Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

Krillolie

Krill oil

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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Beoordeling

Inleiding

Aan de orde is een tweede beoordeling volgens de Europese Verordening 258/97, over het gebruik van krillolie als een nieuw voedselingrediënt. De aanvraag is ingediend door de firma Neptune Technologies and Bioressources (Canada) die de olie isoleert uit garnaalachtige diertjes, zogeheten krill[a]. Deze olie komt niet direct beschikbaar voor de consument, maar de aanvrager wil de olie gaan verhandelen als bron van visolievetzuren onder de merknaam Neptune krillolie (NKO^{TM}). Het nieuwe product zal op de markt komen als voedingssupplement. Daarnaast zal het worden verwerkt in dieetvoeding voor bijzondere medische doeleinden en in gewone levensmiddelen zoals yoghurt, melk en melkachtige dranken, sappen, 'eiwitrepen', maaltijdvervangers.

Krillolie werd in de EU niet in de voeding toegepast vóór 15 mei 1997 toen de verordening in werking trad. Een veiligheidsbeoordeling als nieuw voedingsmiddel is daarom 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’.

Eerste beoordeling

De eerste beoordeling van de aanvraag voor markttoelating is verricht in Finland door de *Novel Food Board* (NFB). Volgens de NFB geeft de informatie in het dossier geen aanleiding om te twijfelen aan de veiligheid van het product. Wel menen de Finse beoordelaars dat beheersmaatregelen moeten worden overwogen om mogelijke overconsumptie van visolievetzuren te voorkomen. Indien nodig zou het aantal productcategorieën beperkt moeten worden, omdat ook inname met andere bronnen van visolievetzuren hierbij in beschouwing moeten worden genomen. Afgezien van deze kanttekening lijkt het dat de NFB geen bezwaar heeft tegen toelating van krillolie als nieuw ingrediënt.

Bevindingen van de commissie VNV

De commissie VNV heeft bezwaar tegen de toelating van krillolie als nieuw voedingsmiddel omdat er onvoldoende gegevens zijn om de veiligheid te kunnen beoordelen. Zij baseert haar oordeel op de informatie in het dossier (zie de samenvatting in bijlage A), de website van de aanvrager (http://www.neptunebiotech.com/) en de eerste beoordeling van de NFB (bijlage B).

De aanvrager meent dat toxicologische informatie over het nieuwe product overbodig is gezien de geschiedenis van gebruik van krill in verschillende delen van de wereld. De

[a] Krill is een Noors woord voor voedsel van baleinwalvissen en bestaat uit kreeftjes en andere kleine schaaldiertjes.

commissie VNV vindt dit niet acceptabel, in tegenstelling de Finse beoordelaars. De commissie VNV constateert dat de geschiedenis van gebruik waar de aanvrager zich op beroept niet gedocumenteerd is. Het betreft consumptie van krill sinds 1970 voornamelijk in Japan, maar ook in de Oekraïne, Rusland en Frankrijk. Niet alleen is de omvang van de krillconsumptie onbekend, ook zijn bevindingen over het uitblijven van mogelijke gezondheidsklachten niet gerapporteerd. Een ander belangrijk argument is dat het product van deze aanvraag niet de krill zelf betreft, maar een extract hiervan. De commissie VNV concludeert daarom dat de veiligheid van krillolie voor de consument beoordeeld moet worden op basis van wetenschappelijke criteria beschreven in de Aanbeveling van de Commissie 97/618/EG.

Bron

De aanvrager koopt diepgevroren krill van een Japans bedrijf die krill opvist uit de Atlantische oceaan van het zuidpoolgebied. De commissie VNV tekent aan dat de identiteit van deze Japanse toeleverancier onvermeld blijft. Ook geeft het dossier geen uitsluitsel hoeveel natriumwaterstofsulfiet, dat als conserveringsmiddel wordt toegevoegd bij het invriezen van krill [1], achterblijft in de olie.

De commissie VNV vraagt zich af of de aanvrager terecht het nieuwe product definieert als een extract van de diersoort *Euphausia superba.* De opgeviste krill zal ongetwijfeld ook verwante organismen uit de dierenrijkfamilie *Euphausiidae* bevatten. Deze familie van garnaalachtige ongewervelde dieren vormt een belangrijk deel van het zoöplankton. Echter, kwantitatieve informatie over de diersoorten waaruit de gebruikte krill is opgebouwd ontbreekt.

Proces

Een belangrijk kritiekpunt van de commissie VNV is dat het productieproces niet duidelijk is beschreven. Het dossier vermeldt dat de diepgevroren krill wordt vermalen en behandeld met een organisch oplosmiddel, maar het is onduidelijk hoe vervolgens de schaaldelen en eiwitten worden verwijderd. Om de chemische kenmerken van het nieuwe product te kunnen beoordelen zou in het bijzonder de scheiding van eiwitten en vetten moeten worden toegelicht. Ook is aanvullende informatie nodig over de verdere zuivering van de krillolie.

Productspecificatie

Aanvullend op de eerste beoordeling constateert de Commissie VNV dat de samenstellingsgegevens niet eenduidig zijn weergegeven. Bij de productspecificatie maakt de Commissie VNV er bezwaar tegen dat voor bijna alle bestanddelen slechts een minimumgehalte wordt vermeld (zie Bijlage A, Tabel I.1). Het dossier vermeldt dat de visolievetzuren eicosapentaeenzuur (EPA) en docosahexaeenzuur (DHA) in krillolie aanwezig zijn in de vorm van fosfolipiden[b], maar de productspecificatie geeft hier geen uitsluitsel over. Ook ontbreekt informatie over de vorm waarin andere aanwezige vetzuren

[b] Fosfolipiden lijken op triacylglycerolen met het verschil dat in plaats van een derde vetzuurketen er een fosfaat-alcoholgroep aan het glycerolhandvat is gekoppeld. Lecithine (fosfatidylcholine of wel 1,2-diacyl-glycerol-fosforylcholine) is één van de meest voorkomende lipiden in membranen van dierlijk weefsel. Ook is het een veel gebruikte emulgator en goegekeurd levensmiddelenadditief (E322).

voorkomen, te weten triacylglycerolen, fosfolipiden of vrije vetzuren. Op verzoek van het Bureau Nieuwe Voedingsmiddelen heeft de aanvrager de samenstellingsgegevens nader toegelicht. Uit aanvullende analysegegevens blijkt dat 100 g krillolie ongeveer 43 g fosfolipiden, 35 g triacylglycerolen en 16 g vrije vetzuren bevat. Uit de informatie van meerdere productiepartijen blijkt dat de verdeling van de verschillende vetzuren over deze fracties niet consistent is. De hoeveelheid visolievetzuren in de fosfolipidenfractie lijkt ongeveer tweemaal zo groot als die in de beide andere fracties samen (vrije vetzuren en triacylglycerolen). Van de gedocumenteerde productiepartijen varieert het gemiddeld gehalte aan EPA plus DHA van 26,2 tot 27,9 g per 100 g krillolie. De overige vetzuren bestaan voor het grootste deel uit palmitinezuur, myristinezuur, vacceenzuur, oliezuur en palmitolinezuur. Meer dan 80 % van de fosfolipiden bevat choline gekoppeld aan de fosfaatgroep [2] en deze groep verbindingen is ook bekend onder de naam lecithine[b]. De krillolie bevat een kleine hoeveelheid cholesterol. Naast vetten zijn er carotenoïden en vetoplosbare vitaminen aanwezig (zie Bijlage A, Tabel I.1). Andere bronnen melden dat de olie ook het carotenoïde canthaxanthine en vitamine D bevatten [2]. Deze bestanddelen worden echter niet in het dossier genoemd.

Eén van de kwaliteitskenmerken van consumptieoliën is het zogeheten zuurgetal. Dit is een maat voor de hoeveelheid vrije vetzuren waarvoor maximumwaarden staan vermeld in de internationale standaard voor consumptieoliën van de CODEX [3]. De commissie VNV constateert dat de aanvrager het zuurgetal nergens heeft gespecificeerd. De van nature aanwezige antioxidanten blijken voldoende om de stabiliteit van het product te waarborgen. De lage peroxidewaarde en de lage p-anisidinewaarde (zie Tabel I.1 in Bijlage A) geven aan dat er nauwelijks primaire en secundaire oxidatieproducten aanwezig zijn. Stabiliteits-gegevens van de krillolie in zogeheten zachte gelcapsules ondersteunen dit. De commissie VNV tekent aan dat de aanvrager geen stabiliteitstesten heeft uitgevoerd met producten uit de voorgestelde categorieën levensmiddelen waaraan krillolie is toegevoegd.

Contaminanten[c]

De commissie VNV is het eens met de Finse beoordelaars dat de krillolie afdoende is gecontroleerd op milieuverontreinigingen en residuen van bestrijdingsmiddelen. Ook worden de microbiologische risico's voldoende beheerst.

Het is de commissie VNV opgevallen dat de gebruikte analysemethoden niet in alle gevallen overeenkomen met die welke genoemd staan in de eerdere genoemde CODEX standaard (bijvoorbeeld arseen, koper, lood) [3]. Bovendien zijn de maximumwaarden in de productspecificatie voor het kopergehalte hoger dan die uit de CODEX standaard.

Voedingswaarde

Vanuit voedingskundig oogpunt lijkt er geen bezwaar tegen het gebruik van de olie waarvan de geïdentificeerde bestanddelen al in bepaalde mate in onze gewone voeding aanwezig zijn. De commissie VNV merkt op dat de voedingswaarde van de individuele vetzuren gelijkwaardig is voor de verschillende chemische vorm waarin deze worden geconsumeerd.

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c Op pagina 18 en 19 van het dossier vergelijkt de aanvrager de maximumwaarden van enkele zware metalen met de aanvaardbare bovengrenzen die de JECFA heeft afgeleid. Alleen voor cadmium lijkt de berekening correct.

