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

Re: GRAS Notice No. GRN 000777

Dear Dr. Griffiths:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000777. We received Fermentalg's notice on March 30, 2018, and filed it on May 14, 2018. Fermentalg submitted amendments to the notice on August 24, 2018, and September 4, 2018, that provided additional information on the source organism, composition, manufacturing, specifications, and exposure.

The subject of the notice is algal oil (55% docosahexaenoic acid) from *Schizochytrium* sp. strain FCC-3204 (algal oil (55% DHA)) for use as an ingredient in non-exempt and exempt infant formulas for term and pre-term infants[1] at use levels up to 0.5% (wt/wt) of fatty acids as DHA in combination with a safe and suitable source of arachidonic acid (ARA) at a ratio ranging from 1:1 to 1:2 of DHA to ARA. The notice informs us of Fermentalg's view that these uses of algal oil (55% DHA) are GRAS through scientific procedures.

Our use of the term, "algal oil (55% 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 Code of Federal Regulations (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 (55% DHA)."

Fermentalg provides information about the identity and composition of algal oil (55% DHA). Fermentalg describes algal oil (55% DHA) as light yellow to orange in color. Fermentalg states that algal oil (55% DHA) consists of a mixture of triglycerides, of which the predominant fatty acid is DHA (>55%). Fermentalg states that DHA is a long chain, polyunsaturated fatty acid, with the empirical formula $C_{22}H_{32}O_2$, chemical name

[1] Fermentalg notes that algal oil (55% DHA) is intended for use in both milk- and soy-based infant formulas, and that the intended use is substitutional for other sources of DHA.

4,7,10,13,16,19-docosahexaenoic acid (CAS Reg. No. 6217-54-5), and shorthand nomenclature 22:6 n-3. Fermentalg discusses the fatty acid profile of algal oil (55% DHA) and states that the major fatty acids other than DHA (mean approximately 61%) are palmitic acid (16:0) and docosapentaenoic acid (22:5 n-6), present at mean levels of 20.6 and 10.5%, respectively. Fermentalg states that all detected fatty acids[2] are common dietary fatty acids and are present in other *Schizochytrium* sp. algal oils that are GRAS for use in infant formula.[3] Sterols comprise ~1-2% of the algal oil (55% DHA) and are qualitatively similar to sterols in the aforementioned algal oils.

Fermentalg discusses the manufacture of algal oil (55% DHA) and states that it is produced by the marine alga *Schizochytrium* sp. strain FCC-3204. There are no reports of pathogenicity or toxigenicity associated with this or related *Schizochytrium* sp. strains used in the production of DHA algal oils.[4,5] A pure culture of *Schizochytrium* sp. strain FCC-3204 is grown under batch fed, axenic fermentation conditions with controlled pH and temperature. To minimize oxidation, the process is carried out under an inert atmosphere, and antioxidants (e.g., mixed tocopherols from sunflower, ascorbyl palmitate) are added. Following fermentation, the algal cell walls are enzymatically[6] disrupted to release the intracellular oil. The crude algal oil is separated and recovered from the algal biomass by centrifugation. As an optional step, the crude oil may be filtered using safe and suitable filtration materials (e.g., diatomaceous earth and perlite). The oil is winterized (optional), refined, bleached, and deodorized. Fermentalg states that 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 (55% DHA) are food grade and the method complies with current good manufacturing practices.

Fermentalg provides specifications for algal oil (55% DHA) that include a minimum content of DHA (≥55%) 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), and cadmium (<0.01 mg/kg), as well as specified limits for microorganisms.

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[2] In addition to the major fatty acids present in algal oil (55% DHA), the following fatty acids are present at levels less than 1%: dihomo-gamma-linolenic (20:3 n6), arachidonic (20:4 n6), eicosatetraenoic (20:4 n3), eicosapentaenoic (20:5 n3), lauric (12:0), myristoleic (14:1), pentadecanoic (15:0), palmitoleic (16:1 n7), stearic (18:0), oleic (18:1 n9), linoleic (18:2 n6), α-linolenic (18:3 n-3), stearidonic (18:4 n3), arachidonic (20:0), gondoic (20:1 n-9), behenic (22:0), lignoceric (24:0), and nervonic (24:1 n-9). Erucic acid (18:0) is present at 1.0% and myristic acid is present at 1.3%.

[3] Algal oil from *Schizochytrium* sp. was the subject of GRN 000553; DHA oil from *Schizochytrium* sp. was the subject of GRN 000677. We evaluated these notices and responded in letters dated June 19, 2015, and May 2, 2017, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

[4] Fermentalg states that the production organism strain FCC-3204 is closely related to *Schizochytrium* sp. strain ATCC-20888 described in GRN 000137 (according to 18S ribosomal DNA sequence comparison).

