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SCIENTIFIC OPINION

Scientific Opinion on the extension of use for DHA and EPA-rich algal oil from *Schizochytrium* sp. as a Novel Food ingredient[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

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ABSTRACT

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on an extension of use for docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-rich algal oil from *Schizochytrium* sp. as a novel food ingredient (NFI) in the context of Regulation (EC) No 258/97. The NFI is already authorised for use in a range of foodstuffs at specified maximum levels. The applicant requests an extension of use of the NFI in food supplements up to a maximum DHA and EPA content of 3 g per daily dose for the adult population, excluding pregnant and lactating women. In a previous opinion on the Tolerable Upper Intake Level of EPA, DHA and docosapentaenoic acid (DPA), the Panel concluded that supplemental intake of EPA and DHA combined at doses up to 5 g/day, does not give rise to safety concerns for adults. Based on estimations of high intake of DHA and EPA from the NFI which are considered to be conservative, the Panel considers that this level will not be exceeded by the use of the NFI. The conclusion that there are no safety concerns for the NFI is supported by a 90-day study in which no adverse effect was observed at the highest dose tested of 5 %, equivalent to 3.149 and 3.343 g NFI/kg body weight per day for male and female rats. Following a request from a Member State, the Panel reviewed the evidence for an association between DHA and/or EPA intake and risk of prostate cancer. The Panel considers that, on the basis of available data, there is no evidence for a role of EPA and/or DHA intake in the development of prostate cancer. The Panel concludes that the NFI is safe under the proposed extension of use.

KEY WORDS

docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), *Schizochytrium* sp., algal oil, novel food, ingredient

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on a request for the extension of use for docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-rich algal oil from *Schizochytrium* sp. as a novel food ingredient (NFI) in the context of Regulation (EC) No 258/97, taking into account the comments and objections of a scientific nature raised by Member States.

The NFI is already authorised for use in a range of foodstuffs at specified maximum levels of inclusion. The present application relates to the extension of the use of the NFI in food supplements up to a maximum DHA and EPA content of 3 g per daily dose for the adult population, excluding pregnant and lactating women.

The NFI is an algal oil derived from *Schizochytrium* sp. with minimum contents of 22.5 % DHA and 10 % EPA. No changes are proposed to the specification, the source and the production process of the authorised ingredient.

In a previous opinion on the Tolerable Upper Intake Level (UL) of EPA, DHA and docosapentaenoic acid (DPA), the Panel concluded that available data were insufficient to establish a UL for n-3 long-chain polyunsaturated fatty acids (EFSA NDA Panel, 2012). The Panel considered that supplemental intake of EPA and DHA combined at doses up to 5 g/day, does not give rise to safety concerns for adults.

Anticipated intake of DHA and EPA from the NFI was estimated by combining intake of the NFI through enriched foods and food supplements. High intakes of 4.65 g/day (combination of enriched foods and food supplements), based on consumption data from the UK, and 5.37 g (combination of conventional foods, enriched foods and food supplements), based on consumption data from Germany, were estimated. These assessments are considered conservative in that they assume that all food items within a food category contain the NFI at the maximum authorised level of use and that an individual consumes all food categories enriched with the NFI together with food supplements. The Panel considers that the long-term level of no concern of 5 g/day for supplemental DHA and EPA will not be exceeded by the use of the NFI.

The conclusion that there are no safety concerns for the NFI is further supported by a 90-day study carried out with the NFI in rats, in which no adverse effect was observed with the highest dose tested of 5 % which is equivalent to 3.149 and 3.343 g NFI/kg body weight per day for male and female rats, respectively.

Following a request from a Member State, the Panel reviewed the evidence for an association between DHA and/or EPA intake and risk of prostate cancer. The Panel considers that, on the basis of available data, there is no evidence for a role of EPA and/or DHA intake in the development of prostate cancer.

The Panel concludes that the NFI is safe under the proposed extension of use.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The use of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) rich algal oil from *Schizochytrium* has been authorised for use as a novel food ingredient in a range of foodstuffs by the United Kingdom in accordance with Article 4(2) of Regulation (EC) No 258/97.

On 19 November 2012, the company DSM Nutritional Products submitted a request under Article 4 of the Novel Food Regulation (EC) No 258/97 to extend the use of this oil in food supplements intended for normal population.

