

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) June 2019

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 triacetate. FSCJ considered that the NOAEL of 0.239 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.



Toxicity study		Iminoctadir	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	0, 50, 150, 300 ppm	Parent animals PM: 3.6 (0.957)	0, 25, 50, 100 ppm	Parent animals PM: 2.93 (1.94)	

Table 1. Levels relevant to toxicological evaluation

(Values in parenthesis are converted	to the values for iminoctadine)
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¹, Major adverse effect observed at LOAEL ², Major adverse effect observed at LOAEL



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Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
		_	NOAEL	_	NOAEL
Species	Study	Dose	(mg/kg bw/day) and	Dose	(mg/kg bw/day) and
1	5	(mg/kg bw/day)	Critical endpoints ¹	(mg/kg bw/day)	Critical endpoints ²
		PM: 0. 3.6. 10.6.	PF: 12.1 (3.21)		PF: 3.50 (2.32)
		21.5 (0. 0.957. 2.81.	F_1M : 4.2 (1.11)	$\mathbf{DM}_{1} = 0 + 1 + 46 + 2 + 02$	F ₁ M: 3.57 (2.37)
		5 71)	$F_1F \cdot 134(356)$	FW1: 0, 1.40, 2.95,	$F_1F' = 3.97(2.63)$
		PF 0 4 0 12 1	Offspring	3.84(0, 0.969, 1.04, 2.87)	Offspring
		240(0, 106, 321)	$P M \cdot 10.6 (2.81)$	1.94, 3.87)	P M: 5 84 (3 87)
		6 38)	$PE \cdot 12 + (3 \cdot 21)$	PF: 0, 1.75, 3.50,	PE: 6.98 (34.63)
		$F_{1}M_{1} \cap A = 12.3$	$F_{1}M \cdot 12 \cdot 3 (3 \cdot 27)$	6.98 (0, 1.16, 2.32,	$F_{1}M_{1} = 6.90 (4.58)$
		(0, 1, 11, 3, 27)	$F_{1}F_{1}F_{1}F_{1}F_{1}F_{1}F_{1}F_{1}$	4.63)	F_{1} [101. 0.90 (4.30) F_{2} F_{2} $F_$
		(0, 1.11, 5.27) E.E. 0 4 6 12 4 (0	Poproductivity	$F_1M: 0, 1.76, 3.57,$	Paproductivity
		$\Gamma_1\Gamma_1, 0, 4.0, 13.4(0, 1.2)$	$PM \cdot 2.6 (0.057)$	6.90 (0, 1.16, 2.37,	\mathbf{DM} , 2.02 (1.04)
		1.22, 3.30)	PWI. 5.0 (0.957)	4.58)	PM. 2.93 (1.94) $DE. 2.50 (2.22)$
			FF. 4.0 (1.00) FM. 4.2 (1.11)	$F_1F: 0, 1.94, 3.97,$	$PF: 5.30 (2.52) \\ E M: 2.57 (2.27)$
			$F_1M1: 4.2(1.11)$	7.76 (0, 1.28, 2.63,	F_1 M: 5.57 (2.57) F_1 F_1 F_2 F_2 F_3 F_4 F_2 F_3 F_4 F
			F_1F : 4.6 (1.22)	5.15)	$F_1F: 3.97 (2.63)$
			Donomt on Serve 1-		Downet or in -1
			Parent animals		Parent animals
			M: Spermatogranulomas		M: Degeneration/
			F: Loss of corpora lutea		regeneration of
			Offspring: Lower body		epithelial cells in
			weight		epididymis
			Reproductivity		F: Hypertrophy of
			M/F: Slight delay of		renal distal tubular
			mating establishment		epithlium.
