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

# Risk Assessment Report

## Xylazine

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
May 2019

## ABSTRACT

FSCJ conducted a risk assessment of xylazine (CAS No. 7361-61-7), a sedative, based on a set of data submitted to the Ministry of Health, Labour and Welfare (MHLW), and the published documents evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Medicines Agency (EMEA) and others.

Data used in the assessment include ADME (absorption, distribution, metabolism and excretion) (rats, cattle and horses), residues (cattle and horses), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats), developmental toxicity (rats), and others.

The ADME studies in rats indicated that orally administered xylazine was rapidly absorbed, and 70% of the administered dose was excreted in urine and 30% of that was in stools in either case of oral or intravenous administration. The half-time, $T_{1/2}$, of the intravenously administered xylazine was 2~3 hours. In the case of a single intramuscular administration in cattle, xylazine was rapidly metabolized and excreted.
In the residue study in cattle, concentration of xylazine treated in muscles and tissues was below the detection limit after 48 hours of administration.

ADME studies in rats, cattle and horses reported that 2,6-xylidine (CAS No. 87-62-7) was detected in urine as a metabolite of xylazine. JECFA concluded that ADI for xylidine should not be specified since 2,6-xylidine was suggested genotoxic. On the other hand, EMEA conducted an assessment of xylazine after JECFA, and concluded that 2,6-xylidine was not detected in ADME and residue studies.
FSCJ used data of JECFA and EMEA and the findings obtained after the assessment by EMEA evaluation for the evaluation. FSCJ considered as follows: If xylazine is administered in cattle, 2,6-xylidine might be formed transiently in the metabolic processes. However, 2,6-xylidine unlikely remains in food products from the relevant cattle, since it will be rapidly metabolized and excreted if the administration is suspended for an appropriate period.
Based on various toxicity studies, xylazine was considered to have no genotoxicity relevant to human health.

FSCJ considered that xylazine has low carcinogenic potential, because it has no genotoxicity relevant to human health. Precancerous lesion was not observed in subacute toxicity studies, although carcinogenicity study was not conducted.

Among NOAELs obtained in various toxicity studies, an appropriate NOAEL for specifying ADI was 4mg/kg bw/day obtained from the NOAEL for either dams or fetuses in the developmental toxicity studies in rats.
On the other hand, FSCJ considered the following points important at the evaluation: 1) xylazine has a long history of use as a veterinary medicinal product, 2) Xylazine is rapidly metabolized *in vivo* after the absorption and excreted from the body, 3) the use is restricted to case such as surgical operations, 4) EMEA, who evaluated xylazine after JECFA, specified no ADI and MRL of xylazine.
On the basis of comprehensive consideration, FSCJ concluded that it is not necessary to specify ADI of xylazine as long as it is used appropriately as a veterinary medicinal product.

The exposure levels shall be confirmed based on this assessment when the provisional standards will be reviewed.

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

| Species | Study | Dose (mg/kg bw/day) | NOAEL (mg/kg bw/day) and Critical endpoints[1] |
|---|---|---|---|
| Rat | Developmental toxicity study (the 1st study) | 0, 1, 4, 16<br>Gavage administration<br>(from gestation day 6 to15) | 4<br><br>Dams: Partial closure of the eyelids, decreased activity, suppressed body weight<br>Fetuses: Decreased weight |
| Dog | 13-week subacute toxicity study | 0, 10, 30, 100 ppm<br>(0, 0.3, 0.9, 3)<br>dietary administration | Could not specify |
| Toxicological ADI | | | - |
| The critical study for setting toxicological ADI | | | - |
| ADI | | | - |

[1] Major adverse effect observed at LOAEL