



## NATURAL HEALTH PRODUCT

### FISH OIL

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

There are many *N*-3 polyunsaturated fatty acids, popularly known as omega-3 acids/ $\omega$ -3 fatty acids (Ph.Eur. 2012). This monograph is specific to eicosapentaenoic acid (C20:5 n-3; EPA) and docosahexaenoic acid (C22:6 n-3; DHA).

#### Notes

- ▶ Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant’s discretion.
- ▶ The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

#### Date

September 25, 2018

#### Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)	
		Organism group(s)	Part(s)
Fish oil	Fish oil	<ul style="list-style-type: none"> <li>▶ Ammodytidae</li> <li>▶ Carangidae</li> <li>▶ Clupeidae</li> <li>▶ Engraulidae</li> <li>▶ Osmeridae</li> <li>▶ Salmonidae</li> <li>▶ Scombridae</li> </ul>	Whole

References: Proper name: BP 2012, Ph.Eur. 2012; Common name: BP 2012, Ph.Eur. 2012; Source materials: Froese and Pauly 2018, BP 2012, Ph.Eur. 2012, Froese and Pauly 2011, Martindale 2011.

#### Route of administration

Oral

## Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

### Acceptable dosage forms by age group:

**Children 1-2 years:** The acceptable dosage forms are limited to emulsion/suspension and solution/liquid preparations (Giacoaia et al. 2008; EMEA/CHMP 2006).

**Children 3-5 years:** The acceptable dosage forms are limited to chewables, emulsion/suspension, powders and solution/liquid preparations (Giacoaia et al. 2008; EMEA/CHMP 2006).

**Children 6-11 years, Adolescents 12-17 years, and Adults 18 years and older:** The acceptable dosage forms for this age category and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

## Use(s) or Purpose(s)

*Products providing 100-5,000 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), per day*

- ▶ Source of omega-3 fatty acids for the maintenance of good health (EFSA 2012; Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999).
- ▶ Source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (EFSA 2012; Simopoulos 2007; Oh 2005; IOM 2002; Simopoulos 1999) for the maintenance of good health

*Products providing 100-5,000 mg EPA and DHA including at least 100 mg DHA, per day*

Helps support cognitive health and/or brain function (EFSA 2012; van de Rest et al. 2008; Freund-Levi et al. 2006; Fontani et al. 2005a,b; Haag 2003; Morris et al. 2003; IOM 2002).

*Products providing 150-2,000 mg EPA and DHA including at least 150 mg DHA, per day (maximum doses of EPA + DHA in Table 2 below will apply)*

Helps support (healthy) development of brain/(and), eyes/(and) nerves in children up to 12 years of age (Marszalek and Lodish 2005; Haag 2003; IOM 2002; Giedd et al. 1999; Mills 1999).

*Products providing 200-5,000 mg EPA and DHA, per day and containing a ratio of EPA:DHA between 0.5:1 and 2:1*

Helps maintain/support cardiovascular health (EFSA 2012; Oh 2005; Wang et al. 2004; Leaf et al. 2003; Kris-Etherton et al. 2002).

*Products providing 1,000-5,000 mg EPA and DHA, per day and containing a ratio of EPA:DHA between 0.5:1 and 2:1*

- ▶ Helps to reduce serum triglycerides/triacylglycerols (EFSA 2012; Oh 2005; Balk et al. 2004; Hooper et al. 2004; Nilsen et al. 2001; Sirtori et al. 1998).
- ▶ Helps to reduce serum triglycerides and maintain/support cardiovascular health (EFSA 2012; Oh 2005; Balk et al. 2004; Hooper et al. 2004; Wang et al. 2004; Leaf et al. 2003; Kris-Etherton et al. 2002; Nilsen et al. 2001; Sirtori et al. 1998).

*Products providing 2,800-5,000 mg EPA and DHA, per day and containing a ratio of EPA:DHA between 0.5:1 and 2:1*

In conjunction with conventional therapy, helps to reduce the pain of rheumatoid arthritis in adults (EFSA 2012; Volker et al. 2000; Sköldstam et al. 1992).

*Products providing 1,500-5,000 mg EPA and DHA including at least 1000 mg EPA, per day and a ratio of EPA:DHA between 1.75:1 and 2:1*

Helps to promote healthy mood balance (EFSA 2012; Nemets et al. 2006; Sontrop and Campbell 2006; Fontani et al. 2005a,b; Zanarini and Frankenburg 2003; Peet and Horrobin 2002; Stoll et al. 1999).

## **Dose(s)**

### **Subpopulation(s)**

As specified below.

### **Quantity(ies)**

Method of preparation: Standardized fixed oil

Potency must be expressed as the quantity (milligrams) and/or percent (%) of EPA and DHA (% w/w) relative to the total quantity of fish oil.

Table 2. Daily dose for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in fish oil.

Subpopulation(s)		EPA + DHA (mg/day)	
		Minimum <sup>1</sup>	Maximum <sup>2</sup>
Children	1-8 years	100	1,500
	9-11 years	100	2,000
Adolescents	12-13 years	100	2,000
	14-17 years	100	2,500
Adults <sup>3</sup>	18 years	100	2,500
	19 years and older	100	5,000

<sup>1</sup> Restrictions to minimum dose may apply according to Use(s) or Purpose(s) section above.

<sup>2</sup> Adult maximum dose is supported by US FDA 1997. Children and adolescent maximum doses are calculated as a fraction of the adult dose, are relative to body weight and caloric intake.

<sup>3</sup> Includes pregnant and breastfeeding women.

### Direction(s) for use

No statement required.

### Duration(s) of use

No statement required.

### Risk information

#### Caution(s) and warning(s)

No statement required.

#### Contraindication(s)

No statement required.

#### Known adverse reaction(s)

No statement required.

## Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

## Storage conditions

### *All products*

Store in airtight container, protected from light (Ph.Eur. 2012; USP 35 2012).

### *All products, except those encapsulated*

Refrigerate after opening (Wille and Gonus 1989).

## Specifications

- ▶ The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- ▶ The medicinal ingredient must comply with the requirements outlined in the NHPID.
- ▶ Peroxide, anisidine, and totox values of fish oil and omega-3 fatty acids derived from fish oil must be in accordance with the methods set out by the Association of Analytical Community (AOAC) and/or Pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the fish oil and the omega-3 fatty acids from fish oil (HC 2015). The maximum peroxide value (PV) must be 5 mEq/kg, the maximum anisidine value (AV) must be 20 while the maximum Totox value must be 26 (calculated as  $2 \times PV + AV$ ).
- ▶ The dioxins, polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs); the dioxin-like polychlorinated biphenyls (DL PCBs); and the polychlorinated biphenyls (PCBs) are contaminants in oils from marine sources. Testing for these contaminants is required. Testing should be performed using appropriate analytical methods, such as method No. 1613 revision B of the Environmental Protection Agency for PCDDs and PCDFs and method No. 1668B of the Environmental Protection Agency for chlorinated biphenyl congeners (Ph. Eur: EPA 2008; EPA 1994). Licence holders are advised to consult the Commission of the European Communities documents on dioxins and dioxin-like PCB contaminants in marine oil for further information (EU 2006a,b; EU 2001). Refer to Section 3.3.8 of the Quality of Natural Health Products Guide for more information on the acceptable limits of dioxins and dioxin-like PCBs.



## References cited

- Balk E, Chung M, Lichtenstein A, Chew P, Kupelnick B, Lawrence A, DeVine D, Lau J. 2004 Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease. Summary, Evidence Report/Technology Assessment No. 93. AHRQ Publication No. 04-E010-1. Rockville (MD): Agency for Healthcare Research and Quality.
- BP 2012: British Pharmacopoeia 2012. London (GB): The Stationary Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA); 2012.
- EFSA 2012: European Food Safety Authority. Scientific Opinion: Scientific opinion on the tolerable upper intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). EFSA Journal 2012;10(7):2815. [Internet]. [Accessed 2018 July 11]. Available from: <http://www.efsa.europa.eu/en/efsajournal/doc/2815.pdf>
- EMA/CHMP 2006: European Medicines Agency: Pre-authorization Evaluation of Medicines for Human Use. Committee for Medicinal Products for Human Use. Reflection Paper: Formulations of choice for the paediatric population.[Accessed 2018 June 1]. Available from:
- EU 2011: European Commission. Commission Regulation (EU) No 1259/2011 of 2 December 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for dioxins, dioxinlike PCBs and non dioxin-like PCBs in foodstuffs. Official Journal of the European Union L 320/18 3.12.2011 [Internet]. [Accessed 2018 July 11]. Available from: <http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:320:0018:0023:EN:PDF>
- Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. 2005a. Cognitive and physiological effects of omega-3 polyunsaturated fatty acid supplementation in healthy subjects. European Journal of Clinical Investigation 35(11):691-699.
- Fontani G, Corradeschi F, Felici A, Alfatti F, Bugarini R, Fiaschi AI, Cerretani D, Montorfano G, Rizzo AM, Berra B. 2005b. Blood profiles, body fat and mood state in healthy subjects on different diets supplemented with omega-3 polyunsaturated fatty acids. European Journal of Clinical Investigation 35(8):499-507.
- Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. 2006.  $\omega$ -3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: omegAD study. Archives of Neurology 63(10):1402-1408.
- Froese R, Pauly D, editors. 2018. FishBase: A Global Information System on Fishes. [Internet]. Penang (MY): WorldFish Center. [Accessed 2018 July 11]. Available from: <http://www.fishbase.org>

Giacoa GP, Taylor-Zapata P, Mattison D. Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Formulation Initiative: selected reports from working groups. *Clinical Therapeutics* 2008; 30(11):2097-2101.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. 1999. Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience* 2(10):861-863.