			required date.		Offspring: No
					toxicity
					Reproductivity:
					Decrease in
					conception rate
				0, 0.1, 1, 10, 30,	Dams: 1 (0.664)
	Developmental			60, 100 (0, 0.0664,	Fetuses: 10 (6.64)
	toxicity study			3.32, 6.64)	
	(A preliminary				Dams: Decreased
	study)				feed intake
					Fetuses: Death
		0, 10, 30, 100	Dams: 30 (7.98)	0, 1, 5, 10	Dams: 10 (6.64)
		(0, 2.66, 7.98, 26.6)	Fetuses: 100 (26.6)	(0, 0.664, 3.32,	Fetuses: 10 (6.64)
				6.64)	
	Developmental		Dams: Suppressed body		Dams: No toxicity
	tovicity study		weight, decreased feed		Fetuses: No toxicity
	toxicity study		intake		
			Fetuses: No toxicity		(No teratogenicity)
			(No teratogenicity)		
	Overall score of			Dams: 5 (3.32)	
	assessment			Fetuses: 10 (6.64)	
Mouse	18-month	0, 30, 80, 200, 400	M: 32 (8.51)		



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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)	,	Toxicity study	Iminoctadir	ne tris (albesilate)	Iminoctad	line triacetate
Species Study Dose (mg/kg bw/day) Consecting (mg/kg bw/day) Dose (mg/kg bw/day) Consecting (mg/kg bw/day) <thconsecting (mg/kg bw/day) Consecting</thconsecting 			_	NOAEL	_	NOAEL
1 (mg/kg bw/day) Critical endpoints1 (mg/kg bw/day) Critical endpoints2 2 carcinogenicity study pm F: 6 (1.59) F: 6 (1.59) Critical endpoints2 1 F: 0, 6, 15, 40, 82 F: 10 (1.57, 40, 82 F: 10 (1.59, 3.99, 10.6, 21.8) M: Hypertrophy of renal tubular ceils with collid-like cast/ basophilic changes in renal tubules. M: 0, 833, 0.553 2 (No carcinogenicity) 0, 10, 100, 300 M: 0.833, 0.553) F: 0, 0, 12, 12, 12, 12, 12, 12, 12, 12, 12, 12	Species	Study	Dose	(mg/kg bw/day) and	Dose	(mg/kg bw/day) and
carcinogenicity study ppm F: 6 (1.59) M: 0, 5, 13, 32, 66 (0, 1.33, 3.45, 8.51, 17.5) H: Hypertrophy of renal ubular epithelium. F: 0, 6, 15, 40, 82 (0, 1.59, 3.99, 10.6, 21.8) F: Dilatation of renal ubular cells with colloid-like cast/ basophilic changes in renal tubules. Two-year (No carcinogenicity) 0, 10, 100, 300 M: 0.833 (0.553) Two-year (No carcinogenicity) 0, 10, 100, 300 M: 0.833 (0.553) Two-year (No carcinogenicity) 0, 10, 100, 300 M: 0.833 (0.553) Carcinogenicity study Developmental toxicity study Dams: 3, 0.798) 5.67, 17.2) F: 0.0.787, 7.94, 29.5 (0, 0.522, 41.20) Rabbit 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) 0, 4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 42.65) Petvelopmental toxicity study Dams: Sign of miscarriage Dams: Sign of miscarriage Dams: Anorexia Poday subacute toxicity study Dams: Sign of miscarriage MF: degeneration/ 90-day subacute toxicity study Dams: Sign of miscarriage NH: 0, 1.01, 3.14, 8.34 (0, 0.57), 1.91, 4.58) MF: degeneration/ 90-day subacute 0, 0, 5, 0, 0.597, 1.91, 4.58) Dams: Anorexia <t< td=""><td>1</td><td>5</td><td>(mg/kg bw/day)</td><td>Critical endpoints¹</td><td>(mg/kg bw/day)</td><td>Critical endpoints²</td></t<>	1	5	(mg/kg bw/day)	Critical endpoints ¹	(mg/kg bw/day)	Critical endpoints ²
Rabbit Developmental toxicity study 0, 3, 10, 30 (0, 0, 798, 2.66, 7.98) Dans: 3, (0, 798) 0, 4, 8, 12 (0, 2.50) Feuses: 10 (2.66) Rabbit Developmental toxicity study 0, 3, 10, 30 (0, 0, 798, 2.66, 7.98) Dans: 3, (0, 798) 0, 4, 8, 12 (0, 2.55) Feuses: 10 (2.66) 90-day subacute toxicity study 0, 3, 10, 30 (0, 0, 798, 2.66, 7.98) Dams: Sign of miscarriage 0, 25, 100, 250 MF: - ppm. 90-day subacute toxicity study 0, 24, 100, 6370, 13, 14, 40 0, 25, 100, 250 MF: - ppm. 90-day subacute 0, 0, 573, 19, 10, 61 Dams: Sign of miscarriage MF: - ppm. MF: - ppm. 90-day subacute 0, 0, 0, 0, 0, 71, 91, 13, 44 MF: - ppm. MF: - ppm. 90-day subacute 0, 5, 100, 250 ppm. MF: - ppm. 90-day subacute 0, 5, 100, 751 19, 4, 58) Dams: Anorexia 90-day subacute 0, 5, 100, 757 19, 4, 58) Dams: Anorexia		carcinogenicity study	ppm	F: 6 (1.59)	/	/
