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

Risk Assessment Report

Mono, bis (trimethylammoniummethylene chloride)-alkyltoluene

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of mono, bis (trimethylammoniummethylene chloride)-alkyltoluene (TAMCA), a disinfectant, based on documents including the summary of data submitted from the applicant.

The data used in the assessment include pharmokinetics (mice and chickens), residues (cattle, pigs and chickens), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats and rabbits), chronic toxicity (rats and dogs) as well as reproductive and developmental toxicity.

Data on *in vitro* genotoxcity studies of TAMCA, including reverse mutation tests, were all negative though there were in vivo genotoxicity study submitted. FSCJ judged that TAMCA is unlikely to be genotoxic *in vivo* and has no genotoxicity relevant to human health as following reasons : 1) *in vitro* genotoxicity study including reverse mutation tests gave negative results; 2) it is highly unlikely that TAMCA has mutagenic potential (DNA reactivity) based on their chemical structure; and 3) a quaternary ammonium compound such as benzalkonium chloride, an analogous compound of TAMCA, has been used as a disinfectant for a long time in the medical field.

Major adverse effects of TAMCA include diarrhea, loose stool, suppressed body weight, and decreased feed consumption.

No teratogenicity was observed in developmental toxicity study in mice and during organogenesis in rats.

The effects observed at the lowest dose in various toxicological studies were abnormalities in general conditions such as diarrhea and loose stool as well as changes observed in the hematological and blood biochemical examinations such as increase in WBC and decrease in Cl in a five-week subacute toxicity study in rats [-]. The NOAEL in this study was 2.5 mg/kg bw/day.

Since the data used for the assessment of TAMCA was limited, data for evaluation of chronic toxicity and reproductive and developmental toxicity studies were insufficient, and no *in vivo* genotoxicity study has been

conducted, FSCJ was considered an additional safety factor to be necessary for the toxicological evaluation. Considering the overseas assessment results of a quaternary ammonium compound, an analogous compound of TAMCA, and the long history of use in the medical field, FSCJ concluded that an additional safety factor of 2 is appropriate as long as TAMCA is used appropriately as a veterinary medicine.

Consequently, FSCJ specified the ADI for TAMCA at 0.013 mg/kg bw/day, based on NOAEL of 2.5 mg/kg bw/day, obtained in rats in the five-week subacute toxicity study applying a safety factor of 200 (including a safety factor of 2).

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and critical endpoints
Mouse	Developmental toxicity study	0, 5, 25, 50 (Gavage administration)	Parent: 5 Suppressed body weight Embryo: 50 Not teratogenic
Rat	30-day subacute toxicity study	0, 7.0 (Gavage administration)	- Suppressed body weight and decreased feed consumption
	5-week subacute toxicity study	0, 2.5, 10, 40 (Gavage administration)	2.5 Loose stool, diarrhea, stridor, increase in WBC, decrease in blood Cl^-, increase in ALP (F), and decrease in Chol (M)
	6-week subacute toxicity study	0, 0.02, 0.2, 1, 10% (Dermal administration)	- Suppressed body weight
	47-day subacute toxicity study	0, 0.02, 0.2, 1, 10% (Dermal administration	- Suppressed body weight Skin hardening, skin thickening, crust formation and others
	4-month subacute toxicity study	0, 0.01, 0.02, 0.04, 0.08% (Exposure via drinking water)	0.01% (Equivalent to 10) Decrease in feed consumption and drinking water
	Two-year combined chronic toxicity/carcinogenicity study	0, 50, 200, 1 000, 2 500, 5 000 ppm (Dietary administration)	200 ppm (Equivalent to 10) Caecum distension Not carcinogenic
	Administration during organogenesis	0, 5, 25, 50 (Gavage administration)	Parent: 25 Loose stool, diarrhea and weakness Offspring: 50 Not teratogenic
	Fecal and cecal microbial populations	0, 50, 200, 1 000, 2 500, 5 000 ppm (Dietary administration)	1 000 ppm (Equivalent to 50) Reduction of gram positive flora and relative increase in gram negative flora
Rabbit	4-week subacute toxicity study	0.05% (Dermal administration)	- No toxic effects
Gerbil	Effect on intracellular calcium storage	0.001% (Exposure via drinking water)	- Decrease of intracellular calcium level in the uterine smooth muscle (0.001%: equivalent to 1)

Toxicological ADI (mg/kg bw/day)	0.013 NOAEL: 2.5 SF: 200
The critical study for setting ADI	5-week subacute toxicity study in rats
ADI (mg/kg bw/day)	0.013

-, NOAEL could not be specified, and toxicity was not listed in the table due to subcutaneous injection