Madhu G. Soni, Ph.D.
Soni & Associates Inc.
749 46th Square
Vero Beach, FL 32968

Re: GRAS Notice No. GRN 000978

Dear Dr. Soni:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000978. We received the notice that you submitted on behalf of Oliphenol LLC (Oliphenol) on November 13, 2020 and filed it on February 23, 2021. Oliphenol submitted amendments to the notice on July 12, 2021 and October 11, 2021, providing additional information regarding the manufacturing process, specifications, analytical methods, and safety of the notified substance.

The subject of the notice is hydrolyzed aqueous olive pulp extract (HAOPE) for use as an antioxidant and ingredient in snack crackers and croutons; sport drinks, "energy" drinks, flavored water, fruit-flavored drinks, and milk-based meal replacements; fruit juices and nectars; butter, margarine, oil and shortening; salad dressings; mayonnaise; mayonnaise-type sandwich spreads; dry coating mixes for meat, poultry and fish; dry seasoning mixes; sauces, dips and gravies; catsup; snacks; and vegetable juices at a level providing 5 mg of hydroxytyrosol (HT) per serving and in grain-based, protein-based, meal replacement and energy bars; yogurt; frozen yogurt; and chewing gum at a level providing 10 mg of HT per serving.[1] The notice informs us of Oliphenol's view that the use of HAOPE is GRAS through scientific procedures.

Our use of the terms, "hydrolyzed aqueous olive pulp extract" and "HAOPE," 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 (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual names for "hydrolyzed aqueous olive pulp extract" or "HAOPE."

[1] Oliphenol states that HAOPE is not intended for use in infant formula, infant and toddler foods, and products under the jurisdiction of the United States Department of Agriculture.

Oliphenol provides information about the identity and composition of the two forms of HAOPE, which include a golden brown to purplish colored powder and a brown to dark purplish colored liquid. HAOPE is obtained from the fruits of *Olea europaea*, commonly known as olives. Oliphenol describes the powder and liquid forms of HAOPE as containing 12-16% and 7.5-8.5% polyphenols, respectively, as well as carbohydrates, protein, fat, and ash. Oliphenol states that the major phenolic compound present in HAOPE is HT (3.5-4.5% and 3.0-4.0% in the powder and liquid forms, respectively). Oliphenol states that other phenolic compounds in HAOPE include oleuropein, tyrosol, oleuropein aglycone and gallic acid, and notes that these compounds are also found in olive oil.

Oliphenol describes the method of manufacture for HAOPE produced from the byproducts of olive oil processing. Olive pulp, obtained by milling olives, is stirred and then centrifuged to separate the vegetation water from the oil and solids. The vegetation water is collected, centrifuged to remove residual oil and large particulates, and adjusted to a pH of 3.5–4.5 using citric acid. The acid-treated vegetation water is stored from 2 to 8 months at room temperature allowing for the hydrolysis of oleuropein to HT and elenoic acid until a conversion ratio of at least 5:1 is attained. The liquid is then filtered to remove any remaining insoluble particulates and microorganisms. The filtered liquid containing 0.3–0.5% total polyphenols is concentrated at low temperature using high vacuum evaporation to produce a semi-viscous liquid containing 2% polyphenols. The liquid concentrate is then either standardized to 3-4% HT to yield the final liquid form of HAOPE or freeze-dried into a powder containing 3.4%-4.5% HT. Oliphenol states that HAOPE is manufactured according to current good manufacturing practices and that all materials in the manufacturing process are used in accordance with U.S. regulations.

Oliphenol provides the specifications for the powder and liquid forms of HAOPE. The specifications include the content of simple phenols and polyphenols (12-16 % for the powder and 7.5-8.5% for the liquid), HT (3.5-4.5% for the powder and 3-4% for the liquid), carbohydrates (45-74% for the powder and 30-45% for the liquid), fat (8-18% for the powder and 8-15% for the liquid), protein (3-8% for the powder and 3-6% for the liquid), ash (12-20%), pH (3-4 in 1 g/10 mL water), moisture (<5% for the powder and 30-45% for the liquid), lead (<0.1 mg/kg), total arsenic (<0.1 mg/kg), cadmium (<0.1 mg/kg), mercury (<0.01 mg/kg), and limits for microorganisms. Oliphenol provides the results from three non-consecutive batch analyses each for the powder and liquid forms to demonstrate that HAOPE can be manufactured to meet these specifications. Oliphenol states that HAOPE has a shelf-life of 2 years based on an accelerated stability study conducted on the powder form.

