to evaluate reproductive and developmental toxicity applying results from forced feeding test during the period of organogenesis in rats and rabbits. In this forced feeding test during organogenesis in rats, dams had loose stools, and fetuses showed increased early resorptions and delayed ossification after administration of 1,400 mg /kg bw per day. Hence, the NOAEL was estimated for both dams and fetuses to be 700 mg (titer) /kg bw per day. In the forced feeding test during the period of organogenesis in rabbits, none of adverse effects was observed at any dose in the dams and fetuses. Therefore, the NOAEL for both dams and fetuses was estimated to be the highest dose, 420 mg /kg bw per day. Fosfomycin was not teratogenic in rats and rabbits. The lowest NOAEL was 420 mg/kg bw per day in dams and fetuses of rabbits.

Genotoxicity/carcinogenicity test

The results of genotoxicity tests, including reverse mutation, DNA damage, and mutation tests, were negative. The results of both dominant lethal and micronucleus tests were also negative in rodents. Hence, it was confirmed that fosfomycin had no genotoxicity to be concerned for human health.
Although neither chronic toxicity nor carcinogenicity tests were conducted, none of the toxicological effects of fosfomycin to suggest cytotoxicity and proliferative effects was observed in a 182-day administration test in rats and dogs. These results indicated that fosfomycin is not a genotoxic carcinogen.

Toxicological ADI

Since fosfomycin is unlikely to be a genotoxic carcinogen, we considered estimation of the ADI for fosfomycin to be relevant. Among reported results from toxicity tests, the lowest NOAEL and LOAEL were 175 mg/kg bw per day in a 35-day subacute toxicity test in rats. This LOAEL should be used appropriately to determine the ADI.

Although chronic toxicity test was not conducted, no considerable difference was noted in toxic effects between 35- and 182-day subacute toxicity tests. Administration for the prolonged period did not enhance any effect. Toxicity observed in the tests for up to 182 days was mild but not severe.

Teratogenicity was not observed in the forced feeding tests during the period of organogenesis in rats and rabbits, and no effects were observed on the reproductive potential of the dams, although two generation reproduction test was not conducted.

Therefore, we decided that the ADI to ensure sufficient safety can be estimated by converting the LOAEL in the 35-day subacute toxicity test in rats to NOAEL, and by introducing an additional factor of 10. Additional factor was set at 10 because fosfomycin was administered for 6 days a week, not 7 days, and because neither chronic toxicity nor carcinogenicity tests were conducted.

As a result, the toxicological ADI of fosfomycin was established to be 0.175 mg/kg bw per day by applying a safety factor of 1,000 (i.e. species difference of 10, individual difference of 10, and additional factor of 10) to the LOAEL of 175 mg (titer)/kg bw per day in the 35-day subacute toxicity test in rats.

2. Microbiological ADI

In this risk assessment, it was 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 the internationally recognized formula available in the VICH guidelines. In calculating a microbiological ADI, we applied 0.004397 mg/ml that is calculated minimum inhibitory concentration ([MIC_{calc}]), 84% indicating fraction of exposed bacteria based on the urine recovery rate of about 16.4% at 24 h after 500 mg [titer] administration in humans, 220 g/day for mass of colon content, and 60 kg as bw of person to the VICH formula as follows:

$$\text{ADI (mg/kg bw per day)} = \frac{0.004397\ *^1 \times 220*^2}{(1\text{-}0.16)*^3 \times 60*^4} = 0.01919 \text{ mg/kg bw per day}$$

*1: The MIC_{calc} is derived from the lower 90% confidence limit for the mean MIC_{50} of the relevant genera for which the drug is active, as described in the VICH guidelines.
*2: Mass of colon content/g.
*3: Ratio of biologically available oral dose that is estimated from the urine excretion rate of about 16.4% of total dose in an oral administration test in humans.)[1]
*4: Body weight of person/kg.

3. ADI calculation

It was decided that the ADI for fosfomycin can be established because the substance is not a genotoxic carcinogen.

The lowest LOAEL obtained in the toxicological test was 175 mg (titer)/kg bw per day in a 35-day subacute toxicity test in rats. On the basis of this result, FSCJ established the ADI to be 0.175 mg/kg bw per day by converting the LOAEL in the 35-day subacute toxicity test in rats to NOAEL, and by applying a safety factor of 1,000 (i.e. species difference of 10, individual difference of 10, and additional factor of 10). The additional factor of 10 above was set because fosfomycin was administered for 6 days a week, not 7 days, and because neither chronic toxicity nor carcinogenicity tests were conducted.

On the other hand, the microbiological ADI of 0.019 mg/kg bw per day calculated using the VICH formula is much smaller than the toxicological ADI of 0.175 mg/kg bw per day. Thus, it was appropriate to set the ADI at 0.019 mg/kg bw/day.

4. Conclusion

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

Fosfomycin: 0.019 mg/kg bw per day

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

[1] Report of clinical applications of fosfomycin calcium in surgery. T.Kawahata et al. Chemotherapy, 23(5), 1975, p.1880-1885