De dagelijkse inname van 280 mg visolievetzuren die de aanvrager voorstelt (overeenkomend met 1 gram krillolie als supplement), is minder dan de 450 mg die de Gezondheidsraad aanbeveelt in haar recente Richtlijn Goede Voeding [4] om het risico op sterfte door hart en vaatziekten te verminderen. Dit sluit aan bij recente aanbevelingen van Amerikaanse en Engelse deskundigencommissies.

Verwachte inname

De aanvrager gaat uit van toepassing van krillolie in een breed assortiment voedingsmiddelen om zo de inname van visolievetzuren met de dagelijkse voeding aan te vullen. Per portie zullen deze producten 500 mg krillolie bevatten. Dit wordt bestempeld als maximum aanbevolen dagelijkse hoeveelheid, maar de aanvrager is hierin niet eenduidig. Voor het gebruik van voedingsupplementen wordt een dubbele hoeveelheid krillolie aangeraden, te weten 1000 mg per persoon per dag (zie onderdeel IX in Bijlage A). Dit komt overeen met ongeveer 280 mg visolievetzuren. Om te kunnen schatten wat consumenten dagelijks aan krillolie binnen zullen krijgen is voedselconsumptieonderzoek onontbeerlijk, maar dergelijke gegevens ontbreken in het dossier. Ook zijn de portiegroottes niet gespecificeerd. Het lijkt onwaarschijnlijk dat de aanvrager zicht houdt op alle mogelijke toepassingen. De commissie VNV heeft daarom grote twijfels of duidelijke etikettering van de met krillolie verrijkte producten voldoende garantie biedt dat consumenten hun inname zullen beperken tot de hoeveelheid die de aanvrager wenselijk acht. Het kan niet worden uitgesloten dat grootverbruikers van bepaalde levensmiddelen waaraan krillolie is toegevoegd tevens een krilloliesupplement gaan gebruiken.

Voor wat de visolievetzuren betreft sluit de commissie VNV zich aan bij de Finse beoordelaars die verwijzen naar de bovengrens van inname van 3 g EPA plus DHA, die door de Amerikaanse Food and Drug Administration als veilig wordt beschouwd. In dit verband herhaalt de commissie VNV haar eerdere standpunt [5] dat er behoefte is aan een betere wetenschappelijke onderbouwing van het maximaal veilige innameniveau van visolievetzuren om meer duidelijkheid te krijgen over mogelijke langetermijneffecten. Hoewel er effecten op de bloedstolling zijn aangetoond bij overschrijding van de bovengrens, is met de huidige stand van wetenschap de vraag of dit zou kunnen leiden tot nadelige gezondheidseffecten niet te beantwoorden. Een belangrijk aandachtspunt is dat er in de supermarkten al producten met verhoogde gehalten aan visolievetzuren liggen. Volgens de commissie VNV zijn er daarom maatregelen nodig ten aanzien van de mogelijk inname van visolievetzuren uit alle DHA-rijke en/of EPA-rijke bronnen. Alleen dan kan de consument zijn dagelijkse consumptie van visolievetzuren verantwoord regelen en kan overschrijding van de genoemde veilige bovengrens worden voorkomen [6].

Toxicologische informatie

De commissie VNV concludeert dat aanvullend onderzoek nodig is waaruit moet blijken dat onbekende (niet-geïdentificeerde) verbindingen in de krillolie geen nadelige gevolgen zullen hebben voor gezondheid van de consument. Dit wordt hieronder toegelicht.

Voor een gezuiverde olie bevat het nieuwe product een aanzienlijke hoeveelheid eiwit, te weten tussen 0,5 en 3,5 g per 100 g olie (zie Bijlage A, Tabel I.1). Net als bij de Finse beoordelaars is dit een belangrijk aandachtspunt van de commissie VNV omdat niet bekend is welke eiwitten dit zijn. Daarnaast tekent de commissie aan dat de aanvrager het heeft nagelaten om de zogeheten niet-verzeepbare vetbestanddelen te onderzoeken op

ongewenste verbindingen. Uit verschillende informatiebronnen [7-9] blijkt dat de nieuwe olie een bijzonder bestanddeel zou bevatten. Het gehalte van deze verbinding wordt echter niet in de productspecificatie vermeld. Het betreft een bepaald flavonoïde dat structureel overeenkomsten lijkt te vertonen met 6,8-di-c-glucosylluteolin. Ook in een recent gepubliceerd onderzoeksrapport [10] wordt hiervan melding gemaakt. De commissie VNV kan de biologische effecten niet evalueren omdat voedingskundige en toxicologische informatie over dit flavonoïde ontbreekt in het dossier.

Er is geen veiligheidsonderzoek met laboratoriumdieren uitgevoerd conform internationale toxicologische richtlijnen. De resultaten met immuundeficiënte muizen, die met krillolie werden behandeld in het kader van een tumormodelonderzoek, zijn niet relevant voor de veiligheidsbeoordeling.

Net als de Finse beoordelaars meent de commissie VNV dat de beschikbare gegevens over mensgebonden onderzoek beperkt zijn. Omdat dit dossieronderdeel toegespitst is op vermeende gezondheidsbevorderende effecten, benadrukt de commissie VNV dat evaluatie van de veronderstelde gunstige werking géén onderdeel is van deze veiligheidsbeoordeling. De aanvrager heeft in één onderzoek[d] een aantal veiligheidskenmerken onderzocht maar hiervan is alleen een beknopte samenvatting in het dossier opgenomen. Omdat details van de onderzoekmethode en individuele laboratoriumuitslagen niet beschikbaar zijn, kan de commissie VNV deze veiligheidsgegevens niet beoordelen. De commissie constateert dat in twee andere onderzoeksrapporten ongewenste bijwerkingen niet systematisch werden bijgehouden maar gezondheidsbedreigende incidenten lijken zich niet te hebben voorgedaan; de commissie kan niet nagaan of deze onderzoekingen volgens Good Clinical Practice (GCP) zijn uitgevoerd. Volgens recent gepubliceerde onderzoeksresultaten [10] lijkt een dagelijkse dosering van 300 mg krillolie het immuunsysteem te kunnen beïnvloeden. De door de aanvrager voorgestelde toepassing betreft een hogere dosering die mogelijk langdurig door voedingsbewuste consumenten zal worden gebruikt. De commissie VNV dringt daarom aan op onderzoek dat de veiligheid van het gebruik ondersteunt.

Conclusie

De commissie VNV stelt vast dat aanvullende gegevens nodig zijn voordat het product op de Europese markt kan worden toegelaten. Er is onvoldoende zekerheid over de afwezigheid van mogelijk van nature aanwezige, schadelijke verbindingen. Niet alleen zal de samenstelling duidelijker gespecificeerd moeten worden waarbij de aanvrager ook bovengrenzen voor de bestanddelen moet aangeven, ook is toxicologisch onderzoek nodig om een veilige bovengrens van inname te kunnen vaststellen.

[d] Inzake de onderzochte groep personen, gezonde vrijwilligers óf patiënten, is de tekst in het dossier niet consistent met het betreffende onderzoeksrapport "Neptune 2002 Confidential".

Referenties

1. http://www.fda.gov/ohrms/dockets/dailys/03/Feb03/020503/8004dafd.pdf.
According to page 9 of this document, frozen krill contains 100 mg sodium hydrogen sulphite per kg. This complies with European limits for sulphite. The applicant has submitted this document to the United States Food and Drug Administration (US FDA).
(Volgens dit document, dat de aanvrager heeft verstrekt aan de Amerikaanse Food and Drug Administration, bevat diepgevroren krill ongeveer 100 mg natriumwaterstofsulfiet (natriumbisulfiet) per kg. Dit voldoet aan de Europese sulfietnorm voor schaaldieren.)

2. www.neptunebiotech.com/products/nko_factsheet%20.pdf
www.mercola.com/products/krill_oil.htm
www.rejuvenation-science.com/neptune-krill-oil.html

3. CODEX Standard for edible fats and oils not covered by individual standards. CODEX STAN 19-1981 (Rev.2-1999) (www.codexalimentarius.net/download/standards/74/CXS_019e.pdf)

4. Health Council of the Netherlands. Guidelines for a healthy diet 2006. The Hague: Health Council of the Netherlands, 2006; publication no. 2006/21
Gezondheidsraad. Richtlijnen goede voeding 2006. Den Haag: Gezondheidsraad, 2006; publicatie nr 2006/21
(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. Health Council of the Netherlands: Committee on the Safety Assessment of Novel Foods. Docosahexaenoic acid rich oil. The Hague: Health Council of the Netherlands, 2002; publication no. 2002/03VNV.
Gezondheidsraad: Commissie Veiligheidsbeoordeling nieuwe voedingsmiddelen (VNV) Docosahexaeenzuurrijke olie. Den Haag: Gezondheidsraad, 2002; publicatie nr. 2002/03VNV
(http://www.cbg-meb.nl/nl/docs/nwvoeding/docosahexaeenzuurrijke%20olie.pdf)

6. Statement of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the addition of DHA-rich oil from micro algae to an extended range of foods
(http://www.efsa.europa.eu/en/science/nda/nda_statements/nda_statement_dha_microalgae.htm)

7. "Nutraceutical products. First target market: nutraceutical products. As the first company to offer NKO™, the true krill oil that optimally contains all the naturally occurring bioactive ingredients like Omega-3 fatty acids (EPA & DHA) functionalised with phospholipids, esterified astaxanthin and a novel flavonoid." (http://www.neptunebiotech.com/markets.html)

8. Neptune Technologies & Bioressources Inc. Discovers a New Molecule Novel Flavonoid. Business Wire, Oct 10, 2001
(http://www.findarticles.com/p/articles/mi_m0EIN/is_2001_Oct_10/ai_79018633)

9. Bunea R, El Farrah K, Deutsch L (2004). Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. Altern Med Rev 9(4): 420-428

10. L Deutsch (2007). Evaluation of the Effect of Neptune Krill Oil on Chronic Inflammation and Arthritic Symptoms. J Amer College Nutrition, 26: 39-48
A short summary of this study is included in the dossier, ie "Neptune, 2004. CONFIDENTIAL"

Assessment - English courtesy translation (May 1, 2007)

Introduction

The subject in question is a so-called second assessment, in accordance with European Regulation 258/97, regarding the use of krill oil as a novel food ingredient. The application was submitted by Neptune Technologies and Bioressources (Canada), a company which extracts the oil from shrimp-like creatures known as krill[a]. This oil will not be made directly available to consumers. The applicant proposes to market the oil as a source of fish-oil fatty acids, under the brand name of Neptune krillolie (NKO™). The novel product will be positioned on the market as a food supplement. In addition, it will be incorporated into dietary foods for special medical purposes and in ordinary foods such as yoghurt, milk and milky drinks, juices, 'protein bars', and meal replacements.

