Claire L. Kruger, PhD, DABT
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Re: GRAS Notice No. GRN 000934

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000934 that you submitted on behalf of CABIO Biotech (Wuhan) Co., Ltd (CABIO). We received this notice on April 21, 2020 and filed it on July 20, 2020. CABIO submitted amendments to the notice on August 7, 2020, October 14, 2020, November 11, 2020, March 2, 2021, March 10, 2021 and June 4, 2021 that clarified the identity, composition, intended uses, production organism, manufacturing process, and stability of the ingredient, and amended fatty acid and microbial specifications.

The subject of the notice is algal oil from *Schizochytrium* sp. strain CABIO-A-2 containing ≥35% docosahexaenoic acid (algal oil (≥35% DHA)), for use as an ingredient in the food categories listed in 21 CFR 184.1472(a)(3) (Menhaden oil) at levels up to 29% of the levels specified, excluding products under USDA jurisdiction, and as the sole added source of DHA in any given food category so that the total dietary exposure to DHA will be no more than 1.5 g/person (p)/day (d). CABIO also intends to use algal oil (≥35% DHA) as an ingredient in cow milk- and soy-based, non-exempt infant formula for 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 DHA to ARA. The notice informs us of CABIO'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 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 (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "algal oil (≥35% DHA)."

CABIO describes the identity of algal oil (≥35% DHA). CABIO states that algal oil (≥35% DHA) has a color from light yellow to orange yellow and is composed predominantly of triglycerides (95%), with minor amounts of diglycerides (3%) and monoglycerides (1%). DHA (22:6 n-3) is the major fatty acid; other fatty acids present in algal oil include myristic (14:0), palmitic (16:0), docosapentaenoic (22:5 n-6), and oleic (18:1 n-9) acid.[1] CABIO notes the similarity of its algal oil to other *Schizochytrium* sp. algal oils (e.g., GRN 000553)[2] that have been determined to be GRAS for the intended uses.

CABIO describes the method of manufacture for algal oil (≥35% DHA) produced via fermentation of a pure culture of the marine alga *Schizochytrium* sp. strain CABIO-A-2 under controlled conditions. CABIO states that *Schizochytrium* sp. strain CABIO-A-2 is non-pathogenic and non-toxigenic. Following fermentation, the algal biomass is treated with a protease[3] to release the crude algal oil. The protease is heat inactivated and the crude algal oil is separated from the biomass by hexane extraction and centrifugation. Crude oil is stored up to 24 months in nitrogen-flushed, high density polyethylene (HDPE) containers at temperatures held at -18 to -13 °C. Crude algal oil is then refined using standard procedures of degumming, bleaching, and deodorization. The refined algal oil may optionally undergo winterization. The resulting algal oil (≥35% DHA) is treated with ascorbyl palmitate, α-tocopherol, lecithin and sunflower oil, and packaged in nitrogen flushed HDPE drums or heat-sealed food grade aluminum bags and stored at temperatures ranging from -18 to -13 °C. CABIO states that the manufacture of algal oil (≥35% DHA) is consistent with current good manufacturing practices (cGMP) and that the processing aids and food contact materials used are food-grade and compliant with applicable U.S. regulations for use in food.

CABIO provides the following specifications for algal oil (≥35% DHA), expressed on a weight percent basis: DHA (≥35.0%), eicosapentaenoic acid (EPA) (≤3.0%), acid value (≤0.5 mg KOH/g),peroxide value (≤5 meq/kg), moisture (≤0.05%), unsaponifiable matter (≤3.5%), trans fatty acid (≤1.0%), total arsenic (≤0.1 mg/kg), cadmium (≤0.1 mg/kg), copper (≤0.05 mg/kg), iron (≤0.2 mg/kg), mercury (≤0.04 mg/kg), lead (≤0.1 mg/kg), and limits for microbes, including *Salmonella* serovars (negative in 25 g) and *Cronobacter* sp. (negative in 10 g). CABIO also provides data on the fatty acid composition of algal oil (≥35% DHA), and sterol content (approximately 1%). CABIO identifies the major sterols as cholesterol and stigmasterol, noting these are similar to the sterol profile observed for other *Schizochytrium* sp. oils. CABIO provides the results from three non-consecutive batches to demonstrate that the algal oil (≥35% DHA) can be produced to meet the stated specifications.

