Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

Docosahexaeenzuurrijke olie (2)

Docosahexaenoic acid rich oil (2)

Tweede beoordeling van de veiligheid voor de consument, volgens de Europese verordening 258/97 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten

Second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

aan/to:

de Minister van Volksgezondheid, Welzijn en Sport
the Minister of Health, Welfare and Sport

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Aan de orde is een tweede beoordeling volgens de Europese Verordening 258/97, over het gebruik van een algenolie met minimaal 32 % docosahexaeenzuur (DHA, een afkorting van *docosahexaenoic acid*). De aanvraag is ingediend door Martek Biosciences Corporation. Deze DHA-rijke olie is sinds 2003 toegelaten op de Europese markt als nieuw voedselingrediënt voor voedingsupplementen en bijzondere voeding, en daarnaast ook voor een beperkt aantal categorieën gewone levensmiddelen [1]. Voor deze laatste groep wil de aanvrager de toepassing van DHA-rijke olie uitbreiden met in het bijzonder allerlei dranken.

Voor het verbreden van het productassortiment van nieuwe voedingsmiddelen is een veiligheidsbeoordeling vereist. In het kader van de desbetreffende Europese toelatingsprocedure is deze tweede beoordeling uitgevoerd door het Bureau Nieuwe Voedingsmiddelen van het College ter Beoordeling van Geneesmiddelen. Het bureau heeft hiervoor de Commissie Veiligheidsbeoordeling Nieuwe Voedingsmiddelen geraadpleegd, hierna genoemd 'de commissie VNV'.

Achtergrond

De DHA-rijke olie is afkomstig van de microalg *Schizochytrium sp*. Behalve DHA komen de overige geïdentificeerde bestanddelen van de olie ook in onze gewone voeding voor. Bij de eerste aanvraag[a] voor het gebruik van de DHA-rijke olie oordeelde de commissie VNV in 2002 positief, onder voorbehoud dat het productassortiment beperkt en goed gedefinieerd moest zijn [2]. De commissie deed de aanbeveling om het maximum aantal te consumeren porties per dag, waarmee de veilig geachte bovengrens[b] van 1500 mg DHA niet wordt overschreden, op het etiket te noemen.

Als gevolg van de besprekingen tussen de bevoegde autoriteiten in de EU over geschikte beheersmaatregelen om overconsumptie te voorkomen, werd besloten het aantal productcategorieën te beperken. Dit resulteerde in 2003 in een toelating voor zuivelproducten met uitzondering van op melk gebaseerde dranken, zuivelvervangers met uitzondering van dranken, smeerbare vetten, dressings en ontbijtgranen. Ook mag de DHA-rijke olie worden toegevoegd aan voedingssupplementen, dieetvoeding voor medisch gebruik en dieetproducten voor gewichtsvermindering zoals maaltijdvervangers[c] [1].

Met de huidige aanvraag verzoekt de firma markttoelating voor die productcategorieën die niet in de handelsvergunning maar die wel in de oorspronkelijke aanvraag waren opgenomen. Dit zijn bakkerijproducten, niet-alcoholische dranken, melk en dranken op basis van melk, dranken op basis van zuivelvervangers (bijvoorbeeld sojadranken) en voedingsrepen, zie ook pagina 3 van bijlage A en pagina 5 van bijlage B.

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[a] In 2001 door de firma OmegaTech. Deze firma is later door Martek Biosciences Corporation overgenomen.

[b] De commissie VNV verwijst naar de Amerikaanse *Food and Drug Administration* die 3 g EPA plus DHA per dag aanhoudt als veilige bovengrens van inname.

[c] Voeding gebruikt in energiebeperkte diëten voor gewichtsvermindering.

Eerste beoordeling

De eerste beoordeling van de aanvraag voor markttoelating is verricht in het Verenigd Koninkrijk door de *Advisory Committee on Novel Foods and Processes* (ACNFP). Deze Engelse deskundigencommissie heeft geen bezwaar tegen uitbreiding van het assortiment van producten waaraan DHA-rijke olie mag worden toegevoegd. De wetenschappelijke gegevens die de aanvrager heeft verstrekt hebben de ACNFP overtuigd dat er geen aanleiding is tot bezorgdheid over de veiligheid bij een realistisch consumptiepatroon. Wel is de ACNFP kritisch op een aantal punten. Het dossier bevat nauwelijks gegevens over de hoeveelheid DHA die inwoners van de verschillende Europese lidstaten dagelijks binnenkrijgen met de gewone voeding. De aanvrager houdt geen rekening met consumenten die naast het gebruik van DHA-verrijkte levensmiddelen dagelijks ook een voedingssupplement met DHA nemen. Volgens de ACNFP heeft de aanvrager überhaupt te hoge verwachtingen van de bekwaamheid van de consument om zijn of haar dagelijkse DHA inname te regelen aan de hand van informatie op het etiket. Gezien deze tekortkomingen in het dossier betwijfelt de ACNFP of het in de praktijk mogelijk is, dat consumenten de juiste hoeveelheid DHA kunnen berekenen die volgens de aanvrager een zinvolle aanvulling vormt op hun dagelijkse voeding. Daarnaast is het zo dat de effecten van langdurig verhoogde blootstelling aan DHA op de gezondheid niet bekend zijn. De ACNFP vindt het daarom belangrijk dat niet alleen de omvang van de DHA-consumptie op nationaal en/of Europees niveau wordt gecontroleerd (marktmonitoring), maar dat ook de gevolgen voor de volksgezondheid worden geëvalueerd.

Bevindingen van de commissie VNV

De commissie VNV heeft geen bezwaar tegen uitbreiding van het gebruik van DHA-rijke olie naar productgroepen die de aanvrager voorstelt. Aanvullend op de veiligheidsbeoordeling van de ACNFP maakt zij enkele opmerkingen. De commissie VNV baseert haar oordeel op de informatie in het dossier (waarvan de samenvatting is opgenomen als bijlage A) en de eerste beoordeling door de ACNFP (bijlage B).

