

ORIGINAL SUBMISSION

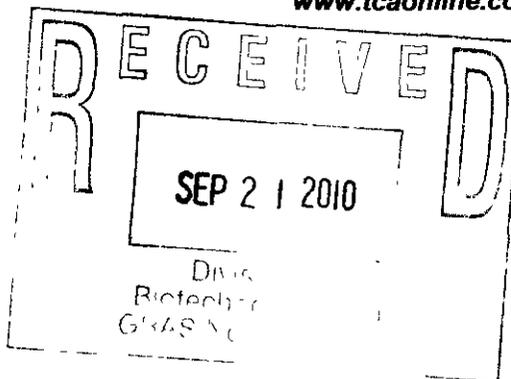


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13 September 2010

Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835



Re Notification of GRAS Determination for Natural Astaxanthin Complex (AstaPure),
a *Haematococcus pluvialis* extract characterized by component astaxanthin
esters of common edible fatty acids

Dear Sir/Madam:

I represent Algatechnologies (1998) Ltd., Kibbutz Ketura 88840, Israel, a company manufacturing *Natural Astaxanthin Complex (AstaPure)*, a natural carotenoid ester ingredient extracted from algae, and currently sold in the United States as a dietary supplement and dietary ingredient. In 2007, FDA accepted a New Dietary Ingredient Notification pursuant to 21 U.S.C. 350b(a) for Algatechnologies' AstaPure (Natural Astaxanthin Complex) based on its identical nature to other astaxanthin oleoresins allowed by the FDA for use in the United States.

In accordance with proposed 21CFR §170.36 (Notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR18939-18964), I am now submitting in triplicate, as the agent for Algatechnologies, a GRAS Notification for Natural Astaxanthin Complex (AstaPure), a *Haematococcus pluvialis* extract characterized by component astaxanthin esters of common edible fatty acids, to be used as a nutrient in baked goods, beverages, cereals, chewing gum, coffee and tea, dairy product analogs, frozen dairy desserts and mixes, hard candy, milk products, processed fruits and fruit juices, processed vegetables and vegetable juices, and soft candy at use levels of 0.5 mg astaxanthin per serving (reference amounts customarily consumed, 21 CFR 101.12).

Please contact me should you have questions concerning this submittal

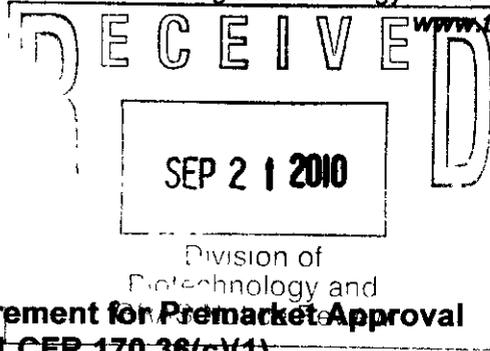
Sincerely yours, *[Signature]*

(b) (6)

Richard F. Taylor, Ph.D.
President

TC Associates Inc.

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1. GRAS Exemption Claim

A. Claim of Exemption from the Requirement for Premarket Approval Requirements Pursuant to Proposed 21 CFR 170.36(c)(1)

Algatechnologies (1998) Ltd , Kibbutz Ketura 88840, Israel, hereby notifies the Food and Drug Administration that it has determined Natural Astaxanthin Complex (AstaPure), a *Haematococcus pluvialis* extract characterized by component astaxanthin esters of common edible fatty acids, is Generally Recognized As Safe (GRAS) for use as a nutrient and, therefore, exempt from the requirement of premarket approval under the conditions of its intended use as described herein. The basis for this finding is detailed in this notification.

(b) (6)



Date 13 SEPTEMBER 2010

Richard F Taylor, Ph D.V

Agent for:

Algatechnologies (1998) Ltd.
Kibbutz Ketura 88840
Israel

B. Name and Address of Notifier

Richard F. Taylor, Ph.D.
President
TC Associates Inc.
PO Box 285
West Boxford, MA 01885

Telephone/Fax: 978-352-7047
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C. Common or Usual Name of the Notified Substance

The common name of the substance of this notification is Natural Astaxanthin Complex, also known by its trade name, AstaPure. Astaxanthin itself is a forty carbon carotenoid occurring naturally in algae and yeast. The substance is a complex mixture of primarily lipids with astaxanthin esterified with common edible fatty acids as the primary carotenoid present. Astaxanthin esters provide a source of astaxanthin when ingested. Hereafter, the term *Natural Astaxanthin Complex (AstaPure)* is used to describe the mixture of carotenoids and fatty acids that is the subject of this GRAS determination, and the term *esterified astaxanthin* to describe the principal component of the substance.