Image: Non-Internet Network M: Hypertrophy of renal tubular epithelium. Image: Non-Internet Network F: 0, 6, 15, 40, 82 tubular epithelium. Image: Non-Internet Network F: Dilatation of renal tubular esite with colloid-like cast/ basophilic changes in renal tubular. N: Hypertrophy of renal tubular. Image: Non-Internet Network N: M: Hypertrophy of renal tubular. N: Hypertrophy of renal tubular. Image: Non-Internet Network N: M:			$M \cdot 0 = 5 = 13 = 32 = 66$			
Instruction of the intervention of the interventintery intervention of the intervention of the interven			$(0 \ 1 \ 33 \ 3 \ 45 \ 8 \ 51$	M. Hypertrophy of renal		
P: 0, 6, 15, 40, 82 (0, 1.59, 3.99, 10.6, 21.8) P: Diatation of renal tubular cells with colloid-like cast/ basophile changes in renal tubules. M: 0.833 (0.553) Two-year carcinogenicity study (No carcinogenicity) 0, 10, 100, 300 ppm M: 0.833 (0.553) Two-year carcinogenicity study 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) M. 2, 0.787, 7.94, 29.5 (0, 0.252, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 10 (2.66) Developmental toxicity study Dams: 3, (0.798) 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) Dams: 4 (2.65) 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Po-day subacute toxicity study Dams: Sign of miscarriage Fetuses: increases in skeletal anomaly (Connection of the center of the skull) 0, 25, 100, 250 ppm M/F: - ppm 90-day subacute 90-day subacute 0, 5, 10 ppm M/F: degeneration/ regeneration of renal tubular epithelial cells			17 5)	tubular enithelium		
Instruction of the state of the st			$F: 0 \in 15 = 40 = 82$	F: Dilatation of renal		
Correction Correction Construction Construction <td></td> <td></td> <td>$(0 \ 1 \ 59 \ 3 \ 99 \ 10 \ 6)$</td> <td>tubular cells with</td> <td></td> <td></td>			$(0 \ 1 \ 59 \ 3 \ 99 \ 10 \ 6)$	tubular cells with		
Provide Construction Description Masses (No carcinogenicity) 0, 10, 100, 300 M: 0.833 (0.553) Two-year 0, 10, 100, 300 ppm carcinogenicity study 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0			(0, 1.5), 5.55, 10.0,	colloid-like cast/		
Base in renal tubules. Million charges in renal tubules. (No carcinogenicity) 0, 10, 100, 300 ppm M: 0.833 (0.553) F: 0.787 (0.522) Two-year carcinogenicity study 5.67, 17.2) F: 0.0787, 7.94, 29.5 (0, 0.0522, 5.27, 19.5) M/F: swelling of renal proximal tubular epithelian tubularen tubular			21.0)	basophilic changes in		
Image: Constraint of the standard state in the state is the state in the state is the state in the				renal tubules		
Image: carcinogenicity study (No carcinogenicity) M: 0.100, 300 ppm M: 0.833 (0.553) F: 0.787 (0.522) Two-year carcinogenicity study N: 0.033, 8.55, 26.0 (0.0553, 5.67, 17.2) F: 0.0787, 7.94, 29.5 (0.0522, 5.27, 19.5) M/F: swelling of renal proximal tubular epithelium F: 0.0787, 7.94, 29.5 (0.0522, 5.27, 19.5) Rabbit 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) 0, 4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Developmental toxicity study 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) 0, 4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Developmental toxicity study Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull) Dams: Anorexia Fetuses: No toxicity (No teratogenicity) Dog 90-day subacute toxicity study (the 1 st study) M/F: - ppm (the 1 st study) M/F: - ppm (the 1 st study) M/F: - ppm (the 1 st study) 90-day subacute 0, 5, 10 ppm M: -				Tellal tubules.		
