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Re: GRAS Notice No. GRN 000677

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000677. We received the notice you submitted on behalf of Mara Renewables Corporation (Mara) on November 1, 2016, and filed it on November 21, 2016. We received amendments to the notice on January 20, 2017, and January 23, 2017. These amendments provide clarification about the intended use, specifications, batch analyses, and the source organism and enzyme preparation involved in the manufacture.

The subject of the notice is algal oil derived from *Schizochytrium* sp. strain ONC-T18 (algal oil). The notice informs FDA of the view of Mara that algal oil is GRAS, through scientific procedures, for use as an ingredient in non-exempt and preterm exempt infant formula,¹ at a maximum level of 0.5% total fat as docosahexaenoic acid (DHA) and in combination with a safe and suitable source of arachidonic acid (ARA). The ratio of DHA to ARA would range from 1:1 to 1:2.

Our use of “algal oil” in this letter should not be considered an endorsement or recommendation of that term as an appropriate common or usual name for the purpose of declaring the substance in the ingredient statement of foods that contain that ingredient. 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.”

Mara provides information about the identity and composition of algal oil. Mara describes algal oil as a yellow to orange-colored, semi-solid to liquid oil that is extracted from the microalgae *Schizochytrium* sp. strain ONC-T18. Mara states that algal oil consists of a mixture of triglycerides, of which the predominant fatty acid is DHA

¹ Mara notes that algal oil is intended for use in both milk- and soy-based infant formula, and that the intended use is substitutional for other sources of DHA.

(>35%). Mara states that DHA is a long chain, polyunsaturated fatty acid, with empirical formula $C_{22}H_{32}O_2$, chemical name 4,7,10,13,16,19-docosahexaenoic acid, and shorthand nomenclature 22:6 n-3. Mara discusses the fatty acid profile of algal oil and states that the major fatty acids other than DHA are myristic acid (14:0), palmitic acid (16:0), docosapentaenoic acid (22:5 n-6), and cis-vaccenic acid (18:1). Mara states that all of the fatty acids detected are well known and present in the diet from vegetable and animal sources.

Mara provides a description of the manufacturing method for algal oil. *Schizochytrium* sp. ONC-T18 is grown under batch fed, axenic fermentation conditions with controlled pH and temperature. Following fermentation, the algal cell walls are enzymatically² disrupted to release the intracellular oil. The crude algal oil is separated and recovered from the algal biomass by centrifugation. Mara states that safe and suitable antioxidants (e.g. mixed tocopherols) may be added to the product. The oil is refined through degumming, bleaching, and deodorization. Mara states that sunflower oil may be added to algal oil as a diluent. Mara states that all reagents and processing aids used in the manufacture of algal oil are food grade and the method is in accordance with current good manufacturing practices.

Mara provides specifications for algal oil that include a minimum content of DHA ($\geq 35\%$), and limits for acid value (< 0.5 mg potassium hydroxide/g), peroxide value (< 5.0 meq/kg), trans-fatty acids ($\leq 2\%$), unsaponifiable matter ($\leq 3.5\%$), moisture ($\leq 0.05\%$), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), copper (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), and iron (≤ 0.2 mg/kg). Mara also provides limits for microbial contaminants, including no detectable *Chronobacter sakazakii* or *Salmonella* in a 25 g sample. Mara provides six non-consecutive batch analyses to demonstrate that algal oil can be produced in accordance with the specifications.

Mara provides estimates of dietary exposure to DHA from algal oil based on the intended use in infant formula and the assumption that infants consume 100 to 120 kcal/kg body weight (bw)/d, about 50% of which is fat. Mara states 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, Mara calculates that the dietary exposure to DHA is 27 to 33 mg/kg bw/d. Based on a minimum specified content of 35% DHA in algal oil, OFAS notes that the estimated dietary exposure to algal oil is equivalent to 77 to 94 mg/kg bw/d.

Mara discusses published studies supporting the safety of algal oil. Mara discusses that the metabolic fate of dietary DHA is well understood and similar to other dietary fatty acids. Mara summarizes published toxicity testing, including a study in which algal oil was administered to rats at concentrations up to 50,000 mg/kg for 13 weeks. There were

² Mara states that the enzyme is a protease preparation produced by a selected strain of *Bacillus licheniformis*. Mara states that the enzyme is food grade, complies with specifications established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006) and Food Chemicals Codex (FCC, 2016) for food grade enzymes, and is not present in the final algal oil product. Mara states that the final algal oil product is analyzed for residual proteins at a detection limit of 0.15%, and concludes that the enzyme is removed during the manufacturing process and not present in the final product.

no adverse effects at the highest dose tested, equivalent to 3,305 and 3,679 mg/kg bw/d in male and female rats, respectively. Mara also discusses a published developmental toxicity study and a 3-month dietary toxicity study in rats and noted the absence of maternal and developmental toxicity at any dose level tested in either study.

To further support its view that algal oil is GRAS for the intended use, Mara discusses the results of published *in vitro* and *in vivo* genotoxicity tests (microbial reverse mutation assay, *in vivo* rat bone marrow micronucleus assay, and chromosomal aberration assay in cultured human peripheral blood lymphocytes). Mara states that algal oil was neither mutagenic nor genotoxic in any of the assays.

As part of its notice, Mara includes the report of a panel of individuals (Mara's GRAS panel). Based on its review, Mara's GRAS panel concluded that algal oil is safe under the conditions of its intended use.

Based on the data and information described above, Mara concludes that algal oil is GRAS for its intended use in infant formula.

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). The notice raises a potential issue under these labeling provisions. In the notice, Mara cites data that demonstrate that algal oil has a similar lipid (fatty acid and sterol) profile to that of currently marketed oil from *Schizochytrium* sp. Mara subsequently cites studies that describe DHA as having a benefit on growth and neurodevelopment and reducing morbidity. 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Mara notes that algal oil has a yellow to orange color. As such, the use of algal oil in food products may constitute the use of a color additive 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 000677 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 Petition Review in OFAS.

Intended Use in Infant Formula

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 Mara'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.

Section 301(II) of the FD&C Act

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of Mara's notice concluding that algal oil is GRAS under its intended conditions of use, we did not consider whether section 301(II) 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(II).

Conclusions

Based on the information that Mara provided, as well as other information available to FDA, we have no questions at this time regarding Mara'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 000677 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -

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Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A. Adams -S
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