D. Conditions of Use

Natural Astaxanthin Complex (AstaPure) derived from a *Haematococcus pluvialis* is intended for use as a nutrient in baked goods, beverages, cereals, chewing gum, coffee and tea, dairy product analogs, frozen dairy desserts and mixes, hard candy, milk products, processed fruits and fruit juices, processed vegetables and vegetable juices, and soft candy at use levels of 0.5mg astaxanthin per serving (reference amounts customarily consumed, 21CFR 101.12). Estimates of possible daily intake from the intended use levels of Natural Astaxanthin Complex are the same as determined using the CSFII 2003-04 (USDA 2004) database by Fuji Chemical Industry Co. Ltd., GRAS Notice No. GRN 000294. As reported in the latter Notification, the intended use of Natural Astaxanthin Complex in the above mentioned food categories results in an estimated daily intake of astaxanthin for 'users only' at mean and 90th percentile of 3.2 mg/person (<0.1 mg/Kg body weight/day) and 5.4 mg/person (0.1 mg/Kg body weight/day), respectively.

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E. Equivalence to Other GRAS Substances

We reference the entire GRAS submission for astaxanthin extract submitted by EAS Consulting Group, Alexandria, Virginia, on behalf of Fuji Chemical Industry Co., Ltd., on July 2009, and the response of FDA, Michael A. Cheeseman dated 6 January 2010 (GRAS Notice No. GRN 000294, Notification of GRAS Determination for Astaxanthin Oleoresin, a *Haematococcus pluvialis* extract characterized by component astaxanthin esters of common edible fatty acids) finding no questions by FDA for the astaxanthin GRAS exemption. The information and data in the Fuji astaxanthin extract GRAS submission with respect to chemical composition, identity, toxicity, manufacturing process, estimated daily intake, intended use levels, consumption, expert panel conclusions, *et al.*, are directly applicable to the Algatechnologies' Natural Astaxanthin Complex (AstaPure). Our GRAS Notification claims equivalence of Algatechnologies' Natural Astaxanthin Complex and the astaxanthin extract of Fuji Chemical Industry Co., Ltd.

F. Basis for GRAS Determination

As required by 21 CFR 170.30, the intended use of Natural Astaxanthin Complex (AstaPure) has been determined to be Generally Recognized As Safe (GRAS) based on scientific analysis and procedures.

A significant body of qualitative and quantitative scientific evidence including human and animal and clinical studies exists in support safety-in-use for Natural Astaxanthin Complex. In support of this GRAS determination for Natural Astaxanthin Complex, we cite all toxicological studies on the equivalent astaxanthin esters cited in the Fuji GRAS Notice GRN 000294.

Fuji Chemical Industry Co., Ltd. (2007). Notification of GRAS Determination for *Haematococcus pluvialis* extract characterized by component astaxanthin esters (of common edible fatty acids). GRN 000294.
http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn0294.pdf

This document cites studies which have shown that no adverse effects of astaxanthin have been noted at doses of up to 40 mg/day in humans, and up to 465 and 557 mg astaxanthin/kg/day (highest dose tested) in male and female rats, respectively. Given that the daily intake of astaxanthin from the intended uses of Natural Astaxanthin Complex at the 90th percentile of 5.4 mg/person (0.1 mg/kg body weight/day) is approximately seven-fold lower than the demonstrated safe levels of human intake of at

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least 40 mg astaxanthin per day (0.67 mg/kg body weight/day), the estimated daily intake in humans is from 500 to 5000-fold lower than the demonstrated safe level.

In support of their GRAS determination for astaxanthin esters, the report of an Expert Panel is also included in the above cited document which considered the safety of astaxanthin and astaxanthin esters (Expert Panel Statement: Determination of the Generally Recognized As Safe (GRAS) Status of Astaxanthine Esters as a Nutrient, GRN 000294, pp. 11-49). The three member expert panel concluded the following:

*Based on a critical evaluation of the publicly available data summarized herein, the Expert Panel members whose signatures appear below, have individually and collectively concluded that astaxanthin esters derived from *Haematococcus pluvialis*, meeting the specifications cited herein, and when used as a nutrient in Baked Goods, Beverages, Cereals, Chewing Gum, Coffee and Tea, Dairy Product Analogs, Frozen Dairy Desserts and Mixes, Hard Candy, Milk Products, Processed Fruits and Fruit Juices, Processed Vegetables and Vegetable Juices, and Soft Candy at use levels of 0.5 mg astaxanthin per serving (reference amounts customarily consumed, 21 CFR 101.12) and when not otherwise precluded by Standards of Identity are safe*

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that astaxanthin esters, when used as described, are GRAS based on scientific procedures

These findings are directly applicable to Natural Astaxanthin Complex, which is equivalent to the cited astaxanthin esters.