Two-year 0, 10, 100, 300 M: 0.833 (0.553) racinogenicity study M: 0, 0.833, 8.55, 26, 0 (0, 0.553, 567, 17.2) M/F: swelling of real proximal tubular epithelium reacting encirty study S.67, 17.2) F: 0.0787, 7.94, 29.5 (0, 0.522, 5.27, 19.5) M/F: swelling of proximal tubular epithelium Rabbit 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) S.31, 7.96) Fetuses: 12 (7.96) Developmental toxicity study Dams: Sign of miscarriage Petuses: Increases in skeletal anomaly (Connection of the center of the skull) Dams: Anorexia Petuses: No toxicity 90-day subacute toxicity study M/F: - <u>ppm</u> M/F: degeneration/ M/F: degeneration/ 90-day subacute 0, 5, 10 ppm M/F: - M/F: degeneration/ 90-day subacute 0, 5, 10 ppm M: -				(No carcinogenicity)		
Two-year carcinogenicity studyF: 0.787 (0.522)Two-year carcinogenicity studyM: 0, 0.833, 8.55, 20.60 (0, 0.553, 5.67, 17.2)M/F: swelling of renal proximal tubular epithelial epithelial tumors in the kidneyRabbit0, 3, 10, 30 (0, 0.798, 2.66, 7.98)Dams: 3, (0.798) Fetuses: 10 (2.66)0, 4, 8, 12 (0, 2.65, 5.31, 7.96)Dams: 4 (2.65) Fetuses: 12 (7.96)Developmental toxicity study0, 3, 10, 30 (0, 0.798, 2.66, 7.98)Dams: 3, (0.798) Fetuses: 10 (2.66)0, 4, 8, 12 (0, 2.65, 5.31, 7.96)Dams: 4 (2.65) Fetuses: 12 (7.96)Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)0, 25, 100, 250 ppmM/F: - ppm90-day subacute toxicity study0, 25, 100, 250 (the 1st study)M/F: degeneration/ regeneration of renal tubular epithelial cells90-day subacute90-day subacute0, 5, 10 ppmM/F: degeneration/ scarning90-day subacute90-day subacute0, 5, 10 ppmM: -			/	(itto eareningementy)	0, 10, 100, 300	M: 0.833 (0.553)
Two-year carcinogenicity studyNo. 100 (doed)Two-year carcinogenicity studyN. 0, 0.833, 8.55, 26.0 (0, 0.553, 5.67, 17.2)M/F: swelling of renal proximal ubular epitheliumRabbit0, 3, 10, 30 (0, 0.798, 2.66, 7.98)Dams: 3, (0.798) Fetuses: 10 (2.66)0, 4, 8, 12 (0, 2.65, 5.31, 7.96)Dams: 4 (2.65) Fetuses: 12 (7.96)RabbitDevelopmental toxicity study0, 3, 10, 30 (0, 0.798, 2.66, 7.98)Dams: 3, (0.798) Fetuses: 10 (2.66)0, 4, 8, 12 (0, 2.65, 5.31, 7.96)Dams: 4 (2.65) Fetuses: 12 (7.96)Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)Dams: Anorexia Fetuses: No toxicity (No teratogenicity)Po90-day subacute toxicity study (the 1 st study)N/F: - ppm90-day subacute90-day subacute0, 5, 10 ppm90-day subacute0, 5, 10 ppmM: -					ppm	F: 0.787 (0.522)
Two-year carcinogenicity studyM: 0, 0.833, 8.55, 26, 0 (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0					PP	
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carcinogenicity study 5.67, 17.2) tubular epithelium F: 0, 0.787, 7.94, 29.5 (0, 0.522, 5.27, 19.5) At 300 ppm; Renal epithelial tumors in the kidney 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) 0.4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Developmental toxicity study Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull) Dams: Anorexia Fetuses: No toxicity 90-day subacute toxicity study (the 1 st study) 0, 25, 100, 250 (the 1 st study) M/F: - ppm 90-day subacute 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0		Two-vear			26.0 (0. 0.553.	renal proximal
