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CFSAN/Office of Food Additive Safety
February 12, 2004

Agency Response Letter
GRAS Notice No. GRN 000137

Sam Zeller, Ph.D.
Martek Biosciences Corporation
6480 Dobbin Road
Columbia, MD 21045

Re: GRAS Notice No. GRN 000137

Dear Dr. Zeller:

The Food and Drug Administration (FDA) is responding to the notice, dated August 18, 2003, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on August 21, 2003, filed it on August 21, 2003, and designated it as GRAS Notice No. GRN 000137.

The subject of the notice is algal oil (*Schizochytrium* sp.). For the purpose of this letter, FDA refers to this ingredient as "algal oil." The notice informs FDA of the view of Martek Biosciences Corporation (Martek) that algal oil is GRAS, through scientific procedures, for use as a direct food ingredient at the levels listed in Table 1. At this time, Martek intends for algal oil to be used in the same food categories as those currently listed in 21 CFR 184.1472(a)(3) (menhaden oil) at levels that are no more than 29 percent of the levels specified in that regulation. Martek also intends for algal oil to be used in several additional food categories (soy protein bars; processed vegetable drinks; hard candy; soft candy; non-dairy and powdered cream substitutes; jams and jellies; non-dairy milk, imitation and soy milk) at specified maximum use levels. These use levels are listed in Table 1 as "Initial Intended Use Levels." Martek notes that the FDA issued a proposed rule (the menhaden oil proposal; 67 FR 8744, February 26, 2002) amending 21 CFR 184.1472 (a) (3) by changing the maximum use levels and food categories in which menhaden oil may be used. Martek asked that the agency apply any such amendments to algal oil. These values are incorporated in the column labeled "Future Intended Use Levels" in Table 1. Subsequent to receiving Martek's notice, FDA issued a tentative final rule amending 21 CFR 184.1472 (69 FR 2313; January 15, 2004).

Martek acknowledges that FDA raised concerns about the consumption of high levels of two fatty acids (i.e., docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)), which may increase bleeding time, increase levels of low-density lipoprotein cholesterol, and have an effect on glycemic control in non-insulin dependent diabetics (menhaden oil final rule; 62 FR 30751; June 5, 1997). In affirming the GRAS status of menhaden oil, FDA concluded that the use of menhaden oil as a direct food ingredient is GRAS, provided that the combined daily intake of EPA and DHA from consumption of menhaden oil does not exceed 3 g/p/d. To assure that the combined exposure to EPA and DHA would not exceed 3 g/p/d, FDA established maximum levels of use of menhaden oil that would be permitted in specified food categories (21 CFR 184.1472(a)(3)). In an amendment

dated December 5, 2003, Martek notes that algal oil would be used as the sole added source of DHA in any given food category and that algal oil would not be combined or augmented with any other oil that is rich in the fatty acids DHA or EPA.

As part of its notice, Martek includes the report of a panel of individuals (Martek's GRAS panel) who evaluated the data and information that are the basis for Martek's GRAS determination. Martek considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Martek's GRAS panel evaluated information on the safety of the source microorganism, composition of the product, the method of manufacture, product specifications, intended use levels, consumption estimates, and data from toxicity studies. Martek's GRAS panel concludes that algal oil derived from *Schizochytrium* sp. is GRAS when used in foods at a level such that the daily intake of DHA would not exceed 1.5 g/p/d. Martek explains that Martek's GRAS panel did not consider whether an intake above 1.5 g/p/d would be safe because 1.5 g/p/d was the amount considered to be needed to accomplish the intended nutritional effect of including DHA in the diet.

Martek describes the intended use of algal oil in foods and provides a table that lists the food categories and intended use level in each food category (Table 1). Algal oil is intended to be used as a direct food ingredient in food categories listed in 21 CFR 184.1472(a)(3) at maximum use levels that are 29 percent of those specified in the regulation. Martek notes that a GRAS notice (GRN 000105) for the use of fish oil concentrate as a direct food ingredient described the use of that ingredient in several food categories in addition to those already listed in 21 CFR 184.1472(a)(3) and provided a basis to conclude that the intake of DHA and EPA would remain below 3 g/p/d even if that fish oil concentrate was used in those additional food categories. Likewise, Martek intends that algal oil be used in the same food categories as those specified in GRN 000105, at maximum use levels that are 50 percent of the use levels specified in GRN 000105. Martek estimates that the use of algal oil at the maximum proposed use levels would result in a mean dietary exposure of no more than 1.5 grams of DHA per day.

Table 1
Maximum Intended Use Levels of Algal Oil*

Food Category	Initial Intended Use Levels (Percent by Weight)	Future Intended Use Levels (Percent by Weight)
Cookies, crackers (1)**	1.45	-
Breads, Rolls (white and dark) (1)**	0.29	-
Fruit pies, custard pies (1)**	2.03	-
Cakes (1)**	2.9	-
Cereals (4)	1.16	1.16
Baked goods and baking mixes (1)	1.16	1.45

Fats, oils (12) (not including infant formula)	5.8	3.48
Yogurt (31)***	1.16	-
Milk products (31)	1.45	1.45
Cheese products (5)	1.45	1.45
Frozen dairy products (20)	1.45	1.45
Meat products (29)	2.9	1.45
Egg products (11)	1.45	1.45
Fish products (13)	5.8	1.45
Condiments (8)	1.45	1.45
Soup mixes (40)	0.87	0.87
Snack foods (37)	1.45	1.45
Nut Products (32)	1.45	1.45
Gravies and sauces (24)	1.45	1.45
Soy protein bars (33)****	1.45	-
Plant protein products (33)	-	1.45
Processed vegetable drinks (36)	0.29	0.29
Hard candy (25)	2.9	2.9
Soft candy (38)	1.16	1.16