Oliphenol discusses the cumulative dietary exposure to HAOPE and HT from the intended use of HAOPE. Oliphenol estimates the mean and 90th percentile eaters-only cumulative dietary exposures to HAOPE to be 843 mg/person (p)/day (d) and 1500 mg/p/d, respectively. Oliphenol states that, based on the use levels of HT, the intended use of HAOPE is substitutional for the uses described in GRN 000726.[2] Therefore, the

[2] The subject of GRN 000726 was phenolic preparation from olive fruit containing ≥40% HT. We evaluated this notice and responded in letter dated February 28, 2018, stating that we had no questions at

intended use of HAOPE is not expected to increase the cumulative dietary exposure to HT reported in GRN 000726 for the U.S. population aged 2 years and older (i.e., 30 mg/person (p)/day (d) (0.5 mg/kg body weight (bw)/d) at the mean and 52 mg/p/d (0.9 mg/kg bw/d) at the 90th percentile).

Oliphenol states that olives, the source material for HAOPE, and olive oil have a long history of food use. Oliphenol notes FDA evaluated two GRAS notices (GRNs 000600 and 000876)[3] for HT (a component of HAOPE) and one GRAS notice (GRN 000726) for a phenolic preparation from olive fruit (PPOF).

Oliphenol summarizes published acute, subchronic, and reproductive and developmental toxicity studies on HAOPE. In the subchronic toxicity and the reproductive and developmental toxicity studies, no adverse effects were observed in rats at 2,000 mg/kg bw/d. To further support the safety of HAOPE, Oliphenol also discusses safety studies on PPOF, HT-rich aqueous virgin olive oil (VOO), and pure HT. No toxicologically relevant effects were reported in published 90-day studies in rats administered olive extract containing 35% HT at doses up to 691 mg/kg bw/d (equivalent to 250 mg HT/kg bw/d), 1,000 mg HT (from VOO)/kg bw/d, or 50 mg pure HT/kg bw/d. Oliphenol states that HAOPE, olive extracts in general, and HT are not mutagenic and genotoxic under the conditions of the study. Additionally, in a double-blind, randomized, placebo-controlled trial, 400 mg phenolic-rich olive extract/d for eight weeks did not cause adverse effects.

Oliphenol includes the statement of a panel of individuals (Oliphenol's GRAS panel). Based on its review, Oliphenol's GRAS panel concluded that HAOPE is safe under the conditions of its intended use.

Based on the totality of the data and information described above, Oliphenol concludes that HAOPE is GRAS for its intended use.

Standards of Identity

In the notice, Oliphenol states its intention to use HAOPE 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.

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

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that time regarding the notifier's GRAS conclusion.

[3] We evaluated GRNs 000600 and 000876 and responded in letters dated May 13, 2016 and January 21, 2020, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

referred to as nutrient content claims and health claims). If products containing HAOPE 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 ONFL in CFSAN. 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(a) 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. Oliphenol's intended use of HAOPE constitutes use as a preservative. Therefore, the ingredient statement on labels of food products containing HAOPE 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 in CFSAN.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Oliphenol describes HAOPE as a golden brown to purplish-colored powder and a brown to dark-purplish-colored liquid. As such, the use of HAOPE 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 000978 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 Food Ingredients in OFAS.

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 Oliphenol's notice concluding that HAOPE 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 HAOPE. Accordingly,

our response should not be construed to be a statement that foods containing HAOPE, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Oliphenol provided, as well as other information available to FDA, we have no questions at this time regarding Oliphenol's conclusion that HAOPE is GRAS under its intended conditions of use. This letter is not an affirmation that HAOPE 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 000978 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.12.10 14:29:10 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
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