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Risk Assessment Report

Paraquat (Pesticides)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of a bipyridinium herbicide, paraquat (CAS No. 1910-42-5), based on results from various studies. Major adverse effects of paraquat in experimental animals were observed in body weight (suppressed weight gain), lungs (increased weight, alveolar epithelium hyperplasia, and pneumonia), kidneys (renal tubule dilatation) and eyes (cataract in rats and dogs). The effects on the lung were considered to be the most critical endpoints in the assessment. Neither carcinogenicity, effects on fertility, teratogenicity, genotoxicity, or immunotoxicity was observed. FSCJ reasonably concluded no obvious concern of paraquat-residue in foods to yield neurotoxicity through human dietary exposure, as long as paraquat is applied following the registered standard use of the pesticide. The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.45 mg paraquat ion*/kg bw per day in one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.0045 mg paraquat ion/kg bw per day by applying a safety factor of 100 to the NOAEL. FSCJ judged these effects also as the end-point of the acute reference dose (ARfD). The lowest NOAEL was 0.45 mg paraquat ion/kg bw per day in one-year chronic toxicity study in dogs. For potential adverse effects of a single oral administration of paraquat, FSCJ specified an ARfD to be 0.0045 mg paraquat ion/kg bw by applying a safety factor of 100 to the NOAEL.

Conclusion in Brief

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of a bipyridinium herbicide, paraquat (CAS No. 1910-42-5), based on results from various studies.

The data used in the assessment includes the fate in animals (rats, mice, cattle, chicken and others), fate in plants (lettuce and soy beans and others), residues in crops, and tests of acute neurotoxicity (rats), subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats and mice), carcinogenicity (mice), two- and three- generation reproductive toxicity (rats), developmental toxicity (rats and mice), genotoxicity and immunotoxicity (rats). Scientific findings in human are also included.

The major adverse effects of paraquat in experimental animals were observed in body weight (suppressed weight gain), lungs (increased weight, alveolar epithelium hyperplasia, and pneumonia), kidneys (renal tubule dilatation) and eyes (cataract in rats and dogs). The effects on the lung and respiratory organs were considered to be the most critical endpoints in the assessment. Neither carcinogenicity, effects on fertility, teratogenicity, genotoxicity, or immunotoxicity was observed. After reviewing of currently available results

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*[1]Paraquat ion corresponds to 1,1'-dimethyl-4,4'-bipyridinium.

*[2]Because of structural similarity of paraquat to a dopaminergic neurotoxic substance, 1-methyl-4-phenyl-1, 2, 3, 6-tetrathydropyridine (MPTP), neurotoxicity of paraquat is of concern. FSCJ thus examined this hypothetical neurotoxicity by available data.

This is an English translation of excerpts from the original full report (June-FS/337/2022)[1)]. Only original Japanese texts have legal effect. The original full report is available in Japanese at http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20130612175&fileId=210

Abbreviations: ADI, Acceptable daily intake; ARfD, Acute reference dose; NOAEL, No-observed-adverse-effect level; FSCJ, Food Safety Commission of Japan

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of non-clinical studies and scientific findings in human, FSCJ reasonably concluded no obvious concern of paraquat-residue in foods to yield neurotoxicity through human dietary exposure, as long as paraquat is applied following the registered standard use of the pesticide.

Based on the results from various studies, paraquat (parent compound only) was identified as the substance relevant to the residue definition for dietary risk assessment in agricultural products and livestock products.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 0.45 mg paraquat ion*1/kg bw per day in one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.0045 mg paraquat ion/kg bw per day by applying a safety factor of 100 to the NOAEL.

The sensitive and critical endpoints of paraquat after the oral administration appeared on the lung and respiratory organs throughout the studies examined. Effects on the lung were detected even in animals of impending sacrifice and of dead state in acute toxicity studies. These data suggested the gradual time dependent deterioration of the lung after the paraquat exposure. Thus, paraquat was possible to initiate the lung and respiratory organ damages after single exposure, which is consistent with the histopathological findings in the repeated dose study. Accordingly, FSCJ judged the consequence as the end-point of the acute reference dose (ARfD). The lowest NOAEL was 0.45 mg paraquat ion/kg bw per day in one-year chronic toxicity study in dogs. For potential adverse effects of a single oral administration of paraquat, FSCJ specified an ARfD to be 0.0045 mg paraquat ion/kg bw by applying a safety factor of 100 to the NOAEL.

