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

Risk Assessment Report

MCPA (Third edition)

(Pesticides)

Food Safety Commission of Japan (FSCJ)

June 2021

ABSTRACT

The FSCJ conducted a risk assessment of MCPA (CAS No. 94-74-6), a phenoxy herbicide, based on submitted documents. For this third edition, a risk managing organization presented new data including residue in crops (tea).

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

Major adverse effects of MCPA (including MCPA-ethyl, MCPA-DMA and MCPA-EHE) were observed in the body weight (suppressed weight gain), the nervous system (including abnormal gait and ataxia in rats and mice), the liver (including hepatocellular hypertrophy) and the kidneys (renal dysfunctions and related renal lesions). No carcinogenicity or biologically significant genotoxicity was observed.

In a developmental toxicity study in rats, skeletal anomaly and skeletal variations were observed in fetuses at maternally toxic doses, whereas no adverse effect was observed in fetuses at doses that are not maternally toxic. In a developmental toxicity study in mice, fetal skeletal variation (an increased occurrence of supernumerary 14th rib) was observed in fetuses in the C3H/He strain at maternally toxic doses, whereas no effect was observed in fetuses of other strains at doses that were not maternally toxic. No teratogenicity was observed in mice. In a developmental toxicity study in rabbits, no adverse effect was observed in fetuses even at maternally toxic doses. Moreover, in a developmental toxicity study in rats, no adverse effect was observed in the offspring at maternally toxic doses. This outcome suggested that the likelihood of MCPA eliciting adverse effects on the fetus and/or the offspring at doses that are not maternally toxic is minimal.

Based on the results from these studies, the FSCJ specified MCPA, which includes its salts (sodium salt and dimethylamine salt) and MCPA esters (ethyl and ethylhexyl esters), as the relevant substances for the residue definition for dietary risk assessment in agricultural products, livestock products and fishery products.

No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values were compared, of which the lowest value was a NOAEL of 0.19 mg/kg bw per day in a one-year chronic toxicity study in dogs (MCPA-2). The FSCJ specified an acceptable daily intake (ADI) of 0.0019 mg/kg bw per day by applying a safety factor of 100 to this NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of MCPA was 32 mg/kg bw per day in a developmental toxicity study in mice (MCPA, interstrain comparison study). The FSCJ specified an acute reference dose (ARfD) of 0.32 mg/kg bw by applying a safety factor of 100 to this NOAEL.

