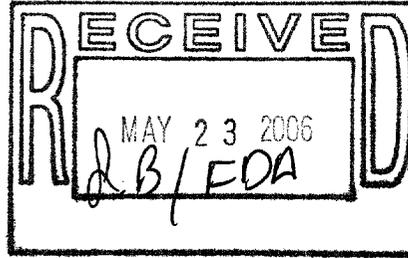


 natural

Natural ASA
Strandveien 15
Pb 165, 1325 Lysaker
NORWAY
Phone: +47 67 11 45 00
Fax: +47 67 11 45 01
Org. No.: 950 293 225



Natural ASA
Industriveien 42
N-6160 Hovdebygda
NORWAY
Phone: +47 70 04 91 00
Fax: +47 70 04 91 01

May 15, 2006

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD,
20740

Dear Sir or Madam:

Re: Premarket Notification for a New Dietary Ingredient

In accordance with 21 CFR, Part 190, Sec. 190.6 "Requirement for premarket notification," we are submitting this new dietary ingredient notification for the dietary ingredient Omega-3 Phospholipids. Please note the following:

1. Name and Address of the Manufacturer of the New Dietary Ingredient

Natural ASA
Strandveien 15
N - 1325 Lysaker
Norway

2. Name of the New Dietary Ingredient

Omega-3 Phospholipids

3. Description of the Dietary Supplement that will contain the New Dietary Ingredient

Omega-3 Phospholipids is a dark, viscous liquid containing a mixture of phospholipids and triglycerides, with a small amount of ethyl esters and free fatty acids. Omega-3 Phospholipids is rich in the long-chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid. Each gram of Omega-3 Phospholipids contains 105 to 135 mg of EPA and 50 to 75 mg of DHA, and 155 to 210 mg combined EPA+DHA, with an EPA:DHA ratio of approximately 2:1. The recommended use of Omega-3 PL is the consumption of up to 4 g/day.

4. Evidence of Safety

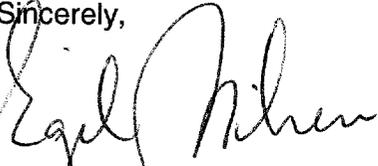
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May 15, 2006

Data supporting that Omega-3 Phospholipids is expected to be reasonably safe under the conditions of indicated use are provided in the attachment.

The original and two copies of the Notification are attached, including appendices and references. We trust that the information provided meets the requirements of a New Dietary Ingredient Notification as indicated in 21 CFR §190.6. If you have any questions or comments regarding the content of this submission, please do not hesitate to contact Egil Nilsen at +47 91 18 66 67

Sincerely,

A handwritten signature in black ink, appearing to read "Egil Nilsen". The signature is fluid and cursive, with a large initial "E" and "N".

Egil Nilsen
Business Development Manager

**NEW DIETARY INGREDIENT NOTIFICATION FOR
OMEGA-3 PHOSPHOLIPIDS**

Natural ASA
Strandveien 15
N – 1325 Lysaker
Norway

May 15, 2006

NEW DIETARY INGREDIENT NOTIFICATION FOR OMEGA-3 PHOSPHOLIPIDS

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NEW DIETARY INGREDIENT NOTIFICATION FOR OMEGA-3 PHOSPHOLIPIDS

In accordance with the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 U.S.C. §350b (a) (2), and with final regulations (21 CFR § 190.6) published in the Federal Register (FDA, 1997a) "Requirement for Premarket Notification", the following information is submitted by Natural ASA in support of a New Dietary Ingredient Notification for Omega-3 phospholipids (Omega-3 PL). Natural ASA intends to market Omega-3 PL as a dietary supplement in the United States. The term "dietary supplement" is defined in 21 U.S.C. 321(ff) as, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)." Omega-3 PL is a dietary ingredient that may be lawfully used in dietary supplements, in accordance with 21 U.S.C. 321 (ff)(1)(E). As per the statutes of the DSHEA, 21 U.S.C. § 350b (a) (2), Natural ASA will not introduce, market, distribute or sell Omega-3 PL until at least 75 days following official acknowledgement of the receipt of this notification by the U.S. Food and Drug Administration (FDA).

SECTION 1

The name and complete address of the manufacturer of the dietary supplement that contains the dietary ingredient, or the dietary ingredient.

Natural ASA
Strandveien 15
N - 1325 Lysaker
Norway

Contact: Egil Nilsen
Natural ASA
Business Development Manager
Strandveien 15
N - 1325 Lysaker
Norway
Tel: +47 91 18 66 67
Fax: +47 92 37 54 92
E-mail: egil@natural.no

SECTION 2

2.1 The Name of the Dietary Ingredient

The name of the new dietary ingredient manufactured by Natural ASA is Omega-3 Phospholipids (Omega-3 PL). Omega-3 PL is predominantly a mixture of phospholipids (PL) and triglycerides (TG), with a small amount of ethyl esters and free fatty acids.

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SECTION 3

Description of the dietary supplement or dietary supplements that contain the dietary ingredient including (i) the level of dietary ingredient in the dietary supplement, and (ii) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement.

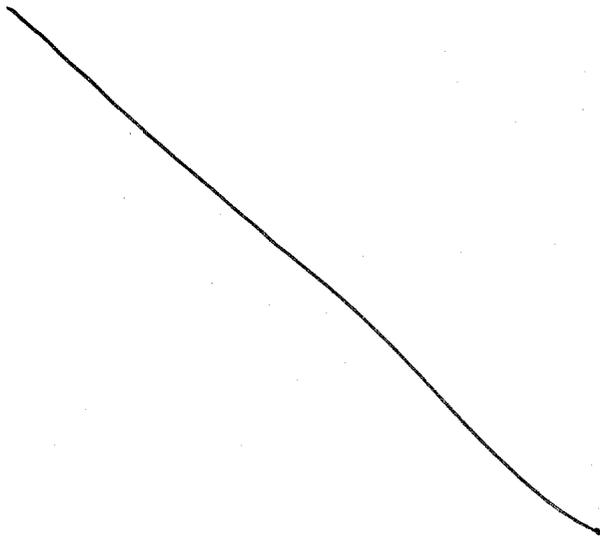
Omega-3 PL is a fish oil supplement in which the long-chain omega-3 fatty acids, EPA and DHA, are present primarily in TG form, and secondarily, in PL form. The fatty acid composition of Omega-3 PL is presented in Table 3-1, and the fractional lipid composition of Omega-3 PL is presented in Table 3-2. Certificates of Analysis for fatty acid profiles and fractional lipid analyses of different batches of Omega-3 PL can be found in Appendix C. Final product specifications can be found in Appendix B.

PAGE 8

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Omega-3 PL is a dark viscous liquid. Each gram of Omega-3 PL will contain 105 to 135 mg of EPA and 50 to 75 mg of DHA, providing a total EPA+DHA intake of approximately 155 to 210 mg and an EPA:DHA ratio of approximately 2:1. The recommended use of Omega-3 PL is the consumption of up to 4 g/day. Assuming the maximum levels of EPA and DHA, this usage would provide a daily intake of up to 540 mg EPA, 300 mg DHA, 840 mg combined EPA+DHA. Usage of Omega-3 PL is not restricted to any target population; the only subpopulations excluded from using Omega-3 PL are individuals allergic to fish and persons taking anticoagulants. There is no limitation on the duration of Omega-3 PL use.

Several fish oils are currently approved for use as dietary supplements in the United States. These fish oils, as well as their recommended doses, are summarized in Table 3-3. The combined intake of EPA+DHA from recommended intakes of these supplements ranges from approximately 300 mg/day to just over 1,000 mg/day. The proposed intake of up to 4 g/day of Omega-3 PL would result in the intake of up to 840 mg/day combined EPA+DHA, which is within the range of intakes from the recommended use of other long-chain omega-3 fatty acid supplements. In addition, the ratio of EPA:DHA in Omega-3 PL is essentially identical to the ratio found in Krill Oil™ (approximately 2:1).

Table 3-3 Fish Oils Approved as New Dietary Ingredients in Dietary Supplements: Indications of Use							
Company	Document Number	New Dietary Ingredient	Indications for Use	Total Daily Intake (mg)			Ratio of EPA:DHA
				EPA+DHA	EPA	DHA	
Natural ASA							
Neptune Technologies and Bioresources	RPT 131	Neptune Krill Oil™	1 gram of oil per gel-cap with a recommended daily intake of 1 to 3 gel-caps per day. No limitation on the duration of use. The only subpopulations excluded from using Krill Oil are persons with seafood allergies and those taking anticoagulants.	278.8 to 836.4	183 to 549	95.8 to 287.4	1.9:1
Martek BioSciences Corporation**	RPT 110	DHA GOLD® Golden Algae	Up to 6 g/day.	1260	90	1080	1:12
Clover Corporation Ltd.	RPT 130	Hi®DHA Tuna Oil	One gram per day.	360	80	280	1:3.5
Monsanto Company	RPT 17	DHA Gold™ Marine Microalgae Oil***	One gram per day.	376.3	26.3	350	1:13

* The specifications for EPA, DHA, and EPA+DHA are 105 to 135 mg/g, 50 to 75 mg/g, and 155 to 210 mg/g, respectively. These intake levels were calculated using the maximum levels of EPA and DHA indicated in the specifications.

** Acquired original manufacturer, OmegaTech Inc.

*** Formerly called SeaGold™ DHA-rich Oil.

The recommended intake of Omega-3 PL results in a combined EPA+DHA intake that is below the FDA limit of 3,000 mg/day combined EPA+DHA. Also, the amount of DHA and EPA provided by the recommended use of Omega-3 PL is well below the 2,000 mg/day maximum dose that FDA recommends for dietary supplements containing fish oil (FDA, 2000b [Docket No. 91N-0103]). The recommended use of Omega-3 PL would also provide up to 1.0 g PC, which corresponds to about 130 mg choline. This amount of choline is approximately 3.7% of the Tolerable Upper Intake Level for choline (i.e., 3.5 g/day) (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine).

SECTION 4

The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer has concluded that the dietary supplement will reasonably be expected to be safe.

4.1 Introduction

PL are naturally present in all cell membranes (Houtsmüller, 1979), where they play a pivotal role in the regulation of cell membrane properties such as fluidity, permeability, and membrane-bound enzyme activity (Wang *et al.*, 2000). In addition to being important sources of energy, PL are also important sources of long-chain polyunsaturated fatty acids (LC-PUFA), such as EPA, DHA, and arachidonic acid (AA), which are necessary for normal infant growth and brain development. Very high concentrations of LC-PUFA are found in brain PL of grey matter and retinal membranes, especially in photoreceptor cells (Wang *et al.*, 2000).

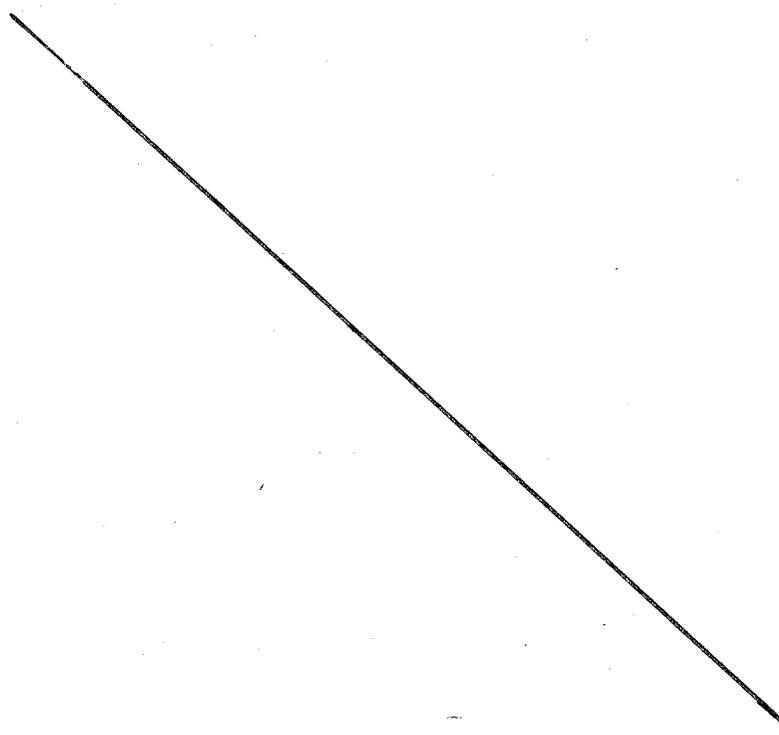
While the majority of dietary ingredients used in fish oil supplements provide EPA and/or DHA in TG form, in Omega-3 PL, these LC-PUFA are provided both in TG form and in PL form. Thus, in the safety evaluation of Omega-3 PL, these constituents, namely PL and the fish oils (EPA and DHA), were examined individually and in combination as "Omega-3 PL". Several aspects were considered in the safety evaluation of Omega-3 PL, including current FDA regulations regarding lecithin, EPA, and DHA, background exposure in the diet, metabolism, genotoxicity, general and developmental toxicity, and human clinical trials. Because other fatty acids are present in Omega-3 PL, the safety of these fatty acids was evaluated with reference to their natural abundance in the diet.

4.2 Regulatory Status

4.2.1 Omega-3 PL

While there are regulations in the United States pertaining to the maximum amount of EPA and DHA that can be consumed safely from foods and from dietary supplements, regulations pertaining to the form of these fatty acids do not exist (*i.e.*, these fatty acids can be administered in TG form or in the form of PL, ethyl esters, or as free fatty acids). An EPA/DHA formulation that is predominantly in PL form and that is currently being regulated as a dietary supplement in the U.S. (Docket No. 95S-0316), Canada, and Japan is Krill Oil (Neptune Technologies, Quebec, Canada).

Krill Oil is isolated from the Krill, which is a small shrimp-like marine crustacean. Although Krill Oil and Omega-3 PL vary in their fatty acid compositions and fractional lipid profiles, they are similar in the ratio of EPA:DHA, as well as in the total amount of phospholipids



4.2.2 Lecithin

Lecithin, meeting FCC specifications, has GRAS status in foods with no limitations other than current GMP [21 CFR § 184.1400(c)] (CFR, 2005a). Lecithin also has GRAS status as a general purpose food additive (21 CFR § 582.1400) (CFR, 2005b). The Meat and Poultry Inspection Division lists lecithin as an "Emulsifying Agent", and approves its use as an emulsifier

and an antioxidant in oleomargarine (up to a maximum of 0.5%), and in shortening and various meat and poultry products (in amounts "sufficient for purpose").

4.2.3 EPA/DHA

The FDA has established a maximum daily intake of 3.0 g of DHA and EPA. This level was initially established in 1997 when the FDA determined that menhaden oil was GRAS up to a level which provided a maximum of 3.0 g DHA+EPA/day. Since this ruling, FDA has received notices from several other companies that have concluded that fish oils, other than menhaden oil, are GRAS for use in the same food categories as those listed in 21 CFR 184.1472(a) (3) at maximum use levels that are designed to assure that the combined daily intake of EPA and DHA would not exceed 3 g per person per day (CFR, 2005a). As in the final ruling for menhaden oil, the GRAS status of these fish oils was based on the use of the fish oil product as the sole added source of EPA and DHA, and not in combination with other EPA/DHA-rich oils. A summary of fish oils that have self-affirmed GRAS status can be found in Table 4.2-2. Some of these oils have a total content of EPA+DHA that is greater than the level in menhaden oil, which is 20%. In addition, the ratio of EPA:DHA varies from 1:12 in algal oil (Martek Biosciences Corp.) to 1.6:1 in the 18/12 TG oil (Ocean Nutrition Canada Ltd.). In Omega-3 PL, EPA+DHA are present in amounts up to 21.0% total, by weight, and the ratio of EPA:DHA is approximately 2:1. Thus, Omega-3 PL has an EPA and DHA composition that is typical of other fish oils.

Company	GRAS Notice Number (Date)	Oil	Source	% Total EPA+DHA*	% EPA*	%, DHA*	Ratio of EPA:DHA
Natural ASA**	Not applicable						
Not applicable	Not applicable	Menhaden	Menhaden	20.0	12	8	1.5:1
Jedwards International	000146 (August 17, 2004 – FDA, 2004b)	Salmon	Salmon	20.0	8	12	1:1.5
Ocean Nutrition Canada Ltd. (c/o Jheimbach LLC)	000138 (April 20, 2004 – FDA, 2004a)	18/12 TG	Anchovy (95 – 99%), sardine (1 – 5%), jack mackerel, Pacific mackerel, and other occasional species.	30.3	18.5	11.8	1.6:1
Martek Biosciences Corp.	000137 (February 12, 2004 – FDA, 2004c)	Algal	<i>Schizochytrium</i> sp.	38.0	3	35	1:12

Table 4.2-2 Sources of Omega-3 Fatty Acids with Self-Affirmed GRAS Status for Direct Use in Food

Company	GRAS Notice Number (Date)	Oil	Source	% Total EPA+DHA*	% EPA*	%, DHA*	Ratio of EPA:DHA
Clover Corporation (c/o Piper Rudnick, LLP)	000109 (December 4, 2002 – FDA, 2002a)	Tuna	Tuna (skipjack, yellowfin, albacore, bigeye)	32.5	6	26.5	1:4.4
Unilver United States Inc.	000105 (October 15, 2002 – FDA, 2002b)	Fish Oil Concentrate (Marinal Oil Omega-3 Concentrate)	Anchovy, sardine, jack mackerel, mackerel	38	20	18	1.1:1
Jedwards International	000102 (September 3, 2002 – FDA, 2002c)	Small planktivorous pelagic fish body oil (SPPFBO)	Sardine, anchovy	30.0	18	12	1.5:1

* Percentages of the long-chain omega-3 fatty acids are expressed by weight.

