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

Risk Assessment Report

Butachlor (Second edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)
November 2023

ABSTRACT

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of butachlor (CAS No. 23184-66-9), an amide herbicide, based on results from submitted documents. For the second edition, a request for reevaluation was made in accordance with the Agricultural Chemicals Regulation Act, whereby additional test results were submitted by the Ministry of Agriculture, Forestry and Fisheries, including results from residue analysis for crops (paddy rice), acute toxicity study (oral administration in rats), reverse mutation test, and reports on published scientific literature.

Test data used in the assessment include fate in plants (paddy rice), residues in crops, fate in animals (rats, mice and monkeys), subacute toxicity (rats and mice), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), and genotoxicity.

Major adverse effects of butachlor were observed in the liver (including hepatocellular hypertrophy), the kidneys (including organ weight changes and chronic progressive nephropathy), glandular stomach (mucosal atrophy), nasal cavity (hyperplasia of goblet cells), thyroid gland (hyperplasia) and blood (anemia) (Table 1). No adverse effects on fertility, teratogenicity, or biologically significant genotoxicity were observed .

The mode of action was considered to be non-genotoxic, and it was deemed possible to establish a threshold for evaluation, although increased incidences of tumor formation in the stomach, thyroid gland and nose were observed. Furthermore, the mechanisms of development of all tumors suggested that their extrapolation to humans or sensitivity in humans was considered to be low.

Based on these results, butachlor (parent compound only) was identified as the relevant substance for the residue definition for dietary risk assessment in agricultural and fishery products.

The lowest no-observed-adverse-effect level (NOAEL) was 1.0 mg/kg bw per day from a comprehensive evaluation of the two-year combined chronic toxicity/carcinogenicity studies (the 2nd study) and (the 3rd study) in rats (Table 1). The FSCJ specified an acceptable daily intake (ADI) of 0.01 mg/kg bw per day by applying a safety factor of 100 to the NOAEL.

