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

Risk Assessment Report

Comparing Assessment of Iminoctadines

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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Iminoctadine is a guanidine fungicide currently used in one of forms of two salts, iminoctadine tris (albesilate) and iminoctadine triacetate. Studies of iminoctadine are generally subjecting distinctively to each of two salts. Therefore, FSCJ conducted a comparing assessment of each compound based on the risk assessment of each compound in this report. The results of assessments on the individual compounds were summarized in Abstract 1 and Abstract 2, respectively.

ABSTRACT-1: Iminoctadine tris (albesilate)

FSCJ conducted the risk assessment of iminoctadine tris (albesilate) (CAS No.169202-06-6) based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (apples and tomatoes), residues in crops, subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction (rats), developmental toxicity (rats and rabbits), genotoxicity and mechanism on testicular toxicity in dogs and spermatogranuloma in rats.

Major adverse effects of iminoctadine tris (albesilate) observed are degeneration of renal tubular epithelial cells in the kidney (dogs), effects on the male reproductive organs such as agenesis of sperm (dogs) and spermatogranulomas (rats). Iminoctadine tris (albesilate) showed neither carcinogenicity nor genotoxicity.
In a two-generation reproduction study in rats, decreases in fertility and conception rate, decreases in number of implantations and litter size were observed. FSCJ attributed these decreases to the decrease in the sperm due to the above mentioned spermmatogranulomas.
In a developmental toxicity study, skeletal anomaly such as fused in the center of skull, was observed in rabbit fetuses at the dose with maternal toxicity. No teratogenicity was observed in rats.
From the above results, FSCJ identified the relevant substance for the residue definition for dietary risk assessment in agricultural products as iminoctadine tris (albesilate) and iminoctadine.

The lowest value of the no-observed-adverse-effect level (NOAEL) of iminoctadine tris (albesilate) in all tests was 0.90 mg/kg bw/day in a chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.009 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.

The lowest NOAEL for potential adverse effects of a single oral administration of iminoctadine tris (albesilate) was 10 mg/kg bw/day obtained in a developmental toxicity study in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.1 mg/kg bw by applying a safety factor of 100 to the NOAEL.

ABSTRACT-2: Iminoctadine triacetate

FSCJ conducted the risk assessment of iminoctadine triacetate (CAS No. 57520-17-9) based on various documents.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice and apples), residues in crops, subacute toxicity (dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproduction (rats), developmental toxicity (rats and rabbits), genotoxicity, and a mechanism of increased incidence of adrenal pheochromocytoma in rats.

Major adverse effects of iminoctadine triacetate observed are degeneration of renal tubular epithelial cells in the kidney (dogs), effects on the male reproductive organs such as agenesis of sperm (dogs) and spermatogranulomas (rats). No teratogenicity and genotoxicity relevant to human health were observed.

The incidence of adrenal pheochromocytomas in both male and female rats, mononuclear cell leukemia in male rats, and incidence of epithelial tumors in the kidney in both male and female mice were increased in carcinogenicity tests. However, a genotoxic mechanism was unlikely involved in the tumor induction. FSCJ thus considered it possible to establish a threshold dose in the assessment.
In a two-generation reproductive toxicity study in rats, conception rate decreased. FSCJ attributed this decrease to the decrease in the sperm due to the abovementioned spermatogranulomas.
From the above results, FSCJ identified the relevant substance for the residue definition for dietary risk assessment in agricultural products as iminoctadine triacetate and iminoctadine.

The lowest value of the no-observed-adverse-effect level (NOAEL) of iminoctadine triacetate in all tests was 0.20 mg/kg bw/day in a 90-day subacute toxicity study and in a one-year chronic toxicity study in dogs. FSCJ specified an acceptable daily intake (ADI) of 0.002 mg/kg bw/day by applying a safety factor of 100 to the NOAEL.
The lowest NOAEL for potential adverse effects of a single oral administration of iminoctadine triacetate was 8 mg/kg bw/day obtained in a developmental toxicity study 1 in rabbits. FSCJ specified an acute reference dose (ARfD) to be 0.08 mg/kg bw by applying a safety factor of 100 to the NOAEL.

