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# Agency Response Letter GRAS Notice No. GRN 000424

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## CFSAN/Office of Food Additive Safety

December 6, 2012

Mr. Howard Newman  
Desert Lake Technologies, LLC  
3735 Washburn Way  
Klamath Falls, Oregon 97603

Re: GRAS Notice No. GRN 000424

Dear Mr. Newman:

The Food and Drug Administration (FDA) is responding to the notice, dated March 12, 2012, 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 March 13, 2012, filed it on March 20, 2012, and designated it as GRAS Notice No. GRN 000424.

The subject of the notice is c-c-phycocyanin-enriched water extract of the cyanobacterium *Arthrospira maxima* or *Arthrospira platensis*, (also known as *Spirulina maxima* or *Spirulina platensis*), referred to here as "phycocyanin water extract."<sup>(1)</sup> The notice informs FDA of the view of Desert Lake Technologies, LLC (Desert Lake) that phycocyanin water extract is GRAS, through scientific procedures, for use as an ingredient in all foods except infant formulas and foods under USDA's jurisdiction at levels up to a maximum of 250 milligrams per serving (mg/serving).

Our use of “phycocyanin water extract” 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. Title 21 CFR 101.4 states that 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 appropriate common or usual name of a food are the responsibility of the Office of Nutrition, Labeling, and Dietary Supplements (ONLDS) in the Center for Food Safety and Applied Nutrition.

As part of its notice, Desert Lake includes a statement from a panel of individuals (Desert Lake’s GRAS panel) who evaluated the data and information that are the basis for Desert Lake’s GRAS determination. Desert Lake considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Desert Lake’s GRAS panel considered the identity and source of phycocyanin water extract and evaluated estimates of dietary exposure, method of production, and product specifications as well as published and unpublished studies. Based on this review, Desert Lake’s GRAS panel concluded that phycocyanin water extract that meets its established food grade specifications is GRAS under the conditions of its intended use.

Desert Lake provides information about the identity, method of manufacture, and specifications for phycocyanin water extract. Desert Lake does not grow the spirulina and obtains it from one or more suppliers and notes that the feedstock and the final product meet the company’s specifications.

Desert Lake provides a manufacturing process for phycocyanin water extract. The process consists of the reconstitution of spirulina powder with water, followed by the separation of the aqueous portion using centrifugation. The aqueous portion is then dried and packaged. Desert Lake describes the phycocyanin water extract product as a blue powder. Desert Lake states that the manufacturing process for phycocyanin water extract is performed using current good manufacturing processes.

Desert Lake provides specifications for phycocyanin water extract. Desert Lake notes that a major constituent of its product is the water-soluble phycobiliprotein phycocyanin (CAS Reg. No. 11016-15-2). The chromophore of phycocyanin is phycocyanobilin.

In addition, Desert Lake provides specifications for color, moisture (2-7%), heavy metals (arsenic, cadmium, lead and mercury, each at less than 1 mg/kilogram, (mg/kg)), microcystin toxin (less than the limit of detection at 0.16 mg/kg), and provides microbial limits. Desert Lake provides batch analyses for three lots of the product that comply with the specifications. Based on these analyses, Desert Lake states that a typical batch of the final product contains 42-47% phycocyanin compared with an average content of 20% phycocyanin in the spirulina starting material.

Desert Lake provides estimated daily intakes (EDI) of phycocyanin water extract from the intended uses. A publication from the United States Department of Agriculture Center for Nutrition Policy and Promotion (October 2000) states that males aged 51 and older consume the largest number of servings of food per day at 18.2 servings per day (servings/day). Using this estimate of the number servings/day, Desert Lake bases its dietary intake calculations on the assumption that 10% of daily servings of food, or 1.8 servings, would contain phycocyanin water extract. If 10% of a person’s daily food servings contained phycocyanin water extract, then the person would consume 455 mg phycocyanin water extract/day, or approximately 228 mg phycocyanin/day (equivalent to 4 mg/kg body weight per day (mg/kg bw/d) for a 60 kg individual).

Desert Lake also calculated a conservative intake estimate assuming 50% of a person’s daily food servings (approximately 9.1 servings/day) contained phycocyanin water extract. Under this assumption, a person would consume approximately 2280 mg of phycocyanin water extract/day, resulting in consumption of about 1140 mg phycocyanin/day (equivalent to 19 mg phycocyanin/kg bw/d for a 60 kg individual). This would be equivalent to consuming approximately 5700 mg of spirulina/day based on 20% phycocyanin content from the spirulina starting material. Desert Lake’s amendment dated June 22, 2012 notes that very few consumers would consume this much

of the ingredient daily over a lifetime. Additionally, Desert Lake elaborates on the limit of consumption of phycocyanin. Desert Lake expects that the addition of phycocyanin water extract to foods sold in the United States will not result in increased human exposure to phycocyanin because the use is expected to be substitutional rather than additive.

Desert Lake cites published studies conducted with phycocyanin, as well as published studies conducted with whole spirulina, to support the safety of phycocyanin water extract. The toxicological studies performed using phycocyanin isolated from whole spirulina are discussed below in brief. Desert Lake discusses the similarity between *A. platensis* and *A. maxima* based on published molecular taxonomic evidence. Furthermore, Desert Lake considers *A. platensis* and *A. maxima* as indistinguishable.