NOAEL and lowest-observed-adverse-effect level (LOAEL) values from these studies were compared to assess potential adverse effects after a single oral administration of butachlor. The lowest NOAEL was 49 mg/kg bw per day in developmental toxicity studies in rabbits (Table 2). TheFSCJ established an acute reference dose (ARfD) of 0.49 mg/kg bw by applying a safety factor of 100 to this NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
Rat	90-day subacute toxicity study (the 1st study)	0, 300, 1 000, 3 000, 5 000 ppm M: 0, 17.5, 58.7, 177, 305 F: 0, 19.0, 62.7, 186, 313	M: 17.5 F: 19.0	M: 58.7 F: 62.7	M: Suppressed body weight gain, etc. F: Epithelial hyperplasia in the urinary bladder, etc.
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 10, 100, 1 000 ppm M: 0, 0.365, 3.65, 37.1 F: 0, 0.432, 4.33, 43.4	M: 3.65 F: 4.33	M: 37.1 F: 43.4	M/F: Suppressed body weight gain, etc. (No carcinogenicity observed)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 100, 1 000, 3 000 ppm M: 0, 4.5, 45.6, 139 F: 0, 5.7, 58.5, 190	M: - F: -	M: 4.5 F: 5.7	M/F: Chronic kidney disease (Tumorigenesis in the stomach, thyroid gland and nose)
	Two-year combined chronic toxicity/carcinogenicity study (the 3rd study)	0, 5, 20, 100 ppm M: 0, 0.2, 1.0, 4.9 F: 0, 0.3, 1.2, 6.1	M: 4.9 F: 6.1	M: - F: -	M/F: No toxicity (No carcinogenicity observed)
	Comprehensive evaluation of the 2nd and 3rd two-year combined chronic toxicity/carcinogenicity studies		M: 1.0 F: 1.2	M: 4.5 F: 5.7	M/F: Chronic kidney disease (Tumorigenesis in the stomach, thyroid gland and nose)
	Two-generation reproductive toxicity study	0, 100, 1 000, 3 000 ppm PM: 0, 6.74, 67.2, 198 PF: 0, 8.40, 84.8, 246 F_1M: 0, 8.13, 84.0, 283 F_1F: 0, 9.58, 103, 320	Parents PM: 6.74 PF: 84.8 F_1M: 8.13 F_1F: 103 Offspring PM: 6.74 PF: 8.40 F_1M: 8.13 F_1F : 9.58	Parents PM: 67.2 PF: 246 F_1M: 84.0 F_1F: 320 Offspring PM: 67.2 PF: 84.8 F_1M: 84.0 F_1F : 103	Parents M/F: Suppressed body weight gain Offspring M/F: Suppressed body weight gain (No effect on fertility observed)
	Developmental toxicity study	0, 49, 147, 490	Dams: 147 Fetuses: 490	Dams: 490 Fetuses: -	Dams: Loss of body weight/suppressed body weight gain, etc. Fetuses: No toxicity (No teratogenicity observed)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)	Critical endpoints[1)]
Mouse	90-day subacute toxicity study	0, 1 000, 3 000, 6 000 ppm M: 0, 214, 673, 1 290 F: 0, 248, 729, 1 490	M: 214 F: 248	M: 673 F: 729	M/F: Suppressed body weight gain, etc.
	Two-year carcinogenicity study	0, 50, 500, 2 000 ppm M: 0, 7.13, 72.5, 304 F: 0, 8.56, 85.6, 382	M: 7.13 F: 8.56	M: 72.5 F: 85.6	M/F: Cataract, etc. (No carcinogenicity observed)
Rabbit	Developmental toxicity study	0, 49, 147, 245	Dams: 49 Fetuses: 49	Dams: 147 Fetuses: 147	Dams: Increased mortality, etc. Fetuses: Average fetal weight loss (No teratogenicity observed)
Dog	One-year chronic toxicity study	0, 1, 5, 25	M/F: 5	M/F: 25	M/F: Increased relative and absolute weights of the liver, etc.
ADI			NOAEL: 1.0 SF: 100 ADI: 0.01		
The critical study for setting ADI			Comprehensive evaluation of the 2nd and 3rd two-year combined chronic toxicity/carcinogenicity studies		

ADI, Acceptable daily intake; LOAEL, Lowest-observed-adverse-effect level; NOAEL, No-observed-adverse-effect level; SF, Safety factor

[1)] The adverse effect observed at LOAEL

-: NOAEL/LOAEL could not be specified.

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

Species	Study	Dose (mg/kg bw or mg/kg bw per day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw per day)[1)]
Rat	Acute toxicity study*	M: 1 500, 1 740, 2 018, 2 341, 2 716, 3 151, 3 655, 4 239, 4 918 F: 2 018, 2 341, 2 715, 3 150, 3 654, 4 238, 4 917, 5 703	M/F: - M/F: Inactivation, piloerection, lacrimation
	Acute toxicity study*	F: 2 000	F: 2 000 No toxicity
	Developmental toxicity study	49, 147, 490	Dams: 147 Dams: Decrease in weight (6 to 9 days of pregnancy)
Mouse	Acute toxicity study	M: 3 000, 3 600, 4 320, 5 184, 6 221 F: 3 600, 4 320, 5 184, 6 221, 7 465	M/F: - M/F: Piloerection, tail discoloration, loose feces, decreases in skin temperature
	90-day subacute toxicity study	M: 214, 673, 1 290 F: 248, 729, 1 490	M: 214 F: 729 M/F: Decrease in weight (at week one of administration)
Rabbit	Developmental toxicity study	49, 147, 245	Dams: 49 Dams: Decrease in weight / suppressed body weight gain (after 6 to 12 days of pregnancy)
ARfD			NOAEL: 49 SF: 100 ARfD: 0.49
The critical study for setting ARfD			Developmental toxicity study (rabbit)

ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; SF, Safety factor
- NOAEL could not be specified.
[1)] The adverse effect observed at LOAEL
*: Each extracted from different test results.