On 29 April 2013, the competent authorities of the United Kingdom forwarded to the Commission their initial assessment report, which came to the conclusion that this algal oil, at levels up to 3 000 mg EPA and DHA per day in food supplements and not exceeding the maximum use levels previously described for other foods, meets the criteria for acceptance of a novel food defined in Article (3)1 of Regulation (EC) No 258/97.

On 9 July 2013, the Commission forwarded the initial assessment report to the other Member States. Some Member States submitted comments or raised objections.

In consequence, a decision is now required by the Commission under Article 7(1) of Regulation (EC) No 258/97.

The concerns of a scientific nature raised by the Member States can be summarised as follows:

- If food supplements containing 3 000 mg DHA/EPA per daily dose are authorised, consumption of DHA and EPA could exceed the supplemental intake of 5 g per day, which EFSA considers not to cause safety concerns (EFSA NDA Panel, 2012).

- Although, overall, evidence from studies is inconsistent, a positive association between a) high intake levels and b) high plasma concentrations of DHA/EPA and the risk of high-grade prostatic intraepithelial neoplasia, a precursor of prostate cancer, has been found in some meta-analyses (Chua et al., 2012; Dahm et al., 2012; Chua et al., 2013; Sorongon-Legaspi et al., 2013). It was noted that a placebo-controlled, double-blind intervention study is in progress in the US which investigates the possibility of a link between intake of vitamin D (50 µg/day) and DHA/EPA (1 g/day) and the incidence of cancer and cardiovascular disease (Manson et al., 2012).

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,[4] the European Commission asks the European Food Safety Authority to provide one scientific opinion by carrying out the additional assessment for extension of use for docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) rich algal oil from *Schizochytrium* as a novel food ingredient in the context of Regulation (EC) No 258/97.

[4] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

ASSESSMENT

"Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-rich algal oil from *Schizochytrium* sp." (hereinafter "DHA and EPA-rich oil") from DSM Nutritional Products (formerly Martek Biosciences Corporation) has been approved in the European Union (EU) by the competent authority of the UK as a novel food ingredient (NFI) in accordance with Regulation (EC) No 258/97[5] (ACNFP, 2012; FSA, 2012). The NFI is authorised for use in a range of foodstuffs at specified maximum levels of inclusion (Appendix A). Food supplements are included in the current authorisation at a maximum DHA and EPA content of 0.25 g per daily dose as recommended by the manufacturer for the normal population and 0.45 g per daily dose as recommended by the manufacturer for pregnant and lactating women (ACNFP, 2012; FSA, 2012).

The present application relates to the extension of the use of DHA and EPA-rich oil in food supplements up to a maximum DHA and EPA content of 3 g per daily dose as recommended by the manufacturer for normal population.

The assessment is based on data supplied in the original application, the initial assessment by the competent authority of the UK, the concerns and objections of the other Member States and the responses of the applicant. The present assessment is restricted to the aspects relevant to the application for an extension of use of the NFI. The extension of use is requested in relation to the authorisation of two health claims that were assessed positively by the EFSA NDA Panel, which related to the intake of DHA and maintenance of normal (fasting) blood concentrations of triglycerides, with conditions of use of 2 g DHA per day (EFSA NDA Panel, 2010a), and to the intake of DHA and EPA and maintenance of normal blood pressure, with conditions of use of about 3 g EPA and DHA per day (EFSA NDA Panel, 2010b). This assessment concerns only risk that might be associated with the request for extension of use, and is not an assessment of the efficacy of DHA and EPA-rich oil with regard to any claimed benefit.

1. Specification and production process of NFI

The NFI is an algal oil with minimum contents of 22.5 % DHA and 10 % EPA (Martek Biosciences Corporation, 2010; ACNFP, 2012; FSA, 2012). The specification of the NFI is laid down in Table 1. The source of the NFI is a microalgae, which is a member of the genus *Schizochytrium* sp.

Table 1: Specification of DHA and EPA-rich oil from *Schizochytrium* sp.

Test	Specification
Acid value	Not more than 0.5 mg KOH/g
Peroxide value (PV)	Not more than 5.0 meq/kg oil
Moisture and volatiles	Not more than 0.05 %
Unsaponifiables	Not more than 4.5 %
Trans-fatty acids	Not more than 1 %
DHA content	Not less than 22.5 %
EPA content	Not less than 10 %

DHA, docosahexaenoic acid; EPA, eicosapentaenoic; KOH, potassium hydroxide.
Note: All food products containing DHA and EPA-rich oil from *Schizochytrium* sp. should demonstrate oxidative stability by appropriate and recognised national/international test methodology (e.g. AOAC).

