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

Risk Assessment Report
Mebendazole (veterinary medicines)

Food Safety Commission of Japan (FSCJ)
March 2010

Executive summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of mebendazole (CAS No. 31431-39-7), a parasiticide, using a number of data in different risk assessment reports, i.e. reports from the European Medicines Evaluation Agency (EMEA)[1,2] and from Government of Australia[3].

The data used for the risk assessment includes: pharmacokinetic studies in rats, dogs, humans, sheep, and *in vitro*; residue studies in horses, sheep, and goats; acute toxicity studies in mice, rats, guinea pigs, rabbits, and dogs; subacute toxicity studies in rats and dogs; chronic toxicity studies in dogs; genotoxicity studies and carcinogenicity studies in mice and rats; reproductive and developmental toxicity studies in mice, rats, hamsters, rabbits, dogs, cats, sheep, pigs, and horses; and findings in humans.

In these reports, the genotoxicity studies suggested that mebendazole induces aneuploidy. Howevere, a threshold has been established for genotoxicity (i.e. aneuploidy induction), and the carcinogenicity study failed to provide clear evidences of carcinogenicity though the study was insufficient. Hence, FSCJ concluded that mebendazole was not a genotoxic carcinogen to be considered for human health, and that the acceptable daily intake (ADI) could be established.

The adverse effect evoked by the lowest dose in the reported toxicity studies was maternal toxicity found in a teratogenicity study in rats, at the dose of 2.5 mg/kg bw per day, and EMEA considered this value as no observed adverse effect level (NOAEL) for evaluation of the ADI.

For evaluation of the ADI by FSCJ using various data from these reports, a safety factor of 1,000 was applied to the LOAEL of 2.5 mg/kg bw per day which was converted from NOAEL. The safety factor of 1,000 was composed of species difference of 10, individual difference of 10, and additional factor of 10. The additional factor of 10 above was set because the LOAEL was used and the chronic toxicity and carcinogenicity studies were insufficient. As a result, an appropriate ADI of mebendazole was calculated to be 0.0025 mg/kg bw per day.

In conclusion, FSCJ established the ADI to be 0.0025 mg/kg bw per day in the food safety risk assessment of mebendazole.

[1] EMEA, Committee for Veterinary Medical Products. Mebendazole Summary Report(1), 1999.
[2] EMEA, Committee for Veterinary Medical Products. Mebendazole Summary Report(2), 2001.
[3] Report from Government of Australia.

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

1. Assessment by EMEA

In the risk assessment by EMEA, the ADI was calculated to be 0.0125 mg/kg bw per day using a safety factor of 200 to the no observed adverse effect level (NOAEL) of 2.5 mg/kg bw per day, which was obtained in a 13-week subacute toxicity study in dogs and teratogenicity studies in rats and mice. The safety factor of 200 was justified because the dogs were treated only 6 days per week. EMEA considered that this ADI would offer a satisfactory margin of safety with respect to teratogenic effects of the substance. EMEA noted that mebendazole caused teratogenicity after oral administration of 40 mg/kg bw per day and after forced feeding of 10 mg/kg bw per day. It was also noted that oral administration of 40 mg/kg body weight caused no teratogenicity in rabbits.

In a study in which humans were given an oral dose of 25 mg/kg body weight, plasma mebendazole levels of 27–42 ng/mL after 2 to 4 hours have been reported according to EMEA. These concentrations were 2 to 3 times lower than the in vitro NOEL (85 ng/ml) for aneugenic effects and 3 to 4 times lower than the threshold level at a dose of 2,000 times higher than the proposed ADI. EMEA concluded that the aneugenic effects of mebendazole are therefore covered sufficientry by the ADI.

2. ADI evaluation by FSCJ

Mebendazole induced aneuploidy in a genotoxicity study conducted by EMEA. Very probably, mebendazole acts on the spindle and spindle fibers to cause chromosome instability and nondisjunction, resulting in abnormal chromosome numbers. Since aneuploidy has been observed in almost all cancer cells, mebendazole is likely to promote carcinogenicity. However its target is a protein when a substance promotes carcinogenicity, and therefore a threshold concentration of the substance for its carcinogenicity is thought to be detected, unlike other carcinogens that target DNA.

Additionally, no evidence to indicate clear carcinogenicity of mebendazole has been obtained in the genotoxicity study conducted by EMEA, though the histopathological examinations are insufficient. Hence, FSCJ considered that mebendazole was not a genotoxic carcinogen to be seriously concerned for human health, and thusconcluded that the ADI could be established.

The adverse effect evoked by the lowest dose in the reported toxicity studies was maternal toxicity found in a teratogenicity study in rats, at the dose of 2.5 mg/kg bw per day which was taken as NOAEL into the calculation of the ADI by EMEA. FSCJ converted this value to LOAEL for evaluation of the ADI, and set a safety factor of 1,000 which composed of species difference of 10, individual difference of 10, and additional factor of 10. The additional factor of 10 above was set because the LOAEL was used and the chronic toxicity and carcinogenicity studies were insufficient. As a result, the appropriate ADI of mebendazole was evaluated to be 0.0025 mg/kg bw per day.

3.Conclusion

FSCJ concluded that the following value should be used as an ADI for mebendazole:

Mebendazole: 0.0025 mg/kg bw per day

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