



Stella Si
Anchor Center for Certification
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CHINA

Re: GRAS Notice No. GRN 001236

Dear Ms. Si:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001236. We received the notice that you submitted on behalf of Shaanxi Healthful Bioengineering Co., Ltd. (Shaanxi) on October 1, 2024, and filed it on February 14, 2025. Shaanxi submitted amendments to the notice on May 5, 2025, and May 13, 2025, that clarified the intended use, manufacturing, specifications, and aspects of the safety narrative.

The subject of the notice is algal oil ($\geq 40\%$ docosahexaenoic acid) from *Aurantiochytrium limacinum* H Sc-01¹ (algal oil ($\geq 40\%$ DHA)) for use as an ingredient in the same food categories as those listed in 21 CFR 184.1472(a)(3) (Menhaden oil)² at use levels that are no more than 25% of the levels specified for menhaden oil in that regulation. Shaanxi states that if algal oil ($\geq 40\%$ DHA) is blended with another source of DHA or eicosapentaenoic acid (EPA), the use levels will result in dietary exposure that is no more than 1.5 g of DHA/person (p)/d and no more than 3.0 g/p/d of DHA and EPA combined. Algal oil ($\geq 40\%$ DHA) is also intended for use as an ingredient in milk-, soy-, amino acid-, and extensively hydrolyzed protein-based, non-exempt infant formula for term infants and exempt infant formula for pre-term infants, at a maximum level of 0.5% (w/w) of total fat 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 Shaanxi's view that these uses of algal oil ($\geq 40\%$ DHA) are GRAS through scientific procedures.

Our use of the term "algal oil ($\geq 40\%$ 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 Shaanxi notes that *Aurantiochytrium* is synonymous with *Schizochytrium*.

² Shaanxi states that algal oil ($\geq 40\%$ DHA) is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.

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 Nutrition Center of Excellence. The Office of Pre-Market Additive Safety (OPMAS) did not consult with ONFL regarding the appropriate common or usual name for “algal oil ($\geq 40\%$ DHA).”

Shaanxi provides information about the identity and composition of algal oil ($\geq 40\%$ DHA), which is described as a yellow to light-yellow liquid produced from the microalgae *A. limacinum* H Sc-01. Algal oil ($\geq 40\%$ DHA) consists of a mixture of triglycerides, with DHA as the predominant fatty acid (on average 44.3% of total fatty acids) and the other major fatty acids being palmitic acid (15.1%), docosapentaenoic acid (DPA) (11.9%), and linoleic acid (8.0%). Minor fatty acids include oleic acid (2.2%), stearic acid (1.2%), pentadecanoic acid (1.0%), and other fatty acids present at levels $< 1\%$, including EPA (0.4%) and ARA (0.07%). Shaanxi states that all fatty acids that were detected are well known and present in the diet from vegetable and animal sources.

Shaanxi describes the production organism used in the manufacture of algal oil ($\geq 40\%$ DHA). Shaanxi states that *A. limacinum* H Sc-01 is non-pathogenic and non-toxicogenic and is deposited in the China General Microbiological Culture Collection Center (CGMCC) under the deposition number CGMCC No. 27700. Shaanxi concludes that the identity is similar to *A. limacinum* G3 described in GRN 000913,³ based on a 99.2% similarity in 18s rRNA sequence.

Shaanxi describes the method of manufacture for algal oil ($\geq 40\%$ DHA) and states that the crude algal oil is obtained from a culture of *A. limacinum* H Sc-01 grown under controlled conditions in a medium composed of yeast extract, glucose, and minerals. Following fermentation, the *A. limacinum* H Sc-01 cells are enzymatically disrupted using an alkaline protease that meets 21 CFR 184.1027⁴ to release the oil. The crude algal oil is separated and recovered from the biomass by centrifugation. The oil is then degummed, neutralized, bleached with activated carbon and bentonite clay, filtered, optionally winterized, deodorized under vacuum, cooled, and filtered. Shaanxi states that tocopherol is then added to prevent oxidation, and the refined algal oil is optionally filtered before being packaged under nitrogen. Shaanxi states that algal oil ($\geq 40\%$ DHA) is produced in accordance with current good manufacturing practices and that all processing aids, components, and food contact materials are food-grade and comply with applicable U.S. regulations, are GRAS for their intended use, or are the subject of an effective food contact notification.

