



Susan Potter, Ph.D.
Tate & Lyle Americas, LLC
5450 Prairie Stone Parkway
Hoffman Estates, IL 60192

Re: GRAS Notice No. GRN 000780

Dear Dr. Potter:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000780. We received Tate & Lyle Americas LLC's (Tate & Lyle) notice on April 30, 2018, and filed it on May 14, 2018.

The subject of the notice is rebaudioside M obtained by enzyme treatment of steviol glycosides (SGs) purified from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni (rebaudioside M) for use as a general purpose sweetener in foods, excluding infant formula and meat and poultry products, at levels determined by good manufacturing practices. The notice informs us of Tate & Lyle's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 000780 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 rebaudioside M, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "rebaudioside M obtained by enzyme treatment of steviol glycosides purified from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni," "rebaudioside M" "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 (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 "rebaudioside M."

U.S. Food and Drug Administration
Center for Food Safety Applied Nutrition
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Tate & Lyle provides information about the identity and composition of rebaudioside M. Rebaudioside M (CAS No. 1220616-44-3), a glycoside of steviol, is identified as 13-[(O-β-D-glucopyranosyl-(1-2)-O-[β-D-glucosylpyranosyl-(1-3)]-β-D-glucosylpyranosyl)oxy]-kaur-16-en-18-oic acid (4-α)-O-β-D-glucosylpyranosyl-(1-2)-O-[β-D-glucosylpyranosyl-(1-3)]-β-D-glucosylpyranosyl ester. Rebaudioside M is one of a group of known SGs which differ from each other by the number of glycoside moieties and bonding order.

Tate & Lyle provides information about the manufacturing process for rebaudioside M. Tate & Lyle states that the manufacturing process starts with the production of a purified extract of *S. rebaudiana* (stevia) leaves and that this process is described in GRN 000275.¹ Briefly, stevia leaves are extracted with a suitable solvent and then subjected to purification steps to obtain an extract containing ≥ 95% SGs. Tate & Lyle describes a non-pathogenic and non-toxicogenic strain of *Escherichia coli* K-12 engineered to express two glucosyltransferases and a sucrose synthase that are used to catalyze the conversion of SGs to rebaudioside M. The *E. coli* strain is grown in culture medium and at the end of the fermentation step, triethanolamine is added to the medium and cells are mechanically disrupted. The solution is heat treated, flocculant added, and the mixture centrifuged to remove solids. The supernatant is concentrated by filtration and freeze-dried to obtain the enzyme preparation. The enzyme preparation is added to an aqueous solution of sucrose and the stevia extract containing ≥ 95% SGs, and the reaction allowed to proceed until the desired conversion of SGs to rebaudioside M is complete. The enzymes are denatured and removed by filtration. Rebaudioside M is precipitated from the solution, removed by filtration and then dried to obtain the final product.

Tate & Lyle provides specifications for rebaudioside M that include the content of total SGs (≥ 95%) and rebaudioside M (≥ 85 %). Specifications also include limits for total ash (≤ 1%), loss on drying (≤ 6%), lead (≤ 1 mg/kg), arsenic (≤ 1 mg/kg), mercury (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), methanol (≤ 200 mg/kg), ethanol (≤ 5000 mg/kg), and microorganisms. Tate & Lyle provides results from three, non-consecutive batch analyses to demonstrate that rebaudioside M can be produced to meet specifications.

Tate & Lyle provides estimates of dietary exposure to rebaudioside M. Tate & Lyle 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 208 times that of sucrose, Tate & Lyle estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.1 mg/kg body weight (bw)/day (d) and in children to be 1.2 mg/kg bw/d. Tate & Lyle states that the use of rebaudioside M in food is self-limiting due to organoleptic factors and consumer taste considerations.

Tate & Lyle summarizes published studies pertaining to the metabolic fate and safety of rebaudioside M. Based on pharmacokinetic studies, Tate & Lyle concludes that microorganisms in the colon hydrolyze SGs completely to steviol and thus rebaudioside

¹ GRN 000275 was submitted on behalf of McNeil Nutritionals, LLC (McNeil) for the use of purified steviol glycosides, with rebaudioside A as the principal component, obtained from the leaves of *S. rebaudiana*. We evaluated this notice and responded in a letter on June 11, 2009, stating that we had no questions at that time regarding McNeil's GRAS conclusion.

M shares a common metabolic fate. Tate & Lyle 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 its safety conclusion of rebaudioside M. Tate & Lyle includes an update of the literature regarding the safety of rebaudioside M through March 2018 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that rebaudioside M is GRAS for the intended use, Tate & Lyle summarizes the decisions on the safety of SGs 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. Tate & Lyle notes that JECFA 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.

Tate & Lyle includes the statement of a panel of individuals (Tate & Lyle's GRAS panel). Based on its review, Tate & Lyle's GRAS panel concluded that rebaudioside M is safe under the conditions of its intended use.

Based on all the available scientific information, Tate & Lyle concludes that rebaudioside M is GRAS for its intended use in foods.

Standards of Identity

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

Conclusions

Based on the information that Tate & Lyle provided, as well as other information available to FDA, we have no questions at this time regarding Tate & Lyle's conclusion that rebaudioside M is GRAS under its intended conditions of use. This letter is not an affirmation that rebaudioside M 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 000780 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
Michael A.
Adams -S

Digitally signed by Michael
A. Adams -S
Date: 2018.07.31 15:31:51
-04'00'

Dennis M. Keefe, Ph.D.
Director
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.