Request for an opinion on the substantial equivalence of an astaxanthin-rich extract of *Haematococcus pluvialis* algae (AstaPure™) with the existing algal meal product for use in human dietary supplements

Submitted by:

Algatechnologies (1998) Ltd.
Kibbutz Ketura 88840
Israel

Contents

Introduction 2
Composition 2
Carotenoid profiles. 3
Fatty acids 5
Other constituents 5
Nutritional value 8
Metabolism 8
Intended use 9
Level of undesirable substances 9
Trace elements 9
Pesticide contamination 11
Microbiological contamination 11
Manufacturing quality control 12
Conclusion 12

Appendices

Appendix A ACNFP Opinion on the substantial equivalence of astaxanthin-rich carotenoid oleoresin extracted from *Haematococcus pluvialis*. FSA June 2004.

Appendix B Algatechnologies Ltd. Production flow chart. (Confidential)

Appendix C Supercritical carbon dioxide extraction process description. (Confidential)

Appendix D Analytical comparison of samples of astaxanthin oleoresins derived from the same source but extracted in different extraction facilities. Food Chemical Risk Analysis, UK. 2006.

Appendix E Manufacturers Safety Data Sheet.

Appendix F Sample copy of product label.

Appendix G Screening for pesticide residues.

Appendix H Microbiological test report and certificates of analysis

Appendix I Certificates of compliance with ISO 9001 and HACCP quality control programmes. (Confidential)

Introduction

Algatechnologies Ltd. (1998) wishes to market its natural astaxanthin product, AstaPure™, in the EU for use in dietary supplements. The company intends to notify the European Commission using the simplified procedure provided under the terms of Article 5 of the Novel Foods Regulation (EC) 258/97. To satisfy the Regulation it is necessary for the company to provide an opinion delivered by one of the competent bodies referred to in Article 4(3), that the food or ingredient is substantially equivalent to existing foods or food ingredients as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained therein. Accordingly the company is submitting this request for an opinion from the UK Food Standards Agency on the substantial equivalence of AstaPure oleoresin to *Haematococcus pluvialis* algal meal and oleoresins already available on European markets.

The substantial equivalence of algal oleoresin derived from Algatechnologies algal meal to the whole-algal product was established in an opinion given by the ACNFP to Valensa (US Nutra) in 2004 (Appendix A). At that time Algatechnologies was the supplier of *H.pluvialis* to Valensa. The substantial equivalence of Cyanotech Corporation's oleoresin extracted from *H.pluvialis* by supercritical CO_2 to whole algal meal was also recently confirmed by the ACNFP[1]. Substantial equivalence for both products was based on the whole algal meal marketed by the Swedish company AstaCarotene (now a subsidiary of Fuji Chemical Industry Co, Ltd.) in the EU since before 1995. In October 2005 UK Food Standards Agency confirmed that it was lawful for Algatechnologies to market their product, processed by Valensa in Europe. Algatechnologies now intends to extract the oleoresin at a European plant using the same CO_2 technology used by Valensa and Cyanotech and to market the product in the EU.

Algatechnologies will demonstrate that oleoresin produced by supercritical CO_2 extraction at their European plant is indistinguishable from the Valensa product produced from the identical starting material, and by implication is also substantially equivalent to whole algal meal. As required by Article 3(4) of Regulation (EC) No 258/97, the company will provide comparative data and information on the composition, nutritional value, metabolism, intended use and level of undesirable substances relating to AstaPure algal bioresin.

Composition

Algatechnologies' proprietary and patented cultivation process employs a closed tubular system for cultivating enriched cells that provide a high concentration of astaxanthin in the algal biomass. The two-stage (green and red) process, including optimised growth conditions and strain selection, produces a fine, free-flowing red flake (Appendix B). By improving control of

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[1] UK Competent Authority Opinion on substantial equivalence of Astaxanthin-rich oleoresin extracted from *Haematococcus pluvialis* considered under article 5 of the Novel Foods Regulation. February 2007.

various parameters, Algatechnologies' closed-system production techniques eliminate significant disadvantages of open pond algae systems, such as the introduction of heavy metal and microbiological contaminants.

