William J. Rowe
President
GRAS Associates, LLC
11810 Grand Park Ave
North Bethesda, MD 20852

Re: GRAS Notice No. GRN 000999

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000999. We received the notice that you submitted on behalf of Zhucheng Haotian Pharm Co., Ltd (ZCHT) on March 16, 2021 and filed it on July 6, 2021. We received amendments to the notice on September 9, 2021 and November 8, 2021, confirming the intended use as a flavor modifier, and providing additional information on the intended use and dietary exposure.

The subject of the notice is enzyme-modified steviol glycosides (EMSG) for use as a general-purpose sweetener in foods[1] at levels determined by current good manufacturing practices and as a flavor modifier in foods at up to 600 mg/kg and in chewing gum at up to 1500 mg/kg.[2] The notice informs us of ZCHT's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 000999 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

[1] ZCHT states that EMSG is not intended for use in infant formula nor meat and poultry products under the jurisdiction of the United States Department of Agriculture (USDA).

[2] ZCHT states that the use of EMSG as a flavor modifier is not expected to result in a sweetening effect in foods at the intended use levels.

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."

ZCHT provides information about the identity and composition of EMSG. ZCHT describes the composition of two forms of EMSG that contain either ≥80% total steviol glycosides (SGs) (≥75% glucosylated SGs) and ≤ 20% dextrin[3] or ≥95% total SGs (≥75% glucosylated SGs) and ≤5% dextrin. SGs are a group of structurally related sweet compounds that are constituents of *Stevia rebaudiana* leaves and consist of a common steviol backbone linked to varying numbers and combinations of glucose, rhamnose, xylose, fructose, deoxyglucose, galactose, and arabinose. EMSG is produced by the treatment of a stevia leaf extract preparation that contains a minimum of 95% total SGs with a source of glucose and food-grade cyclomaltodextrin glucanotransferase (CGTase).[4] The reaction results in the formation of glucosylated forms of the starting SGs.

ZCHT 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 a purified extract of the leaves of *S. rebaudiana* (Bertoni) Bertoni (stevia extract). Dried stevia leaves are extracted with water or ethanol and the extract is then flocculated with calcium oxide and ferrous sulfate. The extract is filtered, subjected to ion exchange resins and an adsorption resin that retains SGs that are then eluted from the resin with ethanol. The extract is decolorized, concentrated by membranes and evaporation, and crystallized to obtain a stevia extract that contains ≥95% total SGs and ≥50% rebaudioside A. The stevia extract is combined with water, glucose source,[5] and CGTase and the reaction allowed to proceed under specified conditions. The reaction mixture is subsequently heated to deactivate the enzyme and then filtered. The resulting solution may be optionally subjected to a resin column to reduce levels of residual dextrin. The solution is evaporated, dried, and milled to obtain the final EMSG product.

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[3] OFAS notes that a specification of ≥ 80% total SGs does not meet the minimum criteria specified in FDA Import Alert #45-06 for highly purified stevia products, which states that products that contain ≥ 95% SGs on a dried weight basis are not subject to detention. However, the manufacturing process for EMSG described in GRN 000999 includes the production of a purified intermediate which contains ≥ 95% total SGs that meets the Import Alert criteria but is then subjected to further processing that may result in a product containing ≥ 80% total SGs and ≤ 20% residual dextrin.

[4] ZCHT states that the CGTase used in the manufacture of EMSG is a food grade enzyme produced by submerged fermentation of a genetically engineered stain of *Bacillus licheniformis* and that the enzyme is removed during the manufacture of EMSG.

[5] ZCHT states that the sources of glucose that may be used in the manufacture of EMSG include maltodextrin, dextrin, or ß-cyclodextrin.

ZCHT provides specifications for the two forms of EMSG that differ in the content of total SGs (≥ 95% and ≥ 80%) and the limit for dextrin (≤ 5% and ≤ 20%). Specifications for both forms for EMSG include the content of total glucosylated SGs (≥ 75%) and limits for ethanol (≤ 5000 mg/kg), methanol (≤ 200 mg/kg), moisture (≤ 5%), ash (≤ 1%), lead (≤ 0.5 mg/kg), arsenic (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), mercury (≤ 0.1 mg/kg), as well as limits for microorganisms. ZCHT provides results of five, non-consecutive batch analyses for each form of EMSG to demonstrate that EMSG can be manufactured to meet these specifications.

ZCHT provides estimates of dietary exposure to EMSG for the intended use as a sweetener and discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref. 1, a relative sweetness intensity of 100 times that of sucrose, and an estimate of the steviol equivalence of EMSG, ZCHT estimates maximum dietary exposure for adults (expressed as steviol equivalents) to be 3.15 mg/kg body weight (bw)/day (d) and for children to be 3.47 mg/kg bw/d. ZCHT states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations. ZCHT also estimates the dietary exposure to EMSG for the intended use of EMSG as a flavor modifier based on information provided in GRN 000607[6] that included an estimate of dietary exposure using the anticipated average use levels of EMSG and estimates of food consumption based on frequency data from the Market Research Corporation of America and portion size data from USDA. ZCHT estimates dietary exposure to EMSG from use a flavor modifier to be up to 0.57 mg/kg bw/d on a steviol basis. ZCHT concludes that total dietary exposure to EMSG on a steviol basis is less than 4.0 mg/kg bw/d.

ZCHT summarizes published studies pertaining to the metabolic fate and safety of SGs. ZCHT concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. ZCHT discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies, published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A, and *in vitro* and *in vivo* mutagenicity/genotoxicity studies for the safety conclusion of EMSG. ZCHT includes an update of the literature regarding the safety of SGs through November 2020 and reports that no toxicology studies were found that would alter its safety conclusion.

To further support its view that EMSG is GRAS for the intended use, ZCHT summarizes the decisions on the safety of SGs by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. ZCHT notes that JECFA has established an acceptable daily intake (ADI) for SGs of 0-4 mg/kg bw/d (expressed as

[6] The subject of GRN 000607 was EMSG intended for use in foods at up to 600 mg/kg and in chewing gum at up to 1500 mg/kg as a flavor modifier. We evaluated GRN 000607 and responded in a letter dated October 14, 2016 stating that we had no questions at that time regarding the notifier's GRAS conclusion.

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.

ZCHT includes the report of a panel of individuals (ZCHT's GRAS panel). Based on its review, ZCHT's GRAS panel concluded that EMSG is safe under the conditions of its intended use.

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

Standards of Identity

In the notice, ZCHT 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 ZCHT'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 ZCHT provided, as well as other information available to FDA, we have no questions at this time regarding ZCHT'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 000999 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.12.03 17:43:37 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

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.