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

Risk Assessment Report

Gentamicin

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
August 2018

ABSTRACT

FSCJ conducted a risk assessment of an antibiotics, Gentamicin (CAS No. 1403-66-3), based on the evaluation report from JECFA and from EMEA, and a written application for the marketing approval of new veterinary medicinal products and its attached documents.

Data used in the assessment include pharmacokinetics (dogs, cattle, pigs and chicken), residues (cattle, pigs and chicken), genotoxicity, acute toxicity (mice, rats, guinea pigs and dogs), sub-acute toxicity (rats, rabbits, dogs and monkeys), chronic toxicity and carcinogenicity (rats and dogs), reproductive developmental toxicity (mice, rats, guinea pigs and rabbits), and microbiological effects.

Although some data in *in vitro* studies on genotoxicity were positive, FSCJ considered these data to be unreliable because the methods of these studies were partly inappropriate and the positive data were likely pseudo-positive. In contrast, *in vitro* gene mutation test and chromosomal aberration tests using CHO cells, and an *in vivo* bone marrow micronucleus test in mice were conducted according to GLP, negative data from these studies were considered to be reliable. In addition, data from 4 bacterial reverse mutation tests were reported to be negative as a reference information, though the concentration used was unknown. Therefore, FSCJ concluded that gentamicin had no genotoxicity relevant to human health, thus an ADI for gentamicin could be specified.
FSCJ judged that gentamicin was of no carcinogenic concern, supporting the conclusion of JECFA to deny a structural alert in gentamicin although carcinogenicity study was not conducted, based on the fact that aminoglycoside antibiotics are known to be non-carcinogenic, and based on data from the genotoxicity studies.
The major effect observed in a toxicity study was the nephrotoxicity.
Data from all the studies of reproductive developmental toxicity were referred, and FSCJ judged that gentamicin has no teratogenicity based on the data from studies with oral administration and with muscular and subcutaneous injection that ensure the systemic exposure to gentamicin.

FSCJ specified the toxicological ADI for gentamicin to be 0.1 mg/kg bw/day, applying the safety factor of 100 to the NOAEL of 10 mg/kg bw/day which was obtained in 14-week sub-acute toxicity study in dogs.

Microbiological ADI was estimated to be 0.011 mg/kg bw/day.

FSCJ specified the ADI for gentamicin as 0.011 mg/kg bw/day as the microbiological ADI is smaller than the toxicological ADI.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	4-week subacute toxicity study	0, 400, 2 000, 10 000, 50 000 ppm	M: 25.4 F: 24.5 The degenerative changes in the tubular epithelial cells, and epithelial hyperplasia of the cecal mucosa
	13-week subacute toxicity study	0, 4, 19, 116	19 Ketone bodies in the urine
Dog	14-week subacute toxicity study	0, 2, 10, 60	10 Interstitial nephritis in the kidney
Monkey	Ototoxicity study	0, 25, 50 Intramuscular administration	–
Toxicological ADI (mg/kg bw/day)			0.1 mg/kg bw/day
The critical study for setting toxicological ADI			14-week subacute toxicity study in dogs. S.F.: 100
Microbiological ADI (mg/kg bw/day)			0.011 mg/kg bw/day
The critical study for setting microbiological ADI			MICcalc derived from MIC_{50} of the isolated strain from human enterobacterial flora: 0.003 mg/mL
ADI			0.011 mg/kg bw/day

– : Not specified

[1] Major adverse effect observed at LOAEL