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

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
Rat	90-day subacute toxicity study (MCPA-1)	0, 40, 160, 640, 2 560 ppm M: 0, 2.51, 10.2, 41.4, 163 F: 0, 2.85, 11.5, 45.9, 186	M: 10.2 F: 45.9 M: Increased absolute and relative kidney weights F: Suppressed body weight gain, etc.
	90-day subacute toxicity study (MCPA-2)	0, 50, 150, 450 ppm M: 0, 3.6, 10.9, 32.6 F: 0, 4.0, 12.1, 35.8	M: 10.9 F:12.1 M/F: Urinary calculi
	90-day subacute toxicity study (MCPA-ethyl)	0, 40, 160, 640, 2 560 ppm M: 0, 2.37, 9.35, 37.5, 151 F: 0, 2.61, 10.2, 41.7, 169	M: 2.37 F: 10.2 (Expressed as MCPA equivalents: M: 2.08, F: 8.95) M: Reduced TP, T.Chol and Glob levels F: Alopecia
	90-day combined subacute toxicity/neurotoxicity study (MCPA)	0, 50, 500, 2 500 ppm M: 0, 3, 34, 177 F: 0, 4, 42, 188	M: 3 F: 4 M/F: Increased adrenocortical lipids
	90-day combined subacute toxicity/neurotoxicity study (MCPA-DMA)	0, 60, 600, 3 000 ppm M: 0, 4, 42, 208 F: 0, 5, 48, 232	M: 42 F: 48 (Expressed as MCPA equivalents: M: 34.3, F:39.2) M/F: Suppressed body weight gain, single cell necrosis of the hepatocyte, etc.
	90-day combined subacute toxicity/neurotoxicity study (MCPA-EHE)	0, 75, 750, 3 750 ppm M: 0, 5, 54, 261 F: 0, 6, 63, 296	M: 5 F: 6 (Expressed as MCPA equivalents: M: 3.21, F: 3.85) M/F: Decrease of bone marrow cells, etc.
	Two-year combined chronic toxicity/carcinogenicity study (MCPA-1)	0, 20, 200, 2 000 ppm M: 0, 0.698, 7.11, 71.8 F: 0, 0.875, 8.71, 98.6	M: 0.698 F: 8.71 M: Perilobular/diffuse hepatocyte hypertrophy, etc. F: Suppressed body weight gain, etc. (No carcinogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
	Two-year combined chronic toxicity/carcinogenicity study (MCPA-2)	0, 20, 80, 320 ppm M: 0, 1.1/1.2, 4.4/4.8, 17.6/19 F: 0, 1.4/1.5, 5.7/6.1, 23/24.3	M: 4.4/4.8 F: 5.7/6.1 M/F: Decreased TG, etc. (No carcinogenicity is observed.)
	Three-generation reproductive toxicity study (MCPA)	0, 50, 200, 1 000 ppm PM: 0, 4.2, 16.5, 85.8 PF: 0, 4.6, 17.7, 89.0 F_1M: 0, 3.2, 13.0, 65.2 F_1F: 0, 3.5, 14.1, 76.7 F_2M: 0, 3.4, 13.3, 69.3 F_2F: 0, 3.6, 14.6, 82.7	Parent and offspring: PM: 4.2 PF: 4.6 F_1M: 3.2 F_1F: 3.5 F_2M: 3.4 F_2F: 3.6 Parent: M/F: Reduced conception rate, etc. Offspring: Suppressed body weight gain
	One-generation reproductive toxicity study (MCPA)	0, 20, 50, 1 000 ppm M: 0, 1.34, 3.28, 65.9 F: 0, 1.55, 3.87, 79.0	Parent and offspring: M: 3.28 F: 3.87 Parent: Suppressed body weight gain, etc. Offspring: Pyelectasis (fetuses), suppressed body weight gain (pups) (No effect on fertility is observed.)
	Two-generation reproductive toxicity study (MCPA)	0, 50 150, 450 ppm PM: 0, 3.6, 10.7, 39.6 PF: 0, 4.4, 12.7, 41.0 F_1M: 0, 4.5, 13.4, 41.5 F_1F: 0, 5.2, 15.5, 45.8	Parent and offspring: PM: 10.7 PF: 12.7 F_1M: 13.4 F_1F: 15.5 Parent: M: Suppressed body weight gain F: Increased absolute and relative ovarian weights, suppressed body weight gain Offspring: Suppressed body weight gain (No effect on fertility is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
	One-generation reproductive toxicity study (MCPA)	0, 450/300, 750/500, and 1 000/667 ppm	Parent: - Offspring: M/F: 115
		PM: 0, 38.9, 67.1, 88.9 PF: 0, 35.7 ~ 41.7, 57.0 ~ 98.8, 75.4 ~ 122 F_1M: 0, 76.1, 115, 157 F_1F: 0, 72.2, 115, 156	Parent: - Suppressed body weight gain, reduced feed intake Offspring: Suppressed body weight gain (No effect on fertility is observed.)
	One-generation reproductive toxicity study (MCPA-EHE)	0, 700/647, 1 200/800, and 1 600/1 070 ppm	Parent: - Offspring: 90.3
		PM: 0, 64.6, 106, 145 PF: 0, 54.0 ~ 91.6, 90.3 ~ 163, 126 ~ 217 F_1M: 0, 107, 178, 232 F_1F: 0, 107, 188, 249 (MCPA equivalent)	Parent: - Suppressed body weight gain Offspring: Suppressed bodyweight gain (No effect on fertility is observed.)
	Developmental toxicity study (MCPA-1)	0, 25, 70, 200	Dams and fetuses: 25 Dams: Suppressed body weight gain, etc. Fetuses: Low body weight (No teratogenicity is observed.)
	Developmental toxicity study (MCPA-2)	0, 15, 60, 120	Dams and fetuses: 60 Dams: Suppressed body weight gain, etc. Fetuses: Low body weight, etc. (No teratogenicity is observed.)
	Developmental toxicity study (MCPA-ethyl)	0, 25, 70, 200	Dams: 70 (Expressed as MCPA equivalent: 61.4) Fetuses: 25 (Expressed as MCPA equivalent: 21.9) Dams: Suppressed body weight gain, etc. Fetuses: Low body weight (No teratogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
	Developmental toxicity study (MCPA-DMA)	0, 18.5, 62, 185	Dams and fetuses: 62 (Expressed as MCPA equivalent: 50.6) Dams: Decreased body weight, suppressed body weight gain, etc. Fetuses: Low body weight, skeletal anomaly, skeletal variation, etc.
	Developmental toxicity study (MCPA-EHE)	0, 23.5, 62.7, 188	Dams and fetuses: 62.7 (Expressed as MCPA equivalent: 40.3) Dams: Decreased body weight/suppressed body weight gain, etc. Fetuses: Low body weight, hydrocephalus, forelimb bone, etc.
Mouse	90-day subacute toxicity study (MCPA)	0, 80, 250, 800, 2 560 ppm M: 0, 9.15, 29.1, 91.3, 296 F: 0, 11.5, 36.1, 118, 368	M: 91.3 F: 36.1 M: Suppressed body weight gain, etc. F: Decreased PLT, increased MCV, etc.
	90-day subacute toxicity study (MCPA-ethyl)	0, 80, 250, 800, 2 560 ppm M: 0, 9.05, 28.2, 92.5, 282 F: 0, 10.8, 32.5, 103, 318	M: 28.2 F: 32.5 (Expressed as MCPA equivalents: M: 24.7, F: 28.5) M/F: Suppressed body weight gain, etc.
	Two-year carcinogenicity study (MCPA-1)	0, 20, 200, 1 500 ppm M: 0, 1.86, 18.2, 139 F: 0, 1.82, 18.0, 136	M: 18.2 F: 18.0 M/F: Suppressed body weight gain, etc. (No carcinogenicity is observed.)
	Two-year carcinogenicity study (MCPA-2)	0, 20, 100, 500 ppm M: 0, 3.2/3.4, 15.7/16, 79.5/83 F: 0, 3.9/4.2, 19.5/21, 97.2/103	M: 15.7/16 F: 3.9/4.2 M: Localized hyperplasia of renal tubular epithelium, etc. F: Localized hyperplasia of renal tubular epithelium (No carcinogenicity is observed.)