** Omega-3 PL has been included in the table only for reference.

In 2004, the FDA reaffirmed that the intake of DHA and EPA must not exceed 3.0 g/day from all fish oil sources (FDA, 2004d), and recommended that dietary supplements provide a maximum of 2 g/day combined EPA and DHA (FDA, 2000b [Docket No. 91N-0103]).

4.3 Background Exposure From the Diet

4.3.1 Omega 3 Phospholipids

Omega-3 PL occur naturally in several foods, including food sources of marine origin, eggs (both regular and omega-3 enriched), human milk, and infant formula. In addition, Omega-3 PL has a similar fatty acid composition and fractional lipid profile as Krill Oil (Neptune Technologies and Bioresources, Quebec, Canada), an ingredient that is currently approved for use in dietary supplements in the United States (Docket No. 95S-0316). Krill Oil is discussed in Section 4.2.1.

4.3.1.1 *Omega-3 Phospholipids in Marine Foods*

EPA- and DHA-rich PL are known to occur naturally in many marine food sources, including fish, shellfish, and algae. An analysis of lipid classes, fatty acids, and sterols in samples of fish and seafood from Gilbert Bay, South Labrador has recently been conducted (Copeman and Parrish, 2004). These results are summarized in Table 4.3-1. The PL fraction in fish and seafood can account for up to 75% of total lipids, with the flesh of fish generally having a greater composition than fish livers. EPA and DHA are also fairly concentrated in fish and seafood, and are within the range found in Omega-3 PL. These data suggest that a 100 g serving of cooked blue mussels, which contains 4.48 g of fat (USDA, 2005) would provide approximately 1.47 g EPA+DHA and 1.69 g PL, and a 100 g serving of cooked Atlantic herring, which contains

11.59 g of fat (USDA, 2005) would provide approximately 1.83 g EPA+DHA and 0.74 g PL. For comparison, the highest recommended intake of Omega-3 PL (4 g/day) would result in an intake of up to 840 mg EPA+DHA and 2.2 g PL.

Species	Phospholipids (% Total Lipids)		Long Chain Omega-3 Fatty Acids (% Total Fatty Acids)			
			EPA		DHA	
	Flesh	Liver	Flesh	Liver	Flesh	Liver
Fish						
<i>Gadus morhua</i> (northern cod)	54.9 ± 6.5	12.3 ± 7.0	19.1 ± 0.4	12.2 ± 1.7	32.6 ± 1.5	12.7 ± 1.2
<i>Gadus morhua</i> (golden cod)	55.5 ± 3.3	13.3 ± 4.4	18.2 ± 1.4	14.3 ± 0.9	33.1 ± 2.6	15.0 ± 1.4
<i>Gadus ogac</i> (rock cod)	43.9 ± 5.4	11.6 ± 2.3	19.6 ± 0.6	15.0 ± 7.6	29.2 ± 1.4	12.7 ± 6.4
<i>Clupea harengus</i> (herring)	6.4 ± 2.1	35.8 ± 7.8	7.0 ± 1.4	14.4 ± 1.5	8.8 ± 0.5	23.5 ± 3.3
Seafood	Whole Body		Whole Body		Whole Body	
<i>Serripes groenlandicus</i> (Greenland cockle)	49.9 ± 7.6		22.6 ± 1.3		16.5 ± 1.0	
<i>Mytilus edulis</i> (blue mussel)	37.8 ± 3.1		19.6 ± 1.3		13.2 ± 1.0	
<i>Chlamys islandica</i> (Icelandic scallops)	74.6 ± 3.7		26.9 ± 2.9		25.9 ± 2.6	
<i>Spisula solidissima</i> (little surf clam)	63.3		22.9		14.3	

Data are mean ± SD; adapted from Copeman and Parrish, 2004.

4.3.1.2 Omega-3 Phospholipids in Eggs

Although foods of marine origin represent the primary sources of omega-3 PL, consumption of these foods is low in many parts of the world, including the U.S. As an example, in 1995, the per capita fish consumption in Japan was 45 lb whereas in the U.S., it was 3-fold less, averaging about 15 lb (National Marine Fisheries Service, UN Food and Agriculture Organization, 1996). In an effort to increase the intake of DHA in the U.S., DHA-enriched eggs were produced. The fatty acid composition of regular and DHA-enriched eggs, with respect to their omega-3 fatty acid content, is shown in Table 4.3-2. The PL and TG fatty acid distribution of DHA-enriched eggs is shown in Table 4.3-3. The consumption of 2 DHA-enriched eggs would result in an intake of 290.4 mg combined EPA+DHA, which is approximately 34.5% of the highest proposed intake of EPA+DHA from Omega-3 PL.

Fatty Acid	Control Egg (mg/egg)	DHA-enriched Egg (mg/egg)
C18:3n-3 (ALA)	15.0	94.9
C20:5n-3 (EPA)	0.0	10.2
C22:6n-3 (DHA)	27.6	135.1
Total omega-3 fatty acids	43.0	248.0
Long-chain omega-3 fatty acids	28.0	153.0
Short-chain omega-3 fatty acids	15.0	95.0
Omega-6 to omega-3 ratio	19:1	2:1

* Adapted from Abril and Barclay, 1998.

Fatty Acid	PL (% total fatty acids)	Triacylglycerol (% total fatty acids)
C18:3n-3 (ALA)	0.00	1.73
C20:5n-3 (EPA)	0.20	0.00
C22:6n-3 (DHA)	8.80	0.39

* Adapted from Abril and Barclay, 1998.

4.3.1.3 *Omega-3 Phospholipids in Human Milk and Infant Formula*

Human milk and infant formula also contain omega-3 PL. The level of PL in human milk ranges from 20 to 40 mg/100 mL; the relative concentration of PC, phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), and spingomyelin in human milk is 30%, 28%, 5.3%, 4%, and 31%, respectively (Jensen, 1989; cited in Gorbunov *et al.*, 2001). The DHA content of human milk has been shown to vary widely across women living in different countries of the world, and is dependent on the maternal dietary intake of DHA (Sala-Vila *et al.*, 2003). Women in the marine region of China have the highest level of breast milk DHA (approximately 2.75 g/100 g total fatty acids), followed by Canadian Inuit women (approximately 1.25 g/100 g total fatty acids) (Sala-Vila *et al.*, 2003). DHA levels in lactating women living in the United States average 0.1 g/100 g total fatty acids (Innis, 2004).

A recent study assessing the fatty acid composition of total lipids and PL in breast milk from Japanese women reported that 10.1% of DHA (1.09% of total lipids) and 33.06% of EPA (0.13% of total lipids) are in the form of PL (Wang *et al.*, 2000). Using these values and the total fat content of mature breast milk (USDA, 2005), the total daily intake of DHA and EPA, as well as the amount in PL form, were estimated (Table 4.3-4).

On a per kilogram basis, the intake of EPA+DHA in infants who are exclusively breastfed for the first 3 months of life (10.22 mg/kg body weight/day) is very similar to the intake of EPA+DHA for a 70 kg adult from the proposed use of Omega-3 PL (up to 12 mg/kg body weight/day). In the calculations presented in Table 4.3.1-4, the levels of DHA and EPA were each assumed to be 100 mg/100 g total fatty acids (Innis, 2004); however, these levels are conservative, as a very wide range of DHA and EPA levels in breast milk from lactating women residing in the U.S. have been reported (DHA, up to 400 mg/100 g total fatty acids; EPA, up to 300 mg/100 g total fatty acids; Innis, 2004). Thus, on a per kilogram basis, the daily intake of DHA and EPA from breast milk may actually exceed the levels proposed in Omega-3 PL.

In recognition of the need to match the long-chain polyunsaturated fatty acid (LC-PUFA) composition of infant formula to that of breast milk, the European Society of Pediatric Gastroenterology and Nutrition (ESPGHAN) Committee on Nutrition (Aggett *et al.*, 1991), the FAO/WHO Expert Committee on Fats and Oils in Human Nutrition (FAO/WHO, 1994), and the Commission of the European Union (European Commission, 1996), recommended that AA and DHA be included in infant formula at levels that are equivalent to those found in breast milk. A variety of purified lipid sources are being used to supplement infant formula with LC-PUFA, including egg yolk lipids, in which the LC-PUFA are in PL form, and single-cell cyanoficeae algae, fungi, and fish, in which the LC-PUFA are predominantly in the form of TG (Gil *et al.*, 2003). While formula-fed infants receiving an egg-PL DHA+AA enriched formula ingest a larger proportion of DHA in the form of PL, overall, they consume roughly half the amount of DHA as breastfed infants, and no EPA (Table 4.3-4).

		DHA (mg)				EPA (mg)				Combined DHA+EPA (mg)			
		Total ⁴		From PL ⁴		Total ⁴		From PL ⁴		Total ⁴		From PL ⁴	
		mg	mg/kg bw ³	mg	mg/kg bw ³	mg	mg/kg bw ³	mg	mg/kg bw ³	mg	mg/kg bw ³	mg	mg/kg bw ³
Breast milk	Intake per 100 g ¹	4.38	0.71	0.44	0.07	4.38	0.71	1.45	0.23	8.76	1.42	1.89	0.30
	Intake per day ²	31.67	5.11	3.20	0.52	31.67	5.11	10.47	1.69	63.34	10.22	13.67	2.21
Egg PL DHA+AA enriched formula ⁵	Intake per 100 g ¹	5.73	0.92	5.73	0.92	0	0	0	0	5.73	0.92	5.73	0.92
	Intake per day ²	41.4	6.67	41.4	6.68	0	0	0	0	41.4	6.68	41.4	6.68

¹ The value for total fat content of human mature milk (4.38 g/100 g) was derived from the USDA National Nutrient database (USDA, 2005). The same value was used in the calculations pertaining to the infant formula.

² The value for daily intake of breast milk (723 g/day) in exclusively breast-fed infants at 3 months of age was derived from the Child-Specific Exposure Factors Handbook (U.S. EPA, 2002). The same value was used in the calculations pertaining to the infant formula.

³ The value for the body weight of a 3-month-old infant (6.2 kg) was derived from the Child-Specific Exposure Factors Handbook (U.S. EPA, 2002). The same value was used in the calculations pertaining to the infant formula.

⁴ DHA and EPA levels in breast milk were each considered to be 100 mg/100 g total fatty acids (Innis, 2004). 10.1% of DHA and 33.06% of EPA were considered to be in PL form (Wang *et al.*, 2000).

⁵ The amount of DHA and EPA in the egg PL DHA+AA enriched infant formula was 130 mg/100 g total fatty acids and 0 mg/100 g total fatty acids, respectively (Carlson *et al.*, 1998).

Abbreviations: AA, arachidonic acid; BW, body weight; DHA, docosahexaenoic acid; EPA, eicosahexaenoic acid; PL, phospholipid.

4.3.2 Lecithin

The term lecithin is often used interchangeably with the term PC. Commercial lecithin, made from processed soybeans and used as a food additive in nutrition supplements, is actually a mixture of PC (about 23%) and other PL (Canty *et al.*, 1994). PC contains about 13% choline, by weight (Canty *et al.*, 1994). Lecithin is an important source of the essential nutrient, choline. Adequate intakes (AI) and Tolerable Upper Intake Levels (UL) for choline have been established by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. The Adequate Intake (AI) for adults is 550 mg daily for men and 425 mg daily for women. The UL is 3.5 g/day.

Lecithin is a component of all biomembranes; thus, most foods contain some lecithin (Zeisel *et al.*, 1982). While egg yolks, organ meats, spinach, nuts, and wheat germ are especially good sources of lecithin, there are many other sources of lecithin in the diet (Table 4.3-5). In addition, lecithin is used widely as an emulsifier in food manufacturing. Omega-3 PL contains 400 to 550 mg/g total PL and 150 to 250 mg/g PC. With the daily intake of up to 4 g/day Omega-3 PL, the maximum intake of total PL and PC is 2.2 g and 1.0 g, respectively, corresponding to a maximum choline intake of 130 mg/day.

JECFA reported that the average diet provided about 1 to 5 g daily of lecithin (JECFA, 1974). Similarly, using data collected from the 1970s, Zeisel *et al.* (1982) estimated that Americans ingest about 6 g lecithin daily, corresponding to approximately 300 to 1,000 mg choline daily. An additional 100 mg/day are consumed from food products containing added lecithin (Zeisel *et al.*, 1982). Studies on lecithin intakes were conducted over 30 years ago and, since then, dietary intake patterns have changed considerably (Wurtman, 1979). Intakes of processed foods and away-from-home dinners have increased substantially, thus increasing lecithin intakes (Wurtman, 1979). At the same time, health-conscious Americans have reduced their consumption of cholesterol-rich fatty foods that are also a good source of lecithin (*i.e.*, eggs, meat, and dairy products). Lecithin-containing food supplements have become popular in maintaining neurological and cardiovascular health, and have contributed to an increase in lecithin consumption (Wurtman, 1979). Thus, true lecithin intake levels are unknown; however, it seems likely that dietary patterns associated with a reduction in lecithin consumption are counterbalanced by those associated with increased lecithin intakes through supplementation.

Food	Serving Size	Lecithin (mg/serving)	Choline (mg/serving)
Apple	1 medium	29.87	0.39
Banana	1 medium	3.26	2.85
Beef liver	3.5 oz	3362.55	60.64
Beef steak	3.5 oz	446.12	0.78
Butter	1 tsp	6.8	0.02
Cauliflower	1/2 cup	107.06	6.79
Corn oil	1 tbsp	0.13	0.004
Coffee	6 oz	2.05	18.59
Cucumber	1/2 cup	3.06	1.18
Egg	1 large	2009.80	0.22
Ginger ale	12 oz	1.11	0.07
Grape juice	6 oz	2.11	8.99
Human milk	1 cup	27.08	2.10
Iceberg lettuce	1 oz	2.86	8.53
Infant formula	1 oz	2.97	0.818
Margarine	1 tsp	1.74	0.02
Milk (whole)	1 cup	27.91	3.81
Orange	1 medium	53.03	2.91
Peanut butter	2 tbsp	97.39	12.96
Peanuts	1 oz	107.35	13.24
Potato	1 medium	25.97	5.95
Tomato	1 medium	4.94	5.50
Whole wheat bread	1 slice	6.57	2.52

4.3.3 EPA/DHA

Foods of marine origin are the most concentrated sources of EPA and DHA; thus, the prevalence of these foods in the diet is the primary factor affecting dietary intake of EPA and DHA. A 2.5-year study examining the eating habits of individuals residing in France revealed that the average DHA intake is 273 and 226 mg/day in men and women, respectively, and the average EPA intake is 150 and 118 mg/day in men and women, respectively (Astorg *et al.*, 2004). In contrast, the average daily intakes of DHA and EPA were reported to be 106 and 56 mg/day, respectively, in Australia (Meyer *et al.*, 2003). In a study of the dietary intake of pregnant Canadian women, it was reported that the average intakes of DHA and EPA were 160 and 78 mg/day, respectively (Innis and Elias, 2003). The recent production of DHA-enriched eggs and the incorporation of AA and DHA in infant formula have resulted in an increase in DHA

intake (see Section 4.3.1). In addition, DHA and EPA are being added to a multitude of foods such as yoghurt, cheese, milk, and margarine.

4.3.4 Other Fatty Acids and Components Present in Omega-3 Phospholipids

4.3.4.1 Other Fatty Acids Present in Omega-3 Phospholipids

In addition to EPA and DHA, Omega-3 PL contains several other fatty acids (Table 4.3-6). As discussed in the following sections below, these fatty acids are naturally present in the diet.

Fatty Acid Formula	Trivial Name	Level in Omega-3 PL (mg/g)**
C14:0	Myristic acid	
C16:0	Palmitic acid	
C16:1	Palmitoleic acid	
C18:0	Stearic acid	
C18:1	Oleic acid	
C18:2 (n-6)	Linoleic acid	
C18:3 (n-3)	α -Linolenic acid	
C18:4 (n-3)	Stearidonic acid	
C20:0	Eicosanoic acid	
C20:1	Eicosenoic acid	
C20:4 (n-6)	Arachidonic acid	
C20:4 (n-3)	Eicosatetraenoic acid	
C20:5 (n-3)	Eicosapentaenoic acid (EPA)	
C22:1 (n-11)	Cetoleic acid	
C22:5 (n-3)	Docosapentaenoic acid	
C22:6 (n-3)	Docosahexaenoic acid (DHA)	
C24:1	Tetracosanoic acid	

* Only fatty acids present in amounts greater than 5 mg/g are presented.

** The level of each fatty acid is shown as a mean of five different analyses (see Appendix C for the Certificate of Analysis for each data set).