Het DHA-gehalte van de producten waaraan de olie wordt toegevoegd varieert van 60 mg per 100 ml drank tot 600 mg per 100 gram voor kaas en smeerbare vetten, zie pagina 5 van bijlage B. De dagelijkse consumptie van DHA uit verrijkte levensmiddelen die volgens de aanvrager aansluit op aanbevelingen over visolievetzuren[d] in verschillende Europese landen, zou tussen de 200 en 500 mg liggen [3]. Om dit te bereiken kunnen één of meerdere porties van de voorgestelde producten worden genuttigd om de consumptie van DHA met de gewone voeding aan te vullen. Voor wat betreft dit laatste deelt de commissie VNV de kritiek van de ACNFP. Het dossier bevat onvoldoende gegevens over de hoogte van de achtergrondinname en hoe dit varieert binnen de Europese Unie.

Volgens de Richtlijnen Goede Voeding van de Nederlandse Gezondheidsraad in 2006 is een dagelijkse inname van 450 mg visolievetzuren, bij voorkeur door het eten van vis, nodig om het risico op sterfte door hart en vaatziekten te verminderen [4]. Uit voedselconsumptie-

[d] Eicosapentaeenzuur (EPA) en docosahexaeenzuur (DHA) zijn meervoudig onverzadigde (n-3) langeketenvetzuren

onderzoek in 2003 blijkt dat Nederlandse jongvolwassenen in de leeftijd van 19-30 jaar gemiddeld maar 94 mg visolievetzuren per dag binnenkrijgen [5]. De Gezondheidsraad meent dat voor niet-viseters het gebruik van met visolievetzuren verrijkte voedingsmiddelen een aanvaardbaar alternatief zou kunnen zijn.

De aanvrager heeft een inschatting gemaakt van de dagelijkse DHA consumptie gebaseerd op individuele voedselconsumptiegegevens uit het Verenigd Koninkrijk. Bij deze berekeningen is uitgegaan van het doemscenario dat men uitsluitend de voorgestelde levensmiddelen met DHA (in de maximaal toegestane concentratie) zal nuttigen in het huidige eetpatroon. Een samenvatting van de resultaten is te vinden op pagina 6 van bijlage B. Onder gebruikers is de gemiddelde DHA consumptie het hoogste voor jonge mannen en komt uit op 0,87 gram per dag. Bij volwassen mannen zou de DHA inname voor grootverbruikers van alle voorgestelde producten 1,66 gram bedragen (97,5 percentiel). De commissie VNV is zich ervan bewust dat de traditionele benadering, zoals die is toegepast, een overschatting van de DHA-inname zal betekenen omdat geen rekening wordt gehouden met een bewuste keuze voor deze speciale producten. Gegevens uit consumenten-onderzoek om dit in kaart te brengen ontbreken. De commissie VNV sluit zich aan bij de kritiek van de ACNFP die de bruikbaarheid van de innamegegevens ter discussie stelt omdat het gebruik van voedingssupplementen met DHA-rijke olie niet in het onderzoek is meegenomen. Het is niet ondenkbaar is dat consumenten op één dag zowel supplementen als andere producten met DHA gebruiken. De ACNFP concludeert dat er in zijn algemeenheid meer consumptieonderzoek nodig is naar gecombineerd gebruik van voedingssupplementen én levensmiddelen waaraan een bioactief ingrediënt is toegevoegd. De commissie VNV onderschrijft deze aanbeveling.

Algemeen kan worden gesteld dat de resultaten die de aanvrager verstrekt geruststellend zijn in de zin dat mensen met hun huidige voedingspatroon niet veel meer DHA zullen binnenkrijgen dan 1,5 gram. Het is echter onbekend in hoeverre de Engelse consument representatief is voor de Europese bevolking met betrekking tot de voorgestelde productgroepen.

Op basis van de resultaten van voedselconsumptieonderzoek bij Nederlandse jongvolwassenen in 2003 stelt de commissie vast dat het innameniveau van DHA aanvaardbaar is bij normaal gebruik van de voorgestelde producten [6]. Kijkend naar de meest gebruikte producten binnen enkele van de voorgestelde categorieën, dan bedraagt bijvoorbeeld de gemiddelde inname van DHA bij gebruikers ruwweg 300 mg met brood en broodjes, 160 mg met melk, 190 mg met kaas en 460 mg met de overige zuivelproducten en 170 mg voor vetten inclusief dressings, en ongeveer 300 mg voor niet-koolzuurhoudende dranken. Echter, grootverbruikers van bijvoorbeeld brood of zuivel die verrijkte producten uit verschillende categorieën levensmiddelen combineren, kunnen de veilig geachte bovengrens[b] van 1,5 gram DHA makkelijk overschrijden. Voor in het bijzonder de verschillende groepen dranken is dit lastig in te schatten. In het geval alle niet-koolzuurhoudende dranken (uitgezonderd die op basis van zuivel) het maximale DHA-gehalte van 60 mg per 100 ml bevatten dan consumeren jongvolwassen ruim één gram DHA gebaseerd op een gemiddelde inname van 1,7 liter [6].

Nederland beschikt recent ook over consumptiegegevens van jonge kinderen in de leeftijd van twee tot zes jaar [6]. Hieruit kan worden afgeleid dat als er brood en melk met DHA-rijke olie zou worden geconsumeerd, de gemiddelde DHA-inname ongeveer 300 mg bedraagt. Als bijvoorbeeld alle zuivelproducten de maximale hoeveelheid DHA-rijke olie zou

bevatten, dan zouden jonge kinderen alleen al hiermee gemiddeld 600 mg DHA binnenkrijgen. Een dergelijke blootstelling is globaal te vergelijken met die van de totale hoeveelheid visolievetzuren bij tweemaal vette vis per week (600 mg EPA plus DHA). De commissie VNV concludeert dat het niveau van DHA-inname veilig is bij een normaal consumptiepatroon van gewone levensmiddelen en producten met DHA-rijke olie. Zij is het hierin eens met de ACNFP.

