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

Risk Assessment Report

Salinomycin

(Veterinary Medicinal Products and Feed Additives)

Food Safety Commission of Japan (FSCJ)
May 2018

SUMMARY

FSCJ conducted a risk assessment of an antibiotic/paraciticide, salinomycin (CAS No. 53003-10-4), using documents for evaluation of salinomycin sodium salt (CAS No. 55721-31-8) such as assessment reports and the documents for revising the residue standards by EFSA.

The data used for the assessment are pharmacokinetics (mice, rats, rabbits, cattle, pigs and chicken), residues (cattle and chicken), genotoxicity, acute toxicity (mice, rats, rabbits, dogs and chicken), subacute toxicity (mice, rats and dogs), chronic toxicity and carcinogenicity (mice and rats), reproductive developmental toxicity (mice, rats and rabbits), and microbiological effects.

FSCJ considered that salinomycin has no genotoxicity relevant to human health based on the genotoxicity study, and thus concluded that the ADI for salinomycin can be specified.

Major adverse effects observed in subacute toxicity study, and chronic toxicity and carcinogenicity study were decreased motor activity and suppressed body weight in mice and rats, and neurotoxicity in dogs. Carcinogenicity was not observed.
In reproductive developmental toxicity studies, suppressed body weight was observed in parental animals and offsprings, but teratogenicity was not observed.

FSCJ estimated the toxicological ADI as 0.005 mg/kg bw/day applying a safety factor of 100 to the NOAEL of 0.5 mg (as sodium salts)/kg bw/day obtained in 90-day subacute toxicity study in dogs and in a developmental toxicity study in rabbits.
The microbiological ADI was estimated as 0.025 mg/kg bw/day.
FSCJ specified the ADI for salinomycin to be 0.005 mg (as sodium salts)/kg bw/day since the toxicological ADI was smaller than the microbiological ADI.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Mice	Three-month subacute toxicity study	Feed grade 0, 150, 450, 900, 1 350 ppm	M: 27 F: 28 Death, Suppressed increase of body weight, etc.
	Six-month subacute toxicity study	Purified grade 0, 10, 30, 100, 300 ppm	13 Decreased locomotor activity, suppressed increase of body weight
	Two-year chronic toxicity and carcinogenicity study (the 1st study)	0, 10, 30, 100, 300 ppm	M: 14 F: 12 Decreased locomotor activity, suppressed increase of body weight, cloudy swelling in the liver, etc. No carcinogenicity
	Two-year chronic toxicity and carcinogenicity study (the 2nd study)	Feed grade 0, 50, 100, 200, 400 ppm	M**:** 7.7 or 7.9 F**:** 8.6 or 8.8 Wasting, suppressed increase of body weight, etc. No carcinogenicity
	Two-year carcinogenicity study	Biomass containing salinomycin Na 0, 50, 200, 800 (600 after 32 weeks)	5.8 (as a sodium salt) Increased incident rate of caudal lesions, suppressed increase of body weight, etc. No carcinogenicity
	Two-generation reproductive toxicity study	0, 10, 30, 100 ppm	Parent and offspring: 4.3 ~ 5.3 Parent and offspring: Suppressed increase of body weight
	Developmental toxicity study	Purified grade 0, 4, 12, 36	Dams, offspring and fetuses: 11 Dams: Death Offspring: Decrease ratio of number of birth to total number of implantation, decreased body weight of offspring. Fetuses: decreased body weight No teratogenicity
Rat	One-month subacute toxicity study	Purified grade 0, 2.5, 5.0, 10, 20	4.8 Death, decreased locomotor activity, suppressed increase of body weight, cardiac cloudy

