Donald Schmitt, MPH
ToxStrategies, Inc.
931 W. 75th St., Suite 137, PMB 255
Naperville, IL 60565

Re: GRAS Notice No. GRN 000913

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000913. We received the notice that you submitted on behalf of Mara Renewables Corporation (Mara) on March 25, 2020 and filed it on April 13, 2020. Mara submitted amendments to the notice on June 26, 2020, July 28, 2020, and September 1, 2020 that provided additional information on the reagents, production microorganism, and shelf life and clarified the manufacturing methods, use levels in meat and poultry products, and estimated dietary exposure.

The subject of the notice is algal oil (minimum 35% docosahexaenoic acid (DHA)) from *Aurantiochytrium limacinum*[1,2] strain G3 (*Aurantiochytrium* sp. strain G3) (algal oil (≥ 35% DHA)) for use as an ingredient in the food categories listed in 21 CFR 184.1472(a)(3) at up to 20% of the levels specified, 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 Mara'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

[1] Mara states that *Schizochytrium limacinum* strain G3 was reclassified as *Aurantiochytrium limacinum* strain G3.

[2] Yokoyama, R., & Honda, D. (2007). Taxonomic rearrangement of the genus *Schizochytrium* sensu lato based on morphology, chemotaxonomic characteristics, and 18S rRNA gene phylogeny (Thraustochytriaceae, Labyrinthulomycetes): emendation for *Schizochytrium* and erection of *Aurantiochytrium* and *Oblongichytrium* gen. nov. *Mycoscience, 48*, 199-211. doi: 10.1007/s10267-006-0362-0

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)."

Mara provides information about the identity and composition of algal oil (≥ 35% DHA). Algal oil (≥ 35% DHA) is extracted from the microalgae *Aurantiochytrium* sp. strain G3 and is described as a liquid, white to orange oil that is predominantly triglycerides with polyunsaturated fatty acids. Mara states that algal oil (≥ 35% DHA) contains a minimum of 35% DHA, which is a long chain, polyunsaturated fatty acid with the empirical formula $C_{22}H_{32}O_2$, the chemical name docosa-4,7,10,13,16,19-hexaenoic acid, and the shorthand nomenclature 22:6 n-3. Mara states that all fatty acids that were detected are well-known components of the human diet and are found in both animal- and vegetable-based food sources.

Mara describes the method of manufacture for algal oil (≥ 35% DHA). A pure culture of *Aurantiochytrium* sp. strain G3 is fermented under controlled axenic conditions in a medium that consists primarily of dextrose, soy peptone, yeast extract, ammonium sulfate, and sodium chloride. Following fermentation, the algal cell walls are enzymatically disrupted after a pH adjustment using sodium hydroxide to release the intracellular oil.[3] The crude oil layer is separated from the fermentation biomass by centrifugation and then treated with antioxidants as necessary. The oil can then undergo an optional fractionation/winterization step in which the oil is cooled and centrifuged. The oil may also be further treated with citric or phosphoric acid and refined using water degumming. The oil is then bleached and deodorized. Antioxidants can be added as necessary and sunflower or low erucic acid rapeseed oil can be added to the refined oil to standardize the DHA content. Mara states that all reagents and processing aids used in the manufacture of algal oil (≥ 35% DHA) are food grade and the ingredient is manufactured in accordance with current good manufacturing practices.

Mara provides specifications for algal oil (≥ 35% DHA) that include a minimum content of DHA (≥ 35%) and limits for acid value (≤ 0.5 mg potassium hydroxide/g), peroxide value (≤ 5.0 milliequivalents/kg), *trans* fatty acids (≤ 2.0%), moisture (≤ 0.05%), unsaponifiable matter (≤ 3.5%), lead (< 0.1 mg/kg), arsenic (< 0.1 mg/kg), mercury (< 0.1 mg/kg), and microorganisms. Mara provides results of three non-consecutive batch analyses of algal oil (≥ 35% DHA) to demonstrate that algal oil (≥ 35% DHA) can be produced to meet the stated specifications.

Mara states that the maximum use levels for algal oil (≥ 35% DHA) in food are based on the maximum use levels for menhaden oil specified in 21 CFR 184.1472(a)(3). Mara states that the intended use of algal oil (≥ 35% DHA) is substitutional for existing uses of DHA-containing oils and therefore, the intended use of algal oil (≥ 35% DHA) in food will not result in an increase in the dietary exposure to DHA.