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4.4 Metabolism

4.4.1 Biosynthesis

4.4.1.1 *Lecithin*

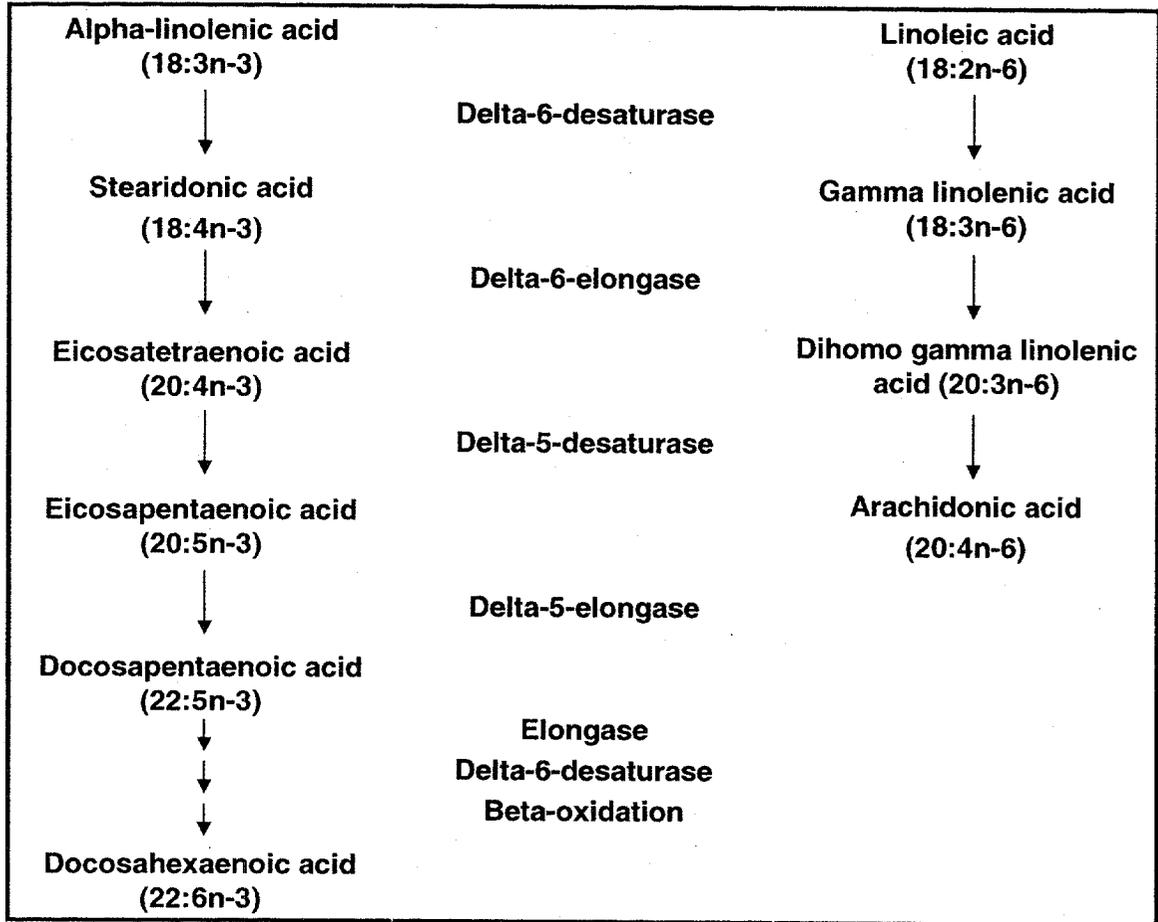
PC, a normal and abundant human cell membrane constituent (Houtsmüller, 1979), can also be synthesized *de novo* via 3 distinct pathways (Zeisel *et al.*, 1979). In the first pathway, called the cytidine diphosphate (CDP) choline pathway, choline is phosphorylated to phosphocholine *via* the enzyme choline kinase; phosphocholine is then converted to CDP-choline (*via* CTP:phosphocholine cytidyltransferase) and subsequently to PC (*via* CDP:choline: diacylglycerol cholinephosphotransferase). PC can also be synthesized *via* the base-exchange pathway, where a free nitrogenous base (*i.e.*, choline) is interchanged with a PL-bound base (*i.e.*, serine, inositol, ethanolamine). The base-exchange pathway is also reversible, resulting in choline displacement from PC. Another pathway to PC synthesis involves the conversion of either PS or PE to PC. The conversion of PS to PC first requires decarboxylation of PS to yield PE; PE then undergoes a series of 3 methylation reactions utilizing S-adenosylmethionine (SAM) as a methyl group donor.

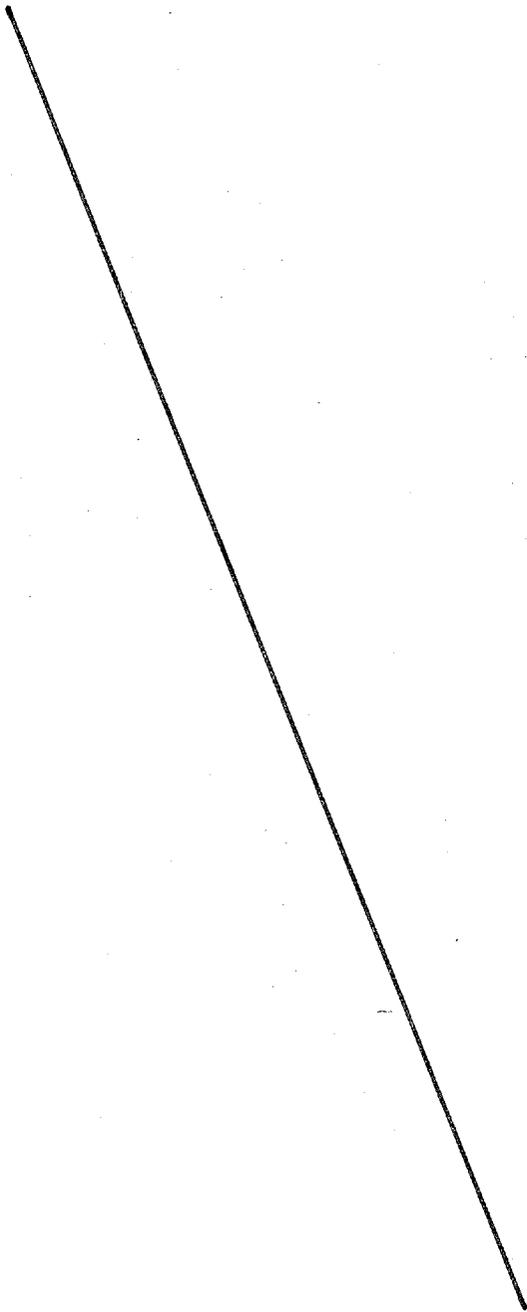
PC is an important source of the essential nutrient, choline. In addition to the metabolic pathways of biosynthesis outlined in the preceding paragraph, choline is utilized in 3 other metabolic pathways, including acetylation to the neurotransmitter acetylcholine, irreversible oxidation to betaine (a methyl donor), and generation of sphingomyelin.

4.4.1.2 *EPA and DHA*

EPA and DHA can be synthesized from their 18-carbon precursor, alpha-linolenic acid, *via* the desaturation-elongation pathway. While alpha-linolenic acid is considered to be an essential fatty acid, DHA has come to be known as conditionally essential, since infants, particularly pre-term infants and those who are exclusively formula-fed, have a limited capacity to synthesize DHA endogenously (Cunnane *et al.*, 2000). It is noteworthy that the same enzymes involved in the synthesis of EPA and DHA from α -linolenic acid are also involved in the synthesis of AA from its precursor, linoleic acid (Figure 4-1). Thus, α -linolenic acid and linoleic acid compete for the same elongation and desaturation enzymes.

Figure 4-1 Synthesis of Long-Chain Polyunsaturated Fatty Acids from Their 18-Carbon Precursors





4.4.3 Phospholipid Metabolism

PL are present in every cell of the human body, where they function to compartmentalize and protect cellular components from the outside environment. While TG synthesis occurs only in the liver, adipose tissue, lactating mammary glands, and intestinal mucosal cells, *all cells*, except mature erythrocytes, are capable of PL synthesis. In addition, in cellular membranes, PL are continually being degraded, resynthesized, and remodeled. The following enzymes are important in the metabolism of phospholipids:

- Phospholipase A₂ catalyzes the hydrolysis of the ester bond in the *sn-2* position of the PL, resulting in the formation of one free fatty acid and lysophospholipid;
- Phospholipase A₁ causes cleavage of the ester bond at the *sn-1* position of the PL, resulting in the formation of one free fatty acid and lysophospholipid;
- Phospholipase B cleaves the ester bond either at the *sn-1* or *sn-2* positions of the PL, resulting in the formation of one free fatty acid and lysophospholipid;
- Phospholipase C catalyzes hydrolysis of the ester bond at the *sn-3* position of the PL (liberating the base and 1,2-diacylglycerol); and
- Phospholipase D, which hydrolyzes the nitrogenous base from PL and is involved in signal transduction.

Clearly, PL represent an important class of membrane lipids in all body cells. Because PL are important in the maintenance of membrane stability and in signal transduction, they are constantly being remodeled and restructured.

4.5 Animal Studies

4.5.1 Acute Single Dose Toxicity

No acute single dose toxicity studies for lecithin and for EPA and DHA were identified in the literature.

4.5.2 Repeated Dose Toxicity

4.5.2.1 Lecithin

The repeated dose toxicity of lecithin has been assessed in both short-term and long-term feeding studies. Short-term feeding studies of lecithin (*i.e.*, 2 weeks in duration) were conducted in mice, rats, and rabbits (Table 4.5-1). Deaths were not observed in any of the studies, and the oral LD₅₀ ranged from 4.75 ± 0.64 g/kg (in rabbits) to >16 g/kg (in rats and mice).

Reference*	Animals	Sample Size	Lecithin Dose and Study Duration	Results
FDRL, 1973a	Albino CD-1 outbred mice.	5 groups (n=5 males and 5 females per group).	1, 2, 4, 8, or 16 g/kg/day for 2 weeks.	None of the animals died. Oral LD ₅₀ was >16 g/kg.
FDRL, 1973b	Albino Wistar rats.	5 groups (n=5 males and 5 females per group).	1, 2, 4, 8, or 16 g/kg/day for 2 weeks.	None of the animals died. Oral LD ₅₀ was >16 g/kg.
FDRL, 1973c	Dutch-Belted rabbits.	5 groups (n=5 males and 5 females per group).	3, 4, 8, 9, or 16 g/kg/day for 2 weeks.	None of the animals died. Oral LD ₅₀ was 4.75 ± 0.64 g/kg.

* All studies cited in CIR, 2001.

Lechowski *et al.* (1999) studied the effects of long-term administration of a lecithin-supplemented diet on the biochemical profile and morphological changes in the liver of rats fed different animal fats. Male Wistar rats (8 weeks old) were randomly divided into 8 groups (n=8/group) and fed fully synthetic diets containing various animal fats (beef tallow, pork fat, or fish oil) with or without lecithin supplementation for 36 days. Two control groups consumed a diet without added fat, either with or without lecithin. Lecithin was supplemented at a level of 5%, by weight. Lecithin supplementation did not result in any pathological lesions in the liver. Fatty degeneration of hepatocytes was less pronounced in all groups that were supplemented with lecithin. Lecithin supplementation had favorable effects on total and HDL cholesterol.

Brantom *et al.* (1973) assessed the effects of chronic consumption of a diet containing 4% soya lecithin in 48 male and 48 female SPF Wistar rats. Rats consumed the lecithin-enriched diet for 2 years, and feed consumption, body weights, mortality, hematology, organ weights, and gross and microscopic organ pathologies were compared to rats consuming a control diet. The mean lecithin intake was 1,470 and 2,280 mg/kg/day for males and females, respectively. Although there was a trend to increased feed consumption and body weight in the lecithin-supplemented group, there were no significant differences observed between groups in any of the other parameters measured.

4.5.2.2 DHA and EPA Studies

Several animal studies were identified in which the safety of DHA and EPA consumption was examined. In one study, 5-week-old male Otsuka Long-Evans Tokushima Fatty (OLETF) rats (which are used to model Type 2 diabetes) were provided with diets containing 1.0 g EPA/kg body weight/day, 1.0 g oleic acid/kg body weight/day or a non-supplemented rat chow diet until they were 30 weeks of age (Minami *et al.*, 2002). No adverse events or signs of toxicity were reported in OLETF rats consuming a diet providing 1.0 g EPA/kg body weight/day. Moreover, consumption of the EPA-containing diet had beneficial effects on various lipid and biochemical parameters, causing significant reductions in plasma TG levels and abdominal fat accumulation, and significantly improving insulin resistance. Thus, EPA was found to have a potentially beneficial role in improving insulin sensitivity in Type 2 diabetes.

In another animal study, diets containing corn oil, corn oil and 0.1 g EPA/kg body weight/day, or corn oil and 1.0 g EPA/kg body weight/day were fed to ovariectomised rats for 9 weeks (Poulsen and Kruger, 2004). No significant differences were noted between the bone breaking strength and serum type-1 collagen concentrations of the treatment and control rats. Ovariectomised rats consuming 1.0 g EPA/kg body weight/day were reported to have a significantly lower femur bone density, which was attributed to a decrease in bone density, possibly caused by an increase in bone resorption. In contrast to these findings, the administration of EPA to older women (mean age 79.5 years) had beneficial effects on bone density (Kruger *et al.*, 1998).

The administration of a diet containing 2% DHA or EPA ethyl esters, representing a dose of approximately 1,000 mg/kg body weight/day, to normal Sprague-Dawley rats for 3 weeks did not result in any adverse events (Hung *et al.*, 2000). In contrast, consumption of EPA and DHA had beneficial effects on lipid metabolism and leukotriene synthesis, with the effects elicited by EPA consumption being stronger than those elicited by consumption of DHA. In another study the administration, by gavage, of diets containing 0 (control), 0.5, or 1.25 g/kg body weight/day of an oil containing 40 to 50% DHA for 90 days to normal CD rats did not result in significant differences in any of the parameters examined (*i.e.*, hematology, clinical chemistry, pathology, ophthalmology, neurobehavioral, and neuropathological indices) (Arterburn *et al.*, 2000). The No-Observed-Adverse-Effect Level (NOAEL) for normal CD rats was calculated from the highest dose of DHA administered, and corresponded to a dose of approximately 0.5 to 0.625 g DHA/kg body weight/day.

One study was identified in which the safety of DHA, purified from tuna oil, was examined in pigs (Merritt *et al.*, 2003). Newborn piglets were administered formula providing approximately 387 or 653 mg DHA/kg body weight/day for male piglets and 412 or 691 mg DHA/kg body weight/day for female piglets. The consumption of either dose of DHA did not result in any significant effects on body weight, clinical signs, food consumption, clinical chemistry, hematology, organ weight, or gross or histopathology in the male and female piglets. These

study findings further corroborate the safety of DHA supplementation, and specifically provided support for the use of DHA from tuna oil in infant formulations.

4.5.3 Genotoxicity

The results of studies examining the mutagenic potential and genotoxic potential of lecithin are summarized in Table 4.5-2. Lecithin was neither mutagenic nor genotoxic in any study. On the contrary, the addition of lecithin to incubations of TA98 and 1,8-dinitropyrene reduced mutagenicity, though the reduction in mutagenicity was less than that seen with uninduced S9 (Shah *et al.*, 1991).

Reference*	Test System	Assay	Dose	Results
Litton Bionetics Inc., 1975	<i>Salmonella typhimurium</i> TA1535, TA1537, TA1538	Bacterial mutation	0.2% lecithin for plate tests; 0.01% to 0.04% for suspension tests	Negative
	<i>Saccharomyces cerevisiae</i> D4	Yeast mutation	1.875% to 5%	Negative

*All studies cited in CIR, 2001.

4.5.4 Developmental Toxicology

In a series of studies conducted by Food and Drug Research Laboratories (FDRL, 1973d,e, 1974), the effects of lecithin supplementation during gestation were assessed in mice, rats, and rabbits (Table 4.5-3). The administration of lecithin in doses ranging from 4.75 to 1,600 mg/kg/day for 10 to 13 consecutive days during gestation did not result in increased maternal or fetal mortality, or any maternal tissue abnormalities.

Reference*	Animals	Sample Size	Lecithin Dose and Study Duration	Results
FDRL, 1973d	Gravid albino CD-1 outbred mice.	5 groups (n=21 to 23 female mice per group).	0, 16.0, 74.3, 345.0, or 1600.0 mg/kg/day during days 6 to 15 of gestation.	The administration of up to 1,600 mg/kg/day lecithin to pregnant mice for 10 consecutive days had no effect on nidation or on maternal or fetal survival. The number of abnormalities in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control group.
FDRL, 1973e	Gravid albino Wistar rats.	5 groups (n=22 to 24 female rats per group).	0, 16.0, 74.3, 345.0, or 1600.0 mg/kg/day during days 6 to 15 of gestation.	The administration of up to 1,600 mg/kg/day lecithin to pregnant rats for 10 consecutive days had no effect on nidation or on maternal or fetal survival. The number of abnormalities in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control group.

Table 4.5-3 Reproductive Toxicity of Lecithin				
Reference*	Animals	Sample Size	Lecithin Dose and Study Duration	Results
FDRL, 1974	Gravid Dutch-Belted rabbits.	5 groups (n=10 to 12 female rabbits per group).	0, 4.75, 22.1, 100.3, or 475.0 mg/kg/day during days 6 to 18 of gestation.	One gravid animal in the 4.75 mg/kg/day group aborted on day 12 of gestation. Neonatal deaths were reported in all groups. The administration of up to 475 mg/kg/day lecithin to pregnant rabbits for 13 consecutive days had no effect on nidation, maternal, or fetal survival. The number of abnormalities in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control group.

