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# 2,3-Diethylpyrazine

## Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of 2,3-diethylpyrazine (CAS No.15707–24-1) based on results from various studies. This additive, 2,3-diethylpyrazine, has no apparent toxicity relevant to human health based on the results of studies including the genotoxicity and repeated dose toxicity. The additive (flavoring) was categorized into Structural class II of the report of "Working group on safety assessment method of flavorings" (November 4, 2003) (classification criteria of Structural classes I, II and III are based on Cramer *et al*. (1978), which are similar to those of Joint FAO/WHO Expert Committee on Food Additives (JECFA)). The safety margin exceeds 1,000 which is regarded as the appropriate safety margin for a 90-day repeated dose toxicity study. The predicted amount of intake (1–2 µg/person/day) is also lower than the acceptable daily intake of Structural class II (540 µg/person/day). FSCJ concluded that 2,3-diethylpyrazine, an additive (flavoring), has no concern relevant to human health when it is used for the purpose of flavoring food.

### Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of 2,3-diethylpyrazine (CAS No.15707–24-1) for a flavor use, based on results from various studies.

Data used in the assessment includes genotoxicity and repeated dose toxicity.

This additive, 2,3-diethylpyrazine, has no apparent toxicity relevant to human health based on the results of studies including the genotoxicity and repeated dose toxicity. In addition, FSCJ confirmed that the additive (flavoring) was categorized into Structural class II of the report of "Working group on safety assessment method of flavorings"* (November 4, 2003) (classification criteria of Structural classes I, II and III are based on Cramer *et al*. (1978)**, which are similar to those of Joint FAO/WHO Expert Committee on Food Additives (JECFA)). The safety margin (11,000–22,000) exceeds 1,000 which is regarded as the appropriate safety margin for a 90-day repeated dose toxicity study. The predicted amount of intake (1–2 µg/person/day) is also lower than the acceptable daily intake of Structural class II (540 µg/person/day).

Hence, FSCJ concluded that 2,3-diethylpyrazine, an additive (flavoring), has no concern relevant to human health when it is used for the purpose of flavoring food.

* The report is available at: http://www.fsc.go.jp/senmon/tenkabutu/tenkabutu-kouryo-kokusaihyouka.pdf (Japanese)

** Cramer GM, Ford RA, Hall RL. Estimation of toxic hazard—a decision tree approach. Food and Cosmetics Toxicology. 1978; **16**: 255–276.

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## Supplementary Note on Genotoxicity of 2,3-diethylpyrazine

In the micronucleus test using the medium dose of 2,3-diethylpyrazine (125 mg/kg body weight/day) and the high dose (250 mg/kg body weight/day), micronucleated polychromatic erythrocytes (MNPCE) has been detected. The applicant claimed the occurrence of MNPCE as an effect secondary to the chemical-induced hypothermia. Although body temperature of the test animals was not measured in this micronucleus test using the low dose of 2,3-diethylpyrazine (62.5 mg/kg body weight/day), FSCJ discussed the interpretation in consideration with the hypothermia data reported by Boulet (2012).

Regarding the occurrence of MNPCE with the low dose in the micronucleus test, FSCJ could not verify it to be the hypothermic effect due to the lack of body temperature data of the test animals. Nevertheless FSCJ considered it to be of no biological significance, since MNPCE incidence in the low dose (0.24%) was much lower than that in the medium dose (0.70%) or that in the high dose (0.62%), and also within the historical control data (0.05–0.24%) at the test facility.

Positive results suggesting the chromosomal structural changes were obtained from chromosomal aberration tests in cultured mammalian cells. The direct DNA damage is unlikely to occur *in vivo* because of no biological significance of the above micronucleus test. FSCJ concluded that the threshold could be specified for a slight increase in polyploid cells without showing the dose-dependency. Human exposure to 2,3-diethylpyrazine as a food additive for flavoring (estimated amount of intake) is so low and will never reach to the exposure level to induce numerical chromosome aberration or decrease in body temperature.

Therefore, FSCJ concluded that 2,3-diethylpyrazine has no genotoxicity relevant to human health as long as it is used for the purpose of flavoring food.