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

Risk Assessment Report

Amoxicillin

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
July 2018

ABSTRACT

FSCJ conducted a risk assessment of amoxicillin (CAS No. 26787-78-0), an antimicrobial, based on JECFA evaluation report and a set of data submitted to the Ministry of Health, Labour and Welfare (MHLW).

Although DNA damage was observed in *in-vitro* comet assays at the maximum dose of amoxicillin in a genotoxicity study, FSCJ considered it as an indirect effect from reactive oxygen species. In addition, data from the other *in-vitro* studies and *in-vivo* studies with amoxicillin-clavulanate combination were all negative. Therefore, FSCJ considered that amoxicillin had no genotoxicity relevant to human health, thus concluded that the ADI for amoxicillion could be specified.

FSCJ considered that amoxicillin is unlikely to be carcinogenic based on conclusion of JECFA's evaluation, data from genotoxicity study, and based on the fact that tumors and/or prepeoplastic lesions were not observed in a 6-month subacute toxicity study.

The value of NOAEL in various toxicological studies (500 mg ~ 4.0 g/kg bw/day) was obtained at the highest dose in each study.

Hypesensitivity was the mostly concerned toxicological effect. Amoxicillin is specifically absorbed through dipeptide transporters in the digestive tract, while impurities and the degraded-products are hardly absorbed. Moreover, *in-vivo* absorption of protein complexes with amoxicillin and/or its metabolites is considered to be low because those complexes show extreamly low bioavailabilities after oral administration. Therefore, FSCJ considered it very unlikely that the amount ingested with food consumption potentially induce allergy. However, a quantitative index for allergenicity could not be established because of lack of data, thus FSCJ did not consider quantitatively the toxicological ADI.

Microbiological ADI was estimated to be 0.0013 mg/kg bw/day.

As a conclusion, FSCJ specified the ADI for amoxicillin to be 0.0013 mg/kg bw/day.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Mice	Reproductive toxicity	0, 0.4, 1.3, 4.0 g/kg bw/day	Dams, Fetuses, Offspring: 4.0 g/kg bw/day (the highest dose) No teratogenicity
	Developmental toxicity	0, 200, 500, 2 000	－ (NOAEL could not specified)
Rat	21-day subacute toxicity study (the 1st study)	0, 500	－
	21-day subacute toxicity study (the 2nd study)	0, 500	－
	One-month subacute toxicity study	0, 0.4, 0.9, 1.9, 4.0 g/kg bw/day	4.0 g/kg bw/day (the highest dose)
	Six-month subacute toxicity study	0, 0.4, 0.9, 1.9, 4.0 g/kg bw/day	4.0 g/kg bw/day (the highest dose)
	26-week subacute toxicity study	0, 200, 500, 2 000	2 000 (the highest dose)
	Reproductive toxicity (the 1st study)	0, 200, 500	Parents, embryo, fetuses, offspring: 500 (the highest dose)
	Reproductive toxicity (the 2nd study)	0, 0.4, 1.3, 4.0 g/kg bw/day	Dams, fetuses, offspring: 4.0 g/kg bw/day (the highest dose) No teratogenicity
	Reproductive toxicity (the 3rd study)	0, 200, 500	Dams, offspring : 500 (the highest dose)
	Developmental toxicity	0, 200, 500, 2 000	2 000 (the highest dose) No teratogenicity
Dog	14-day subacute toxicity study	250	－
	6-month subacute toxicity study	0, 200, 500, 2 000	2 000 (the highest dose)
Cat	4-week subacute toxicity study	0, 100, 300, 500 mg/head/day	－
Toxicological ADI (mg/kg bw/day)			Not specified

[1] Major adverse effect observed at LOAEL

The critical study for setting toxicological ADI	–
Microbiological ADI (mg/kg bw/day)	0.0013
The critical study for setting microbiological ADI	MICcalc derived from MIC_{50} of the isolated strain from human enterobacterial flora: 0.0002 mg/mL
ADI	0.0013

*; Dietary concentration at 1 000 or 10 000 equivalent to 75 or 750 mg/kg bw/day