Haag M. 2003. Essential fatty acids and the brain. *The Canadian Journal of Psychiatry* 48(3):195-203.

HC 2015: Health Canada. Quality of Natural Health Products Guide. Version 3.1 [Internet]. Ottawa (ON): Natural Health Products Directorate, Health Canada. [Accessed 2018 July 11]. Available from: [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/pdf/prodnatur/legislation/docs/eq-paq-eng.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodnatur/legislation/docs/eq-paq-eng.pdf)

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Moore H, Worthington HV, Durrington PN, Ness AR, Capps NE, Davey Smith G, Riemersma RA, Ebrahim SBJ. 2004. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. *Cochrane Database of Systematic Reviews* Issue 4. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub2.

IOM 2002: Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board, Institute of Medicine. 2002. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington (DC): The National Academies Press.

Kris-Etherton PM, Harris WS, Appel LJ, American Heart Association Nutrition Committee. 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106(21):2747-2757.

Leaf A, Kang JX, Xiao YF, Billman GE. 2003. Clinical prevention of sudden cardiac death by n3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 107(21):2646-2652.

Marszalek JR, Lodish HF. 2005. Docosahexaenoic acid, fatty acid-interacting protein, and neuronal function: breastmilk and fish are good for you. *Annual Review of Cell and Developmental Biology* 21:633-657.

Martindale 2011: Sweetman SC, editor. Martindale: The Complete Drug Reference. [Internet]. London (GB): Pharmaceutical Press. [Omega-3 Fatty Acids latest modification: 04-Nov-2011; Accessed 2018 July 11]. Available from: <http://www.medicinescomplete.com>

- Mills MD. 1999. The eye in childhood. *American Family Physician* 60(3):907-918.
- Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. 2003. Consumption of fish and n-3 fatty acid and risk of incident alzheimer disease. *Archives of Neurology* 60(7):940-946.
- Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. 2006. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *The American Journal of Psychiatry* 163(6):1098-1100.
- Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. 2001. Effects of a highdose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *The American Journal of Clinical Nutrition* 74(1):50-56.
- Oh R. 2005. Practical applications of fish oil ( $\Omega$ -3 fatty acids) in primary care. *The Journal of the American Board of Family Practice* 18(1):28-36.
- Peet M, Horrobin DF. 2002. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives of General Psychiatry* 59(10):913-919.
- Ph.Eur. 2012: European Pharmacopoeia. 8<sup>th</sup> edition. Strasbourg (FR): Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM), 2012.
- Simopoulos AP. 2007. Omega-3 fatty acids and athletics. *Current Sports Medicine Reports* 6(4):230-236.
- Simopoulos AP. 1999. Essential fatty acids in health and chronic disease. *The American Journal of Clinical Nutrition* 70(Suppl 3):560S-569S.
- Sirtori CR, Crepaldi G, Manzato E, Mancini M, Rivellesse A, Paoletti R, Pazzucconi F, Pamparana F, Stragliotto E. 1998. One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance: reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations. *Atherosclerosis* 137(2):419-427.
- Sköldstam L, Börjesson O, Kjällman A, Seiving B, Akesson B. 1992. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. *Scandinavian Journal of Rheumatology* 21(4):178-185.
- Sontrop J, Campbell MK. 2006.  $\omega$ -3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. *Preventative Medicine* 42(1):4-13.



Stoll AL, Locke CA, Marangell LB, Severus WE. 1999. Omega-3 fatty acids and bipolar disorder: a review. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 60(5-6):329-337.

US FDA 1997: United States Food and Drug Administration. 21 CFR 184 Substances Affirmed as Generally Recognized as Safe: Menhaden Oil [Internet]. Washington (DC): Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2018 July 11]. Available from: <https://www.federalregister.gov/documents/2004/01/15/04-811/substances-affirmed-as-generally-recognized-as-safe-menhaden-oil>

USP 35 2012: United States Pharmacopeia and the National Formulary (USP 35 - NF 30). Rockville (MD): The United States Pharmacopeial Convention; 2012.

van de Rest O, Geleijnse JM, Kok JF, van Staveren WA, Dullemeijer C, OldeRikkert MGM, Beekman ATF, de Groot CPGM. 2008. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. *Neurology* 71(6):430-438.

Volker D, Fitzgerald P, Major G, Garg M. 2000. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *The Journal of Rheumatology* 27(10):2343-2346.

Wang C, Chung M, Balk E, Kupelnick B, DeVine D, Lawrence A, Lichtenstein A, Lau J. 2004. Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Summary, Evidence Report/Technology Assessment No. 94. AHRQ No. 04-E009-2. Rockville (MD): Agency for Healthcare Research and Quality.

WHO 2005: World Health Organization. 2005 Re-evaluation of human and mammalian toxic equivalency factors (TEFs). [Last updated 2011 November 16; Accessed 2018 July 11]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/16829543>

Wille HJ, Gonus P. 1989. Preparation of Fish Oil for Dietary Applications. In: Galli C, Simopolous AP, editors. *Dietary  $\omega$ 3 and  $\omega$ 6 Fatty Acids. Biological Effects and Nutritional Essentiality*. New York (NY): Plenum Press.

Zanarini MC, Frankenburg FR. 2003. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *The American Journal of Psychiatry* 160(1):167-169.

## References reviewed

Ackman RG. 1992. The absorption of fish oils and concentrates. *Lipids* 27(11):858-862.

Addis PB. 1990. Fish oil and your health [Internet]. Duluth (MN): Minnesota Sea Grant Research and Education. [Accessed 2012 January 30]. Available from: <http://www.seagrants.umn.edu/downloads/f9.pdf>



Aggett PJ, Antoine JM, Asp NG, Bellisle F, Contor L, Cummings JH, Howlett J, Müller DJ, Persin C, Pijls LT, Rechkemmer G, Tuijelaars S, Verhagen H. 2005. PASSCLAIM: consensus on criteria. *European Journal of Nutrition* 44(Suppl 1):i5-i30.

Agostini C, Massetto N, Biasucci G, Rottoli A, Bonvissuto M, Bruzzese MG, Giovannini M, Riva E. 2000. Effects of long-chain polyunsaturated fatty acid supplementation on fatty acid status and visual function in treated children with hyperphenylalaninemia. *Journal of Pediatrics* 137(4):504-509.

Ahmed AA, Holub BJ. 1984. Alteration and recovery of bleeding times, platelet aggregation and fatty acid composition of individual phospholipids in platelets of human subjects receiving a supplement of cod liver oil. *Lipids* 19(8):617-624.

Allen KG, Harris MA. 2001. The role of n-3 fatty acids in gestation and parturition. *Experimental Biology and Medicine* 226(6):498-506.

Angerer P, Kothny W, Störk S, von Schacky C. 2002. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovascular Research* 54(1):183-190.

Annuzzi G, Rivellesse A, Capaldo B, Di Marino L, Iovine C, Marotta G, Riccardi G. 1991. A controlled study on the effects of n-3 fatty acids on lipid and glucose metabolism in non-insulindependent diabetic patients. *Atherosclerosis* 87(1):65-73.

Appel LJ, Miller ER, Seidler AJ, Whelton PK. 1993. Does supplementation of diet with 'fish oil' reduce blood pressure? *Archives of Internal Medicine* 153(12):1429-1438.

Bairati I, Roy L, Meyer F. 1992. Effects of a fish oil supplement on blood pressure and serum lipids in patients treated for coronary artery disease. *The Canadian Journal of Cardiology* 8(1):41-46.

Beblo S, Reinhardt H, Demmelmair H, Muntau A, Koletzko B. 2007. Effects of fish oil supplementation on fatty acid status, coordination, and fine motor skills in children with phenylketonuria. *Journal of Pediatrics* 150(5):479-484.

Beblo S, Reinhardt H, Muntau AC, Mueller-Felber W, Roscher AA, Koletzko B. 2001. Fish oil supplementation improves visual evoked potentials in children with phenylketonuria. *Neurology* 57(8):1488-1491.

Bender NK, Kraynak MA, Chiquette E, Linn WD, Clark GM, Bussey HI. 1998. Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. *Journal of Thrombosis and Thrombolysis* 5(3):257-261.

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(2):131-136.

Birberg-Thornberg U, Karlsson T, Gustafsson PA, Duchon K. 2006. Nutrition and theory of mind – the role of polyunsaturated fatty acids (PUFA) in the development of theory of mind. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 75(1):33-41.

Birch EE, Castaneda YS, Wheaton DH, Birch DG, Uauy RD, Hoffman DR. 2005. Visual maturation of term infants fed long-chain polyunsaturated fatty-acid supplemented or control formula for 12 mo. *The American Journal of Clinical Nutrition* 81(4):871-879.

Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. 2000. A randomized controlled trial of early long-chain polyunsaturated fatty acids and mental development in term infants. *Developmental Medicine and Child Neurology* 42(3):174-181.

Birch EE, Hoffman DR, Castañeda YS, Fawcett SL, Birch DG, Uauy RD. 2002. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. *The American Journal of Clinical Nutrition* 75(3):570-580.

Blonk MC, Bilo HJ, Nauta JJ, Popp-Snijders C, Mulder C, Donker AJ. 1990. Dose-response effects of fish-oil supplementation in healthy volunteers. *The American Journal of Clinical Nutrition* 52(1):120-127.

Børnaa KH, Bjerve KS, Nordøy A. 1992. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. *Arteriosclerosis and Thrombosis* 12(6):675-681.

Bonnema SJ, Jespersen LT, Marving J, Gregersen G. 1995. Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. *Diabetes, Nutrition & Metabolism* 8(2):81-87.

Bourre JM. 2006. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. *Journal of Nutritional Health and Aging* 10(5):386-399.

Brinker F. 2010. Final updates and additions for Herb Contraindications and Drug Interactions, 3rd edition. including extensive Appendices addressing common problematic conditions, medications and nutritional supplements, and influences on Phase I, II & III metabolism with new appendix on botanicals as complementary adjuncts with drugs. [Internet]. Sandy (OR): Eclectic Medical Publications. [Updated July 13, 2010; Accessed 2012 January 30]. Available from: <http://www.eclecticherb.com/emp/updatesHCIDI.html>

Brinker F. 2001. Herb Contraindication and Drug Interactions. 3<sup>rd</sup> edition. Sandy (OR): Eclectic Medical Publications.

- Buckley MS, Goff AD, Knapp WE. 2004. Fish oil interaction with warfarin. *Annals of Pharmacotherapy* 38(1):50-53.
- Buckley R, Shewring B, Turner R, Yaqoob P, Minihaue AM. 2004. Circulating triacylglycerol and apoE levels in response to EPA and docosahexaenoic acid supplementation in adult human subjects. *The British Journal of Nutrition* 92(3):477-483.
- Burgess JR, Stevens L, Zhang W, Peck L. 2000. Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *The American Journal of Clinical Nutrition* 71(Suppl 1):327S-30S.
- Cairns JA, Gill J, Morton B, Roberts R, Gent M, Hirsh J, Holder D, Finnie K, Marquis JF, Naqvi S, Cohen E. 1996. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study. *Circulation* 94(7):1553-1560.
- Calder PC. 2004. n-3 fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clinical Science* 107(1):1-11.
- Calder PC. 2006. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *The American Journal of Clinical Nutrition* 83(Suppl 6):1505S-1519S.
- Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, Santini M. 2005. N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *Journal of the American College of Cardiology* 45(10):1723-1728.
- Calon F, Lim GP, Yang F, Morihara T, Teter B, Ubeda O, Rostaing P, Triller A, Salem N Jr, Ashe KH, Frautschy SA, Cole GM. 2004. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron* 43(5):596-599.
- Carlson SE. 1996. Arachidonic acid status of human infants: influence of gestational age at birth and diets with very long chain n-3 and n-6 fatty acids. *The Journal of Nutrition* 126(Suppl 4):1092S-1098S.
- Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. 1993. Arachidonic acid status correlates with first year growth in preterm infants. *Proceedings of the National Academy of Sciences* 90(3):1073-1077.
- Carroll DN, Roth MT. 2002. Evidence for the cardioprotective effects of omega-3 fatty acids. *The Annals of Pharmacotherapy* 36(12):1950-1956.



Cazzola R, Russo-Volpe S, Miles EA, Rees D, Banerjee T, Roynette CE, Wells SJ, Goua M, Wahle KW, Calder PC, Cestaro B. 2007. Age- and dose-dependent effects of an eicosapentaenoic acid-rich oil on cardiovascular risk factors in healthy male subjects. *Atherosclerosis* 193(1):159-167.

Chee KM, Gong JX, Rees DM, Meydani M, Ausman L, Johnson J, Siguel EN, Schaefer EJ. 1990. Fatty acid content of marine oil capsules. *Lipids* 25(9):523-528.

Cleary MA, Feillet F, White FJ, Vidailhet M, MacDonald A, Grimsley A, Maurin N, Ogier de Baulny H, Rutherford PJ. 2006. Randomised controlled trial of essential fatty acid supplementation in phenylketonuria. *European Journal of Clinical Nutrition* 60(7):915-920.

Cleland LG, French JK, Betts WH, Murphy GA, Elliot MJ. 1988. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. *The Journal of Rheumatology* 15(10):1471-1475.

Colter AL, Cutler C, Meckling KA. 2008. Fatty acid status and behavioural symptoms of attention deficit hyperactivity disorder in adolescents: a case-control study. *Nutrition Journal* 7:8.

Commission of the European Communities. Commission Regulation (EC) No 1883/2006 of 19 December 2006 laying down the methods of sampling and analysis for the official control of levels of dioxins and dioxin-like PCBs in certain foodstuffs. *Official Journal of the European Union* L 364/32 20.12.2006 [Internet]. [Accessed 2012 March 23]. Available from: <http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:364:0032:0043:EN:PDF>

Commission of the European Communities. Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Union* L 364/5 20.12.2006 [Internet]. [Accessed 2012 March 23]. Available from: <http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:364:0005:0024:EN:PDF>

Commission of the European Communities. Commission Regulation (EC) No 199/2006 of 3 February 2006 amending Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs as regards dioxins and dioxin-like PCBs. *Official Journal of the European Union* L 32/34 4.2.2006 [Internet]. [Accessed 2012 January 30]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:032:0034:0038:EN:PDF>

Commission of the European Communities. Commission Directive 2004/44/EC of 13 April 2004 amending Directive 2002/69/EC laying down the sampling methods and the methods of analysis for the official control of dioxins and the determination of dioxin-like PCBs in foodstuffs. *Official Journal of the European Union* L 113/17 20.4.2004 [Internet]. [Accessed 2012 January 30]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:209:0005:0014:EN:PDF>

Commission of the European Communities. Commission Regulation (EC) No 466/2001 of 8 March 2001 setting maximum levels for certain contaminants in foodstuffs. Official Journal of the European Union L 77/1 16.3.2001 [Internet]. [Accessed 2012 January 30]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:077:0001:0013:EN:PDF>

Council of the European Union. Commission Regulation (EC) No 2375/2001 of 29 November 2001 amending Regulation (EC) No 466/2001 setting maximum levels for certain contaminants in foodstuffs. Official Journal of the European Communities L 321/1 6.12.2001 [Internet]. [Accessed 2012 January 30]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:321:0001:0005:EN:PDF>

Conklin SM, Gianaros PJ, Brown SM, Yao JK, Hariri AR, Manuck SB, Muldoon MF. 2007. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neuroscience Letter* 421(3):209-212.

Connor WE, DeFrancesco CA, Connor SL. 1993. N-3 fatty acids from fish oil. Effects on plasma lipoproteins and hypertriglyceridemic patients. *Annals of the New York Academy of Sciences* 683:16-34.

Connor WE, Prince MJ, Ullmann D, Riddle M, Hatcher L, Smith FE, Wilson D. 1993. The hypotriglyceridemic effect of fish oil in adult-onset diabetes without adverse glucose control. *Annals of the New York Academy of Science* 683:337-340.

Council for Responsible Nutrition. March 2006. VOLUNTARY MONOGRAPH for Omega-3 DHA, Omega-3 EPA, Omega-3 DHA & EPA. [Accessed 2012 January 30]. Available at: <http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf>

Cunnane S, Drevon CA, Harris B, Sinclair A, Spector A. 2004. Recommendations for intake of polyunsaturated fatty acids in healthy adults [Internet]. Devon (GB): International Society for the Study of Fatty Acids and Lipids. [Accessed 2012 January 30]. Available from: <http://www.issfal.org/news-links/resources/publications/PUFAIntakeReccomdFinalReport.pdf>

Dangour AD, Uauy R. 2008. N-3 long-chain polyunsaturated fatty acids for optimal function during brain development and ageing. *Asian Pacific Journal of Clinical Nutrition* 17(Suppl 1):185-188.

De Groot RHM, Hornstra G, Jolles J. 2007. Exploratory study into the relation between plasma phospholipid fatty acid status and cognitive performance. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 76(3):165-172.

Deutch B, Jørgensen EB, Hansen JC. 2000. Menstrual discomfort in Danish women reduced by dietary supplements of omega-3 PUFA and B<sub>12</sub> (fish oil or seal oil capsules). *Nutrition Research* 20(5):621-631.



