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

Risk Assessment Report
Monepantel (veterinary medicines)

Food Safety Commission of Japan (FSCJ)
September 2010

Executive Summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of monepantel (CAS No. 887148-69-8), a parasiticide, using published and unpublished reports compiled in a dossier submitted through the Ministry of Health Labour and Welfare (MHLW). The data used for the assessment includes pharmacokinetic tests (rats, dogs, and sheep), residue tests (sheep), acute toxicity tests (rats), subacute toxicity tests (mice, rats, and dogs), chronic toxicity tests (rats and dogs), carcinogenicity tests (mice and rats), reproductive and developmental toxicity tests (rats and rabbits), genotoxicity tests, and general pharmacological tests.

It turned out that monepantel was noncarcinogenic in two carcinogenicity tests, one in rats and the other in mice, and was nongenotoxic in three *in vitro* tests:the Ames' assay; chromosomal aberration test; and micronucleus test, hence monepantel was considered not to be genotoxic carcinogen. It was decided that an acceptable daily intake (ADI) could be established accordingly.

A toxicity effect observed at the lowest dose in toxicity tests in various animals was centrilobular hepatocyte hypertrophy in a 78-week carcinogenicity test in mice. The lowest observed adverse effect level (LOAEL) was 1 mg/kg bw per day. The FSCJ established an ADI of 0.001 mg/kg body weight/day, by applying a safety factor of 1,000 to the LOAEL. The safety factor of 1,000 was composed of 10 for interspecies differences, 10 for interindividual differences, and 10 for additional factor for the uncertainty due to the use of LOAEL instead of NOAEL.

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

1. Toxicological effects

Subacute toxicity test

Three subacute toxicity studies: a 13-week subacute toxicity test in mice ; a 4-week and a 90-day subacute toxicity test in rats ; and a 4- and 13-week subacute toxicity test in dogs were conducted. A toxicity effect observed at the lowest dose in these tests was dilated small intestine in male dogs in a 13-week subacute toxicity test in dogs. The LOAEL was 10 mg/kg body weight/day. The lowest no observed adverse effect level (NOAEL) was 5 mg/kg body weight/day based on increased aspartate aminotransferase (AST) levels in female mice in the 13-week subacute toxicity test in mice.

Chronic toxicity test

A 52-week chronic toxicity tests in rats and dogs were conducted. Increases in the absolute and relative weight of the male liverwere observed at the lowest dose in the 52-week chronic toxicity test in rats, while no pathological findings such as hepatocyte hypertrophy were found. The NOAEL was 14 mg/kg body weight/day. The 52-week chronic toxicity test in dogs demonstrated hypertrophy of hepatocytes and adrenocortical cells in all treatment groups. The severity of hepatocyte hypertrophy was independent of the dose. Hepatocyte hypertrophy was observed in more than half of the male and female mice in all treatment groups, but was not observed in male and female mice in the control groups. Thus, hepatocyte hypertrophy was considered to be a toxic effect and the LOAEL was set at 3 mg/kg body weight/day.

Carcinogenicity test

A 78-week carcinogenicity test in mice and a 104-week carcinogenicity test in rats were conducted. The 78-week carcinogenicity test in mice demonstrated centrilobular hepatocyte hypertrophy in male and female mice in all treatment groups. The incidence of centrilobular hepatocyte hypertrophy was significantly increased in all treatment groups except for female mice in the highest dose group. The incidence of centrilobular hepatocyte hypertrophy was independent of dose in both male and female mice. This dose independence might be caused by dose-dependent fatty liver in male and female mice in this study. Specifically, hepatocyte hypertrophy might be masked by fatty liver when these pathologies are regarded as a series of alterations, thereby influencing the incidence of hepatocyte hypertrophy. Nonsignificant differences in the female mice in the highest dose group may be similarly explained. Thus, the hepatocyte hypertrophy observed in this study might be caused by monepantel administration. The LOAEL was set at 1 mg/kg body weight/day. The 104-week carcinogenicity test in rats demonstrated increases in the absolute and relative weights of the kidneys and heart, but caused no other effects. Monepantel was noncarcinogenic in all the carcinogenicity tests.

Reproductive and developmental toxicity tests

A two-generation reproductive test in rats and a teratogenicity test in rats and rabbits were conducted. In the two-generation reproductive tests in rats, the NOAEL in parent animals was set at 200 ppm (13.5 mg/kg body weight/day) in light of the hepatomegaly, increased absolute and relative weights of the adrenal glands and liver, centrilobular hepatocyte hypertrophy, and cell hypertrophy in the zona glomerulosa of the adrenal cortex in parent animals. The LOAEL in pups was set at 200 ppm (13.5 mg/kg body weight/day) in light of the increased absolute and relative weight of the liver in pups. No effects of monepantel administration were observed in the teratogenicity test in rats and rabbits. Thus, the NOAEL in dams and fetuses was set at 1,000 mg/kg body weight/day. Monepantel was nonteratogenic. A LOAEL of 13.5 mg/kg body weight/day in pups in the two-generation reproduction test in rats was observed.

Genotoxicity test

An *in vitro* Ames test, chromosomal aberration test, and *in vivo* micronucleus test in rodents using monepantel and *in vitro* Ames and micronucleus tests using monepantel metabolites were conducted. All the tests were negative. Thus, monepantel was nongenotoxic in the living body.

2. ADI calculation

Monepantel was noncarcinogenic in a carcinogenicity test and nongenotoxic in various genotoxicity tests. Hence, monepantel is non-genotoxic. Thus, an ADI could be determined.A toxicity effect observed at the lowest dose in toxicity tests in various animals was centrilobular hepatocyte hypertrophy in a 78-week carcinogenicity test in mice. The LOAEL was 1 mg/kg body weight/day. The ADI of monepantel should be calculated to be 0.001 mg/kg body weight/day by applying a safety factor of 1,000 to the LOAEL. The additional factor of 10 was set to account for using the LOAEL in place of NOAEL.

3. Conclusion

FSCJ concludes that the following value should be used as an ADI for monepantel:

Monepantel: 0.001 mg/kg body weight/day

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