Donald F. Schmitt, MPH
ToxStrategies, Inc.
931 W. 75th St., Suite 137, PMB 255
Naperville, IL 60565

Re: GRAS Notice No. GRN 000862

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000862. We received the notice that you submitted on behalf of BASF Corporation (BASF) on May 15, 2019, and filed it on July 22, 2019. We received amendments on September 27, 2019, October 31, 2019, December 11, 2019, January 22, 2020, May 6, 2020, and May 26, 2020 that provide clarifying information on the production strain, the method of manufacture, batch analyses, stability, specifications, use level in meat and poultry, dietary exposure, and narrative. We received an amendment to the notice on October 31, 2019, that modifies the scope of the intended use by excluding use of the powder formulation in products under USDA jurisdiction.

The subject of the notice is algal oil from *Schizochytrium* sp. strain ONC-T18 (algal oil) as an oil formulation (40% docosahexaenoic acid (DHA)) or as a powder formulation (10% DHA). For clarity, in the remainder of this letter, we use the term "algal oil" to denote both the oil formulation and the powder formulation and include the term "formulation" to denote the specific formulation. Algal oil is intended for use in milk- and soy based non-exempt infant formula for term infants and milk- and soy based exempt infant formula for pre-term infants at levels up to 0.5% (w/w) of total fat as DHA with the provision that algal oil will be used in infant formula 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 oil formulation is intended for use in the food categories listed in 21 CFR 184.1472(a)(3) at up to 25% of the levels specified and the powder formulation is intended for use in the food categories listed in 21 CFR 184.1472(a)(3), excluding those products under USDA jurisdiction, at up to 100% of the levels specified; and, with the provision that if algal oil 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)/day (d) and no more than 3.0 g/p/d of DHA and EPA combined. The notice informs us of BASF's view that these uses of algal oil are GRAS, through scientific procedures.

Our use of the term "algal oil" 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 Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "algal oil."

BASF provides information about the identity and composition of algal oil. BASF describes it as a yellow to orange colored liquid that is produced from the microalgae *Schizochytrium* sp. strain ONC-T18. BASF states that algal oil consists of a mixture of triglycerides in which the predominant fatty acid is DHA (approximately 40% when as the oil formulation; 10% when as the powder formulation). BASF states that the fatty acid profile of algal oil includes myristic acid (14:0), palmitic acid (16:0), docosapentaenoic acid (22:5 n-6), and oleic and vaccenic acids (sum 18:1). BASF states that all fatty acids are well-known components of the human diet and are found in both animal- and vegetable-based food sources.

BASF provides a description of the manufacturing for algal oil and cites the source to be the crude algal oil produced in GRN 000677.[1,2] BASF discusses the taxonomy and safety of *Schizochytrium* sp. strain ONC-T18; *Schizochytrium* sp. is well-characterized in the published literature and has been used for a number of years in the production of DHA algal oils for use in human foods. BASF states that *Schizochytrium* sp. strain ONC-T18 is non-pathogenic and toxin production is unlikely because there are no known reports of toxin production by thraustochytrids, of which *Schizochytrium* is a member. BASF starts the manufacturing with an optional vacuum distillation,[3] and proceeds to bleaching with activated carbon and bleaching earth, and deodorization. The algal oil is packaged under nitrogen until use; alternatively, it may be further processed by microencapsulation using corn starch to produce algal oil powder. BASF lists casein (derived from milk) and soy lecithin among the substances used in this microencapsulation to produce the algal oil powder formulation. To formulate the powder, algal oil is emulsified, homogenized, spray dried, and standardized to 10% DHA. BASF states that algal oil is produced in accordance with current good manufacturing practices and all processing aids and formulation ingredients are food-grade and commonly used in food.

BASF provides specifications for algal oil that include a minimum content of DHA (38% as triglyceride when as the oil formulation; 10% as triglyceride when as the powder formulation) and limits for total *trans* fat (1.0% of fatty acids), unsaponifiables (≤3.5% by weight of oil), arsenic (≤0.1 mg/kg), lead (≤0.1 mg/kg when as the oil formulation; ≤0.02 mg/kg when as the powder formulation) and microorganisms. For the powder formulation, BASF provides additional limits for microorganisms, including

[1] Algal oil with 40% DHA 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.
[2] BASF considers that the subject of GRN 000862 differs from the subject of GRN 000677 in the manufacture (addition of optional distillation step and elimination of optional degumming and winterization steps), specifications (microbiological), composition (concentration of DHA), and inclusion of additional uses in foods listed in 21 CFR 184.1472(a)(3).
[3] The distillation step is optional and will be applied if levels of free fatty acids in the oil exceed 0.5% or levels of unsaponifiables in the oil exceed 3.5%.

Cronobacter sakazakii (negative in 10 g) and *Salmonella* serovars (negative in 25 g). BASF provides specifications that meet Food Chemicals Codex (FCC 11, 2018) specifications. BASF provides results of at least three non-consecutive batch analyses to demonstrate that algal oil can be produced to meet the stated specifications. Based on the results of stability studies, BASF concludes that algal oil is stable for a minimum of 12 months at 2-8 °C and 24 months at ≤ -18 °C.

