

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

ANTARCTIC KRILL OIL

Issue

The Finnish Competent Authority has prepared an initial opinion on an application for the authorisation of Antarctic Krill Oil as a novel food ingredient under the Novel Food Regulation (EC) No. 258/97. The Committee is asked whether it agrees with the initial opinion and whether it has any further comments or objections to make on the application. The Committee's advice will form the basis for the UK's formal response.

Introduction

1. On 20 February 2006, the European Commission forwarded the Finnish Competent Authority's (CA) initial opinion on an application made by Neptune Technologies & Bioresources Inc. under Article 4(1) of Regulation (EC) 258/97, for the authorisation of Antarctic Krill Oil (Neptune Krill Oil, NKO™) as a novel food ingredient. Under the time scales set out in the regulation, the UK and other Member States have until 19 April 2007 to provide comments and/or reasoned objections to the initial opinion.
2. The Finnish CA has sought advice from their Novel Food Board. The Finnish Initial Assessment Report is attached as **Annex 1**. The full dossier provided by the applicant is attached as **Annex 2** (restricted).

Background

3. This application from Neptune Technologies & Bioresources Inc. is for the placing on the market of an oil extracted from the crustacean *Euphasia superba* (Antarctic Krill) as a novel food ingredient (NI), for use in a number of food categories as a source of omega-3 fatty acids and as a food supplement in the EU. The NI is a whole lipid extract of Antarctic Krill and is an opaque reddish oil

with an intense seafood odour. The major components of the NI are eicosapentaenoic acid (EPA), docosahexanoic acid (DHA) and several phospholipids, the most prominent of which is lecithin.

4. In accordance with the European Commission Regulation 258/97, the Finnish CA considers that the NI falls under the category described under Article 1(2)(e), which is a food or food ingredient consisting of or isolated from plants or animals. This corresponds to class 2.2 under Commission Recommendation 97/518/EC, which sets out the guidelines for novel food applications. The requirements for a submission for this class are as follows:

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

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

5. The key issues for consideration are presented below under these headings. The Secretariat would also note that the applicant has additionally provided information under scheme X.

I. Specification of the novel food

Annex 2, p.4-11

6. The Antarctic Krill used to obtain the NI is fished in the Atlantic section of the Antarctic Ocean. The krill is supplied by a Japanese firm that has been fishing Antarctic Krill for more than two decades. Within a few hours of harvest the krill

are frozen and transported to Canada while maintained at temperatures of -20°C to -30°C, where they are inspected and approved by the Canadian Food Inspection Agency (CFIA). The applicant produces the NI under Good Manufacturing Practice (GMP) and the production method is controlled under an internal HACCP system. The final product is also regularly tested to ensure compliance with international standards for residual solvents, micro-organisms, heavy metals and pesticides.

7. The specification of the NI is provided in the dossier (Annex 2 p.8, Table I.7.2-1). According to the specifications, the NI consists of at least 32g/100g of polyunsaturated fatty acids of which there is 15g/100g EPA and 9g/100g DHA. The minimum level of monounsaturated fatty acids is 12g/100g and 30g/100g for saturated fatty acids. The NI contains 0.8-1.2g/100g of cholesterol and 0.5-3.5g/100g of protein. In addition, it contains the naturally occurring antioxidants esterified astaxanthin (1.5mg/g min), vitamin A (100IU/g min) and vitamin E 0.5 IU/g min).
8. The applicant analysed three different batches of the NI (Annex 2 p.9, Table I.7.2-2) and was of the view that the results were representative of the NI when produced on commercial scale. The Finnish CA was satisfied with the compositional data provided and commented that the compositional assessment had used generally accepted methods and quality assurance indicators had been included.

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

Annex 2, p.12-20

9. The oil is obtained by first crushing the frozen krill. The lipids and protein are extracted from the crushed krill using acetone¹ under cold extraction conditions. The proteins and lipids are filtered and separated leaving an oil/acetone mix. The acetone is then evaporated off and the NI undergoes filtration and purification before it is packaged and stored under nitrogen.
10. The applicant is of the view that any potential impurities present in the NI arise due to environmental exposure of the Antarctic krill. Each production lot of the NI

is analysed for the presence of 17 pesticides, as well as dioxins, PCBs, heavy metals, fluorine and various micro-organisms.

11. The applicant has provided the results of batch analysis of 3 lots of the NI (Annex 2, p.16-17 Tables II.2.3-2 and II.2.3-3). Analysis shows that the sum of dioxins, furans and dioxin-like PCBs in the NI are within a maximum of 10.0pg/g fat as defined in Commission Regulation (EC) 199/2006. Both mercury and lead levels are below 0.1mg/kg which is the maximum levels prescribed in Commission Directive 2001/22/EC. Levels of arsenic, cadmium and tin are below the weekly levels (Provisional Tolerable Weekly Intake, PTWI) proposed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for 70kg adults and copper levels are below the maximum daily levels (Provisional Maximum Tolerable Daily Intake, PMTDI). JECFA has not set a PTWI or PMTDI for antimony however levels in the NI are below 1mg/kg in the NI. The levels of pesticide residues in the NI were below 0.1mg/kg.
12. The applicant also provided results of stability tests conducted on the NI. The tests determined the peroxide value of the NI and indicate the prominence of oxidation with oils, the Oil Stability Index (OSI) and the Oxygen Radical Absorption Capacity (ORAC). The peroxide value of the NI was found to be 0.05mEq peroxide/kg indicating it does not have a high potential for rancidity. The test to measure the resistance of the NI to oxidation at high temperatures over time, indicated the peroxide value remained <0.1mEq peroxide/kg for over 50 hours at a temperature of 97.8°C. Long term stability testing indicated there is no significant change in the composition of the NI in 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.
13. The Finnish CA was of the view that the analyses used were generally accepted methods and their description was sufficiently detailed. Although the stability tests were conducted correctly the Finnish CA notes that the high temperature used for OSI is not relevant to shelf life and ORAC in its part does not describe antioxidant capacity because it does not measure lipid oxidation.

¹ Acetone is generally permitted for use as an extraction solvent in the manufacture of foods and food

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

Annex 2, p. 21-22

14. Antarctic Krill (*Euphausia superba*) is native to the Atlantic section of the Austral-Antarctic Circumpolar Ocean and is closely related to shrimp and often consumed as food in a similar fashion. It has a history of consumption in Japan, Russia, Ukraine and France dating back to the mid-70's.

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

Annex 2, p.23-27

15. The NI is intended to be added into yoghurt, milk and milk drinks, juices, protein bars, and meal replacements, Foods for Special Medical Purposes and encapsulated as food supplement. The applicant proposes to incorporate the NI in each of the foods at 500mg per serving, which is the maximum recommended daily intake. The applicant notes that one serving provides approximately 140mg combined EPA and DHA. All food products containing the NI would be clearly marked so as to discourage consumption of more than one NI product/day. The product will also be available in food supplements, the NI will be available with a recommended intake of up to 1000 mg/day. For Foods for Special Medical Purposes, the level of the NI would be governed by the requirements of Directive 1999/21/EC.

16. The applicant points out that the proposed food uses of yoghurt and meal replacements are directly comparable to those of Martek Biosciences Corporation who were given authorisation in 2003 to market their novel DHA-rich oil obtained from algae source (Commission Decision 2003/427/EC). The proposed dose of the NI will provide less LC omega-3 polyunsaturated fatty acids (PUFAs) than permitted for Martek's DHA-rich oil (140mg combined EPA and DHA compared to 200mg DHA).

17. It is proposed that the NI will be used to replace fish oils and LC omega-3 PUFA oils currently on the market. The applicant does not recommend the product to be used in conjunction with any other LC omega-3 PUFA oil-containing products or supplement and all products containing the NI would clearly labelled so as to discourage consumption of more than one NI product/day.

18. The applicant states that in populations' traditionally consuming fish, coagulopathy (defective blood clotting) is reported due to prolonged exposure to PUFA's (Bang and Dyerberg, 1980; Hsia *et al.*, 1989). However consumption of the NI at the recommended daily dose will provide 140mg/day of EPA and DHA combined which is substantially less than the amount determined to be required to produce elongation of bleeding times which is more than 3.0g EPA and DHA/day (Hsia *et al.*, 1989). For food supplements containing the NI, the applicant recommends a special indication stating that people with coagulopathy or those who are taking anticoagulants or other medications should consult their doctor before taking the food supplement. No similar warning is proposed for foodstuffs containing the NI, where the recommended dose is lower.
19. The applicant also states that although the NI contains lipids separated from protein, its consumption by individuals with allergies to shellfish may produce allergic reactions even if minimal protein is present. The NI will therefore be labelled in accordance with the Allergen Labelling Directive 2000/13/EC with the statement "contains oil from crustaceans (Antarctic Krill)".
20. The Finnish CA was content with the applicant's proposal for allergen labelling of the NI noted that the special warning they intend to label food supplements containing the NI was sufficient for to enable the product to be additionally marketed in this form.
21. The Finnish CA highlights that the applicant proposes to incorporate the NI in several different products by adding 500mg/serving which is also the recommended maximum daily intake. Since the planned range of use is broad and since it is possible that consumers would consume several of the products per day any decision on allowing the product onto the market should take account of whether the range of enriched foods should be restricted.

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

Annex 2, p.28-30

22. Antarctic Krill has a history of consumption in Japan, Russia, Ukraine and France since the mid-70's.
23. The NI has also been available as dietary supplement products in North America and Asia since mid 2000. The recommended daily intake of the NI is 1-2 soft gel

capsules/day, with each capsule containing 500mg of the NI which corresponds to an intake of 500-1000mg/day.

XI. Nutritional information on the novel food

Annex 2, p.31-34

24. The NI is a whole lipid extract of Antarctic krill and its major components are EPA, DHA and several phospholipids of which lecithin is the major form. EPA and DHA 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.
25. The applicant states that combined intakes of EPA and DHA vary within the EU. For example, it is 0.835 g/day in Norway, 0.325 g/day in Sweden, 0.203 g/day in Germany and in Portugal it ranges from 0.083 g/day in a rural village to 0.754 in a fishing village. The applicant's recommended dose of the NI from suggested foods will provide 140mg combined EPA and DHA/day, which is within the range of current documented consumption in the EU.
26. The applicant refers to a previously approved DHA-rich oil (Martek Biosciences Co.), where the maximum daily dose of DHA must not exceed 200mg/day. In comparison the NI will provide approximately 48mg DHA and 92mg EPA per recommended dose of 500 mg of the NI. The combined amount of EPA and DHA per daily serving from food (140 mg) is below the amount of DHA approved per daily dose (200 mg) from food supplements. For encapsulated food supplement the intake of EPA and DHA resulting from the consumption of 1000 mg NI/day will be 95.8 mg DHA/day and 183 mg EPA/day for a total of 278.8 mg/person/day.
27. The applicant highlights that several authorities have published recommended daily intakes of LC omega-3 PUFA. 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 lifestyle by developing European dietary guidelines. The daily recommended intake of EPA and DHA provided by the NI in foods is 140 mg/day which is less than the "population goal" for very long chain omega-3 PUFA by the Eurodiet² report (200 mg/day) and much less than the population guideline recommendation for LC omega-3 PUFA, established by the

² Eurodiet: Nutrition & Diet for Healthy Lifestyles in Europe. Core Report 2000, http://ec.europa.eu/health/ph_determinants/life_style/nutrition/report01_en.pdf.

Scientific Advisory Committee on Nutrition (SACN) (450 mg/day) in their 2004 document *Advice on fish consumption: benefits and risks* (SACN, 2004)

28. The major components of the NI, EPA and DHA, have been shown to have beneficial effects on risk factors for cardiovascular disease (CVD). Although not relevant in the context of a safety evaluation under (EC) 258/97, the applicant has referred to several studies which are thought to support this view.
29. The Finnish CA concluded that the intake levels suggested by the applicant are similar or lower than levels in countries where considerable amounts of fish are consumed as food. For food supplements although the combined levels of EPA and DHA (278 mg/day) exceeds the requirement for maximum DHA (200 mg) in Commission Decision 2003/427/EC and the Eurodiet level (200 mg) this remains below the UK recommendation (450 mg).

XII. Microbiological information on the novel food

Annex 2, p.35-37

30. The production method is controlled by reference to a HACCP system where potential points for contamination and corruption of the NI have been identified.
31. To ensure the quality of the final NI product, lots will be regularly tested to ensure compliance with international standards addressing residual solvents, micro-organisms, heavy metals, arsenic and pesticides. The applicant has provided results of the batch analysis of the NI for the presence of micro-organisms (Annex 2, p.36, Table XII.1-2.)
32. The applicant was granted a fish processing establishment licence (Certificate number 5111) in 2005 and is on the list of authorised Canadian exporters to the EU.
33. The Finnish CA was content that the HACCP system presented in the application and the verifications conducted in accordance with Canadian standards are in line with the general requirements of the EU.

XIII. Toxicological information on the novel food

Annex 2, p.38-45

34. In order to show the safety of the NI, data relating to the absorption, distribution, metabolism and excretion of both the NI and its main constituents EPA and DHA, as well as pre-clinical and clinical studies using the NI were reviewed. The applicant has also referred to rat and mice studies which show omega-3 fatty acids attached to phospholipids (as present in the NI) are more bio available than for example fatty acids in the triglyceride form.
35. The applicant conducted a repeat-dose toxicity study on 96 C57BL6 Nude Congenic Mice to examine the safety of consumption of the NI. The mice were administered diets in which the NI represented 16.6% of their daily dietary intake which is equivalent to 28.3 g NI/kg body weight/day, for over a period of six months. No clinical adverse effects were observed and no histopathological abnormalities were observed in any of the organs examined.
36. The safety of the NI was studied in 25 individuals who consumed 6 soft gel capsules daily for a period of two months. Each capsule contained 1000 mg of the NI and provided 386 mg of omega-3 fatty acids, 416 mg of phospholipids and 0.16 mg astaxanthin. One individual withdrew from the study due to a known salt intolerance and two others withdrew due to increasing greasiness of their facial skin which they attributed to the consumption of the NI. In the remaining 22 subjects, no adverse effects were observed over the course of the two-month experimental period.
37. In a trial designed to examine the effect of the NI on hyperlipidemia, 120 subjects were administered NI doses of 300 to 3000 mg/person/day for a minimum of 12 weeks. No adverse effects were reported.
38. In a trial designed to examine the effect of the NI on the management of premenstrual syndrome (PMS) and dysmenorrhoea, 70 females were selected at random to receive either the NI or fish oil treatments. During the first month of the trial, subjects consumed two 1000 mg capsules once daily with meals. During the second and third months of the trial, they consumed two 1000 mg capsules once daily for 8 days prior to menstruation and 2 days during menstruation. Although minor increases in the oiliness of the facial skin was observed by individuals in

the NI group, no serious adverse effects were reported by the subjects during the duration of the trial.

39. The effects of the NI (300 mg/day) on markers of chronic inflammation were examined in comparison to a placebo, on 90 patients. The subjects were followed for a period of one month during which time no adverse effects associated with the consumption of the NI were reported by the authors.
40. The applicant states that despite the minimal amount of protein present in the NI, a warning will be placed on the labelling of all products containing the NI which states that persons with food allergies, coagulopathy or who are taking anticoagulants or other medication should consult their doctor before taking nutritional supplements.
41. The Finnish CA notes that although no studies on krill allergens have been published, there is no reason to assume that krill also contains protein(s) similar to tropomyosin which is the main allergen in shrimp. According to the specification, the NI contains approximately 0.5-3.5 g/100 g of residual protein. The recommended daily intake (500 mg) may thus contain 2.5-17.5 mg of protein originating from krill. On this basis the Finnish CA therefore accepted that the warning labels on packaging concerning the products unsuitability for individuals with allergies to fish or crustaceans are necessary.
42. The Finnish CA was of the view that for a toxicity study, the experiment conducted on C57BL/6 Nude mice is very poorly reported and limited in scope. The scope of the human trials is also 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.
43. The Finnish CA was content with 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 is appropriate.

Committee Action Required

44. The Committee is asked whether it agrees with the initial opinion from the Finnish CA that Antarctic Krill oil produced by Neptune Technologies & Bioresources Inc should be granted authorisation as a novel food ingredient in food supplements and in other foods, and whether it wishes to make any additional comments on the application.

Secretariat

March 2007

Annexes attached:

Annex 1 – Finnish Competent Authority's initial assessment report.

Annex 2 - Application dossier submitted by Neptune Technologies & Bioresources Inc. for the approval of Antarctic Krill oil as a novel food ingredient. **(RESTRICTED)**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Finnish Competent Authority's Initial Assessment Report

**Secretariat
March 2007**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

RESTRICTED

Application dossier submitted by Neptune Technologies & Bioresources Inc. for the approval of Antarctic Krill oil as a novel food ingredient.

**Secretariat
March 2007**