

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

ASTAXANTHIN DERIVED FROM *Haematococcus pluvialis* algae

Issue

The Finnish Competent Authority has prepared an initial opinion on an application for the authorisation of Astaxanthin derived from *Haematococcus pluvialis* green alga-rich in astaxanthin as a novel food ingredient (NI) under the Novel Food Regulation (EC) No. 258/97. The Committee is asked whether it agrees with the conclusions of the Finnish CA or whether it has any further comments or objections to make on the application. The Committee's advice will form the basis for the UK's formal response.

Introduction

1. On 23 January 2009, the European Commission forwarded the Finnish Competent Authority's (CA) initial opinion on an application made by BioReal (Sweden) AB under Article 4(1) of Regulation (EC) 258/97, for the authorisation of for two astaxanthin-rich preparations derived from *Haematococcus pluvialis* algae as a novel food ingredient in arrange of drinks. Under the time scales set out in the regulation, the UK and other Member States have until 23 March 2009 to provide comments and/or reasoned objections to the initial opinion.
2. The Finnish Initial Assessment Report is attached as **Annex 1** (restricted). The full dossier provided by the applicant is attached as **Annex 2** (restricted).

Background

3. This application from BioReal (Sweden AB) is for the use of astaxanthin in two forms. Astaxanthin is an ingredient originating from an algal source has a history of use in the EU in food supplements since 1995. However, its use in other food products is considered novel and requires a pre-market safety assessment.
4. In accordance with the European Commission Regulation 258/97, the applicant considers that the novel ingredient (NI) falls under Article 1(2)(e): foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals. Although the Finnish CA considered the application to fall under category (d): foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae, they noted that the difference in category has no

significance on the safety assessment because both categories correspond to class 1.1 under Commission Recommendation 97/518/EC, which sets out the guidelines for novel food applications. The requirements for a submission for this class are as follows:

I	Specification of the NF	X
II	Effect of the production process applied to the NF	X
III	History of the organism used as the source of the NF	X
IV	Effect of the genetic modification on the properties of the host organism	-
V	Genetic stability of the GMO	-
VI	Specificity of expression of novel genetic material	-
VII	Transfer of genetic material from GM microorganisms	-

VIII	Ability to survive in and colonise the human gut	-
IX	Anticipated intake/extent of use of the NF	X
X	Information from previous human exposure to the NF or its source	X
XI	Nutritional information on the NF	X
XII	Microbiological information on the NF	X
XIII	Toxicological information on the NF	X

5. The key issues for consideration are presented below under these headings.

I. Specification of the novel food

Annex 2, p.14-20

6. *Haematococcus pluvialis* is a green algae found in fresh and brackish waters and is the strain used to produce the NI. During environmental stress and nutrient limitation, individual algal cells accumulate lipids and astaxanthin to protect against oxidation and turn into dark-red highly resistant aplanospores and it the NI is obtained from these bodies.

7. The NI will be available in two forms, and for these will be referred to in this paper as a cell powder and an oleoresin :

- The cell powder consists of crushed and spray-dried aplanospores (5.0-5.6% natural astaxanthin, referred to as **AstaReal A1010** in the dossier)
- The oleoresin has an astaxanthin content of 10-12%, and an encapsulated form (astaxanthin content 2.5-2.7%, referred to as **AstaREAL L10** in the dossier)

8. The cell powder product is a spray-dried product consisting of biomass containing 10% protein, 42% fat, 40% carbohydrates and 5.0-5.6 % astaxanthin.

9. The oleoresin consists of the lipid component found in algae biomass, mainly triglycerides, fatty acids and carotenoids, which are collected by supercritical carbon dioxide extraction of the spray-dried algal meal. The carotenoid component and the extractable fatty acids are increased by a factor of 2.5. The typical composition of the oleoresin is 73% fatty acids and triglycerides and moisture <0.5%, total astaxanthin content of 10-12 g astaxanthin/100g viscous oil and astaxanthin is typically present as 80% monoester, 18% diester and 2% free astaxanthin.
10. The oleoresin is encapsulated using modified starch and is in powder form, and improves the emulsification of the product in the water-containing food matrix. Total astaxanthin content is typically 2.5-2.7%.
11. The applicant has provided information on the carotenoid component of both forms in Table 1, and similar data for the fatty acid component can be seen in Table 1, p18 of Annex 2. The applicant states that the anticipated daily intake of natural astaxanthin will be the same, despite which form of their novel ingredient will be used as a source of astaxanthin in the final end products:

Table 1. Typical carotenoid content in AstaREAL1010 and AstaREAL L10. Values given as % w/w (min-max).