Krill oil was not used in foods in the EU prior to 15 May 1997, when the Regulation came into effect. This oil therefore requires a safety assessment as a novel food in the EU. 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”).

Initial assessment

The initial assessment of the application for market authorization was carried out in Finland by the Novel Food Board (NFB). According to the NFB, on the basis of the information contained in the dossier there is no reason to doubt the safety of the product. Nevertheless, the Finnish assessors do take the view that consideration should be given to the use of control measures for the prevention of possible over-consumption of fish-oil fatty acids. If necessary, the number of product categories should be limited, to allow for the possibility of fish-oil fatty acid intake from other sources. Aside from this comment, it seems that the NFB has no objection to the authorisation of krill oil as a novel ingredient.

Findings of the VNV Committee

The VNV Committee objects to the authorisation of krill oil as a novel food as there is insufficient data to conduct a safety assessment. The Committee bases its view on the information contained in the dossier (see Annex A for the summary), on the applicant’s website (http://www.neptunebiotech.com/) and on the report of the first assessment by the NFB (see Annex B).

The applicant feels that toxicological information pertaining to the novel product is unnecessary, in view of the history of consumption of krill in various parts of the world. Unlike the Finnish assessors, the VNV Committee feels that this is unacceptable. The VNV Committee notes that the history of use referred to by the applicant is not documented. This

[a] Krill is a Norwegian term for the food consumed by baleen whales. It consists of various small crustaceans.

pertains to the consumption of krill since 1970, mainly in Japan, but also in the Ukraine, Russia, and France. Aside from the fact that nothing known about the scale of the krill consumption in question, no findings concerning the absence of possible health problems have been reported. Another important argument is that the product to which this application relates is an extract of krill, and not the krill itself. The VNV Committee therefore concludes that the issue of whether krill oil is safe for consumers should be assessed on the basis of scientific criteria, as described in European Commission Recommendation No. 97/618/EC.

Source

The applicant purchases deep-frozen krill from a Japanese company that harvests krill from the waters of the South Atlantic, close to Antarctica. The VNV Committee notes the absence of any details concerning the identity of this Japanese supplier. Nor does the dossier provide any definitive answers concerning the quantity of sodium hydrogen sulphite (which is added to the krill as a preservative during the freezing process [1]) that remains in the oil.

The VNV Committee wonders whether the applicant can justifiably define the novel product as an extract of the animal species *Euphausia superba.* The catch undoubtedly also includes related organisms from this family of organisms, the *Euphausiidae*. This family of shrimp-like invertebrates represents a major part of the zooplankton. However, no quantitative information has been provided concerning the animal species that are present in the krill used here.

Process

One major criticism expressed by the VNV Committee is that no clear description has been provided of the production process in question. The dossier states that the deep-frozen krill is milled and treated with an organic solvent, but it is not clear how the proteins and fragments of shell are subsequently removed. In order to assess the novel product's chemical characteristics, further clarification will be required concerning the separation of proteins and fats in particular. Additional information is also required concerning the further purification of the krill oil.

Product specification

As a supplement to the initial assessment, the VNV Committee concludes that compositional data are not clearly indicated. With regard to the product specification, the VNV Committee objects to the fact that only a minimum level is indicated for almost all of the components (see Annex A, Table I.1). The dossier states that the fish-oil fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are present in krill oil as phospholipids[b], but the product specification provides no definite answer on this matter. Other fatty acids are also present, namely triacylglycerols, phospholipids, or free fatty acids, yet there is no information regarding the form in which they occur. At the request of the Novel Foods Unit,

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b Phospholipids resemble triacylglycerols, except that a phosphate-alcohol group is attached to the glycerol backbone, where there would otherwise be a third fatty acid chain. Lecithin (phosphatidylcholine or rather 1,2-diacylglycerol phosphorylcholine) is one of the most commonly occurring lipids in the membranes of animal tissue. It is also a frequently used emulsifying agent and an approved food additive (E322).

the applicant has provided further details with regard to the compositional data. Additional analytical data shows that 100 g of krill oil contains approximately 43 g of phospholipids, 35 g of triacylglycerols, and 16 g of free fatty acids. The information provided shows that, for a number of production lots, the distribution of the various fatty acids throughout these fractions is not consistent. The amount of fish-oil fatty acid in the phospholipid fraction appears to be approximately twice the combined total of the two other fractions (free fatty acids and triacylglycerols). In the documented production lots, the average levels of EPA plus DHA vary from 26.2 g to 27.9 g per 100 g of krill oil. The other major fatty acids are palmitic acid, myristic acid, vaccenic acid, oleic acid, and palmitoleic acid. More than 80 % of the phospholipids contain choline bound to the phosphate group [2]. This group of compounds is also known as lecithin[b]. The krill oil contains little cholesterol. Besides fats, carotenoids and fat-soluble vitamins are also present (see Annex A, Table I.1). According to other sources of information, the oil is also said to contain the carotenoid canthaxanthin and vitamin D [2]. These components are however not cited in the dossier.

One of the quality characteristics of edible oils is the so-called acid value. This is a measure of the quantity of free fatty acids, for which maximum values have been indicated in the CODEX international standard for edible oils [3]. The VNV Committee notes that the applicant has failed to provide any details of the acid value. It appears that there are sufficient naturally occurring antioxidants to safeguard the stability of the product. The low peroxide value and the low p-anisidine value (see Table I.1 in Annex A) indicate that virtually no primary or secondary oxidation products are present. This is supported by stability data on krill oil in soft gelatin capsules. The VNV Committee notes that the applicant has not performed any stability tests on products in the proposed categories of foods to which krill oil is added.

Contaminants[c]

The VNV Committee agrees with the Finnish assessors that the krill oil has been adequately tested for environmental contaminants and pesticide residues. The applicant is also quite capable of dealing with the microbiological risks involved.

It has come to the attention of the VNV Committee that, in some cases, the analytical methods used differ from those set out in the above-mentioned CODEX standard (e.g. arsenic, copper, lead) [3]. In addition, the maximum values for copper levels cited in the product specification are higher than those used by the CODEX standard.

Nutritional value

From the nutritional point of view, there would seem to be no objection to the use of an oil whose identified ingredients are already present in our normal diet to some extent. The VNV Committee notes that the nutritional value of the individual fatty acids is independent of the chemical form in which they are consumed.

The daily intake of 280 mg of fish-oil fatty acids (equivalent to 1 gram of krill oil in supplements) proposed by the applicant, is less than the 450 mg that the Health Council of

[c] On pages 18 and 19 of the dossier, the applicant compares the maximum values of several heavy metals with the tolerable upper intake levels derived by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Only in the case of cadmium does the calculation appear to be correct.

the Netherlands recommended in its recent Healthy Diet Guidelines [4] to reduce the mortality risk from cardiovascular disease. This is in keeping with recent recommendations by American and British expert committees.

Anticipated intake

The applicant assumes that krill oil will be used in a wide range of foods, in order to supplement the intake of fish-oil fatty acids in the daily diet. These products will contain 500 mg of krill oil per portion. This is seen as the maximum recommended daily intake, but this has not been clearly identified as such by the applicant. Double the above amount is recommended with regard to the use of food supplements, i.e. 1000 mg per individual per day (see section IX in Annex A). This is equivalent to approximately 280 mg of fish-oil fatty acids. Food consumption surveys are indispensable as a means of estimating the amount of krill oil that consumers will ingest on a daily basis. However, the dossier contains no information of this kind. Nor indeed are the portion sizes specified. It seems unlikely that the applicant will monitor all possible uses of the new ingredient. Accordingly, the VNV Committee very much doubts that clear labelling of the products enriched with krill oil would provide adequate assurance that consumers will restrict their intake to the level that the applicant considers to be appropriate. In addition, the possibility cannot be excluded that "heavy users" of certain foods to which krill oil has been added will not also use a krill oil supplement.

With regard to the fish-oil fatty acids, the VNV Committee endorses the conclusions of the Finnish assessors. The latter cite an upper intake level of 3 g of EPA plus DHA, which is considered by the US Food and Drug Administration to be safe. In this connection, the VNV Committee reiterates its previous standpoint [5] that there is a need for improved scientific support for the maximum safe fish-oil fatty acid intake level, in order to provide greater clarity concerning possible long-term effects. While exceeding the upper intake level has been shown to have an effect on blood coagulation, given the current scientific situation it is not possible to say whether this could result in adverse health effects. A major focal point is that Dutch supermarkets already stock products with elevated fish-oil fatty acid levels. The VNV Committee therefore takes the view that measures are needed to address the potential intake of fish-oil fatty acids from all DHA-rich and/or EPA-rich sources. Only then can consumers manage their daily consumption of fish-oil fatty acids in a responsible fashion, thereby preventing the safe upper intake level in question from being exceeded [6].

Toxicological information

The VNV Committee concludes that supplementary research is required, to demonstrate that unknown (non-identified) compounds in the krill oil have no adverse effects on the health of consumers. This conclusion is explained below.

