



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

Re: GRAS Notice No. GRN 000673

Dear Dr. Matulka:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000673. We received the notice, dated September 23, 2016, that you submitted on behalf of TerraVia Holdings, Inc. (TerraVia) under the format of the agency's final rule (81 FR 54960; August 17, 2016; Substances Generally Recognized as Safe (GRAS)) on October 6, 2016, and filed it on October 13, 2016. We received amendments on December 13 and December 20, 2016. These amendments included additional information on studies supporting the safety of algal fat under the conditions of its intended use, a re-write of sections that TerraVia initially blackened out, and clarification on the Freedom of Information Act exemption statement.¹

The subject of the notice is algal fat derived from *Prototheca moriformis* (S7737) (algal fat) for use as a partial replacement for stearic acid-containing dietary fats or oils in margarine and margarine-like spreads, butter-like spreads, vegetable shortenings, nut spreads, milk products, non-dairy products, baked goods, chocolate-based sauces and syrups, baked desserts, cookies, and frozen dairy desserts at levels resulting in exposure up to 9.1 g per person per day (g/p/d). Intended uses exclude food products for which a standard of identity does not permit the use of the algal fat. The notice informs us of TerraVia's view that this use of algal fat is GRAS through scientific procedures.

Our use of the term, "algal fat," 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. We did not consult with ONFL regarding the appropriate common or usual name for algal fat.

TerraVia describes the identity and composition of algal fat. TerraVia describes algal fat as pale yellow to wheat-yellow in appearance. TerraVia notes that algal fat almost exclusively consists of triglycerides ($\geq 95\%$) with small amounts of diglycerides ($\leq 5\%$) and trace amounts of monoglycerides ($\leq 0.5\%$). TerraVia states that algal fat contains approximately 55% stearic acid and 35% oleic acid as a percentage of the total fatty acid content and that the fatty acid composition of algal fat is similar to other stearic-rich plant-derived solid fats in the food supply.

¹ GRN 000673 included information that TerraVia initially blackened out in the notice dated September 23, 2016. In the December 13, 2016, amendment, TerraVia provided a re-write of these blackened out sections.

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TerraVia describes the manufacturing process for algal fat, beginning with the development of the production strain. *P. moriformis* strain S376 was chemically mutagenized to increase triglyceride synthesis. An intermediate strain was chosen based on increased synthesis of oleic acid and then genetically modified in three separate transformation steps. The final strain, *P. moriformis* S7737, was chosen based on high stearic acid and low linoleic acid content and desired triglyceride profiles of the resulting fat. *P. moriformis* strain S7737 is used for fermentation under controlled pH, temperature, agitation, and aeration rates in a medium containing glucose or sucrose, as well as other nutrients. Following fermentation, the culture is heat treated to inactivate the algal cells and the algal biomass is then concentrated and dried. The dried biomass is mechanically extracted using soybean hulls as an extraction aid to release the crude algal oil. The crude algal oil is refined using standard edible oil refining techniques including degumming, bleaching, and deodorization. To ensure product stability, a food-grade antioxidant may be added to the product prior to packaging.

TerraVia provides specifications for algal fat, including appearance, peroxide value (≤ 2 milliequivalents/kg), stearic acid ($\geq 50\%$ total fatty acid (TFA)), oleic acid ($\geq 30\%$ TFA), linoleic acid ($\leq 2\%$ TFA), and free fatty acids ($\leq 1\%$ TFA). Specifications also include limits for lead, arsenic, and mercury (each < 0.2 mg/kg). TerraVia provides analytical data from three batches of algal fat to demonstrate the ability to produce a product in compliance with these specifications.

TerraVia intends to use algal fat as a partial replacement for stearic acid-containing dietary fats and oils. TerraVia estimates the daily dietary exposure to algal fat using intended use levels and consumption data from What We Eat in America (WWEIA), National Health and Nutrition Examination Survey (NHANES), 2011–2012. The estimated mean and 90th percentile exposures to algal fat are 63.67 mg/kg body weight (bw)/d (or 3.82 g/p/d) and 152 mg/kg bw/d (or 9.1 g/p/d), respectively. TerraVia states that the use level of algal fat in foods would be self-limiting because excessive addition would affect the food's palatability.

TerraVia discusses subacute and subchronic toxicity studies, a reproductive toxicity study, and *in vitro* and *in vivo* genotoxicity studies to support its safety conclusion of the use of algal fat. TerraVia summarizes a published subacute toxicity study in which no adverse effects were reported after the administration of 30,000 mg of glyceryl monostearate/kg bw/d, a stearic acid-rich product, for three weeks in weanling mice. TerraVia also discusses a published subchronic toxicity study in which no treatment-related adverse effects occurred in rats consuming algal fat for 13 weeks at up to the highest dietary level of approximately 5,000 mg/kg bw/d. TerraVia summarizes a published 19-week rat study in which no toxicity was reported following the administration of diets containing approximately 4,000 mg/kg bw/d fats rich in stearic acid. No adverse effects were reported in a published 13-week rat study at the highest dietary level of approximately 5,000 mg/kg bw/d oleic-rich oil. TerraVia discusses a published three-generation rat reproductive toxicity study that showed that mango kernel oil, a stearic acid/oleic acid-rich fat similar to algal fat in stearic acid content, when consumed at 5,000 mg/kg bw/d of the diet for 22-weeks, did not cause toxicological or reproductive adverse effects. According to TerraVia, algal fat was not mutagenic in bacterial reverse mutation assays and was not clastogenic in an *in vivo* mouse bone marrow chromosome aberration assay at up to 2,000 mg/kg bw. TerraVia states that *P. moriformis* is not recognized in the scientific literature to be associated with pathogenicity and is non-toxicogenic. TerraVia further states that a closely related *P. moriformis* strain was evaluated for toxigenicity and pathogenicity in a corroborative study in which rats were acutely dosed *via* gavage with live *P. moriformis* S2014 at approximately 2.5×10^8 colony forming units/rat, with no viable counts detected in any tissues and no adverse effects reported.

Based on the data and information described above, TerraVia concludes that algal fat is GRAS for its intended use in food.

We note that GRN 000673 referred to a panel of individuals (TerraVia's GRAS panel). The notice did not provide a GRAS panel report as a basis for TerraVia's conclusion of GRAS status. TerraVia stated that the report contained confidential information and offered to provide a redacted version of the GRAS panel report, which FDA declined. Nonetheless, because the notice provided publicly available information supporting TerraVia's conclusion, we completed our evaluation without considering the deliberations of TerraVia's GRAS panel.

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 TerraVia's notice concluding that algal fat 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 fat. Accordingly, our response should not be construed to be a statement that foods containing algal fat, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that TerraVia provided, as well as other information available to FDA, we have no questions at this time regarding TerraVia's conclusion that algal fat is GRAS under its intended conditions of use. This letter is not an affirmation that algal fat 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 000673 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
**Michael A.
Adams -S**

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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