Juan Cristián Santa María
Senior Director, Global Regulatory & Scientific Affairs
Tate & Lyle
5450 Prairie Stone Parkway
Hoffman Estates, IL 60192

Re: GRAS Notice No. GRN 001140

Dear Mr. Santa María:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001140. We received the notice that you submitted on behalf of Tate & Lyle on March 30, 2023 and filed it on July 6, 2023. We received an amendment to the notice on September 25, 2023, which provides additional information on the manufacturing process.

The subject of the notice is enzyme-modified steviol glycosides (EMSG) for use as a general-purpose sweetener in foods, excluding infant formula and meat and poultry products, at levels determined by current good manufacturing practices (cGMP). The notice informs us of Tate & Lyle's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 001140 is made from highly purified components of the leaves of the stevia plant. We note that a GRAS notice for the use of specific purified components of stevia, such as EMSG, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "EMSG," and "steviol glycosides," or "SGs" in this letter is not our recommendation of these terms as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "EMSG."

Tate & Lyle provides information about the identity and composition of EMSG. Tate & Lyle describes EMSG as a white to off-white powder that contains ≥ 95% total steviol glycosides (SGs). SGs are a group of structurally-related sweet compounds that are

constituents of *Stevia rebaudiana* (Bertoni) Bertoni leaves and consist of a common steviol backbone linked to varying numbers and combinations of glucose, rhamnose, xylose, fructose, deoxyglucose, galactose, and arabinose.

Tate & Lyle describes the method of manufacture of EMSG and states that all materials and processing aids used to manufacture EMSG are food-grade and that EMSG is produced under current good manufacturing practices. The manufacturing process starts with an extract of the leaves of *S. rebaudiana* (stevia extract). Dried stevia leaves are extracted with water and the extract may then be treated with activated charcoal and ion-exchange chromatography. Tate & Lyle states that the stevia extract contains ≥ 60% total SGs on a dry basis. The stevia extract is combined with glycosyltransferase and sucrose synthase enzymes[1] and sucrose, and the enzymatic reaction is allowed to proceed to obtain the desired distribution of SGs. The resulting mixture is subjected to a heat treatment step to inactivate and denature the enzymes and then filtered to remove the enzymes. The second stage of the manufacturing process includes a series of purification steps using 1 of 2 alternative process streams that may include additional filtration, treatment with ion exchange resins, and adsorption resins to remove impurities. The product is then concentrated and dried. Tate & Lyle describes additional steps that are optional in which the dried product is crystallized with water and alcohol, washed with alcohol, and then dried and granulated to obtain the final EMSG product.

Tate & Lyle provides specifications for EMSG that includes the content of total SGs (≥ 95%, dry basis) and limits for moisture (≤ 6%), ash (≤ 1%), ethanol (≤ 5000 mg/kg), methanol (≤ 200 mg/kg), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), mercury (≤ 0.1 mg/kg), and microorganisms. Tate & Lyle provides a summary of the results of analyses of nine non-consecutive batches to demonstrate that EMSG can be produced to meet these specifications.

Tate & Lyle discusses published data and information regarding dietary exposure to SGs and EMSG. Tate & Lyle discusses a published study on dietary exposures to rebaudioside A (Ref. 1) that reported the estimated average and upper percentile dietary exposures to rebaudioside A, as steviol equivalents, in various population groups, such as non-diabetic and diabetic adults and children, that were based on the sweetness intensity of rebaudioside A relative to sucrose. Tate & Lyle also summarizes the conclusions about dietary exposures to SGs by Joint FAO/WHO Expert Committee on Food Additives (JECFA). Tate & Lyle states that EMSG has a sweetness intensity of 200-300 times that of sucrose and notes this is similar to the sweetness intensity of other high-purity SGs and EMSG preparations in the marketplace that are intended for use as general purpose sweeteners. Tate & Lyle states that the intended use of EMSG is substitutional for other sources of SGs and EMSG. Therefore, Tate & Lyle concludes that

[1] Tate & Lyle states that the glycosyltransferase and sucrose synthase are obtained from a genetically engineered strain of *Escherichia coli* K-12 W3110 that is non-pathogenic and nontoxigenic. Tate & Lyle states that the enzymes used are consistent with those described in the JECFA (2021) monograph for enzyme modified steviol glycosides and are considered safe for their intended use in the production of EMSG. The enzymes are manufactured in accordance with cGMP and specifications for the enzymes comply with the requirements for enzyme preparations established in the Food Chemicals Codex (13th Edition).

the intended uses of EMSG is not expected to change current dietary exposure to SGs and that dietary exposures to EMSG will be within the current acceptable dietary intake (ADI) of 4 mg/kg body weight (bw)/day (as steviol). Tate & Lyle note that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

Tate & Lyle summarizes published studies pertaining to the metabolic fate and safety of SGs. Tate & Lyle concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. Tate & Lyle discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies, published multi-generational reproductive and developmental toxicology studies conducted with SGs, and *in vitro* and *in vivo* mutagenicity/genotoxicity studies for the safety conclusion of EMSG. Tate & Lyle includes an update of the literature regarding the safety of SGs through December 2022 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that EMSG is GRAS for the intended use, Tate & Lyle summarizes the decisions on the safety of SGs by the JECFA, the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. Tate & Lyle notes that JECFA has established an ADI for SGs of 0-4 mg/kg bw/day (expressed as steviol equivalents). This ADI was based on a no observed adverse effect level of 970 mg/kg bw/d (383 mg/kg bw/d, as steviol equivalents) from a two-year rat study, and the application of a safety factor of 100 to account for intra- and inter-species differences.

Based on all the available scientific information, Tate & Lyle concludes that EMSG is GRAS for its intended use in foods.

Standards of Identity

In the notice, Tate & Lyle states its intention to use EMSG in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In its review of Tate & Lyle's notice that EMSG is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing EMSG. Accordingly, this response should not be construed to be a statement that foods that contain EMSG, if introduced or delivered for introduction

into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Tate & Lyle provided, as well as other information available to FDA, we have no questions at this time regarding Tate & Lyle's conclusion that EMSG is GRAS under its intended conditions of use. This letter is not an affirmation that EMSG is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001140 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.10.17 18:11:26 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
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Reference

1. Renwick, A.G. 2008. The use of a sweetener substitution method to predict dietary exposures for the intense sweetener rebaudioside A. Food and Chemical Toxicology 46:S61–S69.