* All studies cited in CIR, 2001.

4.6 Clinical Studies

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4.6.2 Lecithin

Clinical studies of lecithin have been conducted in a wide range of patient populations, including patients with Alzheimer's disease, tardive dyskinesia, Parkinson's disease, and other neurological disorders (Table 4.6-2). Lecithin has been administered in doses ranging from 1.2 to 105 g for 1 day to 36 weeks. In Omega-3 PL, the amount of total PL is 400 to 550 mg/g, and the amount of PC is 150 to 250 mg/g. With an intake of up to 4 g/day Omega-3 PL, the maximum intake of total PL and PC is 2.2 g and 1.0 g, respectively. It is generally accepted that most individuals can tolerate at least 25 g PC per day, without experiencing adverse gastrointestinal side effects (*i.e.*, nausea, vomiting, diarrhea) (Wood and Allison, 1982). In some studies, consumption of lecithin doses as high as 50 to 100 g for up to 10 weeks have been well-tolerated (Jackson *et al.*, 1981; Wilbur *et al.*, 1982; Yackulic *et al.*, 1982; Anderson *et al.*, 1983; Randels *et al.*, 1984; Volavka *et al.*, 1986). Long-term consumption of high doses of lecithin has been associated with weight gain; this results from the high caloric density of lecithin.

Table 4.6-2 Summary of Clinical Studies Evaluating the Effects of Lecithin Consumption

Study Design	Study Population	Lecithin/Choline Dose	Duration	Adverse Events	Reference
Clinical Studies of Lecithin in Patients with Alzheimer's Disease					
Randomized, double blind, placebo-controlled study assessing the effects of lecithin, administered with or without tarcine, in patients with AD.	32 patients (17 males and 15 females, aged 52 to 84 years) with AD.	9 X 1,200 mg lecithin with (n=14) or without (n=18) 25 to 100 mg tarcine daily.	36 weeks	Raised aminotransferase concentration in one subject receiving lecithin only.	Maltby <i>et al.</i> , 1994
Multi-center, double blind, randomized, placebo-controlled, crossover clinical trial assessing the effects of lecithin, administered with or without tarcine, in patients with AD.	67 outpatients (24 males and 43 females, aged 53 to 81 years) with AD.	1,200 mg lecithin daily with or without 114 mg tarcine.	1 month	Mild GI side effects reported in 4 subjects consuming lecithin alone and in 20 subjects consuming both lecithin and tarcine.	Chatellier <i>et al.</i> , 1990
Randomized, double blind, placebo-controlled, crossover study assessing the effects of piracetam, administered with or without PC, in patients with AD.	18 patients (5 males and 13 females, aged 56 to 75 years) with AD.	2.4 to 9.9 g piracetam and/or 18 g lecithin (80% PC) were administered daily.	3 to 4 weeks	Fasting plasma choline increased significantly from 11.5 ± 2.9 nmol/L to 40.8 ± 14.3 nmol/L ($P < 0.01$). No adverse events reported for PC.	Growdon <i>et al.</i> , 1986
Open label study assessing the effects of lecithin in patients with AD.	6 subjects (2 males and 4 females, aged 62 to 82 years) with AD.	A single oral dose of lecithin (15 g/70 kg, consisting of approximately 95% PC).	Acute (single) oral dose	Significant increases in plasma and red blood cell choline at 3 and 6 h post ingestion ($P < 0.01$). One or more episodes of diarrhea reported in some subjects.	Pomara <i>et al.</i> , 1983
Randomized, double blind, placebo-controlled, crossover study assessing the effects of memory training and lecithin administration on cognitive performance in patients with AD.	10 patients (7 males and 3 females, aged 54 to 73 years) with AD.	35 g/day of a mixture containing 53% PC orally.	2 weeks	Diarrhea reported in one patient that resolved on its own, without discontinuation of treatment.	Brinkman <i>et al.</i> , 1982

Table 4.6-2 Summary of Clinical Studies Evaluating the Effects of Lecithin Consumption

Study Design	Study Population	Lecithin/Choline Dose	Duration	Adverse Events	Reference
Clinical Studies of Lecithin in Patients with Dyskinesia					
Double blind, placebo-controlled, cross-over clinical trial assessing the effects of lecithin in patients with tardive dyskinesia.	14 patients (7 males and 7 females, aged 25 to 70 years) with tardive dyskinesia.	20 g/day PC for 8 weeks, preceded and followed by a 2- to 4-week baseline/washout.	8 weeks	Serum choline more than doubled during lecithin treatment (from 11.1 ± 3.1 nmol/L to 23.4 ± 11.3 nmol/L). No clinically significant adverse events associated with lecithin consumption; however, GI symptoms were reported by 7 (50%) of patients during lecithin treatment, compared with 3 (21%) during placebo treatment. Symptoms included diarrhea, nausea, and abdominal pain.	Gelenberg <i>et al.</i> , 1990
Double blind, placebo-controlled study assessing the effects of lithium, administered with or without lecithin, in patients with tardive dyskinesia.	18 psychiatric inpatients (11 males and 6 females; mean age, 49.7 years) with tardive dyskinesia.	The dose of lithium administered was sufficient to maintain a serum level of 0.6 mEq/L. Lecithin (containing 93.5% PC) was administered at 50 g/70 kg/day.	5 weeks	None reported.	Volavka <i>et al.</i> , 1986
Randomized, double-blind study assessing the effects of lithium, lecithin, and lithium+lecithin in patients with tardive dyskinesia.	9 inpatients (4 males and 5 females, aged 41 to 72 years) with tardive dyskinesia.	After 2 baseline weeks, subjects were divided into 2 groups and administered lithium (n=5) or lecithin (n=4) throughout the entire study (weeks 3 to 11) and combined (lithium + lecithin) during weeks 6 to 8. The dose of lithium administered was sufficient to maintain a serum level of 0.6 mEq/L. Lecithin (containing 93.5% PC) was administered at 50 g/70 kg/day.	8 weeks	None reported.	Anderson <i>et al.</i> , 1983

Table 4.6-2 Summary of Clinical Studies Evaluating the Effects of Lecithin Consumption

Study Design	Study Population	Lecithin/Choline Dose	Duration	Adverse Events	Reference
Randomized, double blind, placebo-controlled study assessing the effects of lecithin in patients with tardive dyskinesia.	5 female inpatients (aged 32 to 77 years) with tardive dyskinesia.	Three doses of lecithin were studied in three separate studies: (i) 31.5 or 50 g/70 kg/day lecithin (derived from soyabean extract and containing 93.5% PC), consumed daily for 4 weeks or 50 g/70 kg/day lecithin (derived from egg yolk and containing 54% PC) for 3 weeks.	3 to 4 weeks	All treatments caused significant increases in serum choline. No adverse events noted in any of the studies.	Anderson <i>et al.</i> , 1982
Case report of a patient with tardive dyskinesia administered lecithin.	74-year-old woman with idiopathic dyskinesia	650 mg lecithin (5 tablets of 130 mg each) 3 times daily for 2 years, followed by 500 mg lecithin (2 tablets of 250 mg each) 6 times daily for a prolonged time period.	> 2 years	None reported.	Vickar, 1982
Case report of a patient with tardive dyskinesia administered lecithin.	68-year-old female with tardive dyskinesia.	A dose of 72 g lecithin (containing 21 to 24% PC) was introduced gradually over a period of 16 days, and maintained for another 7 days.	23 days	None reported.	Wilbur <i>et al.</i> , 1982
Randomized, double blind, placebo-controlled study assessing the effects of lecithin in patients with tardive dyskinesia.	12 subjects (3 males and 9 females) with tardive dyskinesia and schizophrenia.	Three doses of lecithin were studied in three separate studies: (i) 31.5 or 50 g/70 kg/day lecithin (derived from soyabean extract and containing 93.5% PC), consumed daily or 50 g/70 kg/day lecithin (derived from egg yolk and containing 54% PC).	Up to 6 weeks	Three-fold increase in serum choline. One patient developed insomnia during the last 2 weeks of a 4-week trial, and reported feeling depressed. Weight gain (up to 2.7 kg in one patient) occurred during lecithin treatment, but did not reach statistical significance.	Yackulic <i>et al.</i> , 1982
Randomized, double-blind placebo-controlled, crossover study assessing the effects of lecithin in patients with tardive dyskinesia.	6 inpatients (1 male and 5 females, aged 49 to 60 years) with tardive dyskinesia.	50 g lecithin (containing 70% PC) daily for 14 days, preceded and followed by a 10-day baseline/washout.	14 days	Significant increase in serum choline. No adverse events reported.	Jackson <i>et al.</i> , 1981

Table 4.6-2 Summary of Clinical Studies Evaluating the Effects of Lecithin Consumption

Study Design	Study Population	Lecithin/Choline Dose	Duration	Adverse Events	Reference
Open label study assessing the effects of lecithin in subjects with ataxia.	4 subjects (2 males and 2 females, aged 18 to 56 years) with Friedreich's ataxia.	Lecithin (containing 22% PC) was consumed at a dose of 50 g/day for 8 weeks and 100 g/day for another 8 weeks.	16 weeks	Plasma choline increased significantly during treatment but tended to drop towards baseline levels despite continued lecithin ingestion. Two subjects could not tolerate lecithin doses in excess of 50 g/day, and 1 subject could only tolerate a maximum dose of 75 g/day. One patient became depressed, gained 6 kg during the study and withdrew at 11 weeks. All patients reported diarrhea and nausea during treatment and 2 experienced flushing of the skin.	Chamberlain <i>et al.</i> , 1980
Open label study assessing the effects of lecithin (containing 20% PC) in patients with tardive dyskinesia.	7 patients with tardive dyskinesia.	60 to 80 g lecithin (<i>i.e.</i> , equivalent to 12 to 16 g PC or 1.8 to 2.4 g choline) daily.	6 weeks to 6 months	Significant increases in serum choline in all patients. Mild GI disturbances reported, including indigestion, weight gain, and diarrhea.	Zeisel <i>et al.</i> , 1980
Open label study comparing the effects of choline chloride and lecithin (containing 20% PC) in patients with tardive dyskinesia.	5 male outpatients (aged 27 to 32 years) with tardive dyskinesia.	150 to 200 mg/kg/ choline chloride (<i>i.e.</i> , 12 to 17 g) daily for 6 to 8 weeks; after a washout (18 to 35 days), 42 to 105 g lecithin (<i>i.e.</i> , 8.4 to 21 g PC) daily for up to 6 months.	6 to 8 months	Both choline and lecithin resulted in a significant increase in serum choline. Adverse reactions to choline included a "fishy" body odor and GI irritation. No adverse reactions to lecithin, but 1 patient had a 7% increase in weight.	Gelenberg <i>et al.</i> , 1979a
Open label study assessing the effects of lecithin (containing 20% PC) in patients with tardive dyskinesia.	3 patients (2 males and 1 female, aged 48 to 70 years) with tardive dyskinesia.	45 to 95 g lecithin (<i>i.e.</i> , 9 to 19 g PC) daily.	2 to 8 weeks	Mild to severe bouts of diarrhea were reported, which resolved once the lecithin dose was reduced.	Gelenberg <i>et al.</i> , 1979b
Randomized, double, blind, placebo-controlled, crossover study assessing the effects of lecithin in patients with tardive dyskinesia.	6 patients (1 male and 5 females, aged 49 to 60 years) with tardive dyskinesia.	50 g lecithin daily.	2 weeks	Nausea and vomiting reported in 1 subject, who was withdrawn from the study.	Jackson <i>et al.</i> , 1979

Table 4.6-2 Summary of Clinical Studies Evaluating the Effects of Lecithin Consumption

Study Design	Study Population	Lecithin/Choline Dose	Duration	Adverse Events	Reference
Clinical Studies of Lecithin in Patients with Other Neurological Diseases					
Open label study assessing the effects of lecithin in patients with manic-depressive illness.	8 subjects (7 males and 1 female, aged 17 to 36 years) with manic-depressive illness.	4 patients received Lethicon wax/granules (containing 51 to 55% PC) and 4 received Phospholipon 100 wax (which contains >90% PC). All subjects received 15 g/day in the first week, and 30 g/day in the second week.	2 weeks	Of the patients receiving Lethicon, 3 could not consume > 15 g/day due to diarrhea and vomiting. The 4 th subject experienced mild nausea on 15 g/day, and nausea, diarrhea, and motor restlessness on 30 g/day. All subjects consuming Phospholipon 100 tolerated 30 g/day, showed significant improvements, and reported no adverse events.	Cohen <i>et al.</i> , 1980
Randomized, double blind, placebo-controlled study assessing the effects of lecithin in patients with Parkinsonian dementia.	16 patients (12 males and 4 females, aged 56 to 84 years) with Parkinsonian dementia.	30 g soybean lecithin (containing 25% PC) or placebo (skim milk powder) were consumed daily.	9 weeks	None reported.	Garcia <i>et al.</i> , 1982
Other Clinical Studies of Lecithin					
Randomized, double blind, placebo-controlled study of lecithin (n=5) vs. placebo (n=7) in increasing plasma choline and decreasing hepatic steatosis in TPN patients.	12 subjects receiving long-term TPN (<i>i.e.</i> , for 7.0 ± 1.1 years) and had low plasma choline levels.	40 g soy lecithin or 40 g placebo (soybean oil) daily.	6 weeks.	By the end of the study, plasma free choline increased significantly from baseline in the treated group (5.5 ± 1.7 mmol/L vs. 7.90 ± 2.51 mmol/L; $P=0.04$) and decreased significantly from baseline in the placebo group (6.5 ± 0.9 mmol/L vs. 4.85 ± 0.73 mmol/L; $P=0.01$). One subject in lecithin group withdrew from the study due to diarrhea.	Buchman <i>et al.</i> , 1992

Abbreviations: AD, Alzheimer's Disease; GI, gastrointestinal; PC, phosphatidylcholine; TPN, total parenteral nutrition.

4.6.3 EPA/DHA

The FDA addressed the safety of DHA and EPA supplementation in the 1997 final rule on the approved use of menhaden oil as a direct food ingredient (FDA, 1997b) and regarding the use of ω -3 fatty acids as a dietary supplement (FDA, 2000b). In both of these decisions, the FDA set a maximum intake of 3 g/day DHA+EPA based on information in the scientific literature on increased bleeding times, increases in low-density lipoprotein (LDL) cholesterol levels, and on the control of fasting glucose levels in individuals with non-insulin dependent diabetes mellitus (NIDDM). The 1997 FDA final ruling was that menhaden oil is GRAS for direct addition to various categories of foods in amounts ranging from 1 to 20%, depending on the food category, and that the combined intake of EPA+DHA should not exceed 3 g/person/day. Since this ruling, FDA has received notices from several other companies that have concluded that fish oils and other sources of EPA and/or DHA, other than menhaden oil, are GRAS for use in the same food categories as those listed in 21 CFR 184.1472(a) (3) at maximum use levels that are designed to assure that the combined daily intake of EPA and DHA would not exceed 3 g per person per day (see Table 4.2-2) (CFR, 2005a). As in the final ruling for menhaden oil, the GRAS status of these fish oils was based on the use of the fish oil product as the sole added source of EPA and DHA, and not in combination with other EPA/DHA-rich oils. Several sources of EPA and DHA that have GRAS status are derived from the same fish (anchovies and sardines) as Omega-3 PL (*i.e.*, Ocean Nutrition Canada, 18/12 TG; Unilever Unites States Inc., Marinal Oil Omega-3 Concentrate; Jewards International, Small Planktivorous Pelagic Fish Body Oil). Details on these EPA and DHA sources can be found in Section 4.2.3 of this submission.

FDA also recommended that the total amount of EPA+DHA provided by dietary supplements be less than 2,000 mg/day (FDA, 2000b [Docket No. 91N-0103]). The intake of EPA+DHA from the maximum recommended dosage of Omega-3 PL (*i.e.*, up to 4 g/day) is below 2,000 mg/day (in fact, it is below 1,000 mg/day); thus, it was deemed unnecessary to assess, from clinical studies, the safety of the total amount of EPA and DHA, as the proposed levels of intended use for Omega-3 PL are fully compliant with FDA's regulations and recommendations.

There are two factors that separate Omega-3 PL from most other fish oil supplements: 1) EPA and DHA exist both in TG form and in PL form; and 2) The formulation contains a relatively higher ratio of EPA:DHA than most fish oil supplements. Clinical trials in which DHA and/or EPA were administered in PL form were reviewed in Section 4.6.1-1. Clinical trials in which a high ratio of EPA:DHA was administered, irrespective of lipid form, are reviewed in Table 4.6-3. The ratio of EPA:DHA in Omega-3 PL is approximately 2:1; thus, clinical studies in which subjects were administered a fish oil supplement with an EPA:DHA ratio of 1.5:1 to 2.5:1 were reviewed.

Although Silva *et al.* (1996) reported significant increases in blood glucose levels in diabetics and non-diabetics with the administration of 3.6 g/day EPA+DHA in a ratio of 1.5:1 (EPA:DHA), these effects were most likely due to the high level of EPA and DHA administered, rather than to the ratio of EPA:DHA. Other studies reported no alterations in glycemic control when the EPA+DHA intake was limited to 3.0 g/day and the ratio of EPA:DHA was 1.5:1 (McGrath *et al.*, 1996; McVeigh *et al.*, 1994). One minor hematoma was reported in a patient with angiographically confirmed coronary artery disease who was administered 3.32 g EPA+DHA in a ratio of 1.6:1 (EPA:DHA) (von Schacky *et al.*, 1999); however, the subjects participating in this study were taking platelet inhibitors, and it is impossible to delineate whether the hematoma was the result of the platelet inhibitor(s), the fish oil supplement, or some sort of synergy between the two compounds. Many platelet inhibitors function by altering eicosanoid production in favor of anti-aggregatory mediators; thus, that EPA and DHA can act additively or synergistically with platelet inhibitors to exert a compounded anti-platelet effect is a possibility that cannot be ruled out. It is of note that, as specified in Section 3 of this submission, the labeling of Omega-3 PL will indicate that people taking anticoagulants should not use Omega-3 PL.

It is apparent that the most common adverse events associated with the administration of a fish oil supplement containing EPA and DHA in a ratio of 1.5:1 to 2.5:1 are gastrointestinal (belching, nausea, diarrhea, unacceptable aftertaste, *etc.*). While such side effects may occur with the use of Omega-3 PL, these adverse events are highly unlikely, particularly since the recommended dosage of Omega-3 PL results in an EPA+DHA intake less than 1 g/day. Also, it may be noteworthy to reiterate that the ratio of EPA:DHA in Omega-3 PL (approximately 2:1) is practically identical to that found in Krill Oil (which is approved as a New Dietary Ingredient and is marketed widely in the United States as an EPA+DHA supplement) and very similar to that found in menhaden oil (1.5:1).

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of a fish oil supplement on renal function, symptoms, and serum lipids in patients with lupus nephritis.	21 patients with confirmed systemic lupus nephritis, aged 22 to 66 years.	<u>Treatment:</u> 15, 1-gram fish oil capsules (MaxEPA), providing, in TG form, 2.7 g EPA, 1.7 g DHA, 4.4 g EPA+DHA, and an EPA:DHA ratio of 1.6:1. <u>Placebo:</u> 15, 1-gram capsules of olive oil.	1 year, with a 10-week washout period prior to the crossover	None reported.	Clark <i>et al.</i> , 1993
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement in patients with coronary atherosclerosis.	59 patients, aged 55 to 66 years, with $\geq 30\%$ narrowing of lumen diameter of a major coronary artery.	<u>Treatment:</u> 12, 1-gram capsules (Promega, Park-Davis), providing (in unknown form) 2.88 g EPA, 1.92 g DHA, 4.8 g combined EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 12, 1-gram capsules of olive oil.	28 months.	3/31 (9.7%) of subjects in the fish oil group withdrew from the study due to "intolerance" (presumably GI) to the fish oil capsules.	Sacks <i>et al.</i> , 1995
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on survival in Stage III patients with generalized solid tumors.	60 patients with generalized solid tumors, aged 56 to 60 years.	<u>Treatment:</u> 18, 1-gram capsules of MaxEPA, providing, in TG form, 3.06 g EPA, 2.07 g DHA, 5.13 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> sugar tablets.	Until death (up to 28 months).	None reported. Survival was significantly increased in subjects in the treatment group.	Gogos <i>et al.</i> , 1998
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on the course of coronary atherosclerosis.	223 patients with angiographically confirmed coronary artery disease.	<u>Treatment:</u> 6, 1-gram capsules of a fish oil supplement, providing (in unknown form) 2.12 g EPA, 1.29 g DHA, 3.41 g EPA+DHA, and an EPA:DHA ratio of 1.6:1. <u>Placebo:</u> 6, 1-gram capsules of a non-marine oil.	3 months; the dose was subsequently reduced to 3, 1-gram capsules for 21 months.	3 patients in the placebo group and 4 in the treatment group reported mild GI discomfort and withdrew from the study. One subject in the treatment group developed a slightly itchy rash determined by the authors to not be causally linked with treatment. One minor hematoma was reported in a subject in the treatment group undergoing a repeat angiography	von Schacky <i>et al.</i> , 1999

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Open label study assessing the effects of fish oil supplementation in 5 children with cystic fibrosis.	5 female patients with cystic fibrosis, aged 4, 6, 10, 12, and 16 years.	<u>Treatment:</u> The 2 youngest children (<25 kg) were administered 6, 1-gram capsules of Himega (Sigma Clayton, Victoria, Australia) providing, in unknown form, 1.8 g EPA, 1.2 g DHA, 3.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. The other children were administered 9, 1-gram capsules, providing 2.7 g EPA, 1.8 g DHA, 4.5 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	Capsules were administered in 6-week cycles (6 weeks on and 6 weeks off) for 12 months.	None reported. There was an indication that fish oil supplementation may benefit children with cystic fibrosis who do not have end-stage disease.	Thies, 1997
Randomized, double-blind, placebo-controlled study assessing the effects of mesalazine administered with or without a fish oil supplement in patients with Crohn's disease.	38 patients with Crohn's Disease in remission, aged 5 to 16 years (mean age, 10.13 years).	<u>Treatment:</u> 50 mg/kg body weight/day mesalazine and 3, 1-gram capsules of TRIOLIP (SOFAR, Italy) providing, in TG form, 1.2 g EPA, 0.6 g DHA, 1.8 g EPA:DHA, and an EPA:DHA ratio of 2:1. <u>Placebo:</u> 50 mg/kg body weight/day mesalazine and 3, 1-gram capsules of olive oil.	12 months	The number of patients who relapsed at 1 year was significantly lower in the treatment group than in the placebo group. No side effects were reported in patients of either group.	Romano <i>et al.</i> , 2005
Randomized, double-blind, placebo-controlled study assessing the effects of a low fat diet and omega-3 fatty acids in patients with multiple sclerosis.	31 patients with multiple sclerosis, aged 42.5 years.	<u>Treatment:</u> A very low fat diet (<15% of energy) in addition to 6, 1-gram capsules of EPAX 5500 EE (Tishcon Corp., USA) providing, in ethyl ester form, 1.98 g EPA, 1.32 g DHA, 3.3 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> The American Heart Association Step I diet and 6, 1-gram capsules of olive oil.	12 months	Both diets resulted in a significant reduction in the relapse rate; however, quality of life scores were significantly improved only in the fish oil group. No adverse events were reported.	Weinstock-Guttman <i>et al.</i> , 2005

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Randomized, double-blind, placebo-controlled study assessing the effects of fish oil supplementation in children with bronchial asthma.	30 children with bronchial asthma, with an approximate age of 11 years.	<p><u>Treatment:</u> Each 300 mg fish oil capsule contained, in unknown form, 84 mg EPA, 36 mg DHA, 120 mg EPA+DHA, and an EPA:DHA ratio of 2.3:1. Children were dosed as follows: 18.8 to 24.2 kg, 6 capsules/day; 24.8 to 32.6 kg, 8 capsules/day; 34.0 to 41.4 kg, 10 capsules/day; 45.3 to 59.2 kg, 12 capsules/day.</p> <p><u>Placebo:</u> 300 mg capsules of olive oil, dosed in the same manner as described for the treatment group.</p>	10 months	One child dropped out of the study because of inability to swallow the capsules. No side effects, such as prolonged epistaxis, bleeding tendency, or menstrual problems, were reported during the study in the fish oil group. Significant improvement in asthma scores were observed in the treatment group.	Nagakura <i>et al.</i> , 2000
Randomized study assessing the effects of a fish oil supplement on hemostatic variables, bleeding episodes, and restenosis.	610 patients, approximately 59 years of age, with coronary artery disease undergoing coronary artery bypass surgery.	<p><u>Treatment:</u> 4, 1-gram capsules of Omacor™ providing, in ethyl ester form, 2.04 g EPA, 1.28 g DHA, 3.32 g EPA+DHA, and an EPA:DHA ratio of 1.6:1. Approximately half of the patients received aspirin, while the other half received warfarin.</p>	9 months following the surgery.	The frequency of bleeding episodes was similar in the control and treatment groups. Other measures of hemostatic function were also similar between the two groups. Glycemic control was not significantly altered with fish oil supplementation, nor was the concentration of thiobarbituric acid-reactive substances. The group receiving the n-3 fatty acid supplement had a reduced incidence of vein graft occlusion, and a significant inverse relation between relative change in serum PL n-3 fatty acids and vein graft occlusions was observed.	Eritsland <i>et al.</i> , 1995a,b, 1996
Open label study assessing the effects of fish oil supplementation in patients with cystic fibrosis.	30 patients with cystic fibrosis with a mean age of 12.4 years (range, 0.8 to 24 years).	<p><u>Treatment:</u> Subjects were administered either 1.0 or 0.5 g capsules of Triolip (SOFAR, Milan Italy) providing, per gram in unknown form, 400 mg EPA, 200 mg DHA, 600 mg EPA+DHA, and an EPA:DHA ratio of 2:1. Subjects were also encouraged to eat fish and seafood. The mean daily intake of EPA and</p>	8 months	No serious adverse events were reported. Side effects of fish oil supplementation, such as nausea and diarrhea, were kept low, presumably because of the use of enteric-coated capsules. Long-term fish oil supplementation in patients with cystic fibrosis was found to reduce markers of	De Vizia <i>et al.</i> , 2003

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
		DHA was 1.28 g and 0.93 g, respectively.		inflammation, enhance pulmonary function, and reduce the length of antibiotic therapy as compared with the preceding 8-month period.	
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on hypertension.	156 patients, aged 49.5 ± 6.6 years, with previously untreated stable mild hypertension.	<u>Treatment:</u> 6, 1-gram capsules of K85 (Norsk Hydro AS, Norway), providing, in ethyl ester form, 3.26 g EPA, 1.82 g DHA, 5.08 g EPA+DHA, and an EPA:DHA ratio of 1.8:1. <u>Placebo:</u> 6, 1-gram capsules of corn oil.	10 weeks	At 5 weeks, reports of mild or moderate GI problems (belching, self-limited diarrhea, constipation) were similar between the 2 groups; after 10 weeks, 19 patients in the placebo group and 9 in the treatment group reported such problems. Body weight increased significantly from baseline in both groups, by 0.70 kg and 0.56 kg in the treatment and placebo groups, respectively. Bleeding time, platelet count, and plasma fibrinogen levels did not change significantly in either group.	Bønaa <i>et al.</i> , 1990
Randomized study assessing the effects of a fish oil supplement on blood lipid profiles, glycemic control, and hemostatic factors.	57 moderately hypertriglyceridemic patients, approximately 61 years of age, undergoing coronary artery bypass surgery.	<u>Treatment:</u> 4, 1-gram capsules of K85 (Pronova AS, Oslo, Norway), providing, in ethyl ester form, 2.07 g EPA, 1.28 g DHA, 3.4 g EPA+DHA, and an EPA:DHA ratio of 1.6:1.	6 months following the surgery.	None reported.	Eritsland <i>et al.</i> , 1994a,b
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on the rate of restenosis following percutaneous intraluminal coronary angioplasty.	551 patients requiring coronary angioplasty.	<u>Treatment:</u> 10, 1-gram capsules of a fish oil supplement, providing, in ethyl ester form, 4.1 g EPA, 2.8 g DHA, 6.9 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 10, 1-gram capsules of corn oil.	6 months	No significant differences occurred between the 2 groups for any of the adverse events. The incidence of bleeding episodes was 3% in each group, and of infections, 4% in each group. GI symptoms were reported in 8% of the placebo group and 7% of the	Leaf <i>et al.</i> , 1994

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1					
Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
				treatment group. Withdrawal due to adverse cardiovascular disease events was 1% and 3% in the treatment and placebo groups, respectively. Bleeding time and platelet count were not affected by either treatment.	
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of a fish oil supplement on blood lipid profiles and glycemic control in subjects with non-insulin-dependent diabetes mellitus.	16 subjects with non-insulin-dependent diabetes mellitus, aged 46 to 72 years.	<u>Treatment</u> : 15, 1-gram capsules of Promega (Parke Davis Warner Lambert, Pennsylvania), providing, in unknown form, 4.1 g EPA, 1.9 g DHA, 6.0 g EPA+DHA, and an EPA:DHA ratio of 2.2:1. <u>Placebo</u> : 10, 1-gram capsules of olive oil.	6 months for each intervention.	None reported. No significant effects on total blood count or bleeding time.	Connor <i>et al.</i> , 1993
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on platelet PL fatty acid composition and function.	20 healthy males aged 32 ± 4 years.	<u>Treatment</u> : 4, 1-gram capsules of Esapent (Farmitalia, Italy), providing, in ethyl ester form, 2.04 g EPA, 1.4 g DHA, 3.44 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo</u> : 4, 1-gram capsules of olive oil.	4 months	20% of subjects in the placebo group reported abdominal discomfort and diarrhea after 1 to 2 weeks of treatment, necessitating a transient reduction in placebo dose from 4 to 2 capsules. 50% of subjects in the treatment group reported occasional fish aftertaste. No other side effects were experienced.	Prisco <i>et al.</i> , 1994, 1995
Open label study assessing the effects of fish oil supplementation on psoriasis.	30 patients with plaque psoriasis, aged 12 to 69 years (mean, 37 years).	<u>Treatment</u> : Subjects consumed a low fat diet and 30 mL of fish oil (MaxEPA) providing, in TG form, 5.4 g EPA, 3.6 g DHA, 9.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	4 months	2 subjects were lost to follow-up, and 2 subjects withdrew due to difficulties complying with the study diet. 58% of subjects experienced moderate or excellent improvement in their condition, while mild or no improvement was observed in 19% and 23% of subjects, respectively. LTB ₅ (an anti-	Kragballe and Fogh, 1989

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1					
Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
				inflammatory marker), which was undetectable before the study, became detectable after 1 month.	
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on ventricular arrhythmias and blood lipid profiles.	35 subjects with a diagnosis of ventricular tachyarrhythmia, aged 48 to 73 years.	<u>Treatment:</u> 8, 1-gram capsules of Pिकासол (Pronova Biocare, Norway), providing, in re-esterified TG form, 2.67 g EPA, 1.63 g DHA, 4.3 g EPA+DHA, and an EPA:DHA ratio of 1.6:1. <u>Placebo:</u> 8, 1-gram capsules of corn oil.	16 weeks	None reported.	Christensen <i>et al.</i> , 1995
Randomized, controlled study assessing the safety and efficacy of dietary and exercise counseling with and without fish oil supplementation for the treatment of antiretroviral therapy-induced hypertriglyceridemia.	52 HIV-infected adults receiving ≥3 antiretroviral drugs and with a fasting TG level >200 mg/dL (mean age, 43.7 years).	<u>Treatment:</u> A standard diet and exercise program with or without fish oil supplementation (a liquid formulation) providing, in unknown form, 1.75 g EPA, 1.15 g DHA, 2.9 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	16 weeks	In the fish oil supplement group, 1 subject withdrew from the study because of the discomfort of phlebotomy, 1 because nausea and vomiting, one was lost to follow-up, and one because of toxicity. There was no significant change from baseline in platelet function, and no reports of increased bleeding tendency were made by any of the subjects. Fish oil supplementation was associated with significant reductions in TG levels, but significant increases in LDL-C, making the benefits of TG-lowering difficult to interpret.	Wohl <i>et al.</i> , 2005
Randomized, double-blind, placebo-controlled study assessing the effects of fish oil supplementation in patients with atopic dermatitis.	31 patients aged 16 to 56 years with atopic dermatitis.	<u>Treatment:</u> 10, 1-gram capsules of Max-Epa®, providing, in TG form, 1.8 g EPA, 1.2 g DHA, 3.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 10, 1-gram capsules of olive oil.	12 weeks	4 subjects dropped out of the study from each group due to inability to swallow the capsules. Results favored the treatment group with respect to scale (P<0.05), itch (P<0.05), and overall subjective severity (P<0.02). After 12 weeks, the serum concentration of alpha-tocopherol was significantly lower	Bjørneboe <i>et al.</i> , 1987

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1					
Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
				in the treatment group than in the placebo group.	
Open label study assessing the effects of fish oil supplementation on the progression of cancer cachexia.	18 patients with unresectable pancreatic cancer.	<u>Treatment:</u> 2, 1-gram capsules of MaxEPA (Seven Seas Health Care, UK), providing in TG form, 0.36 g EPA, 0.24 g DHA, 0.6 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. The dosage was increased by 2 g at weekly intervals until a maximum dose of 16, 1-gram capsules were consumed, providing 2.88 g EPA, 1.92 g DHA, 4.8 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	3 months (median)	Most patients tolerated a maximum dose of 12 g/day fish oil. Several patients reported offensive taste or transient diarrhea. All patients were losing weight prior to supplementation (2.9 kg/month), whereas on receiving fish oil supplementation, there was a median weight gain of 0.3 kg/month (P<0.002).	Wigmore <i>et al.</i> , 1996
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on blood lipid profiles.	53 patients with dyslipidemia, with recent acute myocardial infarction.	<u>Treatment:</u> 4, 1-gram capsules of K85 (Norsk Hydro AS, Norway), providing, in ethyl ester form, 1.96 g EPA, 1.29 g DHA, 2.53 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 4, 1-gram capsules of corn oil.	12 weeks	None reported.	Swahn <i>et al.</i> , 1998
Open label study assessing the effects of fish oil supplementation in children with hydroa vacciniforme.	3 male patients with hydroa vacciniforme aged 5, 7, and 8 years.	<u>Treatment:</u> 5, 1-gram capsules of MaxEPA (Seven Seas Ltd., Marfleet, UK) providing, in unknown form, 900 mg EPA, 600 mg DHA, 1500 mg EPA+DHA, and an EPA:DHA ratio of 1.5:1.	3 months	None reported. All the patients showed reduced erythema sensitivity to UVA and one also showed reduced sensitivity to UVB.	Rhodes and White, 1998
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement in the management of recurrent migraines.	27 adolescents with a mean age of 15 ± 1 years with chronic, recurrent migraine headaches.	<u>Treatment:</u> 2, 1-g capsules of a fish oil supplement, providing, in ethyl ester form, 756 mg EPA, 498 mg DHA, 1.25 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 2, 1-gram capsules of olive oil (fatty acids were in ethyl ester form).	Each intervention period lasted 2 months and was separated by a 1-month washout period.	4 patients dropped out of the study, one because of difficulty swallowing the capsules, the other 3 because of failure to comply. No adverse events were reported. Both treatments resulted in significant reductions in the frequency, duration, and severity of headaches.	Harel <i>et al.</i> , 2002

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on blood lipid profiles.	35 patients with hypertriglyceridemia or mixed hyperlipidemia, aged 47 to 58 years.	<u>Treatment:</u> 12, 1-g capsules of a fish oil supplement, providing, in unknown form, 2.16 g EPA, 1.44 g DHA, 3.6 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 12, 1-gram capsules of soy oil.	2 months	5 subjects, all in the placebo group, dropped out of the study due to adverse events, including acute pancreatitis, eructations, nausea, sensation of repletion, meteorism, and epigastralgiias. Minor and transitory side effects were reported by 5 subjects in the treatment group and 1 in the placebo group. Significant increases in blood glucose were observed in diabetics and non-diabetics.	Silva <i>et al.</i> , 1996
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on blood pressure and blood lipid profiles.	19 males whose blood pressure was not adequately controlled with antihypertensive drugs, aged 52.8 to 60.4 years.	<u>Treatment:</u> 18, 1-gram capsules of a fish oil supplement, providing, in an unknown form, 2.16 g EPA, 1.28 g DHA, 3.44 g EPA+DHA, and an EPA:DHA ratio of 1.7:1.	8 weeks	No subjects withdrew from the study due to adverse events. 4 subjects in the treatment group complained of intermittent headaches, and 3 in the placebo group complained of mild GI symptoms, including nausea, indigestion, and diarrhea. Blood chemistry tests were not affected by administration of either the treatment or placebo. Platelet count decreased significantly from baseline in the treatment group; however, prothrombin and partial thromboplastin time were not affected.	Gray <i>et al.</i> , 1996
Open label study assessing the effects of fish oil supplementation on hyperlipidemia in children and adolescents with end-stage renal disease.	16 patients, 7 to 18 years of age, with end-stage renal disease and receiving renal replacement therapy.	<u>Treatment:</u> Subjects were administered EPAGIS (Agis Commercial Agencies Ltd., Yeruham, Israel), providing, per 1-gram capsule, 180 mg EPA, 120 mg DHA, 300 mg EPA+DHA, and an EPA:DHA ratio of 1.5:1. Doses were adjusted as follows: 10 to 20 kg, 3 g/day; 20 to 30 kg, 4 g/day; 30 to 40 kg, 6 g/day; >40	8 weeks	2 subjects reported abdominal cramps, which subsided spontaneously, and 2 reported diarrhea. Platelet count and mean diastolic and systolic blood pressure remained unchanged from baseline. Favorable alterations in blood lipid profiles were achieved with fish oil	Goren <i>et al.</i> , 1991

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1					
Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
		kg, 8 g/day.		supplementation, including significant reductions in TG and in the ratio of total cholesterol:HDL-C.	
Open label study assessing the effects of omega-3 fatty acids in patients with postpartum depression.	16 females aged 20 to 42 years (mean, 31 years) with diagnosed post-partum depression.	<u>Treatment:</u> Subjects were administered either 0.5, 1.4, or 2.8 g/day EPA+DHA (from EPAX 5500 (Pronova, Lysker, Norway), providing EPA and DHA in a ratio of 1.5:1.	8 weeks	Depression was significantly improved in all three groups (as assessed by the HAM-D and EPDS scales), irrespective of omega-3 dose. No adverse events were reported.	Freeman <i>et al.</i> , 2006
Randomized, double-blind, placebo-controlled study comparing the effects of fish oil supplements in ethyl ester vs. TG form on blood lipid profiles, hemostasis, and platelet function.	31 healthy normolipaemic men, aged 21 to 47 years.	<u>Treatment:</u> 4, 1-gram capsules of K85 (Norsk Hydro, Norway), providing, in ethyl ester form, 2.2 g EPA, 1.2 g DHA, 3.4 g EPA+DHA, and an EPA:DHA ratio of 1.8:1 or 12, 1-gram capsules of ACTIVEPA 30 (JC Martens, Norway), providing, in TG form, 2.2 g EPA, 1.4 g DHA, and an EPA:DHA ratio of 1.6:1. <u>Placebo:</u> 4, 1-gram capsules of corn oil.	7 weeks	Hematological (hemoglobin, red blood cell count, white blood cell count, platelet number, and mean platelet volume) and serum chemistries (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase) were not affected by any of the treatments. No adverse side effects were reported.	Hansen <i>et al.</i> , 1993b
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of a fish oil supplement on serum lipid peroxidation.	23 patients with non-insulin-dependent diabetes mellitus, aged 46 to 61 years.	<u>Treatment:</u> 6, 1-gram capsules of MaxEPA (Duncan Flockhart, UK), providing, (in unknown form), 1.8 g EPA, 1.2 g DHA, 3.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 6, 1-gram capsules of olive oil.	Each intervention lasted 6 weeks, with a 6-week washout period prior to the crossover.	Glycemic control (including blood glucose, glycosylated hemoglobin, and glycosylated LDL-C) was not affected by either treatment. Fish oil administration resulted in significant reductions in plasma vitamin E levels as compared with baseline and the placebo, and significant elevations in plasma malondialdehyde, as compared with baseline and the placebo. No side effects were reported.	McGrath <i>et al.</i> , 1996

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Open label study assessing the effects of fish oil supplementation on dislipoproteinemia in pediatric patients with systemic lupus erythematosus.	24 adolescents aged 12 to 21 years fulfilling systemic lupus erythematosus criteria.	<u>Treatment:</u> During Phase I of the study, subjects followed the National Cholesterol Education Program Step I Diet. During Phase II of the study, subjects continued with the diet and were administered 3 capsules of Twinepa extra strength fish oil concentrate, providing, in unknown form, 1.8 g EPA, 0.72 g DHA, 2.5 g EPA+DHA, and an EPA:DHA ratio of 2.5:1.	Each Phase lasted 6 weeks.	Dietary modification and fish oil supplementation were found to be effective at reducing serum TG. No adverse events were reported.	Ilowite <i>et al.</i> , 1995
Randomized, double-blind, placebo-controlled study comparing absorption of omega-3 fatty acids in patients with cystic fibrosis who have pancreatic insufficiency and in healthy controls.	12 cystic fibrosis patients with pancreatic insufficiency and 13 age-matched controls.	<u>Treatment:</u> 8, 1-gram capsules of a fish oil supplement, providing, in ethyl ester form, 3.19 g EPA, 2.21 g DHA, 5.4 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 8, 1-gram capsules of olive oil.	6 weeks	2/7 (29%) and 2/5 (40%) patients with cystic fibrosis who received fish and olive oils, respectively, and 1/8 (13%) and 0/5 (0%) healthy subjects discontinued taking the capsules prior to 6 weeks because of eructation or diarrhea. There were no significant effects of any of the treatments on vitamin A or E, alkaline phosphatase, alanine aminotransferase, bilirubin, glucose, albumin total leukocyte count, hemoglobin, hamatocrit, prothrombin time, bleeding incidence or platelet aggregation (in response to collagen or adenosine diphosphate).	Henderson <i>et al.</i> , 1994
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of omega-3 supplementation on endothelium-dependent vasodilation in patients with chronic heart failure.	20 patients with chronic heart failure on maximal medication management with a mean age of 73 years.	<u>Treatment:</u> 10 mL of High-strength Cod Liver Oil (Seven Seas, Hull, United Kingdom) providing, in unknown form, 1.8 g EPA, 1.2 g DHA, 3.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 10 mL of olive oil.	Each phase lasted 6 weeks, with a 6-week washout period between phases.	Fish oil supplementation was shown to have beneficial effects in patients with chronic heart failure. No adverse events were reported.	Morgan <i>et al.</i> , 2006

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Open label study assessing the effects of fish oil supplementation on blood pressure, hyperinsulinemia, and dyslipidemia in Indians.	20 hypertensive subjects with hyperinsulinemia, aged 30 to 60 years.	<u>Treatment:</u> 1 or 2 capsules of Cap MaxEPA providing, in unknown form, 180 or 360 mg EPA, 120 or 240 mg DHA, 300 or 600 mg EPA+DHA, and an EPA:DHA ratio of 1.5:1.	6 weeks	Significant reductions in plasma insulin, systolic and diastolic blood pressure, serum TG, total cholesterol, and LDL-C were observed in both treatment groups. No adverse events were reported.	Bhise <i>et al.</i> , 2005
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of fish oil supplementation on inflammation in children with cystic fibrosis.	14 patients with cystic fibrosis aged 6 – 16 years (mean age, 10.5 years).	<u>Treatment:</u> Sufficient capsules of fish oil to provide 100 mg EPA+DHA/kg body weight/day. Each capsule provided, in ethyl ester form per gram, 440 mg EPA, 240 mg DHA, 680 mg EPA+DHA, and an EPA:DHA ratio of 1.8:1. <u>Placebo:</u> Safflower oil (fatty acids were in ethyl ester form) and sufficient 1-gram capsules were consumed to provide 100 mg omega-6 fatty acids/kg body weight/day.	Each treatment lasted for 6 weeks, and was separated by a 6-week washout.	Fish oil supplementation resulted in a significant reduction in serum leukotriene B ₄ (a marker of inflammation). No adverse events were observed or reported.	Kurlandsky <i>et al.</i> , 1994
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of a fish oil supplement on arterial compliance in patients with NIDDM.	20 patients with NIDDM, aged 45 to 64 years.	<u>Treatment:</u> 10, 1-gram capsules of MaxEPA (Duncan Flockhart, UK), providing, in unknown form, 1.8 g EPA, 1.2 g DHA, 3.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 10, 1-gram capsules of olive oil.	Each intervention lasted 6 weeks, with a 6-week washout period prior to the crossover.	No alterations occurred in fasting blood glucose levels. No side effects were reported.	McVeigh <i>et al.</i> , 1994
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement in patients awaiting coronary angioplasty.	18 patients with stable angina pectoris and awaiting coronary artery bypass surgery, aged 48 to 69 years.	<u>Treatment:</u> 6, 1-gram capsules of K85 (Norsk Hydro, Norway), providing, in ethyl ester form, 3.15 g EPA, 1.89 g DHA, 5.04 g EPA+DHA, and an EPA:DHA ratio of 1.7:1. <u>Placebo:</u> 6, 1-gram capsules of corn oil.	≥6 weeks prior to coronary angioplasty.	None reported.	Almdahl <i>et al.</i> , 1993
Randomized, double-blind, placebo-controlled, crossover study comparing the effects of a	14 patients with familial hypercholesterolemia (type IIa), aged 29	<u>Treatment 1:</u> 6, 1-gram capsules of K85 (Pronova A/S, Norway), providing, in ethyl ester form, 3.3 g EPA, 1.74 g DHA, 5.04 g EPA+DHA, and an	The study included 3 intervention periods, which	No adverse events were reported. Resting bleeding time was not affected by any of the treatments. Standardized exercise shortened	Hansen <i>et al.</i> , 1993a

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
fish oil supplement and a HMG-CoA reductase inhibitor on lipid metabolism and bleeding time.	to 59 years.	EPA:DHA ratio of 1.9:1. <u>Treatment 2:</u> 40 mg of an HMG-CoA reductase inhibitor (Mevacor, MSD Norway). <u>Treatment 3:</u> A combination of treatments 1 and 2.	each lasted 6 weeks and were separated by a 6-8 week washout.	bleeding time by 19% (P<0.001) and 16% (P<0.001) before and after lovastatin treatment, respectively. Administration of K-85, alone or in combination with lovastatin, caused an inhibition in the exercise-induced reduction in bleeding time.	
Randomized, double-blind, placebo-controlled study comparing the effects of a fish oil supplement and another lipid supplement.	60 patients undergoing elective coronary artery bypass surgery.	<u>Group 1:</u> 3.2 g evening primrose oil. <u>Group 2:</u> 3.2 g marine fish oil, providing, in unknown form, 1.9 g EPA, 1.26 g DHA, 3.16 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Group 3:</u> 3.4 g evening primrose oil and marine fish oil in a ratio of 3:1. <u>Group 4:</u> Gelatin capsules.	4 weeks (before surgery)	None reported.	Brister and Buchanan, 1998
Randomized, double-blind, placebo-controlled study assessing the effects of a fish oil supplement on platelet aggregation.	12 healthy volunteers, aged 23 to 40 years.	<u>Treatment:</u> 12, 1-gram capsules of MaxEPA (Lipitac, Reckitt and Colman Products Pty Ltd., Australia), providing, in unknown form, 2.16 g EPA, 1.44 g DHA, 3.6 g EPA+DHA, and an EPA:DHA ratio of 1.5:1. <u>Placebo:</u> 12, 1-gram capsules of olive oil.	2, 4-week intervention periods, separated by a 4-week washout period.	None reported.	Misso and Thompson, 1995
Open label study assessing the effects of a fish oil supplement on endothelial dysfunction.	6 hypercholesterolemic subjects, aged 39 to 49 years.	<u>Treatment:</u> 20, 1-gram capsules of MaxEPA, providing, in unknown form, 3.56 g EPA, 2.32 g DHA, 5.88 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	4 weeks.	None reported.	Chin and Dart, 1994
Randomized, double-blind, placebo-controlled, crossover study assessing the effects of a fish oil supplement on atherosclerosis risk factors.	10 mildly hypertriglyceridemic but otherwise healthy subjects, aged 34 to 68 years.	<u>Treatment:</u> Approximately 9, 1-gram capsules of a fish oil supplement, providing, in ethyl ester form, 3.70 g EPA, 2.06 g DHA, 5.76 g EPA+DHA, and an EPA:DHA ratio of 1.8:1. <u>Placebo:</u> Approximately 9, 1-gram capsules of olive oil.	2, 4-week intervention periods separated by a 1-week washout period.	None reported. Bleeding times were not significantly prolonged with either fish oil or olive oil treatment.	Harris <i>et al.</i> , 1993

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1

Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
Randomized study assessing the effects of a diet low in saturated fat and containing either n-3 or n-6 fatty acids on plasma lipoproteins and hemostatic factors.	26 healthy, non-obese males, aged 18 to 34 years.	<u>Treatment:</u> Following a 3-week baseline period, during which subjects consumed a diet containing 30% of energy as fat (8% monounsaturated fat; 4% polyunsaturated fat; 16% saturated fat), subjects consumed, in a crossover fashion, diets containing 30% of energy as fat (14% monounsaturated fat; 6% polyunsaturated fat; 8% saturated fat), with either n-3 or n-6 fatty acids. The n-3 fatty acid diet provided 3.0 g EPA, 2.0 g DHA, 5.0 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	Each dietary intervention lasted 3 weeks, followed by an 8-week washout.	None reported.	Sanders <i>et al.</i> , 1997
Randomized study assessing the effects of dietary fat and saturated fat content on eicosanoid production and hemostatic parameters.	6 healthy non-smoking males, aged 27 to 58 years.	<u>Treatment:</u> Subjects consumed, in a crossover fashion, a diet either high or low in saturated fat and 9, 1-gram capsules of EPAX 5000 TG (Martens A/S, Sandefjord, Norway), providing, in TG form, 3.15 g EPA, 1.71 g DHA, 4.86 g EPA+DHA, and an EPA:DHA ratio of 1.8:1.	Each diet was followed for 3 weeks, separated by an 8-week washout.	No significant changes in bleeding time or hemostatic parameters as compared with controls. No adverse events were reported.	Nordøy <i>et al.</i> , 1994
Open label study assessing the maximum tolerated dose and dose-limiting toxicities of fish oil supplementation.	22 patients, aged 34 to 76 years, with neoplastic disease not amenable to curative therapy who showed signs of cachexia.	<u>Treatment:</u> Subjects were given an escalating dose of a fish oil supplement providing, per gram in ethyl ester form, 378 mg EPA, 249 mg DHA, 728 mg EPA+DHA, and an EPA:DHA ratio of 1.5:1. The maximum tolerated dose was found to be 21, 1-gram capsules, providing 7.94 g EPA, 5.23 g DHA, and 12.72 g EPA+DHA.	2 weeks per dose.	Dose-limiting toxicity was GI, mainly diarrhea and a poorly described toxicity described as "unable to tolerate in stomach or esophagus".	Burns <i>et al.</i> , 1999
Randomized, double-blind, placebo-controlled, crossover study comparing the effects of a fish oil supplement vs. gemfibrozil.	10 hyperlipidemic patients with NIDDM, aged 61.1 ± 6.2 years.	<u>Treatment 1:</u> Fish oil supplements providing, in TG form, 2.89 g EPA, 1.78 g DHA, 4.68 g EPA+DHA, and an EPA:DHA ratio of 1.6:1. <u>Treatment 2:</u> 900 mg gemfibrozil.	2, 2-week intervention periods separated by an 8-week washout.	Mild epigastric discomfort was reported in 2 subjects receiving fish oil supplementation and in 1 subject receiving gemfibrozil. Blood chemistries, and hepatic and renal blood measures were	Fasching <i>et al.</i> , 1996

Table 4.6.3-1 Summary of Clinical Studies in which EPA and DHA were Administered in a Ratio of 1.5:1 to 2.5:1					
Study Design	Study Population	EPA and DHA Daily Dose and Form	Duration	Adverse Events	Reference
				unaffected by either treatment. No significant changes were detected in glycemic control.	
Randomized study assessing the enrichment of EPA and DHA in total plasma lipids and PL when administered in TG vs. ethyl ester form.	40 healthy male volunteers, aged 18 to 55 years.	<u>Treatment 1:</u> 4 to 14, 1-gram capsules of K85, providing, in ethyl ester form, 2.18 to 7.62 g EPA, 1.21 to 4.24 g DHA, 3.39 to 11.86 g EPA+DHA, and an EPA:DHA ratio of 1.8:1. <u>Treatment 2:</u> 12 or 24, 1-gram capsules of TG30, providing, in TG form, 2.16 or 4.32 g EPA, 1.44 or 2.88 g DHA, 3.60 or 7.20 g EPA+DHA, and an EPA:DHA ratio of 1.5:1.	15 days	None of the volunteers suffered from adverse events or discomforts, and all volunteers completed the treatment period without reduction of the dose. The enteral absorption of EPA and DHA was at least as good from a synthetic ethyl ester as it was from a natural TG containing equivalent amounts of these fatty acids.	Krokan <i>et al.</i> , 1993

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPDS, Edinburgh Postnatal Depression Scale; GI, gastrointestinal; HAM-D, Hamilton Rating Scale for Depression; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, Low-density lipoprotein cholesterol; PL, phospholipids; TG, triglycerides.

4.7 Summary of Safety

4.7.1 Lecithin

Lecithin, meeting FCC specifications, is GRAS for direct addition to food with no limitations other than GMP [21 CFR § 184.1400(c)] (CFR, 2005a). Lecithin is comprised of PL, with PC being the most abundant PL species. The maximum amount of total PL that would be ingested from the consumption of 4 g/day Omega-3 PL is 2.2 g. At least 25 g of lecithin, containing up to 95% PC, has been consumed daily without side effects, and some studies have reported no adverse events from the consumption of up to 100 g lecithin per day. Thus, the intake of total PL from the proposed intake of Omega-3 PL is very low in comparison with lecithin doses that have been administered in clinical trials in which no adverse events were observed. In addition, the amount of choline provided by the highest recommended dose of Omega-3 PL is approximately 130 mg, and this is well below the UL of 3.5 g/day for choline.

4.7.2 EPA/DHA

The amount of DHA and EPA provided by the highest recommended daily use of Omega-3 PL is 840 mg, a level well below the 3.0 g/day limit established by the FDA (1997b, 2004d). Also, the amount of DHA and EPA is below the 2 g/day maximum dose that FDA recommends for fish oil dietary supplements (FDA, 2000b [Docket No. 91N-0103]). Subchronic and chronic animals trials have indicated that DHA and EPA possess low oral toxicity. As a result, the amount of DHA and EPA provided by the recommended daily intake of Omega-3 PL is not expected to pose any safety concerns.

4.7.3 Omega-3 PL

Omega-3 PL has a fatty acid composition and fractional lipid profile similar to marine sources of EPA and DHA (fish, shellfish). Krill Oil, which is currently marketed as a dietary supplement in Canada, Japan, and the United States, contains, per gram, similar amounts of EPA and DHA, and the ratio of EPA:DHA in Krill Oil and Omega-3 PL is essentially identical (approximately 2:1). Moreover, Krill Oil and Omega-3 PL contain similar amounts of phospholipids and neutral lipids. The primary difference between Krill Oil and Omega-3 PL is that the former is extracted from the Krill while the latter is synthesized enzymatically *via* interesterification of soy lecithin and a concentrated fish oil ethyl ester. The specifications for Omega-3 PL indicate that the product is a concentrated source of EPA and DHA, and that levels of heavy metal contaminants and other contaminants (PCBs, PCDDs, PCDFs, PAHs) are very low, even lower than those found in other fish oil supplements. Analytical reports from accredited laboratories attest to the purity of Omega-3 PL with respect to heavy metals and contaminants (Appendix C). In addition, fatty acid analyses from laboratories across Europe and in North America confirm that the production of Omega-3 PL results in a consistent fatty acid profile, particularly with respect to

the levels of EPA and DHA (Appendix C). All other fatty acids present in Omega-3 PL are naturally present in the diet. Finally, the careful study of over 45 clinical studies in which EPA and DHA were administered in a ratio similar to that found in Omega-3 PL confirms the safety of Omega-3 PL.

Overall, the safety of the proposed New Dietary Ingredient, Omega-3 PL, is fully supported by extensive safety data relating to its primary components, lecithin and the omega-3 fatty acids, DHA and EPA. The safety of Omega-3 PL is also inferred from background dietary exposure to EPA and DHA in PL form, as well as to each of the individual components. Omega-3 PL complies fully with the FDA limitation of 3 g/day combined EPA and DHA and the FDA recommendation of a maximum of 2 g/day combined EPA and DHA from dietary supplements.

GLOSSARY

AA, arachidonic acid
ALC, American Lecithin Company
AD, Alzheimer's Disease
BMI, body mass index
CDP, cytidine diphosphate
DG, diacylglycerides or diglycerides
DHA, docosahexaenoic acid
DSM-III, Diagnostic and Statistical Manual of Mental Disorders
EPA, eicosapentaenoic acid
FAO/WHO, Food and Agriculture Organization/World Health Organization
FCC, Food Chemicals Codex
FDA, Food and Drug Administration
EPDS, Edinburgh Postnatal Depression Scale
ESPGHAN, European Society of Pediatric Gastroenterology and Nutrition
GI, gastrointestinal
GMO, genetically modified organism
GMP, Good Manufacturing Practice
GRAS, Generally Recognized as Safe
HAM-D, Hamilton Rating Scale for Depression
HDL-C, high density lipoprotein cholesterol
HIV, human immunodeficiency virus
JECFA, Joint Expert Committee on Food Additives
LCAT, lecithin:cholesterol acyltransferase
LC-PUFA, long-chain polyunsaturated fatty acids
LDL-C, low density lipoprotein cholesterol
NE, necrotizing enterocolitis
NIDDM, non-insulin dependent diabetes mellitus
NOAEL, No Observed Adverse Effect Level
OLETF, Otsuka Long-Evans Tokushima Fatty
Omega-3 PL, Omega-3 Phospholipids
PC, phosphatidylcholine
PCDDs, polychlorinated dibenzo-*p*-dioxins
PCDFs, polychlorinated dibenzofurans
PCBs, polychlorinated biphenyls
PE, phosphatidylethanolamine
PI, phosphatidylinositol
PL, phospholipids
PS, phosphatidylserine
PTMI, Provisional Tolerable Monthly Intake
PTWI, Provisional Tolerable Weekly Intake
RBC, red blood cells
SAM, S-adenosylmethionine
TEQ-WHO, Toxicity Equivalents – World Health Organization
TG, triglycerides
TPN, total parenteral nutrition

REFERENCES

- Abril, R.; Barclay, W. 1998. Production of docosahexaenoic acid-enriched poultry eggs and meat using an algae-based feed ingredient. In: Simopoulos, A.P. (Ed.). *The Return of ω -3 Fatty Acids into the Food Supply: International Conference on ...* 1. Land-based Animal Food Products, Sep. 18-19, 1997, Bethesda, Maryland. S. Karger; Basel, Switz./New York, *World Review of Nutrition and Dietetics*, Vol. 83, pp. 77-88.
- Ackman, R.G.; Eaton, C.A.; Sipos, J.C.; Loew, F.M.; Hancock, D. 1977. A comparison of fatty acids from high levels of docosenoic acids of rapeseed oil (erucic acid) and of partially hydrogenated fish oil (primarily cetoleic acid) in a non-human primate species in a short-term exploratory study. *Bibl Nutr Dieta* 25:170-185.
- Aggett, P.J.; Haschke, F.; Heine, W.; Hernell, O.; Koletzko, B.; Launiala, K.; Rey, J.; Rubino, A.; Schöch, G.; Senterre, J.; Tormo, R. (ESPGHAN Committee on Nutrition). 1991. Comment on the content and composition of lipids in infant formulas. *Acta Paediatr Scand* 80(8&9):887-896.
- Almdahl, S.M.; Nilsen, D.W.T.; Østerud, B.; Sørli, D.G.; Vaag, J. 1993. Thromboplastin activities and monocytes in the coronary circulation of reperfused human myocardium. *Scand J Thorac Cardiovasc Surg* 27(1):81-86.
- Amate, L.; Gil, A.; Ramirez, M. 2001. Feeding infant piglets formula with long-chain polyunsaturated fatty acids as triacylglycerols or phospholipids influences the distribution of these fatty acids in plasma lipoprotein fractions. *J Nutr* 131(4):1250-1255.
- Anderson, B.G.; Reker, D.; Ristich, M.; Friedman, E.; Banay-Schwartz, M.; Volavka, J. 1982. Lecithin treatment of tardive dyskinesia--A progress report. *Psychopharmacol Bull* 18(1):87-88.
- Anderson, B.G.; Reker, D.; Banay-Schwartz, M.; Webb, E.; Volavka, J. 1983. Lecithin plus lithium in tardive dyskinesia. *Psychopharmacol Bull* 19(1):124-126.
- Arterburn, L.M.; Boswell, K.D.; Koskelo, E.; Kassner, S.L.; Kelly, C.; Kyle, D.J. 2000. A combined subchronic (90-day) toxicity and neurotoxicity study of a single-cell source of docosahexaenoic acid triglyceride (DHASCO® oil). *Food Chem Toxicol* 38(1):35-49.
- Astorg, P.; Arnault, N.; Czernichow, S.; Noisette, N.; Galan, P.; Hercberg, S. 2004. Dietary intakes and food sources of n-6 and n-3 PUFA in French adult men and women. *Lipids* 39(6):527-535.
- Bhise, A.; Krishnan, P.V.; Aggarwal, R.; Gaiha, M.; Bhattacharjee, J. 2005. Effect of low-dose omega-3 fatty acids substitution on blood pressure, hyperinsulinemia and dyslipidemia in Indians with essential hypertension: A pilot study. *Indian J Clin Biochem* 20(2):4-9.
- Bjorneboë, A.; Soyland, E.; Bjorneboe, G.E.; Rajka, G.; Drevon, C.A. 1987. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. *Br J Dermatol* 117(4):463-469.

- Bønnaa, K.H.; Bjerve, K.S.; Straume, B.; Gram, I.T.; Thelle, D. 1990. Effect of eicosapentaenoic and docosahexaenoic acids on blood pressure in hypertension. A population-based intervention trial from the Tromsø study. *N Engl J Med* 322(12):795-801.
- Bondía-Martínez, E.; López-Sabater, M.C.; Castellote-Bargalló, A.I.; Rodríguez-Palmero, M.; González-Corbella, M.J.; Rivero-Urgell, M.; Campoy-Folgozo, C.; Bayés-García, R. 1998. Fatty acid composition of plasma and erythrocytes in term infants fed human milk and formulae with and without docosahexaenoic and arachidonic acids from egg yolk lecithin. *Early Hum Dev* 53(Suppl.):S109-S119.
- Brantom, P.G.; Gaunt, I.F.; Hardy, J.; Grasso, P. 1973. Long term feeding and reproduction studies on emulsifier YN in rats. *Food Cosmet Toxicol* 11(5):755-769.
- Brinkman, S.D.; Smith, R.C.; Meyer, J.S.; Vroulis, G.; Shaw, T.; Gordon, J.R.; Allen, R.H. 1982. Lecithin and memory training in suspected Alzheimer's disease. *J Gerontol* 37(1):4-9.
- Brister, S.J.; Buchanan, M.R. 1998. Effects of linoleic acid and/or marine fish oil supplements on vessel wall thromboresistance in patients undergoing cardiac surgery. In: Sinzinger, H.; Samuelsson, B.; Vane, J.R.; Paoletti, R.; Ramwell, P.; Wong, P.Y.-K. (Eds.). *Recent Advances in Prostaglandin, Thromboxane, and Leukotriene Research. 10th International Conference on Prostaglandins and Related Compounds - Proceedings, Sep. 22-27, 1996, Vienna, Austria. Plenum Press; New York, Advances in Experimental Medicine and Biology, Vol. 433, pp. 275-278.*
- Buchman, A.L.; Dubin, M.; Jenden, D.; Moukarzel, A.; Roch, M.H.; Rice, K.; Gornbein, J.; Ament, M.E.; Eckhart, C.D. 1992. Lecithin increases plasma free choline and decreases hepatic steatosis in long-term total parenteral nutrition patients. *Gastroenterology* 102(4, Part 1):1363-1370.
- Bunea, R.; El Farrah, K.; Deutsch, L. 2004. Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. *Altern Med Rev* 9(4):420-428.
- Burns, C.P.; Halabi, S.; Clamon, G.H.; Hars, V.; Wagner, B.A.; Hohl, R.J.; Lester, E.; Kirshner, J.J.; Vinciguerra, V.; Paskett, E. 1999. Phase I clinical study of fish oil fatty acid capsules for patients with cancer cachexia: Cancer and Leukemia Group B Study 9473. *Clin Cancer Res* 5(12):3942-3947.
- Canty, D.J.; Zeisel, S.H. 1994. Lecithin and choline in human health and disease. *Nutr Rev* 52(10):327-339.
- Carlson, S.E.; Ford, A.J.; Werkman, S.H.; Peeples, J.M.; Koo, W.W.K. 1996. Visual acuity and fatty acid status of term infants fed human milk and formulas with and without docosahexaenoate and arachidonate from egg yolk lecithin. *Pediatr Res* 39(5):882-888.
- Carlson, S.E.; Montalto, M.B.; Ponder, D.L.; Werkman, S.H.; Korones, S.B. 1998. Lower incidence of necrotizing enterocolitis in infants fed a preterm formula with egg phospholipids. *Pediatr Res* 44(4):491-498.

- CFR. 2005a. Part 184—Direct food substances affirmed as generally recognized as safe. Subpart B—Listing of specific substances affirmed as GRAS. Sections § 184.1065, 184.1259, 184.1400, 184.1472, 184.1555—[Linoleic acid, Cocoa butter substitute, Lecithin, Menhaden oil, Rapeseed oil]. In: Code of Federal Regulations Title 21—Food and Drugs. U.S. Government Printing Office; Washington, DC, pp. 489, 510-511, 532, 541-544 & 548-550, . Available from:
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr184_05.html.
- CFR. 2005b. Part 582—Substances generally recognized as safe. Subpart B—General purpose food additives. Section § 542.1400—Lecithin. In: Code of Federal Regulations Title 21—Food and Drugs. . U.S. Government Printing Office; Washington, DC, p. 534. Available from:
http://a257.g.akamaitech.net/7/257/2422/01apr20051500/edocket.access.gpo.gov/cfr_2005/aprqr/pdf/21cfr582.1400.pdf.
- CFR. 2005c. Part 182— Substances generally recognized as safe. Sections § 182.10, 184.20 —[Spices and other natural seasonings and flavorings, Essential oils, oleoresins (solvent-free), and natural extractives (including distillates)]. In: Code of Federal Regulations Title 21—Food and Drugs. U.S. Government Printing Office; Washington, DC, pp. 467-471 . Available from:
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr182_05.html.
- CFR. 2005d. Part 172— Food additives permitted for direct addition to food for human consumption. Sections § 172.210, 172.510, 172.615, 172.860—[Coatings on fresh citrus fruit, Natural flavoring substances and natural substances used in conjunction with flavors, Chewing gum base, Fatty acids]. In: Code of Federal Regulations Title 21— Food and Drugs. U.S. Government Printing Office; Washington, DC, pp. 39-40, 57-57, 67-68 & 98-99. Available from:
http://www.access.gpo.gov/nara/cfr/waisidx_05/21cfr172_05.html.
- CFR. 2005e. Part 164— Tree nut and peanut products. Section § 164.150—Peanut butter. In: Code of Federal Regulations Title 21—Food and Drugs. U.S. Government Printing Office; Washington, DC, p. 528. Available from:
http://a257.g.akamaitech.net/7/257/2422/01apr20051500/edocket.access.gpo.gov/cfr_2005/aprqr/pdf/21cfr164.150.pdf.
- CFR. 2005f. Part 101—Food labeling. Section § 101.12— Reference amounts customarily consumed per eating occasion. In: Code of Federal Regulations Title 21—Food and Drugs. U.S. Government Printing Office; Washington, DC, pp. 52-61. Available from:
http://a257.g.akamaitech.net/7/257/2422/01apr20051500/edocket.access.gpo.gov/cfr_2005/aprqr/pdf/21cfr101.12.pdf.
- Chamberlain, S.; Robinson, N.; Walker, J.; Smith, C.; Benton, S.; Kennard, C.; Swash, M.; Kilkeny, B.; Bradbury, S. 1980. Effect of lecithin on disability and plasma free-choline levels in Friedreich's ataxia. *J Neurol Neurosurg Psychiatry* 43(9):843-845.
- Chatellier, G.; Lacomblez, L. 1990. Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: A multicentre trial. (On Behalf of Groupe Francais d'Etude de la Tetrahydroaminoacridine). *BMJ* 300(6723):495-499.