De commissie onderschrijft de kritische opmerkingen van de ACNFP bij de resultaten van veiligheidsonderzoeken verstrekt door de aanvrager (zie pagina's 9-10 van bijlage B). Veel van de onderzochte vetzuurpreparaten zijn afkomstig van visolie en niet geheel representatief voor de DHA-rijke olie omdat de laatstgenoemde nauwelijks EPA bevat. Daarnaast zijn de meeste onderzoeken met de DHA-rijke olie niet opgezet om statistisch gezien voldoende bewijskracht te leveren over het al dan niet optreden van ongewenste neveneffecten. De beschikbare gegevens van mensgebonden onderzoeken geven geen aanleiding tot bezorgdheid voor de volksgezondheid. De commissie VNV benadrukt echter dat er, in het bijzonder voor kinderen, behoefte is aan een betere wetenschappelijke onderbouwing van het maximaal veilige innameniveau van DHA (al dan niet in combinatie met EPA) om meer duidelijkheid te krijgen over mogelijke langetermijneffecten van blootstelling aan verhoogde niveaus. Hoewel effecten op de bloedstolling zijn aangetoond bij overschrijding van meer dan 3 gram visolievetzuren, is met de huidige stand van wetenschap de vraag of dit zou kunnen leiden tot nadelige gezondheidseffecten niet te beantwoorden.

De aanvrager maakt duidelijk dat er op de huidige Europese markt steeds meer producten beschikbaar komen, waaronder brood en frisdranken, waaraan visolievetzuren zijn toegevoegd. Ook andere type producten waarvan het DHA-gehalte is verhoogd zijn te koop, bijvoorbeeld eieren afkomstig van kippen op speciaal voer. De aanvrager gaat ervan uit dat levensmiddelen die worden verrijkt met DHA-rijke olie, de producten met verhoogd DHA-gehalte uit conventionele bron geheel of gedeeltelijk zullen vervangen. Er zijn echter geen onderzoeksgegevens bij consumenten die dit bevestigen. De ACNFP erkent dat ook de bijdrage van deze conventionele bronnen zouden moeten worden meegenomen om de dagelijkse consumptie van DHA, dat wordt toegevoegd aan levensmiddelen, goed te kunnen bepalen.

Conclusie

Samenvattend is de commissie VNV het eens met de positieve beoordeling door de ACNFP maar deelt de twijfel over het vermogen van de consument om zijn dagelijkse consumptie van DHA verantwoord te kunnen regelen. Volgens de commissie VNV zijn er beleidsmaatregelen nodig ten aanzien van de mogelijk inname van DHA uit alle bronnen die rijk zijn aan DHA of visolievetzuren. Uit het totaal aan beschikbare informatie zijn er geen aanwijzingen dat nadelige gezondheidseffecten kunnen optreden bij voorgesteld gebruik. Maar wat de daadwerkelijke DHA inname is bij een breed aanbod van verrijkte producten en hoe zich dit verhoudt tot de consumptie van producten die van nature rijk zijn aan DHA, zal moeten worden onderzocht onder vrije condities van gebruik. Net als de ACNFP meent de commissie dat marktmonitoring nodig is, bij voorkeur op Europees niveau. Bij de verschillende leeftijdsgroepen en in het bijzonder kinderen moet worden geverifieerd of de totale consumptie van DHA uit alle bronnen de veilig geachte bovengrens niet overschrijdt.

Referenties

1. 2003/427/EG, Beschikking van de commissie van 5 juni 2003 tot verlening van een vergunning voor het in de handel brengen van DHA-rijke (docosahexaeenzuurrijke) olie van de microalg *Schizochytrium sp*. als nieuw voedselingrediënt krachtens Verordening (EG) nr. 258/97 van het Europees Parlement en de Raad. Publicatieblad van de Europese Unie L 144 (2003): 13-14. Zie http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:144:0013:0014:NL:PDF

2. Gezondheidsraad: Commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen (VNV) Docosahexaeenzuurrijke olie. Den Haag: Gezondheidsraad, 2002; publicatie nr. 2002/03VNV. Zie http://www.cbg-meb.nl/CBG/nl/nieuwe_voedingsmiddelen/beoordelingen/ onder "Afgeronde beoordelingen", 26 augustus 2002.

3. A summary of international recommendations on dietary fish oil fatty acids is available from the website of the International Society for the Study of Fatty Acids and Lipids (ISSFAL): http://www.issfal.org.uk/index.php?option=com_content&task=view&id=12&Itemid=31

4. Gezondheidsraad. Richtlijnen goede voeding 2006. Den Haag: Gezondheidsraad, 2006; publicatie nr 2006/21. Zie http://www.healthcouncil.nl/pdf.php?ID=1479&p=1
   Voor het bijhorend achtergronddocument, zie http://www.healthcouncil.nl/pdf.php?ID=1478&p=1

5. Kruizinga AG *et al*. De inneming van omega-3 en -6 vetzuren en vitamine A, D en E bij jongvolwassenen. Aanvullende berekeningen op basis van de voedselconsumptiepeiling 2003, TNO rapport V7451. Zeist, 2007.
   Zie ook http://www.voorlichtingmvo.nl/gfx/file/Infokaart_Inname_vet_en_vetzuren.pdf
   Hierbij is gebruik gemaakt van het nieuwe voedingsstoffenbestand (NEVO) uit 2006 met informatie over DHA en EPA.

6. Resultaten van de voedselconsumptiepeilingen 2003. RIVM, Bilthoven: http://www.rivm.nl/vcp/gegevens/

Assessment - English courtesy translation (December 3, 2008)

Introduction

The subject in question is a second assessment, in accordance with European Regulation 258/97, regarding the use of an algal oil containing at least 32% of docosahexaenoic acid (DHA). The application was submitted by Martek Biosciences Corporation. This DHA-rich oil was admitted to the European market in 2003 as a novel food ingredient for dietary supplements and foods intended for a particular nutritional purpose, in addition to a limited number of categories of ordinary foods [1]. With regard to this latter group, the applicant wishes to extend the application of DHA-rich oil, in particular to all kinds of beverages.
A safety assessment is required before the product range of novel foods can be expanded. In the framework of the relevant European approval procedure, this second assessment was prepared by the Novel Foods Unit of the Medicines Evaluation Board, after consulting the Committee on the Safety Assessment of Novel Foods (hereafter referred to as 'the VNV Committee')

Background

The DHA-rich oil is derived from micro algae *Schizochytrium sp*. Aside from DHA, the oil's other identified components already make up part of our normal diet. In the first application[a] for the use of DHA-rich oil, the VNV Committee gave a positive ruling in 2002, provided that the product range was limited and well defined [2]. The Committee recommended that the maximum number of portions consumed per day, at which the upper intake level of 1500 mg DHA (which is deemed to be safe[b]) is not exceeded, be indicated on the label.

