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

Risk Assessment Report

Sethoxydim
(Pesticides)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ established health based guidance values of sethoxydim (CAS No.74051-80-2), a cyclohexanedione herbicide based on results from various studies in the risk assessment.

The data used in the assessment include fate in animals (rats, goats and chickens), fate in plants (corns, tomatoes and others), residue in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), genotoxicity of sethoxydim or metabolites, and mechanism studies on induction of hepatic metabolism enzymes in rats, mice and dogs.

Major adverse effects of sethoxydim were increased liver weight, hepatocellular hypertrophy and hepatocyte fatty degeneration, suppressed body weight in various species and anemia in dogs. No carcinogenicity, reproductive toxicity and genotoxicity relevant to human health was observed.

In one of two developmental toxicity studies in rats, sethoxydim at the dose levels with severe maternal toxicity caused external and skeletal anomalies, however, no teratogenicity was observed in rabbits.

From the above results, sethoxydim and its metabolites B, C, H and K (including all their conjugates); sethoxydim and its metabolites B and C; and sethoxydim (parent compound only) were identified as the relevant substance for the residue definition for dietary risk assessment in the agricultural, livestock and fishery products, respectively.

The lowest no-observed-adverse-effect level (NOAEL) in various toxicological studies was 8.86 mg/kg bw/day in a one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.088 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest value of NOAEL or lowest-observed-adverse-effect level (LOAEL) for adverse effects of eliciting a single oral administration of sethoxydim was NOAEL of 180 mg/kg bw/day obtained in the second developmental toxicity study in rats. FSCJ specified an acute reference dose (ARfD) to be 1.8 mg/kg bw by applying a safety factor of 100 to the NOAEL.

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

Species	Study	Dose (mg/kg bw/day)	Critical endpoints[1)]
Rat	90-day subacute toxicity study	0, 33, 100, 300, 900, 2 700 ppm M: 0, 2.25, 6.75, 20.1, 60.4, 196 F: 0, 2.42, 7.08, 21.4, 66.2, 200	M: 20.1 F: 21.4 M: Increase in T.Bil, increased absolute/relative liver weight and others F: Increase in T.Bil
	13-week subacute neurotoxicity study	0, 300, 980, 3 200 ppm M: 0, 18.4, 59.3, 207 F: 0, 22.2, 72.0, 234	M: 59.3 F: 72.0 FM: Suppressed body weight (No subacute neurotoxicity)
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 40, 120, 360 ppm M: 0, 1.85, 5.54, 16.6 F: 0, 2.35, 6.78, 21.0	M: 16.6 F: 21.0 FM: No toxicological effects (Not carcinogenic)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 360, 1 080 ppm M: 0, 18.2, 55.9 F: 0, 23.0, 71.8	M: 18.2 F: 23.0 FM: Suppressed body weight (Not carcinogenic)
	Two-year combined chronic toxicity/carcinogenicity study (the 3rd study)	0, 300, 1 000, 3 000 ppm M : 0, 12, 48, 143 F : 0, 17, 66, 204	M: 12 F: 17 M: Suppressed body weight and others F: Increase in T.Bil (Not carcinogenic)
	Two generation reproductive toxicity study (the 1st study)	0, 40, 120, 360, 3 240 ppm PM : 0, 2.83, 8.37, 24.9, 163 PF : 0, 3.23, 9.70, 28.8, 193 F_1M : 0, 2.78, －, 25.6, 247 F_1F : 0,3.31, －, 30.9, 273	Parent PM: 24.9 PF: 28.8 F_1M: 25.6 F_1F: 30.9 Offspring PM: 163 PF: 193 F_1M: 247 F_1F: 273 Parent: Slightly suppressed body weight

Species	Study	Dose (mg/kg bw/day)	Critical endpoints[1)]
			Offspring: No toxicological effects (No effect on reproduction)
	Two generation reproductive toxicity study (the 2nd study)	0, 150, 600, 3 000 ppm PM : 0, 10.7, 42.7, 214 PF : 0, 12.4, 48.9, 249 F_1M : 0, 11.0, 45.9, 226 F_1F : 0, 12.7, 50.4, 259	Parent PM: 214 PF: 48.9 F_1M: 226 F_1F: 50.4 Offspring PM: 42.7 PF: 48.9 F_1M: 45.9 F_1F: 50.4 Parent: Slightly suppressed body weight Offspring: Suppressed body weight (No effect on reproduction)
	Developmental toxicity study (the 1st study)	0, 40, 100, 250	Maternal: 40 Embryo/fetus: 250 Maternal: Suppressed body weight Embryo/fetus: No toxicological effects (Not teratogenic)
	Developmental toxicity study (the 2nd study)	0, 50, 180, 650	Maternal: 50 Embryo/fetus: 180 Maternal: Suppressed body weight Embryo/fetus: external/skeletal anomalies and others
Mouse	90-day subacute toxicity study	0, 100, 300, 900, 2 700 ppm M : 0, 15.4, 45.6, 137, 374 F : 0, 17.2, 52.7, 164, 486	M: 137 F: 164 M: Decrease in T.Chol, suppressed body weight and others F: Increase in T.Chol