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[3] Mara states that the enzyme is a food-grade protease preparation produced by *Bacillus licheniformis* and is used in accordance with 21 CFR 184.1027.

Mara states that FDA had no questions about the use of DHA-rich oils from numerous algal and marine sources in infant formula and in food.[4] Mara discusses multiple published studies and states that it performed a literature search through December 2019 to identify any new safety data on DHA and DHA algal oil.

To support the safety of algal oil (≥ 35% DHA), Mara summarizes the safety studies conducted with the subject of GRN 000677, 40% DHA algal oil obtained from *Aurantiochytrium* sp. strain T18. Mara discusses the taxonomy and safety of *Aurantiochytrium* sp. strain G3. Mara states that *Aurantiochytrium* sp. strain G3 is non-pathogenic and toxin production is unlikely because there are no known reports of toxin production by thraustochytrids, of which *Aurantiochytrium* is a member. Mara reports 90% 18S ribosomal RNA sequence similarity between *Aurantiochytrium* sp. strains T18 and G3. Mara states that algal oil (≥ 35% DHA) from *Aurantiochytrium* sp. strain G3 has a fatty acid profile similar to that from *Aurantiochytrium* sp. strain T18. Mara provides a list of published oral toxicity studies in rats that include acute toxicity, subchronic toxicity, reproductive/developmental toxicity, and genotoxicity/ mutagenicity studies. No treatment-related toxicity of DHA oil was identified by the authors in any of these studies. The authors of the subchronic toxicity study stated that no treatment-related adverse effects were observed up to a dose of 3305 mg/kg body weight (bw)/day (d) in male rats and 3679 mg/kg bw/d in female rats. In the reproductive/developmental toxicity study, the study authors reported that no treatment-related adverse effects for maternal toxicity and embryo/fetal development were observed at 2000 mg/kg bw/d, the highest dose tested. Mara states that DHA algal oil did not demonstrate mutagenic or genotoxic potential in a battery of *in vitro* and *in vivo* genotoxicity tests.

Mara summarizes published human studies conducted for varying durations (1 week to more than 1 year) with fish- or marine-derived oils containing DHA and/or EPA, at intakes up to 6 g DHA/person/d, in excess of the dietary exposure to DHA from algal oil (≥ 35% DHA) estimated by Mara. The studies' authors reported no toxicologically relevant effects on LDL cholesterol levels, glycemic control, bleeding time, platelet aggregation, and other hemostatic parameters.

Mara includes the report of a panel of individuals (Mara's GRAS panel). Based on its review, Mara's GRAS panel concluded that algal oil (≥ 35% DHA) is safe under the conditions of its intended use.

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

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[4] Mara lists GRAS notices for DHA-rich oils from algal and marine sources for use in infant formula and conventional food (GRNs 000041, 000094, 000137, 000379, 000553, 000677, 000731, 000732, 000776, 000777, 000836, 000843, 000844, 000862); we evaluated these GRAS notices and responded in letters dated May 17, 2001, February 12, 2004, April 18, 2006, November 8, 2011, June 19, 2015, May 2, 2017, April 6, 2018, October 26, 2018, September 3, 2019, October 18, 2019, and June 15, 2020, stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, Mara states its intention to use algal oil (≥ 35% DHA) in several food categories, including foods for which standards of identity exist, located in 21 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.

Allergen Labeling

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. Algal oil (≥ 35% DHA) may require labeling under the FD&C Act because it may contain protein derived from soybeans. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to ONFL.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Mara describes algal oil (≥ 35% DHA) as white to orange in 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 000913 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 000913, we coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry 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.

FSIS has advised the following with respect to the statutes it administers:

> FSIS has completed its review and has no objection to the use of algal oil (≥ 35% DHA) in nonstandardized egg, meat, and poultry products at levels not to exceed 1.00% by weight of the product formulation for egg and meat products and 0.60% for poultry products. If algal oil (≥ 35% DHA) is found to impart color under conditions of use, it would limit the product categories under FSIS's jurisdiction in which the ingredient may be used.
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> Regarding labeling, when used in the formulation of a meat, poultry, or egg product under FSIS's jurisdiction, the ingredient would need to be listed in the ingredients statement by its common or usual name as "DHA rich algal oil."

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@fsis.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 Mara'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 Mara provided, as well as other information available to FDA, we have no questions at this time regarding Mara'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 000913 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
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Susan Carlson, Ph.D.
Director
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cc: Melvin Carter, Ph.D.
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