[5] Algal oil from *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 Martek Biosciences Corporations' GRAS conclusion.

[6] Fermentalg states that the enzyme is a protease preparation produced by a selected strain of *Bacillus licheniformis* and is used in accordance with 21 CFR 184.1027. Fermentalg states that the enzyme is not present in the algal oil (55% DHA) final product.

Fermentalg provides the results of three non-consecutive batch analyses to demonstrate that algal oil (55% DHA) can be manufactured to meet these specifications.

Fermentalg provides estimates of dietary exposure to DHA from algal oil (55% DHA) based on the intended use in infant formulas and the assumption that infants consume 100 to 120 kcal/kg body weight (bw)/day (d), about 50% of which is fat. Fermentalg states that infants consume approximately 5.5 to 6.7 g fat/kg bw/d. Based on a maximum use level of 0.5% total fat as DHA, Fermentalg calculates that the dietary exposure to DHA is 27 to 33 mg/kg bw/d. Fermentalg notes that this estimate is in agreement with estimates provided in GRNs 000553 and 000677[3]. Based on a minimum specified content of 55% DHA in algal oil, Fermentalg notes that the estimated dietary exposure to algal oil (55% DHA) is equivalent to 49 to 60 mg/kg bw/d.

Fermentalg provides a summary of published safety studies on *Schizochytrium* sp., as well as published safety studies on algal oil (55% DHA) evaluated by FDA in GRNs 000137,[5] 000553, and 000677.[3] Fermentalg describes published studies showing no toxicologically relevant effect in rats following gavage administration up to 5,000 mg/kg bw/d of algal oil (55% DHA) or dietary administration up to 5% algal oil (55% DHA) in piglets. Several published studies demonstrated that algal oil (55% DHA) from *Schizochytrium* sp. is not mutagenic or genotoxic. Fermentalg conducted an updated literature search through August 2017 and found a developmental and reproductive study of algal oil (55% DHA) from *Schizochytrium* sp. and ARA-rich oil from *Mortierella alpina* in rats, which Fermentalg discusses in detail. From this study, Fermentalg concludes that up to 5,000 mg/kg bw/d of algal oil (55% DHA), the highest dose administered by gavage, was safe in terms of maternal toxicity, embryo/fetal development, and parental reproductive toxicity.

To support its GRAS conclusion, Fermentalg refers to published studies discussed in GRNs 000137,[5] 000553, and 000677[3] conducted in adults, children, and infants that used DHA-containing fish and marine-based oils. Additionally, Fermentalg discusses a recently published 106-day study where healthy term infants from 14 to 120 days of age were fed a milk-based formula that was well tolerated containing 17 mg/100 kcal DHA from either *Crypthecodinium cohnii* or *Schizochytrium* sp. algae. In the August 24, 2018 amendment to the notice, Fermentalg briefly discusses some published studies in pre-term infants and notes that these studies did not report any adverse effects from parental reports of fussiness, diarrhea, or constipation, and no adverse effects were reported from the blood/serum analyses.

Fermentalg includes the report of a panel of individuals (Fermentalg's GRAS panel). Based on its review, Fermentalg's GRAS panel concluded that algal oil (55% DHA) is safe under the conditions of its intended use.

Based on the data and information described above, Fermentalg concludes that algal oil (55% DHA) is GRAS for its intended use.

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). The notice raises a potential issue under these labeling provisions. In the notice, Fermentalg cites data demonstrating that algal oil (55% DHA), intended for use as an ingredient, has a similar lipid (fatty acid and sterol) profile to that of currently marketed oil from *Schizochytrium* sp. If products containing 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Fermentalg notes that algal oil (55% DHA) has a light yellow to orange color. As such, the use of algal oil (55% DHA) in food products may constitute a color additive use under section 201(t)(1) of the Federal Food, Drug, & Cosmetic (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 000777 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.

Intended Use in Infant Formulas

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Fermentalg's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing algal oil (55% DHA) to make the submission required by section 412. Infant formulas are the purview of 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 Fermentalg's notice concluding that algal oil (55% 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 (55% DHA). Accordingly, our response should not be construed to be a statement that foods containing algal oil (55% 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 (55% DHA) is GRAS under its intended conditions of use. This letter is not an affirmation that algal oil (55% 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 000777 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M. Keefe -S

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Date: 2018.10.26 13:17:04 -04'00'

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