As a result of discussions between the competent authorities on appropriate measures to prevent overconsumption, it was decided that the number of product categories should be restricted. In 2003, this resulted in an authorization for dairy products with the exception of milk-based drinks, dairy analogues excluding drinks, spreadable fats, dressings, and breakfast cereals. The DHA-rich oil can also be added to food supplements, dietary foods for special medical purposes, and dietary products for weight reduction, such as meal replacements[c] [1].

The company is using the current application to request market authorization for those product categories that were not included in the Commission Decision [1] but which were part of the original application. These are bakery products, non-alcoholic beverages, milk and milk-based drinks, beverages based on dairy analogues (such as soy beverages) and nutrition bars (see also page 3 of Annex A and page 5 of Annex B).

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a By the OmegaTech company, In 2001. This company was later acquired by Martek Biosciences Corporation.

b The VNV Committee refers to the U.S. Food and Drug Administration which uses 3 g EPA plus DHA per day as a safe upper intake level.

c Foods intended for use in energy-restricted diets for weight reduction.

Initial assessment

The initial assessment of the application for market authorization was carried out in the United Kingdom, by the Advisory Committee on Novel Foods and Processes (ACNFP). This British expert committee has no objection to extending the range of products to which DHA-rich oil may be added. The scientific data supplied by the applicant has convinced the ACNFP that, where there is a realistic pattern of consumption, the novel ingredient does not give rise to specific concerns over safety. However, the ACNFP has expressed criticism on a number of points. The dossier contains little information on the amount of DHA ingested by residents of various EU member states as part of their normal diet. The applicant takes no account of consumers who, in addition to the consumption of DHA-enriched foods, take daily dietary supplements containing DHA. According to the ACNFP, the applicant clearly has unrealistic high expectations of consumers' ability to regulate their daily DHA intake on the basis of information printed on the label. Given these shortcomings in the dossier, the ACNFP doubts whether it is feasible in practice for consumers to correctly calculate the amount of DHA which, according to the applicant, would constitute a meaningful supplement to their daily diet. Furthermore, nothing is known about the effects on health of prolonged exposure to elevated DHA levels. The ACNFP therefore considers it important that, in addition to verifying the scale of DHA consumption at national and/or European level (market monitoring), its impact on public health should be evaluated.

Findings of the VNV Committee

The VNV Committee has no objection to extending the use of DHA-rich oil to the other product groups proposed by the applicant. It has supplemented the ACNFP's safety assessment with various comments. The VNV Committee bases its views on the information in the dossier (the summary of which is contained in Annex A), and on the initial assessment by the ACNFP (Annex B).

The DHA content of products to which the oil is added varies from 60 mg per 100 ml for beverages to 600 mg per 100 grams for cheeses and spreadable fats (see page 5 of Annex B). The daily consumption of DHA from fortified foods which, according to the applicant, is in keeping with the recommendations of several European countries concerning fish-oil fatty acids[d], is claimed to be between 200 and 500 mg [3]. This can be achieved by eating one or more portions of the proposed products, to supplement the consumption of DHA in the normal diet. With regard to the latter point, the VNV Committee concurs with the criticisms expressed by the ACNFP. The file contains insufficient data about the level of background intake, and the way in which this varies within the European Union.

According to the Health Council of the Netherlands' Guidelines for a Healthy Diet (2006), a daily intake of 450 mg fish-oil fatty acids (preferably obtained by eating fish) is required to reduce the risk of mortality from cardiovascular diseases [4]. A 2003 food consumption survey showed that, on average, young Dutch adults (aged from 19 to 30) consumed only 94 mg fish-oil fatty acids per day [5]. The Health Council believes that the consumption of food

[d] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are polyunsaturated long-chain fatty acids (n-3)

products fortified with fish-oil fatty acids could be an acceptable alternative for those who do not eat fish.

The applicant has prepared an estimate of daily DHA consumption, based on individual food consumption data from the United Kingdom. These calculations are based on a worst case scenario in which only the proposed foods containing the maximum level of DHA will be consumed as part of the current eating pattern. A summary of the results is given on page 6 of Annex B. Of all consumers, young men exhibit the highest average DHA consumption (0.87 grams per day). In adult men, DHA intake for 'heavy users' of all the proposed products would amount to 1.66 grams (97.5th percentile). The VNV Committee is aware that a traditional approach of the type used here gives an overestimate of DHA intake. This is because it fails to take account of those who intentionally select these special products. The lack of relevant consumer research data prevents an accurate assessment of this phenomenon. The VNV Committee endorses the ACNFP's criticism, which questions the usefulness of the intake data on the grounds that the study in question did not address the use of food supplements containing DHA-rich oil. It is not inconceivable that some consumers will ingest both supplements and other DHA-containing products in a single day. The ACNFP concludes that, in general, there is a need for further consumption studies into the combined use of food supplements and foods to which a bioactive ingredient has been added. The VNV Committee endorses this recommendation.

In general, the results provided by the applicant can be said to be reassuring inasmuch as, with current dietary patterns, people will not ingest much more than 1.5 grams DHA. With regard to the proposed product groups, however, nothing is known about the extent to which British consumers are representative of the population of Europe as a whole.

Based on the results of a 2003 food consumption survey in young Dutch adults, the Committee finds that normal use of the proposed products corresponds to an acceptable DHA intake level [6]. If we examine the most widely used products in some of the proposed categories, then consumers' average DHA intakes would be roughly 300 mg in the case of bread and rolls, for example. In other foods, it would be 160 mg for milk, 190 mg for cheese, 460 mg for the remaining dairy products, 170 mg for fats (including dressings), and about 300 mg for non-carbonated beverages. There is, however, a risk that 'heavy users' of bread or dairy foods, for example, who combine fortified products from different food categories, may easily exceed the upper intake level of 1.5 grams of DHA (which is deemed to be safe[b]). With regard to the various groups of beverages in particular, this can be difficult to estimate. If all non-carbonated beverages (except those based on dairy products) contain the maximum DHA content of 60 mg per 100 ml, then, based on an average intake of 1.7 litres [6], young adults would consume well over one gram of DHA.