Best Field F: 0, 0.787, 7.94, 29.5 (0, 0.522, 5.27, 19.5) At 300 ppm; Renal epithelial tumors in the kidney Rabbit 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) 0, 4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Developmental toxicity study Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull) Dams: Anorexia Fetuses: No toxicity 90-day subacute toxicity study (the 1 st study) 0, 25, 100, 250 (the 1 st study) M/F: - ppm (S: 0, 0.90, 2.89, 6.90 (0, 0.597, 1.91, 4.58) M/F: degeneration/ regeneration of renal tubular epithelial cells 90-day subacute 0, 5, 10 ppm M: -		carcinogenicity study			5.67.17.2)	tubular epithelium
Pevelopmental toxicity study 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) 0, 4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Developmental toxicity study Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull) Dams: Anorexia Fetuses: No toxicity (No teratogenicity) 90-day subacute toxicity study 0, 25, 100, 250 (the 1 st study) M/F: - 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: - pm M: - 90-day subacute 0, 5, 10 ppm M: -		·····			F: 0, 0,787, 7,94.	···· ···· · · · · · · · · · · · · · ·
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RabbitDevelopmental toxicity study0, 3, 10, 30 (0, 0.798, 2.66, 7.98)Dams: 3, (0.798) Fetuses: 10 (2.66)0, 4, 8, 12 (0, 2.65, 5.31, 7.96)Dams: 4 (2.65) Fetuses: 12 (7.96)Developmental toxicity studyDams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)Dams: Anorexia Fetuses: No toxicity (No teratogenicity)90-day subacute toxicity study0, 25, 100, 250 Ppm (the 1study)M/F: - Ppm 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: - Ppm M: -					5.27. 19.5)	epithelial tumors in
Rabbit 0, 3, 10, 30 (0, 0.798, 2.66, 7.98) Dams: 3, (0.798) Fetuses: 10 (2.66) 0, 4, 8, 12 (0, 2.65, 5.31, 7.96) Dams: 4 (2.65) Fetuses: 12 (7.96) Developmental toxicity study 0.798, 2.66, 7.98) Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull) 0, 25, 100, 250 ppm Dams: Anorexia Fetuses: No toxicity 90-day subacute toxicity study (the 1 st study) 0, 25, 100, 250 (the 1 st study) M/F: - 90-day subacute 0, 0, 0.577, 1.91, 4.58) M/F: - 90-day subacute 0, 5, 10 ppm M: -					0.27, 19.09	the kidney
RabbitDevelopmental toxicity study0.798, 2.66, 7.98)Fetuses: 10 (2.66)5.31, 7.96)Fetuses: 12 (7.96)Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)Dams: Anorexia Fetuses: No toxicity (No teratogenicity)Dog90-day subacute toxicity study (the 1st study)0, 25, 100, 250 PPMM/F: - PPMDog90-day subacute toxicity study (the 1st study)0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0			0. 3. 10. 30 (0.	Dams: 3. (0.798)	0. 4. 8. 12 (0. 2.65.	Dams: 4 (2.65)
Rabbit Developmental toxicity study Dams: Sign of miscarriage Dams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull) 0, 25, 100, 250 M/F: - 90-day subacute toxicity study (the 1 st study) 0, 25, 100, 0.597, 1.91, 4.58) M/F: degeneration/ regeneration of renal tubular epithelial cells 90-day subacute 0, 5, 10 ppm M: -			0.798 2.66 7.98)	Fetuses: 10 (2.66)	5 31 7 96)	Fetuses: 12 (7 96)
RabbitDevelopmental toxicity studyDams: Sign of miscarriage Fetuses: Increases in skeletal anomaly (Connection of the center of the skull)Dams: Anorexia Fetuses: No toxicity (No teratogenicity)Dog90-day subacute toxicity study (the 1 st 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 cells90-day subacute0, 25, 100, 250 ppmM/F: - center of the skull)90-day subacute0, 0, 0, 0, 0, 2.89, 6.90 (0, 0.597, 1.91, 4.58)M/F: degeneration/ regeneration of renal tubular epithelial cells			0.170, 2.00, 1.90)	10(0000)	5.51, 7.50)	1 etuses: 12 (7.90)
