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Mr Andreas Klepsch
European Commission
By email

4 September 2008 Reference: NFU 515

INITIAL OPINION: EXTENSION OF USE OF DHA RICH ALGAL OIL FROM *SCHIZCHYTRIUM* SP

Dear Mr Klepsch,

On 14 January 2008, the UK Competent Authority accepted an application from Martek Biosciences Corporation for the extension of use of DHA rich algal oil from *Schizochytrium* sp as a novel food ingredient, in accordance with Article 4 of regulation (EC) 258/97. The Advisory Committee on Novel Foods and Processes (ACNFP) reviewed this application and their opinion is attached. I apologise for the delay in submitting this opinion as the ACNFP's evaluation was extended while we obtained additional information from the applicant.

In view of the ACNFP's opinion, the UK Competent Authority considers that the additional uses of DHA rich algal oil from *Schizochytrium* sp, at levels not exceeding the maximum use levels described, meets the criteria for acceptance of a novel food defined in Article 3(1) of regulation 258/97.

The UK notes that the purpose of incorporating this novel ingredient is to increase daily consumption of DHA, which has perceived health benefits. However, any health claims that are attributed to the consumption of DHA are not considered in this opinion. Any health or nutrition claims that may be made by the applicant would be subject to separate authorisation procedures under the terms of regulation (EC) 1924/2006.

I am copying this letter and the ACNFP's opinion to the applicant.

Yours sincerely,

(By e-mail only)
Dr Chris Jones
For the UK Competent Authority

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON THE EXTENSION OF USE OF DHA RICH ALGAL OIL FROM *SCHIZCHYTRIUM* SP

Applicant	**Martek Biosciences Corporation**
Responsible Person	**Dr Rodney Gray**
EC Classification	**2.2**

Background

1. An application was submitted from Martek Biosciences Corporation for the extension of use of a docosahexaenoic acid (DHA) rich algal oil from the microalgae *Schizochytrium* sp. The applicant sought authorisation for the use of this novel ingredient (NI) in a range of food products including dairy products, bakery products and soft drinks

2. The ACNFP first considered an application for the authorisation of this DHA rich oil, in 2001 and following the issuing of a favourable UK initial opinion in 2002, the oil was authorised in 2003[1], with a reduction in the number of food categories.

3. Later in 2003, the company Nutrinova notified the Commission of its intention to market a similar DHA rich oil obtained from the microalga *Ulkenia sp.* in accordance with Article 5 of the Novel Food Regulation (EC) 258/97. Nutrinova subsequently made a novel food application via the German authorities to extend the range of use to include baked goods, non alcoholic beverages, fats and oils. The German Competent Authority highlighted a number of safety concerns that, in their view, could be attributed to consumption of more than 1.5g per day of DHA and noted that the dietary intake data provided by the applicant did not provide sufficient reassurance that this figure of 1.5 g/day would not be exceeded, if the additional food categories were authorised.

4. These concerns were consistent with those made by certain other Member States when they considered the 2002 UK initial opinion, which had resulted in the authorisation being given for a reduced number of food categories. The Nutrinova dossier was therefore referred to the European Food Safety Authority (EFSA) for a view on the potential concerns of high level consumption of the DHA. The EFSA Panel on Dietetic Products, Nutrition and Allergies concluded that:

> "In the light of the information provided, the Panel was unable to draw a conclusion as to whether the intake of DHA from micro algae in the EU population would exceed or not 1.5 g per person per day. Representative intake data for existing

[1] Commission Decision of 5 June 2003 authorising the placing on the market of oil rich in DHA (docosahexaenoic acid) from the microlagae *Schizochytrium sp.* as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (2003/427/EC)

and proposed uses of DHA from micro algae would be required for such a conclusion." [2]

5. Martek consider that their new application contains sufficient new data to demonstrate that 1.5g/day should not be viewed as a safety limit. They have additionally provided detailed intake estimates for the UK and other Member States, to address the lack of data identified by EFSA.

6. This application for DHA rich oil was prepared pursuant to the scheme set out in Commission Recommendation 97/618/EC, concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. DHA rich oil has been classified as a complex novel food from non-GM sources source with no history of consumption in the EU (Class 2.2).

