



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

Re: GRAS Notice No. GRN 000744

Dear Dr. Purkayastha:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000744. We received the notice that you submitted on November 8, 2017, and filed it on December 11, 2017. PureCircle submitted an amendment to the notice on February 13, 2018, that provides the results of batch analyses of the notified substance and specifies the date of the updated literature review.

The subject of the notice is steviol glycosides from *Saccharomyces cerevisiae* (SGs). The notice informs FDA of the view of PureCircle that SGs is GRAS, through scientific procedures, 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, as well as use as a table top sweetener.

Our use of the terms “steviol glycosides from *Saccharomyces cerevisiae*,” “SGs” or “steviol glycosides” in this letter is not our recommendation of that term 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 “SGs.”

PureCircle provides information about the identity and composition of SGs. PureCircle describes SGs as a white to off-white powder that contains $\geq 95\%$ steviol glycosides, and is primarily rebaudioside M. Rebaudioside M (CAS Reg. No. 1220616-44-3) is one of a group of known steviol glycosides, which differ from each other by the number of glycoside moieties and bonding order.

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PureCircle describes the method of manufacture of SGs. SGs is obtained from *S. cerevisiae* that is engineered to produce steviol glycosides. PureCircle provides information on the parent *S. cerevisiae* strain, methodology used to construct the production strain, referred to as CEN.PK113-7D, and a summary of the enzymes and their functions that are expressed by the production strain. PureCircle states that the production strain is neither toxigenic nor pathogenic. Corn sugar or sucrose is mixed with a fermentation medium, inoculated with the production strain, and cultured under controlled conditions; e.g., pH and temperature. After fermentation is complete, the mixture is centrifuged to remove cell biomass and insoluble matter. The supernatant is heated to inactivate residual yeast cells, concentrated by evaporation, and optionally spray dried. In the second stage of manufacture, the concentrate is treated with a flocculant (e.g., calcium hydroxide) and then filtered. The filtrate is deionized with ion-exchange resins and then subjected to a macroporous adsorption resin that retains the SGs. The resin is washed with deionized water and the SGs eluted with aqueous ethanol. The resulting solution containing SGs is treated with activated carbon and then filtered. Ethanol is removed from the solution by evaporation and the resulting solution is deionized with ion-exchange resins. The solution is concentrated by membrane filtration and then spray dried. The dry powder is dissolved in aqueous ethanol, SGs allowed to crystallize, and then separated by centrifugation and dried under vacuum.

PureCircle provides specifications for SGs that includes the minimum content of total SGs ($\geq 95\%$) and limits for total ash ($\leq 1\%$), loss on drying ($\leq 6\%$), lead (< 1 mg/kg), arsenic (< 1 mg/kg), cadmium (< 1 mg/kg), mercury (< 1 mg/kg), methanol ($< 0.02\%$), ethanol ($< 0.30\%$), and specified limits for microbial contaminants. PureCircle provides results of non-consecutive batch analyses to demonstrate that SGs can be produced in accordance with these specifications.

PureCircle provides estimates of dietary exposures to SGs. PureCircle discusses a published study on dietary exposures to rebaudioside A (Ref. 1), and based on the methodology described in that study and a relative sweetness intensity of 250 times that of sucrose, PureCircle reports the maximum dietary exposure (expressed as steviol equivalents) in adults to be 0.90 mg/kg body weight/day (bw/d) and in children to be 0.99 mg/kg bw/d. PureCircle states that the use of SGs in food is self-limiting due to organoleptic factors and consumer taste considerations.

PureCircle summarizes published studies pertaining to the metabolic fate and safety of SGs. Based on the pharmacokinetic studies, PureCircle concludes that microbes in the colon hydrolyze all steviol glycosides completely to steviol and thus SGs shares a common metabolic fate. PureCircle discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies; published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A as well as *in vitro* and *in vivo* mutagenicity/genotoxicity studies for the safety conclusion of SGs. PureCircle includes an update of the literature regarding the safety of steviol glycosides through September 2017 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that SGs is GRAS for the intended use, PureCircle summarizes the decisions on the safety of steviol glycosides 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. PureCircle notes that JECFA has established an acceptable daily intake (ADI) for steviol glycosides 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.

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

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

Standards of Identity

In the notice, PureCircle states its intention to use SGs 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 SGs is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing SGs. Accordingly, this response should not be construed to be a statement that foods that contain SGs, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that PureCircle provided, as well as other information available to FDA, we have no questions at this time regarding PureCircle's conclusion that SGs is GRAS under its intended conditions of use. This letter is not an affirmation that SGs 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 000744 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**

 Digitally signed by Michael A.
Adams -S
Date: 2018.03.23 16:25:18
-04'00'

Dennis M. Keefe, Ph.D.
Director
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.