Susan Cho, Ph.D.
NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029

Re: GRAS Notice No. GRN 000732

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000732. We received the notice you submitted on behalf of Linyi Youkang Biology Co., Ltd (Linyi Youkang) on September 21, 2017, and filed it on October 16, 2017. We received amendments to the notice on November 7, 2017, and January 29, 2018, containing additional safety information and signed statements and certifications, and on March 7, 2018, containing a revised Part 1 of the notice.

The subject of the notice is algal oil from *Schizochytrium* sp. strain LU310 (algal oil) for use as an ingredient in food categories as listed in 21 CFR 184.1472(a)(3) excluding products under USDA jurisdiction, at up to 22.22% of the levels specified in 21 CFR 184.1472(a)(3), and for algal oil powder at up to 125% of the levels specified in 21 CFR 184.1472(a)(3).[1] The notice informs us of Linyi Youkang's view that this use of algal oil is GRAS through scientific procedures.

Our use of "algal oil" in this letter should not be considered an endorsement or recommendation of that term as an appropriate common or usual name for the purpose of declaring the substance in the ingredient statement of foods that contain that ingredient. 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."

[1] Linyi Youkang states that the use of algal oil is intended to be the sole source of docosahexaenoic acid (DHA) in food, and if blended with another source of DHA or eicosapentaenoic acid (EPA), the levels would be appropriate to provide no more than 1.5 g of DHA/person/day and no more than 3.0 g/person/day of DHA and EPA combined.

Linyi Youkang provides information about the identity and composition of algal oil. Algal oil is extracted from the microalgae *Schizochytrium* sp. LU 310 and is described as a free flowing, yellow oil that is predominantly triglycerides (>95%). Linyi Youkang states that algal oil contains >45% of docosahexaenoic acid (DHA), which is a long chain, polyunsaturated fatty acid, with 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. Based on data provided in the notice, the remaining major fatty acids are palmitic acid (16:0) and the omega 6 fatty acid docosapentaenoic acid (DPA, 22:5 n-6), which comprise approximately 21% and 10%, respectively of the algal oil.

Linyi Youkang provides a description of the method of manufacture for algal oil. A pure culture of *Schizochytrium* sp. LU310 is fermented under controlled conditions. Following fermentation, the algal cell walls are enzymatically[2] disrupted to release the intracellular oil. The oil layer is separated from the fermentation biomass by centrifugation, and then refined through degumming, decolorization, and deodorization. Linyi Youkang states that vitamin E is added to the finished algal oil. Linyi Youkang states that algal oil may be used to produce a powdered form by the addition of sodium ascorbate, lecithin, ascorbyl palmitate, lactose derived from milk, and modified starch. The mixture is then spray dried to obtain algal oil powder. Linyi Youkang states that all reagents and processing aids used in the manufacture of algal oil are food grade and the method is in accordance with current good manufacturing practices.

Linyi Youkang provides specifications for algal oil and algal oil powder that include minimum content of DHA (>45% of total fatty acids for algal oil and >8% for algal oil powder), and limits for acid value (<0.5 mg potassium hydroxide/g), peroxide value (<5.0 milliequivalents/kg), free fatty acids (<0.1%), moisture (<0.1% for algal oil and <5% for algal oil powder), lead (<0.1 mg/kg for algal oil and <0.05 mg/kg for algal oil powder), arsenic (<0.1 mg/kg), mercury (<0.04 mg/kg for algal oil and <0.01 mg/kg for algal oil powder), as well as limits for microbes. Linyi Youkang provides the results of three, non-consecutive batch analyses of algal oil to demonstrate that specifications can be met.

Linyi Youkang discusses dietary exposure to DHA from the intended use of algal oil. Linyi Youkang states that the use of algal oil is based on the maximum use levels of menhaden oil in specific food categories, excluding use in egg, fish, meat, and poultry products under USDA jurisdiction, established by FDA in the menhaden oil regulation (21 CFR 184.1472) such that the intake would not exceed 3.0 g of omega 3 fatty acid (i.e., EPA and DHA) per person (p) per day (d). The notifier states the intended use of algal oil is as a substitute for other DHA-containing oils currently used in food and, therefore, dietary exposure to DHA is not expected to change. The notifier discusses estimates of

[2] Linyi Youkang notes that the enzyme used is an alkaline protease derived from the non-pathogenic, non-toxigenic bacterium, *Bacillus licheniformis*.

dietary exposure reported in GRN 000137[3] and concludes that the maximum mean dietary exposure to DHA is 1.5 g/p/d.

