Martin J. Hahn
Hogan Lovells US LLP
555 Thirteenth Street, NW
Washington, DC 20004

Re: GRAS Notice No. GRN 000791

Dear Mr. Hahn:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000791. We received the notice that you submitted on behalf of Amazentis SA (Amazentis) on June 15, 2018, and filed it on July 9, 2018.

The subject of the notice is urolithin A for use as an ingredient in protein shakes, meal replacement drinks, instant oatmeal, protein and nutrition bars, and yogurt drinks at levels up to 500 mg/serving and in Greek yogurts, high protein yogurts, and milk-based protein shakes at levels up to 1000 mg/serving. The notice informs us of Amazentis' view that this use of urolithin A is GRAS through scientific procedures.

Amazentis states that urolithin A (3,8-dihydroxybenzo[c]chromen-6-one) is designated by CAS Registry Number 1143-70-0 and has a molecular weight of 228.20 g/mol. Amazentis describes urolithin A as a beige to yellow powder.

Amazentis provides a description of the manufacturing method for urolithin A and states that urolithin A is produced in accordance with current good manufacturing practices. Urolithin A is chemically synthesized using one of two alternative processes, process 1 or process 2. Process 1 starts with a copper-catalyzed reaction of resorcinol with 1,2-bromo-5-methoxybenzoic acid under alkaline conditions in methanol as a solvent. The resulting intermediate A is isolated by filtration, dried, and then treated with aluminum chloride in toluene and hydrolyzed by addition of water. The crude urolithin A is filtered, dried, dissolved in dimethyl sulfoxide, and then precipitated by the addition of water. The precipitate is filtered and rinsed with water followed by methanol. The filtered product is triturated with acetic acid, filtered, rinsed with acetic acid followed by *tert*-butyl methyl ether, and then dried to yield the final urolithin A product. Process 2 starts with a copper-catalyzed reaction of resorcinol with 2-bromo-5-hydroxybenzoic acid under alkaline conditions in water as a solvent that results in the formation of crude urolithin A product and its sodium salts. Sodium salts of urolithin A are neutralized with acetic acid to yield the crude urolithin A product. The crude urolithin A is triturated with acetic acid, filtered, and dried to yield the final urolithin A product.

Amazentis provides specifications for urolithin A that include a minimum content of urolithin A (≥97%), limits for intermediate A[1] (≤0.5%), impurity AZX1[2] (≤0.4%), cadmium (≤0.5 mg/kg), lead (≤0.5 mg/kg), arsenic (≤1.5 mg/kg), mercury (≤0.1 mg/kg), copper (≤100 mg/kg), aluminum (≤2000 mg/kg), methanol (≤3000 mg/kg), *tert*-butyl methyl ether (≤1000 mg/kg), toluene (≤890 mg/kg), dimethyl sulfoxide (≤5000 mg/kg), and acetic acid (≤5000 mg/kg), as well as limits on microorganisms. Amazentis provides the results of four batch analyses of urolithin A made by process 1 and three batches made by process 2 to demonstrate that urolithin A can be manufactured to meet the specifications. Amazentis states that urolithin A is stable for a period of three years at room temperature.

Amazentis provides estimates of dietary exposure to urolithin A based on the intended use and food consumption data from the 2013-2014 National Health and Nutrition Examination Survey. For consumers 12 years and older, Amazentis reports the mean and 90th percentile exposure to urolithin A to be 1,183 and 2,421 mg/person(p)/day(d) (15.5 and 34.1 mg/kg body weight (bw)/d), respectively. Amazentis reports the mean and 90th percentile exposures in children up to 3 years old would be 446 and 944 mg/p/d (38.0 and 80.4 mg/kg bw/d), respectively, and in children ages 3 to 11 years would be 500 and 1,418 mg/p/d (18.2 and 42.7 mg/kg bw/d).

Amazentis discusses published data and information supporting the safety of urolithin A. Amazentis states that urolithin A is identical in structure to the compound formed endogenously in humans following consumption of ellagitannins and ellagic acid present in various fruits and nuts. Amazentis summarizes a published rat study on the absorption, distribution, metabolism and excretion of ^{14}C radiolabeled urolithin A that demonstrates low absorption (<2.2%) and complete elimination of urolithin A. Amazentis discusses published safety studies, including 28-day and 90-day oral toxicity studies, conducted on urolithin A that is the subject of this notice. Amazentis states that no toxicologically significant effects were observed in the 28-day toxicity study in which rats were fed a diet corresponding to levels of urolithin A up to 4,165 mg/kg bw/d and 4,706 mg/kg bw/d, the highest levels tested in males and females, respectively. Amazentis states that no adverse toxicological effects were observed in the 90-day toxicity study in which rats were fed a diet corresponding to levels of urolithin A up to 3,451 mg/kg bw/d and 3,826 mg/kg bw/d, the highest levels tested in males and females, respectively. Amazentis also discusses published genotoxicity studies conducted on urolithin A that is the subject of this notice. Based on the results of these studies, Amazentis states that urolithin A is neither mutagenic nor genotoxic.

Amazentis includes the report of a panel of individuals (Amazentis' GRAS panel). Based on its review, Amazentis' GRAS panel concluded that urolithin A is safe under the conditions of its intended use.

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[1]FDA notes that the intermediate A structure provided in the notice corresponds to urolithin A 8-methyl ether.

[2]Amazentis states that both manufacturing processes may result in an impurity, referred to as AZX1, that is identified as an ionized dimer of urolithin A based on chemical analysis. However, Amazentis states that due to the low levels of the impurity found in the product, the identity of AZX1 was not fully characterized.

Based on the information presented in the notice, Amazentis concludes that urolithin A is GRAS for its intended use in foods.

Standards of Identity

In the notice, Amazentis states its intention to use urolithin A 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). The notice raises a potential issue under these labeling provisions. In the notice, Amazentis cites studies that describe urolithin A as having certain health benefits. If products containing urolithin A 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Amazentis describes urolithin A as a beige to yellow powder. As such, the use of urolithin A in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 000791 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Petition Review in OFAS.

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 Amazentis' notice concluding that urolithin A 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 urolithin A. Accordingly, our response should not be construed to be a statement that foods containing urolithin A, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Amazentis provided, as well as other information available to FDA, we have no questions at this time regarding Amazentis' conclusion that urolithin A is GRAS under its intended conditions of use. This letter is not an affirmation that urolithin A 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 000791 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M. Keefe -S

Digitally signed by Dennis M. Keefe -S
Date: 2018.12.20 11:45:42 -05'00'

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