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

Risk Assessment Report

Isopropyl ester of methionine hydroxy analog (HMBi)

(Feed Additive)

Food Safety Commission of Japan (FSCJ)
May 2024

ABSTRACT

The FSCJ conducted a risk assessment of a feed additive, Isopropyl ester of methionine hydroxy analog (HMBi), referring to the submitted documents for feed additive designation.

HMBi is a synthetic product bonded with ester for 2-deamino-2hydroxymethionine (HMTBa) and 2-propanol. This feed additive is added to cattle and calf feed to supplement methionine. The recommended amount is 47.3 mg/kg bw per day.

HMTBa, a component of HMBi, is designated as a feed additive by the Minister of Agriculture, Forestry and Fisheries to supplement methionine, the same as the assessed additive. 2-propanol is designated as a food additive by the Minister of Health, Labour and Welfare.

The FSCJ determined that the effects on human health by the excipients and others contained in this feed additive would be negligible if humans take this feed additive as a contained substance, considering its usage, existing assessments, directions, and dose.

From the study results of fate in animals and residues, the FSCJ viewed the following sequences and determined a low probability that HMBi would remain in the tissues and milk:

- HMBi is hydrolyzed into HMTBa and 2-propanol after being administered to the cattle. After that, those additives are absorbed through the first rumen wall; and
- HMTBa becomes a source of methionine and 2-propanol is oxidized reversibly to acetone in the liver.

Among the metabolites, methionine is produced *in vivo*. It has been assessed as having no concern about adverse effects on human health through residues in food as long as it is normally used as a veterinary medicinal product or a feed additive. Meanwhile, acetone produced from 2-propanol remained in the milk. However, the average acetone concentration in milk after HMBi administration was far below the concentration that causes metabolic acidosis in cattle. This concentration was not a problem for the cattle. Further, the intake of acetone per body weight of a human child was estimated based on acetone concentration in the milk observed in the HMBi-administered group of a residue study. The amount was less than the RfD (Reference Dose) for chronic oral exposure of acetone to humans computed by the U.S. EPA (United States Environmental Protection Agency) despite the fact of overestimated assumption that such acetone concentration could be applied for all the milk that a child consumes per day. Acetone is volatile. As dairy-derived products distributed on the market are generally sterilized, the amount of acetone

becomes even lower during sterilization. Accordingly, the probability that humans exposed to acetone due to the intake of dairy products would be lower. Based on these facts, the FSCJ determined that the probability of adverse effects on humans derived from the concentration of acetone in the milk due to the administration of HMBi would be significantly low as long as HMBi is normally applied by the expected usage method.

In the genotoxicity study, the FSCJ determined that HMBi is not genotoxic.

In the subacute toxicity study, the primary adverse effects were abnormalities in the liver (hepatocyte vacuolation or pigmentation), kidneys (hyaline droplet deposition), spleen (hemosiderin deposition/ hemosiderosis), and blood (anemia). These studies' lowest no-observed-adverse-effect level (NOAEL) was 100 mg/kg bw per day.

Chronic toxicity, carcinogenicity, and reproductive/developmental toxicity studies have not been conducted. Meanwhile, the FSCJ assumed no safety issue with HMTBa and 2-propanol which HMBi is promptly hydrolyzed into these additives right after an animal takes it. This assumption was on the ground that no concern about chronic toxicity, carcinogenicity or teratogenicity had been reported.

In the safety study for the targeted animals, the FSCJ viewed that there would be no safety issue for the cattle when administering this feed additive to them with the recommended amount.

Given the above, the FSCJ concluded that the probability of affecting human health would be negligible as long as this feed additive is appropriately used.