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

Risk Assessment Report

Dimetridazole

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
April 2015

ABSTRACT

FSCJ conducted a risk assessment of dimetridazole (CAS No. 551-92-8), a paraciticide and antiprotozoan agent, based on evaluataion documents from Joint FAO/WHO Expert Committee on Food Additives (JECFA) , European Medical Agency (EMEA), Australian Pesticides and Veterinary Medicines Authority (APVMA), and others.

Data used in the assessment include pharmacokinetics (rats, pigs and turkeys), residues (pigs, chickens and turkeys), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats and dogs), carcinogenicity (rats) and reproductive and developmental toxicity (rats and rabbits).

Dimetridazole is degraded *in vivo* into small molecules which contain biological components. In addition, pharmacokinetic studies suggested that its active metabolites or metablic intermediates may form covalent binding with tissue proteins or nucleic acids as its analogue ronidazole does.

Data of various genotoxicity studies suggested a potential association between *in vitro* genotoxicity of dimetridazole and nitroreductase activity. Genotoxicity studies also suggested that dimetridazole has a genotoxic potential to humans in aerobic circumstances. In contrast, dimetridazole was found to be negative in all *in vivo* ginotoxicity studies, and thus dimetridazole was suggested to be non-genotoxic *in vivo*. However, since DNA damage has been reported for its analogue metronidazole, FSCJ could not judge the genotoxicity of metronidazole relevant to human health.
In a 122-week carcinogenicity study in rats, increased incidence of benign mammary tumors was observed suggesting carcinogenicity of dimetridazole. However, its carcinogenicity study was conducted so far only in rats, and association between its genotoxicity and carcinogenicity is obscure.

The lowest no-observed-adverse-effect level (NOAEL) and others in the toxicological studies was the lowest-observed-adverse-effect level (LOAEL) of 30 mg/kg body weight/day for maternal toxicity in a developmental toxicity study in rabbits. However, it is considered that an acceptable daily intake (ADI) can not be specified based on this LOAEL because of insufficient profiles of the dimetridazole toxicity.

In conclusion, FSCJ could not specify an ADI of dimetridazole, since 1) covalent binding residues were thought to be formed, 2) the potential of genotoxicity could not be judged while carcinogenicity was suggested, and 3) an appropriate NOAEL for specifying an ADI could not be obtained.