Information on the production process of the NFI was described in the initial application dossier (Martek Biosciences Corporation, 2010). Briefly, the oil is recovered from a fermented culture of the algae. The crude oil is refined into the finished product using processes commonly used in the

[5] Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.

vegetable oil industry. Antioxidants are added to the oil to provide stability. DHA and EPA percentage may be standardised by the addition of food-grade vegetable oil, such as sunflower oil.

The NFI contains a range of fatty acids, of which DHA and EPA, together with palmitic acid, are the most abundant. In the initial application dossier, the applicant provided the analyses of three batches of the NFI, which complied with the specifications (Martek Biosciences Corporation, 2010). DHA and EPA contents were 32.7–35.1 % and 14.9–17.7 %, respectively.

The Panel notes that no changes are proposed to the specification, the source and the production process of the authorised ingredient (Martek Biosciences Corporation, 2010; ACNFP, 2012; FSA, 2012).

2. Anticipated intake/extent of use of the NFI

The NFI is proposed for use as a replacement for fish and other algal oil supplements in the European diet.

The current application relates to the extension of the use of DHA and EPA-rich oil in food supplements up to a maximum DHA and EPA content of 3 g per daily dose for the normal population instead of the maximum DHA and EPA content of 0.25 g per daily dose for the normal population set in the current authorisation (ACNFP, 2012; FSA, 2012). Upon request for clarification, the applicant indicated that the food supplements are recommended for adults only.

Considering that the NFI consists of ca. 50 % DHA and EPA, the Panel notes that this corresponds to a daily intake of 6 g NFI. This represents a daily dose of 0.09 g NFI/kg body weight for a 70 kg adult.

The Panel notes that no change is proposed to the current authorised maximum intake level intended for pregnant and lactating women of 0.45 g per daily dose.

The applicant indicates that food supplement products may be presented in various dosed forms, including capsules or a liquid, depending on desired dose. Food supplement use is controlled under the conditions laid down by Directive 2002/46/EC[6] on food supplements, including provisions for labelling.

2.1. Estimated intake of DHA and EPA from diet, food supplements and enriched foods in the EU

Available data on intake of DHA and EPA in the EU have been summarised by the Panel in an earlier opinion (EFSA NDA Panel, 2012).

Mean daily intake of EPA and DHA from food only was between 0.127 g/day (Germany, women, 18-24 years) and 0.295 g/day (Germany, men, 45–54 years). Daily intake of EPA and DHA in the highest percentiles of consumption (95th percentile) was between 0.285 g/day (The Netherlands, women, 19–30 years) and 1.115 g/day (Belgium, women, 18–39 years). Mean intake of EPA and DHA in high fish consumers from food only was up to 2.700 g/day (France, 18 years, fifth quintile of EPA–DHA intake).

The highest intake estimate (95th percentile) of DHA and EPA was 1.278 g/day (Ireland, 51–64 years) when food and food supplements were considered together. No surveys reported on EPA and DHA intake from food and supplements combined in high seafood consumers.

One survey specifically reported intake of DHA and EPA from enriched foods. Sioen et al. (2010) estimated the intake of DHA and EPA from conventional foods, enriched foods and food supplements in a sample of Flemish women (n = 414, 18–39 years). A market survey was conducted in 2008 in

[6] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, OJ L 183, 12.07.2002, p. 51–57.

order to identify enriched food items and food supplements together with their n-3 polyunsaturated fatty acids (n-3 PUFA) content. Most identified food items were enriched with alpha-linolenic acid (ALA). One brand of eggs and four brands of margarine contained EPA and DHA, besides ALA. A food frequency questionnaire was designed to collect data on the consumption of n-3 PUFA supplements, food items enriched with n-3 PUFA, and food items naturally rich in n-3 long-chain PUFA (n-3 LCPUFA) (seafood and seaweed). EPA and DHA intake was estimated as follows (mean ± standard deviation (SD) (range)): 0.181 ± 0.209 (0–0.871) g/day among non-consumers of n-3 LCPUFA enriched foods and supplements (n = 19), 0.281 ± 0.368 (0–4.642) g/day among consumers of enriched foods (n = 395), 1.067 ± 0.997 (0.026–4.642) g/day among supplement users (n = 19).

