Kristi O. Smedley, Ph.D.
Center for Regulatory Services, Inc.
5200 Wolf Run Shoals Rd.
Woodbridge, VA 22192

Daniel Tusé, Ph.D.
DT/Consulting Group
2695 13th Street
Sacramento, CA 95818

Re: GRAS Notice No. GRN 000738

Dear Dr. Smedley and Dr. Tusé:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000738. We received the notice that you submitted on behalf of Nomad Bioscience GmbH (Nomad) on October 18, 2017, and filed it on November 8, 2017. We received an amendment to the notice on January 11, 2018, that modifies the scope of the intended use by excluding use as a flavor modifier and also provides additional information pertaining to specifications and stability.

The subjects of the notice are thaumatin I, thaumatin II or combinations thereof for use as a sweetener in the food categories listed in Table 1. For the purpose of this letter, FDA describes the subject of the notice as "thaumatin." The notice informs us of Nomad's view that the use of thaumatin is GRAS through scientific procedures.

Table 1. Food categories and intended maximum use levels of thaumatin

Food category	**Use level (mg/kg)**
Wine, beer, and other fermented beverages; jams, jellies, marmalades	5
Potato-based and similar snacks; breakfast cereals	10
Chewing gum (with other sweeteners)	10
Chewing gum (without other sweeteners)	50
Ice cream and other edible ices; cocoa and chocolate products; breath mints and similar; confectionary; decorations, coatings, and fillings	50
Fine bakery items	30
Dietary supplements (capsules, tablets, syrups, and similar)	400
Table-top sweeteners	GMP*

*Levels determined by current good manufacturing practices

Our use of the term "thaumatin" 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 "thaumatin."

Nomad provides information about the identity and composition of thaumatin. Nomad describes thaumatin as a powder that contains thaumatin I and/or thaumatin II proteins and has a sweetness of 3,000 times that of sucrose. Each thaumatin protein consists of a single non-glycosylated polypeptide chain of 207 amino acids. The two proteins have highly similar sequences, differing by five amino acid residues. The molecular weight of each thaumatin protein is ~22 kDa.

Nomad describes the manufacturing process of thaumatin as a plant-based process using spinach (*Spinacia oleracea*), red beet (*Beta vulgaris*) or lettuce (*Lactuca sativa*) in which genes expressing thaumatin have been introduced. Nomad describes two methods used to induce the expression of a thaumatin gene in host plants: *Agrobacterium tumefaciens*-mediated induction and ethanol induction of transgenic plants. After induction by either method, the plants are incubated for 5–10 days to allow for accumulation of the desired thaumatin protein. The leaves and part of the stems are harvested and homogenized. After removal of insoluble material, a thaumatin protein is purified by a series of acid precipitations, centrifugation, and filtration steps. The resulting thaumatin solution is then spray-dried to produce a powder. In the final formulation, thaumatins I and II can be used individually or combined in different ratios. Nomad states that the manufacturing processes of thaumatins I and II are conducted according to current good manufacturing practices. All raw materials and processing aids are food grade. All plants are grown indoors under environmentally controlled conditions and good agriculture and collection practices are applied.

Nomad provides food grade specifications for thaumatin. These include thaumatin content (≥ 98% as total protein), as well as limits for heavy metals (≤30 mg/kg as sum including lead ≤5 mg/kg) and microorganisms. Nomad states that the thaumatin is stable for up to 6 months.

Nomad states that thaumatin is intended for use as a sweetener in the same food categories and at the same maximum permitted use levels as specified by the European Food Safety Authority. Nomad reports that the high level dietary exposure to thaumatin based on the maximum permitted use levels and consumption data derived from European diets is up to 77 mg/person (p)/day (d) (1.1 mg/kg body weight (bw)/d for a 70 kg individual). Nomad assumes the thaumatin that is the subject of the notice may replace all current commercial thaumatin and expand the market to twice its current size.

Nomad describes published studies and publicly available information supporting the safety of thaumatin. Nomad discusses two published 13-week subchronic toxicity studies. In the first study rats were exposed to thaumatin in their diets providing average daily intakes of up to 2502 mg/kg bw/d in male rats and 2889 mg/kg bw/d in female rats. In the second study rats and dogs were exposed to thaumatin in their diets providing average daily intakes of up to 2417 mg/kg bw/d in male rats, 2822 mg/kg bw/d in female rats, and 1400 mg/kg bw/d in male and female dogs. No adverse effects were reported at the highest dose levels tested in either study. Thaumatin was not teratogenic when administered by gavage to rats at up to 2000 mg/kg bw/d from day 6 to 15 of gestation and was without effect on the incidence of dominant lethal mutations when administered on five consecutive days to male mice at up to 2000 mg/kg bw/d. The lack of mutagenic potential was confirmed in bacterial mutagenic assays with *Salmonella typhimurium* and *Escherichia coli* WP2. Nomad also summarizes the results of an *in vivo* digestibility study, *in silico* allergenicity assessments, and preclinical and human clinical studies to determine the allergenic potential of thaumatin. Based on the weight of evidence approach Nomad concludes that thaumatin has a low allergenic potential.

Based on the information presented in the notice, Nomad concludes that thaumatin is GRAS for its intended uses in foods.

Standards of Identity

In the notice, Nomad states its intention to use thaumatin 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 Nomad's notice concluding that thaumatin 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 thaumatin. Accordingly, our response should not be construed to be a statement that foods containing thaumatin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Nomad provided, as well as other information available to FDA, we have no questions at this time regarding Nomad's conclusion that thaumatin

is GRAS under its intended conditions of use. This letter is not an affirmation that thaumatin 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 000738 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2018.04.18 16:36:07 -04'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
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