We also cite the safety of astaxanthin as evidenced by its use as a dietary supplement for over 10 years in the United States without any adverse effects. All these astaxanthin products are extracts of *Haematococcus pluvialis*, and comprised of astaxanthin esters of common fatty acids and other trace carotenoids, and are equivalent to the subject Natural Astaxanthin Complex. Typical recommended doses of these astaxanthin extracts are approximately 6mg/day (range: 2 to 12 mg/day). At 6 mg/day, the daily estimated 90th percentile intake is 5.4 mg astaxanthin per day.

The following New Dietary Ingredient Notifications submitted to the FDA contain detailed toxicological and clinical studies in support of *Haematococcus* astaxanthin extracts equivalent to Natural Astaxanthin Complex which were reviewed and allowed by the FDA.

Aquasearch Inc. (1999, 2000). *New Dietary Ingredient Notification for Haematococcus Algae and Amendments*. FDA filing date 22 February 2000, Report #65, parts 1 and 2, docket 95s-0316.
www.fda/ohrms/dockets/dockets/95s0316/rpt0065_0.1pdf and [0.2pdf](http://www.fda/ohrms/dockets/dockets/95s0316/rpt0065_0.2pdf)

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Cyanotech Corporation. (1999). *New Dietary Ingredient Notification for Haematococcus Algae*. FDA filing date 25 May 1999, Report #50, Docket 95S-0316 www.fda.gov/dockets/dockets/95s0316/rpt0050_02_appendix4.pdf

Fuji Chemical Industry Co., Ltd. (2004). *New Dietary Ingredient Notification for Astaxanthin Extracted from Haematococcus Algae*. FDA filing date 10 June 2004, Report #236, Docket 95S-0316

U S Nutra, LLC. (2005). *New Dietary Ingredient Notification for Haematococcus pluvialis*. FDA filing date 15 June 2005, Report #278, docket 95S-0316.

Algatechnologies' Natural Astaxanthin Complex is equivalent to the subject NDIN astaxanthin extracts from these other companies. Thus, all toxicological studies submitted as parts of the NDINs from these other companies apply to Algatechnologies' Natural Astaxanthin Complex and are directly applicable to our GRAS determination.

Based on the cited studies, and the equivalence of Algatechnologies' Natural Astaxanthin Complex, the use of Natural Astaxanthin Complex at the estimated daily intake suggested, is considered safe.

G. Availability of Information

The data and information that serve as the basis for this GRAS determination are available for the Food & Drug Administration's review and copying at a reasonable time and with reasonable notice at the office of:

Richard F. Taylor, Ph.D.
President
TC Associates Inc
PO Box 285
West Boyford, MA 01885

Telephone/Fax: 978-352-7047
eMail: TCAdtaylor@cs.com

Alternatively, copies of data and information can be provided to the FDA upon request by Dr. Taylor.

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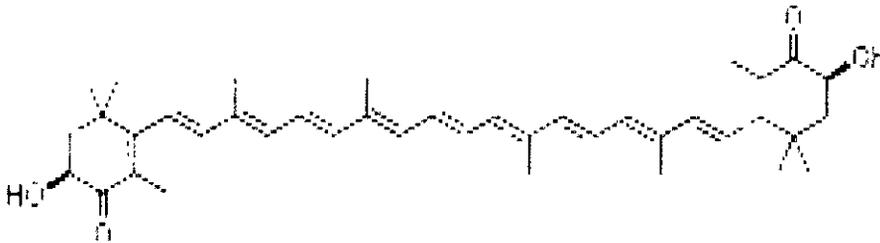
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2. Detailed Information About the Identity of the Notified Substance

A. Identity

Natural Astaxanthin Complex (AstaPure) products will be marketed under the tradename AstaPure, and will contain up to 25% astaxanthin esters. Natural Astaxanthin Complex is produced by carbon dioxide supercritical fluid extraction from *Haematococcus pluvialis* (Phylum: Chlorophyta, Class: Chlorophyceae, Order: Volvocales, Family: Haematococcaceae). The remainder of the oleoresin is comprised of mainly common edible fatty acids.

