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

Risk Assessment Report

Norfloxacin

(Veterinary medicinal products)

Food Safety Commission of Japan (FSCJ)
January 2014

ABSTRACT

FSCJ conducted a risk assessment of "norfloxacin" (CAS No. 70458-96-7), a synthetic fluoroquinolone antimicrobial drug, based on a set of data submitted by the applicant for a reexamination of veterinary medicinal products.

The data used in the assessment are on: pharmacokinetics (rats, mice, rabbits, dogs, monkeys, pigs and chickens), residues (pigs and chickens), genotoxicity and acute toxicity (rats and mice), subacute toxicity (rats and dogs), chronic toxicity and carcinogenicity (rats and dogs), reproductive and developmental toxicity (mice and rabbits), microbiological effects and others.

Although norfloxacin showed positive results suggesting chromosomal aberrations in *in vitro* tests for genotoxicity, the effect was not considered to be attributed to direct effects on DNA. In addition, norfloxacin was negative in all *in vivo* tests for genotoxicity, therefore FSCJ concluded that it was possible to establish a threshold dose in the assessment. Chronic toxicity study and carcinogenicity study did not demonstrate any pathological changes to suggest carcinogenicity of norfloxacin. While norfloxacin showed a positive result in an *in vivo* liver initiation assay and its confirming test in rats, the occurrence of liver tumors was not observed. Based on these data, FSCJ considered that norfloxacin is not a genotoxic carcinogen and the ADI can be specified.

The minimum value of NOAEL or LOAEL in the toxicological studies was LOAEL of 18 mg/kg bw/day in an 81-week combined chronic toxicity/carcinogenicity study in rats. Applying a safety factor of 1,000 (10 for species difference, 10 for individual difference and 10 for the adopted LOAEL value and insufficient data on carcinogenicity and reproductive-developmental toxicity) to the LOAEL, FSCJ specified the toxicological ADI to be 0.018 mg/kg bw/day.

Microbiological ADI was calculated to be 0.014 mg/kg bw/day based on the VICH (the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline 36. FSCJ specified the ADI of norfloxacin as 0.014 mg/kg bw/day because the microbiological ADI is smaller than the toxicological ADI.