The Netherlands also has recent consumption data on young children aged from two to six [6]. It can be inferred from this data that if bread and milk containing DHA-rich oil were to be consumed, this would correspond to an average DHA intake of approximately 300 mg. For example, if all dairy products were to contain the maximum amount of DHA-rich oil then, on this basis alone, young children would ingest an average of 600 mg DHA. This level of exposure is broadly similar to that of the total amount of fish-oil fatty acids ingested by consuming oily fish twice per week (600 mg EPA plus DHA). The VNV Committee concludes that a normal consumption pattern of ordinary foods and products containing DHA-rich oil corresponds to a safe level of DHA intake. This is in keeping with the views of the ACNFP.

The Committee endorses the ACNFP's critical comments concerning the results of safety studies provided by the applicant (see pages 9-10 of Annex B). Many of the fatty acid preparations examined were derived from fish oil and were not fully representative of DHA-rich oil, as the latter contains very little EPA. Furthermore, most of the studies into DHA-rich oil were not designed to generate statistically significant evidence about the occurrence (or absence) of adverse side effects. The available data from human studies gives no cause for concern with regard to public health. However, the VNV Committee has stressed that, for children in particular, there is a need for better scientific support for the maximum safe intake level of DHA (whether or not in combination with EPA). The aim is to obtain clarification concerning the possible long-term effects of exposure to elevated levels of this substance. Although effects on blood clotting have been demonstrated at levels in excess of 3 grams of fish-oil fatty acids, the question of whether this could lead to adverse health effects cannot be answered given the current level of scientific knowledge.

The applicant makes it clear that more and more products are currently becoming available on the European market, including bread and soft drinks to which fish-oil fatty acids have been added. Other type of products with elevated levels of DHA are also on sale, such as eggs from chickens reared on special feeds. The applicant assumes that foods fortified with DHA-rich oil will partially or completely replace products containing elevated levels of DHA from conventional sources. However, there is no consumer research data to confirm this view. The ACNFP acknowledges that the contribution of these conventional sources should also be taken into account, in order to be able to effectively determine the actual daily consumption of DHA that has been added to foods.

Conclusion

In summary, the VNV Committee concurs with the favourable assessment by the ACNFP, while sharing the latter's doubts about consumers' ability to reliably regulate their daily consumption of DHA. The VNV Committee takes the view that policy measures are needed with regard to the possible intake of DHA from all sources that are rich in DHA or in fish-oil fatty acids. None of the available information indicates that adverse health effects can occur when the ingredient in question is used as described in the proposal. However, the actual DHA intake associated with a wide range of fortified products and its relationship to the consumption of products that are naturally rich in DHA will have to be investigated in the context of everyday use. Like the ACNFP, the Committee believes that market monitoring is required, preferably at European level. For each of the various age groups, and for children in particular, the question of whether the total consumption of DHA from all sources exceeds the 'safe upper limit' needs to be verified.

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Samenvatting van het dossier / Summary of the dossier

Martek Biosciences Corporation
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Application for the Authorization of DHA-rich Algal Oil from *Schizochytrium* sp. to Additional Food Groups

Submitted pursuant to
Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients

For all correspondence regarding this dossier, please refer to:

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December 12, 2007

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INTRODUCTION

In March 2001, an application was submitted under Regulation No 258/97 of 27th January 1997 concerning novel foods and novel food ingredients, for the approval of DHA-rich oil produced from *Schizochytrium* sp. (hereinafter "DHA-rich algal oil"), a marine microalgae, for general use as a nutritional ingredient in foods.

The above application and subsequent negotiations resulted in the following approval:

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

The current authorized uses for DHA-rich algal oil under this decision (as detailed in its Annex 2) are reproduced in Table 1.

Table 1 Authorized Uses of DHA-rich Algal Oil Pursuant to Decision 2003/427/EC

Food Category Use Group	Maximum Use Level of DHA
Dairy products except milk-based drinks	200 mg/100 g or for cheese products 600 mg/100 g
Dairy analogues except drinks	200 mg/100 g or for analogues to cheese products 600 mg/100 g
Spreadable fat and dressings	600 mg/100 g
Breakfast cereals	500 mg/100 g
Food supplements	200 mg per daily dose as recommended by the manufacturer
Dietary foods for special medical purposes	In accordance with the particular nutritional requirements of the persons for whom the products are intended
Foods intended for use in energy-restricted diets for weight reduction	200 mg/meal replacement

In the initial assessment report, the United Kingdom's ACNFP came to the conclusion that DHA-rich algal oil is safe for human consumption. More specifically, it stated:

> "The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by OmegaTech that DHA Gold® [DHA-rich oil from the microalgae *Schizochytrium* sp.] is safe for use as a nutritional food ingredient, for the types of uses as described in the application dossier, subject to the labelling requirements described above".

The Commission forwarded the initial assessment report to all Member States, opening the second stage of the procedure and the 60-day period laid down in Article 6(4) of Regulation (EC) No 258/97 (European Parliament and the Council of the European Union, 1997).

During this period, a number of comments regarding the marketing of the product were raised. In response to those comments, and most importantly, in the interest of timely progress to approval of some applications, OmegaTech amended the food applications of the DHA-rich oil.

With this application, Martek requests authorization of DHA-rich algal oil to an extended range of foods. More specifically, Martek hereby submits for authorization, additional food categories and use levels for DHA from DHA-rich algal oil as detailed in Table 2, below.

Table 2 Proposed Food Categories and Use Levels

Proposed Food Category Use Groups	Maximum Use Level of DHA
Bakery products Breads and rolls	200 mg/100g 200 mg/100g
Nutrition bars	500 mg/100g
Non-alcoholic beverages Milk-based drinks Dairy analogue drinks	60 mg/100 mL 60 mg/100 mL 60 mg/100 mL

This application has been prepared in accordance with the EU recommendation of 29 July 1997, where relevant (Commission of the European Communities, 1997). Consistent with the original application of 2001, Sections IV to VIII of the EU recommendation are not applicable to DHA-rich algal oil. Consistent with the original application submitted in 2001, DHA-rich algal oil is classified as Class 2.2, *i.e.*, "complex Novel Food From non-GM Source", the source of the NF has no history of use in the Community.