Dokholyan RS, Albert CM, Appel LJ, Cook NR, Whelton PK, Hennekens CH. 2004. A trial of omega-3 fatty acids for prevention of hypertension. *The American Journal of Cardiology* 93(8):1041-1043.

Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. 2003. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *Journal of Allergy and Clinical Immunology* 112(6):1178-1184.

Dunstan JA, Roper J, Mitoulas L, Hartmann PE, Simmer K, Prescott SL. 2004. The effect of supplementation with fish oil during pregnancy on breast milk immunoglobulin A, soluble CD14, cytokine levels, and fatty acid composition. *Clinical and Experimental Allergy* 34(8):1237-1242.

Engeset D, Alsaker E, Lund E, Welch A, Khaw KT, Clavel-Chapelon F, Thiébaud A, Chajès V, Key TJ, Allen NE, Amiano P, Dorronsoro M, Tjønneland A, Stripp C, Peeters PH, van Gils CH, Chirlaque MD, Nagel G, Linseisen J, Ocké MC, Bueno-de-Mesquita HB, Sacerdote C, Tumino R, Ardanaz E, Sánchez MJ, Panico S, Palli D, Trichopoulou A, Kalapothaki V, Benetou V, Quirós JR, Agudo A, Overvad K, Bjerregaard L, Wirfält E, Schulz M, Boeing H, Slimani N, Riboli E. 2006. Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). *International Journal of Cancer* 119(1):175-182.

Engler MM, Engler MB, Malloy MJ, Paul SM, Kulkarni KR, Mietus-Snyder ML. 2005. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *The American Journal of Cardiology* 95(7):869-871.

Eritsland J. 2000. Safety considerations of polyunsaturated fatty acids. *The American Journal of Clinical Nutrition* 71(Suppl 1):197S-201S.

Eritsland J, Arnesen H, Seljeflot I, Høstmark AT. 1995. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. *The American Journal of Clinical Nutrition* 61(4):831-836.

Eritsland J, Arnesen H, Seljeflot I, Kierulf P. 1995. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagulation and Fibrinolysis* 6(1):17-22.

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen PA. 1994. Long-term effects of n-3 fatty acids on serum lipids and glycemic control. *Scandinavian Journal of Clinical and Laboratory Investigation* 54(4):273-280.

European Commission. Commission Recommendation of 23 August 2011 on the reduction of the presence of dioxins, furans and PCBs in feed and food (2011/516/EU) *Official Journal of the*

European Union L 218/23 24.8.2011 [Internet]. [Accessed 2012 January 30]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:218:0023:0025:EN:PDF>

European Food Safety Authority. 2008. Scientific substantiation of a health claim related to Docosahexaenoic Acid (DHA) and Arachidonic Acid (ARA) and support of the neural development of the brain and eyes pursuant to Article 14 of Regulation (EC) No 1924/2006. The EFSA Journal 794:1-11.

European Food Safety Authority. 2008. Scientific substantiation of a health claim related to  $\alpha$ -linolenic acid and linoleic acid and growth and development of children pursuant to Article 14 of Regulation (EC) No 1924/2006. The EFSA Journal 783:1-9.

Fitzpatrick KC. 2005. Invitational Consultation on Fatty Acids. Winnipeg (MB): Nutritech Consulting.

Food Chemicals Codex. Seventh edition. Rockville (MD): The United States Pharmacopeial Convention; 2011.

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. The Journal of Clinical Epidemiology 48(11):1379-1390.

Frais AT. 2007. Depression and the causal role of specific memory system degenerations: Link may be supported by reported therapeutic benefits of omega 3 fatty acids. Medical Hypothesis 69(1):67-69.

Frangou S, Lewis M, McCrone P. 2006. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. The British Journal of Psychiatry 188:46-50.

Franzen D, Schannwell M, Oette K, Höpp HW. 1993. A prospective, randomized, and doubleblind trial on the effect of fish oil on the incidence of restenosis following PTCA. Catheterization and Cardiovascular Diagnosis 28(4):301-310.

Freese R, Mutanen N. 1997. Alpha-linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. The American Journal of Clinical Nutrition 66(3):591-598.

Fregni F, Schachter SC, Pascual-Leone A. 2005. Review: Transcranial magnetic stimulation treatment for epilepsy: can it also improve depression and vice versa? Epilepsy and Behavior 7(2):182-189.

Friedberg CE, Janssen MJ, Heine RJ, Grobbee DE. 1998. Fish oil and glycemic control in diabetes. A meta-analysis. Diabetes Care 21(4):494-500.





Fux M, Benjamin J, Nemets B. 2004. A placebo-controlled crossover trial of adjunctive EPA in OCD. *Journal of Psychiatric Research* 38(3):323-325.

Gadoth N. 2008. On fish oil and omega-3 supplementation in children: the role of such supplementation on attention and cognitive dysfunction. *Brain and Development* 30(5):309-312.

Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS. 1993. Preventing restenosis with fish oils following coronary angioplasty: a meta-analysis. *Archives of Internal Medicine* 153(13):1595-1601.

Geelen A, Brouwer IA, Schouten EG, Maan AC, Katan MB, Zock PL. 2005. Effects of n-3 fatty acids from fish on premature ventricular complexes and heart rate in humans. *The American Journal of Clinical Nutrition* 81(2):416-420.

Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. 2002. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *Journal of Hypertension* 20(8):1493-1499.

Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J. 1994. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis: a 12-month, double-blind, controlled study. *Arthritis & Rheumatism* 37(6):824-829.

Goodnight SH, Harris WS, Connor WE. 1981. The effects of dietary omega-3 fatty acids on platelet composition and function in man: a prospective, controlled study. *Blood* 58(5):880-885.

Grimsgaard S, Bonna KH, Hansen JB, Nordøy A. 1997. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *The American Journal of Clinical Nutrition* 66(3):649-659.

Guivernau N, Meza N, Barja P, Roman O. 1994. Clinical and experimental study on the longterm effect of dietary gamma-linolenic acid on plasma lipids, platelet aggregation, thromboxane formation, and prostacyclin production. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 51(5):311-316.

Haglund O, Luostarinen R, Wallin R, Wibell L, Saldeen T. 1991. The effects of fish oil on triglycerides, cholesterol, fibrinogen and malondialdehyde in humans supplemented with vitamin E. *European Journal of Nutrition* 121(2):165-169.

Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. 2004. Food and nutrient intake in relation to mental well being. *Nutritional Journal* 3(14):1-5.

Halldorsson TI, Meltzer HM, Thorsdottir I, Knudsen V, Olsen SF. 2007. Is high consumption of fatty fish during pregnancy a risk factor for fetal growth retardation? A study of 44,824 Danish pregnant women. *American Journal of Epidemiology* 166(6):687-696.

Halliwell B, Chirico S. 1993. Lipid peroxidation: its mechanism, measurement, and significance. *The American Journal of Clinical Nutrition* 57(Suppl 5):715S-725S.

Hamazaki T, Sawazaki S, Nagao Y, Kuwamori T, Yazawa K, Mizushima Y, Kobayashi M. 1998. Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions. A randomized, placebo-controlled, double-blind study. *Lipids* 33(7):663-667.

Hamazaki T, Sawazaki S, Itomura M, Asaoka E, Nagao Y, Nishimura N, Yazawa K, Kuwamori T, Kobayashi M. 1996. The effect of docosahexaenoic acid on aggression in young adults: a placebo-controlled double-blind study. *Journal Clinical Investigation* 97(4):1129-1134.

Harel Z, Biro FM, Kottenhahn RK, Rosenthal SL. 1996. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. *The American Journal of Obstetrics and Gynecology* 174(4):1335-1338.

Harris WS. 2010. Omega-3 Fatty Acids. In: Coates PM, Betz JM, Blackman MR, Cragg GM, Levine M, Moss J, White JD, editors. *Encyclopedia of Dietary Supplements*. Second edition. New York (NY): Informa Healthcare.

Harris WS. 2007. International recommendations for consumption of long-chain omega-3 fatty acids. *The Journal of Cardiovascular Medicine* 8(1):S50-S52.

Harrison N, Abhyankar B. 2005. The mechanism of action of omega-3 fatty acids in secondary prevention post-myocardial infarction. *Current Medical Research and Opinion* 21(1):95-100.

Health Canada. MedEffect Canada: Adverse Reaction Reporting [Internet]. Ottawa (ON): Health Canada. [Accessed 2012 January 30]. Available from: [http://www.hc-sc.gc.ca/dhpmpps/medeff/report-declaration/index\\_e.html](http://www.hc-sc.gc.ca/dhpmpps/medeff/report-declaration/index_e.html)

Health Canada. Food Rulings Proposal – EPA and DHA: Level of Addition to Foods. Ottawa (ON): Bureau of Nutritional Sciences, Health Canada; 2006.

Health Canada. Product Licensing Guidance Document, Version 2.0 [Internet]. Ottawa (ON): Natural Health Products Directorate, Health Canada; 2006. [Accessed 2012 January 30]. Available from: [http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/licenselicence\\_guide\\_tc-tm-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/licenselicence_guide_tc-tm-eng.php)

Health Canada. Evidence for Safety and Efficacy of Finished Natural Health Products. Ottawa (ON): Natural Health Products Directorate, Health Canada; 2006. [Accessed 2012 January 30]. <http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/efe-paie-eng.php>

- He K, Song Y, Daviglius ML, Liu K, Van Horn L, Dyer AR, Goldbourt U, Greenland P. 2004. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke* 35(7):1538-1542.
- Hendler SS, Rorvik D, editors. 2001. *PDR for Nutritional Supplements*, 1<sup>st</sup> edition. Montvale (NJ): Thomson PDR.
- Hibbeln JR, Ferguson TA, Blasbalg TL. 2006. Omega-3 fatty acid deficiencies in neurodevelopment, aggression and autonomic dysregulation: opportunities for intervention. *International Review of Psychiatry* 18(2):107-118.
- Hjerkinn EM, Seljeflot I, Ellingsen I, Berstad P, Hjermmann I, Sandvik L, Arnesen H. 2005. Influence of long-term intervention with dietary counselling, long-chain n-3 fatty acid supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. *The American Journal of Clinical Nutrition* 81(3):583-589.
- Hodge W, Barnes D, Schachter HM, Pan Y, Lowcock EC, Zhang L, Sampson M, Morrison A, Tran K, Miguelez M, Lewin G. 2005. Effects of Omega-3 Fatty Acids on Eye Health. Summary, Evidence Report/Technology Assessment No. 117. AHRQ No. 05-E008-2. Rockville (MD): Agency for Healthcare Research and Quality.
- Hodge L, Salome CM, Hughes JM, Liu-Brennan D, Rimmer J, Allman M, Pang D, Armour C, Woolcock AJ. 1998. Effect of dietary intake of omega-3 and omega-6 fatty acids on severity of asthma in children. *European Respiratory Journal* 11(2):361-365.
- Hoffman DR, Locke KG, Wheaton DH, Fish GE, Spencer R, Birth DG. 2004. A randomized, placebo-controlled clinical trial of docosahexaenoic acid supplementation for X-linked retinitis pigmentosa. *American Journal of Ophthalmology* 137(4):704-718.
- Holguin F, Téllez-Rojo MM, Lazo M, Mannino D, Schwartz J, Hernández M, Romieu I. 2005. Cardiac autonomic changes associated with fish oil vs soy oil supplementation in the elderly. *Chest* 127(4):1102-1107.
- Hornstra G. 2000. Essential fatty acids in mothers and their neonates. *The American Journal of Clinical Nutrition* 71(Suppl 5):1262S-1269S.
- Iacoviello L, Amore C, De Curtis A, Tacconi MT, de Gaetano G, Cerletti C, Donati MB. 1992. Modulation of fibrinolytic response to venous occlusion in humans by a combination of lowdose aspirin and n-3 polyunsaturated fatty acids. *Arteriosclerosis, Thrombosis and Vascular Biology* 12(10):1191-1197.
- iHerb Products List [Internet]. Irwindale (CA): iHerb Inc. [Accessed 2012 January 30]. Available from: <http://www.iherb.com/ProductsList.aspx?c=1&cid=1546>

Innis SM. 2007. Dietary (n-3) fatty acids and brain development. *The Journal of Nutrition* 137(4):855-859.

Institute of Medicine Committee on Nutrient Relationships in Seafood Selection to Balance Benefits and Risks, Food and Nutrition Board, Institute of Medicine. 2007. *Seafood Choices: Balancing Benefits and Risks*. Washington (DC): National Academies Press.

Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Hennekens CH. 2001. Intake of fish and omega-3 fatty acids and risk of stroke in women. *The Journal of the American Medical Association* 285(3):304-312.

Jellin JM editor. 2007. *Natural Medicines Comprehensive Database*. Fish Oil. [Internet]. Stockton (CA): 1995-2012 Therapeutic Research Faculty. [Last updated 2012 January 27 Accessed 2012 January 30]. Available from: <http://naturaldatabase.therapeuticresearch.com>

Johansen O, Brekke M, Seljeflot I, Abdelnoor M, Arnesen H. 1999. n-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. *Journal of the American College of Cardiology* 33(6):1619-1626.

Johnson EJ, Chung HY, Caldarella SM, Snodderly DM. 2008. The influence of supplemental lutein and docosahexaenoic acid on serum, lipoproteins, and macular pigmentation. *The American Journal of Clinical Nutrition* 87(5):1521-1529.

Kalmijn S, van Boxten PJ, Ocke M, Verschuren WMM, Kromhout D, Launer LJ. 2004. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 62(2):275-280.

Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. 1997. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *American Journal of Epidemiology* 145(1):33-41.

Kaul U, Sanghvi S, Bahl VK, Dev V, Wasir HS. 1992. Fish oil supplements for prevention of restenosis after coronary angioplasty. *International Journal of Cardiology* 35(1):87-93.

Kelley DS, Siegel D, Vemuri M, Mackey BE. 2007. Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic men. *The American Journal of Clinical Nutrition* 86(2):324-333.

Kidd PM. 2007. Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids. *Alternative Medical Review* 12(3):207-227.

Kjeldsen-Kragh J, Lund JA, Riise T, Finnanger B, Haaland K, Finstad R, Mikkelsen K, Førre Ø. 1992. Dietary omega-3 fatty acid supplementation and naproxen treatment in patients with rheumatoid arthritis. *The Journal of Rheumatology* 19(10):1531-1536.



Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. 2006. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. *Neuroscience Research* 56(2):159-164.

Kremer JM, Bigauoette J, Michalek AV, Timchalk MA, Lininger L, Rynes RI, Huyck C, Zieminski J, Bartholomew LE. 1985. Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. *Lancet* 1(8422):184-187.

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 and Rheumatism* 33(6):810-819.

Kremer JM, Lawrence DA, Petrillo GF, Litts LL, Mullaly PM, Rynes RI, Stocker RP, Parhami N, Greenstein NS, Fuchs BR, Mathur A, Robinson DR, Sperling RI, Bigauoette J. 1995. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal anti-inflammatory drugs. *Arthritis & Rheumatism* 38(8):1107-1114.

Krokan HE, Bjerve KS, Mork E. 1993. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. *Biochimica et Biophysica Acta* 1168(1):59-67.

Kyrozis A, Psaltopoulou T, Stathopoulos P, Trichopoulos D, Vassilopoulos D, Trichopoulou A. 2009. Dietary lipids and geriatric depression scale score among elders: the EPIC-Greece cohort. *Journal of Psychiatric Research* 43(8):763-769..

Lau CS, McLaren M, Belch JJ. 1995. Effects of fish oil on plasma fibrinolysis in patients with mild rheumatoid arthritis. *Clinical and Experimental Rheumatology* 13(1):87-90.

Lau CS, Morley KD, Belch JJ. 1993. Effects of fish oil supplementation on non-steroidal antiinflammatory drug requirement in patients with mild rheumatoid arthritis – a double-blind placebo controlled study. *British Journal of Rheumatology* 32(11):982-989.

Lauritzen L, Kjaer TM, Fruekilde MB, Michaelsen KF, Frokiaer H. 2005. Fish oil supplementation of lactating mothers affects cytokine production in 2 ½-year-old children. *Lipids* 40(7):669-676.

Lawson LD, Hughes BG. 1988. Absorption of eicosapentaenoic acid and docosahexaenoic acid from fish oil triacylglycerols or fish oil ethyl esters co-ingested with a high-fat meal. *Biochemical and Biophysical Research Communications* 156(2):960-963.

Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, Weiner BH, Slack JD, Kellett MA, Raizner AE, Weber PC, Mahrer PR, Rossouw JE. 1994. Do fish oils prevent coronary angioplasty? *Circulation* 90(5):2248-2257.

Leigh-Firbank EC, Minihane AM, Leake DS, Wright JW, Murphy MC, Griffin BA, Williams CM. 2002. Eicosapentaenoic acid and docosahexaenoic acid from fish oils: differential associations with lipid responses. *The British Journal of Nutrition* 87(5):435-445.

Lewin GA, Schachter HM, Yuen D, Merchant P, Mamaladze V, Tsertsvadze A, Clifford T, Kourad K, Barnes D, Armour T, Yazdi F, MacNeil J, McGahern C, Senechal H, Fang M, Barrowman N, Sampson M, Morrison A, Elien D, Saint-Martin M, Sambasivan A, Lowcock E, Pan Y, Lemyre B. 2005. Effects of Omega-3 Fatty Acids on Child and Maternal Health. Summary, Evidence Report/Technology Assessment No. 118. AHRQ No. 05-E025-2. Rockville (MD): Agency for Healthcare Research and Quality.

Linday LA, Dolitsky JN, Shindlecker RD. 2004. Nutritional supplements as adjunctive therapy for children with chronic/recurrent sinusitis: pilot research. *International Journal of Pediatric Otorhinolaryngology* 68(6):785-793.

Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. 2003. Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *American Journal Obstetrics and Gynecology* 188(5):1348-1353.

Logan AC. 2004. Review: omega-3 fatty acids and major depression: a primer for the mental health professional. *Lipids in Health and Disease* 3(25):1-8.

Lorenz R, Spengler U, Fischer S, Duhm J, Weber PC. 1983. Platelet function, thromboxanes formation and blood pressure control during supplementation of the western diet with cod liver oil. *Circulation* 67(3):504-511.

MacLean CH, Issa AM, Newberry SJ, Mojica WA, Morton SC, Garland RH, Hilton LG, Traina SB, Shekelle PG. 2005. Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. Summary, Evidence Report/Technology Assessment No. 114. AHRQ No. 05-E011-2. Rockville (MD): Agency for Healthcare Research and Quality.

MacLean CH, Mojica WA, Morton SC, Pencharz J, Hasenfeld Garland R, Tu W, Newberry SJ, Jungvig LK, Grossman J, Khanna P, Rhodes S, Shekelle P. 2004. Effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Summary, Evidence Report/Technology Assessment No. 89. AHRQ No. 04E012-2. Rockville (MD): Agency for Healthcare Research and Quality.

MacLean CH, Newberry SJ, Mojica WA, Issa A, Khanna P, Lim YW, Morton SC, Suttorp M, Tu W, Hilton LG, Garland RH, Traina SB, Shekelle PG. 2005. Effects of Omega-3 Fatty Acids on Cancer. Summary, Evidence Report/Technology Assessment No. 113. AHRQ No. 05-E010-2. Rockville (MD): Agency for Healthcare Research and Quality.



Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. 1999. Lowered omega-3 polyunsaturated fatty acids in serum phospholipids and cholesterol esters of depressed patients. *Psychiatry Research* 85(3):275-291.

Maes M, Mihaylova I, Kubera M, Bosmans E. 2007. Why fish oils may not always be adequate treatments for depression or other inflammatory illnesses: docosahexaenoic acid, an omega-3 polyunsaturated fatty acid, induces a Th-1-like immune response. *Neuroendocrinology Letters* 28(6):875-880.

Maes M, Mihaylova I, Leunis JC. 2005. In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. *Neuroendocrinology Letters* 26(6):745-751.

Maillard V, Bougnoux P, Ferrari P, Jourdan ML, Pinault M, Lavillonnière M, Body G, Le Floch O, Chajès V. 2002. n-3 and n-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours, France. *International Journal of Cancer* 98(1):78-83.

Makrides M. 2008. Commentary: outcomes for mothers and their babies: do n-3 long-chain polyunsaturated fatty acids and seafoods make a difference? *Journal of the American Dietetic Association* 108(10):1622-1626.

Marangell LB, Martinez JM, Zboyan HA, Chong H, Puryear LJ. 2004. Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depression and Anxiety* 19(1):20-23.

Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ. 2003. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *American Journal Psychiatry* 160(5):996-998.

Maresta A, Balducci M, Varani E, Marzilli M, Galli C, Heiman F, Lavezzari M, Stragliotto E, De Caterina R; ESPRIT Investigators. 2002. Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the Esapent for Prevention of Restenosis Italian study (ESPRIT). *American Heart Journal* 143(6):E5.

Martin RE, Carter EP, Flick GJ, Davis LM, editors. 2000. *Marine & Freshwater Products Handbook*. Lancaster (PA): Technomic Publishing Company, Inc.

McCann JC, Ames BN. 2005. Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *The American Journal of Clinical Nutrition* 82(2):281-295.

Merck 2011: *The Merck Index Version 14.1*. [Internet]. Whitehouse Station (NJ): Merck & Co., Inc. [Published 2006; Updated 2011; Accessed 2011 December 9]. Available from:



<http://www.medicinescomplete.com>

Meydani M, Natiello F, Goldin B, Free N, Woods M, Schaefer E, Blumberg JB, Gorbach SL. 1991. Effect of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. *Journal of Nutrition* 121(4):484-491.

Mickleborough TD, Ionescu AA, Rundell KW. 2004. Omega-3 fatty acids and airway hyperresponsiveness in asthma. *The Journal of Alternative and Complementary Medicine* 10(6):1067-1075.

Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. 2006. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 129(1):39-49.

Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM. 2004. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. *Pediatric Allergy and Immunology* 15(6):517-522.

Montgomery C, Speake BK, Cameron A, Sattar N, Weaver LT. 2003. Maternal docosahexaenoic acid supplementation and fetal accretion. *The British Journal of Nutrition* 90(1):135-140.

Moore CS, Bryant SP, Mishra GD, Krebs JD, Browning LM, Miller GJ, Jebb SA. 2006. Oily fish reduces plasma triacylglycerols: a primary prevention study in overweight men and women. *Nutrition* 22(10):1012-1024.

Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ. 1999. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension* 34(2):253-260.

Mori TA, Burke V, Puddey IB, Watts GF, O'Neal DN, Best JD, Beilin LJ. 2000. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *The American Journal of Clinical Nutrition* 71(5):1085-1094.

Morris MC, Sacks F, Rosner B. 1993. Regulation of blood pressure: does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation* 8(2):523-533.

Mueller BA, Talbert RL, Tegeler CH, Prihoda TJ. 1991. The bleeding time effects of a single dose of aspirin in subjects receiving omega-3 fatty acid dietary supplementation. *Journal of Clinical Pharmacology* 31(2):185-190.

Nagakura T, Matsuda S, Shichijyo K, Sugimoto H, Hata K. 2000. Dietary supplementation with fish oil rich in  $\omega$ -3 polyunsaturated fatty acids in children with bronchial asthma. *European Respiratory Journal* 16(5):861-865.



Nakamura K, Kariyazono H, Komokata T, Hamada N, Sakata R, Yamada K. 2005. Influence of preoperative administration of  $\omega$ -3 fatty acid-enriched supplement on inflammatory and immune responses in patients undergoing major surgery for cancer. *Nutrition* 21(6):639-645.

National Institute of Mental Health. Teenage brain: a work in progress 2001. [Internet]. Bethesda (MD): United States Department of Health and Human Services. [Accessed 2012 January 30]. Available from: <http://wwwapps.nimh.nih.gov/health/publications/teenage-brain-a-work-inprogress.shtml>

Nelson GJ, Schmidt PS, Bartolini GL, Kelley DS, Kyle D. 1997. The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. *Lipids* 32(11):1129-1136.

Nemets B, Osher Y, Belmaker RH. 2004. Omega-3 fatty acids and augmentation strategies in treating resistant depression. *Essential Psychopharmacology* 6(1):59-64.

Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. 2006. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *American Journal of Psychiatry* 163(6):1098-1100.

Nemets B, Stahl Z, Belmaker RH. 2002. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *American Journal of Psychiatry* 159(3):477-479.

Nettleton JA, Katz R. 2005. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. *Journal of the American Dietetic Association* 105(3):428-440.

Nielsen GL, Faarvang KL, Thomsen BS, Teglbjærg 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 randomized, double blind trial. *European Journal of Clinical Investigation* 22(10):687-691.

Nordic Naturals. Why Nordic Naturals? [Internet] Watsonville (CA): Nordic Naturals, Inc. [Accessed 2012 January 30]. Available from: [http://www.nordicnaturals.com/en/Search\\_Results/My\\_Search/130/](http://www.nordicnaturals.com/en/Search_Results/My_Search/130/)

Noaghiul S, Hibbeln JR. 2003. Review: Cross-national comparisons of seafood consumption and rates of bipolar disorders. *The American Journal of Psychiatry* 160(12):2222-2227.

Nordoy A, Barstad L, Connor WE, Hatcher L. 1991. Absorption of the n-3 eicosapentaenoic and docosahexaenoic acids as ethyl esters and triglycerides by humans. *The American Journal of Clinical Nutrition* 53(5):1185-1190.

Nordström DC, Honkanen VE, Nasu Y, Antila E, Friman C, Kontinen YT. 1995. Alpha-linolenic acid in the treatment of rheumatoid arthritis. A double-blind, placebo-controlled and randomized study: flaxseed vs. safflower seed. *Rheumatology International* 14(6):231-234.

Ocean Nutrition Canada. Our Products: Dietary Supplements [Internet]. Dartmouth (NS): Ocean Nutrition Canada Limited. [Accessed 2012 January 30]. Available from: <http://www.oceannutrition.com/products>

O'Connor GT, Malenka DJ, Olmstead EM. 1992. A meta-analysis of randomized trials of fish oil in prevention of restenosis following coronary angioplasty. *American Journal of Preventive Medicine* 8(3):186-192.

Olafsdottir AS, Magnusardottir AR, Thorgeirsdottir H, Hauksson A, Skuladottir GV, Steingrimsdottir L. 2005. Relationship between dietary intake of cod liver oil in early pregnancy and birthweight. *BJOG: an International Journal of Obstetrics and Gynaecology* 112(4):424-429.

Olsen SF, Secher NJ. 2002. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *British Medical Journal* 324(7335):447-450.

Omacor: Abbreviated Prescribing Information [Internet]. Southampton (GB): Solvay Healthcare Ltd. [Accessed 2012 January 30]. Available from: <http://www.omacor.co.uk/hcp/omacor-pi.html>

Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. 1995. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. *British Journal of Obstetrics and Gynaecology* 102(2):95-100.

Osher Y, Bersudsky U, Belmaker, RH. 2005. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *The Journal of Clinical Psychiatry* 66(6):726-729.

Parker G G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D. 2006. Review: omega-3 fatty acids and mood disorders. *American Journal of Psychiatry* 163(6):969-978.

Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC. 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science* 283(5409):1908-1911.

Pawlosky RJ, Bacher J, Salem N. 2001. Ethanol consumption alters electroretinograms and depletes neural tissues of docosahexaenoic acid in rhesus monkeys: nutritional consequences of a low n-3 fatty acid diet. *Alcoholism: Clinical and Experimental Research* 25(12):1758-1765.

Peat JK, Mhrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K, Mellis CM, Leeder SR. 2004. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *The Journal of Allergy and Clinical Immunology* 114(4):807-813.



Pedersen HS, Mulvad G, Seidelin KN, Malcom GT, Boudreau DA. 1999. N-3 fatty acids as a risk factor for haemorrhagic stroke. *Lancet* 353(9155):812-813.

Peet M. 2003. Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 69(6):477-485.

Picado C, Castillo JA, Schinca N, Pujades M, Ordinas A, Coronas A, Agusti-Vidal A. 1988. Effects of a fish oil enriched diet on aspirin intolerant asthmatic patients: a pilot study. *Thorax* 43(2):93-97.

Radack K, Deck C, Huster G. 1990. The comparative effects of n-3 and n-6 polyunsaturated fatty acids on plasma fibrinogen levels: a controlled clinical trial in hypertriglyceridemic subjects. *Journal of the American College of Nutrition* 9(4):352-357.

Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, Connor SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McAnulty J. 2005. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *The Journal of the American Medical Association* 293(23):2884-2891.

Reddy BS. 2004. Omega-3 fatty acids in colorectal cancer prevention. *International Journal of Cancer* 112(1):1-7.

Reis GJ, Silverman DI, Boucher TM, Sipperly ME, Horowitz GL, Sacks FM, Pasternak RC. 1990. Effects of two types of fish oil supplements on serum lipids and plasma phospholipids fatty acids in coronary artery disease. *The American Journal of Cardiology* 15(66):1171-1175.

Richardson AJ. 2004. Clinical trials of fatty acid treatment in ADHD, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 70(4):383-390.

Richardson AJ, Montgomery P. 2005. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 115(5):1360-1366.

Richardson AJ, Puri BK. 2002. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuropsychopharmacology and Biological Psychiatry* 26(2):233-239.

Richardson AJ, Puri BK. 2000. The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 63(1-2):79-87.

- Rose DP, Connolly JM. 1999. Omega-3 fatty acids as cancer chemopreventive agents. *Pharmacology & Therapeutics* 83(3):217-244.
- Ryan AS, Nelson EB. 2008. Assessing the effect of docosahexaenoic acid on cognitive functions in healthy preschool children: a randomized, placebo-controlled, double-blind study. *Clinical Pediatrics* 47(4):355-362.
- Sagduyu K, Docucu ME, Eddy BA, Craigen G, Baldassano CF, Yildiz A. 2005. Omega-3 fatty acids decreased irritability of patients with bipolar disorder in an add-on, open label study. *Nutrition Journal* 4:6.
- Sagredos AN. 1991. [Fatty Acid Composition of Fish Oil Capsules]. *Fett Wissenschaft Technologie* 93(5):184-191 [article in German].
- Samieri C, Feart C, Letenneur L, Dartigues JF, Peres K, Auriacombe S, Peuchant E, Delcourt C, Barberger-Gateau P. 2008. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. *The American Journal of Clinical Nutrition* 88(3):714-721.
- Sanders TA, Hinds A. 1992. The influence of a fish oil high in docosahexaenoic acid on plasma lipoprotein and vitamin E concentrations and haemostatic function in healthy male volunteers. *The British Journal of Nutrition* 68(1):163-173.
- Saynor R, Gillott T. 1992. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. *Lipids* 27(7):533-538.
- Schachter HM, Kourad K, Merali Z, Lumb A, Tran K, Miguelez M, Lewin G, Sampson M, Barrowmann N, Senechal H, McGahern C, Zhang L, Morrison A, Shlik J, Pan Y, Lowcock EC, Gaboury I, Bradejn J, Duffy A. 2005. Effects of omega-3 fatty acids on mental health. Summary, Evidence Report/Technology Assessment No. 116. AHRQ No. 05-E022-2. Rockville (MD): Agency for Healthcare Research and Quality.
- 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. *Scandinavian Journal of Clinical and Laboratory Investigation* 52(3):221-228.
- Schwellenbach LJ, Olson KL, McConnell KJ, Stolcpart RS, Nash JD, Merenich JA. 2006. The triglyceride-lowering effects of a modest dose of docosahexaenoic acid alone versus in combination with low dose eicosapentaenoic acid in patients with coronary artery disease and elevated triglycerides. *Journal of the American College of Nutrition* 25(6):480-485.



Scientific Advisory Committee on Nutrition, Foods Standard Agency, Department of Health. Advice on Fish Consumption: Benefits and Risks 2004 [Internet]. London (GB): TSO (The Stationery Office). [Accessed 2012 January 30]. Available from: [www.sacn.gov.uk/pdfs/fics\\_sacn\\_advice\\_fish.pdf](http://www.sacn.gov.uk/pdfs/fics_sacn_advice_fish.pdf)

Silverman DI, Ware JA, Sacks FM, Pasternak RC. 1991. Comparison of the absorption and effect of on platelet function of a single dose of n-3 fatty acids given as fish or fish oil. *The American Journal of Clinical Nutrition* 53(5):1165-1170.

Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. 1999. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 72(3):211-218.

Simons LA, Parfitt A, Simons J, Balasubramaniam S. 1990. Effects of an ethyl ester preparation of fish oils (Himega) on lipids and lipoproteins in hyperlipidaemia. *Australian and New Zealand Journal of Medicine* 20(5):689-694.

Simopoulos AP, Leaf A, Salem N. 1999. Workshop on the essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. *Journal of the American College of Nutrition* 18(5):487-489.

Singh M. 2005. Essential fatty acids, DHA and human brain. *Indian Journal of Pediatrics* 72(3):239-242.

Sinn N, Bryan J. 2007. Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. *Journal of Development and Behavioural Pediatrics* 28(2):82-91.

Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Del Parigi A, Capurso SA, Argentieri G, Capurso A, Panza F. 2006. Dietary fatty acids intakes and rate of mild cognitive impairment. *The Italian Longitudinal Study on Aging. Experimental Gerontology* 41(6):619-627.

Sommerfield T, Hiatt WR. 2007. Omega-3 fatty acids for intermittent claudication. *Cochrane Database of Systematic Reviews Issue 1. Art. No.: CD003833. DOI:10.1002/14651858.CD003833.pub2.*

Stehr SN, Heller AR. 2006. Omega-3 fatty acid effects on biochemical indices following cancer surgery. *Clinica Chimica Acta* 373(1-2):1-8.

Stevens LJ, Zentall SS, Abate ML, Kuczek T, Burgess JR. 1996. Omega-3 fatty acids in boys with behavior, learning and health problems. *Physiology and Behavior* 59(4-5):915-920.



- Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR, Burgess JR. 1995. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *The American Journal of Clinical Nutrition* 62(4):761-768.
- Stevens L, Zhang W, Peck L, Kuczek T, Grevstad N, Mahon A, Zentall SS, Arnold LE, Burgess JR. 2003. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids* 38(10):1007-1021.
- Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB. 1999. Omega 3 fatty acids in bipolar disorder: a preliminary double blind, placebocontrolled trial. *Archives of General Psychiatry* 56(5):407-412.
- Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. 2005. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Archives of Internal Medicine* 165(7):725730.
- Su K, Huang S, Chiu C, Shen WW. 2003. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *European Neuropsychopharmacology* 13(4):267-271.
- Sundrarjun T, Komindr S, Archararit N, Dahlan W, Puchaiwatananon O, Angtharak S, Udomsuppayakul U, Chuncharunee S. 2004. Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor- $\alpha$ , and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. *The Journal of International Medical Research* 32(5):443-454.
- Svensson M, Schmidt EB, Jørgensen KA, Christensen JH. 2006. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. *Clinical Journal of the American Society of Nephrology* 1(4):780-786.
- SzajewskaH, Horvath A, Koletzko B. 2006. Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition* 83(6):1337-1344.
- Takemura Y, Sakurai Y, Honjo S, Tokimatsu A, Gibo M, Hara T, Kusakari A, Kugai N. 2002. The relationship between fish intake and the prevalence of asthma: the Tokorozawa Childhood Asthma and Pollinosis Study. *Preventive Medicine* 34(2):221-225.
- Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, Ohashi Y, Tajima K, Tominaga S. 2003. Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. *Nutrition and Cancer* 45(2):160-167.



Takwale A, Tan E, Agarwal S, Barclay G, Ahmed I, Hotchkiss K, Thompson JR, Chapman T, Berth-Jones J. 2003. Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *British Medical Journal* 327(7428):1385.

Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamaki H, Lehtonen J, Vartiainen E. 2001. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatric Services* 52(4):529-531

Terry PD, Terry JB, Rohan TE. 2004. Long-chain (n-3) fatty acid intake and risks of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. *Journal of Nutrition* 134(Suppl 12):3412S-3420S.

Theobald HE, Goodall AH, Sattar N, Talbot DC, Chowienczyk PJ, Sanders TA. 2007. Low-dose docosahexaenoic acid lowers diastolic blood pressure in middle-aged men and women. *Journal of Nutrition* 137(4):973-978.

Theodoratou E, McNeill G, Cetnarskyj R, Farrington SM, Tenesa A, Barnetson R, Porteous M, Dunlop M, Campbell H. 2007. Dietary fatty acids and colorectal cancer: a case-control study. *American Journal of Epidemiology* 166(2):181-195.

Thies F, Nebe-von-Caron G, Powell JR, Yaqoob P, Newsholme EA, Calder PC. 2001. Dietary supplementation with eicosapentaenoic acid, but not with other long-chain n-3 or n-6 polyunsaturated fatty acids, decreases natural killer cell activity in healthy subjects aged >55 y. *The American Journal of Clinical Nutrition* 73(3):539-548.

Tsekos E, Reuter C, Stehle P, Boeden G. 2004. Perioperative administration of parenteral fish oil supplements in a routine clinical setting improves patient outcome after major abdominal surgery. *Clinical Nutrition* 23(3):325-330.

Tulleken JE, Limburg PC, Muskiet FA, van Rijswijk MH. 1990. Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. *Arthritis and Rheumatism* 33(9):1416-1419.

Tulleken JE, Limburg PC, van Rijswijk MH. 1988. Fish oil and plasma fibrinogen. *British Medical Journal* 297(6648):615-616.

Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE. 2003. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *Journal of Pediatrics* 143(Suppl 4):S17-S25

United States Department of Agriculture, Agricultural Research Service, National Genetic Resources Program. The Report of the Dietary Guidelines Advisory Committee on Dietary Guidelines for Americans [Internet]. Beltsville (MD): Departments of Health and Human Services and Agriculture. [Accessed 2012 January 30]. Available from:

<http://www.health.gov/dietaryguidelines/dga2005/report/>

United States Food and Drug Administration. Substances Affirmed as Generally Recognized as Safe: Menhaden Oil [Internet]. Federal Register, Volume 70, Number 55, March 23, 2005, Final Rule. Docket Number 1999P-5332. Washington (DC): Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2012 January 30]. Available from: <http://www.epa.gov/fedrgstr/EPA-IMPACT/2005/March/Day-23/i5641.htm>

United States Food and Drug Administration. Agency Response Letter, Letter Responding to Health Claim Petition dated November 3, 2003 (Martek Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease [Internet]. Washington (DC): Food and Drug Administration, Center for Food Safety and Applied Nutrition. [Accessed 2012 January 30]. Available from: <http://www.fda.gov/food/labelingnutrition/labelclaims/qualifiedhealthclaims/ucm072932.htm>

United States Food and Drug Administration. 2002. Agency Response Letter, GRAS Notice No. GRN 000105 [Internet]. Washington (DC): Food and Drug Administration, Center for Food Safety and Applied Nutrition. [Accessed 2012 January 30]. Available from: <http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt000343-041-appx-E-Ref-29GRAS-vol268.pdf>

Vaisman N, Kaysar N, Zaruk-Adasha Y, Pelled D, Brichon G, Zwingelstein G, Bodennec J. 2008. Correlation between changes in blood fatty acid composition and visual sustained attention performance in children with inattention: effect of dietary n-3 fatty acids containing phospholipids. *The American Journal of Clinical Nutrition* 87(5):1170-1180.

Valagussa F, Franzosi MG, Geraci E, Mininni N, Nicolosi GL, Santini M, Tavazzi L, Vecchio C. 1999. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 354(9177):447-455.

Valk EE, Hornstra G. 2000. Relationship between vitamin E requirement and polyunsaturated fatty acid intake in man: a review. *International Journal for Vitamin and Nutrition Research* 70(2):31-42.

Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto, M, Tysklind J, Walker N, Peterson RE. REVIEW The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicological Sciences* 2006;93(2):223-241.

van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Hoefnagels WH, Beekman ATF, de Groot LCPGM. 2008. Effect of fish-oil supplementation on mental well-being in older subjects: a randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition* 88(3):706-713.





Van der Tempel H, Tulleken JE, Limburg PC, Muskiet FA, van Rijswijk MH. 1990. Effects of fish oil supplementation in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 49(2):76-80.

van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. 2007. Fish consumption, n-3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *The American Journal of Clinical Nutrition* 85(4):1142-1147.

van Gool CJ, Thijs C, Henquet CJ, van Houwelingen AC, Dagnelie PC, Schrandt J, Menheere PP, van den Brandt PA. 2003. Gamma-linolenic acid supplementation for prophylaxis of atopic dermatitis—a randomized controlled trial in infants at high familial risk. *The American Journal of Clinical Nutrition* 77(4):943-951.

Velho S, Marques-Vidal P, Baptista F, Camilo ME. 2008. Dietary intake adequacy and cognitive function in free-living active elderly: a cross-sectional and short-term prospective study. *Clinical Nutrition* 27(1):77-86.

Velzing-Aarts FV, van der Klis FR, van der Dijs FP, van Beusekom CM, Landman H, Capello JJ, Muskiet FA. 2001. Effect of three low-dose fish oil supplements, administered during pregnancy, on neonatal long-chain polyunsaturated fatty acid status at birth. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 65(1):51-57.

Vidgren HM, Ågren JJ, Schwab U, Rissanen T, Hänninen O, Uusitupa MI. 1997. Incorporation of n-3 fatty acids into plasma lipid fractions, and erythrocyte membranes and platelets during dietary supplementation with fish, fish oil, and docosahexaenoic acid-rich oil among healthy young men. *Lipids* 32(7):697-705.

Visioli F, Risé P, Barassi MC, Marangoni F, Galli C. 2003. Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. *Lipids* 38(4):415-418.

Vlaandingerbroek H, Hornstra G, Koning TJ, Smeitink JAM, Bakker HD, Klerk HBC, RubioGozalbo ME. 2006. Essential polyunsaturated fatty acids in plasma and erythrocytes of children with inborn errors of amino acid metabolism. *Molecular Genetics and Metabolism* 88(2):159-165.

Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. 2001. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *The Journal of Pediatrics* 139(2):189-196.

Von Schacky C, Fischer S, Weber PC. 1985. Long-term effects of dietary marine  $\omega$ -3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *The Journal of Clinical Investigation* 76(4):1626-1631.



- Von Schacky C, Weber PC. 1985. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. *The Journal of Clinical Investigation* 76(6):2446-2450.
- Walker T, Singh PK, Wyatt KM, O'Brien PM. 1999. The effect of prostanoid precursors and inhibitors on platelet angiotensin II binding. *Journal of Obstetrics and Gynaecology* 19(1):56-58.
- Wang W, Shinto L, Connor WE, Quinn JF. 2008. Nutritional biomarkers in Alzheimer's disease: the association between carotenoids, n-3 fatty acids, and dementia severity. *Journal of Alzheimers Disease* 13(1):31-38.
- Westenhoefer J, Bellisle F, Blundell JE, de Vries J, Edwards D, Kallus W, Milon H, Pannemans D, Tuijtelars S, Tuorila H. 2004. PASSCLAIM – mental state and performance. *European Journal of Nutrition* 43(Suppl 2):II/85-II/117.
- Whalley LJ, Fox HC, Wahle KW, Starr JM, Deary IJ. 2004. Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids. *The American Journal of Clinical Nutrition* 80(6):1650-1657.
- Whelton SP, He J, Whelton PK, Muntner P. 2004. Meta-analysis of observational studies of fish intake and coronary heart disease. *The American Journal of Cardiology* 93(9):1119-1123.
- Wohl DA, Tien HC, Busby M, Cunningham C, Macintosh B, Napravnik S, Danan E, Donovan K, Hossenipour M, Simpson RJ Jr. 2005. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counselling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. *Clinical Infectious Diseases* 41(10):1498-1504.
- Wong KW. 2005. Clinical efficacy of n-3 fatty acid supplementation in patients with asthma. *Journal of the American Dietetic Association* 105(1):98-105.
- Woodman RJ, Mori TA, Burke V, Puddey IB, Barden A, Watts GF, Beilin LJ. 2003. Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients. *Atherosclerosis* 166(1):85-93.
- Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. 2002. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *The American Journal of Clinical Nutrition* 76(5):1007-1015.
- Yehuda S, Rabinovich S, Mostofsky DI. 1998. Modulation of learning and neuronal membrane composition in the rat by essential fatty acid preparation: time-course analysis. *Neurochemical Research* 23(5):627-634.



Yzebe D, Lievre M. 2004. Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. *Fundamental & Clinical Pharmacology* 18(5):581-592.