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

Risk Assessment Report

Bicyclopyrone

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of bicyclopyrone (CAS No. 352010-68-5), an herbicide, based on results from various studies.
The data used in the assessment include fate in animals (rats, goats and chickens), fate in plants (maize and sugarcane), residues in crops, subacute toxicity (rats, mice and dogs), acute- and subacute neurotoxicity (rats), chronic toxicity (rats), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), 2-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), immunotoxicity (mice) and genotoxicity.

Major adverse effects of bicyclopyrone were ocular toxicity such as corneal opacity, hepatoxocity including centrilobular hypertrophy of hepatocytes, and follicular cell hypertrophy in the thyroid. Bicyclopyrone had no reproductive toxicity, immunotoxicity or genotoxicity relevant to human health.
Chromatolysis and swelling of neurons in the dorsal root ganglion were identified as treatemen-related histopathological changes in a one-year chronic toxicity study in dogs, however no clinical sign indicating neurotoxicity was detected in any toxicity studies.
In developmental toxicity studies in rabbits, costochondral malformation, ventricular septum defect, cervical vertebrae anomalies and others were observed in the fetuses. Bicyclopyrone had no teratogenicity in rats.
Increased incidence of squamous cell papilloma and carcinomas in the cornea was ovserved in male in a 2-year chronic toxicity and carcinogenicity combined study in rats. However, a genotoxic mechanism was unlikely to be involved in the tumor development. It was thus considered possible to establish a threshold in the assessment.

Based on all results evaluated, bicyclopyrone (only parent compound) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural and livestock products.

The lowest value of no-observed-adverse-effect levels (NOAELs) and the lowest-observed-adverse-effect levels (LOAELs) in the toxicological studies was the LOAEL of 0.28 mg/kg bw/day in a 2-year chronic toxicity and carcinogenicity combined study in rats. FSCJ considered that an additional safety factor of 10 was appropriate to specify the ADI for the following reasons: 1) the detection of the focal hyperplasia of thyroid follicular cellsat this LOAEL, and 2) insuffient information on dose-response relationship of this change due to wide common ratio in this study. FSCJ specified the ADI of 0.00028 mg/kg bw/day,

applying the safety factor of 1,000 (10 for species difference, 10 for individual difference and an additional factor of 10 to account for the use of a LOAEL instead of a NOAEL) to this LOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of bicyclopyrone was 1 mg/kg bw/day obtained in a developmental toxicity study③ in rabbits, the observed endpoint was supernumerary ribs in the fetuses observed at the dose without maternal toxicity. FSCJ thus specified an acute reference dose (ARfD) for pregnant women and women suspected of being pregnant to be 0.01 mg/kg bw by applying a safety factor of 100 to the NOAEL. For general population, FSCJ specified ARfD to be 2 mg/kg bw by applying a safety factor of 100 to the NOAEL of 200 mg/kg bw in an acute neurotoxicity study in rats.