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

Re: GRAS Notice No. GRN 000882

Dear Ms. Cuellar-Kingston:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000882. We received the notice that you submitted on behalf of Cargill, Incorporated (Cargill) on September 6, 2019 and filed it on October 7, 2019.

The subject of the notice is rebaudioside M from *Yarrowia lipolytica* (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 Cargill's view that this use of rebaudioside M is GRAS, through scientific procedures.

Our use of the terms "rebaudioside M from *Yarrowia lipolytica"* and "rebaudioside M" 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 "rebaudioside M."

Cargill 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-[(2-O-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]kaur-16-en-18-oic acid, 2-O-β-D-glucopyranosyl-3-O-β-D-glucopyranosyl-β-D-glucopyranosyl ester. Rebaudioside M is one of a group of known steviol glycosides (SGs), which differ from each other by the number of glycoside moieties and bonding order. Cargill states that the notified substance is no less than 95% total SGs that is primarily rebaudioside M and may contain any of the following other SGs: rebaudiosides A, B, C, D, E, and F, stevioside, steviolbioside, rubusoside, and dulcoside A.

Cargill provides information about the manufacturing process for rebaudioside M. Rebaudioside M is produced via a daughter strain of *Y. lipolytica* (ML10371) engineered to express enzymes used in the production of SGs. Cargill provides information on the genetics of the parent strains of *Y. lipolytica* (ML326 and ML350) and describes the genes used to express the enzymes that encompass the production pathway of SGs (e.g., rebaudioside M). Cargill states that the production strain is neither toxigenic nor pathogenic, does not produce allergens, contains no antibiotic resistance genes, and that *Y. lipolytica* has a history of safe use as a production source for food ingredients. The manufacturing process begins with the fermentation of dextrose or sucrose using the *Y. lipolytica* production strain under aerobic conditions. Following fermentation, the production organism is removed by centrifugation, microfiltration, or clarification. The supernatant is filtered, and Cargill states that pH may be lowered and preservatives, such as potassium sorbate or sodium benzoate, may be added. The supernatant is subsequently subjected to an adsorption resin that is then eluted with ethanol. The ethanol extract may then be subjected to ion exchange resin, activated carbon, and pH adjustment to further remove impurities and colored substances, and ethanol is then removed from the extract by evaporation. The extract is recrystallized in either water or aqueous ethanol or methanol, and Cargill states that a second recrystallization step may be used. The crystals are washed with water or ethanol and then dried. Cargill states that the product may be blended to obtain the desired SGs composition for the final rebaudioside M product.

Cargill provides specifications for rebaudioside M that include the content of total SGs (≥ 95 %), 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 (≤ 5,000 mg/kg), as well as limits on microorganisms. Cargill provides results from three, non-consecutive batch analyses to demonstrate that rebaudioside M can be produced to meet the provided specifications.

Cargill provides estimates of dietary exposure to rebaudioside M. 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 200-350 times that of sucrose, Cargill estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 0.64 to 1.12 mg/kg body weight (bw)/day (d) and in children to be 0.71 to 1.24 mg/kg bw/d. Cargill states that the use of rebaudioside M 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 rebaudioside M. Based on pharmacokinetic studies, Cargill concludes that microorganisms in the colon hydrolyze SGs completely to steviol and thus rebaudioside M shares a common metabolic fate. Cargill discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies; published multigenerational 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. Cargill includes an update of the literature regarding the safety of rebaudioside M through March 2019 and reports that no studies

relevant to safety/toxicology were found that would alter its safety conclusion.

To further support its view that rebaudioside M is GRAS for the intended use, Cargill 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. Cargill 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.

Cargill includes the report of a panel of individuals (Cargill's GRAS panel). Based on its review, Cargill's GRAS panel concluded that rebaudioside M is safe under the conditions of its intended use. Based on all the available scientific information, Cargill concludes that rebaudioside M is GRAS for its intended use in foods.

Standards of Identity

In the notice, Cargill state 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 our evaluation of Cargill's notice concluding that rebaudioside M is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing rebaudioside M. Accordingly, our response should not be construed to be a statement that foods that containing rebaudioside M, 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 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 000882 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.01.02 09:35:43 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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.