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

Re: GRAS Notice No. GRN 000910

Dear Dr. Smedley and Dr. Tusé:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000910. We received the notice that you submitted on behalf of Nomad Bioscience GmbH (Nomad) on February 4, 2020 and filed it on March 12, 2020. We received an amendment to the notice on May 8, 2020, that provided clarifications on specifications, test methods, estimated dietary exposure, and safety information.

The subject of the notice is thaumatin II for use as a sweetener in the food categories listed in Table 1. The notice informs us of Nomad's view that these uses of thaumatin II are GRAS through scientific procedures.

Table 1. Food Categories and Intended Maximum Use Levels of Thaumatin

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

*Levels determined by current good manufacturing practices (GMP)

Our use of the term “thaumatin II” 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 (OFAS) did not consult with ONFL regarding the appropriate common or usual name for “thaumatin II.”

Nomad provides information about the identity and composition of thaumatin II. Nomad describes thaumatin II as a powder that is highly water soluble and 2000-3000 times sweeter than sucrose. Nomad states that the thaumatin II protein¹ is a single polypeptide chain consisting of 207 amino acids with eight disulfide linkages. The molecular weight of thaumatin II is ~22kDa.

Nomad describes the manufacturing process of thaumatin II using a non-edible host plant, *Nicotiana benthamiana*, in which genes expressing thaumatin II have been introduced. Nomad describes two methods used to induce the expression of a thaumatin II gene in the host plant: *Agrobacterium tumefaciens*-mediated induction and ethanol induction of transgenic plants. After induction of thaumatin II gene expression by either method, the plants are incubated for 5–10 days to allow for accumulation of the thaumatin II protein. The leaves and part of the stems are mechanically cut and homogenized with an extraction buffer. The insoluble materials are removed, and the thaumatin protein is purified using a series of precipitation, centrifugation and filtration steps. The resulting thaumatin II solution is then spray-dried to produce the final thaumatin II powder. Nomad states that the manufacturing process of thaumatin II is conducted in accordance with current good manufacturing practices. Nomad also states that 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 specifications for thaumatin II. These include thaumatin content ($\geq 95\%$), limits for total heavy metals (sum of lead, cadmium, mercury, arsenic, ≤ 5 nanogram (ng)/mg), lead (≤ 1 ng/mg), nicotine (≤ 20 ng/mg), anabasine (≤ 5 ng/mg), and microorganisms. Nomad provides the results of analyses of five non-consecutive batches of thaumatin II to demonstrate conformance with the specifications for thaumatin content, and from three non-consecutive batches to demonstrate conformance with the specifications for heavy metals, nicotine, and anabasine. Nomad states that the thaumatin II product is stable for more than 6 months at 0-20 °C.

Nomad states that thaumatin is intended for use as a sweetener in the same food

¹ Nomad states that the thaumatin II protein that is the subject of this notice is identical in amino acid composition, sequence, and structure to the thaumatin II that is a subject of GRN 000738, as well as the native thaumatin II that is extracted from *Thaumatococcus danielli*.

categories and at the same maximum permitted use levels as specified by the European Food Safety Authority. Nomad states that the exposure to thaumatin II would be the same as that described in GRN 000738² and that the maximum dietary exposure to thaumatin II is 77 mg/person (p)/d (1.1 mg/kilogram (kg) bodyweight (bw)/d for a 70 kg individual) based on maximum permitted use levels and consumption data derived from European diets.

Nomad discusses results of published safety studies to support the safety of thaumatin II. Nomad incorporates the safety information on thaumatin discussed in GRN 000738, and states that an updated literature search was also conducted which did not identify any new studies that report safety concerns. Nomad discusses a published *in vivo* digestibility study in rats and concludes that thaumatin is readily digested prior to absorption. Nomad also discusses three published subchronic studies, one in dogs and two in rats, in which the animals were exposed to thaumatin in their diets at 0%, 0.3%, 1.0% or 3.0% for 13 weeks. In all these studies, no treatment-related adverse effects were reported at levels up to an average daily intake of 1400 mg/kg bw/d in dogs, and over 2000 mg/kg/bw/d in rats. Thaumatin was not teratogenic when administered by gavage to pregnant rats at dose levels up to 2,000 mg/kg bw/d from day 6 to 15 of gestation. Thaumatin was non-mutagenic by the mouse dominant-lethal test at dose levels up to 2000 mg/kg bw/d, and by the bacterial mutagenicity assays at levels up to 50 mg/plate.

Nomad also discusses published *in silico* allergenicity studies and human clinical studies to determine the allergenicity potential for thaumatin II. Nomad concludes, based on the evidence, that thaumatin II has a low allergenic potential.

Based on the totality of data and information available, Nomad concludes that thaumatin II is GRAS under its intended condition of use.

Standard of Identity

In the notice, Nomad states its intention to use thaumatin II in several food categories including foods for which standards of identity exist, located in Title 21 of the CFR. 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 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

² GRN 000738 describes the use of thaumatin I, thaumatin II or combinations thereof as a sweetener in conventional foods. FDA evaluated this notice and responded in a letter dated April 18, 2018, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

section 301(l)(1)-(4) applies. In our evaluation of Nomad’s notice concluding that thaumatin II is GRAS under its intended conditions of use, we did not consider whether section 301(l) or any of its exemptions apply to foods containing thaumatin II. Accordingly, our response should not be construed to be a statement that foods containing thaumatin II, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

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 II is GRAS under its intended conditions of use. This letter is not an affirmation that thaumatin II 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 000910 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

Digitally signed by Susan
J. Carlson -S
Date: 2020.09.09 18:00:05
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Director
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