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
	Developmental toxicity study (MCPA-1)	0, 30, 100, 300	Dams: 100 Fetuses: 30 Dams: Suppressed body weight gain, etc. Fetuses: Low body weight (No teratogenicity is observed.)
	Developmental toxicity study (MCPA-ethyl)	0, 30, 100, 300	Dams: 30 (Expressed as MCPA equivalent: 26.3) Fetuses: 100 (Expressed as MCPA equivalent: 87.7) Dams: Decreased food intake Fetuses: Low body weight, etc. (No teratogenicity is observed.)
	Developmental toxicity study (MCPA, interstrain comparison)	0, 20, 180, 1 620 ppm --- ICR: 0, 3.7, 33.0, 311 C3H/He: 0, 4.1, 35.6, 322 ddY: 0, 3.5, 32.0, 269	ICR mouse Dams and fetuses: 33.0 C3H/He mouse Dams: 322 Fetuses: 35.6 ddY Mouse Dams and fetuses: 32.0 Dams: Suppressed body weight gain, etc. Fetuses: Low body weight, etc. (No teratogenicity is observed.)
Rabbit	Developmental toxicity study (MCPA-1)	0, 20, 50, 125	Dams: 50 Fetuses: 125 Dams: Sedation, diarrhea, etc. Fetuses: No toxicity (No teratogenicity is observed.)
	Developmental toxicity study (MCPA-2)	0, 15, 30, 60	Dams: 30 Fetuses: 60 Dams: Decreased body weight/Suppressed body weight gain, etc.

Species	Study	Dose (mg/kg bw per day)	NOAEL (mg/kg bw per day)[1)]
			Fetuses: No toxicity (No teratogenicity is observed.)
Dog	90-day subacute toxicity study (MCPA)	(i) 0, 77 ~86, 300 ~ 342, 1 200 ~ 1 370 ppm (ii) 0, 7.5, 25.0, 300 ppm	M/F: 1.0 M/F: Prolonged phenol red retention time of the kidneys
		(i) 0, 3.0, 12.0, 48.0 (ii) 0, 0.3, 1.0, 12	
	90-day subacute toxicity study (MCPA-DMA)	0, 20, 80, 360 ppm	M: 0.6 F: 0.7 (Expressed as MCPA equivalents: M: 0.490, F: 0.571) M/F: Increased BUN and Cre, etc.
		M: 0, 0.6, 2.4, 10.9 F: 0, 0.7, 2.9, 12.8	
	90-day subacute toxicity study (MCPA-EHE)	0, 20, 80, 360 ppm	M: 0.6 F: 0.7 (Expressed as MCPA equivalents: M: 0.385, F: 0.449) M/F: Increased BUN and Cre
	One-year chronic toxicity study (MCPA-1)	0, 1, 3, 10	M: 1 F: 1 M/F: Pigmentation in renal cortex tubules
	One-year chronic toxicity study (MCPA-2)	0, 6, 30, 150 ppm	M: 0.19 F: 0.19
		M: 0, 0.19, 0.96, 5.00 F: 0, 0.19, 0.94, 4.34	M/F: Increased severity in lipofuscin deposits in the epithelial cells of proximal tubules, etc.
ADI			NOAEL: 0.19 SF: 100 ADI: 0.0019
The critical study for setting ADI			One-year chronic toxicity study (MCPA-2) (dog)

ADI, Acceptable daily intake; BUN, Blood urea nitrogen; Cre, Creatinine; cRfD, Chronic reference dose; Glob, Globulin; MCV, Mean corpuscular volume; NOAEL, No-observed-adverse-effect level;PLT, Platelet; SF, Safety factor; T.Chol, Total cholesterol; TG, Triglyceride; TP, Total protein; UF, Uncertainty factor

[1)] The adverse effect observed at LOAEL.

