Dietrich B. Conze, Ph.D.
Spherix Consulting Group, Inc.
751 Rockville Pike Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 001008

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001008. We received the notice that you submitted on behalf of ATK Biotech Co., Ltd[1] (ATK Biotech) on May 10, 2021, and filed it on July 28, 2021. ATK Biotech submitted an amendment to the notice on November 3, 2021, January 3, 2022, and February 3, 2022, that clarified the intended use, manufacturing, specifications, dietary exposure, and the safety narrative.

The subject of the notice is algal oil (≥45% docosahexaenoic acid) from *Aurantiochytrium limacinum*[2] TKD-1 (algal oil (≥45% DHA)) for use as an ingredient in the same food categories as those listed in 21 CFR 184.1472(a)(3) (Menhaden oil)[3] at use levels that are no more than 18% of the levels specified for menhaden oil in that regulation. ATK Biotech states that if algal oil (≥45% DHA) is blended with another source of DHA or eicosapentaenoic acid (EPA), the levels will be 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 (≥45% DHA) also will be used as an ingredient in cow milk- and soy-based, non-exempt and exempt infant formula for term and pre-term infants, respectively, 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 ATK Biotech's view that these uses of algal oil (≥45% DHA) are GRAS through scientific procedures.

Our use of the term, "algal oil (≥45% 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. The Office of Food

[1] We received an update on July 27, 2021, that TK Biohealth Co., Ltd. changed to ATK Biotech, Co., Ltd.
[2] ATK Biotech states that *Schizochytrium limacinum* was reclassified as *A. limacinum*.
[3] ATK Biotech states that algal oil (≥45% DHA) is not intended for use in fish products and other products under the U.S. Department of Agriculture's jurisdiction.

Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "algal oil (≥45% DHA)."

ATK Biotech provides information about the identity and composition of algal oil (≥45% DHA), which is described as a light yellow to orange yellow liquid produced from the microalgae *A. limacinum* TKD-1. ATK Biotech states that algal oil (≥45% DHA) consists of a mixture of triglycerides where the predominant fatty acid is DHA (on average ~57% of total fatty acids). The other major fatty acids are palmitic acid (16-18%) and n-6 docosapentaenoic acid (13-15%). Minor fatty acids include arachidonic and eicosapentaenoic (≤1% each), linoleic (0.04-4%), 0leic (0.3-3%), and myristic, palmitoleic, stearic, behenic, and dihomo-gamma-linolenic (<1% each). ATK Biotech states that all fatty acids that were detected are well known and present in the diet from vegetable and animal sources.

ATK Biotech describes the production organism used in the manufacture of algal oil (≥45% DHA). ATK Biotech states that *A. limacinum* TKD-1 is non-pathogenic and non-toxigenic and is deposited in the China Center for Type Culture Collection with the deposition number M2020378.

ATK Biotech describes the method of manufacture for algal oil (≥45% DHA). Crude algal oil is obtained from a pure culture of *A. limacinum* TKD-1 grown under controlled conditions. Following fermentation, the *A. limacinum* TKD-1 cells are enzymatically disrupted to release the oil.[4] The crude algal oil is separated and recovered from the biomass by centrifugation. The oil is then degummed, neutralized, bleached with activated bentonite clay, and steam deodorized. ATK Biotech states that antioxidants (e.g., mixed tocopherols) and sunflower oil (optional) are added to stabilize and standardize the algal oil. The refined algal oil is filtered and packaged under nitrogen until use. ATK Biotech states that algal oil (≥45% DHA) is produced in accordance with current good manufacturing practices, processing aids and formulation ingredients are food-grade, and filtration materials comply with applicable U.S. regulations.

ATK Biotech provides specifications for algal oil (≥45% DHA) that include content of DHA (45-70%) and n-6 docosapentaenoic acid (10-20%), as well as limits for unsaponifiables (≤3.5%) and microorganisms, including *Cronobacter sakazakii* (negative in 10 g) and *Salmonella* serovars (negative in 25 g). Limits for anisidine value, free fatty acids, peroxide value, arsenic, lead, and mercury that meet the specifications for "DHA algal (*Schizochytrium*) oil" in the FCC 12 monograph (FCC 12, 2021) are also provided. ATK Biotech provides the results of five non-consecutive batch analyses to demonstrate that algal oil (≥45% DHA) can be produced to meet these specifications. Based on the results of stability studies, ATK Biotech concludes that algal oil (≥45% DHA) is stable for a minimum of 18 months at 4 °C and 24 months at ≤-18 °C.