Analysis	AstaREAL A1010	AstaREAL L10
Total astaxanthin	5.0-5.6 (5.0-5.4)	10.0-12.0 (10.3-11.1)
Trans-astaxanthin	4.2 (4.0-4.3)	8.3 (7.9-8.7)
9-cis-astaxanthin	0.63 (0.55-0.69)	1.86 (1.61-2.10)
13-cis-astaxanthin	0.37 (0.35-0.38)	0.46 (0.43-0.50)
Total carotenoids (TC)	5.4 (5.2-5.6)	11.2 (10.9-11.7)
Beta-carotene	0.02	0.03
Lutein	0.02	0.04
Canthaxanthin	0.02	0.06
Other	0.10	0.30

(AstaREAL A1010 is the **Cell Powder** form, AstaREAL L10 is the **Oleoresin** form)

12. The NI is manufactured under strict microbiological controls and in a food manufacturing plant approved by Swedish authorities in accordance with Swedish and European Community legislation. The aerobic plate counts are specified <1000 cfu/g for the oleoresin and <10,000cfu/g for the cell powder. The specification for yeast and mould is <100 cfu/g in total for both forms of the NI. Coliformic bacteria, staphylococcus and salmonella bacteria are not detected in the ingredient according to microbiological tests. The applicant is of the view that AstaREAL ingredients are thus unlikely to contain micro-organisms and/or their metabolites of adverse public health significance.

13. Both forms of the NI contain less than 0.1 ppm heavy metals (cadmium, lead and mercury) and less than 0.05 ppm of arsenic and no traces of aflatoxin nor pesticides. Results of analysis for potential algal toxins such as microcystin and saxitoxin indicate the absence of saxitoxin, however whilst 1 of 3 samples tested positive for microcystin (0.3 µg/g), this was found to be below a US regulatory maximum level (see para 56 below).
14. The applicant proposes to state on labels of foods containing the novel ingredients that one portion contains 2-6 mg astaxanthin and that consumption of one portion of food containing the NI per day is recommended.
15. The **Finnish CA** considered that the compositional analysis provided by the applicant is sufficient.

II. Effect of the production process applied to the novel food

Annex 2, p22-35

16. The applicant provides an overview of the technical process as a flow chart in Appendix 8. The algae are cultivated in sterile flasks where the culture is fed with sterile-filtered water and nutrients from specially prepared media lots (made in-house). The flasks are then transferred to a stainless tank after several cultures have reached a specified level. The algae are matured by limiting nutrient availability and increasing light intensity and harvested by decanter centrifuge. The resulting slurry is homogenised and passed through a ball mill to crush cells. This is collected in a cooling tank and then spray-dried as a batch production where each batch is stored in a freezer. Quality control analyses are conducted on each spray-dried batch before approval according to specifications and release. The algal meal contains ≥5% astaxanthin (w/w) and is pasteurised before being vacuum sealed in aluminium bags ready for shipment. The cell powder based product is then either marketed in this form, or it is further processed to produce the oleoresin.
17. The oleoresin is extracted from the dried algal meal by a supercritical carbon dioxide extraction method (See Section 6.2.2 of Annex 2 for details) which extracts the fat soluble components (40-45%) of the meal. Most other components are excluded from the extract (carbohydrates, proteins, minerals (ash <0.2%), chlorophylls and water)
18. The applicant has conducted studies to determine the effect of the proposed food matrices on the NI. These studies determined the shelf life of each of the products based on recoverable astaxanthin. These studies found the shelf life of drinking yoghurt, flavoured yoghurt and low pasteurised fruit drink in cool storage to be 5

weeks, soya yoghurt (3 weeks), fruit mix (compote type product for addition into yoghurt) (3 months), pasteurised fruit drink and UHT milk (9 months).

19. The **Finnish CA** was of the view that the information provided on the production method of the NI and information on the quality of the end products was sufficient. The Finnish CA had no comments on the use of these ingredients in the manufacture of the final food products.