For a purified oil, the novel product contains a substantial quantity of protein, specifically between 0.5 g and 3.5 g per 100 g of oil (see Annex A, Table I.1). Like the Finnish assessors, the VNV Committee sees this as a major focal point, as nothing is known concerning the identity of the proteins in question. It would like to add that the applicant has neglected to analyse the so-called non-saponifiable fat components for the presence of undesirable compounds. Various sources of information [7-9] identify one component in particular which is claimed to be present in the new oil. Yet the product specification gives no details concerning the concentration of this compound. The compound in question is a

certain flavonoid, the structure of which appears to resemble that of 6,8-di-c-glucosylluteolin. Mention is also made of this in a recently published research report [10]. The VNV Committee is unable to evaluate the associated biological effects, as the dossier contains no nutritional and toxicological information pertaining to this flavonoid.

The applicant has not carried out any safety studies in experimental animals conform international guidelines for toxicological testing. The results of tumour model research, in which immunodeficient mice were treated with krill oil, are not relevant to the safety assessment.

Like the Finnish assessors, the VNV Committee takes the view that there is too little data on research involving human subjects. As this dossier item is specifically aimed at supposedly health-promoting effects, the VNV Committee emphasises that an evaluation of these claims regarding favourable effects does not fall within the scope of this safety assessment. In one study[d] the applicant investigated a number of safety aspects, but the dossier contains only a brief summary of the study's findings. No details are given of the research methods used, nor of individual test results. Accordingly, the VNV Committee is unable to assess the safety data in question. With regard to two other study reports, the VNV Committee notes that there was no systematic recording of adverse effects. However, no incidents that posed a threat to health appear to have taken place. The Committee is unable to determine whether these studies were carried out in accordance with Good Clinical Practice (GCP). Recently published study results [10] indicate that a daily dose of 300 mg of krill oil appears to have an effect on the immune system. The use proposed by the applicant involves a higher dose, which may be consumed over a prolonged period by food-conscious consumers. The VNV Committee therefore urgently requests details of any research which supports the assertion that the product is safe to use.

Conclusion

In summary, the VNV Committee has determined that supplementary data is required before the product can be admitted to the European market. There is insufficient certainty about whether the product is entirely free of any naturally occurring harmful compounds. The applicant must specify the composition more clearly, indicating maximum levels for the various components. A toxicological study is also needed, to establish a safe upper intake level.

[d] With regard to the group of test subjects, healthy volunteers, or patients investigated, the text of the dossier is not consistent with the study report in question "Neptune 2002 Confidential".

Referenties

11. http://www.fda.gov/ohrms/dockets/dailys/03/Feb03/020503/8004dafd.pdf.
According to page 9 of this document, frozen krill contains 100 mg sodium hydrogen sulphite per kg. This complies with European limits for sulphite. The applicant has submitted this document to the United States Food and Drug Administration (US FDA).

12. www.neptunebiotech.com/products/nko_factsheet%20.pdf
www.mercola.com/products/krill_oil.htm
www.rejuvenation-science.com/neptune-krill-oil.html

13. CODEX Standard for edible fats and oils not covered by individual standards. CODEX STAN 19-1981 (Rev.2-1999) (www.codexalimentarius.net/download/standards/74/CXS_019e.pdf)

14. Health Council of the Netherlands. Guidelines for a healthy diet 2006. The Hague: Health Council of the Netherlands, 2006; publication no. 2006/21
(http://www.healthcouncil.nl/pdf.php?ID=1479&p=1)
(Background document, see http://www.healthcouncil.nl/pdf.php?ID=1478&p=1)

15. Health Council of the Netherlands: Committee on the Safety Assessment of Novel Foods. Docosahexaenoic acid rich oil. The Hague: Health Council of the Netherlands, 2002; publication no. 2002/03VNV.
(http://www.cbg-meb.nl/nl/docs/nwvoeding/docosahexaeenzuurrijke%20olie.pdf)

16. Statement of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the addition of DHA-rich oil from micro algae to an extended range of foods.
(http://www.efsa.europa.eu/en/science/nda/nda_statements/nda_statement_dha_microalgae.htm)

17. "Nutraceutical products. First target market: nutraceutical products. As the first company to offer NKO™, the true krill oil that optimally contains all the naturally occurring bioactive ingredients like Omega-3 fatty acids (EPA & DHA) functionalised with phospholipids, esterified astaxanthin and a novel flavonoid." (http://www.neptunebiotech.com/markets.html)

18. Neptune Technologies & Bioressources Inc. Discovers a New Molecule Novel Flavonoid. Business Wire, Oct 10, 2001
(http://www.findarticles.com/p/articles/mi_m0EIN/is_2001_Oct_10/ai_79018633)

19. Bunea R, El Farrah K, Deutsch L (2004). Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. Altern Med Rev 9(4): 420-428

20. L Deutsch (2007). Evaluation of the Effect of Neptune Krill Oil on Chronic Inflammation and Arthritic Symptoms. J Amer College Nutrition, 26: 39-48
A short summary of this study is included in the dossier, ie "Neptune, 2004. CONFIDENTIAL"

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Samenvatting van het dossier / Summary of the dossier

APPLICATION FOR THE APPROVAL OF NEPTUNE KRILL OIL™

REGULATION (EC) NO 258/97 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 27TH JANUARY 1997 CONCERNING NOVEL FOODS AND NOVEL FOOD INGREDIENTS

SUMMARY DOCUMENT

NON-CONFIDENTIAL

Prepared for: Neptune Technologies & Bioressources Inc.
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September 14, 2006

APPLICATION FOR THE APPROVAL OF NEPTUNE KRILL OIL™ (NKO™)

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

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ADMINISTRATIVE DATA

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INTRODUCTION

Neptune Technologies and Bioressources Inc. (Neptune) wishes to market a highly purified oil extracted from the crustacean *Euphausia superba* (Antarctic Krill). For the purpose of this dossier the product will hereafter be called NKO™ (Neptune Krill Oil). NKO™ is a whole lipid extract of *Euphausia superba* (Antarctic Krill) and is an opaque reddish oil with a seafood odour. The major components of NKO™ are eicosapentaenoic acid (EPA, C20:5n-3 fatty acid), docosahexaenoic acid (DHA, C22:6n-3 fatty acid), and several phospholipids, the most prominent of which is lecithin. NKO™ is an oil intended for use as a dietary ingredient as a source of omega-3 fatty acids, which occur in NKO™ in their phospholipid form. No processing aids or additives are included in the final NKO™ product due to naturally occurring anti-oxidants that aid in the preservation of the product. Due to this, there are no variations in excipients or active ingredient overages associated with the production of NKO™. Additionally, no proprietary or colouring ingredients are added to the oil from Antarctic Krill to produce NKO™.

Investigations and discussions have confirmed that whilst there is some minor consumption of Antarctic Krill as a food in the European Union (EU), there had been no widespread consumption of Antarctic Krill as a food prior to May 1997. Therefore NKO™ would be considered a "novel food ingredient" under *Regulation (EC) No 258/97 of the European Parliament and of the Council of 2 January 1997 concerning novel foods and novel food ingredient*s (hereafter referred to as EC/258/97). The most appropriate category for Neptune's NKO™ would be:

> *(e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices, and having a history of safe food use.*

Specifically regarding dossier requirements, *Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients (Commission Recommendation 97/618/EC) (1997), Section 4,* NKO™ would be classified as:

> *Class 2.2: "Complex Novel Food from non-GM source", "the source of the novel food has no history of food use in the Community".*

This submission has been prepared in accordance with these guidelines.

I SPECIFICATIONS OF THE NOVEL FOOD

Neptune Krill Oil (NKO™) is a highly purified oil extracted from the crustacean *Euphausia superba* (Antarctic Krill). The proposed name is Neptune Krill Oil (NKO™). The major components of NKO™ are eicosapentaenoic acid (EPA, C20:5n-3 fatty acid), docosahexaenoic acid (DHA, C22:6n-3 fatty acid), and several phospholipids, the most prominent of which is lecithin. The CAS Number for EPA is 25378-27-2, for DHA is 25167-62-8, and for lecithin is 8002-43-5.

The raw materials employed in the production of NKO™ are Antarctic Krill, which are a non-genetically modified source, as they are fished from the wild and not the result of breeding. The Antarctic Krill transformed to obtain NKO™ is fished in the Atlantic section of the Austral-Antarctic Circumpolar Ocean, originating specifically from Statistical Fishing Area 48, a fishing areas designated by the Commission for the Conservation of Antarctic Marine Living Resources (CCAMLR). The Antarctic Krill processed by Neptune are supplied by a Japanese firm that has been fishing Antarctic Krill for more than two decades. The Antarctic Krill are drained and placed in plastic moulds for quick-freezing at about -30°C on board factory ships within a few hours of its harvest. The resulting 12 kg blocks of Antarctic Krill, individually wrapped in plastic film, are packaged two per carton and exported to Canada, while maintained at temperatures of -30 to -20°C, where they are inspected and approved by the Canadian Food Inspection Agency (CFIA). Source manipulations on board the fishing vessels are made in compliance with regulations as they apply to the handling of Krill intended for human consumption.

The process by which Neptune produces NKO™ occurs under Good Manufacturing Practices (GMP), as certified by the Natural Health Products Directorate (NHPD) of Canada. The compositional specifications for NKO™ determined by Neptune and representative batch analysis results are presented in Table I.1 below.