Algatechnologies produces its extract from the H. pluvialis algal biomass, using supercritical CO_2 extraction. The extraction process is described in Appendix C (Confidential). The manufacturing specification for Algatechnologies' oleoresin is:

Appearance:	Dark red viscous oleoresin
Astaxanthin complex:	Min. 10 % (Spectrophotometric Method)
Moisture:	≤ 5% (Karl Fischer)
Solubility:	Lipid soluble
Heavy metals:	≤ 10 ppm as lead
Microbiological Data:	
Total plate count:	< 1000 cfu/gr
Yeast and moulds:	< 100 cfu/gr
E. coli, Salmonella, P. aeruginosa S. aureus:	Absent

Algatechnologies' oleoresin has been subject to extensive chemical analysis in comparison with the previously authorised oleoresin (US Nutra/Valensa) and the whole biomass. The results have been compiled into a comprehensive report (Appendix D) and are summarised below. In the following tables "extractor 1" indicates oleoresin from Algatechnologies' biomass extracted at the Valensa plant and extractor 2 indicates oleoresin from Algatechnologies' biomass extracted at the extraction facility in Europe.

Carotenoid profiles.

The carotenoids present in *H. pluvialis* biomass and in samples of oleoresin extracts were determined by HPLC with UV/vis detection at 472 nm with and without hydrolysis of esters. Carotenoid profiles of oleoresin extracted from Algatechnologies' biomass at the Valensa facilities and European facilities and of AstaCarotene algal meal and the Cyanotech product (BioAstin) are provided in Table 1. The E-isomer of astaxanthin was dominant in all samples where measured although extracts showed a slight shift towards the Z-form. Shifts between geometric isomers are known to happen as a result of environmental conditions (temperature, solvents, etc.). The majority of astaxanthin was present as the mono-esterified form, with lesser amounts as the di-ester and minimal amounts of free astaxanthin. Esterification did not appear to vary between the biomass and extracted forms.

All samples showed similar profiles of the minor carotenoids present (beta-carotene, canthaxanthin, lutein). Absolute concentrations of total carotenoids would not differ between the two extraction processes because both are adjusted with olive oil to give 10.2% astaxanthin complex (total carotenoids), which will deliver at least 10% pure astaxanthin in the final product.

Table 1. Carotenoid profiles of *H. pluvialis* biomass and samples of oleoresin extracts (%, w/w of product)

	Biomass		**Oleoresin**					
	Asta-Carotene (1)	**Alga-technologies' (2)**	**Algatechnologies' product extracted by Extractor 1 (2)**		**Algatechnologies' product extracted by Extractor 2 (2)**		**BioAstin (3)**	
Batch		**AST00406**	**EXT050809**	**EXT110524**	**EXT060201**	**EXT060211**	**(5%)**	**(10%)**
E-astaxanthin	1.54	3.69	8.35	8.10	7.58	8.25	3.71	7.02
9z-astaxanthin	0.33	0.22	1.05	1.13	1.73	1.33	1.00	1.95
13z-astaxanthin	0.35	0.10	0.51	0.68	0.70	0.42	0.46	1.22
15z-astaxanthin	ND	0.07	0.19	0.19	0.10	0.09	0.04	0.06
diZ astaxanthin	ND	ND	ND	ND	ND	ND	0.07	0.19
Total astaxanthin	**2.22**	**4.02**	**10.05**	**10.01**	**10.08**	**10.04**	**5.28**	**10.47**
Free astaxanthin	ND	0.05	0.22	0.24	0.12	0.18	ND	ND
Mon-esters	ND	3.37	8.66	8.78	8.11	8.49	ND	ND
Di-esters	ND	0.67	1.22	1.08	1.87	1.42	ND	ND
Beta-carotene	0.140	0.01	0.01	0.02	0.01	0.01	0.13	0.26
Canthaxanthin	0.002	0.02	0.05	0.05	0.02	0.04	0.14	0.15
Lutein	0.001	0.04	0.07	0.09	0.08	0.09	0.22	0.18
Zeaxanthin	ND	0.01	0.00	0.01	0.01	0.01	ND	ND
Violaxanthin	ND	0.00	0.01	0.02	0.01	0.01	ND	ND
Total other carotenoids	**0.143**	**0.07**	**0.15**	**0.19**	**0.12**	**0.16**	**0.49**	**0.59**
Total carotenoids	**2.36**	**4.09**	**10.20**	**10.20**	**10.20**	**10.20**	**5.77**	**11.06**

(1) Data reported in US Nutra submission to FDA Dept of Health and Human Services (2005).
(2) Individual carotenoids determined by HPLC, total carotenoids by spectrophotometry (Appendix D).
(3) BioAstin carotenoid profiles reported in Cyanotech submission to UK authorities, May 2006.

