



Antonie J. van der Saag  
BioActor B.V.  
Gaetano Martinolaan 50  
6229 GS Maastricht  
NETHERLANDS

Re: GRAS Notice No. GRN 001119

Dear Antonie van der Saag:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001119. We received BioActor's notice on November 4, 2022, and filed it on March 22, 2023. BioActor submitted amendments to the notice on August 28, 2023, September 27, 2023, November 28, 2023, January 29, 2024, and January 30, 2024. These amendments provided additional information on the composition, method of manufacture, specifications, food categories, dietary exposure estimates, and safety information.

The subject of the notice is *Olea europaea* L. leaf extract (olive leaf extract) for use as an ingredient in various foods at the maximum use levels specified in Table 1.<sup>1</sup> The notice informs us of BioActor's view that these uses of olive leaf extract are GRAS through scientific procedures.

Table 1. Intended food categories and maximum use levels for olive leaf extract

<b>Food Category</b>	<b>Maximum use level (mg/kg)</b>
Yogurts	1111
Flavored Milk Drinks	1042
Dry Powdered Milk and Milk Mixtures (Not Reconstituted)	8333
Coconut Beverages	1042
Cookies (Certain Categories)	8333
Cereal, Granola and Nutrition Bars	8333
Cereals (Certain Categories)	8333
Dried, Raw, or Pickled Plums	6250
Fruit Juices and Nectars (Including Citrus)	1042
Vegetables and Vegetable Juices (e.g., Carrot and Tomato Juice)	1042
Fruit-Flavored Beverages (Ready to Drink and from Powders)	1042

<sup>1</sup> BioActor states that olive leaf extract is not intended for use in infant formula, products under the jurisdiction of the United States Department of Agriculture (USDA), and foods in which a standard of identity precludes its use.

<b>Food Category</b>	<b>Maximum use level (mg/kg)</b>
Vegetable and Fruit Juice Blends	1042
Fortified Water	1042
Carbonated Soft Drinks	1042
Teas	1042
Nutrition Drinks and Powders	1042
Sports Drinks	1042
Margarine and Vegetable Spreads and Olive Oil	16667
Candies (Dark Chocolate, Gum Drops, Hard Candy, Dietetic Candy)	8333
Sugar Free Chewing Gum	83333

Our use of the term, “olive leaf extract,” 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 “olive leaf extract.”

BioActor provides information regarding the identity and composition of olive leaf extract. BioActor describes olive leaf extract as a green to brown powder containing at least 50% polyphenols, of which at least 40% is oleuropein.

BioActor states that olive leaf extract is produced from the leaves of *Olea europaea hojiblanca*, *Olea europaea picual*, and *Olea europaea aberquina* trees. The leaves are cleaned, dried, milled, and extracted multiple times using 70% w/w ethanol. The ethanol is evaporated, and the extract is filtered, purified using a microporous resin, concentrated, and heated at 80-90°C for 16-20 hours. The concentrated extract is then spray dried, milled, and standardized to be at least 40% w/w oleuropein. BioActor states that olive leaf extract is manufactured according to current good manufacturing practices and that all the materials used in the manufacturing process are used in accordance with U.S. regulations or are GRAS for their intended use.

BioActor provides specifications for olive leaf extract that include total polyphenols ( $\geq 50\%$ ), oleuropein ( $\geq 40\%$ ), and limits for loss on drying ( $\leq 8\%$ ), residue by calcination ( $\leq 9\%$ ), residual ethanol ( $\leq 100$  mg/kg), benzo(a)pyrene ( $\leq 0.01$  mg/kg), the sum of benzo(a)pyrene, benzo(a)anthracene, benzo(b)fluoranthene and chrysene ( $\leq 0.05$  mg/kg), lead ( $\leq 0.1$  mg/kg), cadmium ( $\leq 0.05$  mg/kg), mercury ( $\leq 0.05$  mg/kg), arsenic ( $\leq 0.35$  mg/kg), and microorganisms. BioActor provides results from the analyses of five non-consecutive batches of olive leaf extract to demonstrate that the

ingredient can be manufactured to meet the specifications. BioActor provides data that shows that the ingredient is stable for at least 3 years.

BioActor provides estimates of dietary exposure to olive leaf extract based on the intended uses and food consumption data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES). BioActor estimates the mean and 90<sup>th</sup> percentile eaters-only dietary exposures to olive leaf extract to be 779.2 mg/(person) p/d (11.9 mg/kg bw/d) and 1553.2 mg/p/d (23.2 mg/kg bw/d), respectively, for the U.S. population aged 2 years and older.

BioActor summarizes published data and information supporting the safety of consumption of olive leaf extract containing at least 50% polyphenols and 40% oleuropein based on the dry extract of olive (*Olea europaea* L.) leaves. BioActor summarizes many published toxicological studies, such as genotoxicity, acute, subchronic, and reproductive and developmental toxicity studies conducted with olive leaf extracts. Some of these studies were conducted with the subject of the notice. BioActor cites a published subchronic study that concluded that oral administration of up to 1000 mg/kg bw/day of olive leaf extract, the highest dose tested, does not cause adverse effects in both male and female rats. BioActor discusses a published oral bioavailability study in human volunteers. BioActor notes that the study authors concluded that oleuropein is extensively metabolized in the body and most of the identified metabolites were in conjugated form, mainly glucuronide and sulfate conjugates that are steadily excreted in urine. BioActor states that olive leaf extract is not mutagenic or genotoxic. BioActor also states that they had conducted a search of the literature and did not find any data and information that would contradict their safety conclusion.

Based on the totality of the information, BioActor concludes that olive leaf extract is GRAS for its intended use.

### **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 olive leaf extract 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. 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.

### **Standards of Identity**

In the notice, BioActor states its intention to use olive leaf extract 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 Requirement for a Color Additive Petition**

There is no GRAS provision for color additives. In the notice, BioActor describes olive leaf extract as green to brown. As such, the use of olive leaf extract 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 001119 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 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 BioActor's notice concluding that olive leaf extract 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 olive leaf extract. Accordingly, our response should not be construed to be a statement that foods containing olive leaf extract, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

### **Conclusions**

Based on the information that BioActor provided, as well as other information available to FDA, we have no questions at this time regarding BioActor's conclusion that olive leaf extract is GRAS under its intended conditions of use. This letter is not an affirmation that olive leaf extract 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 001119 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.  
Carlson -S

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Susan J. Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition