**SCIENTIFIC OPINION**

# Scientific Opinion on the substantiation of health claims related to EPA, DHA, DPA and maintenance of normal blood pressure (ID 502), maintenance of normal HDL-cholesterol concentrations (ID 515), maintenance of normal (fasting) blood concentrations of triglycerides (ID 517), maintenance of normal LDL-cholesterol concentrations (ID 528, 698) and maintenance of joints (ID 503, 505, 507, 511, 518, 524, 526, 535, 537) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

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

European Food Safety Authority (EFSA), Parma, Italy

## SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to EPA, DHA and DPA and the following claimed effects: maintenance of normal blood pressure, maintenance of normal HDL-cholesterol concentrations, maintenance of normal (fasting) blood concentrations of triglycerides, maintenance of normal LDL-cholesterol concentrations, and maintenance of joints. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The food constituents which are the subject of the health claims are mixed long-chain n-3 polyunsaturated fatty acids (n-3 LCPUFA), namely docosahexaenoic acid (DHA) in combination with eicosapentaenoic acid (EPA) and, for ID 511, with docosapentaenoic acid (DPA). The Panel considers that the food constituents, EPA, DHA and DPA, which are the subject of the health claims are sufficiently characterised.

1 On request from the European Commission, Question No EFSA-Q-2008-1289, EFSA-Q-2008-1290, EFSA-Q-2008-1292, EFSA-Q-2008-1294, EFSA-Q-2008-1298, EFSA-Q-2008-1302, EFSA-Q-2008-1304, EFSA-Q-2008-1305, EFSA-Q-2008-1311, EFSA-Q-2008-1313, EFSA-Q-2008-1315, EFSA-Q-2008-1322, EFSA-Q-2008-1324, EFSA-Q-2008-1485 adopted on 02 July 2009.

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The Panel considers that maintenance of normal blood pressure, maintenance of normal HDL-cholesterol (without increasing LDL-cholesterol) concentrations, maintenance of normal (fasting) blood concentrations of triglycerides, maintenance of normal LDL-cholesterol concentrations, and maintenance of normal joints are beneficial to human health.

On the basis of the data available, the Panel concludes that a cause and effect relationship has been established between the consumption of EPA and DHA and the reduction of blood pressure and of blood concentrations of triglycerides.

Intakes of EPA and DHA of about 2-4 g/d are required to obtain the claimed effect on blood triglycerides. Intakes of EPA and DHA of about 3 g/d are required to obtain the claimed effect on blood pressure. The target population is adult men and women.

On the basis of the data available, the Panel concludes that a cause and effect relationship has not been established between the consumption of EPA and DHA (and DPA for ID 511) and the maintenance of normal HDL-cholesterol concentrations, the maintenance of normal LDL-cholesterol concentrations, or the maintenance of normal joints.

**KEY WORDS**

EPA, DHA, DPA, LCPUFA, blood pressure, blood lipids, triglycerides, HDL-cholesterol, LDL-cholesterol, joints, health claims.

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The members of the Claims Sub-Working Group on Bone/Teeth/Connective Tissue: Rikke Andersen, Olivier Bruyère, Albert Flynn, Ingegerd Johansson, Jukka Meurman and Hildegard Przyrembel.

## INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006[3] submitted by Member States contains main entry claims with corresponding conditions of use and literature from similar health claims. The information provided in the consolidated list for the health claims subject to this opinion is tabulated in Appendix C.

## ASSESSMENT

### 1. Characterisation of the food/constituent

The food constituents which are the subject of the health claims are mixed long-chain n-3 polyunsaturated fatty acids (n-3 LCPUFA), namely docosahexaenoic acid (DHA) in combination with eicosapentaenoic acid (EPA) and, for ID 511, with docosapentaenoic acid (DPA).

The n-3 LCPUFA EPA, DHA and DPA are recognised nutrients and are measureable in foods by established methods. They are well absorbed when consumed in the form of triglycerides. This evaluation applies to EPA, DHA and, for ID 511, DPA from all sources with appropriate bioavailability in the specified amounts.

The Panel considers that the food constituents, EPA, DHA and DPA, which are the subject of the health claims are sufficiently characterised.

### 2. Relevance of the claimed effect to human health

#### 2.1. Maintenance of normal blood pressure (ID 502)

The claimed effect is "helps maintain normal blood pressure". The Panel assumes that the target population is the general population.

Blood pressure (BP) is the pressure (force per unit area) exerted by circulating blood on the walls of blood vessels. Elevated BP, by convention above 140 mmHg (systolic) and/or 90 mmHg (diastolic), may compromise the normal structure and function of the arteries.

The Panel considers that maintenance of a normal blood pressure is beneficial to human health.

#### 2.2. Maintenance of normal HDL-cholesterol concentrations (ID 515)

The claimed effect is "HDL (good) cholesterol". The Panel assumes that the target population is the general population.

High-density lipoproteins (HDL) act as cholesterol scavengers and are involved in the reverse transport of cholesterol in the body (from peripheral tissues back to the liver). Conversely, low-density lipoproteins (LDL) carry cholesterol from the liver to peripheral tissues, including the arteries.

The Panel considers that maintenance of normal HDL-cholesterol (without increasing LDL-cholesterol) concentrations is beneficial to human health.

[3] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

### 2.3. Maintenance of normal (fasting) blood concentrations of triglycerides (ID 517)

The claimed effect is "healthy triglyceride levels". The target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect relates to the maintenance of normal (fasting) blood concentrations of triglycerides.

Triglycerides in plasma are either derived from dietary fats or synthesised in the body from other energy sources like carbohydrates. In fasting conditions, serum triglycerides are mainly transported in very-low-density lipoproteins (VLDL) synthesised in the liver. Excess calorie intake with a meal is converted to triglyceride and transported to the adipose tissue for storage. Hormones regulate the release of triglycerides from adipose tissue in order to meet energy needs between meals.

The Panel considers that maintenance of normal (fasting) blood concentrations of triglycerides is beneficial to human health.

### 2.4. Maintenance of normal LDL-cholesterol concentrations (ID 528, 698)

The claimed effect is "blood lipids". The target population is the general population.

In the context of the proposed, the Panel assumes that the claim refers to the maintenance of normal blood triglycerides, LDL- and HDL-cholesterol concentrations.

The maintenance of normal HDL-cholesterol and blood triglyceride concentrations has been addressed in sections 2.2 and 2.3 of this Opinion, respectively.

Low-density lipoproteins (LDL) carry cholesterol from the liver to peripheral tissues, including the arteries. Elevated LDL-cholesterol, by convention >160 mg/dL, may compromise the normal structure and function of the arteries.

The Panel considers that maintenance of normal LDL-cholesterol concentrations is beneficial to human health.

### 2.5. Maintenance of joints (ID 503, 505, 507, 511, 518, 524, 526, 535, 537)

The claimed effects are "joint health" and "immunity maintenance". The Panel assumes that the target population is the general population.

In the context of the proposed wordings the Panel assumes that these claimed effects relate to the maintenance of normal joints.

The Panel considers that maintenance of normal joints is beneficial to human health.

## 3. Scientific substantiation of the claimed effect

### 3.1. Maintenance of normal blood pressure (ID 502)

The background literature provided includes various statements by authoritative bodies that advocate fish intake (1-2 times per week) and/or EPA plus DHA intake (~250-500 mg/day) for the prevention of coronary heart disease. The statements are based on scientific evidence for a beneficial effect of EPA plus DHA on cardiac mortality. None of the statements recommend increased intake of EPA plus DHA for their antihypertensive properties.

The literature presented refers to three meta-analyses (Appel et al., 1993; Morris et al., 1993; Geleijnse et al., 2002), which include two of the individual clinical trials provided (Knapp, 1989; Schmidt, 1992) and all are considered pertinent to the substantiation of the claim.

Appel et al. (1993) conducted a meta-analysis of 17 clinical trials on the effects of dietary n-3 fatty acids (mainly EPA plus DHA) on BP. Systolic BP was significantly reduced in two out of the 11 trials conducted in normotensive subjects, and in two out of the six trials conducted in untreated hypertensive subjects. Pooled estimates for systolic BP were -1.0 mmHg (95% CI: -2.0 to 0.0) in normotensive subjects and -5.5 mmHg (95% CI: -8.1 to -2.9) in hypertensive subjects. Daily doses of n-3 fatty acids were generally high (>3 g in 11 trials).

Morris et al. (1993) performed a meta-analysis of 31 clinical trials investigating the effects of fish oil consumption (mainly EPA plus DHA) on BP. Systolic BP was reduced on average by -3.0 mmHg (95% CI: -4.5 to -1.5). When grouped by EPA plus DHA dose, effects on systolic BP were -1.3 mmHg at ≤ 3 g/d, -2.9 mmHg at 3.3 to 7 g/d, and -8.1 mmHg at 15 g/d. Both EPA and DHA were related to BP response. Systolic BP was not reduced in "healthy" (i.e., normotensive and normocholesterolemic) subjects, i.e. -0.4 mmHg for a mean fish oil dose of 4.2 g per day. Significant BP reductions were found in hypertensive subjects (-3.4 mmHg at 5.6 g/d of EPA plus DHA) and in hypercholesterolaemic patients (-4.4 mmHg at 4.0 g/d of EPA plus DHA).

More recently, Geleijnse et al. (2002) performed a meta-analysis of 36 randomised controlled trials. Daily doses of fish oil (mainly EPA plus DHA) were <1.0 g in one trial, 1.0-1.9 g/d in five trials, 2.0-2.9 g/d in four trials, and 3.0–15.0 g/d in 26 trials, with a median dose of 3.7 g/d. Fish oil reduced systolic BP by -2.1 mmHg (95% CI: -3.2 to -1.0). Restricting the analysis to randomised controlled trials that were double-blind yielded a systolic BP estimate of -1.7 mmHg (95% CI: -3.1 to -0.3). Effects of EPA plus DHA intake on systolic BP were larger in older (>45y of age) subjects (-2.7 mmHg) and in hypertensive subjects (-3.7 mmHg).

Clinical trials on the effects of low doses of EPA plus DHA on BP are lacking. In a recent trial by Murphy et al. (2007), 86 overweight subjects with high serum triglyceride concentrations were randomised to 1 g of EPA plus DHA daily (by means of enriched foods) or placebo, for 6 months. Dietary intervention with EPA plus DHA improved various cardiovascular risk factors, but did not significantly affect BP (Murphy et al., 2007).

Potential mechanisms by which fish oil could reduce BP were described by Howe (1997). The review refers to animal experiments and results from meta-analyses of clinical trials (Appel et al., 1993; Morris et al., 1993). Howe (1997) concluded that there is uncertainty about the antihypertensive effects of EPA and DHA and about underlying mechanisms in animal models. He also stated that the extent of BP reduction depends on the initial BP level and on the dose of very long chain n-3 fatty acids so that clinically significant effects may be expected in hypertensive but not normotensive subjects, given a mean dose of ~3 g of EPA plus DHA per day.

From the evidence provided, the Panel considers that high doses of EPA + DHA (≥3 grams per day) have a short-term effect on systolic BP in subjects with untreated hypertension (~3-5 mmHg decrease in systolic BP; Mancia et al., 2007), and may have smaller, but statistically significant, effects in normotensives (~1 mmHg decrease in systolic BP).

The Panel concludes that a cause and effect relationship has been established between the consumption of EPA and DHA and the reduction of blood pressure.

### 3.2. Maintenance of normal HDL-cholesterol concentrations (ID 515)

The effects of fish oils (mainly EPA plus DHA) on serum lipids and lipoproteins have been studied in numerous clinical trials. Harris (1997) published a meta-analysis of 72 studies with high doses

(2-4 g/d) of EPA and DHA. In another, more recent systematic review 21 studies were included (Balk et al., 2006).

Generally EPA plus DHA at high doses (2-4 g/d) have shown a small HDL-raising effect in subjects with hypertriglyceridaemia. In the meta-analysis by Harris (1997), an increase of 1-3% was observed, accompanied by an increase of 5-10% in LDL cholesterol. Balk et al. (2006) found a small average increase of 1.6 mg/dl in HDL cholesterol and 6 mg/dl in LDL cholesterol. The probable mechanism is increased lipoprotein lipase-mediated conversion of VLDL triglycerides to LDL and HDL-cholesterol (Jacobson, 2008). In subjects with normal triglyceride levels, no effects on serum total, LDL- or HDL-cholesterol are found (Harris, 1997).

The Panel considers that high doses of EPA plus DHA slightly increase HDL-cholesterol concentrations together with LDL-cholesterol concentrations in subjects with hypertriglyceridaemia, but do not affect HDL-cholesterol concentrations in normal subjects.

The Panel concludes that a cause and effect relationship has not been established between the dietary intake of EPA and DHA and the maintenance of normal HDL-cholesterol (without increasing LDL-cholesterol) concentrations.

### 3.3. Maintenance of normal (fasting) blood concentrations of triglycerides (ID 517)

High doses (2-4 g/d) of EPA plus DHA decrease serum triglycerides in both normo- and hyperlipidaemic individuals. The effect is related both to the dose of EPA plus DHA and to the baseline concentrations of triglycerides (Jacobson, 2008). Harris (1997) observed a mean reduction of 35% in subjects with hypertriglyceridaemia and of 24% in those with serum triglycerides < 2 mmol/L. In the meta-analysis by Balk et al. (2006), a mean reduction of 27% in serum triglyceride concentrations was observed. EPA and DHA seem to have similar effects on serum triglycerides (Grimsgaard et al., 1997). The mechanisms that explain the effect include inhibition of triglyceride synthesis, stimulation of fatty acid beta-oxidation, and increased lipoprotein lipase-mediated clearance of VLDL triglycerides (Jacobsen, 2008).

In the diet and lifestyle recommendations by the American Heart Association (AHA), 2-4 g EPA plus DHA per day provided in capsules under physician's supervision are recommended for individuals with hypertriglyceridaemia (Lichtenstein et al., 2006).

The Panel considers that a cause and effect relationship has been established between the consumption of EPA and DHA and the reduction of (fasting) blood concentrations of triglycerides.

### 3.4. Maintenance of normal LDL-cholesterol concentrations (ID 528, 698)

The effects of DHA and EPA on HDL-cholesterol and on blood triglycerides have been already assessed in sections 3.2. and 3.3.

EPA plus DHA at high doses (2-4 g/d) have multiple effects on blood lipids (Jacobson, 2008). Serum total cholesterol concentrations are generally not affected by this supplementation, but in subjects with hypertriglyceridaemia, LDL-cholesterol concentrations may be increased by 5-10% (Harris, 1997, Balk et al., 2006). The results of more recent studies agree with previous findings (Krebs et al., 2006, Hill et al., 2007).

The Panel concludes that a cause and effect relationship has not been established between the consumption of DHA and EPA and the maintenance of normal LDL-cholesterol concentrations.

### 3.5. Maintenance of joints (ID 503, 505, 507, 511, 518, 524, 526, 535, 537)

A total of 18 human intervention studies, 18 reviews, three meta-analyses and six mechanistic studies on the effects of fish oil/n-3 LCPUFA/DHA plus EPA on joint pain, mobility and inflammation in patients with rheumatoid arthritis (RA) were provided. The submitted references also included two reviews on the treatment of RA with drugs and diet (Rennie et al., 2003; Proudman et al., 2007), several publications on the general properties of n-3 LCPUFA, and some review publications in relation to their effects on bone formation, bone resorption, and chondrocyte metabolism (Watkins et al., 2001; Curtis et al., 2002). The Panel notes that the paper by Curtis et al. (2002) has been retracted by the authors four years after its publication (Curtis et al., 2006).

No dietary requirement of n-3 LCPUFA for the maintenance of joint structure (e.g. of cartilage or other connective tissues) or function (e.g. maintenance of flexibility or mobility of the joints) in healthy humans has been demonstrated by the evidence provided.

All human intervention studies, all reviews and the three meta-analyses presented concern patients with clinical diagnosis of acute or chronic RA. Rheumatoid arthritis is a chronic, symmetric, inflammatory, and destructive autoimmune arthropathy affecting the synovial joints with a prevalence of 0.5 to 2.0% in the population and the pathogenesis of which is not fully understood (Gruenwald et al., 2002; Rennie et al., 2003; Ramsbottom and Lockwood, 2006).

The Panel considers that the evidence provided does not establish that patients with clinical diagnosis of RA are representative of the general population with regard to the status of joint tissues, or that results obtained in subjects with RA relating to the treatment of symptoms of the disease (e.g., joint pain, joint swelling, joint stiffness, erosion of joint cartilage) can be extrapolated to the maintenance of structure and function of joints in the general population. Therefore, no conclusions can be drawn from the human studies presented with respect to the maintenance of normal joints in the general population.

The Panel also considers that the evidence provided in the *in vitro* studies submitted does not predict the occurrence of an effect of n-3 LCPUFA EPA, DHA and DPA supplementation on the maintenance of normal joints in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of EPA, DHA and DPA and the maintenance of normal joints.

## 4. Panel's comments on the proposed wording

### 4.1. Maintenance of normal blood pressure (ID 502)

The Panel considers that the following wording reflects the scientific evidence: "DHA and EPA contribute to the maintenance of normal blood pressure".

### 4.2. Maintenance of normal (fasting) blood concentrations of triglycerides (ID 517)

The Panel considers that the following wording reflects the scientific evidence: "DHA and EPA contribute to the maintenance of normal triglyceride concentrations".

## 5. Conditions and possible restrictions of use

### 5.1. Maintenance of normal blood pressure (ID 502)

The Panel considers that intakes of EPA and DHA of about 3 g/d are required to obtain the claimed effect. The target population is adult men and women.

### 5.2. Maintenance of normal (fasting) blood concentrations of triglycerides (ID 517)

The Panel considers that intakes of EPA and DHA of about 2-4 g/d are required to obtain the claimed effect. The target population is adult men and women.

## CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituents, the n-3 LCPUFA EPA, DHA, and DPA, which are the subject of the health claims, are sufficiently characterised.

**Maintenance of normal blood pressure (ID 502)**

- The claimed effect is "helps maintain normal blood pressure". The target population is assumed to be the general population. Maintenance of normal blood pressure is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of EPA and DHA and the reduction of blood pressure.
- The following wording reflects the scientific evidence: "DHA and EPA contribute to the maintenance of normal blood pressure".
- Intakes of EPA and DHA of about 3 g/d are required to obtain the claimed effect. The target population is adult men and women.

**Maintenance of normal HDL-cholesterol concentrations (ID 515)**

- The claimed effect is "HDL (good) cholesterol". The target population is assumed to be the general population. Maintenance of normal HDL-cholesterol (without increasing LDL-cholesterol) concentrations is beneficial to human health.
- A cause and effect relationship has not been established between the consumption of DHA and EPA and the maintenance of normal HDL-cholesterol (without increasing LDL-cholesterol) concentrations.

**Maintenance of (fasting) blood concentrations of triglycerides (ID 517)**

- The claimed effect is "healthy triglyceride levels". The target population is assumed to be the general population. Maintenance of normal blood triglyceride levels is beneficial to human health.
- A cause and effect relationship has been established between the consumption of EPA and DHA and the reduction of (fasting) blood concentrations of triglycerides.

- The following wording reflects the scientific evidence: "DHA and EPA contribute to the maintenance of normal concentrations of triglycerides".

- Intakes of EPA and DHA of 2-4 g/d are required to obtain the claimed effect. The target population is adult men and women.

**Maintenance of normal LDL-cholesterol concentrations (ID 528, 698)**

- The claimed effect is "blood lipids". The target population is assumed to be the general population. Maintenance of normal LDL-cholesterol concentrations is beneficial to human health.

- A cause and effect relationship has not been established between the consumption of EPA and DHA and the maintenance of normal LDL-cholesterol concentrations.

**Maintenance of joints (ID 503, 505, 507, 511, 518, 524, 526, 535, 537)**

- The claimed effects are "joint health" and "immunity maintenance". The target population is assumed to be the general population. Maintenance of normal joints is beneficial to human health.

- A cause and effect relationship has not been established between the consumption of EPA, DHA and DPA and the maintenance of normal joints.

## DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (EFSA-Q-2008-1289, EFSA-Q-2008-1290, EFSA-Q-2008-1292, EFSA-Q-2008-1294, EFSA-Q-2008-1298, EFSA-Q-2008-1302, EFSA-Q-2008-1304, EFSA-Q-2008-1305, EFSA-Q-2008-1311, EFSA-Q-2008-1313, EFSA-Q-2008-1315, EFSA-Q-2008-1322, EFSA-Q-2008-1324, EFSA-Q-2008-1485). The scientific substantiation is based on the information provided by the Members States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: http://www.efsa.europa.eu/panels/nda/claims/article13.htm

## REFERENCES

Adam O, Beringer C, Kless T, Lemmen C , Adam A, Wiseman M, Adam P, Klimmek R, Forth W, 2003. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. Rheumatol. Int. 23, 27-36.

Adam O, 2003. Dietary fatty acids and immune reactions in synovial tissue. Eur. J. Med. Res. 8, 381-387.

Adam O, 1995. Anti-inflammatory diet in rheumatic diseases. Eur. J. Clin. Nutr. 49, 703-717.

Agency for Health Care Research and Quality (US), 2004. Sydne J. Newberry (ed). Effects of Omega-3 Fatty Acids on Lipids and Glycaemic Control in Type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis. Evidence Report/Tech Assessment No. 89. <http://www.ahrq.gov/downloads/pub/evidence/pdf/o3lipid/o3lipid.pdf>

Appel LJ, Miller ER, 3rd, Seidler AJ, Whelton PK, 1993. Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. Arch. Intern. Med. 153, 1429-1438.

Arita M, Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, Yang R, Petasis N A, and Serhan C N, 2005. Stereochemical assignment, anti-inflammatory properties and receptor for omega-3 lipid mediator resolvin E1. J. Exp. Med. 201, 713-722.

Ariza-Ariza R, Mestanza-Peralta M, Cardiel HH, 1998. Omega-3 fatty acids in rheumatoid arthritis: an overview. Semin. Arthritis Rheum. 27, 366-370.

Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chen P, Lau J, 2006. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: A systematic review. Atherosclerosis 189, 19-30.

Bansai S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM, 2007. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA 298, 309-316.

Belch J Ansell D, Madhok R, O'Dowd A, Sturrock R, 1988. Effects of altering dietary essential fatty acids on requirements for non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis: A double-blind, placebo-controlled study. Annals of Rheumatic Diseases 47, 96-104.

Berbert AA, Kondo CR, Almendra CL, Matsuo T, Dichi I, 2005. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition 21, 131-136.

Briel M , Ferreira-Gonzalez I , You J J, Karanicolas P J, Akl E A , Wu P, Blechacz B, Bassler D, Wei X, Sharman A, Whitt I, Alves da Silva S, Khalid Z, Nordmann A J, Zhou Q, Walter S D, Vale N, Bhatnagar N, O'Regan C, Mills E J, Heiner C Bucher, Montori V M, Guyatt G H, 2009. Association between change in high-density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. BMJ 338:b92 doi:10.1136/bmj.b92.

Calder PC, 2006. n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am. J. Clin. Nutr. 83 (suppl), 1505-1519.

Calder PC, Zurier RB, 2001. Polyunsaturated fatty acids and rheumatoid arthritis. Curr. Opin. Clin. Nutr. Metab. Care 4, 115-121.

Calder PC, 2001. n-3 Polyunsaturated fatty acids, inflammation, and immunity. Lipids 36, 1007-1024.

Calder PC, 2002. Dietary modification of inflammation with lipids. Proc. Nutr. Soc. 61, 345-358.

Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA, 2002. Fatty acids and lymphocyte functions. Br. J. Nutr. 87, Suppl 1, S31-48.

Calder PC and Field CJ, 2002. Fatty acids, inflammation and immunity. In: Nutrition and Immune Function. Calder PC, Fields CJ, Gill HS (Eds).CABI Publishing, Wallingford, 57-92.

Calder PC, 2000. The scientific basis for fish oil supplementation in rheumatoid arthritis. In: Food and Nutritional Supplements – Their role in health and disease. Ransley JK, Donnelly JK, Read NW, (Eds). Springer, Berlin, 75-197.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, 2003. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA, 289, 2560-2572.

Cleland LG, Caughey GE, James MJ, Proudman SM, 2006. Reduction of cardiovascular risk factor with longterm fish oil treatment in early rheumatoid arthritis, J. Rheumatol. 33, 1973-1979.

Cleland LG, James MJ, Proudman SM, 2003. The role of fish oils in the treatment of rheumatoid arthritis. Drugs 63, 845-53.

Cleland, LG, French JK, Betts WH, Murphy GA & Elliott MJ, 1988. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. J. Rheumatol. 15, 1471-1475.

Connor WE, 2000. Importance of n-3 fatty acids in health and disease. Am. J. Clin. Nutr. 71 (1 Suppl), 171S-5S.

Curtis CL, Rees SG, Cramp J, Flannery CR, Hughes CE, Little CB, Williams R, Wilson C, Dent CM, Harwood JL, Caterson B, 2002. Effects of n-3 fatty acids on cartilage metabolism. Proc. Nutr. Soc. 61, 381-389.

Curtis CL, Rees SG, Cramp J, Flannery CR, Hughes CE, Little CB, Williams R, Wilson C, Dent CM, Harwood JL, Caterson B, 2006. Notice of retraction. Effects of n-3 fatty acids on cartilage metabolism. Proc. Nutr. Soc. 65, 434.

Desai S, Lockwood B, 2006. Nutraceuticals in joint health. Mode of action, Nutrafoods 5, 20-33.

Din JN, Newby DE, Flapan AD, 2004. Omega 3 fatty acids and cardiovascular disease-fishing for a natural treatment. BMJ 328, 30-35.

EFSA (European Food Safety Authority), 2005. Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the European Parliament related to the Safety of Wild and Farmed Fish. Question No. EFSA-Q-2004-22. The EFSA Journal (2005) 236, 1-118.

Eriksen W, Sandvik L & Bruusgaard D, 1996. Does dietary supplementation of cod liver oil mitigate musculoskeletal pain? Eur. J. Clin. Nutr. 50, 689-693.

Expert Workshop of the European Academy of Nutritional Sciences, 1998. de Deckere EA, Korver O, Verschuren PM, Katan MB. Health aspects of fish and n-3 polyunsaturated fatty acids from plant and marine origin. Eur. J. Clin. Nutr. 52, 749-753.

Fats and oils in human nutrition, 1994. Food and Agriculture Organization and World Health Organization. Report.

Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, Martin A, Andres-Lacueva C, Senin U, Guralnik JM, 2006. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J. Clin. Endocrinol. Metab. 91, 439-446.

Fortin PR, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC, Sperling RI, 1995. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. J. Clin. Epidemiol. 48, 1379-1390.

Fortin PR and Heath CW Jr, 1992. Epidemiologic studies of rheumatoid arthritis: future directions. J. Rheumatol. Suppl. 32, 74-77.

Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ, 2002. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J. Hypertens. 20, 1493-1499.

Geusens P, Wouters D, Nijs J, Jiang Y & Dequeker J, 1994. Long-term effect of omega 3 fatty acid supplementation in active rheumatoid arthritis. Arthritis Rheumatism 37, 824-829.

Goldberg RJ, Katz J, 2007. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 129, 210-223.

Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Op Reimer WS, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Funck-Brentano C, Filippatos G, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Altiner A, Bonora E, Durrington PN, Fagard R, Giampaoli S, Hemingway H, Hakansson J, Kjeldsen SE, Larsen ML, Mancia G, Manolis AJ, Orth-Gomer K, Pedersen T, Rayner M, Ryden L, Sammut M, Schneiderman N, Stalenhoef AF, Tokgözoglu L, Wiklund O, Zampelas A, 2007. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth

Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts), Eur. Heart J. 28, 2375-2414.

Grimsgaard S, Bonaa KH, Hansen JB, Nordoy A, 2007. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. Am. J. Clin. Nutr. 66, 649-659.

Gruenwald J, Graubaum HJ & Harde A, 2002. Effect of cod liver oil on symptoms of rheumatoid arthritis. Advances in Therapy 19, 101-107.

Harris WS, 1997. n-3 Fatty acids and serum lipoproteins: Human studies. Am. J. Clin. Nutr. 65, 1645-1654.

Hill AM, Buckley JD, Murphy KJ, Howe PR, 2007. Combining fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors. Am. J. Clin. Nutr. 85, 1267-1274.

Howe PR, 1997. Dietary fats and hypertension. Focus on fish oil. Ann N Y Acad. Sci. 827, 339-352.

Jacobsen TA, 2008. Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease. Am. J. Clin. Nutr. 87, 1981S-1890S.

James MJ and Cleland LG, 1997. Dietary n-3 fatty acids and therapy for rheumatoid arthritis. Semin. Arthritis Rheum. 27, 85-97.

Jokela R, Engstroem K, Wallin R, Saldeen T, 1998. Effect of in vitro stability of dietary fish oil on lipid peroxidation and prostanoids in vivo. Ups. J. Med. Sci. 103, 213-221.

Kjeldsen-Kragh J, Lund JA, Riise T, Finnanger B, Haaland K, Finstad R, Mikkelsen K, Førre O, 1992. Dietary omega-3 fatty acid supplementation and naproxen treatment in patients with rheumatoid arthritis. J. Rheumatol. 19, 1531-1536.

Knapp HR and FitzGerald GA, 1989. The antihypertensive effects of fish oil. A controlled study of polyunsaturated fatty acid supplements in essential hypertension. N. Engl. J. Med. 320, 1037-1043.

Krebs JD, Browning LM, McLean NK, Rothwell JL, Mishra GD, Moore CS, Jebb SA, 2006. Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the management of cardiovascular disease risk in overweight hyperinsulinaemic women. International Journal of Obesity 30, 1535-1544.

Kremer JM, Jubiz W, Michalek A, Rynes RI, Bartholomew LE, Bigaouette J, Timchalk M, Beeler D, Lininger L, 1987. Fish-oil fatty acid supplementation in active rheumatoid arthritis. A double-blinded, controlled, crossover study. Ann. Intern. Med. 106, 497-503.

Kremer JM, Lawrence DA, Jubiz W, DiGiacomo R, Rynes R, Bartholomew LE, Sherman M, 1990. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. Clinical and immunologic effects. Arthritis Rheum. 33, 810-820.

Kremer JM, Lawrence DA, Petrillo GF, Litts LL, Mullaly PM, Rynes RI, Stocker RP, Parhami N, Greenstein NS, Fuchs BR, Mathur A, Robinson D R, Sperling R I, Bigaouette J, 1995. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. Arthritis Rheum. 38, 1107-1114.

Kremer JM, 2000. n-3 fatty acid supplements in rheumatoid arthritis, Am. J. Clin. Nutr. 71 (suppl), 349S-51S.

Kremer JM, 1996. Effects of modulation of inflammatory and immune parameters in patients with rheumatic and inflammatory disease receiving dietary supplementation of n-3 and n-6 fatty acids. Lipids 31, Suppl, S243-S247.

Kremer J M, Malamood H, Maliakkal B, Rodgers J B, Ross J S, Cooper J A , 1996. Fish oil dietary supplementation for prevention of indomethacin-induced gastric and small bowel toxicity in healthy volunteers. J. Rheumatol. 23, 1770-1773.

Lau CS, Morley KD, Belch JJ, 1993. Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis – a double-blind placebo controlled study, Br. J. Rheumatol. 32, 982-989.

Lau CS, McLaren M, Belch JJ, 1995. Effects of fish oil on plasma fibrinolysis in patients with mild rheumatoid arthritis. Clin. Exp. Rheumatol. 13, 87-90.

Lau CS, 2006. Collateral benefits of fish oil therapy for rheumatoid arthritis. J. Rheumatol. 33, 1931-1933.

Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Summary of American Heart Association Diet and Lifestyle Recommendations Revision 2006. Arterioscler. Thromb. Vasc. Biol. 26, 2186-2191.

Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology, 2007. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J. Hypertens. 25, 1105-1187.

Morris MC, Sacks F, Rosner B, 1993. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 88, 523-533.

Moyad MA, 2005. An introduction to dietary/supplemental omega-3 fatty acids for general health and prevention: part II. Urol. Oncol. 23, 36-48.

Murphy KJ, Meyer BJ, Mori TA, Burke V, Mansour J, Patch CS, Tapsell LC, Noakes M, Clifton PA, Barden A, Puddey IB, Beilin LJ, Howe PR, 2007. Impact of foods enriched with n-3 long-chain polyunsaturated fatty acids on erythrocyte n-3 levels and cardiovascular risk factors. Br. J. Nutr. 97, 749-757.

Navarro E, Esteve M, Olivé A, Klaassen J, Cabré E, Tena X, Fernández-Bañares F, Pastor C, Gassull MA, 2000. Abnormal fatty acid pattern in rheumatoid arthritis. A rationale for treatment with marine and botanical lipids. J. Rheumatol. 27, 298-303.

Nielsen GL, Faarvang KL, Thomsen BS, Teglbjaerg KL, Jensen LT, Hansen TM, Lervang HH, Schmidt EB, Dyerberg J, Ernst E, 1992. The effects of dietary supplementation with n-3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomised, double-blind trial. Eur. J. Clin. Invest. 22, 687-691.

Oh R, 2005. Practical applications of fish oil (Omega-3 fatty acids) in primary care. J. Am. Board Fam. Pract. 18, 28-36.

Pritchett JW, 2006. Statins and Dietary Fish Oils Improve Lipid Composition in Bone Marrow and Joints. Clin. Orthop. Relat. Res. 456, 233-237.

Proudman SM, Keen HI, Stamp LK, Lee AT, Goldblatt F, Ayres OC, Rischmueller M, James MJ, Hill CL, Caughey GE, Cleland LG, 2007. Response-driven combination therapy with conventional

Disease-Modifying Antirheumatic Drugs can achieve high responses rates in early Rheumatoid Arthritis with minimal Glucocorticoid and Nonsteroidal anti-inflammatory drugs use, Semin. Arthritis Rheum. 37, 99-111.

Ramsbottom H, Lockwood B, 2006. Nutraceuticals for healthy joints, The Pharmaceutical Journal 277, 740-746.

Remans PHJ, Sont JK, Wagenaar LW, Woutres-Wesseling W, Zuijderduin WM, Jongma A, Breedveld FC, van Laar JM, 2004. Nutrient supplementation with polyunsaturated fatty acids and micronutrients in rheumatoid arthritis: clinical and biochemical effects. Eur. J. Clin. Nutr. 58, 839-845.

Rennie KL, Hughes J, Lang R and Jebb SA, 2003. Nutritional management of rheumatoid arthritis: a review of the evidence J. Hum. Nutr. Dietet. 16, 97-109.

Schmidt EB, Lervang HH, Varming K, Madsen P, Dyerberg J, 1992. Long-term supplementation with n-3 fatty acids, I: Effect on blood lipids, haemostasis and blood pressure. Scand. J. Clin. Lab. Invest. 52, 221-228.

Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M, Nelson JL, 1996. Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. Epidemiology 7, 256-263.

Skoldstam L, Borjesson O, Kjallman A, Seiving B & Akesson B, 1992. Effects of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. Scand. J. Rheumatol. 21, 178-185.

Sperling RI, Benincaso AI, Knoell CT and Larkin JK, 1993. Dietary n-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils. J. Clin. Invest. 91, 651-660.

Stamp LK, James MJ, Cleland LG, 2005. Diet and rheumatoid arthritis: a review of the literature. Semin. Arthritis Rheum. 35, 77-94.

Stulnig TM, 2003. Immunomodulation by polyunsaturated fatty acids: mechanisms and effects. Int. Arch. Allergy Immunol. 132, 310-321.

Van der Tempel H, Tulleken JE, Linburg JC, Muskiet AJ and Van Rijswijk MH, 1990. Effects of fish oil supplementation in rheumatoid arthritis. Ann. Rheum. Dis. 49, 76-80.

Volker D, Fitzgerald P, Major G,Garg M, 2000. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. J. Rheumatol., 27, 2343-2436.

Watkins BA, Li Y, Lippman HE and Seifert MF, 2001. Omega-3 polyunsaturated fatty acids and skeletal health. Exp. Biol. Med. 226, 485-497.

WHO (World Health Organization), 2003. Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO expert consultation, Geneva 28 January-1 February 2002. WHO Technical Report Series 916.

# APPENDICES

## APPENDIX A

### BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[4] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

### ISSUES THAT NEED TO BE CONSIDERED

#### IMPORTANCE AND PERTINENCE OF THE FOOD[5]

Foods are commonly involved in many different functions[6] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[4] OJ L12, 18/01/2007
[5] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[6] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

### SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

### WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

## TERMS OF REFERENCE

### HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.

- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.

- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.

- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.

- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.

- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

## APPENDIX B

### EFSA DISCAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

## APPENDIX C

Table 1. Main entry health claims related to EPA, DHA and DPA, including conditions of use from similar claims, as proposed in the Consolidated List.

| ID | Food or Food constituent | Health Relationship | Proposed wording |
|---|---|---|---|
| **502** | Long chain Omega 3 fatty acids | Blood pressure - n-3 LC-PUFA cause relaxation in the neighbouring blood vessel to dilate influencing blood pressure | n-3 LC-PUFA help maintain a healthy blood pressure. |
| | **Conditions of use**<br>- Usual consumption as traditional foodstuff in a normal diet. 340mg total Omega 3 fatty acids daily.<br>- 3 to 4 g per day<br>- 0.43g per day (serving - 1/3 to 1/4 of this)<br>- Tagesdosis > 300 mg Omega-3-Fettsäuren<br>- Food supplement with 450-900 mg of EPA and 200-400 mg of DHA in the daily dose.<br>- Food supplement with 0.5-1.2 g of omega-3 fatty acids in the daily dose.<br>- the quantity of EPA+DHA in the daily diet should be of 200-500 mg. The product shall contain a significant amount of n-3 PUFA compared to the recommended daily allowance. The product shall comply with the conditions of nutrition claim „Source/high omega-3 fatty acids".<br>- 30 Gramm (g). Angenommene durchschnittliche Verzehrsmenge an Rapsspeiseöl pro Tag/entspricht ca. drei Esslöffeln. Entspricht einer täglichen Aufnahme von 2,88 g Omega-3-Fettsäuren durch 30 g Rapsspeiseöl pro Tag | | |
| **503** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Omega-3 fatty acids, DHA/EPA, Marine oils such as fish oil, cod liver oil containing DHA and EPA | Joint health | Helps maintain mobility and flexibility of joints/helps diminish morning stiffness in joints/ helps maintain healthy, flexible, mobile and supple joints |
| | **Conditions of use**<br>- 125-500 mg EPA/DHA Jugendliche, Erwachsene | | |
| **505** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Marine oils such as cod liver oil and fish oil containing eicosapentaenoic acid (EPA : C20:5 n-3) + docosahexaenoic acid (DHA; C22:6 n-3) or long-chain n-3 (omega 3) polyunsaturated fatty acids (LC n-3 PUFA, LC omega 3 PUFA) or 'Omega 3' | Joint health | Long-chain Omega 3 polyunsaturated fatty acids help maintain healthy, flexible, mobile and supple joints |

| | | | |
|---|---|---|---|
| | **Conditions of use**<br>- Up to 2800 mg LC omega-3 PUFA/day | | |
| **507** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Fish oil, omega 3 fatty acids | Joint health | Helps maintain joint mobility and flexibility. Helps diminish morning stiffness in joints. |
| | **Conditions of use**<br>- Min. 2 g DHA and/or EPA daily , min 2.6 g fish oil daily | | |
| **511** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Long chain Omega 3 fatty acids (EPA/DPA/DHA) | Joint health | Helps maintain supple and flexible joints |
| | **Conditions of use**<br>- No conditions of use provided | | |
| **515** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Long chain omega-3 fatty acids EPA and DHA | HDL (good) cholesterol | Long-chain omega-3 fatty acids EPA and DHA help maintain healthy levels of good cholesterol. Normal levels of good cholesterol are important for keeping your heart and blood vessels healthy. Long-chain omega-3 fatty acids EPA and DHA help maintain normal cholesterol levels. |
| | **Conditions of use**<br>- The effective dose required to maintain healthy HDL cholesterol levels is estimated to be 500 mg n-3 LC-PUFAs per day. To carry the claim, a product should contain =30 mg n-3 LC-PUFAs per 100 g or 100 kcal, in accordance with the Update of the ANNEX of the Regulation 1924/2006 (eg., 1% or 2% DHA milk provides ?40 mg DHA per 100 g and 77 mg DHA per 100 kcal, and so would qualify to carry the claim). | | |
| **517** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Long chain omega-3 fatty acids EPA and DHA | Healthy triglyceride levels | Long-chain omega-3 fatty acids EPA and DHA help maintain healthy blood triglyceride levels. Normal triglyceride levels are important for keeping your heart and blood vessels healthy. Long-chain omega-3 fatty acids help maintain normal blood triglycerides |

| | | | |
|---|---|---|---|
| | **Conditions of use**<br>- DHA/EPA Jugendliche, Erwachsene 125 – 500 mg<br>- >1.5g per day (BNF CVD 2005 p.217) min 10% fat (product basis), min 70% UFA (fat basis), mex 2% TFA (fat basis) and 3 to 4 g per day VLC omega 3 (EDA)<br>- > 1.5g per day<br>- General population. Minimum 15% RDI per 100g or 100kcal (RDI for EPA+DHA assumed as 200mg/day)<br>- The effective dose required to maintain healthy triglyceride levels is estimated to be 500 mg n-3 LC-PUFAs per day. To carry the claim, a product should contain =30 mg n-3 LC-PUFAs per 100 g or 100 kcal, in accordance with the Update of the ANNEX of the Regulation 1924/2006 (e.g., 1% or 2% DHA milk provides ?40 mg DHA per 100 g and 77 mg DHA per 100 kcal, and so would qualify to carry the claim).<br>- Salmon - Salmon oil - Fish oil - Daily amount of fish oil corresponding to a daily intake of 300 to 500 mg EPA+DHA Up to 3 g/d of marine omega-3 fatty acids | | |
| **518** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Long Chain Fatty Acids (EPA/DHA) | Joint Mobility | Long tradition of use in helping joint mobility. Renowned for helping maintain Joint Mobility and Flexibility |
| | **Conditions of use**<br>- 5-10 ml per day | | |
| **524** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Omega-3 fish body oil-PUFAs | Immunity maintenance and joint care | Involved in the immune system May help maintain a healthy immune system May help maintain healthy joints Joint care |
| | **Conditions of use**<br>- Usual consumption as traditional foodstuff in a normal diet. 340mg total Omega 3 fatty acids daily | | |
| **526** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Omega-3 stable fish body oil | Joint health | Natural stable omega-3 fatty acids help to maintain supple joints. Natural stable omega-3 fatty acids help manage anti-inflammatory responses. |
| | **Conditions of use**<br>- Approx 2:1 ratio EPA/DHA 130mg/kg of stabilised omega-3 fish oil from the flesh of the fish and not the liver. | | |

| | | | |
|---|---|---|---|
| **528** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Fish oils / Omega 3 fatty acids | Blood lipids | Fish oils / Omega-3 oils from fish / EPA and DHA may help to control / regulate blood lipids / lipid profile Fish oils / Omega-3 oils from fish / EPA and DHA help support a healthy heart |
| | **Conditions of use**<br>- 2-5 g/ d<br>- 1600mg of oils, corresponding to : - 242 mg of EPA - 161 mg of DHA per day | | |
| **535** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Omega-3 stable fish body oil | Joint health | Natural stable omega-3 fatty acids help to maintain supple joints. Natural stable omega-3 fatty acids help manage anti-inflammatory responses. |
| | **Conditions of use**<br>- Minimum 3g fish oil/day equal to on average 960 mg EPA and 660 mg DHA/day<br>- 125-500 mg EPA/DHA Jugendliche, Erwachsene | | |
| **537** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | EPA and DHA Omega-3 fatty acids | Joint health | Omega-3 EPA and DHA help maintain healthy joints |
| | **Conditions of use**<br>- Food supplement with 500-3000 mg of fish oil omega-3-fatty acids (EPA and DHA) in the daily dose.<br>- General population. Minimum 15% RDI per 100g or 100kcal (RDI for EPA+DHA assumed as 200mg/day)<br>- General population | | |
| **698** | **Food or Food constituent** | **Health Relationship** | **Proposed wording** |
| | Fish oils / Omega 3 fatty acids | Blood lipids | Fish oils / Omega-3 oils from fish / EPA and DHA may help to control / regulate blood lipids / lipid profile Fish oils / Omega-3 oils from fish / EPA and DHA help support a healthy heart |
| | **Conditions of use**<br>- Adults: typical dosage should be 300-500 mg of fish-derived Omega-3 oils daily (as per WHO recommendations), typically comprised of around an approximate 60:40 ratio EPA:DHA.<br>- Salmon - Salmon oil - Fish oil - Daily amount of fish oil corresponding to a daily intake of 300 to 500 mg EPA+DHA. Up to 3 g/d of marine omega-3 fatty acids | | |

## GLOSSARY / ABBREVIATIONS

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|---|---|
| BP | Blood pressure |
| DHA | Docosahexaenoic acid |
| DPA | Docosapentaenoic acid |
| EPA | Eicosapentaenoic acid |
| HDL | High-density lipoproteins |
| LCPUFA | Long-chain polyunsaturated fatty acids |
| LDL | Low-density lipoproteins |
| VLDL | Very-low-density lipoproteins |