Acknowledgement

FSCJ wishes to thank the members of the Expert Committee on Pesticides for preparation of the original full report[1)].

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Appendix

FSCJ's View on Paraquat Neurotoxicity*2

No neurotoxicity was detected in acute and 90-day subacute studies of paraquat in rats, so far surveyed[1)]. Neurotoxicity attributed to paraquat was not observed in other toxicological studies.

Paraquat is structurally similar to a dopaminergic neurotoxic substance, 1-methyl-4-phenyl-1, 2, 3, 6-tetrathydropyridine (MPTP). To investigate the possible causal relationship between paraquat and Parkinson disease, various nonclinical experiments had been done[1)].

JMPR, EPA and APVMA concluded, from the available information on the toxicities of paraquat, no concern of neurotoxicity through human dietary exposure to paraquat as pesticide residues in food, and also effects on lung as the most critical endpoints even after dietary intakes.

The rationales are summarized below.

(1) MPTP is transported readily across the blood-brain barrier to get in the brain. MPTP is then converted to $MPDP^+$ (1-methyl-4-phenyl-4-phenyl-2,3-diydropyridinium) and oxidized into the toxic cation MPP^+ (1-methyl-4-phenyl-pyridinium) to cause dopaminergic neurotoxicity. Although an involvement of dopamine transporter is suggested for paraquat[2)], this di-cation chemical is not readily taken up into the brain[3)].

(2) Behavioral, neurological and/or neuropathological effects were detected after subcutaneous, intraperitoneal and intracerebral administrations of paraquat. Inconsistencies were, however, observed within the experimental data.

Due to the difference in the route of administration and tissue distribution, these data have only limited relevances to human exposure through food intakes of paraquat as pesticide residue.

(3) In properly designed tests including positive control groups, no behavioral, neurological or neuropathological effects were observed after the oral administration[1,3)].

Some epidemiological studies suggested the association between paraquat exposure and Parkinson disease. The rationale for such relationship is, however, not yet established from the points of methodologies related to research design, statistical power, diagnostic criteria, exposure assessment, bias, and confounding factors. Enhanced risk of Parkinson disease was not observed in paraquat manufacturing workers. No case report was also available for Parkinson disease symptoms (bradycardia, tremor, stiffness and posture instability) in short or long-term survivors who were exposed to paraquat and manifesting its effects on the lungs.

FSCJ concluded no concern of neurotoxicity of paraquat in food based on the currently available non-clinical test results

and scientific findings in human, as long as the pesticide is used following the registered standard of use. This conclusion is consist with the views of overseas institutions.

