http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=40

http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm154989.htm

U.S. Food and Drug Administration

Agency Response Letter GRAS Notice No. GRN 000253

CFSAN/Office of Food Additive Safety

December 17, 2008

Leslie Lake Curry
Director, Regulatory & Scientific Affairs
Cargill, Incorporated
15407 McGinty Rd West
Wayzata, MN 55345

Re: GRAS Notice No. GRN 000253

Dear Ms. Curry:

The Food and Drug Administration (FDA) is responding to the notice, dated May 15, 2008, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on May 15, 2008, filed it on May 20, 2008, and designated it as GRAS Notice No. GRN 000253.

The subject of the notice is rebaudioside A purified from *Stevia rebaudiana* (Bertoni) Bertoni. The notice informs FDA of the view of Cargill, Incorporated (Cargill) that rebaudioside A is GRAS, through scientific procedures, for use as a general-purpose sweetener in foods, excluding meat and poultry products, provided that food standards of identity do not preclude such use, at levels determined by current good manufacturing practices (cGMP).

The rebaudioside A that is the subject of GRAS Notice No. GRN 000253 is a highly purified component of the stevia plant. As such, FDA notes that the GRAS notice for the use of a specific purified component of stevia, such as rebaudioside A, and FDA's response do not necessarily apply to the uses of other stevia products.

21 CFR 101.4 states that all ingredients must be declared by their common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Our use of "rebaudioside A" in this letter should not be considered an endorsement or recommendation of that term as an appropriate common or usual name for the purpose of declaring the substance in the ingredient statement of foods that contain that ingredient. Issues associated with labeling and the appropriate common or usual name of a food are the responsibility of the Office of Nutrition, Labeling and Dietary Supplements in the Center for Food Safety and Applied Nutrition.

As part of its notice, Cargill includes the report of a panel of individuals (Cargill's GRAS panel) who evaluated the data and information that are the basis for Cargill's GRAS determination. Cargill considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Cargill's GRAS panel evaluated the identity, method of manufacture, product specifications, and the potential exposure resulting from the intended uses of rebaudioside A as well as published and unpublished studies on rebaudioside A and related substances. Based on this review, Cargill's GRAS panel concluded that rebaudioside A, produced consistent with cGMP and meeting appropriate purity and food grade specifications, is GRAS, by scientific procedures, under the conditions of its intended use.

Cargill provides information about the identity, method of manufacture, and specifications for rebaudioside A. Rebaudioside A (CAS Reg. No. 58543-16-1), a glycoside of steviol, is identified as 13-[(2-O-ß-D-glucopyranosyl-3-O-ß-D-glucopyranosyl-ß-D-glucopyranosyl)oxy] kaur-16-en-18-oic acid ß-D-glucopyranosyl ester. Rebaudioside A is obtained from the leaves of *S. rebaudiana* (Bertoni) Bertoni. The leaves are dried, crushed and extracted with water, followed by precipitation and filtration of the extract. An adsorption resin is used to trap the steviol glycosides of the leaf extract. The resin is washed with methanol or ethanol to release the glycosides. The elutant is then concentrated by evaporation or with an adsorption resin, followed by drying to yield a "steviol glycoside primary extract." The primary extract is dissolved in a water-ethanol solvent mixture and further processed by filtration, crystallization, and centrifugation steps. The resulting preparation of crystals is rinsed with ethanol and vacuum-dried to yield the final rebaudioside A product. Cargill provides specifications for rebaudioside A that include the content of rebaudioside A (=97% by weight (w/w)) and limits for other steviol glycosides (=3% w/w), lead (=1 milligrams per kilogram (mg/kg)), residual methanol (=0.02% w/w), residual ethanol (=0.5% w/w), and microbial contaminants (within specified limits). Cargill notes that these specifications are comparable to the specifications for steviol glycosides established by the FAO/WHO Joint Expert Committee on Food Additives (JECFA) in its 68th meeting in June 2007.

Cargill estimates the intake of rebaudioside A resulting from its intended use in foods. Cargill states that the intake was estimated using published dietary exposure data for other approved high intensity sweeteners (e.g., aspartame) with adjustment for their relative sweetness intensities. Cargill assumed a relative sweetness for rebaudioside A of

200 times that of sucrose and a 100 percent rebaudioside A content for its rebaudioside A product. Cargill estimates a mean intake ranging from 1.3 mg/kg body weight per day (mg/kg bw/d), 0.43 mg/kg bw/d as steviol equivalents, for non-diabetic adults to 3.4 mg/kg bw/d (1.12 mg/kg bw/d as steviol equivalents) for children with diabetes. Cargill states that its intake estimate for heavy intake consumers ranged from 3.4 mg/kg bw/d for non-diabetic adults to 5.0 mg/kg bw/d for non-diabetic children. Cargill states that the use of rebaudioside A in food is largely self-limiting due to its organoleptic properties.