I Specification of the Novel Ingredient (NI)

Application dossier & Commission Decision 2003/427/EC

7. The NI is an oil which contains a range of fatty acids, of which DHA is the most abundant (32%). The applicant has indicated that, as no changes have been made to the NI described in the original application, the purity specification which is attached to authorisation Decision (2003/427/EC) applies. The purity specification differs from the original specification submitted in 2001 only in the upper limit for trans-fatty acids, which was reduced from 2% to 1%.

8. In response to concerns expressed by some Member States during their evaluation of the original application, the applicant carried out stability tests to demonstrate that the NI is resistant to oxidation during baking. These analyses did not highlight any stability concerns.

II Effect of the production process applied to the NI

9. No changes have been made to the original application.

III History of the organism used as the source of the NI

10. No changes have been made to the original application.

Discussion *The Committee accepted that the data provided in the original application were sufficient and did not highlight any concerns that have arisen since their 2002 opinion was issued.*

[2] Statement of the Panel on Dietetic products, Nutrition and Allergies on a request from the Commission related to the addition of DHA-rich oil from microalgae to an extended range of foods

IX Anticipated intake and extent of use of the NI

Application Dossier p. 7-19

11. The NI is already authorised for use in a number of food categories and the applicant has proposed an additional range of food categories for the addition of the NI. Existing and proposed food categories are detailed in the table below.

Food use	Maximum use level of the NI, expressed as DHA	Status
Dairy products except milk based drinks	200mg/100g; 600mg/100g for cheese	Permitted
Dairy analogues except drinks	200mg/100g; 600mg/100g for cheese analogues	Permitted
Spreadable fats and dressings	600mg/100g	Permitted
Breakfast cereals	500mg/100g	Permitted
Food supplements	200mg daily dose	Permitted
Dietary foods for special medical purposes	In accordance with the nutritional requirements of the persons for whom the products are intended	Permitted
Foods intended for use in energy restricted diets for weight reduction	200mg/meal replacement	Permitted
Bakery products, breads and rolls	200mg/100g	Proposed
Nutrition bars	500mg/100g	Proposed
Non-alcoholic beverages	60mg/100g	Proposed
Milk based drinks	60mg/100g	Proposed
Dairy analogue drinks	60mg/100g	Proposed

Note: All the newly proposed food categories were included in the original application and were therefore covered by the 2002 initial opinion.

12. The applicant estimated the current and potential dietary intake of DHA and the DHA rich oil using consumption data from the UK National Diet and Nutrition Survey (NDNS) and European market data. These estimates indicate that the maximum level of intake is 1.7g DHA /day. This "worst case" estimate is likely to be an overestimation as consumers are unlikely in practice to consume all food categories containing the NI at the maximum level of incorporation at the same time.

13. In response to Committee's concern that the intake estimates did not include the consumption of dietary supplements, the applicant considers that the co-consumption of DHA rich supplements is unlikely as they are generally taken as an alternative to fish or foods fortified with fish oil, but has not provided any data to support this assertion. UK officials with responsibility for food consumption surveys have also advised that the current NDNS surveys do not provide

sufficient detail to determine whether individuals consuming a fortified food will or will not also consume supplements containing the same ingredient.

NDNS Data
(Application Dossier p9)

14. The applicant has calculated the mean, 90th, 95th and 97.5th percentile "all user[3]" intakes for each of the authorised and proposed food categories. This methodology provides "worst case" estimates, as it is assumed that all products within each category contain the maximum level of the NI. These data indicate that male adults are likely to have the greatest 97.5th percentile all-user intake at 1.7g per day. The figures also indicate that consumption of the NI generally increased with age, and was lower in females. When expressed in terms of body weight, the highest potential consumption is in children. (See Tables below).

Summary of the Estimated Daily Intake of DHA from DHA Rich Algal Oil from all Proposed Food Categories in the U.K. by Population Group – based on NDNS Data

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (mg)	Percentile (mg)			Mean (mg)	Percentile (mg)		
					90	95	97.5		90	95	97.5
Children	1½ -4½	98.8	1,628	418	648	724	829	419	647	725	853
Young People	4-10	99.6	834	662	972	1107	1222	662	972	1107	1222
Female Teenager	11-18	97.8	436	667	1047	1165	1278	665	1038	1144	1250
Male Teenager	11-18	99.5	414	871	1313	1489	1607	869	1312	1489	1607
Female Adult	16-64	94.1	901	619	960	1108	1230	626	962	1119	1231
Male Adult	16-64	94.8	726	795	1247	1502	1664	802	1250	1502	1662

Summary of the Estimated Daily Intake of DHA (relative to body weight) from DHA Rich Algal Oil from All Proposed Food Categories in the U.K. by Population Group – based on NDNS Data

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (mg/kg bw)	Percentile (mg/kg bw)			Mean (mg/kg)	Percentile (mg/kg bw)		
					90	95	97.5		90	95	97.5
Children	1½ -4½	98.8	1,628	29	45	51	57	29	45	51	57
Young People	4-10	99.6	834	26	38	43	49	26	38	43	49
Female Teenager	11-18	97.3	436	12	20	23	26	13	20	23	26
Male Teenager	11-18	99.3	414	16	25	28	31	16	25	28	31
Female Adult	16-64	91.6	901	9	15	17	19	9	15	17	19

[3] The "All user" distribution of intakes is obtained by considering only those individuals who consume the relevant foods, discounting individuals who do not consume them

Male Adult	16-64	91.4	726	9	15	18	21	10	16	18	21

Per capita **data**
(Application dossier p10-15)

15. In recognition of the advice from the EFSA that additional data were required in order to assess the likely consumption of the NI across the EU, the applicant has also sought to estimate likely intake in other member states. In the absence of more comprehensive data on dietary habits, these estimates are based on average consumption data for the relevant food categories together with the maximum proposed levels of DHA. These figures indicate that intake of DHA via fortified foods in other MS would be broadly comparable to those seen in the UK. While this analysis does not provide the same level of detail as the UK NDNS data, the applicant contends that it is a useful basis for comparison and sufficiently robust to be valid.

Guidance Upper Levels
(Application dossier p17-19)

16. Previous concerns regarding the safety of DHA rich algal oil have centred on whether the additional food categories would lead to EU consumers consuming more than 1.5g per day (see para 4 above). The applicant disagrees with the use of this limit and has provided a number of safety studies to justify their position (see section XIII below). In addition, the applicant has highlighted a number of EU (France, Belgium) and non-EU countries (Australia & New Zealand, US, Canada) who have published guidance upper limits for the consumption of omega-3 fatty acids. The applicant considers that these limits are based on nutritional benefit, and that exceeding them will not cause any detrimental health effect. In particular the applicant notes that France has issued a report which states that a maximum recommended intake for nutritional purposes is around 2g per day of omega-3 fatty acids.

17. The applicant also points out that, if there were any safety concerns attributed to the consumption of omega-3 fatty acids, then this would apply equally to fish oils which are widely available as a food ingredient in the EU and which are currently used in a number of the food categories that are requested in this dossier (eg bread, soft drinks) (See XI below).

Discussion *The Committee accepted that, with the notable exception of the NDNS data and similar data available in the Netherlands, there is a paucity of public databases that would allow detailed estimated of dietary intake to be made in individual EU Member States. Given that the NDNS data reflect consumption by the British population the Committee viewed these to be most valid for their consideration, and did not consider the merits of the per capita approach. However, the Committee noted the intake estimates applied only to the addition of DHA to foods and did not include consumption of foods that were naturally rich in n-3 polyunsaturated fatty acids, and the baseline level of consumption may differ across the EU.*

The Committee noted the lack of data to support the applicant's view that co-consumption of fortified products and dietary supplements was unlikely, but recognised that that the discretionary consumption of supplements was a generic issue.

In response to the information regarding guidance upper levels, the Committee noted that there is general acceptance that the UK population does not consume enough n-3 polyunsaturated fatty acids in their diet and that the novel ingredient was an alternative to the fish oil derived products that are currently available. (see also XIII below)

X Information from previous human exposure to the NF or its source

Application Dossier p. 20-21

18. As noted above the NI has undergone a premarket safety evaluation in accordance with Regulation (EC) 258/97 and is authorised in the EU for use in a restricted number of food categories. The applicant has provided labels from some of the products that have been on sale in the EU (Appendix 9 of the application dossier). The applicant has also highlighted that the safety of the NI has been evaluated by a number of bodies outside the EU including the Australia and New Zealand Food Authority[4], who considered the ingredient to be safe for use in various food categories including bakery products, nutrition bars and a range of drinks.

Discussion *The Committee accepted that the NI was currently on the market in the EU, and noted that broadly the same proposed additional food uses had been favourably reviewed by the Australia and New Zealand Food Authority.*

XI Nutritional information on the Novel Food

Application Dossier p24

19. A nutritional profile of the NI is detailed in Appendix 10 of the application dossier. The NI is almost entirely composed of triglyceride fat. The NI is intended to be added to a range of existing foods either as a partial replacement for the fat component, or as a direct replacement for fish oil (added as an ingredient). The applicant does not envisage any significant differences to the non-fat nutritional profile of the food as consumed, and has provided a comparison of milk based drinks fortified with the NI and with fish oil in order to demonstrate that the nutritional profile is unchanged at a macronutrient level (Application Dossier p24, Table 7).

Discussion *The Committee accepted that the nutritional information provided was appropriate and the non-fat nutritional profile of a product containing the novel ingredient would not be significantly different to when compared with an equivalent product fortified with fish oil. The fatty acid profile of the product would not*

[4] http://www.foodstandards.gov.au/standardsdevelopment/applications/ (Application number 428)

necessarily reflect that of existing, fish oil derived products, although this would be unlikely to give rise to safety concerns.

XII Microbiological Information

Application Dossier p28

20. This issue was addressed in the original submission.

Discussion *The Committee accepted the data provided in the original application were sufficient and did not highlight any concerns that have arisen since their 2002 opinion was issued.*

XIII Toxicological information

Application Dossier ppp29-40

21. The applicant contends that safety concerns over the consumption of greater than 1.5g DHA per day that were raised previously (see paras 3-4 above) are not borne out by the available safety data. The applicant has provided an overview of 15 clinical studies in which the highest intake of the NI was 7.2g/day (equivalent to 2.7g DHA) in a 12 week study. Additional information regarding each of the studies is tabulated in Appendix 11 of the dossier. Based on these studies, the applicant concludes that intake of DHA rich oil arising from its use in the proposed food categories does not give rise to any safety concerns, including children and pregnant women.

22. The applicant also highlighted a review by Kroes *et al,* (2003) which considered a number of safety studies for DHA (from fish oil) and indicated that safe levels of consumption of DHA may be higher than 3g/day.

23. The applicant has also implemented procedures for obtaining and evaluating adverse and serious adverse experiences that are related to consumption of their ingredient.

24. The applicant also responded to the following concerns raised by the Committee during its assessment of the toxicological data presented in their dossier.

(i) *The lack of a clearly defined upper limit, and the failure to provide studies to enable the identification of the upper safe limit of intake.*
In response the applicant noted that this is no different from the current position regarding fish oils. In addition the applicant provided an overview of the preclinical studies that were carried out on the NI and were submitted as part of the original (2001) application. These data indicate that the NOEL level is in excess of 340/mg/kg/day of DHA. The applicant also highlighted the results of the study by Howe *et al*, (2002) which show that the NI (2.7g DHA per person per day) was well tolerated over a 12 week period. The applicant noted that, based on the proposed levels of incorporation, this equates to 20-40 servings of food containing the DHA rich oil.

(ii) *The ratio of DHA:EPA in the NI differs from that seen in fish oil and this could mean that studies carried out on fish oils may have reduced relevance, when used to determine the likelihood of potential adverse effects on blood clotting,*

gestation times and the immune system. In addition certain studies provided may report adverse effects, but these are not discussed fully.

In response the applicant highlighted 15 clinical studies in over 1200 adults, children and pregnant/nursing women which, they contend, demonstrates that consumption of the NI is not associated with any adverse experiences related to blood clotting, gestation times or the immune system. The applicant also provided summaries of a number of other studies which show no effect of omega-3 fatty acids on platelet activity, coagulation factors and immune function. The applicant also provided an additional commentary which indicated the adverse effects seen in certain studies, were not related to consumption of the novel ingredient.

Discussion *The Committee accepted that the toxicological data provided by the applicant both in their first dossier in 2001, together with the additional studies that have been carried out in the intervening period, as being of sufficient quality to demonstrate that the additional proposed uses of the NI did not cause significant concern with respect to the composition of the ingredient. The main issue is whether its normal use, as proposed by the applicant, significantly increases the intake of DHA in the population to levels which constitute a risk to health. The Committee noted however that the proposed uses were as an alternative to existing food ingredients that are currently used as a source of DHA. Members identified that there were uncertainties about the potential effects of long term consumption of high levels of DHA per se, but acknowledged these were not solely related to consumption of the NI and could also apply to existing sources. The applicant argues that the data indicate that the product is safe even at the highest intakes they consider. They refer to clinical studies but these studies were, in many cases, looking at different outcomes in individuals in different physiological states and the individual statistical power of these studies to pick up adverse outcomes is limited. The applicant also refers to a study where intakes of 2.7g/day were well tolerated over a 12 week period. This provides some reassurance but the committee notes that the concentrations of fat soluble nutrients such as DHA may continue to increase in tissues over much longer periods of supplementation. Although not part of this evaluation, the Committee wished to highlight the applicant's assertion that there was no effect of the NI on the immune system, although this is generally perceived to be a benefit of the consumption of long chain n-3 polyunsaturated fatty acids such as DHA. They also note that there are well acknowledged effects of high intakes of fish oils which could be detrimental to health, such as clotting.*

Allergenicity and Labelling

25. In its evaluation of the original application in 2001-2002, the Committee concluded that "there is a very low level of residual protein (less than 0.1%) and carbohydrate in the final refined oil. This indicates that the oil is likely to elicit only a low risk of allergenicity".

26. The requirement for the product to be labelled "DHA rich oil from the microalga *Schizochytrium sp.*", which is a condition of the original authorisation, will apply if authorisation is given for an extension of the product range.

Discussion *The Committee accepted that the allergenicity data provided in the original application were sufficient and did not highlight any concerns that have arisen since their 2002 opinion was issued. The Committee also considered that the current labelling requirements were adequate and did not require re-examination.*

Overall Discussion *The Committee accepted that the applicant had provided sufficient scientific data to assure them that the proposed additional uses of the NI did not give rise to specific concerns over safety when consumed at the levels they consider realistic.*

Some omissions in the applicants' submission (e.g. lack of consideration of the impact of supplements, sparse data on baseline variation in DHA intakes between member states, unrealistic expectations of the ability of consumers to titrate their daily intake of DHA) led to uncertainty as to the levels of intake likely to be achieved in practice. There also remains uncertainty about safe upper levels when DHA is consumed over prolonged periods.

Set against these uncertainties the Committee was mindful that current policy in the UK is to encourage the intake of long chain n-3 polyunsaturated fatty acids and that this product may help consumers with low intakes to increase their consumption of n-3 fatty acids (Advice on fish consumption: Benefits and Risks; SACN/COT 2004).

The question remained as to the impact that long term, high-level consumption of these products may have on health and this should be kept under review and intakes of DHA monitored at national and/or EU level. The Committee accepted that this uncertainty was not solely related to the extension of use of this DHA-rich oil and any studies that looked at the impact of consumption of foods fortified with n-3 long chain polyunsaturated fatty acids would have to address all dietary sources and different age groups, particularly children.

Similarly the Committee noted that the extent of co-consumption of dietary supplements and foods fortified with the same ingredients was unknown and recommended that this should be investigated by the FSA as a generic issue. In the present case, the applicant has argued that consumers are likely to modulate supplement use in response to their intake of DHA from foods. Although this would be possible, the Committee is sceptical that consumers would be willing or able to calculate their total daily intake of a component such as DHA. Also, supplements and/or foods containing the same active component may be promoted for different health benefits (e.g. arthritis or cardiovascular disease or brain and retinal function), adding to consumer confusion about relevant intakes.

CONCLUSION

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by the applicant, Martek Bioscience Corporation that the range of uses for

the novel ingredient (DHA rich algal oil from *Schizochytrium* sp.) is acceptable, subject to the labelling requirements described above.

26 August 2008