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

# Risk Assessment Report

## Zeranol (α-zearalanol)

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
December 2020

## ABSTRACT

FSCJ conducted a risk assessment of zeranol (CAS No. 26538-44-3), a hormonal agent, using assessment reports of JECFA and FDA.

Considering results of genotoxicity studies where zeranol and its major metabolites, zearalenone and taleranol, did not show any genotoxicity relevant to human health, FSCJ judged it possible to specify the ADI.

Major adverse effects of zeranol were functional and morphological changes in the reproductive organs implying that zeranol is a weak estrogen. Such hormonal effects were commonly observed in various toxicity studies. No teratogenicity was observed.
In a combined 104-week chronic toxicity and carcinogenicity study, an increased incidence of pituitary anterior adenomas was observed in male mice. FSCJ considered that such neoplastic change was related to hormonal action of zeranol.

Dilation of uterine cavity was observed in female rats administered 1.3 mg/kg bw/day, a LOAEL in a combined 104-week chronic toxicity/carcinogenicity study, while no toxicity was observed in male rats. Consequently, FSCJ determined the NOAEL of 0.13 mg/kg bw/day for female rats.
In two-generation reproductive toxicity studies for the group (parent and offspring) administered 1.5mg/kg bw/day, the LOAEL, the followings were observed: 1) decreased or suppressed body weight; 2) decrease in fertility rate and pregnancy rate in $F_1$ parent animals; and 3) decreased number of birth and low body weight in offspring. On the basis of these results, FSCJ determined the NOAEL of 0.15 mg/kg bw/day for parent and offspring.

FSCJ attributed the characteristic *in-vivo* effects of zeranol to its estrogenic activity, and considered that rat was the most susceptible species to the estrogenic activity of zeranol. Accordingly, FSCJ considered it appropriate to specify an ADI based on the dose without adverse effect that was attributable to estrogenic action observed in the study in rats.

The lowest NOAEL was 0.13 mg/kg body weight/day for dilation of uterine cavity found in a combined 104-week chronic toxicity/carcinogenicity study in rats. Given the above, FSCJ considered it appropriate to specify the ADI of 1.3 μg/kg bw/day applying a SF 100 to the NOAEL of 0.13 mg/kg bw/day.

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

| Species | Study | Dose (mg/kg bw/day) | NOAEL (mg/kg bw/day) |
|---|---|---|---|
| Mouse | 8-week subacute toxicity study | 0, 1, 5, 25, 50, 100 ppm (Feeding) | M: 15<br>No toxicity<br>F: 0.75<br>Decrease in absolute- and relative-organ weight of the ovary |
| | Combined 104-week chronic toxicity/carcinogenicity study | 0, 0.15, 1.5, 15 ppm (Feeding) | 0.23<br>M: Increased subcapsular hyperplasia in the adrenal gland<br>F: Increased mucus production of the cervical canal and vaginal epithelium |
| Rat | Combined 104-week chronic toxicity/carcinogenicity study | 0, 0.25, 2.5, 25 ppm (Feeding) | M: 1.3<br>No toxicity<br>F: 0.13<br>Dilation of the uterine cavity |
| | Two-generation reproductive toxicity study | 0, 0.3, 3, 30 ppm (Feeding) | Parent/Offspring: 0.15<br>Decrease in body weight |
| Dog | 104-week chronic toxicity study | 0, 1, 100, 1 000 ppm (Feeding) | 2.5<br>Severe atrophy of the ovaries accompanied by decrease of cysts, squamous metaplasia and inflammatory changes of the uterus and prostate, and chronic inflammatory changes of the urinary bladder |
| | 7-year chronic toxicity study | 0, 15, 38<br>Cycle method (91 cycle: oral capsule administration)<br>*Female only | 15 (LOAEL)<br>Increase in the average- and relative-weight of the ovaries |
| Monkey | 10-year chronic toxicity study | 0, 15, 75<br>Cycle method (131 cycle: gavage administration)<br>*Female only | 15 (LOAEL)<br>Suppressed body weight, external endometriosis |
| | 3 menstrual cycle administration | 0, 0.05, 0.5, 5<br>(oral administration)<br>*Female only | -a |

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|---|---|---|---|
| | 3 menstrual cycle or 111-day administration | 0, 0.5, 5, 50<br>(oral administration)<br>*Female only | 5<br>cessation or remarkable extention of the menstrual cycle, decreased estradiol concentration |
| | Study in ovariectomized monkeys | 0.05, 0.5, 5<br>(oral administration)<br>*Ovariectomized female | -b |
| Toxicological ADI | | | 0.0013 mg/kg<br>NOEL: 0.13<br>SF: 100 |
| The critical study for setting Toxicological ADI | | | Combined 104-week chronic toxicity/carcinogenicity study in rats Feeding |
| ADI | | | |

a: As there was no effect of administration observed in all groups including the positive controle, FSCJ judged that the estrogenic activity of the test substance was undetectable under conditions of this study.
b: FSCJ described the study as “Other study”, since it was a study on the hormonal activity in ovariectomized monkey.
-: .No description in the assessment report.