1. ADMINISTRATIVE DATA

The present petition is submitted by Martek Biosciences Corporation (Martek), manufacturer of DHA-rich oil from *Schizochytrium* sp.

Address of the applicant is as follows:

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The person responsible for the dossier is:

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I SPECIFICATION OF THE NOVEL FOOD

The specification for DHA-rich algal oil is specified in Annex 1 to the approval Decision 2003/427/EC and is presented in Table 3 below. No changes in the specification of the product are made (Commission of the European Communities, 2003).

Table 3 Specification of DHA-rich Algal Oil Established by Decision 2003/427/EC

Test	Specification
Acid value	Not more than 0,5 mg KOH/g
Peroxide value (PV)	Not more than 5,0 meq/kg oil
Moisture and volatiles	Not more than 0,05%
Unsaponifiables	Not more than 4,5%
Trans-fatty acids	Not more than 1%
DHA content	Not less than 32,0%

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO THE NOVEL FOOD

No changes have been made to the original application.

III HISTORY OF SOURCE ORGANISM

No changes have been made to original application.

IX ANTICIPATED INTAKE/EXTENT OF USE

As stated above, during its initial assessment, the United Kingdom's ACNFP came to the conclusion that DHA-rich algal oil is safe for human consumption. The UK competent authority did not restrict or limit food categories in their opinion and concluded that *"the Advisory Committee on Novel Foods and Processes is satisfied by the evidence … that DHA Gold®* (DHA-rich oil from the microalgae *Schizochytrium* sp.) *is safe for use as a nutritional food ingredient, for the types of uses as described in the application dossier* [which included the food categories authorized under Decision 2003/427/EC and also the food categories that are the object of the present petition]*, subject to the labelling requirements described above"* (Commission of the European Communities, 2003).

Anticipated Intake

Consumption of long-chain omega-3 fatty acids is generally recognized as having considerable heart health benefits. In particular, EFSA recognized intake recommendations by some (such as the UK, the Netherlands, France and the Nordic Countries) authorities of long-chain omega-3 fatty acids (EPA and DHA) in adults for cardio-protective effects (200 to

500 mg/day). Further, specific population groups such as pregnant and nursing women are advised to consume DHA (200 to 300 mg/day). Based on marketed use of DHA-rich algal oil in food products around the world, it is reasonable to assume that food manufacturers will formulate food products containing 100 mg or less DHA per serving. Therefore, it is anticipated that most foods containing DHA will deliver maximally 100 mg DHA per food serving. Given recommendations to increase consumption of long-chain omega-3 fatty acids, individuals are expected to consume 2 to 5 foods containing DHA-rich algal oil per day. Given this scenario, meaningful increases of 200 to 500 mg DHA per day will be introduced into an individual's diet. **Anticipated exposure of DHA from DHA-rich algal oil is 200-500 mg per day.**

Maximum Estimated Intake

In this section we present 2 ways of estimating maximum intake levels. Firstly we estimate maximum intake based on the well-recognised National Diet and Nutrition Survey (NDNS) data from the UK. Secondly, we estimate maximum intake using real market data, which is based on per-capita intakes across Europe[1], to calculate and compare the dietary habits of individuals within member states and to show their similarities. Again this technique makes significant over-estimates based on simple summation of intakes from the various foods. It is also difficult to remove specific foods within the groups that would not be targets for DHA addition, for example due to technological reasons.

Maximum estimated intake is based on the assumption that all of the designated food groups will contain DHA from DHA-rich algal oil. The calculation of intake, based on both NDNS survey data for an all-user individual in the 97.5th percentile, and those on *per capita* consumption is estimated to be 1.7 g/day. This should be considered the maximum possible intake for a dedicated DHA consumer. The intake of the average consumer should clearly be much less.[2]

Bakery Products

Baked goods containing DHA were included in the original DHA-rich algal oil application dossier. The German Competent Authority opened a discussion during the 60-day period regarding trans-fat content and stability during processing for this use group. Additional stability and analysis data has been presented to address these subjects.

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[1] Average daily intake of food is based on EU-wide population databases described in more detail below. Data Food Networking (DAFNE), Zenith International marketing databases, supported by Food and Agriculture Organization of the United Nations Statistics Division (FAOSTAT),

[2] Calculations of anticipated exposure, based on 100% market penetration must of necessity exceed actual exposures. Such calculated estimates can only represent the consumption of extremely high percentile population groups.

Nutrition Bars

Nutrition bars were included in the original application dossier for DHA-rich algal oil. This use group was accepted throughout both 90-day and 60-day periods and was carried forward to the Standing Committee on the Food Chain and Animal Health meeting. It was mentioned that, at the last minute, there was some confusion regarding the definition of "Nutrition Bars" specifically concerning whether this definition was sufficient to exclude pure confectionery products such as "Mars bars". Martek is resubmitting this food group in the present application and is specifically excluding the addition of DHA–rich algal oil to confectionery bars.

Nutrition bars are a fairly new and specific food type and unlike bakery products or non-alcoholic beverages, this category of foods is not broadly consumed by the entire population. Nutrition bars may be consumed frequently by special populations, young people, athletes, hikers, *etc.* Accordingly, it would be a gross underestimate of consumption for those individuals who are "eaters" to compute the *per capita* intake and divide by the entire population. Accordingly, it is assumed that a typical bar is 50 g and that the average dedicated consumer of nutrition bars may eat as much as one bar each day. This gives an estimated average daily intake of 50 g of nutrition bars per day for those individuals who are "eaters".

Product Categories and Nutrient Profiles

In addition to information presented regarding combined consumption of all food categories and mean and high-level intake groups, consideration should also be given to the fact that only certain types of products within each food group/category will actually be suitable for the inclusion of DHA-rich algal oil. The addition of DHA-rich algal oil to fortified food products will involve health and/or nutrition claims being made (there would be no point in adding DHA-rich oil if this were not the case), and as such would be subject to the risk management principles laid down in *Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods* (European Parliament and the Council of the European Union, 2006). As part of this regulation, nutrient profiles will be introduced to control the types of food to which functional ingredients such as DHA-rich algal oil may be added. As a consequence DHA-rich algal oil will be added to "healthier option" foods. This regulation will further limit intake, making the above considerations even more conservative.