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[1] CABIO compares its oil to the Food Chemicals Codex (FCC, ed. 12) monograph for "DHA from algal (*Schizochytrium*) oil" noting that, while differences in fatty acid composition were observed between its algal oil (≥35%) and the FCC monograph, these differences do not affect the safety of the notified ingredient.

[2] Algal oil (40% DHA) derived from *Schizochytrium* sp. was the subject of GRN 000553. We evaluated this notice and responded in a letter dated June 19, 2015, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

[3] CABIO confirms that the protease is subtilisin (EC 3.4.21.62) from *Bacillus longiformis*. CABIO further states this enzyme is GRAS for its intended use and meets the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and FCC specifications for enzymes used in food. CABIO states that the protease is not expected to be present in the refined oil.

CABIO states that the intended uses of its algal oil (≥35% DHA) are substitutional for other DHA-containing algal oils. CABIO estimates the dietary exposure to DHA from the intended use of algal oil (≥35% DHA) in conventional food in relation to food categories and limits for DHA and EPA specified in 21 CFR 184.1472(a)(3). CABIO incorporates the estimated dietary exposure outlined in GRN 000137[4] and states that the estimated mean dietary exposure to DHA, for ages 2 years and above, from the intended uses of algal oil (≥35% DHA) in menhaden oil foods, is 1.5 g/p/d of DHA.

CABIO also estimates the dietary exposure to algal oil (≥35% DHA) from the intended use in infant formula using the assumption that infants consume about 100 to 120 kcal/kg body weight (bw)/day of infant formula, of which 50% is fat. CABIO states this consumption corresponds to about 5.6 to 6.7 g of fat/kg bw/d and estimates a dietary exposure of 27 to 33 mg/kg bw/d to DHA at the maximum use level of 0.5% (w/w) of total fat as DHA.

CABIO indicates that an updated literature search was conducted through January 2020 and describes unpublished and published toxicological studies supporting the safety of algal oil (≥35% DHA), including safety studies that investigated the DHA oil. CABIO indicates that DHA oils are triglycerides, which occur in phospholipids in breast milk and the absorption, distribution, metabolism, and elimination of triglyceride oils are widely known in the scientific community and represent the primary source of dietary lipid for humans. CABIO states that their intended use is identical to the uses for other GRAS algal oils containing similar concentrations of DHA.

CABIO cites several published studies that include acute, sub-chronic, developmental, and reproductive toxicity studies in rats, piglets, and rabbits fed whole cell biomass and algal oil (≥35% DHA) from *Schizochytrium* sp. Collectively, these studies showed no adverse effects. CABIO discusses a published study that examined the developmental and reproductive effects of orally administered DHA oil from *Schizochytrium* sp., as well as the combined effects of orally administered DHA oil from *Schizochytrium* sp. and ARA oil from *Mortierella alpina* up to 5,000 mg/kg bw/day in rats. There were no toxic effects on implantation, number of corpora lutea, fetal viability, fetal weight, and sex ratio. CABIO states that there were no adverse effects observed up to a dose of 5,000 mg/kg bw/day.

Furthermore, based on the unpublished toxicology studies in mice and rats with algal oil (≥35% DHA) derived from S*chizochytrium* sp., CABIO concludes that algal oil (≥35% DHA) derived from *Schizochytrium* sp. did not show any adverse effects, thereby corroborating the safety conclusion derived from the published studies of DHA oil. Additionally, CABIO states that DHA-containing fish and marine-algal oil (*Crypthecodinium cohnii* and *Schizochytrium* sp.) did not display any adverse effects in pre-term, term, and adults based on the published clinical trials cited in GRN 000553

[4] Algal oil (*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 the notifier's GRAS conclusion.

and in the current GRN (000934), thereby underscoring the safety of consumption of DHA containing oils.

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

Standards of Identity

In the notice, CABIO states its intention to use algal oil (≥35% DHA) 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). If products containing algal oil (≥35% 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 in CFSAN. 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 amendment to the notice, CABIO notes that algal oil (≥35% DHA) color is light yellow to orange yellow. As such, the use 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 000934 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 the 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 CABIO's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing algal oil (≥35% DHA) to make the submission required by section 412. Infant formulas are the purview of ONFL in CFSAN.

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 CABIO'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 CABIO provided, as well as other information available to FDA, we have no questions at this time regarding CABIO'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 000934 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.07.20 13:51:24 -04'00'

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