III. History of the source organism

Annex 2, p. 36-38

20. *Haematococcus pluvialis* proprietary strain AC032 is used as the source of the novel food. *H. pluvialis* occurs naturally in the food chain. It is consumed by zooplanktons and crustaceans which in turn are consumed by fish. As it is naturally high in astaxanthin it is used in aqua culture feed for farmed salmon, sea bream, and prawns increase the pink coloration of their flesh. It has been approved as a colour additive in salmon feeds in the US, Japan and Canada and is classified as feed raw material in Sweden where it is also used in poultry feed.
21. The algal meal (cell powder) of *H. pluvialis* has a history of use as dietary supplements in the EU since at least 1995 and in the US since at least 1999.
22. The **Finnish CA** was satisfied with the information provided on the history of use of the production organism and had no further comments.

IX. Anticipated intake/extent of use of the novel food

Annex 2, p.22-27

23. The NI is intended to be added into a range of fermented (yoghurt type) and non-fermented liquid dairy products and their soya based counterparts. The applicant also seeks authorisation for fruit based drinks (e.g. nectars).
24. The applicant has advised that the label and other marketing material will recommend consumers to consume one portion of food containing the NI per day which will contain a maximum of 6 mg astaxanthin. Fermented and non-fermented fluid dairy products, fermented soya products and fruit drinks, with a portion size of 200-250 mg, will therefore contain 0.8-2.4 mg astaxanthin per 100 g or 100 ml.
25. The applicant has used national dietary survey data from Sweden, Finland and Great Britain (GB) to calculate potential high level intake of astaxanthin enriched foods. Consumption of fermented soya products is assumed to be the same as yoghurt-type products as they are likely to be consumed as an alternative. Because the likely daily intake of the NI is dependent on the level of incorporation, the applicant has presented mean and high level intake estimates as a range rather than assuming the higher (6mg) level of incorporation per portion.

26. The applicant has also considered the scenario where consumers do not follow the recommendation to consumer only one portion of astaxanthin-containing foods per day, and they replace all conventional yoghurts, sour milk, juice and nectar with astaxanthin-rich counterparts. In Sweden the cumulative daily intake of astaxanthin would be 3.5-10.4 mg (range 2-6mg.portion) and in Finland and GB, it would be 1.8-21.6 mg respectively.
27. The applicant has estimated high level consumption (95th percentile) could be 8.8-26.6 mg in Sweden and 18.6-56.0 mg per day in Finland and GB. The applicant is of the view that the calculations concerning Swedish consumers are more reliable because real food consumption data are used rather than the theoretical calculations from Finland and GB, For example, the applicant has not used the raw data from the NDNS survey, and high level intake for GB has been estimated simply by adding the high level intakes for the three individual food categories. The applicant also points out that according to data from Finland and GB, the amount of yoghurt, milk and fruit drinks will be over 2.3 kg a day if they are all consumed at a high level.
28. Based on the toxicological information reviewed in XII (below) , the applicant concludes that there is no evidence of any toxic effects with 42 mg daily intake of astaxanthin in a normal 60 kg adult. The applicant therefore contends that the cumulative intake of astaxanthin in Finnish and British consumers (up to 21.6 mg/day) and the high cumulative intake in Swedish consumers (up to 26.6 mg/day) are not expected to be a risk to consumers. The applicant does not discuss the high level (95th percentile) intake figure ('up to' 56 mg/day) for Finland and the UK as they view such cumulative intake to be very unlikely to occur. The applicant does not consider consumption by children as the products will not be targeted at this group of the population.
29. The applicant states that, based on the studies on astaxanthin and the NI, there are no population groups who would be at a specific risk if consuming astaxanthin and notes that all products containing the NI will be targeted solely at adults and not recommended for children, pregnant or breast-feeding women or people with chronic diseases. The applicant anticipates that products containing the NI are intended to be an addition to the diet, or to replace traditional fermented and non-fermented dairy products, fermented soya products or fruit drinks. The limited labelling information provided does not indicate how products containing the NI could be avoided by the non-target groups
30. The Finnish CA is of the view that daily intake of astaxanthin recommended by the applicant has not been observed to have any effects on the nutrition status. The Finnish CA notes that no recommended daily dose or ADI value is defined for astaxanthin but the applicant's proposal for enriched foods to contain 2-6 mg of astaxanthin and a recommendation that only one such dose should be consumed

daily is consistent with the recommended daily intakes for food supplements containing astaxanthin.