3. Comparing Assessment

Iminoctadine tris (albesilate) and iminoctadine triacetate had common major adverse effects in toxicity studies of both compounds, suggesting that these toxicities caused in animals were by iminoctadine. Accordingly, FSCJ conducted comparing assessment of iminoctadine comprehensively using the data of these two iminoctadine compounds. FSCJ expressed the no-observed-adverse-effect level (NOAEL) and

the lowest-observed-adverse-effect level (LOAEL) of iminoctadine and its compounds using values converted to level of iminoctadine.
The NOAELs for each compound observed in relevant studies were shown in Table 1, and potential adverse effects of a single oral administration of each compound were shown in Table 2.

The lowest value of the no-observed-adverse-effect level (NOAEL) for iminoctadine tris (albesilate) in all tests was 0.239 mg/kg bw/day (iminoctadine tris (albesilate): 0.90 mg/kg bw/day) in a one-year chronic toxicity study in dogs. The lowest value of NOAEL for iminoctadine triacetate in all tests was 0.132 mg/kg bw/day (iminoctadine triacetate: 0.20 mg/kg bw/day) in a 90-day subacute toxicity study and in a one-year chronic toxicity study in dogs. This NOAEL of 0.132 mg/kg bw/day for iminoctadine triacetate is the lowest of NOAELs for both iminoctadine compounds based on the LOAEL of 0.272 mg/kg bw/day for iminoctadine triacetate in a one-year chronic toxicity study in dogs.
The lowest NOAEL of 0.239 mg/kg bw/day for iminoctadine tris (albesilate) was lower than the lowest LOAEL of 0.272 mg/kg bw/day for iminoctadine triacetate. FSCJ considered that the NOAEL of 0.239 mg/kg bw/day could secure food safety covering toxicities of both compounds, because similar adverse effects were observed at the LOAELs for both compounds, and the adverse effect (eminiferous tubular atrophy) caused by iminoctadine triacetate at the LOAEL was mild. Consequently, FSCJ specified the ADI for iminoctadine to be 0.0023 mg/kg bw/day by applying a safety factor of 100 to the NOAEL 0.239 mg/kg bw/day.

The lowest NOAEL for potential adverse effects of a single oral administration of iminoctadine tris (albesilate) was 2.66 mg/kg bw/day based on the LOAEL of 7.98 mg/kg bw/day (iminoctadine tris (albesilate): 10 mg/kg bw/day) in a developmental toxicity study in rabbits.
The lowest NOAEL for potential adverse effects of a single oral administration of iminoctadine triacetate was 5.31 mg/kg bw/day (iminoctadine triacetate: 8 mg/kg bw/day) in a developmental toxicity study in rabbits based on the LOAEL of 7.96mg/kg bw/day (iminoctadine tris (albesilate): 12 mg/kg bw/day) in a developmental toxicity study in rabbits. Similar toxicity was observed at the LOAELs in both compounds, which were very similar. Therefore, the difference between two NOAELs was attributed to dose-spacing at dose setting in each study.
FSCJ considered it appropriate to use the NOAEL for potential adverse effects of a single oral administration of iminoctadine as 5.31 mg/kg bw/day. Therefore, FSCF specified an acute reference dose (ARfD) to be 0.053 mg/kg bw by applying a safety factor of 100 to the NOAEL.

The plant metabolite study determined metabolite K as a metabolite/degradate of a TRR over 10%, while the rat metabolite study did not detected it. The repeated dose-oral toxicity of metabolite K was considered weaker than those of iminoctadine tris (albesilate) and iminoctadine triacetate based on the results from a 28-day subacute toxicity study in rats. In addition, metabolite M showed negative in both *in vivo* gene mutation tests and micronucleus tests.
On the basis of the results above, FSCJ identified the relevant substances for the residue definition for dietary risk assessment in agricultural products as iminoctadine tris (albesilate), iminoctadine triacetate and iminoctadine.

ADI and ARfD of iminoctadine

ADI	0.0023 mg/kg bw/day
The critical study for setting ADI	Chronic toxicity study (iminoctadine tris (albesilate))
Species	Dogs
Duration One year	
Route of administration	Dietary administration
NOAEL	0.239 mg/kg bw/day (converted to the value for iminoctadine)
Safety Factor	100
ARfD	0.053 mg/kg bw/day
The critical study for setting ARfD	Developmenal toxicity study (iminoctadine triacetate)
Species	Rabbits
Duration	From gestation day 6 to 18
Route of administration	Gavage administration
NOAEL	5.31 mg/kg bw/day (converted to the value for iminoctadine)
Safety Factor	100

The estimated dietary intakes for chronic or acute exposure shall be confirmed when the provisional standards will be revised based on this assessment.

