DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

Sue Andress
Director of Regulatory Affairs
Whole Earth Sweetener Company LLC
33 N. Dearborn, Suite 200
Chicago, IL 60602

DEC 17 2008

Re: GRAS Notice No. GRN 000252

Dear Ms. Andress:

The Food and Drug Administration (FDA) is responding to the notice, dated May 8, 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 9, 2008, filed it on May 13, 2008, and designated it as GRAS Notice No. GRN 000252.

The subject of the notice is rebaudioside A purified from *Stevia rebaudiana* (Bertoni) Bertoni. The notice informs FDA of the view of Whole Earth Sweetener Company LLC (Whole Earth) that rebaudioside A is GRAS, through scientific procedures, for use as a sweetener in a variety of food categories as described in Table 1, as well as use as a table top sweetener, formulated to provide 30 milligrams of rebaudioside A per gram of the finished product.[1]

Table 1
Intended Uses of Rebaudioside A

Food Category	**Use Level Rebaudioside A (milligrams per kilogram (mg/kg))**
Cereals (oatmeal, cold cereal, cereal bars)	150
Ready-to-drink teas	90 – 450
Fruit juice drinks	150 – 500
Diet soft drinks	150 – 500
Energy drinks	150
Flavored waters	150

The rebaudioside A that is the subject of GRAS Notice No. GRN 000252 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.

[1] The table top use level represents the rebaudioside A level in the sweetener mix, which would be diluted prior to consumption; final sweetener concentrations as consumed would be organoleptically limited to those levels in other pre-sweetened foods and beverages.

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, Whole Earth includes the report of a panel of individuals (Whole Earth's GRAS panel) who evaluated the data and information that are the basis for Whole Earth's GRAS determination. Whole Earth considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Whole Earth'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, Whole Earth's GRAS panel concluded that rebaudioside A, produced consistent with good manufacturing practice and meeting appropriate purity and food grade specifications, is GRAS, by scientific procedures, under the conditions of its intended use.

Whole Earth 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-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 obtained from the leaves of *S. rebaudiana* (Bertoni) Bertoni by extraction with water, ethanol, or methanol and is concentrated with an adsorption resin to trap the desired steviol glycosides. The resin is washed with ethanol or methanol to release the glycosides. The elutant is de-colorized and de-salted by ion exchange and microfiltration to improve the purity of rebaudioside A. Recrystallization with alcohol (methanol or ethanol) and water mixtures results in a final product with a purity of greater than 95 percent. The residual ethanol or methanol is removed and the product is then spray-dried or granulated. Whole Earth provides specifications for rebaudioside A that include the content of rebaudioside A (≥95% by weight (w/w)) and limits for stevioside (<2% w/w), steviol (<0.005% w/w), moisture (<5%), lead (<1 mg/kg), arsenic (<1 mg/kg), cadmium (<1 mg/kg), residual methanol (<300 mg/kg), residual ethanol (<1g/kg), and microbial contaminants (within specified limits). Whole Earth 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.

Whole Earth provides an estimated daily intake (EDI) of rebaudioside A, based on the intended food categories and use levels and data from the most recent National Health and Nutrition Examination Survey (NHANES 2003-2004), which includes table top sweeteners. Whole Earth calculates the total mean and 90th percentile EDI for eaters only, aged 2 years and older, as 2 mg/kg body weight per day (mg/kg bw/d) and 5 mg/kg bw/d, respectively. The range of exposures among population subgroups (age, gender and sex) is similar, ranging from 1.2 to 2.4 mg/kg bw/day (mean) and 2.4 to 5.6 mg/kg bw/day (90th percentile). Whole Earth states that the use of rebaudioside A is self-limiting in that high levels cause a food to be unpalatable.

Whole Earth discusses information pertaining to the safety evaluation of rebaudioside A. This information includes published and unpublished animal studies conducted with rebaudioside A, other steviol glycosides, steviol, and crude stevia extracts. The published animal studies include acute studies in rats, hamsters, and mice; subchronic studies in rats and dogs; chronic/carcinogenicity studies in rats; and reproductive/developmental toxicity studies in rats and hamsters. The unpublished animal studies

include subchronic studies in rats and dogs, and reproductive/developmental toxicity studies in rats. Additional published and unpublished studies include *in vitro* and *in vivo* genotoxicity studies. The unpublished genotoxicity studies are specifically on rebaudioside A.

Whole Earth discusses published and unpublished studies about the absorption, distribution, metabolism, and excretion of rebaudioside A, other steviol glycosides, and steviol in animals and humans. Whole Earth states that all steviol glycosides, including rebaudioside A and stevioside, are metabolized via the same intermediates and hydrolysis pathways and, as such, the safety data for all characterized steviol glycosides are relevant to the safety evaluation of rebaudioside A.

Whole Earth discusses published clinical studies of stevioside, other steviol glycosides and crude stevia extracts in diabetics and nondiabetics and in hypertensive and normotensive subjects. Whole Earth concludes that stevioside, at levels up to 30 mg/kg bw/day, does not affect blood glucose levels. Whole Earth also concludes that, although stevioside administration was associated with clinically relevant reductions in blood pressure for individuals with moderately severe hypertension who were not on antihypertensive therapy, such reductions in blood pressure were not observed in individuals with normal blood pressure or in individuals with hypertension receiving antihypertensive medication.

In its discussion of the published literature, Whole Earth also considers reports on stevia or stevia-derived substances that raised safety concerns about the use of such substances as food ingredients. Whole Earth states that there is now an extensive database on structurally related steviol glycosides including specific studies for which rebaudioside A was the test material, and concludes that, based on the totality-of-the-evidence, there are no remaining safety issues to be resolved with respect to the intended uses of rebaudioside A.

To further support its view that rebaudioside A is safe for the intended uses, Whole Earth 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. Whole Earth 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.[2] In 2007, FSANZ proposed an ADI for steviol glycosides of 4 mg/kg bw/day (expressed as steviol).[3]

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 Whole Earth's notice that rebaudioside A is GRAS for use as a sweetener in

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[2] 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.

[3] 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.

selected cereals or beverages and as a table top sweetener, 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 Whole Earth, as well as other information available to FDA, the agency has no questions at this time regarding Whole Earth'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 Whole Earth 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 000252, 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,

Antonia Mattia for LMT

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