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

Risk Assessment Report

Nicarbazin

(Feed Additive)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

The FSCJ conducted a risk assessment of an anti-parasitic veterinary medicinal product and feed additive of nicarbazin (CAS No. 330-95-0), based on the submitted documents.

To determine an acceptable daily intake (ADI) and safe concentrations for nicarbazin (DNC and HDP), a series of studies were conducted to assess genotoxicity, subacute and chronic toxicity, reproductive and developmental toxicity.

Genotoxicity study: No safety concerns for humans arise from nicarbazin and its components of 4,4'-dinitrocarbanilide (DNC) and 4, 6-dimethyl-2-pyrimidinol (HDP) when nicarbazin is used as a veterinary medicinal product or a feed additive. The FSCJ determined that to specify the ADI would be possible.

Subacute and chronic toxicity studies in rats: The LOAEL of nicarbazin was 100 mg/kg bw per day. The NOAEL of its components (DNC and HDP) were identified as follows, based on the findings mainly from kidneys in the 52-week administration test:
- 20 mg/kg bw per day for DNC; and
- 8 mg/kg bw per day for HDP

In the 91-day oral administration test, the NOAEL of 709 mg/kg bw per day was identified for DNC.

Reproductive and developmental toxicity studies in rabbits: DNC administration test has not been conducted. The NOAEL of 60 mg/kg bw per day was identified for nicarbazin in the findings from the liver of dams. No effect was observed in fetuses and the NOAEL identified was 120 mg/kg bw per day. As for its components, the LOAEL were as follows:
- 580 mg/kg bw per day for DNC; and
- 193 mg/kg bw per day for HDP

To determine the ADI of nicarbazin, the FSCJ considered that the substances to which humans are exposed are not nicarbazin administered to chicken, but its components, DNC and HDP. Comparing DNC and HDP, DNC's residual period was longer. The toxicity study that provides the basis for setting the ADI is the study in which the mixture was administered, not nicarbazin. The FSCJ conducted an evaluation based on toxicity data for the mixture, due to the lack of toxicological data of nicarbazin.

Among various toxicity studies, the lowest values of the NOAEL were identified in 52-week chronic toxicity study in rats as follows:
- 20 mg/kg bw per day for DNC; and
- 8 mg/kg bw per day for HDP

Based on these NOAEL, the FSCJ specified the ADI of 0.2 mg/kg bw per day for DNC and 0.08 mg/kg bw per day for HDP by applying a safety factor of 100.

In the results of the microbiological effect survey, none of nicarbazin, DNC, and HPD showed antibacterial activity. Consequently, the FSCJ thought that establishing a microbiological ADI would not be necessary but adopting a toxicological ADI.

From the study results of fate in animals, pharmacokinetics, and residues, it was identified that the main harmful substance to humans is not nicarbazin, but its component, DNC. Given the above NOAEL, the FSCJ concluded that the ADI should be 0.2 mg/kg per day for DNC, in the case that nicarbazin is used as a veterinary drug or a feed additive.