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

Re: GRAS Notice No. GRN 000933

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000933. We received the notice that you submitted on behalf of Hubei Fuxing BioTechnology, Co., Ltd. (Hubei Fuxing) on April 20, 2020, and filed it on July 21, 2020. Hubei Fuxing submitted amendments to the notice on October 6, 2020, October 9, 2020, and November 13, 2020, that clarified the manufacturing, dietary exposure, specifications, and cited studies.

The subject of the notice is algal oil (≥36% docosahexaenoic acid) from *Schizochytrium* sp. strain DHF (algal oil (≥36% DHA)) for use as an ingredient in the same food categories as those currently listed in 21 CFR 184.1472(a)(3) (Menhaden oil),[1] at use levels of algal oil (≥36% DHA) that are no more than 27.78% of the levels specified for menhaden oil in that regulation, 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 total dietary exposure to DHA will be no more than 1.5 g/person (p)/day (d) and no more than 3.0 g/p/d of DHA and EPA combined. Hubei Fuxing also intends to use algal oil (≥36% DHA) as an ingredient in cow milk-, soy-, amino acid-, and extensively hydrolyzed protein-based, exempt and non-exempt infant formula for pre-term, low birth weight, and term infants at a maximum level of 0.5% 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 Hubei Fuxing's view that this use of algal oil (≥36% DHA) is GRAS through scientific procedures.

Our use of the term "algal oil (≥36% 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

[1] Hubei Fuxing states that algal oil (≥36% DHA) is not intended for use in products under the U.S. Department of Agriculture's jurisdiction or in products defined in 21 CFR 170.3(n)(13).

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 (≥36% DHA)."

Hubei Fuxing provides information on the identity and composition of algal oil (≥36% DHA), which is described as a free flowing, yellow oil consisting of a mixture of triglycerides where the predominant fatty acid is DHA at ≥36%. Hubei Fuxing states that algal oil (≥36% DHA) also contains the fatty acids palmitic acid (C16:0) and docosapentaenoic acid (C22:5 n-6) at approximately 26% and 9%, respectively. Hubei Fuxing states that the fatty acids that are present in algal oil (≥36% DHA) are common to the diet from other food sources.

Hubei Fuxing describes the method of manufacture for algal oil (≥36% DHA), which is obtained through fermentation of a pure culture of the marine alga *Schizochytrium sp.* strain DHF under controlled conditions.[2,3] Following fermentation, the cell walls are enzymatically lysed,[4] and the crude algal oil is separated from the fermentation biomass by disc centrifugation. The crude algal oil is degummed, deacidified, decolorized, filtered, and deodorized. Lastly, antioxidants are added to the algal oil (≥36% DHA) before packaging under nitrogen. Hubei Fuxing states that all growth media, raw materials, and processing aids are food-grade and meet applicable regulations for use in food in the United States.

Hubei Fuxing provides specifications for algal oil (≥36% DHA) that include DHA (≥36%) and limits for acid value (≤0.8 mg KOH/g), free fatty acids (≤0.4% as oleic acid), trans fatty acids (≤1.0%), unsaponifiable matter (≤3.0%), lead (≤0.1 mg/kg), as well as limits on microorganisms, including *Salmonella* serovars (negative in 25 g) and *Cronobacter* sp. (negative in 10 g). Hubei Fuxing provides the results of five non-consecutive batch analyses to demonstrate that algal oil (≥36% DHA) can be manufactured to meet these specifications. Hubei Fuxing states that algal oil (≥36% DHA) is stable for up to 1 year under nitrogen at -25 °C and away from light.

Hubei Fuxing estimates the dietary exposure to DHA from the intended use of algal oil (≥36% DHA) in relation to limits for DHA and EPA specified in 21 CFR 184.1472(a)(3) and GRN 000137.[5] Hubei Fuxing states that the intended use of algal oil (≥36% DHA) is substitutional for other DHA-containing oils on the market; therefore, they do not expect the dietary exposure to DHA to change.

Hubei Fuxing also estimates the dietary exposure to DHA from the intended use in infant formula using the assumption that infants consume 100 to 120 kcal/kg body

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[2] Hubei Fuxing states that the organism was identified as strain DHF by the China Center for Type Culture Collection (CCTCC).
[3] Hubei Fuxing states that *Schizochytrium* sp. strain DHF is non-pathogenic and non-toxigenic.
[4] The enzyme is heat deactivated during the decolorization/deodorization process.
[5] 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.

weight (bw)/d of infant formula, of which ~50% is fat (50-60 kcal/kg bw/d of fat). Hubei Fuxing states that this consumption corresponds to approximately 5.5 to 6.7 g fat/kg bw/d. At a use level of 0.5% total fat as DHA, Hubei Fuxing estimates the dietary exposure to DHA from the use of algal oil (≥36% DHA) for infants to be 27 to 33 mg/kg bw/d.

Hubei Fuxing discusses the safety of algal oil (≥36% DHA) and indicates that an updated literature search was conducted through August 2020. Hubei Fuxing summarizes the results of four published subchronic toxicity studies in rats, one published subchronic toxicity study in pigs, two published combined subchronic and reproductive and/or developmental toxicity studies in rats, four published reproductive and/or developmental toxicity studies in rats, and one published developmental toxicity study in rabbits that received either DHA-rich algal oil or DHA-rich microalgae (DRM). No treatment-related adverse effects were reported at doses up to 5 g DHA-rich algal oil/kg bw/d and 4 g DRM/kg bw/d in rats in the subchronic toxicity studies. No developmental toxicity was reported at doses up to 5 g DHA-rich algal oil/kg bw/d and 21.7 g DRM/kg bw/d in rats and 1.8 g DRM/kg bw/d in rabbits. Furthermore, Hubei Fuxing summarizes multiple published and unpublished *in vitro* and *in vivo* genotoxicity and mutagenicity studies and states that algal oil (≥36% DHA) is neither mutagenic nor genotoxic.

To further support safety, Hubei Fuxing summarizes clinical studies in adults, children, pregnant women and their offspring, and preterm and term infants. Hubei Fuxing states that based on the review of human clinical studies, the intake of DHA is safe as long as the daily intake does not exceed 1.5 g/p/d in adults. Additionally, Hubei Fuxing states that no adverse effects of DHA in infant formula at up to 0.96% of total fatty acids (51-61 mg DHA/kg bw/d) were reported.

Hubei Fuxing includes the statement of a panel of individuals (Hubei Fuxing's GRAS panel). Based on its review, Hubei Fuxing's GRAS panel concluded that algal oil (≥36% DHA) is safe under the conditions of its intended use.

Based on the totality of the data and information in the notice, Hubei Fuxing concludes that algal oil (≥36% DHA) is GRAS under the intended conditions of use.

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 (≥36% 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 the 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Hubei Fuxing describes algal oil (≥36% DHA) as a yellow oil. As such, the use of algal oil (≥36% 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 000933 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.

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 Hubei Fuxing's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing algal oil (≥36% DHA) 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 Hubei Fuxing's notice concluding that algal oil (≥36% 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 (≥36% DHA). Accordingly, our response should not be construed to be a statement that foods containing algal oil (≥36% DHA), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Hubei Fuxing provided, as well as other information available to FDA, we have no questions at this time regarding Hubei Fuxing's conclusion that algal oil (≥36% DHA) is GRAS under its intended conditions of use. This letter is not an affirmation that algal oil (≥36% 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 000933 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.11.13 16:44:26 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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