³ Algal oil (minimum 35% docosahexaenoic acid) from *Aurantiochytrium limacinum* strain G3 was the subject of GRN 000913. We evaluated this notice and responded in a letter dated November 10, 2020, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

⁴ Shaanxi states that the alkaline protease preparation is produced by *Bacillus licheniformis*, a non-toxicogenic and non-pathogenic organism. Shaanxi further states that the enzyme is food-grade and meets the specifications for enzyme preparations in the Food Chemicals Codex and the General Specifications and Considerations for Enzyme Preparations Used in Food Processing established by the FAO/WHO Joint Expert Committee on Food Additives (JECFA, 2006).

Shaanxi provides specifications for algal oil ($\geq 40\%$ DHA) that include content of DHA ($\geq 40.0\%$), as well as limits for EPA ($\leq 3.9\%$), ARA ($\leq 1.3\%$), DPA ($\leq 16.5\%$), dihomo-gamma-linolenic acid ($\leq 2.8\%$), peroxide value (≤ 5.0 milliequivalents/kg), acid value (≤ 0.5 mg potassium hydroxide/g), anisidine value (≤ 20.0), total oxidation value (≤ 26.0), unsaponifiable matter ($\leq 3.5\%$), insoluble impurities ($\leq 0.2\%$), moisture ($\leq 0.1\%$), *trans* fatty acids ($\leq 1.0\%$), free fatty acids ($\leq 0.4\%$), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), lead (≤ 0.1 mg/kg), mercury (≤ 0.04 mg/kg), and microorganisms, including *Cronobacter* sp. (absent in 25 g), *Salmonella* serovars (absent in 25 g), and *Listeria monocytogenes* (absent in 25 g). Shaanxi provides the results of three non-consecutive batch analyses to demonstrate that algal oil ($\geq 40\%$ DHA) can be produced to meet these specifications.

Shaanxi discusses the stability of algal oil ($\geq 40\%$ DHA), notes that the studies on the stability of other DHA-containing algal oils are provided in previous GRAS notices, and concludes that these studies demonstrate algal oil is stable for up to 36 months under frozen conditions and 12 months under refrigerated conditions. In addition, Shaanxi provides the results of studies conducted with three non-consecutive batches of algal oil ($\geq 40\%$ DHA) stored at -20 °C, 5 °C, and 25 °C and 60% relative humidity for six months, concluding that algal oil ($\geq 40\%$ DHA) is stable under the conditions tested. Shaanxi concludes that the stability of algal oil ($\geq 40\%$ DHA) is expected to be similar to the stability of the other algal oils on the market.

Shaanxi discusses the dietary exposure to DHA from algal oil ($\geq 40\%$ DHA) based on the food categories in 21 CFR 184.1472(a)(3) and use levels calculated for a content of 40% DHA in algal oil. These are then adjusted such that the resulting dietary exposure to DHA will not exceed 1.5 g/p/d, which corresponds to approximately 50% of the total estimated dietary exposure to DHA plus EPA from menhaden oil. Shaanxi states that the intended uses of algal oil ($\geq 40\%$ DHA) are substitutional for other DHA-containing oils currently used in foods; therefore, the cumulative dietary exposure to DHA is not expected to change.

Shaanxi estimates the dietary exposure to DHA from the use of algal oil ($\geq 40\%$ DHA) in infant formula for term infants based on published estimates of the mean and 90th percentile energy requirements of infants and infant body weights, the maximum fat content of infant formula per 21 CFR 107.100 (6 g fat/100 kcal), and the maximum intended use level of algal oil ($\geq 40\%$ DHA). Shaanxi estimates the mean dietary exposure to DHA for male term infants to be approximately 120 to 220 mg/p/d (30 to 40 mg/kg body weight (bw)/d) and the 90th percentile dietary exposure to be 140 to 270 mg/p/d (30 to 40 mg/kg bw/d). Shaanxi estimates the dietary exposure to DHA for female infants that are similar on a body weight basis and slightly lower on a per person basis due to their lower daily caloric intakes and median body weights.

Shaanxi estimates the dietary exposure to DHA from the use of algal oil ($\geq 40\%$ DHA) in infant formula for pre-term infants based on published estimates of the maximum energy requirements of low birth weight, very low birth weight, and extremely low birth weight premature infants and infant body weights, the maximum fat content of infant formula per 21 CFR 107.100 (6 g fat/100 kcal), and the maximum intended use level of

algal oil ($\geq 40\%$ DHA). Shaanxi estimates the maximum dietary exposure to DHA to be 112.5 mg/p/d, 67.5 mg/p/d, and 45 mg/p/d for low birth weight, very low birth weight, and extremely low birth weight premature infants, respectively.