2.2. Estimated intake of DHA and EPA from foods enriched with the NFI

In the initial application dossier, the applicant provided estimates for the intake of DHA and EPA from the NFI based on the proposed uses and use levels (Martek Biosciences Corporation, 2010). All food categories subject to the authorisation were considered in the assessment, i.e. bakery products, breads, rolls and sweet biscuits, breakfast cereals, cooking fats, dairy analogues (except drinks), dairy products (except milk-based drinks), non-alcoholic beverages (including dairy analogues and milk-based drinks), nutrition bars and spreadable fats and dressings. Estimates were derived from food consumption data from the UK National Diet and Nutrition Survey (NDNS 2000–2001) considering the maximum use level for each food category. Estimates of the daily intake of DHA and EPA from foods enriched with the NFI were calculated at individual level, and represent projected seven-day averages. The distribution from which mean and high percentile intake estimates were produced was comprised of these average amounts. Intake of DHA and EPA from food supplements was not taken into account. The estimated intake for the adult population are reported in Table 2.

Table 2: Estimated intake of DHA and EPA from all proposed food categories in the UK adult population (NDNS data, 2000–2001) (g/day)

Gender	Age	% User	Number of total users	All-person consumption				All-users consumption			
				Mean	Percentile			Mean	Percentile		
					90th	95th	97.5th		90th	95th	97.5th
Women	16–64	94.3	903	0.60	0.95	1.10	1.21	0.60	0.96	1.12	1.23
Men	16–64	95.0	728	0.76	1.23	1.45	1.66	0.77	1.23	1.45	1.65

For adult all-users, mean estimated daily intake of DHA and EPA from foods enriched with the NFI is 0.77 g in men and 0.60 g in women. For high consumers (97.5th percentile), estimated intake is 1.65 g in men and 1.23 g in women.

One Member State referred to the assessment of potential intake of n-3 LCPUFA from food and enriched foods of the German population performed by the German Federal Institute for Risk Assessment (BfR, 2009). Intake of n-3 LCPUFA from conventional foods was estimated based on food consumption data from the German National Nutrition Survey II (Nationale Verzehrsstudie (NVS) II) and data on the "natural" content of n-3 LCPUFA in foods. Total intake of n-3 LCPUFA from conventional foods and enriched foods was assessed by assuming that nine of the food categories for which the addition of DHA-rich oil was authorised were enriched with DHA/EPA. In this scenario, the DHA/EPA content of these food categories was assumed at the maximum permitted levels. Intake of n-3 LCPUFAs from food supplements was not taken into account in the assessment.

Estimated mean intake of n-3 LCPUFA from conventional foods was 0.34 mg/day in women and 0.46 mg/day in men (Table 3). Mean total intake estimate of n-3 LCPUFA from conventional foods and enriched foods was 0.93 g/day in women and 1.20 g/day in men. For high-level consumers (95th percentile), total intake estimates were 1.77 g/day in women and 2.37 g/day in men, respectively.

Table 3: Estimated intake of DHA, EPA and DPA in the German adult population (NVS II data, 2005–2006) (g/day)

Gender	Diet of conventional foods [(a)]				Diet including enriched foods [(b)]			
	Mean	SD	Median	95th percentile	Mean	SD	Median	95th percentile
Women	0.34	0.35	0.25	0.94	0.93	0.47	0.85	1.77
Men	0.46	0.50	0.31	1.31	1.20	0.68	1.07	2.37

SD, standard deviation.
(a): Intake estimates from background diet, considering the "natural" content of n-3 LCPUFAs in foods.
(b): Intake estimates including intake from nine food categories (enriched bread, bread rolls, margarine, breakfast cereals, muesli bars, yoghurt, cheese, milk-based beverages, sodas), assuming DHA/EPA contents of these food categories at the maximum permitted levels.

The Panel notes that the assessment methodologies used by the applicant and BfR are generally considered to be "worst case" as a result of several conservative assumptions made in the consumption estimates, assuming that all food items within a food category contain the ingredient at the maximum specified level of use and that an individual consumes all food categories enriched with the NFI which were considered in the assessment.

2.3. Discussion and conclusions

In its opinion on the Tolerable Upper Intake Level (UL) of EPA, DHA and docosapentaenoic acid (DPA), the Panel concluded that available data were insufficient to establish a UL for n-3 LCPUFA (EFSA NDA Panel, 2012). The Panel considered that supplemental intake of EPA and DHA combined at doses up to 5 g/day, does not give rise to safety concerns for adults. Some Member States expressed concerns that the daily dose of 5 g for supplemental DHA and EPA may be exceeded if food supplements containing 3 g DHA and EPA per daily dose are authorised, considering estimated intake from foods enriched with DHA and EPA.

Intake up to 1.65 g/day DHA and EPA was calculated by the applicant for high-level consumers (97.5th percentile) in the UK with respect to supplemental intake from enriched foods. If the food supplement would be consumed together with high intake of DHA and EPA from enriched foods, the total intake estimate of DHA and EPA from supplemental sources (i.e. food supplements and enriched foods) reaches 4.65 g/day.

Based on the assessment from BfR including nine food categories to which the NFI may be added, total intake up to 2.37 g/day n-3 LCPUFA was calculated for high-level consumers (95th percentile) in Germany. Considering an additional intake of 3 g from food supplement, this would result in a total intake estimate of 5.37 g/day. The Panel notes that this includes n-3 LCPUFA intake from conventional foods together with enriched foods.

Given that the exposure scenarios are conservative, the Panel considers that the long-term level of no concern of 5 g/day for supplemental DHA and EPA will not be exceeded by the use of the NFI.

3. Nutritional information on the NFI

The initial application dossier provided nutritional information on the NFI (Martek Biosciences Corporation, 2010). Based on available data, the UK Advisory Committee on Novel Foods and Processes (ACNFP) noted that "the fatty acid profile of the product was broadly comparable with existing fish oil derived products and, as such, would be unlikely to give rise to safety concerns" (ACNFP, 2012; FSA, 2012). The UK Committee noted that the NFI is almost entirely composed of triglycerides, with a caloric value of 9 kcal/g.

The Panel considers that in the context of the present request for extension of use of the NFI, the consumption of the NFI is not nutritionally disadvantageous.

4. Toxicological information on the NFI

The initial application dossier provided toxicological information on the NFI (Martek Biosciences Corporation, 2010), which was reviewed by the Advisory Committee on Novel Foods and Processes (ACNFP) (ACNFP, 2012; FSA, 2012). In a 90-day study in rats, a no-observed-adverse-effect level (NOAEL) of 5 % (50 000 mg/kg), which was the highest dose tested, was derived. This is equivalent to 3.149 and 3.343 g NFI/kg body weight per day for male and female rats, respectively. No indication of genotoxicity was found from a reverse mutation (Ames) assay, an *in vitro* mammalian chromosome aberration test and an *in vitro* mouse micronucleus test conducted with the NFI.

The Panel considers that the available toxicity studies do not indicate safety concerns.

5. Risk of prostate cancer

Some mechanisms have been discussed for a putative protective role of DHA and EPA in cancer risk (Astorg, 2004; Larsson et al., 2004; Kobayashi et al., 2006). However, one Member State raised concerns over the consumption of DHA/EPA and the risk of prostate cancer, based on a recent meta-analysis of prospective cohort studies (Chua et al., 2012) which investigated the relationship between EPA and DHA intakes and prostate cancer, a meta-analysis of case–control and nested case–control studies (Chua et al., 2013; Sorongon-Legaspi et al., 2013) which addressed the association between blood biomarkers of EPA and DHA (expressed as a percentage of total fatty acids) and prostate cancer, and a nested case–control study (Dahm et al., 2012). The latter is a re-analysis of the study by Crowe et al. (2008), which was already included in the meta-analyses. The applicant provided another publication (Brasky et al., 2013) which included a meta-analysis of nested case-control studies on the relationship between blood biomarkers of EPA and DHA (expressed as a percentage of total fatty acids) and prostate cancer.

The Panel notes that prospective cohort studies, and to a lower extent nested case-control studies, have a lower risk of reverse causality than case-control studies. The Panel also notes that although blood biomarkers of EPA and DHA (e.g. in total plasma, plasma phospholipids, and red blood cell (RBC) membranes) have the advantage of being objective measurements and, unlike dietary estimates of DHA and EPA intake, are not subject to recall or reporting bias, they do not only reflect intakes of DHA and EPA, but also their absorption, metabolism and incorporation into plasma fractions, cells or tissues (which is determined by genetic background and health/disease status), as well as the intakes of other fatty acids in the diet, particularly if expressed as a percentage of total fatty acids (EFSA NDA Panel, 2014). Therefore, the Panel considers that prospective cohort studies which have investigated the relationship between EPA and DHA intakes and risk of prostate cancer may provide the most robust evidence in relation to a role of EPA and DHA in the development of prostate cancer.