X. Information from previous human exposure to the novel food ingredient

31. The applicant states that *H. pluvialis* and other astaxanthin producing algae are part of the food chain and therefore many types of fish and crustaceans, including trout, salmon etc accumulate astaxanthin in their tissues and skins. Among the seafood, salmon has the highest content of astaxanthin. The applicant provides astaxanthin content of different salmonids in Table 12 of the dossier. Humans have ingested astaxanthin to varying degrees depending on the importance of seafood in the diet of various populations. Salmon and trout are the major dietary sources of astaxanthin in humans in Europe.
32. The applicant highlights a review of the astaxanthin intake in fish conducted by the EFSA FEEDAP Panel (2005) which reported that consumption of Atlantic salmon in Europe is 0.9 kg per head a year and consumption of trout is no more than 0.3 kg per head a year (based on salmon and trout production in Europe). This corresponds to annual astaxanthin intake of 9 mg from salmon and 7.5 mg astaxanthin from trout at most, or a mean daily astaxanthin intake is 0.045 mg. High level (97.5th percentile) consumption of these fish would result in astaxanthin intake of 1.6-4.1 mg.
33. The applicant notes also that astaxanthin has been marketed as dietary supplement by several companies and the most common daily dosage of food supplements is 4 mg astaxanthin. In 2006, the applicant successfully claimed equivalence of their oleoresin product (to be used in dietary supplements) to the cell powder used in existing astaxanthin rich supplements. In Japan, several astaxanthin enriched food supplement type drinks (tea, orange fruit juice etc) are or have been marketed for a number of years. The daily dose of those products varies from 0.5-15 mg. The applicant provides examples of the products marketed in Japan in Appendix 11.
34. The applicant is of the view that foods enriched with their ingredients are unlikely to give any rise to nutritional, microbiological, and toxicological or allergenicity issues because the level of astaxanthin incorporated do not exceed the current levels consumed in food supplements.
35. The Finnish CA notes that the applicant does not provide any information on the previous use of their ingredients, but was satisfied with accounts of the previous use of astaxanthin-enriched products.

XI. Nutritional information on the novel food

Annex 2, p.51-64

36. The cell powder consists of 10% proteins, 42% fat and 40% carbohydrates. Total astaxanthin content is typically 5.0-5.6 % which equates to 5.0-5.6 g astaxanthin /100 g powder. The astaxanthin is esterified with various fatty acids, typically comprised of 80% monoester, 18% diester and 2% free astaxanthin in the biomass.
37. The oleoresin is nutritionally mainly fat. Typical chemical composition is 73% fatty acids and triglycerides and moisture is >0.5% w/w. It also contains 2.5% of DL- α -tocopherol added as a processing antioxidant before spray-drying the microalga. Total astaxanthin content is typically 10.0-12.0% which equates to 10.0-12.0 g astaxanthin/100 g and this is typically comprised of 80% monoester, 18% diester and 2% free astaxanthin. The oleoresin can be encapsulated with modified starch (73%) and added antioxidants for use in powder form.
38. **Metabolism of astaxanthin:** The EFSA FEEDAP panel reviewed astaxanthin metabolism in humans based on a study by Kristler et al. (2002). The study was carried out *in-vitro* in primary human hepatocytes and identified 3-hydroxy-4-oxo-beta-ionol and 3-hydroxy-4-oxo-beta-ionone as the main free metabolites. The same compounds and their reduction products were also present as glucuronides. These four metabolites were also identified in the plasma taken from two human volunteers 24 hours after oral administration of 100 mg astaxanthin. Results showed that the C9, C9' cleavage of the astaxanthin molecule and reduction of the polyenic 7, 8-double bond are common to the human and the rat whereas the reduction of beta-ionone to beta-ionol is specific to the human. Astaxanthin concentration in plasma after dosing with 40 mg of astaxanthin per day during 4 weeks is around 125 $\mu\text{g/l}$ plasma corresponding to 0.2 μM astaxanthin. It is thought that a dose of 6 mg of astaxanthin per day is unlikely to induce the liver enzymes.
39. **Carotenoid interactions:** Based on the findings of a published study, carried out in 1999, the applicant postulates that explanations for carotenoid interaction appear to be competition for incorporation into micelles, carotenoid exchange between lipoproteins in the postprandial state and inhibition of beta-carotene cleavage. In human supplementation studies, a combined dose of beta-carotene and canthaxanthin (both 25 mg) resulted in lower plasma canthaxanthin compared with separate doses (25 mg) but no beta-carotene response occurred. Combined dose of beta-carotene and canthaxanthin (both 25 mg) in another study inhibited canthaxanthin appearance in the VLDL fraction. Based on these results, it looks unlikely that astaxanthin intake would disturb the beta-carotene balance.
40. The applicant states that astaxanthin has perceived nutritional benefits such as reducing symptoms of eye fatigue, enhancing muscle endurance and reducing recovery after exercise, reducing symptoms of functional dyspepsia and

heartburn, enhancing moisture content and elasticity in skin and protecting from UV-induced damages and enhancing sperm functionality. A detailed summary of these benefits has been provided by the applicant, but such functional benefits appears to be of little significance in the context of this safety assessment.