BASF provides an estimate of dietary exposure to DHA from algal oil for the intended use in infant formula. Based on the assumptions that infants consume 100 to 120 kcal/kg body weight (bw)/d, about 50% of which is fat, BASF notes that infants consume about 50 to 60 kcal fat/kg bw/d, which 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, BASF estimates that the dietary exposure to DHA to be 27 to 33 mg/kg bw/d from algal oil.[4]

BASF discusses estimates of dietary exposure to DHA from algal oil based on the DHA and EPA limits specified in 21 CFR 184.1472(a)(3). BASF states that the intended use is as a substitute for other DHA-containing oils currently used in foods, and therefore BASF does not expect dietary exposure to DHA to change.

BASF states that FDA had no questions about the use of numerous DHA-rich oils from algal and marine sources in infant formula and in food.[5] BASF cites published and unpublished studies from the referenced GRAS notices. Additionally, BASF discusses multiple published studies and states that it performed a literature search through September 2019 to identify any new safety data on DHA and DHA algal oil.

BASF summarizes three published 4-week studies and eight published 13-week studies in rats administered either DHA-rich algal oil, DHA-rich microalgae (DRM), or blends of DHA-rich algal oil and ARA-rich fungal oil (oil blend). BASF states that no treatment-related adverse effects were reported by the study authors at doses up to 5,000 mg DHA-rich algal oil/kg bw/day, 4,000 mg DRM/kg bw/day, and 8,900 mg of oil blend/kg bw/day. Additionally, BASF summarizes the results of six published reproductive and/or developmental toxicity studies in rats administered DHA-rich algal oil or DRM and one published developmental toxicity study in rabbits administered DRM. BASF states that no maternal or developmental toxicity was reported by the study authors in rats at doses up to 11,200 mg DHA-rich algal oil/kg bw/day and 21,700 mg DRM/kg bw/day. BASF notes that, in rabbits, no maternal toxicity was reported by the study authors at doses up to 600 mg DRM/kg bw/day and no developmental toxicity was seen by the study authors at doses up to 1,800 mg DRM/kg bw/day. Furthermore,

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[4] Based on the minimum specified contents of DHA, FDA notes that the estimated dietary exposures to the algal oil as an oil formulation and a powder formulation are equivalent to 71 to 87 mg/kg bw/d, and 270 to 330 mg/kg bw/d, respectively.

[5] BASF lists GRAS notices for DHA-rich oils from algal and marine sources for use in infant formula (GRNs 000041, 000094, 000379, 000553, 000677, 000731, 000776, and 000777) and in food (GRNs 000137, 000138, 000319, and 000732); we evaluated these GRAS notices and responded in letters dated May 17, 2001, April 18, 2006, November 8, 2011, June 19, 2015, May 2, 2017, April 6, 2018, and October 26, 2018 (for infant formula) and in letters dated February 12, 2004, April 20, 2004, August 4, 2010, and April 6, 2018 (for food), stating that we had no questions at that time regarding the notifier's GRAS conclusions.

BASF summarizes multiple published and unpublished *in vitro* and *in vivo* genotoxicity/mutagenicity studies and states that DHA algal oil is neither mutagenic nor genotoxic.

Based on the totality of the data and information presented in its GRAS notice, BASF concludes that algal oil is GRAS under its intended conditions of use.

Standards of Identity

In the notice, BASF states its intention to use algal oil in several food categories, including foods for which standards of identity exist, located in 21 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, and 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 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. The algal oil powder formulation requires labeling under the FD&C Act because it contains protein derived from milk and may contain protein derived from soybeans.

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 BASF'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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, BASF describes algal oil as light yellow to orange in color. As such, the use of algal oil 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 000862 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.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000862, we coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers.

FSIS has advised the following with respect to the statutes it administers:

> FSIS has completed its review and has no objection to the use of algal oil when formulated as the oil in meat (including *Siluriformes* fish products) at maximum use levels of 1.25% by weight and in poultry products at maximum use levels of 0.75% by weight. FSIS further advises that the product categories under the USDA jurisdiction in which the ingredient may be used would be limited if algal oil is found to impart color under the conditions of use.
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> Regarding labeling, FSIS states that the ingredient is required to be listed as "DHA Algal Oil" in the ingredients statement of the products in which it is used.

FSIS requested that we advise you to seek regulatory guidance from its Risk Management and Innovations Staff (RMIS) about the use of algal oil in meat, poultry, and egg products. You should direct such an inquiry to Dr. Melvin Carter, Director, RMIS, Office of Policy and Program Development, FSIS by email at Melvin.Carter@fsis.usda.gov.

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 BASF'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 BASF provided, as well as other information available to FDA, we have no questions at this time regarding BASF'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 000862 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
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Susan Carlson, Ph.D.
Director
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cc: Melvin Carter, Ph.D.
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