Prospective cohort studies on EPA and DHA intakes and risk of prostate cancer

Chua et al. (2012) performed a meta-analysis of prospective cohort studies that assessed the relationship between intake of DHA and EPA and incidence of prostate cancer. Three cohorts assessed EPA and DHA intakes separately (Schuurman et al., 1999; Wallstrom et al., 2007; Park et al., 2009). No significant association was found between EPA intake or DHA intake and prostate cancer risk by combining the results from these cohorts, which did not show significant heterogeneity or publication bias. Three cohorts assessed intakes of EPA and DHA in combination (Leitzmann et al., 2004; Wallstrom et al., 2007; Chavarro et al., 2008). No significant association was found between EPA and DHA intake and prostate cancer risk by combining the results from these three cohorts (75 597 participants). In a sensitivity analysis, the authors excluded the study by Leitzmann et al. (2004) to remove the significant heterogeneity found among studies (I^2 = 73 %, p = 0.023). In this subgroup analysis, a significant positive association between the combination of EPA and DHA intake and total prostate cancer incidence (relative risk (RR) = 1.135; 95 % CI = 1.008–1.278; p = 0.036; I^2 = 25 %, p = 0.249) was found by combining the results of only two studies (Wallstrom et al., 2007; Chavarro et al., 2008). The analysis was repeated by adding two cohorts (Schuurman et al., 1999; Park et al., 2007) which had only addressed and analysed intakes of EPA and DHA separately in relation to

prostate cancer risk. This analysis revealed no significant association between DHA and EPA intake and prostate cancer risk and no significant heterogeneity among studies. The Panel notes that it is unclear how and why the results from four cohorts with different intake variables (EPA, DHA, EPA plus DHA) were combined.

The results from the three studies investigating the relationship between the combined intake of EPA and DHA and risk of prostate cancer are inconsistent. Whereas the Malmö Diet Cancer cohort, which involved 10 564 men in Sweden (mean follow-up 11 years; 817 cases), found a positive association between the combined intake of EPA and DHA and risk of prostate cancer (hazard ratio (HR) = 1.28, 95 % CI = 1.01–1.62 for Q5 vs. Q1; p for trend 0.063) (Wallstrom et al., 2007), the Physician's Health study (Chavarro et al., 2008), which involved 20 167 men in the US (22 year follow-up, 2 161 cases), did not. The Health Professionals follow-up study by Leitzmann et al. (2004), which was excluded from the sensitivity analysis, involved 47 866 men in the US (follow-up 14 years, 2 965 cases) and found no significant association between the combined intake of DHA and EPA and total prostate cancer risk. The Panel notes that the Physician's Health study and Health Professionals follow-up study involved about twice the participants and registered more than double the number of cases than the Malmö Diet Cancer cohort.

The Panel notes that there is no evidence from prospective cohort studies for an association between EPA or DHA intake, considered separately, and incidence of prostate cancer. Three prospective studies which considered DHA and EPA in combination provide inconsistent results, with the two larger cohorts finding no association and the smaller cohort finding a positive association with prostate cancer incidence.

Nested case–control and case–control studies on blood biomarkers of EPA and DHA and risk of prostate cancer

Sorongon-Legaspi et al. (2013) and Chua et al. (2013) reported on the same meta-analysis, which assessed the association between blood biomarkers of EPA and DHA and risk of prostate cancer using data from six case-control and six nested case-control studies. Pooled RR were calculated in relation to total prostate cancer risk (six case–control and five nested case–control studies), or risk of prostate cancer subtypes characterised by its extension (i.e. advanced prostate cancer; four nested case–control studies) or its degree of differentiation (i.e. high-grade prostate cancer; one case control study and three nested case–control studies). No significant associations were found between individual blood levels of EPA or DHA and total prostate cancer risk, risk of advanced prostate cancer, or risk of high-grade prostate cancer. In a further analysis, the authors combined the results obtained for DHA and for EPA individually and found a positive association in this combined analysis of EPA and DHA and risk of high-grade prostate cancer (pooled RR = 1.39, 95 % CI = 1.07–1.80; p = 0.021; I^2 = 17.6 %, p = 0.291), based on one case-control and three nested case–control studies (Crowe et al., 2008; Park et al., 2009; Shannon et al., 2010; Brasky et al., 2011). However, the Panel notes that there is no rationale for combining the results obtained for DHA and for EPA individually in a pooled estimate.