Table I.1 Batch Analysis of 3 Lots of NKO™ Assessing the Compositional Guidelines For NKO™

Requirement	**Specifications**	**Lot Number**		
		060116	**060519**	**060224**
Description				
Appearance	Red opaque oil	Complies	Complies	Complies
Odour	light shrimp	Complies	Complies	Complies
Viscosity	< 1,500 cP	564.0	476.5	585.8
Humidity	<0.9%	0.1%	0.2%	0.1%
Identification				
Peroxide value	< 0.2 mEq peroxide/kg	< 0.1	< 0.1	< 0.1

Table I.1 Batch Analysis of 3 Lots of NKO™ Assessing the Compositional Guidelines For NKO™

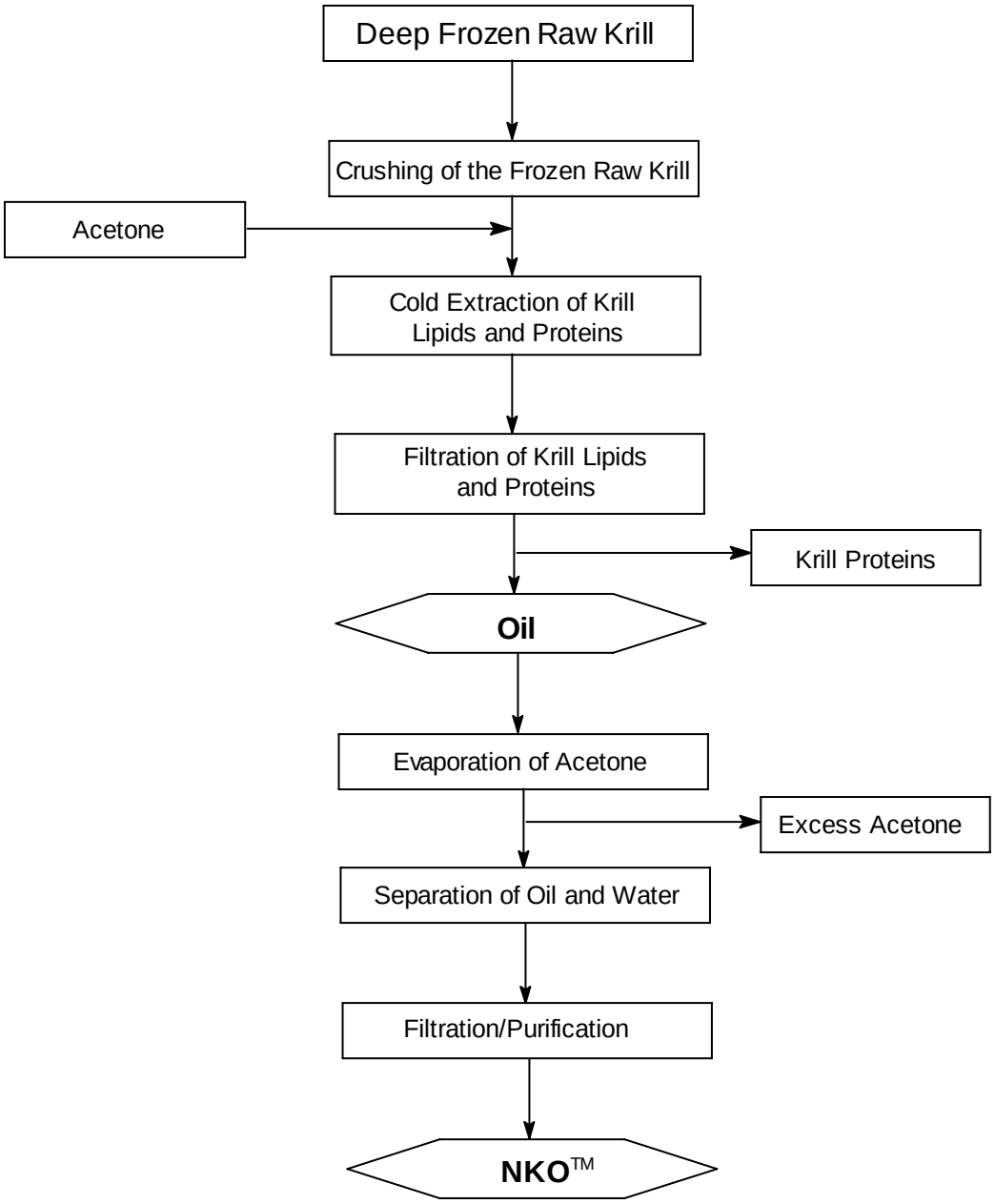
Requirement	Specifications	Lot Number		
		060116	**060519**	**060224**
P-Anisidine	< 1.2	1.0	0.9	0.9
Saponification value	≥165.0 mg KOH/g	174.6	170.8	177.6
Iodine Value	>130.0 gI_2/100 g	137.9	135.6	134.3
Assay				
Total Protein	0.5 – 3.5 g/100g	3.0 g/100 g	0.7 g/100 g	0.8 g/100 g
Total Cholesterol	0.8 – 1.2 g/100g	1.1 g/100 g	1.0 g/100 g	0.9 g/100 g
Total Phospholipids	≥ 40.0 g/100g	47.3 g/100 g	44.8 g/100 g	43.8 g/100 g
Total Lipids as Fatty Acids	≥ 73.0 g/100 g	88.5 g/100 g	81.2 g/100 g	88.2 g/100 g
Saturated fatty acids	< 30.0 g/100 g	29.8 g/100 g	29.2 g/100 g	28.9 g/100 g
Monounsaturated fatty acids	≥ 12.0 g/100 g	22.1 g/100 g	21.6 g/100 g	21.9 g/100 g
Polyunsaturated fatty acids	≥ 32.0 g/100 g	36.7 g/100 g	34.2 g/100 g	37.4 g/100 g
Omega-3 Fatty Acids	≥ 30.0 g/100g	33.6 g/100 g	31.5 g/100 g	34.3 g/100 g
EPA	>15.0 g/100g	17.2 g/100 g	16.6 g/100 g	18.0 g/100 g
DHA	> 9.0 g/100g	11.3 g/100 g	10.3 g/100 g	11.4 g/100 g
DPA	>0.4 g/100 g	0.6 g/100 g	0.5 g/100 g	0.6 g/100 g
Omega –6 Fatty Acids	1.5 – 2.5 g/100g	1.6 g/100 g	1.4 g/100 g	1.6 g/100 g
Linoleic acid	> 1.3 g/100 g	1.4 g/100 g	1.2 g/100 g	1.3 g/100 g
Omega-9 Fatty Acids	≥ 6.0 g/100g	9.6 g/100 g	9.3 g/100 g	9.4 g/100 g
Oleic acid	≥ 5.0 g/100 g	8.6 g/100 g	8.5 g/100 g	8.2 g/100 g
Total *Trans* Fat	< 0.1 g/100 g	< 0.01 g/100 g	0.02 g/100 g	Not detected
Vitamin A	≥ 100.0 IU/g	259.1 IU/g	336.6 IU/g	269.9 IU/g
Vitamin E	≥ 0.5 IU/g	0.65 IU/g	0.67 IU/g	0.70 IU/g
Esterified Astaxanthin	≥ 150.0 mg/100 g	162.6 mg/100 g	160.7 mg/100 g	154.0 mg/100 g

NKO™ is an oil extracted directly from Antarctic Krill and as a result is composed primarily of Antarctic Krill phospholipids. These phospholipids contain a wide variety of naturally occurring fatty acids as their side chains, the most prominent of which are EPA and DHA.

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO THE NOVEL FOOD

A flow diagram is presented below (Figure II.2.1-1) demonstrating the NKO™ manufacturing process.

Figure II.1 Manufacturing Process Employed in the Production of NKO™



The potential impurities and incidental constituents present in NKO™ arise largely from environmental exposure of the Antarctic Krill. Neptune consistently analyses production lots of NKO™ for the presence of 17 pesticides, as well as dioxins, PCBs, heavy metals, fluorine, and various microorganisms and results have been presented in the full dossier.

Three tests have been conducted to ensure the stability of NKO™ over time. These tests determined the peroxide value of NKO™, and indicate the prominence of oxidation with oils, the Oil Stability Index (OSI), and the Oxygen Radical Absorption Capacity (ORAC).

Additionally, long term stability testing has indicated that there is no significant change in the composition of NKO™ softgels following storage at 20°C, with an ambient relative humidity

of 45%, for a period of 36 months, or following storage at 25°C, with an ambient relative humidity of 60%, for a period of 28 months.

III HISTORY OF THE ORGANISM USED AS THE SOURCE

NKO™ is produced from *Euphausia superba* (Antarctic Krill), which are native to the Atlantic section of the Austral-Antarctic Circumpolar Ocean. In terms of their phylogeny, Antarctic Krill are closely related to shrimp and are often consumed as food in a similar fashion. NKO™ is not derived from a genetically modified organism and does not contain any genetically modified products. No toxic constituents are known to be present in NKO™.

IX ANTICIPATED INTAKE/EXTENT OF USE OF NOVEL FOOD

The proposed food uses for NKO™ include:

- Yoghurt;
- Milk and milk drinks;
- Juices;
- Protein bars;
- Meal replacements.
- Foods for Special Medical Purposes (as defined by *Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes*[1]).

With the exception of "foods for special medical purposes", NKO™ is proposed for use as a food ingredient with a maximum use-level corresponding to an NKO™ intake of 500 mg/person/day, providing approximately 140 mg combined EPA and DHA/person/day. The maximum recommended intake of 500 mg NKO™/person/day would be equivalent to 7.14 mg NKO™/kg body weight/day and 1.99 mg combined EPA+DHA/person/day for a 70 kg individual. This use level is below the current recommended dose of 200 mg combined EPA and DHA/day as recommended by the Eurodiet Core Report (Eurodiet, 2000). An intake of 500 mg NKO™/person/day, providing 140 mg combined EPA+DHA/person/day is also below the maximum use level of 200 mg DHA/day provided by an oil rich in DHA marketed by Martek Biosciences Corporation as permitted by the Decision of the European Commission on the 5th of June 2003.