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

Species	Study	Dose# (mg/kg bw per day)	NOAEL# (mg/kg bw per day)[1)]
Rat	90-day subacute toxicity study	0, 6.8, 20.3, 67.6, 203 ppm M: 0, 0.458, 1.35, 4.43,13.2 F: 0, 0.468, 1.43, 4.80, 14.3	M: 4.43 F: 4.80 M/F: Suppressed body weight gain, Decreased food consumption, etc.
	90-day subacute neurotoxicity study	0, 15, 50, 150 ppm M: 0, 1.0, 3.4, 10.2 F: 0, 1.1, 3.9, 11.9	M: 10.2 F: 11.9 M/F: No toxicity (No subacute neurotoxicity is observed)
	Two-year chronic toxicity study	0, 7.1, 21.3, 71, 213 ppm M: 0, 0.251, 0.75, 2.50, 7.53 F: 0, 0.305, 0.95, 3.07, 8.31	M: 0.75 F: 3.07 M/F: Increased alveolar septal cells and alveolar epithelial hyperplasia (No carcinogenicity is observed)
	Two-year combined chronic toxicity/carcinogenicity study (the 1st study)	0, 4.3, 21.3, 71, 213 ppm M: 0, 0.18, 0.89, 2.95, 8.70 F: 0, 0.21, 1.07, 3.64, 10.9	M: 2.95 F: 3.64 M/F: Decrease of RBC, Ht, and Hb, Decrease of TP, etc. (No carcinogenicity is observed)
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	0, 25, 75, 150 ppm M: 0, 1.00, 3.11, 6.26 F: 0, 1.26, 3.93, 7.91	M: 1.00 F: 1.26 M/F: Cataract-like changes, Proliferative lesions of alveolar epithelial cells, etc. (No carcinogenicity is observed)
	Two-generation reproductive toxicity study (the 1st study)	0, 71.4, 143, 286 ppm P M: 0, 4.7, 9.3, 17.9 P F: 0, 5.1, 9.9, 20.9 F_1 M: 0, 6.9, 14.1, 27.6 F_1 F: 0, 7.3, 14.9, 23.5 F_2 M: 0, 6.1, 12.1, 29.2 F_2 F: 0, 6.9, 14.0, 34.8	Parent: P M: 9.3 P F: - F_1 M: 14.1 F_1 F: - F_2 M: 12.1 F_2 F: - Offspring: P M: 9.3 P F: 9.9 F_1 M: 14.1 F_1 F: 14.9 Parent:

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Table 1. *Continued*

Species	Study	Dose[#] (mg/kg bw per day)	NOAEL[#] (mg/kg bw per day)[1)]
			M/F: Alveolar wall thickening/Pulmonary fibrosis and atelectasis Offspring: M: Low body weight F: Decreased weaning rate, Delayed vaginal opening, etc. (No effect on reproductive activity is observed)
	Two-generation reproductive toxicity study (the 2nd study)	0, 14.2, 71, 142 ppm P M: 0, 1.3, 6.1, 12.5 P F: 0, 1.1, 5.9, 12.4 F_1 M: 0, 1.3, 6.2, 12.6 F_1 F: 0, 1.3, 6.1, 12.4 F_2 M: 0, 1.1, 5.6, 10.4 F_2 F: 0, 1.1, 5.5, 10.8	Parent: P M: 6.1 P F: 5.9 F_1 M: 6.2 F_1 F: 6.1 F_2 M: 5.6 F_2 F: 5.5 Offspring: P M: 6.1 P F: 5.9 F_1 M: 6.2 F_1 F: 6.1 Parent: Suppressed body weight gain, Death caused by chronic interstitial pneumonia, etc. Offspring: Suppressed body weight gain (No effect on reproductive activity is observed)
	Three-generation reproductive toxicity study (the 1st study)	0, 25, 75, 150 ppm P M: 0, 3.00, 8.53, 16.5 P F: 0, 3.07, 8.34, 16.5 F_1 M: 0, 2.71, 7.81, 14.7 F_1 F: 0, 2.64, 7.80, 14.6 F_2 M: 0, 2.65, 7.87, 14.1 F_2 F: 0, 2.59, 7.65, 13.7	Parent: P M: 3.00 P F: 3.07 F_1 M: 2.71 F_1 F: 2.64 F_2 M: 2.65 F_2 F: 2.59 Offspring: P M: 8.53 P F: 8.34 F_1 M: 7.81 F_1 F: 7.80 F_2 M: 7.87

