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

Risk Assessment Report
Oxibendazole (veterinary medicines)

Food Safety Commission of Japan (FSCJ)
March 2009

Executive summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of oxibendazole (CAS No. 20559-55-1), a parasiticide belongs to benzimidazole of wide spectrum, using a number of data in different risk assessment reports, i.e. reports from the European Medicines Evaluation Agency (EMEA)[1,2].

The data used for the risk assessment includes: absorption, distribution, metabolism and elimination tests done in cows, sheep, pigs, and horses; acute and subacute toxicity tests in rats and dogs; reproductive and developmental toxicity tests in mice, rats, sheep, cows, and horses; and genotoxicity tests.

Mutagenic potential of oxibendazole was tested in three *in vitro* tests (Ames test; L5178Y TK+/- mous lymphoma mutation assay; and chromosomal aberrations in Chinese hamster ovary (CHO) cells) and in one *in vivo* micronucleus test (mice). Oxibendazole was negative in these tests, noting that polyploidy was observed in cultured Chinese hamster ovary cells with and without S9 metabolic activation for concentration equal or higher than 10μg/ml. These results suggested that oxibendazole was not genotoxic, though neither chronic toxicity nor carcinogenicity tests were conducted[2]. Thus, FSCJ decided that an acceptable daily intake (ADI) oxibendazole could be established.

The lowest value of no observed adverse effect level (NOAEL) obtained in different toxicity tests was 30 mg/kg bw per day in a 98-day subacute toxicity test in rats and dogs. The ADI was calculated by applying to this NOAEL a safety factor of 1,000 that consists of species difference of 10, individual difference of 10, and an additional factor of 10. The additional factor of 10 above was set becauseof the fact that neither chronic toxicity nor carcinogenicity tests was conducted, that the reproductive toxicity test was insufficient, and that the chromosomal aberration test demonstrated polyploidy induction. As a result, an appropriate ADI of oxibendazole was calculated to be 0.03 mg/Kg bw per day.

In conclusion, FSCJ established the ADI to be 0.03 mg/kg bw per day in the food safety risk assessment of oxibendazole.

[1] EMEA, Committee for Veterinary Medical Products. “Oxibendazole”, Summary Report(1). 1996
[2] EMEA, Committee for Veterinary Medical Products. “Oxibendazole”, Summary Report(2), 1997.

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

1. ADI calculation

EMEA calculated the toxicological ADI of oxibendazole, by applying a safety factor of 500 to the NOAEL of 30 mg/kg bw per day which was determined in 98-day subacute toxicity tests in rats and dogs. The safety factor of 500 above consisted of conventional safety factor of 100, and additional factor of 5 that was due to polyploidy inducing effects of oxibendazole. EMEA thus established the toxicological ADI of oxibendazole to be 0.06 mg/kg bw per day (3.6 mg/person per day).

In FSCJ's risk assessment, oxibendazole was suggested to be no genotoxic to be considered for human health, though chronic toxicity and carcinogenicity tests were not conducted。 Thus, it was decided that an acceptable daily intake (ADI) could be established by using a safety factor that includes an additional factor.

FSCJ employed the NOAEL of 30 mg/kg bw per day determined in a 98-day subacute toxicity test in rats and dogs, as EMEA has employed. Howevere, FSCJ considered it desirable to set a different safety factor, namely a value of 1,000 consisting of species difference of 10, individual difference of 10, and additional factor of 10. The additional factor of 10 above was set as an uncertainty factor, because neither chronic toxicity nor carcinogenicity tests were conducted and because the reproductive toxicity test was insufficient, and the chromosomal aberration test demonstrated polyploidy induction.
As a ressult, the ADI of oxibendazole was evaluated to be 0.03 mg/kg bw per day by applying the safety factor of 1,000 to the NOAEL of 30 mg/kg bw per day.

2. Conclusion
FSCJ concluded that the following value should be used as the ADI for oxibendazole:

Oxibendazole: 0.03 mg/kg bw per day

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