Astaxanthin ([3S,3'S]-3,3'-dihydroxy- β,β -carotene-4,4'-dione, CAS Registry Number 472-61-7) has the following structure with an empirical formula of $C_{40}H_{52}O_4$:



In Natural Astaxanthin Complex and astaxanthin esters, the astaxanthin is present esterified to common edible fatty acids.

B. Physical Characteristics

Natural Astaxanthin Complex is a viscous, dark red oil. It is packaged in HDPE or aluminum food grade containers, blanketed with nitrogen, sealed, and stored at 4 to 6°C.

C. Manufacturing Process

H. pluvialis is cultured in indoor and outdoor closed systems. Outdoor cultivation is performed in an array of 40 photo-bioreactors, consisting of one hundred miles of glass tubes, to first accumulate biomass (Green Stage) and then to stress the cells (by exposing them to higher sunlight intensity) to produce astaxanthin (Red Stage). During this process, the cultures are analyzed daily for biomass content, development stage, astaxanthin content, and the absence of any contaminants in the culture, as relevant. After reaching maximal astaxanthin content, the cells are pumped to the down-stream

processing facility and the algal cells precipitated. The algal slurry is collected and analyzed for astaxanthin content, biomass dry weight, and verified again for absence of contaminants.

The collected algal cells are 'cracked' (mechanically fragmented to disrupt the cell walls) and dried. The resulting, flake-like biomass, called 'Dried Algal Meal' or Algal Meal can be used as a standard astaxanthin product *per se* (for example as Salmonid feed pursuant to 21 CFR §73.35) or as the starting material for further extraction and concentration of astaxanthin.

Alternatively, the "Dried Algal Meal" is rehydrated with distilled sterile water and mixed with lecithin (E322, up to 2% of dry weight), ascorbyl palmitate (E304, up to 1% of dry weight), DL-alpha-tocopherol (E307, up to 0.2% of dry weight) and hydroxypropyl methylcellulose (HPMC, E464, up to 3% of dry weight). The mixture is dried by spray drying to form biomass powder, which is used as a standard astaxanthin product *per se*, or as the starting material for various astaxanthin preparations such as astaxanthin capsules and tablets.

Until used, the Algal Meal is vacuum packed into aluminum bags and stored at -4°C. Each lot of Algal Meal is analyzed as appropriate for astaxanthin, cracking efficiency, water content, microbial content, and heavy metals. Samples from each lot are held for further analysis for at least 15 months

For production of Natural Astaxanthin Complex (AstaPure), the dry Algal Meal is sent to pre-certified facilities for SCF (Super Critical Fluid) extraction of the astaxanthin using carbon dioxide as the extractant. Essentially, the Algal Meal is subjected to liquefied carbon dioxide at high pressure and elevated temperature. Under such conditions, non-polar (fat-soluble) materials, such as astaxanthin, astaxanthin fatty acid esters, and fatty acids are solubilized in the carbon dioxide and carried away from the biomass; while polar (water-soluble) materials, such as protein and carbohydrates, are left behind in the biomass. The resulting Natural Astaxanthin Complex (AstaPure) is freed of carbon dioxide by simply returning to ambient pressure and temperature. Samples are then analyzed for astaxanthin content, the oleoresin is standardized, diluted with natural edible oil to an astaxanthin content of 11 to 12%, packed in sealed food-grade containers under nitrogen, and stored at 3°C until shipment or use. A Certificate of Analysis is issued for each lot of AstaPure after microbiological and chemical analysis

AstaPure may be used *per se*, or as the starting material for various astaxanthin preparations such as astaxanthin powder, beadlets or capsules.

The described manufacturing process is near identical to the production of astaxanthin esters as described in Fuji Astaxanthin GRAS Determination GRN 000294. The only significant difference is that the Fuji astaxanthin esters are described as being extracted by a second method using acetone, which then must be removed from the extract. The

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Algatechnologies' astaxanthin oleoresin is only extracted using SCF carbon dioxide, and thus no potential solvent residues are in the product.

