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

Re: GRAS Notice No. GRN 000970

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000970. We received the notice that you submitted on behalf of Shandong Shengxiangyuan Biotechnology Co., Ltd (Shandong) on September 23, 2020 and filed it on December 17, 2020. Shandong submitted amendments to the notice on February 15, 2021 and February 18, 2021 that clarified specifications for the notified substance, information in the certificates of analysis provided in the notice, and 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. The notice informs us of Shandong's view that these uses of EMSG are GRAS through scientific procedures.

The EMSG that is the subject of GRN 000970 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."

Shandong provides information about the identity and composition of EMSG. Shandong describes EMSG as white powder containing ≥ 95% total SGs and up to 5% maltodextrin. 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 (i.e. maltodextrin) and food-grade cyclomaltodextrin glucanotransferase (CGTase).[1] The reaction results in the formation of glucosylated forms of the starting SGs, and Shandong states that EMSG contains ≥ 80% glucosylated SGs and ≤ 15% unreacted SGs.

Shandong 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 and the extract is then flocculated with calcium hydroxide and ferrous sulfate. The extract is filtered, subjected to an adsorption resin that retains SGs that are eluted from the resin with ethanol. The extract is decolorized, concentrated by membranes and evaporation, and then sterile filtered to obtain a stevia extract that contains ≥95% total SGs and ≥50% rebaudioside A. The stevia extract is combined with water, maltodextrin, and CGTase and the reaction allowed to proceed under specified conditions. The reaction mixture is subsequently heated to deactivate the enzyme and then cooled, concentrated, filtered and spray-dried to obtain the final EMSG product.

Shandong provides specifications for EMSG that includes the content of total SGs (≥ 95%), glucosylated SGs (≥ 80%), and unreacted SGs (≤ 15%). Specifications also include limits for maltodextrin (≤ 5%), moisture (≤ 6%), ash (≤ 1%), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), as well as limits for microorganisms.[2] Shandong provides results of five, non-consecutive batch analyses to demonstrate that EMSG can be produced to meet these specifications.

Shandong provides estimates of dietary exposure to EMSG. Shandong discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the

[1] Shandong 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.

[2] Shandong provides specifications for the stevia extract starting material that meet those established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), including limits for ethanol (≤ 5000 mg/kg) and methanol (≤ 200 mg/kg). However, Shandong states that no solvents other than water are used during the manufacture of EMSG, and therefore does not specify limits for ethanol and methanol in EMSG.

methodology described in Ref. 1, a relative sweetness intensity of 200 times that of sucrose, and an estimate of the steviol equivalence of EMSG, Shandong estimates maximum dietary exposure for adults (expressed as steviol equivalents) to be 1.50 mg/kg body weight (bw)/day (d) and for children to be 1.66 mg/kg bw/d. Shandong states that the use of EMSG in food is self-limiting due to organoleptic factors and consumer taste considerations.

Shandong summarizes published studies pertaining to the metabolic fate and safety of SGs. Shandong concludes that microbes in the colon hydrolyze SGs completely to steviol and thus EMSG shares a common metabolic fate. Shandong 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. Shandong includes an update of the literature regarding the safety of SGs through August 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, Shandong 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. Shandong notes that JECFA has established an acceptable daily intake (ADI) for SGs of 0-4 mg/kg bw/d (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.

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

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

Standards of Identity

In the notice, Shandong 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 Shandong'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 Shandong provided, as well as other information available to FDA, we have no questions at this time regarding Shandong'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 000970 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.04.09 14:32:57 -04'00'

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.