			swelling, etc.
	Three-month subacute toxicity study	Feed grade 0, 150, 450, 900, 1 350 ppm	M: 30 F: 34 Death, suppressed increase of body weight, effcts on the biochemical parameters of the blood, etc.
	Two-year chronic toxicity and carcinogenicity study (the 1st study)	0, 20, 50 , 130, 320 ppm	4.6 ~ 5.3 Decreased locomotor activity, suppressed increase of body weight, etc. No carcinogenicity
	Two-year chronic toxicity and carcinogenicity study (the 2nd study)	Salinomycin Na containing fermentation products 0, 1.5, 3.0, 6.0 (as sodium salts)	LOAEL: 1.5 (as sodium salts) effcts on the biochemical parameters of the blood, etc. No carcinogenicity
	Two-year chronic toxicity and carcinogenicity study (the 3rd study)	Feed grade 0, 100, 200, 400, 600 ppm	M: 7.3 or 7.4 F: 8.7 or 8.9 Wasting, suppressed increase of body weight, etc. No carcinogenicity
	30-month chronic toxicity and carcinogenicity study	Feed grade 0, 50, 100, 200 ppm (as salinomycin)	M: ca. 2 F: ca.3 Suppressed increase of body weight
	30-month carcinogenicity study	Salinomycin Na containing mycelium 0, 2.5, 5, 10 (as salinomycin)	5 Suppressed increase of body weight No carcinogenicity
	Reproductive toxicity study	Formulations of salinomycin Na 0, 75, 150, 250 ppm (as slinomycin)	Parent: 4.6 ~ 7.1 Offspring: 7.0 ~ 17.3 Parent and offspring: Suppressed increases of body weight
	Two-generation reproductive toxicity study (the 1st study)	Formulations of salinomycin Na 1.1 ~ 4.8, 2.7 ~ 13.3 or 6.6 ~ 32.6 (as salinomycin)	Parent: 2.7 ~ 13.3 Suppressed increase of body weight Offspring: 1.1 ~ 4.8 Decreased body weight
	Developmental toxicity study (the 1st study)	Formulations of salinomycin Na 0, 1, 3, 10 (as salinomycin)	Dams: 1 piloerection, kyphosis and coarse fur Fetuses: 10 No effect

			No teratogenicity
	Developmental toxicity study (the 2nd study)	Feed grade 0, 2, 6, 20	Dams: 8.6 No effect Fetuses: 8.6 No effect No teratogenicity
Rabbits	Developmental toxicity study (the 1st study)	Salinomycin Na containing fermentation products 0, 0.2, 0.5, 1.1 (as sodium salts)	Dams: 0.5 (as sodium salts) Suppressed increase of body weight Fetuses: 11 (as sodium salt) No effect No teratogenicity
	Developmental toxicity study (the 2nd study)	0, 0.125, 0.25, 0.50	Dams and fetuses: 0.45 No effect No teratogenicity
	Developmental toxicity study (the 3rd study)	Feed grade 0, 2, 5, 10	Dams and fetuses: 4.4 No effect No teratogenicity
	Developmental toxicity study (the 4th study)	Study 1 Salinomycin containing mycelium 0, 0.25, 0.63, 1.60 (as sodium salts) Study 2 Formulations of salinomycin Na 0, 2.3 ~ 4.1, 3.3 ~ 8.5 (as sodium salts)	Dams: 0.63 (as sodium salt) Decreased number of pregnancy maintaining dams Fetuses: 1.60 (as sodium salts) No effect No teratogenicity
	Developmental toxicity study (the 5th study)	Formulations of salinomycin Na 0, 150, 300 ppm	Dams: 3.25 ~ 4.22 No effect Fetuses: 3.25 No effect No teratogenicity
Dogs	90-day sub-acute toxicity study	Salinomycin Na containing fermentation products 0, 0.2, 0.5, 1 (as sodium salts)	0.5 (as sodium salts) Dragging of the hind limbs, degeneration of the axon of the sciatic nerve, etc.
	Six-month subacute toxicity study	Purified grade 0, 0.3, 1.0, 3.0	0.94 Atactic gait, convulsion, trend of suppressed increase of body weight
	One-year chronic toxicity study	Biomass containing salinomycin Na 0, 0.5, 2.5, 12.5	0.52 (as sodium salts) Death, neurotoxicity, etc.

Toxicological ADI (mg/kg bw/day)	0.005 (as sodium salts) NOAEL: 0.5 (as sodium salts) S.F.: 100
The critical study for setting toxicological ADI	90-day subacute toxicity study in dogs, and developmental toxicity study in rabbits (the 2nd study)
Microbiological ADI (mg/kg bw/day)	0.025
The critical study for setting microbiological ADI	MIC_{calc} derived from MIC_{50} of the isolated strain from human enterobacterial flora: 0.000671 µg/mL
ADI	0.005 (as sodium salts)