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

Risk Assessment Report
Eprinomectin (Veterinary medicines)

Food Safety Commission of Japan (FSCJ)
February 2009

Executive summary

The Food Safety Commission Japan (FSCJ) conducted a risk assessment of the parasiticide eprinomectin (CAS No. 123997-26-2) using various test results from industry concerned, which are available in a dossier submitted through the Ministry of Health, Labour and Welfare (MHLW).

The data used for the assessment were obtained from pharmacokinetic tests (rats and cows), residue tests (cows and milk), acute toxicity tests (mice and rats), subacute toxicity tests (dogs), chronic toxicity tests (dogs), two-generation reproductive tests (rats), teratogenicity tests (rats and rabbits), genotoxicity tests, eye irritation tests, and skin sensitization tests.

The test results demonstrated the effects of eprinomectin on the nervous system, including emesis, mydriasis, salivation, ataxia, recumbency, and tremors. Eprinomectin had no effects on reproduction and was neither teratogenic nor genotoxic in vivo.

No carcinogenicity test was conducted on eprinomectin. However, the structurally related drug emamectin is noncarcinogenic, and contains no structural risks alerts. Thus, eprinomectin is unlikely to be carcinogenic, and a threshold could be used to assess this agent.

The lowest no observed adverse effect level in the toxicity tests was 0.4 mg/kg bw/day in the two-generation reproductive test in rats. This value was divided by a safety factor of 100 and the acceptable daily intake (ADI) was set at 0.004 mg/kg bw/day.

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

1. Toxicological effects

(1) Subacute toxicity test

A 6- or 14-week subacute toxicity test was conducted in dogs. Toxicity effects observed at the lowest dose included emesis, mydriasis, salivation, ataxia, recumbency, weight loss or reduced weight gain, and axonal degeneration in sciatic nerves in the 14-week subacute toxicity test. The no observed adverse effect level (NOAEL) was 0.8 mg/kg body weight/day.

(2) Chronic toxicity/carcinogenicity test

A 53-week chronic toxicity test was conducted in dogs. High doses caused localized degeneration in the pons cerebelli and cerebellar nucleus, and vacuolization of swollen degenerated neurons. The NOAEL on the basis of this test result was 1 mg/kg bw/day. The chronic toxicity test was conducted only in dogs and not in any other animal model. Dogs are highly susceptible to both eprinomectin and emamectin according to a chronic toxicity test on emamectin, which is an avermectin compound structurally closely related to eprinomectin. The toxicological endpoint of these compounds is considered to be neurotoxicity. Furthermore, the same NOAEL was obtained in 14-week subacute toxicity and 53-week chronic toxicity tests in dogs. Thus, neurotoxicity does not increase even if the dosing period is extended, and therefore, it was not necessary to conuduct chronic toxicity test of eprinomectin using animals other than dogs.

No carcinogenicity test was conducted on eprinomectin. However, a carcinogenicity test was conducted on the structurally related drug emamectin in mice and rats. No carcinogenicity was observed in these animals.

According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessment, eprinomectin “contains no structural alerts, and the structurally closely related avermectins, emamectin and abamectin, are not carcinogenic in mice or rats”, and thus, “eprinomectin is unlikely to be carcinogenic”.

(3) Reproductive and developmental toxicity tests

A two-generation reproduction test in rats and teratogenicity tests in rats and rabbits were conducted as reproductive and developmental toxicity tests.

The two-generation reproduction test demonstrated reduced feed intake, loss of weight, and low copulation rates among parent animals in the group administered 54 ppm. Increased preweanling mortality, decreased number of surviving pups, and loss of weight were seen in pups. Tremors were observed in the pups in the 18 ppm group, although no effects were observed at 18 ppm in parent animals. In the JECFA assessment, the NOAEL is set at 9 ppm (1.3 mg/kg bw/day). However, the dose level was altered during this test. Thus, the FSCJ did not find the NOAEL calculation backed by sufficient scientific evidence. Therefore, the NOAEL was set at 6 ppm to ensure safety (0.4 mg/kg bw/day).

Teratogenicity was not demonstrated in any tests. Decreased weight gain was seen in rat dams, while no effects of eprinomectin were observed in pups. Delayed pupillary reflex and mydriasis were observed in rabbit dams, but no effects of eprinomectin were observed in pups. The lowest NOAEL derived from these teratogenicity tests was 0.5 mg/kg bw/day.

(4) Genotoxicity test

Genotoxicity tests conducted include: in vitro reverse mutation, alkaline elution, chromosomal aberration, gene mutation, and in vivo micronucleus tests. All these test results were negative. Thus, eprinomectin was not considered to be genotoxic.

2. ADI calculation

Although no carcinogenicity test was conducted on eprinomectin, the structurally related drug emamectin is noncarcinogenic and contains no structural risks alerts. Thus, eprinomectin was unlikely to be carcinogenic. The results of the genotoxicity tests were also all negative. Thus, eprinomectin was considered neither genotoxic nor carcinogenic, and it was appropriate to determine the ADI.

On the basis of tremors observed in juvenile animals at the lowest observed adverse effect level in the two-generation reproduction test in rats, the NOAEL was set at 0.4 mg/kg bw/day. Since this NOAEL was determined to ensure safety, it was not necessary to apply an additional safety factor which takes into account neurotoxicity in juvenile animals.

Accordingly, it was considered appropriate to set the ADI at 0.004 mg/kg bw/day by applying a safety factor of 100 (10 for inter-species differences and 10 for inter-individual variations) to the NOAEL of 0.4 mg/kg bw/day.

3. Conclusion

Given these test results, our risk assessment concluded the ADI for eprinomectin to be set as follows:

Eprinomectin: 0.004 mg/kg bw/day

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