[1] *Official Journal L 091, 07/04/1999 P. 0029 - 0036*

It is proposed that NKO™ be incorporated into each proposed food use at the recommended daily dose of 500 mg NKO™. It is also proposed that all labels of food products containing NKO™ be clearly marked so that the consumer is aware each time a product containing NKO™ is consumed. In accordance with the above statements, each of the proposed food uses (yoghurt, milk and milk-based drinks, juices, protein bars, and meal replacements) would contain 500 mg NKO™/serving, providing 140 mg combined EPA and DHA/serving. As proposed, all food products containing NKO™ would be clearly marked so as to avoid consumption of more than one NKO™ product/day. In addition to its use in food products, NKO™ will be available as a food supplement in an encapsulated form, with a recommended intake of up to 1,000 mg NKO™/day. The encapsulated food supplement will be available as an alternative to using food products containing NKO™, and will be used in place of the fortified food products and not with the food products. Additionally, it has been demonstrated in a clinical trial that consumption of 6,000 mg NKO™/person/day (equivalent to 12 servings of products containing NKO™) did not result in any serious side effects (Neptune, 2002).

In the case of special medical foods, the levels of NKO™ used would be governed by the requirements of Directive 1999/21/EC, which sets out rules for the composition and labelling of foods that are specifically formulated, processed and intended for the dietary management of diseases, disorders or medical conditions of individuals who are being treated under medical supervision.

It is proposed that NKO™ be used to replace fish oils and LC omega-3 PUFA oils currently on the market. It is not recommended that any blend, formulation, or product containing NKO™ be consumed in conjunction with any other blend, formulation, or product containing other fish oils or LC omega-3 PUFA oils or supplements currently on the market.

Consumption of NKO™ at the recommended daily dose will provide 0.139 g/day of EPA and DHA combined, substantially less than the amount determined to be required to produce elongation of bleeding times.

While NKO™ contains Antarctic Krill lipids separated from Antarctic Krill protein, its consumption by individuals with allergies to shellfish may produce allergic reactions. NKO™ is contraindicated for individuals who are allergic to crustaceans, and should be consumed with caution by individuals also consuming anticoagulants or other medications and individuals suffering from coagulopathy. Despite the minimal amount of Antarctic Krill protein contained in NKO™, the following warning will be present on all products containing NKO™:

> WARNING: Persons with seafood allergies, coagulopathy or who are taking anticoagulants or other medications should discuss their situation with their doctor and submit to tests before taking food supplements.

In addition, as discussed in Section I.4, under the terms of Directive 2003/89/EC of the European Parliament and of the Council of 10 November 2003 amending Directive 2000/13/EC as regards indication of the ingredients present in foodstuffs, NKO™ must be labelled as:

> "contains oil from crustaceans (Antarctic Krill)".

X INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO NKO™ OR ITS SOURCE

Antarctic Krill has a history of human consumption as food in Japan, Russia, the Ukraine and France. The consumption of Antarctic Krill began in most nations in the mid-1970s, particularly in Japan where between the years 1977 and 1983, the Japanese Fishing Agency ran a promotional campaign on the use of Antarctic Krill as a food for human consumption (Suzuki and Shibata, 1990; Kawaguchi *et al.*, 1997; Everson, 2000). In February 1994, a report published by "INSERM" provides the results of an exhaustive study on the nutritional value of Antarctic Krill (Ruggiero-Lopez et *al*., 1994).

NKO™ softgels containing the oil proposed for use as a novel food ingredient in the EU have been available as dietary supplement products in North America and Asia for several years. In Canada and the United States, NKO™ has been available for purchase since October of 2002, and in Japan, Korean, Singapore, and Hong Kong, NKO™ has been available since December of 2004. The recommended intake of NKO™ in North America and Asia is 1 to 2 softgel capsules/day, with each softgel containing 500 mg of NKO™.

XI NUTRITIONAL INFORMATION ON THE NOVEL FOOD

Neptune Krill Oil is a whole lipid extract of *Euphausia superba* (Antarctic Krill) and the major components of NKO™ are eicosapentaenoic acid (EPA, C20:5n-3 fatty acid), docosahexaenoic acid (DHA, C22:6n-3 fatty acid), and several phospholipids, the most prominent of which is lecithin. EPA and DHA are long-chain polyunsaturated omega-3 fatty acids (LC omega-3 PUFA) and are present in the diet from several food sources, including fish and seafood, cod liver oil, other omega-3 PUFA-rich oils, and human milk. Lecithin (1,2-diacyl-sn-glycero-3-phosphocholine, E322) is permitted by Directive 95/2/EEC at "*quantum satis*" for general addition to food as an emulsifier.

In the UK the mean consumption of total fish in adults aged 19 to 64 is 217 g/week, including 50 g/week of oily fish, 104 g/week of white fish, and 27 g/week of shellfish. Mean consumption by consumers is 194 g/week of oily fish, 221 g/week of white fish, and 143 g/week of shellfish (Henderson *et al.*, 2002). Estimating LC omega-3 PUFA content at an average of 2 g/100g for oily fish, 0.3 g/100g for white fish, and 0.4 g/100g for shellfish (SACN, 2004), this provides a mean of 0.143 g/day, 0.045 g/day, and 0.015 g/day of LC omega-3 PUFA from oily fish, white fish, and shellfish, respectively, in the total population and 0.554 g/day, 0.095 g/day, and 0.082 g/day of LC omega-3 PUFA in the population consuming oily fish, white fish, and shellfish, respectively.

Combined intakes of EPA and DHA vary within the EU, as well as within individual member states. In Norway, the mean intake of combined EPA and DHA is 0.835 g/day (Johansson *et al.*, 1998), in Sweden, 0.325 g/day, and in Germany, 0.203 g/day (EFSA, 2005). In Portugal, mean intake of combined EPA and DHA ranges from 0.083 g/day in a sampled rural village to 0.754 g/day in a sampled fishing village (Torres *et al.*, 2000).

The recommended daily dose of NKO™ from suggested foods will provide 0.139 g combined EPA+DHA/day, well within the range of current documented consumption in various member states of the EU.

On the 5th of June 2003, the European Commission authorized the placing on the market of an oil rich in DHA marketed by Martek Biosciences Corporation under Regulation EC 258/97 of the European Parliament and of the Council. Martek's DHA-rich oil from *Schizochytrium* sp. has been available to the general European population since 2003The maximum daily dose of DHA-rich oil from *Schizochytrium* sp., when consumed as a food supplement, must contain not more than 200 mg of DHA per daily dose. NKO™ will provide approximately 47.9 mg DHA and 91.5 mg EPA per recommended daily dose of 500 mg NKO™. The combined amount of EPA and DHA per daily serving from food (139 mg) is below the amount of DHA approved per daily dose (200 mg) from food supplements.

For individuals consuming NKO™ as an encapsulated food supplement, the intake of EPA and DHA resulting from the consumption of 1,000 mg NKO™/day will be 95.8 mg DHA/day and 183.0 mg EPA/day, for a total of 278.8 mg/person/day. Human milk also contains EPA and DHA, the levels of which vary with dietary consumption of EPA and DHA (Sala-Vila *et al.*, 2003).

Several authorities have published recommended intakes of LC omega-3 PUFA. In their document titled *Advice on fish consumption: benefits and risks* (SACN, 2004), the SACN recommend an intake of 450 mg LC omega-3 PUFA/day. In 1998, the European Commission funded a project entitled the "Eurodiet" project with the aim of preparing a co-ordinated program on nutrition, diet, and healthy lifestyles by developing European

dietary guidelines. In the Eurodiet core report (Eurodiet, 2000) a population goal of 200 mg LC omega-3 PUFA/day was recommended.

The daily recommended intake of EPA and DHA to be provided by NKO™ from foods is 140 mg/day, which is less than the daily intake recommended by the Eurodiet report (200 mg/day) and much less than the daily intake recommended by the SACN (450 mg/day). As an alternative to consumption in food products, the consumption of 1,000 mg NKO™/day as an encapsulated food supplement will provide 95.8 mg DHA/day and 183.0 mg EPA/day, for a total of 278.8 mg/person/day.

The major components of NKO™, EPA and DHA, have been shown to have beneficial effects on risk factors for cardiovascular disease (CVD). NKO™ has also been researched for potential benefits involving dysmenorrhoea and the emotional symptoms of premenstrual syndrome (Sampalis *et al.*, 2003).

XII MICROBIOLOGICAL INFORMATION ON THE NOVEL FOOD

In accordance with the requirements placed upon all food manufacturers in the EU under *Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs (EC/852/2004)* (2004), the Neptune production method is internally controlled under the Hazard Analysis Critical Control Points (HACCP) system and microorganisms are routinely monitored.

Additionally, a fish processing establishment license (certification number 5111) was granted to Neptune Inc on February 17, 2005 and was renewed on February 17, 2006 by the CFIA following the implementation of a "Quality Management Program - Fish" (QMP). Neptune Inc is on the list of authorized Canadian exporters to the European Union (EU). The official list of imports to the European Union is administered by the EU's Health and Consumer Protection Directorate-General (SANCO).

XIII TOXICOLOGICAL ASSESSMENT OF THE NOVEL FOOD

The safety of NKO™ is predicated on several factors which include the abundant presence of EPA and DHA fatty acids in the diet, the relatively small doses of EPA and DHA resulting from the proposed food use levels of NKO™, and the safety of NKO™ itself as demonstrated in pre-clinical and clinical trials.

Antarctic Krill has a history of human consumption as food in Japan, Russia, the Ukraine and France. Dietary consumption of EPA and DHA has a long history, with several widely consumed foods, including fish and seafood, cod liver oil, other omega-3 PUFA-rich oils, and human milk, reported to be rich in these fatty acids.

As described in Section IX, the maximum proposed use-level of NKO™ corresponds to an intake of intake of 500 mg/person/day, providing approximately 140 mg combined EPA and DHA/person/day. This use level is lower than the current recommended dose of 200 mg combined EPA and DHA/day as recommended by the Eurodiet Core Report and the 200 mg/day maximum use level for a DHA rich oil marketed by Martek Biosciences Corporation as permitted by the Decision of the European Commission on the 5th of June 2003.

In addition to the large amount of available data supporting the safety of DHA and EPA, the safety of NKO™ is supported by pre-clinical and clinical trials conducted by Neptune. In pre-clinical trials, no adverse effects were associated with the consumption of 28.3 g NKO™/kg body weight/day by C57BL6 Nude Congenic mice. In a clinical trial conducted to examine the safety of NKO™, no adverse effects were observed following the consumption of 6,000 mg NKO™/day, providing 1,672.8 mg of combined EPA and DHA/day, for a period of 3 months (Neptune, 2002).

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Eerste beoordeling / First assessment

MINISTRY OF TRADE AND INDUSTRY

49/618/2006

Novel Food Board

29 January 2007

Courtesy translation

Initial assessment report in compliance with Regulation (EC) No 258/97, Article 4

OIL PREPARED FROM ANTARTIC KRILL (*EUPHASIA SUPERBA*) – NEPTUNE KRILL OIL™

Introduction

1. On 29 September 2006, Neptune Technologies & Bioresources Inc. submitted to the Finnish Food Safety Authority Evira an application concerning novel foods and complying with Regulation (EC) No 258/07 of the European Parliament and of the Council. The application concerns placing an oil (Neptune Krill Oil, NKO™) on the market extracted from the crustacean, Antarctic krill (*Euphausia superba*) as a novel food ingredient. Evira submitted the application to the Novel Food Board for an initial assessment in compliance with Article 4 of the above-mentioned Novel Food Regulation.

2. The Novel Food Board has reviewed the application in compliance with European 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 and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. The applicant classifies the application as belonging to the category (e) foods and food ingredients consisting of or isolated from plants or animals, cited in Article 1(2) of the Novel Food Regulation. The object of the application has been further classified, according to Commission Recommendation 97/618/EC, under Class 2.2 comprising complex novel foods from non-genetically modified sources and having no history of food use in the Community. Consequently, the application will be processed in accordance with Schemes I, II, III, IX, XI, XII and XIII presented in the Commission Recommendation. Furthermore, the applicant has provided information under Scheme X, although this is not required by the Commission Recommendation.

I Specifications of the novel food

4. The NKO™ oil destined for the market originates from the crustacean, Antarctic krill (*Euphausia superba*). The crustacean is fished from the Atlantic Antarctic Ocean and cooled within a few hours after capture to a temperature of approximately –30˚C and transported frozen (–20…–30˚C) to Canada. The Canadian Food Inspection Agency CFIA) inspects and approves the raw material. Oil is extracted from the product under Good Manufacturing Practices (GMP).

5. According to the compositional specifications, NKO™ includes at least 32g/100g of polyunsaturated fatty acids, most of which are eicosapentaenoic acid (EPA) and docosahexaenoic

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acid (DHA). Of the product's fatty acids, EPA accounts for over 15g/100g and DHA for over 9g/100g. The minimum level of monosaturated fatty acids is 12g/100g, and 30g/100g for saturated fatty acids. The oil contains 0.8–1.2g/100g of cholesterol and 0.5–3.5 g/100g of protein. In addition, the product includes naturally occurring antioxidants aiding its preservation, such as a minimum of 1.5 mg/g of esterified astaxanthin, a minimum of 100 IU/g of vitamin A and a minimum of 0.5 IU/g of vitamin E. The applicant has provided results from the analysis of three production batches.

Comments from the Novel Food Board:

6. *The presented composition data are sufficient. The composition assessment has used generally accepted methods and quality assurance indicators have been included. In general, the description of the methods is sufficiently detailed and an appropriate reference for the HPLC method for esterified astaxanthin was provided when requested.*

7. *The Board is satisfied with the clarification on the structural formula and molecular weight of EPA obtained from the applicant.*

II Effect of the production process applied to the novel food

8. Neptune manufactures the oil by first crushing the frozen krill. Lipids and proteins are cold extracted from the crushed krill using acetone. The extract is filtered and proteins are separated from the oil, after which the acetone is evaporated. The oil is separated from water, and filtered and purified prior to packaging in a modified nitrogen atmosphere.

9. The potential impurities present in NKO™ are mainly of environmental origin. The application presents results from the analysis of three production lots for the presence of 11 chlorinated pesticides and dioxin-like compounds, heavy metals and micro-organisms.

10. The sum of dioxins, furans and dioxin-like PCBs in NKO™ fulfils, according to the manufacturer's analysis, the requirements of a maximum of 10.0pg/g of fat laid down in the Community provisions (Commission Regulation (EC) No 199/2006). According to the applicant's analysis, both mercury and lead levels in the oil are below 0.1mg/kg, i.e. under the maximum levels prescribed in the related provisions (Commission Directive 2001/22/EC). The levels of arsenic, cadmium and tin remain below the maximum weekly levels proposed by JECFA (Provisional Tolerable Weekly Intake, PTWI), and copper levels below maximum daily levels (Provisional Maximum Tolerable Daily Intake, PMTDI). The product's antimony level is below 1mg/kg (no JECFA recommendations available). The levels of analysed pesticides in NKO™ remain below 0.1mg/kg.

11. The applicant also presents results on the product's stability. The peroxide value of NKO™ is below 0.1mEq peroxide/kg. When the product is heated at a temperature of 97.8˚C for over 50 hours, the peroxide value remains below the cited level. The applicant also presents analytical data on the long-term stability of fatty acids in softgel capsules containing NKO™. The fatty acid level and peroxide value of the capsules do not alter significantly during storage.

Comments from the Novel Food Board:

12. *The analyses have used generally accepted methods and their description is sufficiently detailed.*

13. *The stability tests have been conducted appropriately. The determination of a peroxide value as an indicator of oxidation is a basic analysis and long-term stability (28 and 32 months at different humidity and temperature levels) clearly reveals the stability of the product. Also included are tests (OSI, ORAC) which are not necessary in terms of evaluating the product's safety. The high temperature (97.8˚C) used for OSI (Oil Stability Index) is not relevant to shelf life, and ORAC, for its part, does not describe antioxidant capacity because it does not measure lipid oxidation.*

III History of the organism used as the source of the novel food

14. The Antarctic krill (*Euphausia superba*) originates from the Atlantic section of the Austral-Antarctic Circumpolar Ocean. It is a shrimp-like crustacean and small amounts of it have been used as food in France and outside the EU in Japan, Russia and the Ukraine since the 1970s.

IX Anticipated intake/extent of use of the novel food

15. Proposed uses of NKO™ include adding it to yoghurt, milk and milk drinks, juices, protein bars, meal replacements and foods for special medical purposes. It is proposed that NKO™ be incorporated in each such product at 500mg per serving, which would also correspond to the maximum daily intake. Of this amount, combined EPA and DHA account for approximately 140mg. In addition, plans have been made to place a food supplement on the market with a maximum of 1,000mg NKO™ per daily intake dose (level of EPA+DHA approximately 280mg). In the case of special medical foods, the levels of NKO™ used would be governed by the requirements of Directive 1999/21/EC.

16. The applicant points out that concentrations and intake levels proposed for yoghurt and meal replacements correspond to the levels presented in Commission Decision 2003/427/EC concerning a novel food ingredient (oil rich in DHA from a microalgae, by Martek Biosciences Co.).

17. It is assumed that products containing NKO™ will replace fish oils or other products containing omega-3 fatty acids currently on the market. The applicant does not recommend using products containing NKO™ alongside other corresponding products.

18. The applicant states that individuals with allergies to fish or crustaceans may experience allergic reactions to products containing NKO™, although the level of protein possibly contained in the oil is minimal. Consequently, any products containing NKO™ would be labelled, in accordance with the Labelling Directive 2000/13/EC, with an indication stating that the product contains oil from crustaceans (Antarctic krill).

19. The applicant also states that individuals suffering from coagulopathy may constitute a population at risk due to polyunsaturated fatty acids contained in the product. For food supplements containing NKO™, the applicant recommends a special indication stating that persons with coagulopathy or who are taking anticoagulants or other medications should consult their doctor before taking this particular food supplement.

Comments from the Novel Food Board:

20. *The Board agrees with the applicant that food containing NKO™ obtained from krill be labelled with indications revealing the oil source (crustaceans) in compliance with the requirements of the Labelling Directive 2000/13/EC.*

21. *The applicant proposes that NKO™ be used in several different products by adding 500mg/serving which would also be the oil's maximum daily intake level. Since the planned range of use is broad and since it is possible that consumers consume some products, such as drinks, in several doses per day, the decision on allowing the product onto the market should take account of whether the range of enriched foods should be restricted.*

22. *The applicant proposes special warning indications for food supplements containing NKO™ stating that persons with coagulopathy or who are taking anticoagulants or other medications should consult their doctors before taking this particular food supplement. With regard to food supplements, the proposal can be agreed to, because the levels of NKO™ are higher than in fortified foods. Furthermore, food supplements are used in addition to other nutrition.*

X Information from previous human exposure to the novel food or its source

23. The Antarctic krill originates from the Atlantic section of the Austral-Antarctic Circumpolar Ocean. It is a shrimp-like crustacean and small amounts of it have been used in France and outside the EU in Japan, Russia and Ukraine since the 1970s.

24. In the EU, oil extracted from krill has not been used in food supplements, but similar oils are sold in the Canadian, U.S. and Asian markets. The recommended intake is two softgel capsules per day, corresponding to an NKO™ intake of 1,000mg per day.

XI Nutritional information on the novel food

25. NKO™ is intended for use as a source of omega-3 fatty acids, since their level in the oil is over 30%. NKO contains especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). 100g of the oil includes a minimum of 12g monosaturated fatty acids, less than 30g saturated fatty acids, 0.8–1.2g of cholesterol and 0.5–3.5g of protein. The fatty acids are attached to phospholipids and over 40% of the product comprises phospholipids, lecithin in particular.