41. The applicant states that no clinical studies on children and pregnant and breast-feeding women have been carried out with the NI although a report of a single generation reproductive toxicity (including developmental toxicity was reviewed by the EFSA FEEDAP panel in 2005 which showed that there were no statistically significant adverse effects at 400mg/kg body wt. testing. Given the limited safety studies it is not possible to determine a NOEL (no-effect level) or ADI (acceptable daily intake). The applicant does not recommend that the NI should be consumed by children, pregnant and breast-feeding women because of lack of research.
42. The applicant intends to conduct post-launch monitoring (PLM) of its NI ingredients. The applicant is of the view that the NI will be marketed only by a few companies during the first few years, although does not explain why this would be the case. The applicant advises that some of these companies will perform consumer tests for up to 6 months to check tolerance and adverse effects. The companies will also have a customer service telephone line. The applicant intends to obtain the results from consumer tests and customer services reports from marketing companies. Information of the sale of enriched end products and ingredients will also be gathered yearly by the applicant. The applicant does not indicate what action would be taken in the light of any adverse reactions, and why the initial 6 month period is sufficient to ensure that adverse reactions will be detected.
43. The **Finnish CA** noted that the clinical studies on astaxanthin have mainly focused on its perceived beneficial effects, and as a consequence did not assess nutritional aspects in detail. However as the clinical studies were 3-6 months in duration and no nutritional problems were reported in studies on laboratory animals, it was content that daily astaxanthin intake of 6 mg is not harmful to healthy adults.
44. The **Finnish CA** viewed the assessment of positive health effects of astaxanthin falls under Regulation (EC) 1924/2003 and did not offer any view on perceived benefits that may be attributed to the consumption of the NI. The Finnish CA viewed the applicant's proposal to carry out a programme of PLM to be useful.

XII. Microbiological information on the novel food

Annex 2, p.65-67

45. The ingredients are produced in a food manufacturing plant approved by the Swedish authority in accordance with Swedish and European Community legislation. As stated in the product specifications the aerobic plant count is less

than 10 000 cfu/g (cell powder form) and less than 1000 cfu/g (oleoresin form). Yeast and mould are less than 100 cfu/g in total for both forms. *E. coli*, *Staphylococcus* and *Salmonella* bacteria are not detected in the ingredient in either form. The applicant provides results of microbiological analyses for both products in the Appendix, and states that its ingredients do not contain micro-organisms and/or their metabolites of adverse public health significance.

46. Production and analysis are carried out according to HACCP and under ISO 9001 processes. Only specified and approved food grade raw materials are used in the manufacture of the NI. The applicant conducts all the carotenoid analysis in their validated laboratory and microbiological analyses are conducted by an independent laboratory using accredited analytical methods.
47. The **Finnish CA** notes that the end products are a cell powder form which has undergone heating processes and has low water activity and the oleoresin which is pasteurised before vacuum packing. It notes that microbial flora of such products only contain micro-organisms transferred from the industrial environment, because the heating included in the manufacturing process influences the microbial flora of the initial material. The Finnish CA was content that the manufacturing takes place in a plant approved for food manufacturing.
48. The **Finnish CA** concluded that the information provided on the microbiological quality of the production and end products is sufficient and concludes that the end products are acceptable and stable as regards their microbiological quality.

