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

Risk Assessment Report

Morantel and Pyrantel

(Veterinary Medicinal Products and Feed Additives)

Food Safety Commission of Japan (FSCJ)
March 2021

SUMMARY

FSCJ conducted a risk assessment of tetrahydropyrimidine insecticides, morantel (CAS No. 20574-50-9) and pyrantel (CAS No. 15686-83-6), based on reports of EMEA (European Medicines Agency) and a set of data submitted to the Ministry of Health, Labour and Welfare (MHLW).

As for morantel, FSCJ has conducted a risk assessment in 2013 and specified the ADI of 0.012 mg/kg bw/day. On the basis of this assessment, the MHLW has established the residue standards for morantel. The common metabolite morantel and pyrantel was designated as the marker substance for residue definition. They reported FSCJ the decision.

The present assessment of morantel and pyrantel was conducted in following procedures:
First, FSCJ confirmed nongenotoxicity of morantel and the ADI based on the previous assessment.
Second, FSCJ conducted assessment to establishing an ADI for pyrantel based on the data of toxicokinetics, toxicity, and mechanism of action of morantel and pyrantel.
At the final step, FSCJ assessed reliability of setting a group ADI for morantel and pyrantel based on toxicological characteristics and determination method of residual substance of marantel and pyrantel.

Data used for this assessment of morantel and pyrantel include toxicokinetics, pharmacokinetics and residue (mice, rats, dogs, cattle, sheep, pigs, hoses, donkeys, and human), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats and dogs), chronic toxicity and carcinogenicity (rats and dogs), reproductive and developmental toxicity (mice, rats, rabbits, and dogs), and others.
Results of pharmacokinetic study and residue test of pyrantel suggested that the bioabsorbance was low and the decomposition was relatively fast regardless its salt form.
Regarding genotoxicity of pyrantel, all results were negative in all *in vitro* studies, in *in vitro* studies on metabolites common with morantel, and *in vitro* and *in vivo* studies on morantel. Therefore, FSCJ considered that pyrantel has no genotoxicity relevant to human health through foods as long as is used appropriately as a veterinary medicinal product, and judged that the threshold can be set in the toxicity assessment.

There is no carcinogenicity study available for the evaluation, however; FSCJ considered that pyrantel is of no concern for carcinogenicity if is used appropriately as a veterinary medicinal product because of the following facts; pyrantel has no genotoxicity relevant to human health as long as used appropriately as a veterinary medicinal product, various toxicity studies provided no finding indicative carcinogenic potential, morantel which is the analogous substance has been evaluated to be non-carcinogenic, and of which carcinogenicity study has been judged to be unnecessary by EMA.

FSCJ considered it appropriate to specify the ADI of pyrantel to be 0.012 mg/kg bw/day based on the NOAEL of 1.2 mg/kg bw/day obtained in 13-week subacute toxicity study of pyrantel tartrate in dogs, applying 100 as a safety factor.

FSCJ judged that adverse effects of morantel and pyrantel on human health through foods are common, comprehensively considering their structural similarities, toxicokinetics, their residue levels and their toxicities. Hence, FSCJ specified the group ADI to be 0.012 mg/kg bw/day. Besides this group ADI, the ADIs of morantel and of pyrantel were both 0.012 mg/kg bw/day.