Having regard to the above[3], Martek has addressed herein the questions raised during the 60-day period of the original application for approval of DHA-rich algal oil.

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[3] Also, it should be noted that, in contrast to fish and fish oils, DHA-rich algal oil does not contain contaminants. From an economic standpoint, it is also worth pointing out that the implementation of the requirements of Regulation 183/2005 regulating feed hygiene by fish oil industry seems to raise serious difficulties to such an extent that there are serious concerns of shortage in fish oil supply in the EU after 31 October 2007, the deadline for compliance of feed businesses with the 2005 hygiene rules. See press release from Food

X INFORMATION ON PREVIOUS HUMAN EXPOSURE

The safety of DHA-rich algal oil is supported by its extensive use as a dietary supplement and as a food ingredient in several countries around the world.

In the United States, DHA-rich algal oil has been marketed as a dietary supplement and was the subject of a New Dietary Pre-market Notification submitted to the FDA in December 1997 for SeaGold™ DHA-rich oil (FDA, 1997), the same oil that is the subject of the current application. The use of DHA-rich algal oil as a nutritional food ingredient was previously determined to be GRAS through scientific procedures following review by qualified experts. This conclusion was reviewed by the US FDA as part of GRAS notification GRN 000137, with no objections (FDA, 2004b).

In the United States DHA-rich algal oil has been added to food products including yoghurts, dairy products and analogues, non-alcoholic beverages, nutrition bars and baked goods. Examples of these products are shown in Appendix 8.

DHA-rich algal oil is also approved for use as a novel food ingredient in the European Union 2003/427/EC (Official Journal of the European Union, 2003). In Europe, DHA-rich algal oil has been added to food products including yoghurts, dairy products and analogues. Examples of these products are shown in Appendix 9.

The Australia New Zealand Food Authority (ANZFA) considers DHA-rich algal oil (derived from *Schizochytrium* sp.) and the microorganism itself to be safe for use as a novel food ingredient in various foods including (i) bakery products, breads and rolls; (ii) nutrition bars; and (iii) non-alcoholic beverages, milk-based drinks and dairy analogue drinks (Commonwealth of Australia, 2002).

DHA-rich algal oil was approved by Health Canada for use in a broad range of foods (including bakery products, breads and rolls; nutrition bars; and non-alcoholic beverages, milk-based drinks and dairy analogue drinks) in 2006 (Health Canada, 2006), was approved for use in China by the Ministry of Health in a broad range of foods (including bakery products, breads and rolls; nutrition bars; and non-alcoholic beverages, milk-based drinks and dairy analogue drinks) in 2007 (Chinese Ministry of Health, 2007) and is allowed for use in foods in Mexico following consultation with competent authorities in all food categories proposed herein (Mexico, 2007).

Navigator.com/Europe of 10 July 2007. Because of these difficulties, the Commission and Member States within the Standing Committee on the Food Chain and Animal Health that met on 19 June 2007 agreed to postpone the date of entry into force of hygiene rules to 31 October 2008. Given, however, that most crude fish oil is mainly imported from Peru, Morocco and Chile and that very little is intended for human consumption, despite the postponement of the date, there is little incentive for companies in these countries to invest to meet the new EU hygiene rules, so that the risk of shortage will possibly exist even after 31 October 2008.

X.2 DHA and EPA Exposure - NDNS Survey Data

Previous DHA and EPA human exposure data from the National Diet and Nutrition Survey (NDNS) 1986/1987 were reviewed extensively in the initial application dossier (UKDA, 1991). The principal sources of EPA and DHA in the diet are fatty fish. However, only 35% of UK adults regularly consume fatty fish. In the absence of fatty fish in the diet, average intakes of EPA and DHA would be only 33 mg/day and 54 mg/day, respectively, for the same group of consumers (UKDA, 1991)[4].

Human exposure data from the latest NDNS (Henderson *et al.*, 2002) of adults aged 19 to 64 years shows that the mean consumption of oily fish has increased from 34 g to 53 g/week (97 to 151 mg/day DHA/EPA - from about a quarter to a third of a portion) since the last survey of this age group in 1986/1987. Increased salmon consumption largely accounts for the increase. The intake data has been recently reviewed by the Fish Inter-Committee Sub-Group (FICS) of the UK Scientific Advisory Committee on Nutrition (SACN). This subcommittee has presented recommendations to increase LCPUFA (DHA/EPA) consumption to 450 mg/day (SACN, 2004).

The 2003 AFSSA report on omega-3 fatty acids, referred to previously, recognizes that omega-3 fatty acid intakes are insufficient since the average consumption of fish products by the French population is only to 35 g/day/person. This insufficient intake of omega-3 fatty acids from fish results in the promotion of foods to which they are added (AFSSA, 2003).[5]

The Belgian Superior Council of Hygiene, strongly relying on the comments of the French Agency in the 2003 report, recommends increasing intake of omega-3 fatty acids by pregnant and nursing women, advising the consumption of approximately 250 mg (200 to 300 mg) of DHA on a daily basis.

In the report from the Health Council of the Netherlands of 18 December 2006, experts recommend that the amount of fish fatty acids in the diet be increased substantially in order to meet the norm for these fatty acids of 450 mg/day (Health Council of the Netherlands, 2006).[6] Clearly this has proved difficult to achieve in the EU from fish intake alone, and this fact supports the need for algal oil, a more acceptable, reliable, sustainable, and convenient dietary source of omega-3 DHA.

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[4] National Dietary and Nutrition Surveys (NDNS) of adults aged 16 to 65 (1986/87) which was commissioned jointly by the UK Ministry of Agriculture Foods and Fisheries (MAFF) and Department of Health (DH).
[5] See p. 22 of that report
[6] See in particular p. 13 of the Dutch report entitled “Guidelines for a healthy diet 2006”, N° 2006/21

XI NUTRITIONAL INFORMATION

XI.1 Nutritional Profile of DHA-rich Algal Oil

DHA-rich algal oil is essentially 100% fat (principally in the triglyceride form) and as such has a caloric value of approximately 9 kcal per g. It is highly likely that a food manufacturer will simply use DHA-rich algal oil to replace some or all of the added fish or vegetable oil; therefore, there will be little, if any, change to the nutritional profile of the food product.

