Hywel Griffiths, Ph.D.
Fermentalg
4 Rue Rivière
33500 Libourne
FRANCE

Re: GRAS Notice No. GRN 000843

Dear Dr. Griffiths:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000843. We received Fermentalg's notice on February 11, 2019, and filed it on April 10, 2019. Fermentalg submitted amendments to the notice on April 17, 2019, July 4, 2019, and September 27, 2019, that clarified the dates of the literature search, intended use, use level, and safety discussion.

The subject of the notice is algal oil (35% docosahexaenoic acid) from *Schizochytrium* sp. strain FCC-1324 (algal oil (35% DHA)) for use as an ingredient in food categories listed in 21 CFR 184.1472(a)(3) at levels up to 50% of the levels specified in 21 CFR 184.1472(a)(3) and as the sole added source of DHA in any given food category and, if blended with another source of DHA or eicosapentaenoic acid (EPA), the levels will be no more than 1.5 g of DHA/person (p)/day (d) and no more than 3.0 g/p/d of DHA and EPA combined. The notice informs us of Fermentalg's view that these uses of algal oil (35% DHA) are GRAS through scientific procedures.

Our use of the term, "algal oil (35% DHA)," 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 "algal oil (35% DHA)."

Fermentalg provides information about the identity and composition of algal oil (35% DHA). Fermentalg describes algal oil (35% DHA) as light yellow to orange in color. The final product is a mixture of triglycerides containing 35% DHA. Fermentalg states that the major fatty acids are approximately 45% palmitic, 35% docosahexaenoic, 8% docosapentaenoic acids, and 4% myristic acid, with the rest as other fatty acids. Fermentalg states that all detected fatty acids are common dietary fatty acids and are

present in other *Schizochytrium* sp. algal oils that are GRAS for use in infant formula.[1]

Fermentalg describes the method of manufacture of algal oil (35% DHA). Fermentalg's algal oil (35% DHA) is produced by fermentation of a pure culture of *Schizochytrium* sp. strain FCC-1324 under batch-fed, axenic fermentation conditions with controlled pH and temperature in the absence of light. Following fermentation, the algal cell walls are enzymatically disrupted to release the intracellular oil. The crude algal oil is separated and recovered from the algal biomass by centrifugation. To minimize oxidation, the process is carried out under an inert atmosphere and antioxidants (e.g., mixed tocopherols from sunflower, ascorbyl palmitate) are added. As an optional step, the crude oil may be filtered using safe and suitable filtration materials, including diatomaceous earth and perlite. The oil is winterized (optional), refined, bleached, and deodorized. High-oleic sunflower oil may be added as a diluent. Fermentalg states that all reagents and processing aids used in the manufacture of algal oil (35% DHA) are food grade and the method is in accordance with current good manufacturing practices.

Fermentalg provides specifications for algal oil (35% DHA) that include a minimum content of DHA (≥350 mg/g or 35%), and limits for acid value (≤0.5 mg potassium hydroxide/g), peroxide value (≤5.0 meq O_2/kg), trans fatty acids (≤1%), unsaponifiable matter (≤3.5%), moisture (≤0.05%), lead (<0.01 mg/kg), arsenic (<0.1 mg/kg), mercury (<0.04 mg/kg), iron (<0.2 mg/kg), copper (<0.05 mg/kg), and cadmium (<0.01 mg/kg), as well as limits for microorganisms. Fermentalg provides the results of three non-consecutive batch analyses to demonstrate that algal oil (35% DHA) can be manufactured to meet these specifications.

Fermentalg discusses estimates of dietary exposure to DHA from algal oil (35% DHA) based on the intended use as a substitute for other DHA-containing oils currently used in foods. Therefore, dietary exposure to DHA is not expected to change.

Fermentalg addresses the safety[2] of algal oil (35% DHA) by discussing published acute and subchronic toxicity studies in rats, a 3-week toxicity study in piglets, developmental and reproductive toxicity studies in rats, developmental toxicity studies in rabbits, *in vitro* mutagenicity studies, and *in vitro* and *in vivo* genotoxicity studies that showed no adverse effects. Fermentalg states that it conducted an updated literature search through April 2019, which did not identify any new information that would contradict its conclusion that algal oil (35% DHA) is safe for its intended use.

Fermentalg includes the statement of a panel of individuals (Fermentalg's GRAS panel).

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[1] Algal oil derived from *Schizochytrium* sp. was the subject of GRN 000553; algal oil derived from *Schizochytrium* sp. strain ONC-T18 was the subject of GRN 000677; and algal oil (35% docosahexaenoic acid) from *Schizochytrium* sp. strain FCC-1324 was the subject of GRN 000776. We evaluated these notices and responded in letters dated June 19, 2015, May 2, 2017, and October 26, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

[2] Fermentalg states that it is incorporating into the notice the safety data and information pertaining to the safe use of DHA and EPA per 21 CFR 184.1472 (menhaden oil) discussed in GRN 000137 to support its GRAS conclusion. Algal oil (*Schizochytrium* sp.) was the subject of GRN 000137. We evaluated this notice and responded in a letter dated February 12, 2004, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Based on its review, Fermentalg's GRAS panel concluded that algal oil (35% DHA) is safe under the conditions of its intended use.

Based on the data and information, Fermentalg concludes that algal oil (35% DHA) is GRAS for its intended use.

Standards of Identity

In the notice, Fermentalg states its intention to use algal oil (35% DHA) 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 & Cosmetic (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). These 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.

Potential Requirement for a Color Additive Petition[3]

There is no GRAS provision for color additives. In the notice, Fermentalg notes that algal oil (35% DHA) has a light yellow to orange color. As such, the use of algal oil (35% DHA) 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 000843 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.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000843, we coordinated with FSIS at USDA. Under the Federal Meat Inspection Act, the Poultry

[3] The product categories under the USDA Food Safety and Inspection Service's (FSIS) jurisdiction in which the ingredient may be used would be limited if algal oil (35% DHA) is found to impart color under the conditions of use.

Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers.

Algal oil (35% DHA) is intended for use as an alternative edible oil in the production of various meat and poultry products at levels not to exceed 1.45% by weight of the product formulation for meat products and 0.87% by weight of the product formulation for poultry products. FSIS has completed its review and has no objection to the use of algal oil (35% DHA) in meat and poultry products at these use levels. The oil is required to be listed by its common or usual name in the ingredients statement.

FSIS requested that we advise you to seek regulatory guidance from its Risk Management and Innovations Staff (RMIS) about the use of algal oil (35% DHA) in meat, poultry, and egg products. You should direct such an inquiry to Dr. Melvin Carter, Director, RMIS, Office of Policy and Program Development, FSIS by email at melvin.carter@usda.gov.

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 Fermentalg's notice concluding that algal oil (35% DHA) 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 algal oil (35% DHA). Accordingly, our response should not be construed to be a statement that foods containing algal oil (35% DHA), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Fermentalg provided, as well as other information available to FDA, we have no questions at this time regarding Fermentalg's conclusion that algal oil (35% DHA) is GRAS under its intended conditions of use. This letter is not an affirmation that algal oil (35% DHA) 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 000843 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.10.18 16:08:59 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

cc: Melvin Carter, Ph.D.
Director
USDA/FSIS/OPPD/RMIS
Stop Code 3782, Patriots Plaza III
1400 Independence Ave. SW
Washington, DC 20250-3700