Table 1. *Levels relevant to toxicological evaluation*

(*Values in parenthesis are converted to the values for iminoctadine*)

Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[2]
Rat	90-day subacute toxicity study	0, 160, 400, 1 000 ppm M: 0, 10, 23, 57 (0, 2.66, 6.11, 15.1) F: 0, 11, 30, 66 (0, 2.92, 7.98, 17.5)	M: 10 (2.66) F: 11 (2.92) M/F: Hyperplasia of renal distal tubular epithelium.		
	90-day subacute neurotoxicity study	0, 50, 160, 00 ppm M: 0, 3.17, 10.3, 30.9 (0, 0.843, 2.73, 8.21) F: 0, 3.70, 12.1, 36.0 (0, 0.984, 3.21, 9.57)	M: 10.3 (2.73) F: 12.1 (3.21) M/F: Degeneration/ hyperplasia of renal tubules in the cortex of kidney. (No subacute neurotoxicity)		
	Two-year combined chronic toxicity/ carcinogenicity study	0, 30, 80, 200 ppm M: 0, 1.2, 3.2, 8.1 (0, 0.319, 0.851, 2.15) F: 0, 1.7, 4.3, 10.9 (0, 0.452, 1.14, 2.89)	M: 1.2 (0.319) F: 1.7 (0.452) M: Trend of slight increase in incidence of glomerulonephritis. F: Tubular dilatation /hypertrophy of tubular epithelium in the kidney. (No carcinogenicity)	0, 10, 100, 300 ppm M: 0, 0.356, 3.56, 11.3 (0, 0.23, 2.36, 7.50) F: 0, 0.428, 4.41, 14.2 (0, 0.28, 2.92, 9.42)	M: 0.356 (0.236) F: 0/428 (0.284) M: Spermatogranuloma of the seminal duct F: Suppressed body weight In 300 ppm administered group; M: Increased incidence of mononuclear cell leukemia M/F: Increased incidence of adrenal pheochromocytomas
	Two-generation reproductivity study	0, 50, 150, 300 ppm	Parent animals PM: 3.6 (0.957)	0, 25, 50, 100 ppm	Parent animals PM: 2.93 (1.94)

[1], Major adverse effect observed at LOAEL
[2], Major adverse effect observed at LOAEL

Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[2]
		PM: 0, 3.6, 10.6, 21.5 (0, 0.957, 2.81, 5.71) PF: 0, 4.0,12.1, 24.0 (0, 1.06, 3.21, 6.38) F_1M: 0, 4.2, 12.3 (0, 1.11, 3.27) F_1F: 0, 4.6, 13.4 (0, 1.22, 3.56)	PF: 12.1 (3.21) F_1M: 4.2 (1.11) F_1F: 13.4 (3.56) Offspring P M: 10.6 (2.81) PF: 12.1 (3.21) F_1M: 12.3 (3.27) F_1F: 13.4 (3.56) Reproductiviy PM: 3.6 (0.957) PF: 4.0 (1.06) F_1M: 4.2 (1.11) F_1F: 4.6 (1.22) Parent animals M: Spermatogranulomas F: Loss of corpora lutea Offspring: Lower body weight Reproductivity M/F: Slight delay of mating establishment required date.	PM: 0, 1.46, 2.93, 5.84 (0, 0.969, 1.94, 3.87) PF: 0, 1.75, 3.50, 6.98 (0, 1.16, 2.32, 4.63) F_1M: 0, 1.76, 3.57, 6.90 (0, 1.16, 2.37, 4.58) F_1F: 0, 1.94, 3.97, 7.76 (0, 1.28, 2.63, 5.15)	PF: 3.50 (2.32) F_1M: 3.57 (2.37) F_1F: 3.97 (2.63) Offspring P M: 5.84 (3.87) PF: 6.98 (34.63) F_1M: 6.90 (4.58) F_1F: 7.76 (5.15) Reproductivity PM: 2.93 (1.94) PF: 3.50 (2.32) F_1M: 3.57 (2.37) F_1F: 3.97 (2.63) Parent animals M: Degeneration/ regeneration of epithelial cells in epididymis F: Hypertrophy of renal distal tubular epithlium. Offspring: No toxicity Reproductivity: Decrease in conception rate
	Developmental toxicity study (A preliminary study)			0, 0.1, 1, 10, 30, 60, 100 (0, 0.0664, 3.32, 6.64)	Dams: 1 (0.664) Fetuses: 10 (6.64) Dams: Decreased feed intake Fetuses: Death
	Developmental toxicity study	0, 10, 30, 100 (0, 2.66, 7.98, 26.6)	Dams: 30 (7.98) Fetuses: 100 (26.6) Dams: Suppressed body weight, decreased feed intake Fetuses: No toxicity (No teratogenicity)	0, 1, 5, 10 (0, 0.664, 3.32, 6.64)	Dams: 10 (6.64) Fetuses: 10 (6.64) Dams: No toxicity Fetuses: No toxicity (No teratogenicity)
	Overall score of assessment			Dams: 5 (3.32) Fetuses: 10 (6.64)	
Mouse	18-month	0, 30, 80, 200, 400	M: 32 (8.51)		

Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[2]
	carcinogenicity study	ppm M: 0, 5, 13, 32, 66 (0, 1.33, 3.45, 8.51, 17.5) F: 0, 6, 15, 40, 82 (0, 1.59, 3.99, 10.6, 21.8)	F: 6 (1.59) M: Hypertrophy of renal tubular epithelium. F: Dilatation of renal tubular cells with colloid-like cast/ basophilic changes in renal tubules. (No carcinogenicity)		
	Two-year carcinogenicity study			0, 10, 100, 300 ppm M: 0, 0.833, 8.55, 26.0 (0, 0.553, 5.67, 17.2) F: 0, 0.787, 7.94, 29.5 (0, 0.522, 5.27, 19.5)	M: 0.833 (0.553) F: 0.787 (0.522) M/F: swelling of renal proximal tubular epithelium At 300 ppm; Renal epithelial tumors in the kidney
Rabbit	Developmental toxicity study	0, 3, 10, 30 (0, 0.798, 2.66, 7.98)	Dams: 3, (0.798) Fetuses: 10 (2.66) Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)	0, 4, 8, 12 (0, 2.65, 5.31, 7.96)	Dams: 4 (2.65) Fetuses: 12 (7.96) Dams: Anorexia Fetuses: No toxicity (No teratogenicity)
Dog	90-day subacute toxicity study (the 1st study)			0, 25, 100, 250 ppm M: 0, 1.01, 3.14, 8.34 (0, 0.670, 2.08, 5.53) F: 0, 0.90, 2.89, 6.90 (0, 0.597, 1.91, 4.58)	M/F: - M/F: degeneration/ regeneration of renal tubular epithelial cells
	90-day subacute toxicity study			0, 5, 10 ppm	M: - F: 0.38 (0.252)

Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[2]
	(the 2nd study)			M: 0, 0.19, 0.39 (0, 0.126, 0.258) F: 0, 0.20, 0.38 (0, 0.132, 0.252)	M: Decreased weight of the testis, and histopathological alteration F: No toxicity
	90-day subacute toxicity study (the 3rd study)			0, 5, 10, 225 ppm M: 0, 0.20, 0.38, 0.92 (0, 0.132, 0.252, 0.610)	M: 0.38 (0.252) M: Degeneration/ regeneration of renal tubule in the renal cortex, decreased relative weight of the testis, hypoplasia of seminiferous spermatozoa or azoospermia
	90-day subacute toxicity study	0, 10, 30, 100 ppm M: 0, 0.5, 1.2, 3.6 (0, 0.133, 0.319, 0.957) F: 0, 0.4, 1.4, 4.2 (0, 0.106, 0.372, 1.11)	M: 1.2 (0.319) F: 1.4 (0.372) M/F: Degeneration/ regeneration of renal tubular epithelial cells	Comprehensive evaluation of the results from the 1st to 3rd studies.	M: 0.20 (0.132) F: 0.38 (0.252)
	One-year chronic toxicity study	0, 10, 25, 75 ppm M: 0, 0.37, 0.90, 2.65 (0, 0.0984, 0.239, 0.704) F: 0, 0.41, 0.98, 2.97 (0, 0.109, 0.260, 0.790)	M: 0.90 (0.239) F: 2.97 (0.790) M: Aspermia and others F: No toxicity	0, 5, 10, 25 ppm M: 0, 0.20, 0.41, 1.01 (0, 0.132, 0.272, 0.670) F: 0, 0.22, o.40, 1.03 (0, o.146, 0.265, 0.683)	M: 0.20 (0.132) F: 0.40 (0.265) M: Seminiferous tubular atrophy F: Degeneration/ regeneration of renal proximal tubular epithelium
ADI		NOAEL: 0.90 (0.239) SF: 100 ADI: 0.009 (Value converted to that for iminoctadine: 0.0023)		NOAEL: 0.20 (0.132) SF: 100 ADI: 0.002 (Value converted to that for iminoctadine: 0.0013)	
The critical study for setting ADI		One-year chronic toxicity study in dogs		90-day subacute toxicity study and one-year chronic toxicity study in dogs	

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

Table 2. *Potential adverse effects of a single oral administration*
(*Values in parenthesis are converted to the values for iminoctadine*)

Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]
Rat	General pharmacology (Effects on blood pressure)	M: 0, 1 000, 3 000, 5 000 (0, 266, 798, 1 330)	M: 1 000 (266) M: Decrease in blood pressure		
	Acute toxicity study	500, 800, 1 260, 2 000, 3 200 (133, 212, 335, 532, 851)	M/F: - M/F: Piloerection and diarrhea	134, 181, 244, 329, 444, 600 (0, 88.9, 120, 162, 218, 294, 398)	M: 134 (88.9) F: - M: Red eye discharge F: Diarrhea
	Acute toxicity study			0, 174, 208, 250, 300, 360, 432, 498 (0, 115, 138, 166, 199, 239, 286, 330)	M/F: - M/F: Decreased locomotor activity, decreased respiratory rate
	Developmental toxicity study (preliminary study)			0, 0.1, 1, 10, 30, 60, 100 (0, 0.0664, 0.664, 6.64, 19.9, 39.8, 66.4)	Dams: 10 (6.64) Dams: Decreased body weight/ suppressed body weight
	Developmental toxicity study			0, 1, 5, 10 (0, 0.664, 3.32, 6.64)	Dams: 10 (6.64) Dams: No toxicity
	Overall score of assessment			Dams: 10 (6.64) Dams: Decreased body weight/ suppressed body weight	
Mice	General pharmacology (general condition)			0, 50, 100, 200, 400, 800 (0, 33.2, 66.4, 132, 265, 531)	M/F: 100 (66.4) M/F: Piloerection
	Acute toxicity study	1 260, 2 000, 3 200, 5 000, 8 000 (335, 532, 851, 1 330, 2 120)	M/F: - M/F: Piloerection, suppressed body weight	M: 231, 300, 390, 507, 659 (153, 199, 258, 336, 437) F: 178, 231, 300, 390, 507 (118, 153, 199, 258, 336)	M/F: 231 (153) M/F: Sedation
	Acute toxicity study			M: 0, 200, 240, 288, 346, 415, 498, 598 (0, 132, 159, 191, 229, 275, 330)	M/F: - M/F: Decreased locomotor activity, eye

Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or mg/kg bw/day) [1]
				F: 0, 288, 346, 415, 498, 598, 716 (0, 191, 229, 275, 330, 397, 475)	closing
Rabbit	Developmental toxicity study	0, 3, 10, 30 (0, 0.798, 2.66, 7.98)	Dams: 10 (2.66) Dams: Decreased body weight	0, 4, 8, 12 (0, 2.65, 5.31, 7.96)	Dams: 8 (5.31) Dams: Suppressed body weight
ARfD		NOAEL: 10 (2.66) SF: 100 ARfD: 0.1 (Value converted to that for iminoctadine: 0.026)		NOAEL: 8 (5.31) SF: 100 ARfD: 0.08 (Value converted to that for iminoctadine: 0.053)	
The critical study for setting for ARfD		Developmental toxicity study in rabbits		Developmental toxicity study in rabbits	

ARfD, Acute Reference Dose; NOAEL, No-observed-adverse-effect level; SF, Safety Factor;
-, NOAEL could not be specified
[1], Major adverse effect observed at LOAEL