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

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 (MCPA)	M/F: 0, 267, 361, 487, 658, 888, 1 200	M/F: - M/F: Abnormal gait
	Acute toxicity study (MCPA-ethyl)	M/F: 0, 400, 520, 680, 880, 1 150, 1 500	M/F: - M/F: Limb spasms, suppressed body weight gain
	Acute toxicity study (MCPA-ethyl)	M/F: 558, 804, 1 154, 1 667, 2 400	M/F: - M/F: Decrease in locomotor activity, intermittent tremor, limb spasms
	Acute neurotoxicity study (MCPA)	M: 0, 200, 400, 800 F: 0, 150, 300, 600	M: 200 F: 150 M: Ataxia, decreased activity, abdominal strain F: Abdominal strain
	Acute neurotoxicity study (MCPA-DMA)	M/F: 0, 175, 350, 700	M: 175 (Converted to MCPA: 143) F: - (Expressed as MCPA equivalent: <143) M/F: Abnormal gait (Ataxia)
	Acute neurotoxicity study (MCPA-EHE)	M/F: 0, 250, 500, 1 000	M/F: - (Expressed as MCPA equivalent: <160) M: Abnormal gait (Ataxia) F: Abnormal gait (Ataxia), etc.
	Developmental toxicity study (MCPA-1)	0, 25, 70, 200	Fetuses: 70 Increase in post-implantation embryo mortality
	Developmental toxicity study (MCPA-ethyl)	0, 25, 70, 200	Fetuses: 70 (Converted to MCPA: 61.4) Fetuses: Trend of increase in post-implantation embryo mortality

	Developmental toxicity study (MCPA-DMA)	0, 18.5, 62, 185	Dams and Fetuses: 62 (Expressed as MCPA equivalent: 50.6) Dams: Decreased body weight, reduced food intake Fetuses: Increase in death of embryos and fetuses
	Developmental toxicity study (MCPA-EHE)	0, 23.5, 62.7, 188	Dams and Fetuses: 62.7 (Expressed as MCPA equivalent: 40.3) Dams: Decreased body weight, decreased food intake Fetuses: Increase in post-implantation embryo mortality, etc.
Mouse	General pharmacological study (General condition) (MCPA)	M: 0, 100, 300, 1 000	M: 100 M: Ipsilateral flexion hyperreflexia, mild staggering gait, muscle relaxation, impaired righting reflex
	Acute toxicity study (MCPA)	M/F: 0, 571, 657, 756, 869, 1 000, 1 150	M/F: - M/F: Abnormal gait, hind limbs paralysis, decrease in locomotor activity
	Acute toxicity study (MCPA-ethyl)	M/F: 520, 680, 880, 1 150, 1 500, 1 950	M/F: - M/F: Limb spasms, decrease in locomotor activity, suppressed weight gain
	Acute toxicity study (MCPA-ethyl)	M/F: 720, 1 037, 1 244, 1 493, 1 792	M/F: - M/F: Decrease in locomotor activity, bradypnea, intermittent whole body tremor, limb spasms, etc.
	Developmental toxicity study (MCPA)	0, 30, 100, 300	Fetuses: 100 Fetuses: Increased trend in post-implantation mortality
	Developmental toxicity study (MCPA-ethyl)	0, 30, 100, 300	Fetuses: 100 (Expressed as MCPA equivalent: 87.7) Fetuses: Increased trend in post-implantation mortality, increased occurrence of supernumerary14th rib
	Developmental toxicity study (MCPA, interstrain comparison study)	0, 20, 180, 1 620 ppm ICR: 0, 3.7, 33.0, 311 C3H/He: 0, 4.1, 35.6, 322 ddY: 0, 3.5, 32.0, 269	Fetuses: 32.0 Fetuses: Increased occurrence of supernumerary 14th rib (in ICR, C3H/He, and ddY mice strains)

Rabbit	General pharmacological study (Body temperature) (MCPA)	M: 0, 100, 300, 1 000	M: 300 M: Staggering gait, muscle relaxation, etc.
	General pharmacological study (pupil diameter) (MCPA)	M: 0, 100, 300, 1 000	M: 300 M: Staggering gait
ARfD			NOAEL: 32.0 SF: 100 ARfD: 0.32
The critical study for setting ARfD			Developmental toxicity study in mouse (MCPA, interstrain comparison study)

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