Kevin O'Connor, Ph.D.
Nova Mentis
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Re: GRAS Notice No. GRN 000876

Dear Dr. O'Connor:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000876. We received Nova Mentis' notice on June 17, 2019 and filed it on August 27, 2019. Nova Mentis submitted an amendment to the notice on October 14, 2019, that clarified the intended use of the substance and the analytical methods used to ensure conformance of the substance to the stated specifications.

The subject of the notice is the phenolic compound hydroxytyrosol produced in *Escherichia coli* BL21 (DE3) #145 for use as an antioxidant at a level of 5 to 10 mg per serving in the following foods: bakery products (snack crackers, croutons, grain-based bars with or without filling or coating, protein-based meal replacement and energy bars); beverages (sports drinks, "energy" drinks, milk-based meal replacements, flavored waters, fruit-flavored drinks); yogurt; frozen yogurt; fats and oils (butter, margarine, oil and shortening; salad dressing; mayonnaise; mayonnaise-type sandwich spreads); fruit juices and fruit nectars; dry coating mixes for meat, poultry, and fish; dry seasoning mixes; chewing gum; sauces, dips, gravies, and condiments; snacks (chips, pretzels, popcorn, extruded snacks, fruit chips, grain-based snack mixes); and vegetable juice.[1] The notice informs us of Nova Mentis' view that this use of hydroxytyrosol is GRAS through scientific procedures.

Nova Mentis states its hydroxytyrosol is an off-white powder that is >99% pure. Nova Mentis describes the manufacture of its hydroxytyrosol by fermentation of a culture of non-pathogenic *E. coli* BL21 (DE3) #145. Fermentation takes place until a desired cell density is reached, and cells are then harvested and washed to remove any residual components of the media. Following this, the cells are broken by homogenization to yield a biocatalyst that converts tyrosol to hydroxytyrosol. Tyrosol, ascorbic acid and the biocatalyst are added to a fermenter to start the biosynthesis of hydroxytyrosol. Once hydroxytyrosol conversion is completed, the hydroxytyrosol is extracted, dried, and packaged. Nova Mentis states that all chemicals and processing aids used in the

[1] Infant formula and food products regulated by the United States Department of Agriculture are excluded.

manufacture of its hydroxytyrosol are food grade.

Nova Mentis provides specifications for hydroxytyrosol that include a minimum content of hydroxytyrosol (>99%) and limits for total protein (<200 mg/kg), moisture (<0.5%), ethyl acetate (<500 mg/kg), lead (<0.05 mg/kg), arsenic (<0.05 mg/kg), mercury (<0.05 mg/kg), cadmium (<0.05 mg/kg), and limits for microorganisms. Nova Mentis provides results of three non-consecutive batch analyses to demonstrate that hydroxytyrosol can be produced in accordance with the specifications.

Nova Mentis estimates exposure to hydroxytyrosol from existing dietary sources (i.e., olives and olive oil), the intended uses, and a cumulative dietary exposure from the existing dietary sources and intended uses using food consumption data from the 2007-2010 National Health and Nutrition Examination Surveys. The cumulative eaters-only mean and 90th percentile dietary exposures for the U.S. population aged 2 years and older are 30 mg/person (p)/d (0.5 mg/kg body weight (bw)/d) and 52 mg/p/d (0.9 mg/kg bw/d), respectively.

Nova Mentis discusses published data and information supporting the safety of hydroxytyrosol based on a scientific literature search conducted through April 2019. Nova Mentis also states that FDA reviewed two previous GRAS notices, GRNs 000600 and 000726, for pure hydroxytyrosol and a phenolic preparation from olive fruit containing ≥40% hydroxytyrosol, respectively.[2] Nova Mentis summarizes the results of three published subchronic studies in rats. In all three studies, the test substance was administered by gavage. In one study, no adverse effects were observed at 50 mg/kg bw/d of hydroxytyrosol. In another study, no adverse effects were reported after the administration of 691 mg olive extract containing 35% hydroxytyrosol, equivalent to 250 mg/kg bw/d of hydroxytyrosol. In a third study, no adverse effects were observed after the administration of 2,000 mg/kg bw/d of olive pulp extract (OPE) estimated to provide 48 mg/kg bw/d of hydroxytyrosol. Based on the results of a published reproductive toxicity study and a published developmental toxicity study in rats, Nova Mentis concludes that OPE containing hydroxytyrosol as its major component is unlikely to be a reproductive toxicant and that no maternal or developmental toxicity was reported at up to 2,000 mg/kg bw/d of OPE (or 48 mg/kg bw/d of hydroxytyrosol). Based on the results of multiple published *in vitro* bacterial reverse mutation assays, *in vitro* chromosomal aberration assays, and *in vivo* micronucleus assays, Nova Mentis concludes that hydroxytyrosol is unlikely to be genotoxic or clastogenic. Nova Mentis also states that the results of human studies with olive oil containing phenolics, including hydroxytyrosol, did not reveal any adverse effects.

Based on the totality of data and information summarized above, Nova Mentis concludes that hydroxytyrosol is GRAS under the conditions of its intended use.

Standards of Identity

[2] FDA evaluated GRNs 000600 and 000726 and responded in letters on May 13, 2016, and February 28, 2018, respectively, that we had no questions at that time regarding the notifiers' GRAS conclusions.

In the notice, Nova Mentis states its intention to use hydroxytyrosol 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.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). If products containing hydroxytyrosol bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and 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 on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Under section 403(k) of the FD&C Act, a food is misbranded if it contains any chemical preservative, unless the label states that fact. Under section 403(i)(2) of the FD&C Act, a food is misbranded unless its label bears the common or usual name of each ingredient. Further, under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any way. Nova Mentis's intended use of hydroxytyrosol constitutes use as a preservative. Therefore, the ingredient statement on labels of food products containing hydroxytyrosol must comply with the labeling regulations implemented in sections 403(k) and 403(i)(2) of the FD&C Act. For example, 21 CFR 101.22(j) requires that the label of a food with an added chemical preservative must declare both the common or usual name of the ingredient and a separate description of its function. Further, food that is subjected to any form of preservation, except as provided in 21 CFR 101.95(c), may not be labeled as "fresh." Questions related to food labeling should be directed to ONFL.

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 section 301(ll)(1)-(4) applies. In our evaluation of Nova Mentis' notice concluding that hydroxytyrosol 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 hydroxytyrosol. Accordingly, our response should not be construed to be a statement that foods containing hydroxytyrosol, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Nova Mentis provided, as well as other information available to FDA, we have no questions at this time regarding Nova Mentis' conclusion that hydroxytyrosol is GRAS under its intended conditions of use. This letter is not an affirmation that hydroxytyrosol 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 000876 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.01.21 15:19:38 -05'00'

Susan Carlson, Ph.D.
Director
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