Desert Lake reports on an acute toxicity study in male OF1 mice and male Sprague-Dawley rats using phycocyanin extract from *A. maxima*. According to Desert Lake, the study authors estimated the LD<sub>50</sub> of phycocyanin extract to be greater than 3000 mg/kg bw. No changes in behavior or histopathology were observed, nor were there any statistically significant effects on body weight changes.

Desert Lake reports on another acute toxicity study and a subchronic toxicity study of phycocyanin. These studies used phycocyanin from *A. platensis* as the test article. For the acute toxicity study, groups of adult male and female Wistar rats were administered a single dose of phycocyanin at 0 (control), 250, 500, 1000, 2000, and 5000 mg phycocyanin/kg bw by mixing with basal diet. The animals were kept under observation for a period of 21 days for symptoms of toxicity and mortality. Desert Lake notes that the study authors reported acute treatment with phycocyanin did not induce mortality or any signs of toxicity and the dietary LD<sub>50</sub> of phycocyanin in this study was greater than 5000 mg/kg bw.

Desert Lake discusses the subchronic study in which groups of adult male and female Wistar rats were administered 0 (control), 500, 1000, 2000, and 4000 mg phycocyanin/kg of diet/day for 14 weeks. Daily food intake and body weights were recorded. After 14 weeks, the rats were necropsied. Liver, lung, heart, kidney, spleen, brain, adrenal glands and gonads were collected, organ weights were recorded and histopathological examination was performed. Hematological and serum chemistry analyses were also performed. There were no significant differences between control and treatment groups in terms of food intake, body weight gain, organ weights, hematological or serum chemistry measurements. Desert Lake calculates the amount of phycocyanin consumed/kg bw based on the phycocyanin content of the diet and explains that no adverse effects were observed at the highest level tested, 4000 mg phycocyanin/kg of diet/day (approximately 200 mg phycocyanin/kg bw/day).

## Standards of Identity

In the notice, Desert Lake states its intention to use phycocyanin water extract in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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

In describing the intended use and EDI, Desert Lake notes that many organizations are advocating an increase in consumption levels of phycocyanin water extract. 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 particular. Section 403(r) of the FD&C Act lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. If products that contain phycocyanin water extract bear any claims on the label or in labeling, such claims are the purview of the ONLDS.

The Office of Food Additive Safety (OFAS) neither consulted with ONLDS on this labeling issue nor evaluated the information in Desert Lake's notice to determine whether it would support any claims made about phycocyanin water extract on the label or in labeling.

### Potential Requirement for a Color Additive Petition

In their notice, Desert Lake notes that phycocyanin water extract may impart color to food. As such, the use of phycocyanin water extract 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), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food; except that such term does not include any material which the Secretary,<sup>(2)</sup> by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of color additive can be exempt from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. Given the construct of section 201(t)(1) of the FD&C Act and 21 CFR 70.3(f) and (g), the use of a substance that is capable of imparting color may constitute use as a color additive in addition to use as a food additive or GRAS substance. For example, beta-carotene is both approved for use as a color additive (21 CFR 73.95) and affirmed as GRAS for use as a nutrient supplement (21 CFR 184.1245); in some food products, beta-carotene is used for both purposes. Importantly, if the use of phycocyanin water extract constitutes use as a color additive within the meaning of section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR 70.3(f) and (g), section 721(a) of the FD&C Act requires premarket review and approval of that use by FDA. Under section 402(c) of the FD&C Act, a food product that contains an unapproved color additive would be deemed adulterated.<sup>(3)</sup>

Desert Lake states that phycocyanin water extract is not intended for use as a color additive and, thus, would be exempt from the definition of color additive under section 201(t) of the FD&C Act and FDA's implementing regulations in 21 CFR 70.3(f) and (g). Importantly, FDA's response to GRN 000424 does not include any comment by FDA about Desert Lake's view on this issue. If, after receipt of this letter, Desert Lake has any specific questions about this issue, we recommend that Desert Lake contact the Division of Petition Review in OFAS.

### Section 301(II) of the FD&C Act

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FD&C Act to, among other things, add section 301(II). 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 its review of Desert Lake's notice that phycocyanin water extract is GRAS for the intended uses, FDA did not consider whether section 301(II) or any of its exemptions apply to foods containing phycocyanin water extract. Accordingly, this response should not be construed to be a statement that foods that contain phycocyanin water extract, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

### Conclusions

Based on the information provided by Desert Lake, as well as other information available to FDA, the agency has no questions at this time regarding Desert Lake's conclusion that phycocyanin water extract 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 phycocyanin water extract. As always, it is the continuing responsibility of Desert Lake to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000424, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Dennis M. Keefe, Ph.D.  
Director  
Office of Food Additive Safety  
Center for Food Safety and Applied Nutrition

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(1).....We note that current taxonomy reflects that these species are members of the genus *Arthrospira*, generally referred to in food as spirulina.

(2).....The Secretary of the Department of Health and Human Services.

(3).....We note that section 721(b)(4) of the FD&C Act provides that a color additive shall be deemed to be safe and suitable for the purpose of listing under section 721(b) of the FD&C Act while there is in effect a published finding of the Secretary declaring that the substance is exempt from the definition of "food additive" because of its being generally recognized by qualified experts as safe for its intended use as provided in section 201(s) of the FD&C Act. Importantly, FDA's response to GRN 000424 does not constitute a "finding of the Secretary" within the meaning of section 721(b)(4) of the FD&C Act.

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