Table 1. *Continued*

Species	Study	Dose# (mg/kg bw per day)	NOAEL# (mg/kg bw per day)[1)]
			F_2 F: 7.65 Parent: Suppressed body weight gain, Alveolar histiocytic proliferation Offspring: Perivascular inflammatory cell infiltration in lung (No effect on reproductive activity is observed)
	Three-generation reproductive toxicity study (the 2nd study)	0, 30, 100 ppm 0, 2.0, 6.67	Reference only due to the study with two doses.
	Developmental toxicity study (the 1st study)	0, 1, 3, 8	Dams: 3 Fetuses: 8 Dams: Decreased body weight, Suppressed body weight gain Fetuses: No toxicity (No teratogenicity is observed)
	Developmental toxicity study (the 2nd study)	0, 1, 5, 10	Dams: 1 Fetuses: 1 Dams: Suppressed body weight gain, etc. Fetuses: Low body weight, Anterior and posterior limb phalanges/bones of toe delayed ossification, etc. (No teratogenicity is observed)
Mouse	90-day subacute toxicity study	0, 6.8, 20.3, 67.6, 203 ppm M: 0, 0.80, 2.47, 7.77, 24.2 F: 0, 0.93, 2.64, 9.33, 28.3	M: 7.77 F: 9.33 M/F: Suppressed body weight gain, Eosinophilic swelling of alveolar epithelium, etc.
	Two-year combined chronic toxicity/carcinogenicity study	0, 1.42, 7.1, 21.3, 71 ppm M: 0, 0.18, 0.93, 2.78, 9.29 F: 0, 0.18, 0.94, 2.71, 9.25	M: 2.78 F: 2.71 M/F: Decrease of RBC and Ht, etc. (No carcinogenicity is observed)
	99-week carcinogenicity study	0, 12.5, 37.5, 100/125 ppm M: 0, 1.68, 5.05, 15.9 F: 0, 2.59, 7.72, 24.1	M: 1.68 F: 2.59 M: Renal tubular degeneration, etc.

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Table 1. *Continued*

Species	Study	Dose[#] (mg/kg bw per day)	NOAEL[#] (mg/kg bw per day)[1)]
			F: Renal tubular dilatation (No carcinogenicity is observed)
	Developmental toxicity study (the 1st study)	0, 7.5, 15, 25	Dams: 15 Fetuses: 15 Dams: Death /Emergency slaughter, Suppressed body weight, etc. Fetuses: Low body weight, etc. (No teratogenicity is observed)
	Developmental toxicity study (the 2nd study)	0, 1, 5, 10	Dams: 1 Fetuses: 5 Dams: Suppressed body weight gain Fetuses: Delayed ossification (coccygeal vertebra, calcaneus and sternebra segment) (No teratogenicity is observed)
Dog	90-day subacute toxicity study	0, 7, 20, 60, 120 ppm M: 0, 0.20 , 0.55, 1.75, 3.52 F: 0, 0.24, 0.71, 1.92, 4.26	M: 0.55 F: 0.71 M/F: Increased absolute and relative weights of lungs, Alveolitis, etc.
	One-year chronic toxicity study	0, 15, 30, 50 ppm M: 0, 0.45, 0.93, 1.51 F: 0, 0.48, 1.00, 1.58	M: 0.45 F: 0.48 M/F: Increased vesicular sound, Increased degree of chronic interstitial pneumonia, etc.
ADI			NOAEL: 0.45 SF: 100 ADI: 0.0045
The critical study for setting ADI			One-year chronic toxicity study (dog)

ADI: Acceptable daily intake, SF: Safety factor, NOAEL: No-observed-adverse-effect level
-: NOAEL could not be specified.
[#]: Converted value for paraquat ion
[1)] The adverse effect observed at LOAEL

