



Ray A. Matulka, Ph.D.
Burdock Group Consultants
859 Outer Road
Orlando, FL 32814

Re: GRAS Notice No. GRN 000754

Dear Dr. Matulka:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000754. We received the notice that you submitted on behalf of Corbion Biotech, Inc. (Corbion¹) on February 8, 2018, and filed it on February 14, 2018. We received amendments to the notice on April 10, 2018, May 31, 2018, and June 18, 2018. These amendments included the information regarding stability, the timeframe for the literature search performed, and an updated Part 1 of the notice.

The subject of the notice is high-oleic algal oil from *Prototheca moriformis* strain S6697 (high-oleic algal oil) for use as a partial replacement of conventional vegetable and non-vegetable dietary oils in baked goods; baked desserts; meal replacement bars, drinks and protein supplements; cereals and bars; cheese spreads; margarine and margarine-like spreads; butter-like spreads; vegetable oil and shortening; salad dressing and mayonnaise; sauces, gravies, and dressings; nut spreads, nuts, and seeds; dairy and milk products (including analogs); gelatins and puddings; soups and broth, meat products²; frozen dairy desserts; snacks; soft candy; and confectionery at levels up to 100%. Intended uses exclude food products for which a standard of identity does not permit the use of high-oleic algal oil. The notice informs us of Corbion's view that the use of high-oleic algal oil is GRAS through scientific procedures.

Our use of the term "high-oleic 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

¹ On April 10, 2018, Dr. Matulka of Burdock Group Consultants informed FDA that the original notifier of GRN 000754, TerraVia Holdings, Inc., was acquired by Corbion. On June 18, 2018, Corbion confirmed that Corbion assumes responsibility as the notifier of GRN 000754, providing an updated Part 1 of the notice.

² Meat products (mixtures) include all meats and meat containing dishes, salads, appetizers, frozen multicourse meat meals, and sandwich ingredients prepared by commercial processing or using commercially processed meats with home preparation.

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 did not consult with ONFL regarding the appropriate common or usual name for “high-oleic algal oil.”

Corbion provides information about the identity and composition of high-oleic algal oil. Corbion describes high-oleic algal oil as clear and pale yellow to wheat yellow in appearance. Corbion notes that high-oleic algal oil consists primarily of triglycerides ($\geq 95\%$) with low levels of diglycerides ($\leq 5\%$) and trace amounts of monoglycerides ($< 0.5\%$). Corbion states that the average oleic acid concentration in high-oleic algal oil is 88%, which is higher than that in vegetable oils (olive, canola, and soybean oils contain 71%, 61%, and 22% oleic acid, respectively). Corbion considers that the composition of other major fatty acids in high-oleic algal oil is similar to that in olive, canola, and soybean oils except for the reduced linoleic acid content.

Corbion describes the manufacturing process for high-oleic algal oil, beginning with the development of the production strain. *P. moriformis* strain S376 was chemically mutagenized to yield a variant designated S1331, which underwent further mutagenesis (both chemical and UV) to generate S5100, which was chosen based on increased synthesis of oleic acid. *P. moriformis* strain S5100 was then modified in two separate transformation steps to overexpress an endogenous gene to promote the conversion of palmitic acid to stearic acid, and to lower the expression of an endogenous desaturase to minimize the conversion of oleic acid to polyunsaturated fatty acids. The resulting *P. moriformis* strain S6697 produces approximately 3% palmitic acid, 2% stearic acid, and 90% oleic acid. *P. moriformis* strain S6697 is grown under controlled pH, temperature, agitation and aeration rates in a medium containing glucose or sucrose, as well as other nutrients, including wheat. Following fermentation, the culture is heat-treated to inactivate the cells; the algal biomass is then concentrated in an evaporator before drying. The dried biomass is mechanically extracted to release the crude algal oil using soybean hulls as an extraction aid. The high-oleic algal oil is refined using standard edible oil refining steps to remove proteins and algal cells. The oil is degummed, bleached, and deodorized. To ensure product stability, a food-grade antioxidant may be added to the product prior to packaging.