In addition, Natural Astaxanthin Complex or equivalent astaxanthin ester extracts are extracted from *H. pluvialis* biomass using SCF extraction for use in dietary ingredient and dietary supplement products, reviewed by the FDA and currently sold in the U.S. Examples are listed in Table 1. The SCF extraction method used by Algatechnologies to produce Natural Astaxanthin Complex thus follows established and accepted methods which have been used safely for products in the U.S. for over ten years and meet the requirements of 21 U.S.C 350b(a)(2).

TABLE 1. *Haematococcus* Astaxanthin Dietary Ingredient and Dietary Supplement Products Reviewed and Allowed by the FDA for Sale in the United States

Company	Product(s)	Description
Cyanotech Corp. (Kailua-Kona, HI)	BioAstin® Gel Caps SCE5 SCE7 Beadlets	4mg algal meal in gelatin capsules 5% astaxanthin SCF-CO ₂ extract 7% astaxanthin SCF-CO ₂ extract 1.35% astaxanthin gelatin beadlets
Mera Pharmaceuticals (Kailua-Kona, HI)	AstaFactor®	5 mg astaxanthin algal meal in soft gels
Fuji Health Science BioReal (Maui, HI) BioReal (Sweden)	AstaReal® Gel Caps L-10 P2AF	SCF-CO ₂ extract of algal meal 2 mg astaxanthin gelatin capsules 10% astaxanthin oleoresin 2% astaxanthin water dispersible
Valensa International (Eustis, FL)	Zanthin® Complex Vegetarian softgel Beadlets	SCF-CO ₂ extract of algal meal 5 mg astaxanthin gelcap 2.5% astaxanthin complex 2.0% astaxanthin complex
Algatechnologies Ltd Kibbutz Ketura Israel	AstaPure Oleoresin Capsules Beadlets	SCF-CO ₂ extract of algal meal 10 to 25% Astaxanthin oleoresin 4 mg astaxanthin gelatin capsules 2 to 2.5% astaxanthin granules

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D. Composition

SCF with carbon dioxide extracts almost exclusively lipid soluble materials from a biomass such as *H. pluvialis*, as shown in Table 2.

TABLE 2. Chemical Analysis of *H. pluvialis* SCF Extracted Natural Astaxanthin Complex (AstaPure) from Algal Meal

Component	Biomass (flakes or powder) (n=5)	Astaxanthin Oleoresin (n=10)
<i>g/100g</i>		
Fat ^a	33.4	98.2
Saturated fat	4.8	15.8
Mono-unsaturated	13.3	36.4
PUFA	15.4	46.7
Total fatty acids ^b	4.17	97.9
Total carotenoids ^c	3.81	10.2
Total astaxanthin ^c	3.75	10.1
Of which		
Astaxanthin mono-ester	89.9% (of Ax)	84.25% (of Ax)
Astaxanthin di-ester	7.29% (of Ax)	13.85% (of Ax)
Free astaxanthin	1.62% (of Ax)	2% (of Ax)
Analysis following enzymatic de-esterification:		
E-astaxanthin	80.36% (of Ax)	76.39% (of Ax)
9Z-astaxanthin	8.12% (of Ax)	14.07% (of Ax)
13Z-astaxanthin	10.12% (of Ax)	7.1% (of Ax)
Protein ^d	18.6	0.20
Carbohydrate ^e	24.4	<0.5
Dietary Fibers	18	<0.1
Ash ^f	2.4	0.07
Moisture ^g	3.6	0.35
<i>Major fatty acids (g/100g)</i>		
Palmitic (C16:0)	5.1	9.2
Oleic (C18:1)	9.17	36
Linoleic (C18:2)	8.8	30
Gamma-linolenic (C18:3n3)	6.8	13.5
Arachidonic (C20:4n6)	0.5	1
EPA (C20:5n3)	0.8	2
Total	31.17	91.7

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(Table 2 continues)

	n = 15	n = 15
Arsenic	<0.2 mg/Kg	<0.2 mg/Kg
Lead	<0.06 mg/Kg	<0.06 mg/Kg
Mercury	<0.01 mg/Kg	<0.01 mg/Kg
Cadmium	<0.01 mg/Kg	<0.01 mg/Kg
Total Plate Count, <100 CFU/g	Pass	Pass
Total coliforms, NMT < 10/g	Pass	Pass
<i>Escherichia coli</i> , NMT <10/g	Pass	Pass
Yeast, <10 CFU/g	Pass	Pass
Moulds, <10 CFU/g	Pass	Pass
<i>Salmonella</i> sp, 0 in 25 g	0	0