RabbitDevelopmental toxicity studyDevelopmental miscarriageDevelopmental miscarriageDevelopmental miscarriageRabbittoxicity studyFetuses: Increases in skeletal anomaly (Connection of the center of the skull)Fetuses: No toxicity (No teratogenicity)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 cells90-day subacute0, 5, 10 ppmM: -				Dams. Sign of		Dams: Anorexia
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Products in relation inclusion in skeletal anomaly (Connection of the center of the skull)(No teratogenicity)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: - mission inclusion in mission inclusion in (No teratogenicity)90-day subacute0, 25, 100, 250 ppm M/F: degeneration/ regeneration of renal tubular epithelial cells90-day subacute0, 5, 10 ppm90-day subacute0, 5, 10 ppm	Rubble	toxicity study		Fetuses: Increases in		
90-day subacute toxicity study (the 1 st study) 90-day subacute toxicity study M/F: - ppm (the 1 st study) M/F: - ppm (the 1 st study) 90-day subacute 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: degeneration/ regeneration of renal tubular epithelial cells 90-day subacute 0, 5, 10 ppm M: -				skeletal anomaly		(No teratogenicity)
90-day subacute toxicity study (the 1 st study) 90-day subacute M/F: - 90-day subacute 0, 25, 100, 250 pm M/F: degeneration/ regeneration of renal 2.08, 5.53) 90-day subacute 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0				(Connection of the		(it to teratogenery)
90-day subacute toxicity study (the 1 st study) 90-day subacute 0, 25, 100, 250 ppm M/F: - 90-day subacute toxicity study (the 1 st study) M/F: degeneration/ regeneration of renal tubular epithelial cells M/F: degeneration/ regeneration of renal tubular epithelial cells 90-day subacute 0, 5, 10 ppm M: -				center of the skull)		
90-day subacute toxicity study (the 1 st study) 90-day subacute M/F: degeneration/ 90-day subacute toxicity study 8.34 (0, 0.670, 2.89, 6.90 (0, 0.597, 1.91, 4.58) M/F: degeneration/ 90-day subacute 0, 5, 10 ppm M: -			/	/	0 25 100 250	M/F [.] -
90-day subacute toxicity study (the 1 st study) 90-day subacute M/F: degeneration/ 90-day subacute toxicity study (the 1 st study) 8.34 (0, 0.670, 2.08, 5.53) M/F: degeneration/ 90-day subacute 90-day subacute 90-0.000, 2.89, 6.90 (0, 0.597, 1.91, 4.58) 6.90 (0, 0.597, 1.91, 4.58) 90-day subacute 90-day subacute 0, 5, 10 ppm M: -					nnm	
90-day subacute toxicity study (the 1st study) 101 acgeneration regeneration 90 -day subacute toxicity study (the 1st study) 101 acgeneration study 1.91 , 4.58) 90 -day subacute $0, 5, 10 ppm$ 90 -day subacute $0, 5, 10 ppm$					$M \cdot 0 = 1 \ 01 = 3 \ 14$	M/F· degeneration/
90-day subacute toxicity study (the 1 st study) 0.34 (0, 0.070, 2.08, 5.53) regeneration of reliant tubular epithelial cells 90-day subacute 0.90 (0, 0.597, 1.91, 4.58) regeneration of reliant tubular epithelial cells 90-day subacute 0, 5, 10 ppm M: -					8 34 (0, 0, 670	regeneration of renal
toxicity study (the 1 st study) 2.08, 9.53) tubulal epinetial cells 90-day subacute 0, 5, 10 ppm M: -		90-day subacute			2.08 5 53	tubular epithelial
Dog (the 1 st study) 1°. 0, 0.30, 2.39, 4 cens 90-day subacute 0, 5, 10 ppm M: -		toxicity study			(2.00, 5.55)	
90-day subacute 0, 5, 10 ppm M: -	Dog	(the 1 st study)			F: 0, 0.90, 2.89,	Cells
90-day subacute 0, 5, 10 ppm M: -					0.90(0, 0.39), 1.01 / 59)	
90-day subacute 0, 5, 10 ppm M: -					1.71, 4.30)	
90-day subacute 0, 5, 10 ppm M: -						
90-day subacute 0, 5, 10 ppm M: -		00 day and			0 5 10	М.