XII MICROBIOLOGICAL INFORMATION

This issue was discussed and addressed in the initial submission.

XIII ADDITIONAL TOXICOLOGICAL AND HUMAN SAFETY INFORMATION

Fifteen clinical studies in over 1200 adults, children, and pregnant/lactating women demonstrate that ingestion of DHA-rich algal oil is not associated with any adverse experiences unrelated to oil organoleptic properties. *(In some cases ingestion of DHA-rich algal oil capsules is associated with a fishy like "burp"/reflux, an organoleptic property inherent to any LCPUFA oil consumed at high concentrated doses.)* The product has been evaluated in children, adults with and without cardiac disease and diabetes and pregnant and lactating women. There are no signs of any safety concern in any population. Demonstrating confidence in the safety of DHA-rich algal oil, the US National Institutes of Health is currently supporting a study which involves the use of DHA-rich algal oil in pregnant/nursing women at a dose of 800 mg DHA/day. Martek is unaware of any study or investigation that has been terminated due to safety issues with DHA-rich algal oil. A recent EU recommendation noted that pregnant and lactating women should ingest at least 200 mg per day of DHA with up to one gram per day as appropriate (Koletzko *et al.*, 2007). As the algal source of DHA does not contain mercury or environmental contaminants there is no issue of over-exposure to toxins from this source.

Additionally Martek Biosciences Corporation has a written regulatory, medical, and clinical group procedure for obtaining, evaluating, and reporting AEs and SAEs occurring in clinical trials and in reports from marketed use of its products. Martek monitors product AEs during sponsored clinical studies or during investigator-initiated studies for which product is supplied. Also monitored are AEs reported to Martek through an established toll free (800) phone number and website. However, Martek does not formally monitor AEs reported to manufacturers of infant formulas containing Martek oils since these are considered the responsibility of the infant formula manufacturer.

There is an active component and a passive component to the AE monitoring program. All reports of AEs and SAEs are referred to Martek's medical affairs personnel for evaluation, reporting and recording. Medical affairs and regulatory groups are jointly responsible for collecting and maintaining an AE database for each product.

Discussion of the Safety of DHA and EPA

France and Belgium – The French working group revised recommended nutritional levels for intake of long-chain omega-3 fatty acids. The group decided to establish levels based on daily intake beyond which the nutritional benefit of long-chain omega-3 fatty acids can no longer be shown. The group emphasised that that this level should not be considered a safety limit, *i.e.*, a level of intake beyond which there are health risks.

The Belgian authorities of the Superior Council of Hygiene agree with this position, recalling the French Agency expressly mentions in its 2003 report mentioned above that the 2 g/day recommendation is not a safety limit.

FDA- The FDA has accepted as GRAS, oils whose levels of daily intake of EPA and DHA are estimated at less than 3 g/day.

There exists a strong scientific argument that daily intakes of DHA/EPA up to 3 g/day are safe. This analysis was recently re-affirmed both by FDA and by independent scientific reviewers in the EU.

In 1997, FDA affirmed as GRAS menhaden oil as a direct food ingredient with specific limitations to assure that the total daily intake of EPA and DHA would not exceed 3 g per person per day (FDA, 2007). In 2004, in a subsequent consideration of a Health Claim Petition, FDA reiterated its conclusion that 3 g DHA/EPA per day is GRAS (FDA, 2004a).

CONCLUSIONS

Foods containing DHA at maximum use level will deliver approximately 100 mg DHA per serving. Based on intake recommendations by EU expert bodies, individuals are expected to consume 2 to 5 foods containing DHA-rich algal oil per day. Given this scenario, meaningful increases of 200 to 500 mg DHA per day will be introduced into an individual's diet; anticipated exposure of DHA from DHA-rich algal oil is 200 to 500 mg per day.

In the estimation of maximum intake, care has been exercised to assure that the sources of data are representative of intake across Europe by not only using the well-recognised United Kingdom (UK) National Diet and Nutrition Survey (NDNS) data but also by using market data based on per capita intakes across Europe. The estimated intake using either of these data sources, for both authorised and proposed uses, resulted in the same calculated intake of 1.7g/day, equivalent to an individual who consumes approximately 13 portions of food containing DHA-rich algal oil will ingest approximately 1.7 g of DHA per day. The total maximum estimated DHA intake including both proposed applications and authorized uses of DHA and the background level is approximately 1.7 g /day + 0.2-0.3 g/d = 1.9-2.0 g/day. This is clearly a significant over-estimation.

Clinical studies in over 1200 adults, children, and pregnant/lactating women demonstrate that ingestion of DHA-rich algal oil is not associated with any serious adverse experiences and no adverse experiences other than minor fishy "burps" [reflux, an organoleptic experience associated with other long-chain polyunsaturated fatty acids (LCPUFA)]. Clinical studies support safe use of DHA-rich algal oil up to 7.2 g per day (which equates to approximately 2.7 g DHA per day).

DHA from DHA-rich algal oil is the only vegetarian version of this omega-3 fatty acid that is commercially available to meet the needs of persons that may be vegans, vegetarians or allergic to other sources.

Comments expressed at the time of the submission of the original application are considered and addressed.

The data presented in this submission continues to support both the original opinion of the UK Expert Committee and that of the Standing Committee on the Foodchain and Animal Health (SFCAH). In its 2002 assessment, having led to the issuance of the authorization Decision 2003/427, the UK Advisory Committee on Novel Foods and Processes (ACNFP) concluded that the addition of DHA-rich algal oil to all foods covered in the original list, which importantly included the proposed food categories that are the subject of this application, is "safe for use" (Commission of the European Communities, 2003). The adoption by the SCFAH of Commission Decision 2003/427 acknowledges in Recital 5 that "it is established that DHA-rich oil from the microalgae *Schizochytrium* sp. complies with the criteria laid down in Article 3(1) of the Regulation", specifically that DHA-rich algal oil does not:

- present a danger for the consumer,
- mislead the consumer, or
- differ from foods or food ingredients which they are intended to replace to such an extent that their normal consumption would be nutritionally disadvantageous for the consumer."

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Eerste beoordeling / First assessment

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