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

Risk Assessment Report

Calcium Carbonate (2nd edition)

(Food Additives)

Food Safety Commission of Japan (FSCJ)

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ABSTRACT

FSCJ conducted a risk assessment of an additive, calcium carbonate, designated by the revised specification which newly includes the specification of calcium carbonate containing a calcium double salt of L-(+) tartaric and L-(-) malic acids, based on results from various studies. The assessed item is an additive used as a food manufacturing agent.

FSCJ judged it appropriate to specify the ULS[1] of 2,000 mg/person per day using UF1.5, for an upper limit of extra-dietary intake of calcium, based on each examination of calcium carbonate and of the calcium double salt of L-(+) tartaric and L-(-) malic acids contained in it. FSCJ concluded that calcium carbonate (the specification was revised to include calcium carbonate containing the calcium double salt of L-(+) tartaric and L-(-) malic acids) is of no concern for the food safety as long as used appropriately as a food additive.

1. Calcium carbonate

Calcium carbonate, the additive, is dissociated into carbonate and calcium ions in the stomach after the ingestion as a food additive. FSCJ thus conducted a risk assessment of calcium carbonate using the data on calcium carbonate and the other calcium salts.

No toxicities relevant to human health have been suggested from the data on genotoxicity, acute toxicity, carcinogenicity, and reproductive and developmental toxicity of calcium carbonate and the other calcium salts. Data enough for toxicological evaluation are not available in the repeated dose toxicity studies and thus the no-observed-adverse-effect level (NOAEL) could not be specified only from these studies.

Associations of excessive intake of calcium with milk-alkali syndrome, renal calculi, prostatic carcinomas and circulatory diseases have been suggested in human clinical studies. FSCJ considered the followings: the association of calcium intake with prostatic carcinomas or circulatory diseases is not consistent and not well supported from the point of the biological mechanism and their time course; the association between calcium intake and milk-alkali syndrome would be positive; the association of calcium intake with renal calculi would be also positive, because of the human intervention studies by Burtis et al. (1994) and Jackson et al. (2006); and it would be, however, difficult to specify the NOAEL or the lowest-observed-adverse-effect level (LOAEL) from these study results, because participants were patients of renal calculi in the study of Burtis et al., and participants took vitamin

[1] UL as a supplement. The upper limit of extra dietary intake.

D for facilitating calcium absorption in the study of Jackson et al.

FSCJ, therefore, considered it appropriate to evaluate calcium intake based on the case reports of milk-alkali syndrome in the assessment. As the result, FSCJ judged it appropriate that the LOAEL is specified to be 3,000mg/person per day in pregnant women, based on the report by Gordon et al (2005), in which pregnant women with no medical history were diagnosed to be milk-alkali syndrome after extra-dietary intake of calcium at ca. 3,000 mg/person per day for one month.

Calcium absorption in pregnant women is expected to be augmented and thus have an increasing risk of milk-alkaline syndrome incidence, as was reported by Uenishi et al. (2003) and by Bailey et al. (2008). FSCJ, therefore, judged that the LOAEL for ordinal Japanese population can be also specified based on the report by Gordon et al. (2005), although the data were obtained in Australian with the different amount of dietary calcium intake from that of Japanese. Consequently, FSCJ specified the LOAEL of 3,000 mg/person per day.

Moreover, FSCJ judged that no newly provided findings concerning the safety of calcium carbonate as the major ingredient of the additive (specification: calcium carbonate which contains the calcium double salt of L-(+) tartaric and L-(-) malic acids) changes the results of the previous one, except the documents used for the previous risk assessment of calcium carbonate in 2016 by FSCJ .

Hence, FSCJ concluded it appropriate to specify the ULS[2] of 2,000 mg/person per day using UF1.5, for an upper limit of extra-dietary intake of calcium.

2. Calcium double salt of L-(+) tartaric and L-(-) malic acids

No data of the calcium double salt of L-(+) tartaric and L-(-) malic acids contained in a small amount in calcium carbonate on its relevance to food safety was available. FSCJ thus decided to assess the safety of L-(+) tartaric acid, L-(-) malic acid and calcium each, considering the fact that the calcium double salt dissociates into each ions composing the double salt when it is dissolved in water. In addition, FSCJ judged that food safety of L-(+) tartaric acid and L-(-) malic acid need not be evaluated because of the following facts: 1) L-(+) tartaric acid and DL-(-) malic acid are designated as additives; 2) L-(+) tartaric acid and L-(-) malic acid are ingested through ordinal dietary habit; 3) L-(+) tartaric acid and L-(-) malic acid are normally contained in wine yet to be deacidified; 4) the calcium double salt of L-(+) tartaric and L-(-) malic acids is used as a seed crystal of organic acid salts, therefore is supposed to precipitate as a crystal deposit then to be removed by filtration or other ways; 5) the amount of L-(+) tartaric acid and L-(-) malic acid contained in wine is reduced by the addition of calcium carbonate containing the calcium double salt of L-(+) tartaric and L-(-) malic acids; 6) even if all amount of the added calcium double salt of L-(+) tartaric and L-(-) malic acids remains in the wine, amounts of L-(+) tartaric and L-(-) malic acids additionally produced in the wine from the added double salt is considered to be very low compared to the intake of L-(+) tartaric and L-(-) malic acids originally presented in the wine.

While it was unlikely that all amount of the added calcium double salt of L-(+) tartaric and L-(-) malic acids remains in the wine, none of data from studies on residue and transition of the added calcium double salt in wine was available. Accordingly, FSCJ decided to estimate the intake of the calcium double salt of L-(+) tartaric and L-(-) malic acids and those of the dissociated components of the said salt, assuming a condition that all of the double

[2] UL as a supplement. The upper limit of extra dietary intake.

salt remains in the wine based on the maximum content (2.0 %) designated in the revised content specification draft.

In addition, FSCJ decided to take into account of the estimated intake in the population with a drinking habit in order to avoid under estimation, in consideration of a potential difference in the intake between populations that may be caused when wine is preferentially taken in a particular population.

FSCJ evaluated the increase in exposure to the additive “calcium carbonate” resulting from the revision of the ingredient specification and the standards for use, using the above-mentioned intake estimation. As the results, FSCJ concluded that the increase in the exposure is negligible, even if all of the calcium double salt of L-(+) tartaric and L-(-) malic acids is assumed to remain in the wine with the maximum content (2.0 %) designated in the revised ingredient specification draft.