Shaanxi discusses data and information used to support the safe use of algal oil ($\geq 40\%$ DHA) from prior GRNs for similar substances or from an updated literature search conducted through April 30, 2025. Shaanxi states that algal oil ($\geq 40\%$ DHA) is quantitatively and qualitatively equivalent to the *Schizochytrium* sp.- derived algal oil that is the subject of GRN 000677⁵ by comparing the fatty acid and sterol contents to support this conclusion.

Shaanxi incorporates into the notice published safety data and information, including mutagenicity and genotoxicity, clinical and epidemiological, and acute, sub-chronic, chronic, and developmental toxicity studies in rats discussed in GRNs 000677 and 000913. Shaanxi notes that the metabolic fate of dietary DHA is well understood and similar to other dietary fatty acids. From these data, Shaanxi concludes that *Schizochytrium* sp.-derived algal oils are neither genotoxic nor toxigenic and are well tolerated in test animals at doses up to a nominal feed concentration of 50,000 ppm (equivalent to $\sim 3,305$ mg/kg bw/d in males).

Shaanxi states that two studies were conducted in term infants using infant formula supplemented with *Schizochytrium* sp.-derived DHA-rich oil, which have been extensively discussed in GRNs 000731 and 000776.⁶ Shaanxi states that in these studies, no adverse effects were observed, including growth parameters in the study participants, and concludes that the test articles were safe and well tolerated. Shaanxi also notes that, while there are no published clinical studies conducted in pre-term infants with formulas containing *Schizochytrium* sp.-derived algal oils, refined DHA oil from a number of sources, including *Schizochytrium* sp., was previously reviewed as part of GRNs 000326, 000553, 000677, 000933, and 001008⁷ in support of the safe use of *Schizochytrium* sp.-derived algal oils in this subpopulation.

Based on the totality of the data and information, Shaanxi concludes that algal oil ($\geq 40\%$ DHA) is GRAS for its intended use.

⁵ Algal oil derived from *Schizochytrium* sp. strain ONC-T18 was the subject of GRN 000677. We evaluated this notice and responded in a letter dated May 2, 2017, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

⁶ Algal oil from *Schizochytrium* sp. strain LU310 and algal oil (35% docosahexaenoic acid) from *Schizochytrium* sp. strain FCC-1324 were the subjects of GRNs 000731 and 000776, respectively. We evaluated these notices and responded in letters dated April 6, 2018, and October 26, 2018, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

⁷ Arachidonic acid-rich oil from *M. alpina* strain I₄₉-N₁₈, algal oil derived from *Schizochytrium* sp., algal oil ($\geq 36\%$ docosahexaenoic acid) from *Schizochytrium* sp. strain DHF, and algal oil ($\geq 45\%$ docosahexaenoic acid) from *Aurantiochytrium limacinum* TKD-1 were the subjects of GRNs 000326, 000553, 000933, and 001008, respectively. We evaluated these notices and responded in letters dated February 16, 2011, June 19, 2015, November 13, 2020, and February 25, 2022, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, Shaanxi states its intention to use algal oil ($\geq 40\%$ 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). If products containing algal oil ($\geq 40\%$ DHA) 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. OPMAS 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, Shaanxi describes algal oil ($\geq 40\%$ DHA) as a yellow to light-yellow liquid. As such, the use of algal oil ($\geq 40\%$ 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 001236 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 OPMAS.

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 Shaanxi's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing algal oil ($\geq 40\%$ DHA) to make the submission required by section 412. Infant formulas are the purview of the Office of Critical Foods in the Nutrition Center of Excellence.

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 Shaanxi's notice concluding that algal oil ($\geq 40\%$ 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 ($\geq 40\%$ DHA). Accordingly, our response should not be construed to be a statement that foods containing algal oil ($\geq 40\%$ DHA), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Shaanxi provided, as well as other information available to FDA, we have no questions at this time regarding Shaanxi's conclusion that algal oil ($\geq 40\%$ DHA) is GRAS under its intended conditions of use. This letter is not an affirmation that algal oil ($\geq 40\%$ 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 001236 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

 Digitally signed by Susan J. Carlson -S
Date: 2025.06.10 17:01:33 -04'00'

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