



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

Re: GRAS Notice No. GRN 000731

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000731. 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 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 exempt infant formulas for pre-term infants and non-exempt infant formulas for term infants at a maximum level of 0.5% total fat as docosahexaenoic acid (DHA) and in combination with a safe and suitable source of arachidonic acid (ARA). The ratio of DHA to ARA would range from 1:1 to 1:2. 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."

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 (>95.4%), with diglycerides (3.9%), monoglycerides (1.1%), and glycerol (<1.04%). Linyi Youkang states that algal oil contains >45% 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. The remaining major fatty acids are palmitic acid

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5001 Campus Drive
College Park, MD 20740
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(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 representative data for the fatty acid profile of algal oil and notes that the composition is comparable to algal oils from *Schizochytrium* sp. described in GRNs 000553¹ and 000677.²

Linyi Youkang describes 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 enzymatically³ 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 % 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 <0.01 mg/kg for algal oil powder), as well as limits for microbes, including *Salmonella* serovars (absent in 25 g sample). Linyi Youkang provides the results of three, non-consecutive batch analyses of algal oil to demonstrate that specifications can be met. The batch analyses also included results for *Cronobacter sakazakii* (absent in 25 g samples).

Linyi Youkang provides estimates of dietary exposure to DHA from algal oil based on the intended use level in infant formulas and an assumption that infants consume 100 to 120 kcal/kg body weight (bw)/day (d) of formula, which contains approximately 50% fat. Linyi Youkang states that infants consume about 50 to 60 kcal fat/kg bw/d that corresponds to approximately 5.5 to 6.7 g fat/kg bw/d. Based on a maximum use level of 0.5% total fat as DHA, Linyi Youkang calculates that the dietary exposure to DHA is 27 to 33 mg/kg bw/d.

Linyi Youkang cites published and unpublished toxicological studies to support the

¹ 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 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.

² 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.

³ Linyi Youkang Biology notes that the enzyme used is an alkaline protease derived from the non-pathogenic, non-toxicogenic bacterium, *Bacillus licheniformis*.

intended use of the algal oil that is the subject of GRN 000731. Linyi Youkang states that a literature search on animal data was conducted through July 2017. Linyi Youkang also incorporates into GRN000731 the safety and metabolism studies of DHA algal oils from *Schizochytrium* sp. strains (DHA algal oils) discussed in GRNs 000553 and 000677.

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 LD₅₀ for their algal oil ingredient is greater than 15200 mg/kg bw. In addition, Linyi Youkang cites published acute studies discussed in GRNs 000553 and 000677, where the LD₅₀ 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. 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 studies for DHA algal oil in term and preterm infants not previously included in other GRAS notices to support the safety of consumption of algal oil. Linyi Youkang cites a published DHA algal oil supplementation study that examined the effects of DHA algal oil on stimulated inflammatory cytokine production in white blood cells from term infants at high genetic risk for type 1 diabetes. Mothers in their last trimester of pregnancy received 800 mg/d DHA algal oil, and formula-fed term infants up to 5 months old received up to 10.2 mg DHA algal oil/ounce infant formula. Linyi Youkang and the study's authors conclude that DHA algal oil was well tolerated in both mothers and term infants alike and showed no adverse effects. Linyi Youkang also cites a study in term infants who were formula-fed up to 0.96% DHA algal oil from *Cryptothecodinium cohnii* (with fixed concentration of 0.64% ARA) for 12 months. Linyi Youkang and the study's authors conclude that consumption of DHA algal oil from *C. cohnii* was well tolerated in term infants and showed no adverse effects. Linyi Youkang also cites studies of non-specified sources of DHA algal oil conducted in pre-term infants. Linyi Youkang reports that consumption of DHA algal oil up to 0.86% of total fatty acids (or 32 mg) was well tolerated and no adverse effects were observed. The literature search on published human data was from January 2013 to July 2017 as reported in the amendment received on November 7, 2017.

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

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 OFAS. Questions related to food labeling in general should be directed to 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 notes that algal oil has a yellow color. As such, the use of algal oil in food products may constitute the use of a color additive 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 000731 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 Formula

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 Linyi Youkang's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing algal oil 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 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 000731 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**

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

 Digitally signed by Michael A.
Adams -S
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