[E: 0.20 (0.252)]		toxicity study			0, 3, 10 ppm	1×1 E: 0.38 (0.252)



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Toxicity study		Iminoctadine tris (albesilate)		Iminoctadine triacetate	
		Deer	NOAEL	Deer	NOAEL
Species	Study	Dose (max/laa)	(mg/kg bw/day) and	Dose (ma/laa huu/dau)	(mg/kg bw/day) and
		(mg/kg bw/day)	Critical endpoints ¹	(mg/kg bw/day)	Critical endpoints ²
	(the 2 nd study)			M: 0, 0.19, 0.39	
				(0, 0.126, 0.258)	M: Decreased weight
				F: 0, 0.20, 0.38 (0,	of the testis, and
				0.132, 0.252)	histopathological
					alteration
					F: No toxicity
		/	/	0, 5, 10, 225 ppm	M: 0.38 (0.252)
					M: Degeneration/
				M: 0, 0.20, 0.38,	regeneration of renal
	90-day subacute			0.92 (0, 0.132,	tubule in the renal
	toxicity study			0.252, 0.610)	cortex, decreased
	$(\text{the } 3^{\text{rd}} \text{ study})$				relative weight of the
	(the 5 study)				testis, hypoplasia of
					seminiferous
					spermatozoa or
		/	/		azoospermia
		0, 10, 30, 100 ppm	M: 1.2 (0.319)	Comprehensive	M: 0.20 (0.132)
		M. 0. 0.5. 1.2.2.6	F: 1.4 (0.372)	evaluation of the	F: 0.38 (0.252)
		M: 0, 0.5, 1.2, 3.0		results from the 1 st	
	90-day subacute	(0, 0.133, 0.319, 0.57)	M/F: Degeneration/	to 3 rd studies.	
	toxicity study	(0.937)	regeneration of renal		
		(0, 0.106, 0.372)	tubular epithelial cells		
		(0, 0.100, 0.572, 1.11)			
		0 10 25 75 ppm	$M \cdot 0.90 (0.239)$	0 5 10 25 ppm	M· 0 20 (0 132)
		$M \cdot 0, 0.37, 0.90$	F 2 97 (0.790)	$M \cdot 0 \ 0 \ 20 \ 0 \ 41$	F: 0.40 (0.265)
		2 65 (0, 0, 0984	1.2.97 (0.790)	1 01 (0 0 132	1.0.10 (0.200)
		0.239, 0.704)	M: Aspermia and others	0.272, 0.670)	M: Seminiferous
	One-year chronic	F = 0.041.098	F: No toxicity	F: 0, 0, 22, 0, 40	tubular atrophy
	toxicity study	2.97 (0.0.109		1 03 (0 0 146	F: Degeneration/
		0.260, 0.790)		0 265 0 683)	regeneration of renal
		0.200, 0.170)		0.200, 0.000)	proximal tubular
					epithelium
	1	NOAEL: 0.90 (0.239))	NOAEL: 0.20 (0.13	32)
		SF: 100		SF: 100	,
	ADI	ADI: 0.009		ADI: 0.002	
		(Value converted to	that for iminoctadine:	(Value converted to	that for iminoctadine:
		0.0023)		0.0013)	
The cri	tical study for setting	One-year chronic tox	ticity study in dogs	90-day subacute to	oxicity study and one-
ADI				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



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

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



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Т	oxicity study	Iminoctad	ine tris (albesilate)	Iminoctad	Iminoctadine triacetate	
Species	Study	Dose (mg/kg bw or mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or	Dose (mg/kg bw/day)	Endpoints relevant to setting NOAEL and ARfD (mg/kg bw or	
			mg/kg bw/day) ¹	E. 0. 289, 246, 415	mg/kg bw/day) ¹	
				F: 0, 288, 346, 415, 498, 598, 716 (0,	closing	
				191, 229, 275, 330, 397, 475)		
		0, 3, 10, 30 (0,	Dams: 10 (2.66)	0, 4, 8, 12 (0, 2.65,	Dams: 8 (5.31)	
Dabbit	Developmental	0.798, 2.66, 7.98)		5.31, 7.96)		
Kabbit	toxicity study		Dams: Decreased body		Dams: Suppressed	
			weight		body weight	
		NOAEL: 10 (2.66)		NOAEL: 8 (5.31)		
		SF: 100		SF: 100		
	ARfD	ARfD: 0.1		ARfD: 0.08		
		(Value converted to that for iminoctadine:		(Value converted to that for iminoctadine:		
		0.026)		0.053)		
The c	critical study for	Developmental tox	vicity study in rabbits	Developmental toxic	vity study in rabbits	
sett	ting 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