Although small differences in ratios of *cis* and *trans*-isomers, esterification and other carotenoids can be seen between the algal biomass and oleoresin extracts, these do not appear to be systematic and differences between the two extraction process were not statistically significant at the $p<0.05$ level (paired two-sample t-test). Samples of *H. pluvialis* algal biomass show inherent variation in measured ratios of *cis*- and *trans*-isomers, which probably relate to differences in production systems, growing conditions, etc.

Carotenoids extracted from Algatechnologies' biomass by extractor 1 have been judged to be substantially equivalent to the whole algal meal previously marketed in Europe. The extract produced by extractor 2 has an indistinguishable carotenoid profile and must therefore also be substantially equivalent to the whole algal meal previously marketed in Europe.

Fatty acids

Samples of biomass and oleoresins were analysed for fatty acids in triplicate and average results are summarised with data for AstaCarotene algal meal and the Cyanotech product (BioAstin) in Table 2. The predominant fatty acid present in all samples was C18 (overall average 69%), followed by C16 (20%) and C20 (7%). Ratios of fatty acids varied between extracts but this is to be expected given measured relative standard deviation of up to 38% for the principal fatty acids. For example, three replicates with an average C18:1 content of 26.4% had measured values from 19.9% to 38.2%. Small differences in average fatty acid content between extracts would be insignificant in the context of this degree of analytical variability. There were no significant differences in total C16, total C18 or total C20 levels at the $p<0.05$ level (paired two-sample t-test).

Overall, oleoresin extracts produced by the two extraction facilities would be indistinguishable on the basis of their fatty acid profiles because of natural variations and analytical uncertainties. Both extracts are therefore substantially equivalent to the whole algal meal previously marketed in Europe.

Other constituents

Certificates of analysis for other constituents (protein, moisture, carbohydrate, total fat and ash) are summarised in Table 3. Analyses of protein, fat and ash were conducted in triplicate. No differences between the extract produced by the two suppliers were observed for protein, fat, carbohydrate or ash content. Some differences were observed for moisture content. The company has provided additional data on variability in water content of algal biomass (Table 4). This shows a relatively large degree in variability in moisture content (1.3 – 4.0%), which is probably reflected in variability of moisture content of oleoresin.

Table 2. Fatty acid profiles of *H. pluvialis* biomass and samples of oleoresin extracts (%, w/w of product)

	Biomass		Oleoresin					
	Asta-Carotene (1)	**Alga-technologies' (2)**	**Algatechnologies' product extracted by Extractor 1 (2)**		**Algatechnologies' product extracted by Extractor 2 (2)**		**BioAstin (3)**	
Batch		**AST00406**	**EXT050809**	**EXT110524**	**EXT060201**	**EXT060501**	**(5%)**	**(10%)**
C8:0						0.1		
C12:0			0.2	0.3	0.3	0.2		
C14:0	0.4				0.6		0.3	0.4
C15:0	0.3						0.2	
C16:0	16.6	17.6	19.8	24.7	20.2	20.9	12.0	19.6
C16:1	0.4		2.5	1.5	1.8	7.2	0.5	1.0
C16:2			1.5	1.5	0.9	1.5		
C16:3		4.3	5.3		5.3	5.9		
C17:0	2.4						0.1	0.2
C17:1	2.5						0.7	1.5
C18:0	3.0						1.5	1.9
C18:1	29.5	39.1	26.1	29.9	26.4	24.4	44.1	24.9
C18:2	26.9	35.6	38.5	32.8	36.3	34.4	20.0	32.8
C18:3*	9.7	2.0	1.0		5.6		13.0	15.7
C20:0	1.3		0.8	0.9	0.6	1.1	0.5	0.5
C20:1	0.6		0.7	0.6	0.4	0.5	0.4	0.3
C20:2			1.1	1.2	1.1	1.5	0.2	0.3
C20:3*	1.0		1.3	1.1	1.0	1.2	0.1	
C20:4	4.3	1.4	3.0	2.8			0.5	0.6
C20:5				0.9		1.5		
C21:0	1.3							
C22:0			0.4	0.4		0.6	0.3	0.2
C23:0	0.2							
C24:0						0.2		

* n-6 and n-3 combined
(1) US Nutra submission to FDA.(2) Appendix D. (3) Cyanotech submission to UK.

Table 3. Protein, fat, carbohydrate, ash and moisture content of Algatechnologies' biomass and oleoresin extracts (%, w/w of product)

	Biomass AST00406	Oleoresin - extractor 2 EXT060201			Oleoresin - extractor 2 EXT060501			Oleoresin - extractor 1 EXT110524			Oleoresin - extractor 1 EXT050809		
	%	%	S.D.	RSD %	%	S.D.	RSD %	%	S.D.	RSD %	%	S.D.	RSD %
Protein	16.6	0.39	0.02	5.13	0.30	0.03	8.33	0.32	0.07	21.28	0.31	0.08	25.81
Fat	35.4	98.27	0.46	0.47	98.63	0.12	0.12	98.30	0.20	0.20	98.83	0.31	0.31
Carbohydrate	24.4	<0.5			<0.5			<0.5			<0.5		
Ash	2.4	0.04	0.01	25.00	0.17	0.06	34.80	0.40	0.14	35.00	0.04	0.01	28.57
Moisture	3.6	1.00			0.50			0.40			0.4		

Table 4. Moisture content and fat content of Algatechnologies' algal biomass (%, w/w of product).

Batch number	Moisture (%)	Fat (%)
06504	3.5	35.9
05804	2.6	28.0
05704	2.9	29.1
05504	3.9	30.4
04304	4.0	31.6
02404	2.2	40.2
02104	3.0	36.8
01404	2.5	36.1
01104	2.5	32.5
00104	2.9	33.3
01005	3.7	34.7
00905	2.0	32.6
00805	3.0	31.3
00705	3.3	34.4
00605	3.4	34.8
00505	1.3	30.4
00405	2.3	34.8
00305	2.5	38.6
00205	3.2	46.4
00105	3.4	34.4
Maximum	4.0	46.4
Minimum	1.3	28.0
Average	2.9	34.3
Standard deviation	0.679	4.186
RSD	23%	12%

Nutritional value

The carotenoid profile of Algatechnologies' oleoresin is indistinguishable from that of the US Nutra product that was assessed by the ACNFP in June 2004 (Appendix A). The US Nutra extract was considered to correspond closely to the levels of carotenoids in the existing algal meal so that no differences in nutritional value were expected. Algatechnologies oleoresin can therefore be assumed to be nutritionally equivalent to the US Nutra extract and to the existing algal meal.

Metabolism

The carotenoid and fatty acid profiles of Algatechnologies' oleoresin are indistinguishable from those of the US Nutra product that was assessed by the ACNFP in June 2004. No differences in metabolism between Algatechnologies' oleoresin, the US Nutra extract and the existing algal meal would be expected.

Intended use

Algatechnologies' astaxanthin-rich carotenoid oleoresin will be sold to dietary supplement manufacturers who will then dilute the product in a suitable carrier (e.g. olive oil) to produce capsules containing up to 4 mg of astaxanthin. This dose level is in line with astaxanthin levels found in existing similar products.

The recommended dose level will be communicated to supplement manufactures in the Manufacturers Safety Data Sheet (Appendix E), which includes the following clause:

<u>Product Use</u>	Dietary supplement for human (consumed in capsules, tablets, etc; maximal dose per adult is 40 mg oleoresin per day, equivalent to 4 mg of pure astaxanthin)

A sample copy of the product label is also enclosed (Appendix F).

Level of undesirable substances

<u>Trace elements</u>

Two batches of product from each extractor were analysed for 31 trace elements using inductively coupled plasma (Table 5). Because the method used for CO_2 extraction is designed to concentrate lipophilic compounds, levels of all electrolytes are relatively low.

For some elements the concentration from the two suppliers appeared to be different. However, these differences were not statistically significant at the $p<0.05$ level (paired two-sample t-test). Any differences in trace elements cannot be due to differences in nutrient composition of the production system because these are closely controlled. However, the quality of the process water is not completely constant, but varies between certain permitted limits. Furthermore, most of the cations and some anions are actively accumulated in the algae cells, sometimes to concentrations up to a few hundred-fold higher than in the medium. Therefore, minor changes in the ion concentrations in the media can cause large differences in concentrations in the cells.

Table 5. Trace element content of oleoresin extracts determined by ICP.

Batch number		**50809** Extractor #1	**110524** Extractor #1	**60201** Extractor #2	**60211** Extractor #2
Ag – silver (in-ICP)	mg/kg	<0.100	<0.100	<0.100	<0.100
Aluminium (in-ICP)	mg/kg	<4.0	<0.550	<3.5	<2.5
As – Arsenic (in-ICP)	mg/kg	<0.250	<0.250	<0.250	<0.250
B-Boron (in-ICP)	mg/kg	<0.250	<0.100	<0.100	<0.150
Ba-Barium (in-ICP)	mg/kg	0.15	0.12	0.15	0.15
Be-Beryllium (in-ICP)	mg/kg	<0.020	<0.020	<0.020	<0.020
Ca-Calcium (in-ICP)	mg/kg	65	56	90	65
Cd-Cadmium (in-ICP)	mg/kg	<0.050	<0.050	<0.050	<0.050
Co-Cobalt (in-ICP)	mg/kg	<0.050	<0.050	<0.050	<0.050
Cr-Chromium (in-ICP)	mg/kg	<0.150	<0.050	<0.080	<0.150
Cu-Copper (in-ICP)	mg/kg	0.4	0.3	0.5	0.35
Fe-Iron (in-ICP)	mg/kg	<1.5	0.55	<2.6	<2.0
Hg-Mercury (in-ICP)	mg/kg	<0.100	<0.100	<0.100	<0.100
K-Potassium (in-ICP)	mg/kg	4	1.6	3.5	3.5
Li-Lithium (in-ICP)	mg/kg	<0.100	<0.100	<0.350	<0.250
Mg-Magnesium (in-ICP)	mg/kg	12	11	25	28
Mn-Manganese (in-ICP)	mg/kg	<0.060	<0.020	<0.080	0.05
Mo-Molybdenum (in-ICP)	mg/kg	<0.100	<0.050	<0.050	<0.050
Na-Sodium (in-ICP)	mg/kg	8	6	8	12
Ni-Nickel (in-ICP)	mg/kg	<0.300	<0.050	<0.070	<0.100
P-Phosphorus (in-ICP)	mg/kg	3	1.1	6.5	4.5
Pb-Lead (in-ICP)	mg/kg	<0.100	<0.050	<0.050	<0.050
S-Sulphur (in-ICP)	mg/kg	3.5	3	15	13
Sb-Antimony (in-ICP)	mg/kg	<0.250	<0.100	<0.100	<0.100
Se-Selenium (in-ICP)	mg/kg	<0.300	<0.100	<0.100	<0.100
Si-Silica (in-ICP)	mg/kg	5	3	7	12
Sn-Tin (in-ICP)	mg/kg	<0.500	<0.200	<0.200	<0.200
Sr Strontium (in-ICP)	mg/kg	0.25	0.22	0.6	0.25
Titanium(in-ICP)	mg/kg	<0.050	<0.050	<0.065	<0.350
V-Vanadium(in-ICP)	mg/kg	<0.050	<0.050	<0.050	<0.050
Zn-Zinc(in-ICP)	mg/kg	0.25	0.3	1.2	1.1

To investigate variability in trace elements between batches of algal biomass, the company has provided data for ICP analysis of three batches of product which are summarised in Table 6.

Trace element concentrations are typically around an order of magnitude higher in algal biomass than in oleoresin. However, a similar degree of batch-to-batch variability can be seen for certain elements. This indicates that any differences seen in trace element levels in the oleoresin product are probably due to variation in the algal biomass.

Table 6. Trace element content of algal biomass determined by ICP.

Batch number		**3606**	**2206**	**2806**
Ag – silver (in-ICP)	mg/kg	<0.100	<0.100	<0.100
Aluminium (in-ICP)	mg/kg	16	25	10
As – Arsenic (in-ICP)	mg/kg	<0.100	<0.100	<0.100
B-Boron (in-ICP)	mg/kg	2	1.5	2
Ba-Barium (in-ICP)	mg/kg	1.6	2.5	1.11
Be-Beryllium (in-ICP)	mg/kg	<0.020	<0.020	<0.050
Ca-Calcium (in-ICP)	mg/kg	750	1000	538
Cd-Cadmium (in-ICP)	mg/kg	<0.030	<0.030	<0.030
Co-Cobalt (in-ICP)	mg/kg	1.2	0.45	0.367
Cr-Chromium (in-ICP)	mg/kg	1	1	0.452
Cu-Copper (in-ICP)	mg/kg	3.3	5	2.67
Fe-Iron (in-ICP)	mg/kg	225	250	141
Hg-Mercury (in-ICP)	mg/kg	<0.200	<0.100	<0.050
K-Potassium (in-ICP)	mg/kg	3804	3200	2997
Li-Lithium (in-ICP)	mg/kg	2	<0.100	0.566
Mg-Magnesium (in-ICP)	mg/kg	1100	700	636
Mn-Manganese (in-ICP)	mg/kg	31	37	25.9
Mo-Molybdenum (in-ICP)	mg/kg	0.97	0.8	0.595
Na-Sodium (in-ICP)	mg/kg	1500	1100	581
Ni-Nickel (in-ICP)	mg/kg	1.1	0.7	0.308
P-Phosphorus (in-ICP)	mg/kg	5506	3200	2975
Pb-Lead (in-ICP)	mg/kg	<0.500	<0.500	<0.150
S-Sulphur (in-ICP)	mg/kg	79	300	125
Sb-Antimony (in-ICP)	mg/kg	<0.500	<0.500	<0.500
Se-Selenium (in-ICP)	mg/kg	<0.500	<0.500	<0.500
Si-Silica (in-ICP)	mg/kg	8	35	10
Sn-Tin (in-ICP)	mg/kg	<0.200	0.4	<0.100
Sr Strontium (in-ICP)	mg/kg	9	11	7.2
Titanium(in-ICP)	mg/kg	1.1	2	0.925
V-Vanadium(in-ICP)	mg/kg	<0.100	<0.060	<0.050
Zn-Zinc(in-ICP)	mg/kg	19	15	9

Pesticide contamination

Gas chromatographic screening for pesticide residues has been applied to four batches of product (Appendix G). The screen is capable of detecting up to 198 different pesticide residues with limits of detection (LOD) of 0.005 - 0.05 mg/kg and limits of quantitation (LOQ) of 0.01 - 0.2 mg/kg depending on the sensitivity of the GC detectors to the different compounds and on the sample matrix. No residues were detected.

Microbiological contamination

Batches of algal meal and oleoresin are routinely tested for microbiological contamination using methods compliant with German national standards (§64 LFGB German Food Act, DIN). Analyses include Total Plate Count, detection of yeasts and moulds, coliforms, E. coli, S. aureus, pseudomonas sp. and salmonella. A test report and certificates of analysis are provided for 4 batches at Appendix H.

Manufacturing quality control

Algatechnologies' facilities are certified as compliant with State of Israel Department of Health Good Manufacturing Practices standards and the company is permitted to use the official GMP symbol on its products. The Algal Meal and AstaPure oleoresin are produced in certified ISO 9001 production facilities and externally audited HACCP quality control management systems are in force. Certificates of compliance with GMP, ISO and HACCP principles are provided at Appendix I.

The analytical laboratory used by Algatechnologies in its quality control programmes, Bactochem Ltd. (2 Haharesh Street, Ness-Ziona, Israel), is ISO 9001 accredited by the Israel Laboratory Accreditation Authority for all chemical and microbiological assays cited in this submission.

Algatechnologies certifies that its products are free from genetically modified organisms, free from sources of bovine spongiform encephalopathy and have not bee treated with ionising radiation.

Conclusion

Samples of astaxanthin-rich oleoresin from different supercritical CO_2 extraction systems have been subject to extensive chemical analysis to identify any differences that might exist between them. Analyses have included astaxanthin and its isomers and esterification states, other trace carotenoids present, fatty acid profiles, trace elements, protein, moisture, total fat and ash.

Some small differences in some of the analytes could be seen between the oleoresin extracts. However, these did not appear to be systematic and were not statistically significant and probably related to natural variability in the algal biomass caused by differences in production systems or growing conditions.

Overall, there is no evidence of any systematic differences between oleoresins produced at different CO_2 extraction facilities. There is therefore no reason to believe that they would differ in their chemical, biological or physical properties.

Algatechnologies' oleoresin is made from the same starting material and extracted using the same technology as US Nutra's oleoresin. The two products are chemically indistinguishable and can be regarded as being essentially identical. Algatechnologies oleoresin can therefore be assumed to be nutritionally and metabolically equivalent to the US Nutra extract and to the existing algal meal. The intended use of Algatechnologies' oleoresin is as a food supplement at doses up to 4 mg (astaxanthin) per day, which is identical to the ACNFP's recommendations for the US Nutra product and equivalent to pre-existing use of the bioresin. Levels of undesirable substances are low and equivalent to the US Nutra product.

US Nutra's oleoresin has already been judged to be substantially equivalent to *H. pluvialis* biomass previously available on EU markets. It follows that Algatechnologies' oleoresin must also be substantially equivalent to the biomass because the products are essentially the same.