[4] ATK Biotech states that the enzyme is a protease preparation produced by *Bacillus licheniformis*, a non-pathogenic and non-toxigenic organism. ATK Biotech further states that the enzyme is food-grade and meets the specifications for enzyme preparations in the Food Chemicals Codex 12th Edition (FCC 12, 2021) and the General Specification and Considerations for Enzyme Preparations Used in Food Processing established by the FAO/WHO Joint Expert Committee on Food Additives (JECFA, 2006).

ATK Biotech discusses the dietary exposure to DHA from algal oil (≥45% DHA) based on the food categories in 21 CFR 184.1472(a)(3) at levels providing not more than 1.5 g/p/d DHA, which corresponds to ~50% of the total estimated dietary exposure to DHA plus EPA from menhaden oil. ATK Biotech states that the intended uses of algal oil (≥45% DHA) are substitutional for other DHA-containing oils currently used in foods; therefore, the dietary exposure to DHA is not expected to change. ATK Biotech bases its use levels on the mean content (57%) of DHA in algal oil (≥45% DHA), but states that if higher levels of DHA are present, the use levels would be reduced accordingly to provide an estimated dietary exposure of ≤1.5 g/p/d DHA.

ATK Biotech provides a dietary exposure estimate to DHA from the use of algal oil (≥45% DHA) in infant formula for term and pre-term infants. Based on the assumptions that infants consume 100 to 120 kcal/kg body weight (bw)/d, of which ~50% is fat, ATK Biotech notes that infants consume about 50 to 60 kcal fat/kg bw/d, which corresponds to ~5.5 to 6.7 g fat/kg bw/d. Based on a maximum use level of 0.5% total fat as DHA, ATK Biotech estimates the dietary exposure to DHA for infants to be 27 to 33 mg/kg bw/d. Based on the levels of DHA in algal oil (≥45% DHA) ranging from 53 to 62%, per batch analyses, ATK Biotech estimates the dietary exposure to algal oil (≥45% DHA) to be 43 to 62 mg/kg bw/d.

ATK Biotech discusses data and information to support the safe use of algal oil (≥45% DHA) and indicates that a literature search conducted through March 2021 did not identify any safety concerns. ATK incorporates information from various GRNs for long-chain polyunsaturated fatty acid-containing oils.[5] ATK Biotech states that algal oil (≥45% DHA) is quantitatively and qualitatively equivalent to the *Schizochytrium* sp.-derived algal oil that is the subject of GRN 000677 and compares the fatty acid and sterol profiles between the two ingredients. ATK Biotech notes that the fatty acid levels (other than DHA) and sterols either approximate or are less than those from GRN 000677. Therefore, ATK Biotech incorporates into the notice published genotoxicity, acute, sub-chronic, and developmental toxicity studies from GRN 000677, as well as safety studies from GRNs 000137, 000553, and 000731 that use DHA-containing oils derived from other strains of *Schizochytrium* sp. and *Schizochytrium* sp. biomass. ATK Biotech concludes that DHA-containing oils derived from *Schizochytrium* sp. are neither genotoxic nor toxigenic.

ATK Biotech discusses new clinical studies and incorporates into the notice published clinical studies from prior notices to support the safe use of algal oil (≥45% DHA) in term infants (GRNs 000731 and 000776), pre-term infants (GRNs 000326, 000379, 000553, and 000677), and children and adults (GRNs 000836 and 000934). ATK Biotech concludes that *Schizochytrium* sp.-derived DHA-containing oils are well-tolerated in term and pre-term infants, children, and adults.

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[5] Long-chain polyunsaturated fatty acid-containing oils were the subjects of GRNs 000137, 000326, 000379, 000553, 000677, 000731, 000776, 000836, and 000934. We evaluated these notices and responded in letters stating that we had no questions at that time regarding the notifiers' GRAS conclusions. These letters are available on our GRAS Notice inventory at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices.

Based on the totality of the data and information, ATK Biotech concludes that algal oil (≥45% DHA) is GRAS for its intended 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 (≥45% 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. 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, ATK Biotech describes algal oil (≥45% DHA) as a light yellow to orange yellow oil. As such, the use of algal oil (≥45% 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 001008 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 ATK Biotech's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing algal oil (≥45% 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 ATK Biotech's notice concluding that algal oil (≥45% 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 (≥45% DHA). Accordingly, our response should not be construed to be a statement that foods containing algal oil (≥45% DHA), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that ATK Biotech provided, as well as other information available to FDA, we have no questions at this time regarding ATK Biotech's conclusion that algal oil (≥45% DHA) is GRAS under its intended conditions of use. This letter is not an affirmation that algal oil (≥45% 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 001008 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.02.25 18:02:10 -05'00'

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