Linyi Youkang cites published and unpublished toxicological studies from GRNs 000137,[3] 000553,[4] and 000677,[5] that previously received "no question letters" and reported on algal oils from *Schizochytrium* sp. strains (DHA algal oils). The notifier states that an updated literature search was performed for animal data published up to July 2017. Linyi Youkang reports on three published studies and one unpublished study pertaining to animal data and mutagenicity data. Linyi Youkang reports that there were no treatment-related adverse effects observed. Linyi Youkang cites a published 90 day subchronic rat gavage study. Both Linyi Youkang and the authors reported no treatment-related adverse effects occurred up to 5000 mg/kg bw, the highest dose tested. Linyi Youkang cites an unpublished acute study in rats. Linyi Youkang reports that no animals died during the 14-day observation period and that the LD_{50} for their DHA algal oil ingredient is greater than 15200 mg/kg bw. In addition, Linyi Youkang cites published acute studies discussed in GRNs, where the LD_{50} was also determined to be greater than 5000 mg/kg bw for DHA algal oil in rats. Linyi Youkang cites a published developmental (teratology) and reproductive study performed in rats. The authors of the study and Linyi Youkang both report that due to the absence of maternal, developmental, or reproductive effects, no significant effects occurred up to 5000 mg/kg bw of the DHA algal oil, the highest dose tested and therefore support the safety of the intended uses and use levels, which are below the levels listed for such uses in the menhaden oil regulation (21 CFR 184.1472). Linyi Youkang cites published bacterial reverse mutation assay and chromosomal aberration test using human blood peripheral lymphocytes. The study authors and Linyi Youkang both found that DHA algal oil is not mutagenic and does not induce chromosomal aberrations.

Linyi Youkang reports on several human studies for DHA algal oil not previously included in other GRAS notices based on literature search results to July 2017. The emphasis as illustrated by the published articles that Linyi Youkang cites is on possible health benefits. Linyi Youkang states that the articles report no adverse effects. Linyi Youkang cites a published 14-week human study in which adults with hypertriglyceridemia consumed DHA algal oil containing 2.4 g/d of DHA plus EPA (1.77 g DHA and 0.65 g EPA). The authors reported on a decrease in triglycerides in the DHA

[3] GRN 000137 describes the use of algal oil derived from *Schizochytrium* sp. as an ingredient in certain conventional food categories. We evaluated this notice and responded in a letter on February 12, 2004, stating that we had no questions at that time regarding Martek Biosciences Corporation's GRAS conclusion.

[4] GRN 000553 describes the use of algal oil derived from *Schizochytrium* sp. as an ingredient in infant formulas in combination with a safe and suitable source of arachidonic acid (ARA). We evaluated this notice and responded in a letter on June 19, 2015, stating that we had no questions at that time regarding DSM Nutritional Products' GRAS conclusion.

[5] GRN 000677 describes the use of algal oil derived from *Schizochytrium* sp. strain ONC-T18 as an ingredient in infant formulas in combination with a safe and suitable source of ARA. We evaluated this notice and responded in a letter on May 2, 2017, stating that we had no questions at that time regarding Mara Renewables Corporation's GRAS conclusion.

algal oil group compared to the control. The authors stated that there was no effect to blood pressure or heart rate, and the blood chemistry and hematology.

Based on the data and information described above, Linyi Youkang concludes that algal oil is GRAS for its intended use.

Standards of Identity

In the notice, Linyi Youkang states its intention to use algal oil 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(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). The notice raises a potential issue under these labeling provisions. The notice raises a potential issue under these labeling provisions. In the notice, Linyi Youkang cites studies that describe algal oil as having certain health benefits. If products containing algal oil 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.

Allergen Labeling

The 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 powder may require labeling under the FD&C Act because the formulation contains lactose and may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in the OFAS. Questions related to food labeling in general should be directed to the ONFL in the Center for Food Safety and Applied Nutrition.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Linyi Youkang describes algal oil as yellow. As such, the use of algal oil 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 000732 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 the 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 Linyi Youkang's notice concluding that algal oil 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. Accordingly, our response should not be construed to be a statement that foods containing algal oil, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Linyi Youkang provided, as well as other information available to FDA, we have no questions at this time regarding Linyi Youkang's conclusion that algal oil is GRAS under its intended conditions of use. This letter is not an affirmation that algal oil 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 000732 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2018.04.06 15:03:26 -04'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition