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

Risk Assessment Report

Fluazinam

(Pesticides)

Food Safety Commission of Japan (FSCJ)

November 2013

ABSTRACT

FSCJ conducted a risk assessment of a fungicide "fluazinam" (CAS No. 79622-59-6) having N-phenyl-pyridinamine skeleton based on summary reports made by applicants and the documents from the governments of the US, Canada and Australia.

The data used in the assessment were on: fate in animals (rats, goats, and chickens), fate in plants (kidney beans, apples, etc.), residues in crops, subacute toxicity (rats, mice, and dogs), chronic toxicity (dogs and rats), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and others.

Major adverse effects of fluazinam observed are: hepatocellular hypertrophy and others in the liver and effects on blood such as anemia.

No effect on reproductive abilities or genotoxicity was observed.

Increases in the incidence of thyroid tumors in rats and hepatocellular tumors in mice were identified in carcinogenicity tests. Increased incidence of thyroid tumors in rats, on one hand, was likely a consequence of the following chain of events: Fluazinam increased the hepatic microsomal UDP-glucuronyltransferase (UDPGT) activity. As a result, the serum T4 level decreased while the TSH level increased, leading to enhancement of thyroid cell proliferation and hypertrophy of follicular epithelial cells. Increased incidence of hepatocellular tumors in mice, on the other hand, was likely a consequence of induction of the hepatic drug-metabolizing enzyme and enhanced cell proliferation by fluazinam. These mechanisms for the carcinogenicity are considered unlikely to be genotoxic mechanisms, and FSCJ concluded that the threshold could be specified for fluazinam.

White matter vacuolation in the central nervous system was observed in chronic toxicity studies in dogs and carcinogenicity studies in mice. Tests using technical grade fluazinam and ultra-purified fluazinam indicated involvement of impurity-5 in the vacuolation. Further studies indicated possible reversibility of the white matter vacuolation.

A developmental toxicity study in rats identified a significant increase in the incidence of external anomaly such as a small body, cleft palates and deformed palates in fetuses of mice exposed to the highest dose. However, another developmental toxicity study in rats conducted to confirm these results failed to obtain similar results, although skeletal variations such as unossification in sternebrae etc. were observed. The lack of reproducibility in these results suggests no direct relationship between the external anomaly and exposure of fluazinam. Furthermore, no malformation or increase in the occurrence of mutation was observed in developmental toxicity studies in rabbits. From these results, FSCJ concluded that fluazinam has no teratogenicity.

The minimum no observed adverse effect level (NOAEL) in the toxicological studies was 0.38 mg/kg bw/day obtained in a 2-year combined chronic toxicity/carcinogenicity study in rats. However, the lowest observed adverse effect level (LOAEL) in this study was 3.82 mg/kg bw/day, while the NOAEL of a 2-year chronic toxicity study in rats was 1.9 mg/kg bw/day and the NOAEL of a 2-generation reproductive toxicity study in rats was 1.49 mg/kg bw/day. The discrepancy in NOAELs was due to the difference in dose settings, and FSCJ concluded that the NOAEL of fluazinam for rats was 1.49 mg/kg bw/day. The NOAEL in a 1-year chronic toxicity study in dogs was 1 mg/kg bw/day, and FSCJ concluded that this value was appropriate as the basis of the acceptable daily intake (ADI).

Consequently, FSCJ specified the ADI for fluazinam to be 0.01 mg/kg bw/day, applying the safety factor of 100 to the NOAEL of 1 mg/kg bw/day.