Agency Response Letter GRAS Notice No. GRN 000607

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CFSAN/Office of Food Additive Safety

October 14, 2016

Sidd Purkayastha, Ph.D.
PureCircle Limited
915 Harger Road, Suite 250
Oak Brook, IL 60523

Re: GRAS Notice No. GRN 000607

Dear Dr. Purkayastha:

The Food and Drug Administration (FDA) is responding to the notice, dated October 23, 2015, that you submitted in accordance with the agency’s proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on October 30, 2015, filed it on November 24, 2015, and designated it as GRAS Notice No. GRN 000607. On May 19, 2016, PureCircle Limited (PureCircle) notified FDA that you are the point of contact for GRN 000607. PureCircle provided additional information in amendments on May 20, 2016, August 1, 2016, and August 24, 2016.

The subject of the notice is enzyme-modified steviol glycosides (EMSG). EMSG is obtained by enzyme treatment of steviol glycosides (SGs) purified from the leaves of Stevia rebaudiana (Bertoni) Bertoni (Stevia). The notice informs FDA of the view of PureCircle that EMSG is GRAS, through scientific procedures, for use as a flavor modifier in foods, excluding infant formula and products under jurisdiction of the United States Department of Agriculture (USDA). The maximum recommended use level of EMSG in food is 600 milligrams per kilogram (mg/kg) and in chewing gum is 1500 mg/kg. PureCircle provides data to demonstrate that at the intended use level of EMSG, flavor modification is not accompanied by sweetness.

The EMSG that is the subject of GRN 000607 is made from SGs as defined by international standards. FDA notes that a GRAS notice for the use of a specific modified component of stevia, such as EMSG, as well as FDA’s response, does not necessarily apply to the uses of other stevia products.
Our use of “enzyme-modified steviol glycosides,” “EMSG,” “steviol glycosides,” “SGs,” “glucosylated steviol glycosides,” or “GSGs” in this letter should not be considered an endorsement or recommendation of that term as an appropriate common or usual name for the purpose of declaring the substance in the ingredient statement of foods that contain that ingredient. Title 21 CFR 101.4 states that 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 appropriate common or usual name of a food are the responsibility of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition.

Title 21 CFR 101.22 describes specific food labeling requirements for flavoring ingredients. In its review of PureCircle’s notice that EMSG is GRAS for use as a flavor modifier in food, FDA did not consider whether section 101.22 or any of its exemptions apply to foods containing EMSG. PureCircle should consult with ONFL to understand their obligations as to how their flavor modifier should be declared on the label.

As part of its notice, PureCircle includes a statement from a panel of individuals (PureCircle’s GRAS panel) that evaluated the data and information that are the basis for PureCircle’s GRAS determination. PureCircle considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. PureCircle’s GRAS panel evaluated the identity, composition, method of manufacture, product specifications, and dietary exposure resulting from the intended uses of EMSG, as well as published and unpublished studies related to the metabolic fate and safety evaluation of EMSG. Based on this review, PureCircle’s GRAS panel concluded that EMSG, produced under good manufacturing practices, is GRAS under the conditions of its intended use.

PureCircle provides information about the identity and composition of EMSG. PureCircle describes EMSG as an off-white to white powder that has a clean taste consisting of ≥ 80% glucosylated steviol glycosides (GSGs) and unreacted SGs combined and ≤ 20% dextrin. The GSGs have extended glucose side chains, generally with 1 to 20 additional glucose moieties, as compared to the unreacted SGs. Based on the results of five batch analyses that PureCircle provides, EMSG contains, on average, 7.8% unreacted SGs, 35.6% GSGs with 1 to 2 additional glucose moieties, 22.7% GSGs with 3 to 4 additional glucose moieties, and 19.5% of GSGs with 5 to 20 additional glucose moieties.

PureCircle provides information about the method of manufacture and specifications for EMSG. In this process, stevia leaves are extracted in water and calcium hydroxide is added to the extract solution to precipitate impurities followed by filtration. The filtrate is deionized using ion-exchange resins and the glycoside components are subsequently trapped using an adsorption resin. The GSGs are eluted from the resin with ethanol and then decolorized with activated carbon. The product is deionized again using ion-exchange resins, and the product solution is concentrated using nanofiltration. The concentrated solution is spray dried to yield a purified intermediate that contains > 95% SGs, including > 50% rebaudioside A. This product is added to an aqueous solution containing tapioca starch treated with a food-grade cyclomaltodextrin glycosyltransferase and food-grade alpha-amylase. The mixture is incubated, during which a glycosylation reaction takes place adding glucose moieties to the SGs. The enzymes are deactivated with heat and the product is decolorized with activated carbon, filtered, and then spray dried.

PureCircle provides specifications for EMSG that include the content of GSGs and unreacted SGs combined (≥ 80% on a dry weight basis), residual dextrin (≤ 20%), total ash (≤ 1%), loss on drying (≤ 6%), lead (≤ 1 mg/kg), arsenic (≤ 0.5 mg/kg), residual methanol (≤ 200 mg/kg), residual ethanol (≤ 5000 mg/kg), and limits on microbial contaminants. PureCircle provides results from five batch analyses conducted with EMSG that demonstrate compliance with these specifications.\[1\]
PureCircle provides an estimate of dietary exposure to EMSG resulting from the intended use in foods. PureCircle discusses an estimate of dietary exposure conducted by the Flavor and Extract Manufacturers Association of the United States that used the possible average daily intake methodology. This method uses 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. PureCircle states that the average dietary exposure to EMSG on a steviol equivalent basis is 23 mg/person/day (d), which is equivalent to 0.33 mg/kg body weight (bw)/d for a 70 kg person. PureCircle discusses previous estimates of exposure to SGs based on use as a sweetener in food, and notes that the highest reported upper percentile (≥ 90th percentile) exposure, on a steviol basis, is for children (1.47 mg/kg bw/d). PureCircle concludes that the combined dietary exposure to GSGs and SGs, on a steviol basis, would not exceed 1.8 mg/kg bw/d.

PureCircle discusses published and unpublished studies pertaining to the metabolic fate and safety of EMSG. Based on these studies, PureCircle concludes that the final metabolic fate of GSGs is the same as naturally occurring SGs. PureCircle discusses acute, subchronic, and chronic studies in relation to their safety determination for EMSG. PureCircle cites GRN 000375 that discusses published and unpublished in vitro and in vivo mutagenicity/genotoxicity studies, which showed no effects. Based on its consideration of these studies, PureCircle concludes that EMSG is GRAS for its intended use in foods.

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

**Standards of Identity**

In the notice, PureCircle 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 PureCircle’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 provided by PureCircle, as well as other information available to FDA, the agency has no questions at this time regarding PureCircle’s conclusion that EMSG is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of EMSG. As always, it is the continuing responsibility of PureCircle to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.
In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000607, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying at [www.fda.gov/grasnoticeinventory](https://wayback.archive-it.org/7993/20190426035335/http://www.fda.gov/grasnoticeinventory).

Sincerely,

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

[1] The Office of Food Additive Safety notes that a specification of \( \geq 80\% \) of GSGs and unreacted SGs combined does not meet the minimum criteria specified in FDA Import Alert #45-06 for highly purified stevia products, which states that products that contain \( > 95\% \) steviol glycosides on a dried weight basis are not subject to detention. However, as noted above, the manufacturing process for EMSG described in GRN 000607 includes the production of a purified intermediate which contains \( > 95\% \) total steviol glycosides, which meets the Import Alert criteria, but is then subjected to further processing that results in a product containing \( \geq 80\% \) steviol glycosides and \( \leq 20\% \) residual dextrin.