

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

## Risk Assessment Report

### Ethoxyquin

(Feed Additives and Pesticides)

Food Safety Commission of Japan (FSCJ)

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#### ABSTRACT

FSCJ conducted a risk assessment of ethoxyquin (CAS No. 91-53-2), an antioxidant and a plant growth regulator, based on the JMPR assessment reports and others.

The data used in the assessment are on; pharmacokinetics (mice, rats, dogs and chicken), fate in plants (pear), residues (cattle, pigs, chicken, sheep's, fish and shellfish), genotoxicity and acute toxicity (mice, rats and dogs), subacute toxicity (rats and dogs), chronic toxicity and carcinogenicity (rats and dogs), and reproductive and developmental toxicities (rats, rabbits and dogs).

Concerning the genotoxicity of ethoxyquin, data from all the *in vitro* reverse mutation tests were negative, while positive results were obtained in chromosomal aberration tests using Chinese hamster ovary cells and human peripheral blood lymphocytes and also in the mouse lymphoma TK test. As for *in vivo* studies, ethoxyquin gave a weak positive response in the liver micronucleus test in juvenile rats, but negative responses in the mouse bone marrow micronucleus test and the unscheduled DNA synthesis test using rat liver. Although ethoxyquin and/or its metabolite(s) induce chromosomal aberration, the influence on the chromosomal aberration is likely to be associated with ethoxyquin's action on the functional protein component rather than the direct DNA damage in the body.

Results from the 30-month combined chronic toxicity/carcinogenicity study suggest that ethoxyquin has a carcinogenic potential in the urinary bladder in female rats. In the two-stage carcinogenesis model of the urinary bladder in rats, simple hyperplasia and papillary/nodular hyperplasia of the urinary bladder are observed in animals administered ethoxyquin alone.

However, since the urinary bladder events are attributable to the effect of promotion rather than the initiation, existence of a threshold will be expected for the events. Moreover, the events might be enhanced by continuous prooxidant stimuli derived from ethoxyquin metabolites. Therefore, it is unlikely that ethoxyquin as the food additive exerts the carcinogenicity through a genotoxic mechanism, and FSCJ recognized it as feasible to set the threshold value and to specify the acceptable daily intake (ADI).

Based on various data, FSCJ designated ethoxyquin and its dimer to the residue definition in agricultural products.

Residual ethoxyquin dimer has been found as an ethoxyquin metabolite at a substantial level in cultured fishes such as salmon. Toxicity of the dimer has been studied only in one 90-day subacute toxicity test where the toxicity was not observed at the dose of 12.5 mg/kg body weight/day. Ethoxyquin used for the most of toxicity studies seems to contain ethoxyquin dimer as an impurity. Taking the results from such toxicity studies into consideration, though the findings are limited, it is unlikely that toxicity of the dimer is stronger than that of the parent compound.

The fact that residual ethoxyquin dimer is contained as an ethoxyquin metabolite at a substantial level in cultured fishes such as salmon should be noted in the exposure assessment for revising the Provisional Standards. However, the toxicity of ethoxyquin metabolite, dimer, has not been fully clarified yet. Therefore, residues of the dimer should be confirmed, and collection and discussion of new scientific findings on the toxicity should be continued.

Among the no-observed-adverse-effect levels (NOAELs) obtained in various studies, the lowest NOAEL was 2 mg/kg body weight/day obtained in the 90-day subacute toxicity study in dogs. FSCJ, however, judged that it was more appropriate to adopt the lowest-observed-adverse-effect level (LOAEL) of 2.5 mg/kg body weight/day obtained in the two-generation reproduction toxicity study in dogs which was performed more recently and administered for a longer period of time, as a basis for ADI. Accordingly, FSCJ specified the ADI for ethoxyquin as 0.0083 mg/kg body weight/day, based on this LOAEL and applying a safety factor of 300 (10 for species difference, 10 for individual difference and 3 for the adopted LOAEL value).