



Jimmy Wang, Ph.D.
Chief Scientific Officer
Summit Life Science, Inc.
255 Oser Avenue
Hauppauge, NY 11788

Re: GRAS Notice No. GRN 000702

Dear Dr. Wang:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000702. We received the notice that you submitted on behalf of Xinghua GL Stevia Co., Ltd (Xinghua) on April 26, 2017, and filed it on May 24, 2017. We received an amendment to the notice on July 7, 2017. In the amendment, the notifier clarifies the manufacturing process and estimates of dietary exposure.

The subject of the notice is steviol glycosides purified from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni with rebaudioside A as the principal component (SG-R). The notice informs FDA of the view of Xinghua that SG-R 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 good manufacturing practices, as well as use as a table top sweetener.

The SG-R that is the subject of GRN 000702 is made from a highly purified component of the leaves of the stevia plant. We note that a GRAS notice for the use of a specific purified component of stevia, such as SG-R, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "steviol glycosides with rebaudioside A as the principal component," "SG-R," "steviol glycosides," or "SGs" 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

U.S. Food & Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740

(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 “SG-R.”

Xinghua provides information about the identity and composition of SG-R. Xinghua describes SG-R as a white granular powder that consists of $\geq 95\%$ steviol glycosides with rebaudioside A as the principal component. Xinghua describes four formulations of SG-R that contain $\geq 60\%$, $\geq 95\%$, $\geq 97\%$, or $\geq 98\%$ of rebaudioside A. Rebaudioside A (CAS Reg. No. 58543-16-1) is a steviol glycoside with the chemical name 13-[(2-O- β -D-glucopyranosyl-3-O- β -D-glucopyranosyl- β -D-glucopyranosyl)oxy] kaur-16-en-18-oic acid, β -D-glucopyranosyl ester. Rebaudioside A is one of a group of known steviol glycosides (SGs), which differ from each other by the number of glycoside moieties and bonding order.

Xinghua provides information about the manufacturing process for SG-R. The dried leaves of *S. rebaudiana* are extracted with hot water, filtered, and then subjected to an adsorption resin. The SGs are subsequently eluted from the resin with aqueous ethanol. The eluate is concentrated and spray dried. The dried product is recrystallized using ethanol and the crystalline product obtained by centrifugation and drying. Xinghua states that an additional recrystallization step may be used as well as mixing of crystalline products to obtain the four SG-R formulations with differing concentrations of rebaudioside A.

Xinghua provides specifications for each of the four SG-R formulations that include the minimum content of total steviol glycosides (≥ 95 to $\geq 98\%$) and rebaudioside A (≥ 60 to $\geq 98\%$). Specifications for SG-R also include limits for moisture ($\leq 5\%$), lead (≤ 1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), methanol (≤ 200 mg/kg), ethanol (≤ 5000 mg/kg), and limits on microbial contaminants. Xinghua states that SG-R meets the specifications for SGs established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 73rd meeting in 2010. Xinghua provides the results of five batch analyses for each of the four formulations to demonstrate that SG-R can be produced in accordance with the specifications.

Xinghua provides an estimate of dietary exposures to SG-R. Xinghua 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 times that of sucrose, Xinghua reports the maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.5 mg/kg body weight (bw)/d and in children to be 1.7 mg/kg bw/d. Xinghua states that the use of SG-R in food is self-limiting due to organoleptic factors and consumer taste considerations.

Xinghua summarizes published studies pertaining to the metabolic fate and safety of SG-R. Based on the pharmacokinetic studies, Xinghua concludes that microbes in the colon hydrolyze SGs completely to steviol and thus SG-R shares a common metabolic fate. Xinghua 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 SG-R. Xinghua includes an update of the literature regarding the safety of steviol glycosides through December 2016 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that SG-R is GRAS for the intended use, Xinghua summarizes the decisions on the safety of SGs by JECFA, the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. Xinghua 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. Based on all the publicly available scientific information, Xinghua concludes that SG-R is GRAS for its intended use in foods.

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

Standards of Identity

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

Conclusions

Based on the information that Xinghua provided, as well as other information available to FDA, we have no questions at this time regarding Xinghua's conclusion that SG-R is GRAS under its intended conditions of use. This letter is not an affirmation that SG-R 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 000702 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
Michael A.
Adams -S

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

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300042713,
cn=Michael A. Adams -S
Date: 2017.09.28 14:47:03 -04'00'

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.