Corbion provides food grade specifications for high-oleic algal oil. These include appearance, peroxide value (≤ 5 milliequivalents/kg), *p*-anisidine value ($\leq 10\%$), oleic acid ($\geq 80\%$), linoleic acid ($\leq 10\%$), free fatty acids ($\leq 0.1\%$), and limits for lead, arsenic, mercury (each < 0.2 mg/kg), and cadmium (< 0.1 mg/kg). Corbion provides results of three batch analyses (as a range and average) to demonstrate that high-oleic algal oil can be manufactured to meet specifications. Corbion states that high-oleic algal oil is stable for at least 18 months when stored under defined conditions.

Corbion estimates dietary exposure estimates to high-oleic algal oil based on the maximum intended use levels and food consumption data from the National Health and Nutrition Examination Survey (NHANES; 2009-2012). Corbion reports that the dietary exposure to high-oleic algal oil for the total U.S. population (users only) is estimated to

be 12 g/person (p)/day (d) (0.2 g/kg body weight (bw)/d) at the mean and 27 g/p/d (0.5 g/kg bw/d) at the 90th percentile. Corbion notes that the quantity of the high-oleic algal oil used as a partial replacement for conventional vegetable and non-vegetable dietary oils would be self-limiting due to potential unpalatability.

Corbion discusses published data and information supporting the safety of high-oleic algal oil. The scientific literature search covered the period through June 2016. Corbion states that the lipids found in high-oleic algal oil will undergo the same physiological processes by which other plant-derived oils common to the human diet are digested and utilized. Corbion describes a published 13-week dietary toxicity study in which rats were fed diets containing up to 100 g/kg high-oleic algal oil corresponding to 5.2 g/kg bw/d and 6.4 g/kg bw/d in male and female rats, respectively. Corbion reports that no treatment-related adverse effects were observed. Corbion also describes a published 13-week dietary toxicity study with algal structuring fat (containing 55% stearic acid, 35% oleic acid, and 4.2% palmitic acid) from a different strain genetically related to *P. moriformis* strain 6697. In this study, rats were fed diets containing up to 100 g/kg algal structuring fat corresponding to 5.3 g/kg bw/d and 6.3 g/kg bw/d in male and female rats, respectively. No treatment-related adverse effects were reported. Corbion cites two published genotoxicity studies (including a bacterial reverse mutation assay and an *in vivo* bone marrow chromosome aberration assay), which showed that high-oleic algal oil is neither mutagenic nor clastogenic.

Corbion includes the report of a panel of individuals (Corbion's GRAS panel). Based on its review, Corbion's GRAS panel concluded that high-oleic algal oil is safe under the conditions of its intended use.

Based on the information presented in the notice, Corbion concludes that high-oleic algal oil is GRAS for its intended use in foods.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of GRN 000754, 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 would not object to the use of high-oleic algal oil as an ingredient in meat or poultry products where it does not conflict with any standard of identity in 9 CFR Part 319, Part 381 Subpart P, 21 CFR Part 160 or the Food Standards and Labeling Policy Book. The use of high-oleic algal oil in a standardized meat or poultry product that does not provide for the use of oil would require a descriptive name to distinguish it from the traditional product, e.g., "Italian sausage with high-oleic algal oil." When used in the formulation of

a meat or poultry food product under FSIS jurisdiction, the ingredient would require labeling in the ingredients statement by its common or usual name as “high-oleic algal oil.” Furthermore, the use of the oil cannot conflict with FSIS’ interim policy titled “Statements about Omega Fatty Acid Contents on the Labeling of Meat and Poultry Products.” FSIS’ policy clarifies those statements that imply a level of Omega-3 Fatty Acids is significant or that include an undefined nutrient content claim (e.g., “Provides Omega-3 Fatty Acids,” “Good Source Omega-3 Fatty Acids”) are prohibited.

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

Section 301(II) of the Federal Food, Drug, and Cosmetic Act (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 Corbion’s notice concluding that high-oleic 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 high-oleic algal oil. Accordingly, our response should not be construed to be a statement that foods containing high-oleic algal oil, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Corbion provided, as well as other information available to FDA, we have no questions at this time regarding Corbion’s conclusion that high-oleic algal oil is GRAS under its intended conditions of use. This letter is not an affirmation that high-oleic 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 000754 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Michael A.
Adams -S**

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Dennis M. Keefe, Ph.D.
Director
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cc: William K. Shaw Jr., Ph.D.
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