Species	Study	Dose (mg/kg bw/day)	Critical endpoints[1)]
	Two-year chronic toxicity/carcinogenicity study	0, 40, 120, 360, 1 080 ppm M : 0, 4.48, 13.8, 41.2, 134 F : 0, 4.85, 14.9, 44.3, 143	M: 13.8 F: 44.3 FM: Hepatocellular fatty degeneration and others (Not carcinogenic)
Rabbit	Developmental toxicity study (the 1st study)	0, 40, 160, 480	Maternal : 40 Embryo/fetus : 160 Maternal: Suppressed body weight Embryo/fetus: Decreased embryo survival and others
	Developmental toxicity study (the 2nd study)	0, 80, 160, 320, 400	Maternal: 320 Embryo/fetus: 320 Maternal: Trend for suppressed body weight and others Embryo/fetus: Incomplete ossification of sternebrae 6 (Not teratogenic)
Dog	6-month subacute toxicity study	0, 60, 600, 6 000 ppm M : 0, 1.97, 19.6, 177 F : 0, 2.02, 20.2, 223	M: 19.6 F: 20.2 FM : Decrease in Ht, Hb, RBC and others
	One-year chronic toxicity study	0, 300, 600, 3 600 ppm M : 0, 8.86, 17.5, 110 F : 0, 9.41, 19.9, 129	M : 8.86 F : 19.9 FM : Increase in ALP and others
ADI (cRfD)			NOAEL: 8.86 SF: 100 ADI: 0.088
The critical study for setting the ADI			One-year chronic toxicity study in dogs

NOAEL. No-observed adverse effect level; SF, Safety factor; UF, Uncertainty factor; ADI, Acceptable Daily intake;
[1)] Endpoints, The adverse effect observed at LOAEL

Table 2. *Adverse effects possibly elicited by a single oral administration*

Species	Study	Dose (mg/kg bw or mg/kg bw/day)	NOAEL and end point for establishing acute reference dose (ARfD)[1)] (mg/kg bw or mg/kg bw/day)
Rat	Acute toxicity study (the 1st study)	M: 2 083, 2 500, 2 739, 3 000, 3 286, 3 600 F: 2 200, 2 569, 3 000, 3 503, 4 091, 4 777	M: － F: － FM: Ataxic gate, prone position, muscle weakness and others
	Acute toxicity study (the 2nd study)	FM: 0, 2, 182, 2 836, 3 687, 4 793, 6 231, 8 100	FM : － FM: Ataxic gate, lateral position, flaccidity salivation, tremor, suppressed body weight and others
	Developmental toxicity study (the 2nd study)	0, 50, 180, 650	Maternal: 180 Embryo/fetus: 180 Maternal: Decreased body weight, ataxic gate and others Embryo/fetus: External anomalies (loss of tail, filamentous tail and imperforate anus and skeletal anomalies (defect in formation of sacral/caudal vertebrae and others)
Mouse	Acute toxicity study	FM: 0, 2, 836, 3, 687, 4 793, 6 231, 8 100	FM: － FM: Increase in locomotor activity, ataxic gate, lateral position, sedation with ptosis, suppressed respiration and others
Rabbit	Acute toxicity study	M: 1, 822, 2, 551, 3, 571, 5 000, 7 000, 9 800 F : 3, 571, 4 226, 5 000, 7 000	M: － F: － FM: Ataxic gate, sedation, muscle weakness, prone position and others
Dog	Acute toxicity study	FM: 1 250, 2 500, 5 000	M: 1 250 F: － FM : Ataxic gate, tremor, side position
ARfD			NOAEL: 180 SF: 100 ARfD: 1.8
The critical study for setting the ARfD			Developmental toxicity study in rats (the 2nd study)

ARfD, Acute reference dose; SF, Safety factor; NOAEL, No-observed adverse effect level;
－, NOAEL could not be specified
[1)], The adverse effect observed at LOAEL