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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 000920

Dear Dr. Smedley and Dr. Tusé:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000920. We received the notice that you submitted on behalf of Nomad Bioscience GmbH (Nomad) on March 23, 2020 and filed it on May 18, 2020. We received amendments to the notice on July 7, 2020 and November 16, 2020, that provided clarifications and additional information on the intended use, analytical methods, dietary exposure, and safety information.

The subject of the notice is thaumatin II for use as a flavor modifier in beverages (water-based, non-alcoholic), fruit juice drinks and ades, flavored milks and milk drinks, fruit juices, nectars, smoothies, fermented dairy products, coffee, tea, imitation dairy beverages, and vegetable juices, excluding infant formula and products under jurisdiction of the United States Department of Agriculture. The maximum recommended use level of thaumatin II as a flavor modifier in food is 7 mg/kg in food and mg/L in beverages. Nomad provides data to demonstrate the flavor-modifying properties of thaumatin II[1]. The notice informs us of Nomad's view that this use of thaumatin II is GRAS through scientific procedures.

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

[1] Nomad states that the taste-modifying characteristics evaluated include sweet/sour, sour, and bitter tastes, and its effects on a savory base under low and high salt, and low and high monosodium glutamate levels.

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. Nomad states that the thaumatin II protein[2] is a single polypeptide chain consisting of 207 amino acids with eight disulfide linkages. The molecular weight of thaumatin II is ~22 kDa.

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, which is the same process as described in GRN 000910[3]. 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 (≥ 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 for five nonconsecutive batches of thaumatin II to demonstrate conformance with the specifications for thaumatin content, and from three nonconsecutive 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 provides an estimate of dietary exposure to thaumatin II from the intended use as a flavor modifier in specified food categories. Nomad estimates the dietary exposure from the proposed uses by using food consumption data from the 2013-2016 National

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[2] Nomad states that the thaumatin II protein that is the subject of this notice is identical in amino acid composition, sequence, and structure as the thaumatin II that is the subject of GRN 000738, as well as the native thaumatin II that is extracted from *Thaumatococcus daniellii*.

[3] GRN 000910 describes the use of thaumatin II as a sweetener in specified food categories. FDA evaluated this notice and responded in a letter dated September 9, 2020, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Health and Nutrition Examination Surveys. Nomad estimates the dietary exposure for the U.S. population (eaters only) aged 2 years and older to be 57.3 µg/kg bodyweight (bw)/d at the mean and 120.6 µg/kg bw/d at the 90th percentile. Nomad states that assuming the purity of thaumatin II is 95% and that thaumatin II is consumed in the proposed food categories at a maximum use level of 7 mg/kg, the exposure to host proteins would be 2.9 µg/kg bw/d at the mean and 6 µg/kg bw/d at the 90th percentile. Nomad estimates exposure for the total alkaloid content that could be present from the *N. benthamiana* host to be 0.1 µg/d at the mean and 0.21 µg/d at the 90th percentile for a 70-kg adult.

Nomad discusses results of published safety studies to support the safety of thaumatin II. Nomad incorporates the safety information on thaumatin discussed in GRNs 000738 and 000910, and states that an updated literature search did not identify any new literature that reported 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 3.0% in the feed, equal 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.

Standards 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 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 II 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 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(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 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 000920 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.11.24 14:46:46 -05'00'

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