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

Risk Assessment Report

Gibberellin

(Pesticides)

Food Safety Commission of Japan (FSCJ)
January 2018

ABSTRACT

FSCJ conducted a risk assessment of gibberellin (gibberellin A_3, CAS No. 77-06-5), a plant growth regulator with gibbane ring, based on results from various studies.

The data used in the assessment include fate in animals (rats), residues in crops, subacute toxicity (rats and mice), combined chronic toxicity/carcinogenicity (rats), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity and mechanism of liver tumor observed in rat.

FSCJ noted that the data for specification at dose-response assessment were insufficient in some toxicity studies, as definitive subacute toxicity studies were conducted in rodents only, and the chronic toxicity/carcinogenicity study was conducted in rats only. However, FSCJ considers that the toxicological evaluation can be done by applying an additional safety factor, since data of subacute toxicity in dogs were available from the documents referred but not used at the dose assessment, and specie difference was not observed in subacute toxicity.

Major adverse effects of gibberellin observed are, suppressed body weights, effects on the digestive tract (soft stool) and liver (altered hepatocellular foci, rat only). Gibberellin showed no adverse effects on reproductivity, no teratogenicity and no genotoxicity. An increase in the incidence of hepatocellular adenomas in rats was identified in combined two-year chronic toxicity/carcinogenicity tests. 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 the results from various studies, gibberellin (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

FSCJ considered that the safety factor of 1,000 (10 for specie difference, 10 for individual difference, and 10 for an additional uncertainty factor due to insufficient data on animal species in chronic toxicity and carcinogenicity) is appropriate, since the subacute toxicity was studied only in rodents, and a possibility of different toxicological profiles between short-term and long-term treatment was suggested in rats but it could not be determined due to lack of the data in other species. The lowest no-observed-adverse-effect level (NOAEL) obtained in all tests was 112 mg/kg bw/day in combined two-year chronic

toxicity/carcinogenicity in rats. FSCJ specified an acceptable daily intake (ADI) of 0.11 mg/kg bw/day by applying a safety factor of 1,000 to the NOAEL.

The lowest NOAEL for adverse effects which are likely elicited by a single oral administration of gibberellin was 4,190 mg/kg bw obtained in 90-day subacute toxicity study in mice. FSCJ concluded it was unnecessary to specify the ARfD, since this NOAEL was above the cut-off level (500 mg/kg bw) of specifying ARfD.

Table 1. *Levels relevant to toxicological evaluation of gibberellin*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 1 000, 10 000, 50 000 ppm M: 0, 69.7, 704, 3 740 F: 0, 86.9, 871, 4 440	M: 704 F: 871 M/F: Soft stool
	Combined two-year chronic toxicity/ carcinogenicity study	0, 3 000, 10 000, 30 000 ppm M：0, 112, 379, 1 200 F：0, 135, 460, 1 460	M: 112 F: 135 M/F: Increased volume of drinking water (M/F: Increased incidences of hepatocellular adenoma)
	Two-generation reproductive toxicity study	0, 3 000, 10 000, 30 000 ppm PM: 0, 233, 767, 2 400 PF: 0, 263, 870, 2 700 F_1M: 256, 853, 2 610 F_1F: 0, 299, 997, 3 060	PM: 767 PF: 870 F_1M: 853 F_1F: 997 Parent M/F: Soft stool Offspring Suppressed body weight, Enlargement of caecum (No effect on reproduction)
	Developmental toxicity study	0, 1 000	Dam animals and fetuses: 1 000 Dams and fetuses: No toxic effect (No teratogenicity was observed)
Mouse	90-day subacute toxicity study	0, 3 000, 10 000, 30 000, 100 000 ppm M: 0, 410, 1 250, 4 190, 15 200 F: 0, 420, 1 420, 4 580, 17 600	M: 1 250 F: 1 420 M/F: Soft stool
Rabbit	Developmental toxicity study (the 1st study)	0, 1 000	Dams: - Fetuses: 1 000 Dams: Suppressed body weight and decreased feed consumption Fetuses: No toxic effect

			(No teratogenicity was observed)
	Developmental toxicity study (the 2nd study)	0, 100, 300, 1 000	Dams: 300 Dams: Soft stool, suppressed body weight Fetuses: No toxic effect
	Integrated evaluation based on the developmental toxicity study (the 1st study and 2nd study)		Dams: 300 Fetuses: 1 000 (No teratogenicity was observed)
ADI			NOAEL: 112 SF: 1 000 ADI: 0.11
The critical study for setting ADI			Combined two-year chronic toxicity/carcinogenicity study in rats

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable daily intake
[1)], The adverse effect observed at LOAEL
-, NOAEL could not be specified

Table 2. *Potential adverse effects of a single oral administration of gibberellin*

Species	Study	Dose (mg/kg bw)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw)[1)]
Rat	Acute toxicity study	5 000	M/F: － M/F: Soft stool and soiled perineal region
Mouse	Subacute toxicity study	M: 0, 410, 1 250, 4 190, 15 200 F: 0, 420, 1 420, 4 580, 17 600	M: 4 190 F: 4 580 M/F: Soft stool
ARfD			Unnecessary to specify the ARfD, since the NOAEL was above the cut off level (500 mg/kg bw).

NOAEL, No-observed-adverse-effect level; SF, Safety factor; ADI, Acceptable daily intake
[1)], The adverse effect observed at LOAEL
－：NOAEL could not be specified