Cargill discusses published and unpublished studies related to the safety evaluation of rebaudioside A, including animal studies on rebaudioside A, other steviol glycosides, steviol, and crude stevia extracts. Cargill states that studies on high purity steviol glycosides involving the oral route of exposure are the most relevant to the safety evaluation of rebaudioside A. The published animal studies Cargill discusses include acute toxicity studies in rats, mice, hamsters, and dogs; subchronic toxicity studies in rats, rabbits, and chickens; chronic toxicity/carcinogenicity studies in rats and mice; reproductive/developmental toxicity studies in rats, mice, hamsters, and chickens. Additional published studies include *in vitro* and *in vivo* genotoxicity studies.

Cargill discusses published and unpublished studies about the absorption, distribution, metabolism, and excretion of rebaudioside A, other steviol glycosides, and steviol in animals and humans. Cargill states that the metabolism of rebaudioside A in the rat and humans is equivalent to that of stevioside, a related steviol glycoside, and, as such, the safety data for stevioside are relevant to the safety evaluation of rebaudioside A.

Cargill discusses published and unpublished clinical studies on rebaudioside A, stevioside, steviol glycoside mixtures, and crude stevia extracts in diabetics and nondiabetics and in hypertensive, normotensive and hypotensive subjects. Cargill concludes that steviol glycosides are safe and well-tolerated in groups of normotensive individuals and in subjects with type 2 diabetes following long-term consumption at levels of up to about 25 mg/kg bw/d. Cargill also states that studies conducted specifically on its rebaudioside A product showed no effects on glucose homeostasis or blood pressure at levels of up to about 16 mg/kg bw/d. Cargill notes that this level is more than 3-fold greater than the predicted intake of rebaudioside A in adults and children with diabetes (4.5 mg/kg bw/d).

In its discussion of the published literature, Cargill also considers reports on stevia or stevia derived substances that raised safety concerns about the use of such substances as food ingredients. Cargill concludes that, based on the totality of the available data on rebaudioside A and on other steviol glycosides, rebaudioside A is safe under the conditions of its intended use.

To further support its view that rebaudioside A is safe for the intended uses, Cargill describes recent decisions by JECFA and the Food Standards Australia New Zealand (FSANZ) on the safety of steviol glycosides, one of which is rebaudioside A, for use in food as sweeteners. Cargill notes that in 2006, JECFA established a temporary acceptable daily intake (ADI) for steviol glycosides of 0–2 mg/kg bw/d (expressed as steviol),

pending requirements for further studies on the effects of steviol glycosides on blood glucose and blood pressure in humans.[1] In 2007, FSANZ proposed an ADI for steviol glycosides of 4 mg/kg bw/day (expressed as steviol).[2]

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FFDCA)

The Food and Drug Administration Amendments Act of 2007, that was signed into law on September 27, 2007, amends the FFDCA to, among other things, add section 301(ll). Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FFDCA, 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 rebaudioside A is GRAS for use as a general-purpose sweetener in foods, excluding meat and poultry products, provided that food standards of identity do not preclude such use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing rebaudioside A. Accordingly, this response should not be construed to be a statement that foods that contain rebaudioside A, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by Cargill, as well as other information available to FDA, the agency has no questions at this time regarding Cargill's conclusion that rebaudioside A purified from *S. rebaudiana* (Bertoni) Bertoni is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of rebaudioside A purified from *S. rebaudiana* (Bertoni) Bertoni. As always, it is the continuing responsibility of Cargill to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000253, as well as a copy of the information in this notice that conforms to the information in the proposed GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov. To view or obtain an electronic copy of the text of the letter, follow the hyperlinks from the "Food" topic to the "Food Ingredients and Packaging" section to the "Generally Recognized as Safe (GRAS)" page where the GRAS Inventory is listed.

Sincerely,

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

[(1)] At its 69th meeting in June 2008, JECFA reviewed new data on the effects of steviol glycosides on blood glucose and blood pressure in humans. JECFA concluded that the results of the new studies showed no adverse effects of steviol glycosides at the levels tested. At this meeting, the temporary designation was removed and JECFA established an ADI of 0–4 mg/kg bw/d (expressed as steviol). FDA notes that the equivalent ADI for rebaudioside A is 0-12 mg/kg bw/d, due to the relative molecular weights of rebaudioside A of 967 g/mol and steviol of 318 g/mol.

[(2)] The FSANZ issued a final assessment report on August 6, 2008, stating that the agency has established a full ADI of 4 mg/kg bw/d and recommended the approval of steviol glycosides as a food additive in specified food categories.

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