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January 9, 2002

Via FedEx

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

**Re: New Dietary Ingredient Notification for Astaxanthin Extracted from
Haematococcus Algae**

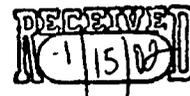
Dear Sir/Madame:

Pursuant to 21 CFR § 190.6, please be advised that Micro Gaia Inc. ("Micro Gaia") of Maui, Hawaii¹, is hereby providing you with notification of its intent to market a New Dietary Ingredient, namely astaxanthin extracted from *Haematococcus* algae. Micro Gaia will commence marketing of its astaxanthin extract 75 days after acknowledgment of your receipt of this notification, unless otherwise instructed by your agency. Enclosed with this original document are two additional copies of Micro Gaia's submission and the attachments thereto.

Based upon the following, Micro Gaia respectfully submits that there are no safety issues relating to its intended marketing of astaxanthin extracted from *Haematococcus* algae:

1. Micro Gaia produces its astaxanthin extract from *Haematococcus* algae grown at the company's facilities in Maui, Hawaii. The algae is cultivated in a proprietary Bio-Dome technology on Maui, which is constructed in a manner designed to ensure that the algae is grown under sterile conditions, free from pollutants and other environmental toxins. The facility has been inspected by the State of Hawaii and has been found to be in compliance with all applicable rules and regulations.

¹The company's facilities are located at: Maui Research and Technology Park, Premier Place, 535 Lipoa Parkway, Suite 177, Kihei, Maui, Hawaii 96753.



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2. The algae produced at the Maui facility will be extracted at Fuji Chemical Company, Ltd. ("Fuji") of Toyama, Japan. Fuji is a pharmaceutical ingredient supplier that has been in operation since 1946. Fuji is one of the leading custom manufacturers of bulk pharmaceuticals and chemicals for utilization in both Japan and the United States. Fuji's Toyama facility operates in compliance with all Current Good Manufacturing Practices applicable to companies whose pharmaceutical products are imported into the United States.
3. The name of the new dietary ingredient is astaxanthin, which will initially be marketed under the trade name AstaReal[™].
4. AstaReal[™] will initially be marketed in tablet form. Each tablet will contain 1mg of astaxanthin extract. The recommended dose of AstaReal will be 1 to 2mg daily. As noted in the attached report of Harry G. Preuss, M.D.² ("the Preuss Report"), this is well within the range of astaxanthin ingested in a .25kg serving of salmon. The Preuss Report specifically notes that the expected intake of astaxanthin from salmon can range from 10.1 mg per .25 kg serving of Sockeye salmon to a low of 1.325 mg per .25 kg serving of Atlantic salmon.
5. Haematococcus algae is found worldwide in nature and is believed to be the organism that can accumulate the highest levels of naturally occurring astaxanthin. The Preuss Report concludes that there are no reports of toxicity associated with Haematococcus algae in the published literature.
6. Astaxanthin is approved for use in Salmonid feeds at a maximum level of 80mg/kg pursuant to 21 CFR § 73.35. The data submitted in support of Color Additive Petition 7C0211(Roche Vitamins, Fine Chemicals, Hoffman LaRoche, Inc.) (the "Roche Petition") includes various toxicity studies involving astaxanthin, which was reviewed in conjunction with the adoption of 21 CFR § 73.35. The level required for acute toxicity for astaxanthin in rats over a 10 day period was at an oral dose in excess of 2000 mg/kg.
7. As noted in the Preuss Report, Haematococcus algae meal has been approved in Japan for use as a natural food color and as a pigment in fish feeds. Moreover, the Preuss Report further notes that the structure of astaxanthin is similar to other carotenoid pigments such as beta carotene and vitamin E. In light of this, and other information cited therein, the Preuss Report concludes that "astaxanthin is a

² Professor of Physiology, Medicine and Pathology, Georgetown University Medical Center, Washington, D.C.

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carotenoid and should be as safe as other carotenoid”.

8. This conclusion is supported by the Preuss Report’s review of the data submitted in conjunction with the Roche Petition. There, FDA was presented with data indicating toxicity in rats at extremely high levels, and an absence of mutagenicity in salmonella testing. Data also indicated that astaxanthin was well tolerated in pregnant rabbits who ingested doses of 100, 200 and 400 mg/kg/day over a 12 day period. Reproductive studies on rats and dogs revealed no perturbations from the high doses administered. Thirteen week tolerance tests on rats indicated an absence of toxic effects.
9. The Preuss Report further cites three toxicity-related studies conducted in humans. None of the studies, involving 78 subjects, indicated any evidence of adverse events from the consumption of astaxanthin.
10. The Preuss Report concludes that there “appears to be no question as to the safety of Micro Gaia’s astaxanthin product” and that “all evidence points to complete safety in the use of astaxanthin.”
11. A report prepared by ISSI Laboratories, Inc., dated October 31, 2001, concluded that, following testing for 62 chlorinated hydrocarbon pesticides, 59 organo-phosphorous/organo-nitrogen pesticides, 11 carbamate pesticides, heavy metals, toxins, and microorganisms, “AstaReal finished product was found to be free of all listed potential contaminants.” A copy of this report is attached hereto.
12. The conclusion to the Preuss Report also states that “Micro Gaia and the Food and Drug Administration can reasonably rely upon the Agency’s prior acceptance of safety data submitted by other companies marketing astaxanthin as a ‘new dietary ingredient’ in the United States.”
13. In light of the above, Micro Gaia hereby incorporates by reference FDA’s acceptance of safety related data in connection with docket number 95S-0316 by the following companies:
 - Igene Biotechnology, Inc May 4, 2000
 - Cyanotech Corp. May 25, 1999
 - Aquasearch, Inc. December 16, 1999
 - Cyanotech Corp. March 22, 1999