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

Species	Study	Dose (mg/kg bw[#] or mg/kg bw per day[#])	Endpoints relevant to setting NOAEL and ARfD[1)] (mg/kg bw[#] or mg/kg bw per day[#])
Rat	Acute toxicity study	18.4, 58.5, 184	F: 18.4 Dyspnea, Lethargy, Ataxia, Pulmonary hemorrhage, etc.
	Acute toxicity study	M: 33, 82.5, 132 F: 33, 82.5, 132, 198	M/F: 33 M/F: Decreased activity, Dehydration, Low body weight, Irregular breathing, Patch or shadowing in lungs, etc.
	Acute neurotoxicity study	0, 8.4, 25.1, 84	M: 8.4 F: 25.1 M/F: Suppressed body weight gain, etc.
	90-day subacute toxicity study	M/F: 0, 6.8, 20.3, 67.6, 203 ppm M: 0, 0.458, 1.35, 4.43,13.2 F: 0, 0.468, 1.43, 4.80, 14.3	M: 4.43 Swelling of alveolar epithelial cells
	Two-year chronic toxicity study	M/F: 0, 7.1, 21.3, 71, 213 ppm M: 0, 0.251, 0.75, 2.50, 7.53 F: 0, 0.305, 0.95, 3.07, 8.31	M: 0.75 F: 3.07 M/F: Proliferation of alveolar septal cells and Hyperplasia of alveolar epithelial cells
	Two-year combined chronic toxicity/carcinogenicity study (the 2nd study)	M/F: 0, 25, 75, 150 ppm M: 0, 1.00, 3.11, 6.26 F: 0, 1.26, 3.93, 7.91	M: 1.00 F: 1.26 M/F: Proliferative lesions of alveolar epithelial cells
	Two-generation reproductive toxicity study (the 1st study)	M/F: 0, 71.4, 143, 286 ppm P generation M: 0, 4.7, 9.3, 17.9 F: 0, 5.1, 9.9, 20.9	PM: 9.3 PF: 9.9 M: Increased alveolar wall thickness of partial lungs/pulmonary fibrosis and accumulation of foam cells
	Two-generation reproductive toxicity study (the 2nd study)	M/F: 0, 14.2, 71, 142 ppm P generation M: 0, 1.3, 6.1, 12.5 F: 0, 1.1, 5.9, 12.4	F: 5.9 F: Chronic interstitial pneumonia
	Three-generation reproductive toxicity study (the 1st study)	M/F:0, 25, 75, 150 ppm P generation M: 0, 3.00, 8.53, 16.5 F: 0, 3.07, 8.34, 16.5	M: 3.00 F: 3.07 Alveolar histiocytic proliferation
	Developmental toxicity study (the 2nd study)	0, 1, 5, 10	Dams: 5 Dams: Dead or Emergency slaughter (one week after administration), Calming, Emaciation, Pulmonary Edema, etc.

Table 2. *Continued*

	Study examining the effects on renal function (the 1st study) (the 2nd study)	M: 91	- Increased urine protein, Alb, Glu, excreted cells and BUN, Proximal renal tubular hydropic degeneration, etc.
	Study examining the effects on renal hematopoiesis	31, 125	M/F: 31 M: Death F: Decrees in systemic circulation associated with dehydration
Mouse	90-day subacute toxicity study	M/F: 0, 6.8, 20.3, 67.6, 203 ppm M: 0, 0.80, 2.47, 7.77. 24.2 F: 0, 0.93, 2.64, 9.33, 28.3	M: 7.77 F: 9.33 M/F: Eosinophilic swelling of alveolar epithelia cells
	99-week carcinogenicity study	M/F:0, 12.5, 37.5, 100/125 ppm M: 0, 1.68, 5.05, 15.9 F: 0, 2.59, 7.72, 24.1	M: 7.72 F: Alveolar wall thickening
	Developmental toxicity study (the 1st study)	0, 7.5, 15, 25	Dams: 15 Dams: Dark red change of lungs
	28-day subacute toxicity study[2)]	M/F: 0, 100, 125, 150 ppm M/F: 0, 15, 18, 22.5	M/F: - M/F: Pulmonary histopathological findings
Dog	90-day subacute toxicity study	M/F: 0, 7, 20, 60, 120 ppm M: 0, 0.20 , 0.55, 1.75, 3.52 F: 0, 0.24, 0.71, 1.92, 4.26	M: 0.55 F: 0.71 M/F: Alveolitis
	One-year chronic toxicity study	M/F: 0, 15, 30, 50 ppm M: 0, 0.45, 0.93, 1.51 F: 0, 0.48, 1.00, 1.58	M: 0.45 F: 0.48 M/F: Worsening chronic interstitial pneumonia and Increased Bronchial lymph node erythrophagocytosis
ARfD		NOAEL: 0.45 SF: 100 ARfD: 0.0045	
The critical study for setting ARfD		One-year chronic toxicity study (dog)	

ARfD: Acute reference dose, NOAEL: No-observed-adverse-effect level, SF: Safety factor
-: NOAEL could not be specified.
[#] as a value converted for paraquat ion.
[1)] The adverse effect observed at LOAEL.
[2)] Study for differences of toxic effects using manufacturing grade and technical grade active ingredients of paraquat.