XIII. Toxicological information on the novel food

Annex 2, p.68-94

49. The applicant points out that astaxanthin is extensively used in fish feed and the EFSA FEEDAP (2005) opinion on the safety of astaxanthin has been used as a data source for studies published before 2005.
50. The applicant describes acute and sub acute oral toxicity studies conducted on Sprague-Dawley rats fed on the NI. The applicant considers that results of the studies indicate acute toxicity is extremely low because doses of 10 g/kg (cell powder) and 2 g/kg (oleoresin) did not product overt toxicity.
51. **Subchronic and chronic toxicity studies with the NI:** In a 13-week study, rats received the biomass at dose levels up to 200,000 ppm. This dose was well tolerated without any adverse signs of toxicity and was associated with minor histopathological changes in the kidney. The applicant considers a dose level of 200,000 ppm (20 g/kg bw/day biomass or 70 mg/kg bw/day astaxanthin) to represent NOAEL under the conditions of the study. In another 13-week toxicity study were rats were fed AstaREAL oil 50F. (The Secretariat notes that this is a different product code to those used for the NI, para 7 above). The non-toxic

dose was estimated to be 925.9 mg/kg. Although not stated in the study report, the applicant considered the NOAEL value to correspond to 50 mg/kg bw/day astaxanthin. The applicant considers that 70 and 50 mg/kg/day are conservative estimates since in both of these studies; the highest dose administered did not produce toxicity. The corresponding ADI values are 0.7 or 0.5 mg/kg bw/day, assuming a safety factor of 100. This translates to 42 or 30 mg/day in a 60 kg adult consumer. The applicant states that no chronic toxicity studies have been carried out with the products.

52. Genotoxic and mutagenicity studies with the NI: A bacterial mutation test of the cell powder form showed no biologically significant increases in the numbers of revertant colonies in any tester strains after treatment with the test material. The applicant therefore concludes that *H. pluvialis* biomass is non-mutagenic. In addition, bacterial mutation, in vitro mammalian and mouse micronucleus test of biomass indicated astaxanthin was not mutagenic or clastogenic.

53. The applicant reports that reproductive and developmental toxicity studies have not been carried out with the NI and refers to studies considered by EFSA in its review of a number of toxicological tests carried out with products containing astaxanthin (the pure compound, biomass, extracts). There were no maternal, embryotoxic or teratogenic effects in a teratology study in rabbits given up to 400 mg astaxanthin/kg over most of the gestation period. No adverse effects were noted in a one-generation reproduction study in rats at the same dose level.

54. Clinical studies: The applicant provides a summary of the clinical studies conducted on astaxanthin in Tables 17 and 18 (Annex 2, p 86 and 89). The applicant notes that only a few clinical studies with astaxanthin have safety-related primary end-points and that the studies are relatively short in duration (4 to 8 weeks). The applicant considers that additional safety assurance can be obtained from the numerous clinical studies addressing the effects of astaxanthin on specific end-points such as dyspepsia, eye function etc. None of these studies revealed clinically significant adverse effects of astaxanthin during up to 6 months of treatment.

55. Toxicity of other compounds present in the oleoresin:

(a) Canthaxanthin: The applicant notes that the cell powder contains 0.02% canthaxanthin, which is a carotenoid previously used in tanning products and which has been reported to cause adverse effects such as depositing on the retina of eyes of primates. The applicant considers that ingestion of the canthaxanthin from the cell powder and oleoresin added in food would be largely below the levels encountered in foods that are considered safe by the U.S Food and Drug Agency (FDA) (a level of 66.1 mg/kg). The applicant contends that it would be impossible to consume the amounts of food resulting to hazardous

canthaxanthin levels. In addition it notes that astaxanthin has not been reported to cause changes in the retina in experimental animals or humans.

