



Nicole Cuellar-Kingston
Cargill, Inc.
15407 McGinty Road West, M.S. 163
Wayzata, MN 55391

Re: GRAS Notice No. GRN 000768

Dear Ms. Cuellar-Kingston:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000768. We received Cargill, Inc.'s (Cargill) notice on March 19, 2018, and filed it on April 11, 2018.

The subject of the notice is purified steviol glycosides (SGs) for use as a general purpose sweetener in foods, excluding infant formulas and USDA regulated products, at levels determined by good manufacturing practices, as well as use as a table top sweetener. The notice informs us of Cargill's view that this use of SGs is GRAS through scientific procedures.

The SGs that is the subject of GRN 000768 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 and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "steviol glycosides," "SGs," "rebaudioside A," or "rebaudioside B" 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 "SGs."

Cargill provides information about the identity and composition of SGs. SGs contains $\geq 95\%$ total steviol glycosides, a group of structurally-related sweet compounds that are constituents of the stevia leaf. Cargill provides information on various steviol glycosides that are identified in the literature and notes that the molecular structures are similar.

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Steviol glycosides consist of a common steviol backbone linked to varying numbers and combinations of glucose, rhamnose, xylose, fructose, deoxyglucose, galactose, and arabinose in varying orientations on the steviol backbone.

Cargill provides information about the method of manufacture of SGs. SGs is obtained from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni through extraction and multiple purification steps. The leaves are first extracted in water. The extract may be treated with a flocculant (e.g., calcium oxide or ferrous sulfate) and then centrifuged or filtered. The filtrate is deionized using ion-exchange resins and then subjected to an adsorption resin that retains the steviol glycosides. The adsorption resin is subsequently washed with a suitable solvent (e.g., ethanol or methanol) to elute the steviol glycosides. The eluate may be filtered, concentrated by evaporation, and dried. Cargill states that the dried product is then processed by one of two methods. In the first method, the dried product is dissolved in either a solvent (e.g., ethanol) or aqueous solvent and the solution cooled to allow crystals to form. The crystals are removed from the mother liquor by centrifugation or filtration, rinsed with water, and then dried to obtain a product that contains steviol glycosides with rebaudioside A as the principal component. Cargill notes that the mother liquor from the crystallization step can be further treated to crystallize other steviol glycosides. Cargill notes that rebaudioside A can be hydrolyzed by temperature or alkaline treatment to obtain rebaudioside B. In the second method, the dried product is dissolved in water and may optionally be subjected to an adsorption resin. The resulting solution may be dried by evaporation and the SGs are crystallized using a solvent, such as ethanol. The crystalline product is separated by centrifugation and filtration, rinsed with water, and dried to obtain the final SGs product.

Cargill provides specifications for SGs that include the content of total steviol glycosides ($\geq 95\%$), limits for moisture ($\leq 6\%$), ethanol ($\leq 0.5\%$), methanol ($\leq 0.02\%$), lead (< 1 mg/kg), arsenic (< 1 mg/kg), cadmium (< 1 mg/kg), mercury (< 1 mg/kg), and microorganisms. Cargill provides the results of three, non-consecutive batch analyses conducted with two SGs preparations to demonstrate that SGs can be produced in accordance with these specifications.

Cargill provides estimates of dietary exposure to SGs. Cargill discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref. 1 and a relative sweetness intensity of 200 to 350 times that of sucrose, Cargill reports the maximum dietary exposure in adults (expressed as steviol equivalents) to be 2.97 mg/kg body weight/day (bw/d) and in children to be 3.28 mg/kg bw/d. Cargill states that the use of SGs in food is self-limiting due to organoleptic factors and consumer taste considerations.

Cargill summarizes published studies pertaining to the metabolic fate and safety of SGs. Based on the pharmacokinetic studies, Cargill concludes that microbes in the colon hydrolyze steviol glycosides completely to steviol and thus SGs shares a common metabolic fate. Cargill 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. Cargill includes an update of the literature regarding the safety of SGs through July 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, Cargill 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. Cargill 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.

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

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

Standards of Identity

In the notice, Cargill 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 Cargill'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 Cargill. 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 Cargill provided, as well as other information available to FDA, we have no questions at this time regarding Cargill'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 000768 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
Michael A.
Adams -S

 Digitally signed by Michael
A. Adams -S
Date: 2018.08.13 09:24:53
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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.