Brasky et al. (2013) performed a meta-analysis of seven nested-case control studies which reported on the associations between blood biomarkers of DHA and EPA and total, low-grade and high-grade prostate cancer risk. The analysis included four of the five nested-case control studies included in the pooled estimates from Sorongon-Legaspi et al. (2013) and Chua et al. (2013), along with three additional studies which were not included before because they were reported to introduce high heterogeneity (Mannisto et al., 2003), for unknown reasons (Chavarro et al., 2007), or for later publication (Brasky et al., 2013). The RR in the highest vs. lowest quantile of plasma DHA was significantly higher for total (RR = 1.16, 95 % CI = 1.03–1.31; I^2 = 60.5 %, p = 0.02), low-grade (RR = 1.20, 95 % CI = 1.04–1.38; I^2 = 57.5 %, p = 0.05) and high-grade prostate cancer (RR = 1.48, 95 % CI = 1.10–1.99; I^2 = 47.3 %, p = 0.11). No significant association was found between blood biomarkers of EPA and prostate cancer risk.

The Panel notes that one meta-analysis of case–control and nested case–control studies found no association between blood biomarkers of EPA or DHA individually and total, advanced and high-grade prostate cancer risk (Chua et al., 2013; Sorongon-Legaspi et al., 2013). A second meta-analysis of nested case–control studies found no association between blood biomarkers of EPA alone and total, low- and high-grade prostate cancer. In contrast to the first meta-analysis, positive associations were found between blood biomarkers of DHA alone and total and high-grade prostate cancer risk, as well as low-grade prostate cancer risk (Brasky et al., 2013). The two meta-analyses differed with respect to the studies included in the pooled estimates, with no clear rationale as regards their inclusion/exclusion criteria. Considering the individual results of available nested case–control studies which looked at DHA alone and total prostate cancer risk, three reported a positive association (Crowe et al., 2008; Brasky et al., 2011; Brasky et al., 2013), three found no significant association (Harvei et al., 1997; Mannisto et al., 2003; Park et al., 2009) and two found a negative association (Norrish et al., 1999; Chavarro et al., 2007); no significant association was found in the five available case–control studies (Godley et al., 1996; Newcomer et al., 2001; Ukoli et al., 2009; Shannon et al., 2010; Ukoli et al., 2010). With respect to DHA and low- or high-grade prostate cancer risk, one nested case–control study reported a positive association for low- but not high-grade prostate cancer (Brasky et al., 2013), while another nested case–control study reported opposite findings (Brasky et al., 2011); three nested-case control (Chavarro et al., 2007; Crowe et al., 2008; Park et al., 2009) and one case–control study (Shannon et al., 2010) found no significant association with either low- or high-grade prostate cancer. Overall, the Panel notes that results from studies on an association between blood biomarkers of DHA and EPA and prostate cancer risk are inconsistent, with a majority of nested case-control and case-control studies finding null or negative associations. No consistent association is observed, whether EPA or DHA are looked at, or whether total incidence or particular subtypes of prostate cancer are considered.

The applicant also refers to cohort studies examining the relationship between fish intake and prostate cancer risk (Iso et al., 2007; Szymanski et al., 2010), as well as a report on the incidence of prostate cancer in Asian countries compared with other regions of the world (ACS, 2011). The Panel notes that DHA and EPA consumption was not assessed in these studies and that no conclusion can be drawn from these studies on an association between DHA and EPA and prostate cancer risk.

No information is available as yet from on-going intervention studies which investigate the effect of DHA and EPA supplementation on cancer risk, such as the VITAL trial (Manson et al., 2012).

Conclusion

The Panel notes that there is no evidence from prospective cohort studies for an association between EPA and/or DHA intake and incidence of prostate cancer. Results from nested case–control and case–control studies which investigated the association between blood biomarkers of DHA and EPA and prostate cancer risk are mostly null or negative and need to be interpreted with caution, owing to the inherent uncertainties related to the use of blood measurements of DHA and EPA as biomarkers of DHA and EPA intake.

The Panel considers that on the basis of available data, there is no evidence for a role of EPA and/or DHA intake in the development of prostate cancer.

6. Allergenicity

The initial application dossier provided information on the potential allergenicity of the NFI. Based on available data, the ACNFP concluded that the NFI did not present an allergic risk.

The conclusion is the same in the context of the present request for extension of use of the NFI.