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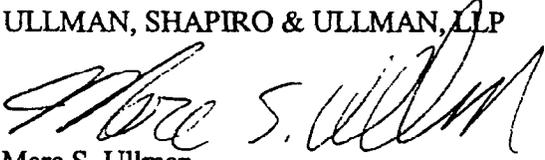
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Based on the foregoing, we believe that FDA should accept this filing on behalf of Micro Gaia as providing sufficient evidence that AstaReal, astaxanthin extracted from Haematococcus algae, when used under the conditions recommended in the product labeling, can reasonably be expected to be safe for human consumption. In support of this, we have also included testing data which reflect the purity of Micro Gaia's product as manufactured.

If you require any additional information, please direct all correspondence to the undersigned.

Very truly yours,

ULLMAN, SHAPIRO & ULLMAN, LLP



Marc S. Ullman

Encls.

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March 1, 2002

VIA FEDERAL EXPRESS

Gloria Chang

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Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)

Center for Food Safety and Applied Nutrition

Food and Drug Administration

5100 Paint Branch Parkway

College Park, MD 20740-3835

Re: Requested Information on New Dietary Ingredient, Astaxanthin.

Dear Ms. Chang:

As per your conversation with Marc S. Ullman, we are providing the following information you requested:

- the cultivation is of Genus-species: *Haematococcus pluvialis*.
 - the product will contain a warning that pregnant and lactating women should consult a physician before use.
 - there is no intention of including limits on duration.
 - recommended dose: 1-2 mg/day (daily).
 - attached are the full studies (or summaries) cited by Harry G. Preuss, MD in the previously submitted "Preuss Report".
1. Torrissen, O.J., R.W. Hardy, K.D. Shearer, Pigmentation of Salmonids -- carotenoid deposition and metabolism. *CRC Crit. Rev. Aquat. Sci.*, 1:209-225, 1989. (See www.astaxanthin.org for summary).
 2. Aquasearch, Inc., Technical Report TR.2102.001, 1999.
 3. Torrissen O.J., Christianson R., Requirement for carotenoids in fish diets, *J. Appl. Ichthyol.*, 11:225-230, 1995.
 4. Roche Laboratories: Carophyll Pink. <http://www.roche.com>

Gloria Chang
Department of Health and Human Services
March 1, 2002
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5. Turujman, S.A., Wamer, W.G., Wei, R.R., Albert R.H., Rapid liquid chromatographic method to distinguish wild salmon from aquacultured salmon fed synthetic astaxanthin, *J. AOAC Int.*, 80(3): 622-632, 1997.
6. Cyanotech Corporation, Technical Bulletin #060, A Technical Review of Haematococcus Algae, 1999.
7. Terao, J., Antioxidant activity of beta-carotene-related carotenoids in solution, *Lipids*, 24(7):659-661, 1989.
8. Miki, W., Biological functions and activities of animal carotenoids: *Pure App. Chem.*, 63:141-146, 1991.
9. Roche Vitamins and Fine Chemicals: Hoffman La Roche, Inc., Astaxanthin as a pigmenter in salmon feed. CAP 7CO211.
10. Ono, A., Sekita, K., Saitoh, M., Umenmura, T., Ogawa, Y., Furuya, T., Kaneko, T., Inoue, T., A 13 week sub-chronic oral toxicity study of haematococcus color in F344 Rats, *Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho Hokoku*, 117:91-98, 1999 [in Japanese; abstract provided].
11. Murillo, E., Hypercholesterolemic effect of canthaxanthin and astaxanthin in rats, *Arch. Latinoam. Nutr.* 42(4):409-413, 1992 [in Spanish; abstract provided].
12. Miki, W.W., Hosoda, K., Konko, K., Itakura, H.: Astaxanthin-containing drink. Patent Application number 10155459. Japanese Patent Office. Publication date June 16, 1998. [in Japanese + English translation].
13. Lignell, A.: Medicament for improvement of duration of muscle function or treatment of muscle disorder or diseases, Patent Cooperation Treaty application #9911251, AstaCarotene AB, Sweden.
14. Aquasearch, Inc.: Technical Report TR.3005.001, 1999.

As per our original filing, Micro Gaia hereby incorporates by reference FDA's acceptance of safety related data in connection with docket number 95S-0316.

Very truly yours,
ULLMAN, SHAPIRO & ULLMAN



Vanessa Riviere
Law Clerk