⁶AOAC Method 963.22⁷AOAC 963.22⁸Validated HPLC method. The only trace carotenoid detected is lutein⁹Tecator ASN 3106¹⁰AOAC 982.14¹¹AOAC 920.17¹²Standards of Israel, Section 2.2.3

The Natural Astaxanthin Complex is comprised primarily of fatty acids, astaxanthin, and minor amounts of other carotenoids and lipids. Three common food fatty acids comprise the fatty acid fraction of the extract: palmitic, oleic, and linoleic acids. The extract contains less than 1% of water soluble materials such as protein and carbohydrate. In addition, extracts showed no or acceptable levels of pesticides and heavy metals, and no traces of diphenylamine or toxins such as aflatoxin.

These analyses are similar and equivalent to the composition of the astaxanthin esters declared GRAS in the GRAS Determination GRN 000294, and to the astaxanthin *H. pluvialis* extracts of the subject NDIN filings listed in Section 1F, above, and further supports the GRAS determination for Algaltechnologies' Natural Astaxanthin Complex.

E. Intended Technical Effects

The intended uses of Natural Astaxanthin Complex (AstaPure) products are for addition to foods as a nutrient. Astaxanthin is found widely in marine animals and crustaceans including salmon, lobster, shrimp, crabs, and krill. It is an antioxidant, and has been shown to protect cellular and mitochondrial membranes against oxidative damage. One intended use for Natural Astaxanthin Complex is addition to foods intended for populations that do not consume animals containing astaxanthin, such as vegetarians. Another is for those who wish to supplement their diets with astaxanthin from algae.

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While the use of Natural Astaxanthin Complex may also impart a color to food products, the intended use of Natural Astaxanthin Complex will fall outside the definition of a 'color additive' for reasons cited by the Expert Panel in the Fuji GRAS Determination GRN 000294. These are: (1) the intended use levels are low enough that they do not impart a significant color to food products (21 CFR 70.3(f)), (2) Natural Astaxanthin Complex is solely added for its nutritive value and thus can be considered an 'unimportant color' (21 CFR 70.3(g)), and (3), the intended use of Natural Astaxanthin Complex in specified foods is to provide consumers with an additional source of dietary astaxanthin and does not relate to any use of Natural Astaxanthin Complex as a color additive (21 CFR 70.3(f)).

3. Summary of the Basis for the Determination that Astaxanthin Oleoresin is GRAS

The determination that AstaPure, Natural Astaxanthin Complex extracted from *Haematococcus pluvialis*, is GRAS is on the basis of scientific procedures, and equivalence of Natural Astaxanthin Complex to other astaxanthin extracts from *H. pluvialis*, including astaxanthin esters as detailed in Fuji Chemical Industry Co., Ltd. GRAS Determination GRN000294.

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SUBMISSION END

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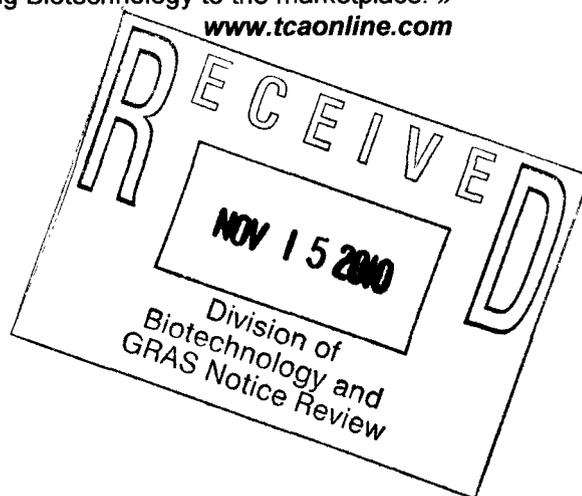
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9 November 2010

Carrie McMahon, Ph.D.
Consumer Safety Officer
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Division of Biotechnology and GRAS Notice Review
5100 Paint Branch Parkway
College Park, MD 20740-3835



Re: GRAS Notice 356

Dear Dr. McMahon:

On behalf of Algatechnologies (1998) Ltd., Kibbutz Ketura 88840, Israel, I hereby withdraw our GRAS Notification of 13 September 2010, *Natural Astaxanthin Complex (AstaPure)*, a *Haematococcus pluvialis* extract characterized by component astaxanthin esters of common edible fatty acids.

For Algatechnologies

Richard F. Taylor, Ph.D.
President
TC Associates Inc.