



Georges Bergen
DSM Nutritional Products, LLC
45 Waterview Blvd.
Parsippany, NJ 07054

Re: GRAS Notice No. GRN 000726

Dear Mr. Bergen:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000726. We received DSM Nutritional Products, LLC's (DSM) notice on August 17, 2017, and filed it on September 14, 2017. DSM submitted amendments to the notice on November 15, 2017, and February 20, 2018, that contain clarification regarding the intended uses and a literature search timeframe.

The subject of the notice is a phenolic preparation from olive fruit (PPOF) for use as an ingredient and as an antioxidant in bakery products; beverages; dairy products and substitutes; desserts; fats and oils; fruit juices and nectars; dry seasoning mixes for meat, poultry, and fish; chewing gum; sauces, dips, gravies, and condiments; snacks; and vegetable juices at levels of 5 to 10 mg of hydroxytyrosol per serving of food.^{1,2} The notice informs us of DSM's view that these uses of PPOF are GRAS through scientific procedures.

Our use of the term, "phenolic preparation from olive fruit" 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 "phenolic preparation from olive fruit."

DSM provides information about the identity and composition of PPOF. DSM describes PPOF as a clear, colorless liquid consisting of $\geq 40\%$ hydroxytyrosol, which is the major phenolic compound found in olives. Hydroxytyrosol is a product of oleuropein

¹ DSM states that the serving sizes are based on reference amounts customarily consumed (21 CFR 101.12).

² DSM states that PPOF is not intended for use in food products regulated by the U.S. Department of Agriculture.

hydrolysis that occurs during the maturation of olives. Hydroxytyrosol is designated by the CAS Registry Number 10597-60-1.

DSM describes the manufacturing process for PPOF, which is produced either by extraction of olive fruit pomace or isolation from the water inherent in the olives (the vegetation water). Olive fruit pomace is mixed with acidified water and subjected to thermal treatment (70–100 °C) for 2–4 h to complete hydrolysis of oleuropein, ligstroside, and their aglycons to hydroxytyrosol and tyrosol, and inactivate enzymes within the fruit. The resulting crude extract is pH-adjusted to neutral and then homogenized. The subsequent centrifugal separation and clarification steps remove olive paste and fine solid particulates yielding a liquid phase containing aqueous olive extract. With vegetation water as the starting material, the manufacturing process begins with a clarification step without the need for thermal treatment under acidic conditions. Chromatographic filtration of the clarified liquid phase yields a purified olive extract that is then concentrated by evaporation to produce a viscous liquid containing $\geq 40\%$ hydroxytyrosol.

DSM provides food grade specifications for PPOF. These include hydroxytyrosol content ($\geq 40\%$); and, limits on ash ($< 3\%$), minor polyphenols ($< 8\%$), lead (≤ 1.0 mg/kg), mercury (≤ 0.1 mg/kg), cadmium (≤ 0.5 mg/kg), arsenic (≤ 1.0 mg/kg), and microbial contaminants. DSM provides results of three non-consecutive batch analyses to demonstrate that PPOF can be manufactured to meet specifications.

DSM provides estimates of cumulative dietary exposure to hydroxytyrosol from background and the intended uses with food consumption data from the National Health and Nutrition Examination Survey (NHANES 2007-2010). DSM reports that the cumulative dietary exposure to hydroxytyrosol for the total users only U.S. population (2 years and older) is 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.

DSM discusses the published safety data and information pertaining to olive extracts containing up to 35% hydroxytyrosol as well as with pure hydroxytyrosol to support the safety of PPOF. DSM states that the scientific literature search covered the period through August 2017. DSM summarizes the published rat and human studies on the absorption, distribution, metabolism, and excretion of hydroxytyrosol itself, as a component of olive oil or olive-derived products. DSM discusses several published acute oral toxicity studies in rodents administered by gavage either pure hydroxytyrosol or olive extracts containing different amounts of hydroxytyrosol and concludes that LD₅₀ for hydroxytyrosol is > 2000 mg/kg bw, the highest dose tested. DSM states that no adverse toxicological effects were reported in a published subchronic 90-day oral toxicity study in rats administered by gavage olive extract containing 35% hydroxytyrosol at doses up to 691 mg/kg bw/d (equivalent to 250 mg hydroxytyrosol/kg bw/d). DSM summarizes published reproductive toxicity and teratogenicity studies in rats administered by gavage hydrolyzed aqueous olive pulp extract containing 2.4% hydroxytyrosol from days 6 to 20 of gestation. No adverse maternal, reproductive, or developmental effects were reported for olive pulp extract at doses up to 2000 mg/kg bw/d (equivalent to 48 mg hydroxytyrosol/kg bw/d), the highest dose tested. In

evaluating the results from published human studies with either pure hydroxytyrosol or olive extract containing 15% hydroxytyrosol for durations up to 8 weeks, DSM concludes that no adverse effects were noted in any of these human studies. DSM states that the results of published *in vitro* and *in vivo* genotoxicity studies on hydroxytyrosol and olive extracts tested indicate that any genotoxic risks for human consumers are negligible.

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

Based on the totality of the data and information described above, DSM concludes that PPOF is GRAS for its intended use in food.

Standards of Identity

In the notice, DSM states its intention to use PPOF 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(k) of the Federal Food, Drug, and Cosmetic Act (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. DSM's intended use of PPOF constitutes use as a preservative. Therefore, the ingredient statement on labels of food products containing PPOF 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.

Under section 403(a) of the 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, DSM describes hydroxytyrosol, the major phenolic compound in PPOF, as an antioxidant having certain health benefits. If products containing PPOF 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 ONFL. 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.

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

Conclusions

Based on the information that DSM provided, as well as other information available to FDA, we have no questions at this time regarding DSM's conclusion that PPOF is GRAS under its intended conditions of use. This letter is not an affirmation that PPOF 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 000726 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

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Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
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