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

Risk Assessment Report

Sarafloxacin

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
May 2018

ABSTRACT

FSCJ conducted a risk assessment of an antibiotic, sarafloxacin (CAS No. 98105-99-8), based on the evaluation reports from JECFA and FDA, and other documents.

Data used in the assessment include pharmacokinetics (mice, rats, rabbits, dogs, chicken, turkies, salmons, trouts, catfishes and humans), residues (chicken, turkies and salmons), genotoxicity, acute toxicity (mice and rats), sub-acute toxicity (mice, rats and dogs), chronic toxicity and carcinogenicity (mice and rats), reproductive developmental toxicity (rats and rabbits), and microbiological effects.

In pharmacokinetics, bioavailability of orally administered sarafloxacin basically depends on the animal species including humans, and it tended to be high in dogs and to decrease as the dose increases. After oral administration of sarafloxancin in mice, rats and rabbits, the related substance mainly detected in the excrement was parent compound. In addition, the glucuronic acid conjugates, N-acetylated metabolites or/and 3'-oxyso compounds were detected as the metabolites. Sarafloxacin-related substances, including unabsorbed parent compound, were detected more in feces than in urine after the oral administration.

Among the residues in the tissues of chicken and turkeis after the last administration, the highest residue was detected in the liver. However, the residues decreased at 72 to ca.120 hrs after the last administration to a trace amount or to below the detection limit. In the case of residue in salmones, residue in the muscle tend to depend on the water temperature and the residue was higher when salmons were reared at the lower temperature.

FSCJ considered that sarafloxacin has no genotoxicity relevant to human health, and thus concluded that the ADI for sarafloxacin could be specified.
Major adverse effects observed in toxicity studies were nephrotoxicity such as interstitial nephritis in the kidney (mice) and tubular nephropathy (rats), decreased blood globlin concentration (rats and dogs), skin erythema, and swelling around eyelid and ear (dogs). Carcinogenicity was not observed.
Reproductive toxicity and teratogenicity were not observed in reporoductive developmental studies.

FSCJ estimated the toxicological ADI for sarafloxacin to be 0.05 mg/kg bw/day by applying a safety factor of 100 to the NOAEL of 5 mg/kg bw/day which was obtained in 90-day sub-acute toxicity study in dogs.

Microbiological ADI was estimated to be 0.0064 mg/kg bw/day.

FSCJ specified the ADI of sarafloxacin as 0.0064 mg/kg bw/day since the microbilogical ADI is smaller than the toxicological ADI.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Mice	78-week carcinogenicity study	150, 750, 3 000	150 Increased mortality, nephrotoxicity. No carcinogenicity
Rat	90-day subacute toxicity study	20, 75, 280, 1 000	280 Death (1 case), the nodule of growth cartilage and auricular chondritis
	52-week chronic toxicity study and 104-week carcinogenicity study	Chronic toxicity study phase: 61, 670, 1 700 Carcinogenicity study phase:54, 580, 1 500	Chronic toxicity study phase: 61 tubular nephropathy, decreased total protein and globulin in the blood. Carcinogenicity study phase: 54 tubular nephropathy, increased relative weight of the kidney No carcinogenicity
	Three generation reproductive toxicity study	75, 275, 1 000	Parents: 75 Decrease in absolute and relative weight of the liver Offspring: 1 000 Reproductive activity: 1 000
	Developmental toxicity study	20, 75, 280, 1 000	Dams**:** 1 000 Fetuses**:** 1 000 No teratogenicity
Rabbit	Developmental toxicity study	15, 35, 75	Dams: － Miscarriage with all examined doses Fetuses: 15 decrease in body weight No teratogenicity
Dog	Two-week subacute toxicity study	2, 20, 50, 125, 300	－
	90-day subacute toxicity study (the 1st study)	5, 25 or 125	5 Decrease in serum globulin
	90-day subacute toxicity study (the 2nd study)	10, 50 or 200 (equivalent to 8, 40, 160 in the first 2 weeks)	8 Erythema of the pinna and muzzles, decrease in serum globulin

[1] Major adverse effect observed at LOAEL

Toxicological ADI (mg/kgbw/day)	0.05
The critical study for setting toxicological ADI	90-day sub-acute toxicity study (the 1st study) (dogs)
Microbiological ADI (mg/kgbw/day)	0.0064
The critical study for setting microbiological ADI	MIC_{calc} of the isolated strain from human enterobacterial flora: 1.23 μg/mL
ADI (mg/kgbw/day)	0.0064 mg/kgbw/day