Non-dairy and powdered cream substitutes (10)	1.45	-
Jams and jellies (28)	2.03	2.03
Milk, dry and powdered mixes (31)*****	0.85	-
Milk-based meal replacements (31)*****	0.29	-
Flavored milk and milk products (31)*****	0.15	-
Non-dairy milk, imitation and soy milk (10)*****	0.3	-
Dairy product analogs (10)	-	1.45
Nonalcoholic beverages (3)	-	0.15
Pastas (23)	-	0.58
Poultry products (34)	-	0.87
Processed fruit juices (35)	-	0.29
White granulated sugar (41)	-	1.16
Sugar substitutes (42)	-	2.9
Chewing gum (6)	-	0.87
Gelatins and puddings (22)	-	0.29
Confections and frosting (9)	-	1.45
Sweet sauces, toppings, and syrups (43)	-	1.45
* The food categories correspond to those listed in 21 CFR 170.3 (n). The number in parenthesis		

following each food category is the paragraph listing of that food category in 21 CFR 170.3 (n).

** Subsumed by "baked goods and baking mixes."

*** Subsumed by "milk products."

**** Subsumed by "plant protein products."

***** Subsumed by "dairy product analogs."

Martek describes generally available information about the identity and composition of algal oil. Martek describes algal oil as a yellow to light orange-colored oil derived from the heterotrophically grown marine alga *Schizochytrium* sp. Algal oil is composed of a mixture of di- and triglycerides, free fatty acids, carotenoids, squalene, and phytosterols. The most abundant fatty acid in algal oil is DHA. Martek provides quantitative information about the fatty acid profile of algal oil, which shows that algal oil contains DHA at a level of approximately 35 percent (by weight), palmitic acid at a level of approximately 24 percent, docosapentaenoic acid at a level of approximately 13.5 percent, myristic acid at a level of approximately 10 percent, and EPA at a level of approximately 3 percent. By comparison, menhaden oil contains DHA at a level of approximately 8 percent and EPA at a level of approximately 12 percent.

Martek describes the manufacturing process for algal oil and provides specifications for the final product. *Schizochytrium* sp. are grown in pure culture in a heterotrophic fed-batch fermentation process. After completion of fermentation, the algae are concentrated and dried. The oil is then separated from the dried biomass by hexane extraction and centrifugation and/or filtration, followed by winterization. The hexane phase undergoes additional centrifugation/filtration to remove solids then the winterized oil is heated and treated with acid. Subsequently, the oil is treated with caustic, centrifuged, bleached and deodorized. Antioxidants are added and the deodorized oil is packaged. Samples of each lot of algal oil are analyzed for compliance with product specifications.

Martek discusses published and unpublished data and information about the identity and safety of the source microorganism. The source of algal oil is a strain of *Schizochytrium* sp. that was derived from a strain of an original wild-type culture (*Schizochytrium* sp. ATCC 20888) by using a classical mutagenesis and screening program. *Schizochytrium* sp. is a thraustochytrid and a member of the Chromista kingdom. Thraustochytrids are widespread throughout the food chain as well as the marine environment and are consumed by man, primarily through consumption of mussels and clams. Two toxic compounds are known to be produced by the Chromista: domoic acid in the genus *Pseudonitzschia* and prymnesin in the genus *Prymnesium* spp; neither of these two organisms is closely related to *Schizochytrium*. Martek found no reports of toxicity or pathogenicity associated with *Schizochytrium* in the literature, and detected no algal toxins by analytical methods.

Martek describes published studies to support its view that algal oil is GRAS for consumption at the recommended levels. Studies conducted using dried *Schizochytrium* sp. algae include a 90 day feeding study in rats, a developmental toxicity study in rats and rabbits, and a single generation rat reproduction study. Genotoxicity studies were conducted using algal oil and dried *Schizochytrium* sp. algae. Martek reports that no treatment related adverse effects were observed in these studies.

Martek also discusses published and unpublished growth studies conducted in poultry and swine using dried *Schizochytrium* sp. algae and reports that no treatment related adverse effects were observed in these studies. Martek notes that a discussion of the absorption, distribution, metabolism, excretion, and safety of the components present in algal oil was provided to the FDA as part of a New Dietary Ingredient Premarket Notification filed in December 1997 by Monsanto for "SeaGold DHA-rich oil."

Based on the information provided by Martek, as well as other information available to FDA, the agency has no questions at this time regarding Martek's conclusion that algal oil is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of algal oil. As always, it is the continuing responsibility of Martek to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

During its evaluation of GRN 000137, FDA consulted with the Labeling and Consumer Protection Staff of the Food Safety and Inspection Service (FSIS) of the United States Department of

Agriculture (USDA). Under the Federal Meat Inspection Act and the Poultry Products Inspection Act, FSIS is responsible for determining the efficacy and suitability of food ingredients in meat and poultry products as well as prescribing safe conditions of use. Suitability relates to the effectiveness of the ingredient in performing the intended purpose of use and the assurance that the conditions of use will not result in an adulterated product, or one that misleads consumers. FSIS advised that Martek seek regulatory guidance about the use of these ingredients in meat and poultry products from Dr. Robert Post, Director, Labeling and Consumer Protection Staff, Office of Policy, Program Development and Evaluation, Food Safety and Inspection Service, 1400 Independence Ave., S.W., Suite 602, Annex, Washington, DC 20250-3700. The telephone number for his office is (202)205-0279 and the telefax number is (202)205-3625.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in your notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at <http://www.cfsan.fda.gov/~lrd/foodadd.html>).

Sincerely,

/s/

George H. Pauli, Ph.D.

Acting Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

cc: Dr. Robert Post, Director
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