DISCUSSION

The NFI, a DHA and EPA rich oil from *Schizochytrium* sp., is already authorised in a range of foodstuffs and in food supplements. The current authorisation sets a maximum content of DHA and EPA in food supplements of 0.25 g per daily dose for the normal population. The present application relates to an extension of the use of the NFI in food supplements up to a maximum DHA and EPA content of 3 g per daily dose for the adult population, excluding pregnant and lactating women.

No changes are proposed to the specification, the source and the production process of the authorised ingredient.

In a previous opinion, the Panel considered that available data were insufficient to establish an UL for EPA and/or DHA (EFSA NDA Panel, 2012). The Panel concluded that supplemental intake of EPA and DHA combined at doses up to 5 g/day does not give rise to safety concerns for adults.

High intakes of DHA and EPA of 4.65 g/day (combination of enriched foods and food supplements), based on consumption data from the UK, and 5.37 g (combination of conventional foods, enriched foods and food supplements), based on consumption data from Germany, were estimated. These assessments are considered conservative in that they assume that all food items within a food category contain the ingredient at the maximum specified level of use and that an individual consumes all food categories enriched with the NFI, considered in the assessment, together with food supplements. The Panel considers that the long-term level of no concern of 5 g/day for supplemental DHA and EPA will not be exceeded by the use of the NFI.

The conclusion that there are no safety concerns for the NFI is further supported by a 90-day study carried out with the NFI in which no adverse effect was observed with the highest dose tested of 5 % which is equivalent to 3.149 and 3.343 g NFI/kg body weight per day for male and female rats, respectively.

The Panel considers that, on the basis of available data, there is no evidence for a role of EPA and/or DHA intake in the development of prostate cancer.

CONCLUSIONS

The Panel concludes that the novel food ingredient, DHA and EPA-rich algal oil from *Schizochytrium* sp., is safe under the proposed extension of use.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier "Application for the extension of authorization of DHA and EPA-rich Algal Oil from *Schizochytrium* sp." received on 28 March 2014. Submitted by DSM Nutritional Products on 19 November 2012. Additional data were provided on 06 June 2014.

2. Letter from the European Commission to the European Food Safety Authority with the request for an opinion on the extension of use from DHA and EPA-rich algal oil from *Schizochytrium*. SANCO.E6/SH/ks D(2014) 889063, dated 25 March 2014.

3. Initial assessment report carried out by the Food Standards Agency of the United Kingdom: "DHA and EPA-rich algal oil from *Schizochytrium* sp. (Extension of use)".

4. Member States' comments and objections.

5. Response by the applicant to the initial assessment report and the Member States' comments and objections.

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APPENDIX

Appendix A. Approved uses of the NFI

Food category	Maximum use level of DHA + EPA (mg/100 g) unless otherwise stated
Food supplements	250 mg per daily dose as recommended by the manufacturer for normal population; 450 mg per daily dose as recommended by the manufacturer for pregnant and lactating women
Dietary foods for special medical purposes	In accordance with the particular nutritional requirements of the persons for whom the products are intended
Foods intended for use in energy-restricted diets for weight reduction	250 mg per meal replacement
Other foods for particular nutritional uses (PARNUTS), as defined in Directive 2009/39/EC (European Parliament and the Council of the European Union, 2009) excluding infant and follow on formula	200 mg/100 g
Bakery products, breads and rolls, sweet biscuits	200 mg/100 g
Breakfast cereals	500 mg/100 g
Cooking fats	360 mg/100 g
Dairy analogues (except drinks)	600 mg/100 g for cheese; 200 mg/100 g for soy and imitation milk products (excluding drinks)
Dairy products (except milk-based drinks)	600 mg/100 g for cheese; 200 mg/100 g for milk products (including milk, fromage frais and yoghurt products; excluding drinks)
Non-alcoholic beverages (including dairy analogue and milk-based drinks)	80 mg/100 g
Cereal/nutrition bars	500 mg/100 g
Spreadable fats and dressings	600 mg/100 g

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
Source: FSA (2012)

ABBREVIATIONS

ACNFP	Advisory Committee on Novel Foods and Processes
ALA	alpha-linolenic acid
BfR	Bundesinstitut für Risikobewertung
CI	confidence interval
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
FSA	Food Standards Agency
HR	hazard ratio
I^2	heterogeneity index
n-3 PUFA	n-3 polyunsaturated fatty acids
n-3 LCPUFA	n-3 long-chain polyunsaturated fatty acids
NFI	novel food ingredient
RR	relative risk
UL	Tolerable Upper Intake Level
UK	United Kingdom