56. **(b) Microcystin and saxitoxin:** The applicant reports that analysis performed on the cell powder product indicated the absence of saxitoxin and in one sample out of three samples tested, 0.3 µg/g of microcystin; however this was below the 1 µg/g maximum the Oregon Department of Health Regulatory allows in blue-green algae containing food supplements. An additional HPLC analysis conducted on the cell powder for four algal toxins did not detect microtoxin-LR, nodularin, anatoxin-a or cylindrospermin. As oleoresin is produced from cell powder, the applicant concluded that this also does not contain these compounds.
57. **Pheophorbide a:** The applicant is aware that the NI contains low levels of pheophorbide a, a decomposition product of chlorophylls which can cause photosensitive dermatitis in humans. *Haematococcus* biomass harvested by the applicant has very low chlorophyll content, typically not more than 0.25%. The level of pheophorbides in its ingredients is low, 17 mg/100 mg or less in the cell powder and much less in the applicant's enriched products. The applicant is of the view that it is not possible that pheophorbide a present in its ingredients would cause any risk for photosensitive dermatitis due to the low level of pheophorbide a.
58. **Allergenicity:** No studies addressing allergenicity have been carried out by the applicant. Based on the marketing of Astaxin, a food supplement consisting mainly of the cell powder and marketed since 1995, of over 30 million units sold, eight allergic-related reactions have been recorded (nettle rash and some cases of swollen eyes and throat). The cell powder contains 10% protein and soy lecithin. In line with EC labelling requirements, all cell powder ingredients and enriched products will be labelled as containing soy lecithin. The oleoresin does not contain any proteins and therefore it is not anticipated to cause allergenic reactions.
59. The **Finnish CA** was of the view that because no teratology studies have been conducted on astaxanthin, the NI should not be used by children or during pregnancy or breast-feeding. There is limited information on astaxanthin metabolism in humans and thus its effect on the absorption of provitamin A carotenoids or other fat-soluble vitamins when used above natural doses has not been established. The Finnish CA notes that in cell models high astaxanthin doses have been shown to influence, among other things, the activity of the CYP3A4 enzyme. This enzyme influences the metabolism of many medicinal substances and thus the potential interaction of astaxanthin and medicines remains unclear. They therefore recommend that the use of astaxanthin-enriched foods should be directed to healthy adults.

60. The Finnish CA accepted the applicant's view that levels of canthaxanthin were too low to be a cause for concern. However, the Secretariat wishes to highlight a 2007 publication which postdates the EFSA FEEDAP opinion and which indicates that, in rats, astaxanthin accumulates in the eye to the same extent as canthaxanthin (**Annex 3**).
61. The Finnish CA notes that no adverse effects were reported in the toxicity studies and clinical trials performed on the applicant's products, which the . An exception was the 13-week toxicity test on oleoresin where elevated prothrombin time and activated partial thromboplastin time values were shown in male rats at the highest dose of astaxanthin used (about 50 mg/kg/day). The researchers did not consider this isolated finding as toxicologically significant. The Finnish CA was not able to assess the significance of the findings because no results or original data were provided in the Appendix to the application. The Finnish CA however notes that the significance is likely to be quite small, because no effects on blood coagulation have been reported in other studies.
62. The Finnish CA notes that although it could have been useful to examine the composition of the protein contained in cell powder in further detail, neither of the applicant's products is likely to pose any significant allergenic risk. Information on soy lecithin contained in cell powder must be given for both the product and food containing the product as set out in the rules for product labelling under Directive 2000/13/EC.
63. The Finnish CA concludes that the applicant has provided sufficient information on cell powder and oleoresin products in order for them to be placed on the market in fermented or non fermented fluid dairy products, fermented soya products or fruit drinks. The Finnish CA notes that the use of astaxanthin-enriched foods should be directed to healthy adults and supports the applicant's proposal concerning the package labelling to give information on the daily intake of astaxanthin. The Finnish CA considers the post-launch monitoring programme by the applicant as useful to follow both the intake and the distribution of the consumption of astaxanthin-enriched foods and recommends its implementation.

Committee Action Required

64. The Committee is asked whether it agrees with the initial opinion from the Finnish CA that astaxanthin-rich cell powder and oleoresin produced by BioReal Sweden AB should be granted authorisation as a novel food ingredient in fermented and non-fermented fluid dairy products, fermented soya products and fruit drinks and whether it wishes to make any additional comments on the application.

Secretariat

Annexes attached:

Annex 1 – Finnish Competent Authority's initial assessment report on Astaxanthin (RESTRICTED)

Annex 2 – Application dossier submitted by BioReal Sweden AB for the approval of natural astaxanthin rich ingredients: AstaREAL A1010 and AstaREAL L10 as a novel food ingredient (RESTRICTED)

Annex 3 – Pietri, D and Lundebyea , A-K (2007). Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology Volume 145, Pages 202-209. "Tissue distribution of astaxanthin in rats following exposure to graded levels in the feed"

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

RESTRICTED

Finnish Competent Authority's Initial Assessment Report

**Secretariat
February 2009**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

RESTRICTED

Application dossier submitted by BioReal Sweden AB for the approval of natural astaxanthin rich ingredients: AstaREAL A1010 and AstaREAL L10 as a novel food ingredient

**Secretariat
February 2009**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology
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"Tissue distribution of astaxanthin in rats following exposure to
graded levels in the feed"

Dietrich Petri and Anne-Katrine Lundebyea,
National Institute of Nutrition and Seafood Research, N-5817 Bergen, Norway

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