26. The intake of combined EPA and DHA varies in the EU. For example, the total combined EPA and DHA intake per day is 0.083g in a rural area of Portugal, 0.203g in Germany and 0.325g in Sweden. In Norway, the intake level rises to 0.835g per day. In the UK, daily intake levels have been estimated to vary from approximately 0.082g to 0.554g, depending on the quantities and types of fish consumed.

27. If NKO™ was used according to the applicant's recommendations, the combined EPA and DHA intake would total approximately 140mg, which falls within the variation range of current intake levels.

28. The Eurodiet[1] project funded by the EU Commission recommended a daily intake of 200mg for LC omega-3 fatty acids. In the UK recommendation is 450mg for LC omega-3 fatty acids (SACN[2]).

29. The Commission Decision 2003/427/EC concerning a novel food ingredient (oil rich in DHA from microalgae, by Martek Biosciences Co.) approves an algae oil to be used in food supplements with a DHA level of 200mg. The intended use of NKO™ involves a daily intake of 1,000mg, corresponding to 95mg DHA and 183mg EPA.

30. The fatty acids EPA and DHA have been stated to have beneficial effects with respect to risk factors for cardiovascular diseases.

Comments from the Novel Food Board:

31. *The fatty acid composition of NKO™ corresponds to that of fish fat and it is rich in EPA and DHA. No official intake recommendations exist for these fatty acids. Nor has a maximum safe intake level been defined for these fatty acids. The intake levels suggested by the applicant are similar or lower than levels in countries where considerable amounts of fish are consumed as a foodstuff.*

32. *For food supplements, the combined EPA+DHA level (278mg/day) exceeds the requirement prescribed for maximum DHA (200mg) in Commission Decision 2003/427/EC. The level also exceeds the Eurodiet recommendation (200mg), but remains below the UK recommendation (450mg).*

XII Microbiological information on the novel food

33. The microbiological quality of NKO™ is controlled by evaluating critical points based on the HACCP (Hazard Analysis Critical Control Points) system principles.

34. The microbial quality is ensured by monitoring the levels of aerobic bacteria, coliforms, yeasts and moulds. Also the presence of pathogenic microbes are monitored by measuring *Salmonella*, *Escherichia coli*, *Staphylococcus aureus*, *Listeria monocytogenes* and *Pseudomonas aeruginosa* in the production lots. In addition to specifications, the applicant presents results from the analysis of three production lots.

35. The company (licence number 5111) is included in the list of authorized importers of products of animal origin to the European Union.

Comments from the Novel Food Board:

36. *The EU does not have special criteria for the microbiology of oil. The general obligations laid down in the Hygiene of Foodstuffs Regulation (EC) 852/2004 apply to microbiological quality. The Board considers that the HACCP presented in the application and the verifications conducted in accordance with Canadian standards are in line with the general requirements of the EU.*

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[1] Eurodiet: Nutrition & diet or healthy life styles in Europe. Core Report 2000, http://ec.europa.eu/health/ph_determinants/life_style/nutrition/report01_en.pdf.

[2] Scientific Advisory Committee on Nutrition (SANC), Food Standards Authority (FSA) and the Department of Health: Advice on Fish Consumption: Benefits and Risks. United Kingdom 2004.

XIII Toxicological information on the novel food

37. In addition to animal experiments and clinical trials on NKO™, the toxicological evaluation of the product involved studies on DHA and EPA fatty acids. The fatty acids in NKO™ are attached to phospholipids and over 40% of the product is namely phospholipids (lecithin in particular). According to the presented data, this form is more readily available to the metabolism than, for example, the triglyceride form.

38. The safety of NKO™ has been evaluated in C57BL/6 Nude mice. The mice were administered 28.3 g NKO™ / kg body weight incorporated into feed for six months. Neither clinical adverse effects nor tissue changes were observed after the experimental period.

39. The safety of NKO™ softgel capsules was studied in 25 individuals who consumed 6 capsules daily for a period of two months. Each capsule contained 1,000 mg of NKO™ and provided 386 mg of omega-3 fatty acids, 416 mg of phospholipids and 0.16 mg of astaxanthin. Two females withdrew from the study because the product caused greasiness of the skin. One individual with a known salt intolerance interrupted the trial because the product caused water retention. No serious adverse effects were reported. For the subjects of the study, levels of total cholesterol, LDL cholesterol, triglycerides, albumin and amylase decreased and their HDL cholesterol level increased. In addition, levels of PTT, creatinin, glucose, alkaline phosphatase and bilirubin were also examined.

40. NKO™ has also been tested on 120 patients suffering from hyperlipidemia, by administering 300–3,000 mg daily doses during (a minimum of) 12 weeks. No adverse effects were reported and the product had a positive effect on blood lipids.

41. The effects of NKO™ were compared with those of fish oil in a study on PMS symptoms in 70 females. During the first month, the subjects consumed two capsules (dose?) daily? with meals and later the same daily dose from 8 days prior to menstruation until the second day of menstruation. No serious adverse effects were reported, but three subjects reported a reduction in the duration of the menstrual cycle during the first month and those who had consumed NKO™ reported minor increases in the greasiness of their skin.

42. The effects of NKO™ (300 mg/day) on markers of chronic inflammation were examined, in comparison to a placebo, on 90 patients. During the one-month period, no adverse effects were reported. The product reduced C-reactive protein levels, and those having used the product reported fewer symptoms and an improved functional capacity.

43. Fish oils may prolong bleeding times but, according to the FDA (USA), coagulation problems should not arise with a dose of less than 3 g/day (EPA +DHA). The applicant has suggested special labels which are discussed in the present evaluation under section IX, chapters 19 and 22.

Comments from the Novel Food Board:

44. *The Antarctic krill is phylogenetically closely related to shrimp, a common cause of allergies. The main allergen in shrimp is tropomyosin, whose recognising antibodies cross-react with e.g. the tropomyosin of cockroaches and dust mites. No studies on krill allergens have been published, but there is reason to assume that krill also contains protein(s) similar to tropomyosin. According to the specification, the evaluated product contains approximately 0.5–3.5 g/100g of residual protein.*

The recommended daily intake (500 mg) may thus contain 2.5–17.5 mg of protein originating from krill. The intended warning labels on packaging concerning the product's unsuitability for individuals with allergies to fish or crustacean are necessary (cf. section IX, chapters 18 and 20 of the present evaluation).

45. *For a toxicity study the experiment conducted on C57BL/6 Nude mice is very poorly reported and limited in scope. Moreover, the scope of the human trials is similarly restricted, since their durations were short and they were conducted on young and healthy individuals. In reality, the product would also be used by completely different types of people. However, considering the fact that krill has long been consumed as a foodstuff, no new safety issues are likely. The animal and human trials can therefore be considered acceptable for the safety evaluation of the product.*

46. *The intended warning labels on food supplement packaging stating that individuals with coagulopathy or who are taking anticoagulants or other medications should consult their doctor before taking the particular food supplement are appropriate (cf. section IX, chapters 19 and 22 in the present evaluation).*

Summary

47. On 29 September 2006, Neptune Technologies & Bioresources Inc. submitted to the Finnish Food Safety Authority, Evira, an application concerning novel foods and complying with Regulation (EC) No 258/07 of the European Parliament and of the Council. The application is related to placing an oil (NKO™) on the market extracted from the crustacean, Antarctic krill (*Euphausia superba*) as a novel food ingredient.

48. The krill is caught from the Atlantic Antarctic Ocean. NKO™ is prepared from frozen and crushed krill by extraction and by separating oil and protein with acetone. After this, the oil is separated, the acetone evaporated and the product purified and filtered. The potential impurities present in the product largely arise from environmental exposure. The application includes results from an analysis performed to detect the presence of pesticides, dioxins, heavy metals and micro-organisms. The stability of the product has been tested and The information provided on the product and the production process is sufficient. The evaluation has used generally accepted methods, quality assurance indicators have been included and the description of the methods is sufficiently detailed.

49. NKO™ is intended for use as a source of omega-3 fatty acids, especially of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Products intended for enrichment include yoghurt, milk and milk drinks, juices, protein bars and foods for special medical purposes. Oil will be incorporated into each product based on a 500mg/serving, corresponding to the product's maximum daily intake. Of this amount, the combined EPA and DHA will account for approximately 140mg. In addition to the above-mentioned, a food supplement will be placed on the market, with a maximum NKO™ level of 1,000mg/day, corresponding to a combined EPA and DHA level of approximately 280mg.

50. The combined EPA and DHA intake levels referred to in the application are similar to or lower than levels in countries where considerable amounts of fish are consumed as a foodstuff. No official intake recommendations exist for these fatty acids. A safe maximum intake level has not been set. The applicant proposes several uses for NKO™. Furthermore, in the EU, oils rich in DHA have been approved as novel food ingredients for use in several foods. In terms of total intake, the Board

states that risk control measures for controlling increasing intake from several sources need to be considered.

51. The research results presented by the applicant do not raise any doubts about the product's safety. Fish oils may prolong bleeding times but, according to the FDA, doses up to 3 g (EPA+DHA) should not cause concern. No clinical adverse effects or histopathological changes were observed in a 6-month trial on C57BL/6 Nude mice, although the Board notes that the scope of the trial was very limited and it was poorly reported. Clinical trials on the product are relatively good but very short-term and conducted on young and healthy individuals. However, since krill has already long been consumed as a foodstuff, no new safety issues are likely.

52. The applicant states that individuals with allergies to fish or crustaceans may experience allergic reactions to products containing NKO™, although the oil contains only minimal amounts of protein. The Board therefore states that any products containing NKO™ should be labelled, in accordance with the Labelling Directive 2000/13/EC, with an indication that the product contains oil from crustaceans (Antarctic krill).

53. The applicant also states that individuals suffering from coagulopathy may constitute a population at risk due to omega fatty acids contained in the product. For food supplements containing NKO™, the applicant recommends a special indication stating that persons with coagulopathy or who are taking anticoagulants or other medications should consult their doctors before taking this particular food supplement. Regarding food supplements, the Board considers the proposal as favourable.