- Chin, J.P.; Dart, A.M. 1994. Therapeutic restoration of endothelial function in hypercholesterolaemic subjects: Effect of fish oils. *Clin Exp Pharmacol Physiol* 21(10):749-755.
- Christensen, J.H.; Gustenhoff, P.; Ejlersen, E.; Jessen, T.; Korup, E.; Rasmussen, K.; Dyerberg, J.; Schmidt, E.B. 1995. n-3 Fatty acids and ventricular extrasystoles in patients with ventricular tachyarrhythmias. *Nutr Res* 15(1):1-8.
- CIR. 2001. Final report on the safety assessment of lecithin and hydrogenated lecithin. *Int J Toxicol* 20(Suppl. 1):21-45.
- Clark, W.F.; Parbtani, A.; Naylor, C.D.; Levinton, C.M.; Muirhead, N.; Spanner, E.; Huff, M.W.; Philbrick, D.J.; Holub, B.J. 1993. Fish oil in lupus nephritis: Clinical findings and methodological implications. *Kidney Int* 44(1):75-85.
- CODEX-STAN 210. 2005. Codex Standard for Named Vegetable Oils. Codex Alimentarius Commission; Rome. [CODEX STAN 210 (Amended 2003, 2005)]. Available from: http://www.codexalimentarius.net/download/standards/336/CXS_210e.pdf.
- Cohen, B.M.; Miller, A.L.; Lipinski, J.F.; Pope, H.G. 1980. Lecithin in mania: A preliminary report. *Am J Psychiatry* 137(2):242-243.
- Connor, W.E.; Prince, M.J.; Ullmann, D.; Riddle, M.; Hatcher, L.; Smith, F. E.; Wilson, D. 1993. The hypotriglyceridemic effect of fish oil in adult-onset diabetes with adverse glucose control. *Ann N Y Acad Sci* 683:337-340.
- Copeman, L.A.; Parrish, C.C. 2004. Lipid classes, fatty acids, and sterols in seafood from Gilbert Bay, Southern Labrador. *J Agric Food Chem* 52(15):4872-4881 & Erratum 53(7):2778.
- Cunnane, S.C.; Francescutti, V.; Brenna, J.T.; Crawford M.A. 2000. Breast-fed infants achieve a higher rate of brain and whole body docosahexaenoate accumulation than formula-fed infants not consuming dietary docosahexaenoate. *Lipids* 35(1):105-111. Cited In: Mathews *et al.*, 2002.
- De Vizia, B.; Raia, V.; Spano, C.; Pavlidis, C.; Coruzzo, A.; Alessio, M. 2003. Effect of an 8-month treatment with omega-3 fatty acids (eicosapentaenoic and docosahexaenoic) in patients with cystic fibrosis. *JPEN* 27(1):52-57.
- Del Castillo, M.L.; Dobson, G.; Brennan, R.; Gordon, S. 2004. Fatty acid content and juice characteristics in black currant (*Ribes nigrum* L.) genotypes. *J Agric Food Chem* 52(4):948-952.
- Eritsland, J.; Seljeflot, M.; Abdelnoor, M.; Arnesen, H. 1994a. Long-term influence of omega-3 fatty acids on fibrinolysis, fibrinogen, and serum lipids. *Fibrinolysis* 8:120-125.
- Eritsland, J.; Seljeflot, M.; Abdelnoor, M.; Arnesen, H.; Torjesen, P.A. 1994b. Long-term effects on N-3 fatty acids on serum lipids and glycemc control. *Scand J Clin Lab Invest* 54:273-280.

- Eritslund, J.; Arnesen, H.; Seljeflot, I.; Kierulf, P. 1995a. Long-term effects of *n*-3 polyunsaturated fatty acids on hemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis* 6(1):17-22.
- Eritslund, J.; Arnesen, H.; Seljeflot, I.; Høstmark, A.T. 1995b. Long-term metabolic effects of *n*-3 polyunsaturated fatty acids in patients with coronary artery disease. *Am J Clin Nutr* 61:831-836.
- Eritslund, J.; Arnesen, H.; Grønseth, K.; Fjeld, N.B.; Abdelnoor, M. 1996. Effect of dietary supplementation with *n*-3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol* 77(1):31-36.
- European Commission. 1996. Commission directive 96/4/EC, Euratom of 16 February 1996 amending Directive 91/321/EEC on infant formulae and follow-on formulae. *Off J Eur Comm* 39(49):12-16.
- FAO/WHO. 1994. Report of a Joint Expert Consultation. Fats and Oils in Human Nutrition. Food and Agriculture Organization of the United Nations (FAO) / World Health Organization (WHO); Geneva, Switz., FOA Food and Nutrition Paper No. 57, pp. 49-55. Available from: <http://www.fao.org/docrep/V4700E/V4700E00.htm>.
- Fasching, P.; Rohac, M.; Liener, K.; Schneider, B.; Nowotny, P.; Waldhausl, W. 1996. Fish oil supplementation *versus* Gemfibrozil treatment in hyperlipidemic NIDDM. *Horm Metab Res* 28(5):230-236.
- FCC. 2003. Lecithin. In: Food Chemicals Codex (5th Ed.). National Academy Press (NAP); Washington, DC, pp. 248-249.
- FDA. 1985. Direct food substances recognized as safe: Low erucic acid rapeseed oil (Final rule - 21 CFR Part 184) [Docket No. 82G-0207]. *Fed Regist (US)* 50(18):3745-3755.
- FDA. 1997a. Premarket notification for a new dietary ingredient; Final rule [21 CFR Part 190 - Docket No. 96N-0232]. *Fed Regist (US)* 62(184):49886-49892.
- FDA. 1997b. Substances affirmed as generally recognized as safe: Menhaden oil (Final rule) [21 CFR, Part 184, Docket No. 86G-0289]. *Fed Regist (US)* 62(108):30751-30757.
- FDA. 2000a. Agency Response Letter GRAS Notice No. GRN 000043 [Lipase Enzyme Preparation, Sep. 22, 2000]. Food and Drug Administration, U.S. (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Premarket Approval; Washington, DC. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g043.html>.
- FDA. 2000b. Letter Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease (Docket No. 91N-0103) [To Jonathan W. Emord, Emord & Associates, P.C. from Christine J. Lewis, Director]. Food and Drug Administration, U.S. (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Nutritional Products, Labeling, and Dietary Supplements. Available from: <http://vm.cfsan.fda.gov/~dms/ds-ltr11.html>.

- FDA. 2001. Agency Response Letter GRAS Notice No. GRN 000080 [ARASCO (Arachidonic Acid-Rich Single-Cell Oil)]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g080.html>.
- FDA. 2002a. Agency Response Letter GRAS Notice No. GRN 000109 [Tuna Oil]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g109.html>.
- FDA. 2002b. Agency Response Letter GRAS Notice No. GRN 000105 [Fish Oil Concentrate]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g105.html>.
- FDA. 2002c. Agency Response Letter GRAS Notice No. GRN 000102 [Small Planktivorous Pelagic Fish Body Oil]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g102.html>.
- FDA. 2004a. Agency Response Letter GRAS Notice No. GRN 000138 [Fish Oil]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g138.html>.
- FDA. 2004b. Agency Response Letter GRAS Notice No. GRN 000146 [Salmon Oil]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g146.html>.
- FDA. 2004c. Agency Response Letter GRAS Notice No. GRN 000137 [Algal oil (Schizochytrium sp.)]. U.S. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety; College Park, Maryland. Available from: <http://www.cfsan.fda.gov/~rdb/opa-g137.html>.
- FDA. 2004d. Substances affirmed as generally recognized as safe: Menhaden oil; Tentative final rule [21 CFR, Part 184, Docket No. 1999P-5332]. Fed Regist (US) 69(10):2313-2317.
- FDRL. 1973a. Approximate LD50 of FDA 71-88 (Lecithin) in Mice. Submitted by FDA in response to a Freedom of Information (FOI) request dated 11/27/95 Re: Food and Drug Research Laboratories Inc. (FDRL). DHEW Contract No. 71-260 ; Lab No. 1762]. Cited In: CIR, 2001.
- FDRL. 1973b. Approximate LD50 of FDA 71-88 (Lecithin) in Rats. Submitted by FDA in response to a FOI request dated 11/27/95 Re: Food and Drug Research Laboratories Inc. (FDRL). [DHEW Contract No. FDA 71-260 ; Lab No. 1763]. Cited In: CIR, 2001.
- FDRL. 1973c. Approximate LD50 of FDA 71-88 (Lecithin) in Rabbits. Submitted by FDA in response to a FOI request dated 11/27/95 Re: Food and Drug Research Laboratories Inc. (FDRL). [DHEW Contract No. 71-260 ; Lab No. 1764]. Cited In: CIR, 2001.

- FDRL. 1973d. Teratologic Evaluation of FDA 71-88 (Lecithin) in Mice. Submitted by FDA in response to a FOI request dated 11/27/95 Re: Food and Drug Research Laboratories Inc. (FDRL). [DHEW Contract No. 71-260 ; Lab No. 1765]. Cited In: CIR, 2001.
- FDRL. 1973e. Teratologic Evaluation of FDA 71-88 (Lecithin) in Rats. Submitted by FDA in response to a FOI request dated 11/27/95 Re: Food and Drug Research Laboratories Inc. (FDRL). [DHEW Contract No. 71-260 ; Lab No. 1766]. Cited In: CIR, 2001.
- FDRL. 1974. Teratologic Evaluation of FDA 71-88 (Lecithin) in Rabbits. Submitted by FDA in response to a FOI request dated 11/27/95 Re: Food and Drug Research Laboratories Inc. (FDRL). [DHEW Contract No. FDA 71-260 ; Lab No. 1767]. Cited In: CIR, 2001.
- Francois, C.A.; Connor, S.L.; Wander, R.C.; Connor, W.E. 1998. Acute effects of dietary fatty acids on the fatty acids of human milk. *Am J Clin Nutr* 67(2):301-308.
- Freeman, M.P.; Hibbeln, J.R.; Wisner, K.L.; Brumbach, B.H.; Watchman, M.; Gelenberg, A.J. 2006. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatr Scand* 113(1):31-35.
- Garcia, C.A.; Tweedy, J.R.; Blass, J.P.; McDowell, F.H. 1982. Lecithin and parkinsonian dementia. In: Corkin, S.; Davis, K.L.; Growdon, J.H.; Usdin, E.; Wurtman, R.J. (Eds.). *Alzheimer's Disease: A Report of Progress in Research*. Raven Press; New York, Aging, Vol. 19, pp. 443-449.
- Gelenberg, A.J.; Wojcik, J.D.; Growdon, J.H. 1979a. Lecithin for the treatment of tardive dyskinesia. In: Barbeau, A.; Growdon, J.H.; Wurtman, R.J. (Eds.). *Choline And Lecithin In Brain Disorders*. Raven Press; New York, Nutrition and The Brain, Vol. 5, pp. 285-303.
- Gelenberg, A.J.; Doller-Wojcik, J.C.; Growdon, J.H. 1979b. Choline and lecithin in the treatment of tardive dyskinesia: Preliminary results from a pilot study. *Am J Psychiatry* 136(6):772-776.
- Gelenberg, A.J.; Dorer, D.J.; Wojcik, J.D.; Falk, W.E.; Brotman, A.W.; Leah, Y.L. 1990. A crossover study of lecithin treatment of tardive dyskinesia. *J Clin Psychiatry* 51(4):149-153.
- Gil, A.; Ramirez, M.; Gil, M. 2003. Role of long-chain polyunsaturated fatty acids in infant nutrition. *Eur J Clin Nutr* 57(Suppl, 1):S31-S34.
- Gogos, C.A.; Ginopoulos, P.; Salsa, B.; Apostolidou, E.; Zoumbos, N.C.; Kalfarentzos, F. 1998. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy: A randomized control trial. *Cancer* 82(2):395-402.
- Gorbunov, D.A.; Semenov, D.V.; Shipitsin, M.V.; Nevinsky, G.A. 2001. Unusual phospholipids of human breast milk. *Dokl Biochem Biophys* 377:62-64.
- Goren, A.; Stankiewicz, H.; Goldstein, R.; Drukker, A. 1991. Fish oil treatment of hyperlipidemia in children and adolescents receiving renal replacement therapy. *Pediatrics* 88(2):265-268.

- Gray, D.R.; Gozzip, C.G.; Eastham, J.H.; Kashyap, M.L. 1996. Fish oil as an adjuvant in the treatment of hypertension. *Pharmacotherapy* 16(2):295-300.
- Growdon, J.H.; Corkin, S.; Huff, F.J.; Rosen, T.J. 1986. Piracetam combined with lecithin in the treatment of Alzheimer's disease. *Neurobiol Aging* 7(4):269-276.
- Hamazaki, K.; Itomura, M.; Huan, M.; Nishizawa, H.; Sawazaki, S.; Tanouchi, M.; Watanabe, S.; Hamazaki, T.; Terasawa, K.; Yazawa, K. 2005. Effect of omega-3 fatty acid-containing phospholipids on blood catecholamine concentrations in healthy volunteers: A randomized, placebo-controlled, double-blind trial. *Nutrition* 21(6):705-710.
- Hansen, J.-B.; Olsen, J.O.; Wilsgard, L.; Lyngmo, V.; Svensson, B. 1993a. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. *Eur J Clin Nutr* 47(7):497-507.
- Hansen, J.-B.; Lyngmo, V.; Svensson, B.; Nordøy, A. 1993b. Inhibition of exercise-induced shortening of bleeding time by fish oil in familial hypercholesterolemia (Type IIa). *Arterioscler Thromb* 13(1):98-104.
- Harel, Z.; Gascon, G.; Riggs, S.; Vaz, R.; Brown, W.; Exil, G. 2002. Supplementation with omega-3 polyunsaturated fatty acids in the management of recurrent migraines in adolescents. *J Adolesc Health* 31(2):154-161.
- Harris, W.S.; Windsor, S.L.; Caspermeier, J.J. 1993. Modification of lipid-related atherosclerosis risk factors by omega-3 fatty acid ethyl esters in hypertriglyceridemic patients. *J Nutr Biochem* 4:706-712.
- Henderson, W.R. (Jr.); Astley, S.J.; McCreedy, M.M.; Kushmerick, P.; Casey, S.; Becker, J.W.; Ramsey, B.W. 1994. Oral absorption of omega-3 fatty acids in patients with cystic fibrosis who have pancreatic insufficiency and in healthy control subjects. *J Pediatr* 124(3):400-408.
- Houtsmüller, U.M.T. 1979. Metabolic fate of dietary lecithin. In: Barbeau, A.; Growdon, J.H.; Wurtman, R.J. (Eds.). *Choline and Lecithin in Brain Disorders*. Raven Press; New York, *Nutrition and the Brain*, Vol. 5, pp. 83-94.
- Hung, P.; Gu, J.Y.; Kaku, S.; Yunoki, S.; Ohkura, K.; Ikeda, I.; Tachibana, H.; Sugano, M.; Yazawa, K.; Yamada, K. 2000. Dietary effects of eicosapentaenoic and docosahexaenoic acid esters on lipid metabolism and immune parameters in Sprague-Dawley rats. *Biosci Biotechnol Biochem* 64(12):2588-2593.
- Ilowite, N.T.; Copperman, N.; Leicht, T.; Kwong, T.; Jacobson, M.S. 1995. Effects of dietary modification and fish oil supplementation on dyslipoproteinemia in pediatric systemic lupus erythematosus. *J Rheumatol* 22(7):1347-1351.
- Innis, S.M. 2004. Polyunsaturated fatty acids in human milk: An essential role in infant development. In: Pickering, L.K.; Morrow, A.L.; Ruiz-Palacios, G.M.; Schanler, R.J. (Eds.). *Protecting Infants through Human Milk: Advancing the Scientific Evidence*. Springer; New York, *Advances in Experimental Medicine and Biology*, Vol. 554, pp. 27-43.

- Innis, S.M.; Elias, S.L. 2003. Intakes of essential n-6 and n-3 polyunsaturated fatty acids among pregnant Canadian women. *Am J Clin Nutr* 77(2):473-478.
- Innis, S.M.; Kuhnlein, H.V. 1988. Long-chain n-3 fatty acids in breast milk of Inuit women consuming traditional foods. *Early Hum Dev* 18(2&3):185-189.
- Jackson, I.V.; Nuttall, E.A.; Ibe, I.O.; Perez-Cruet, J. 1979. Treatment of tardive dyskinesia with lecithin. *Am J Psychiatry* 136(11):1458-1460.
- Jackson, I.V.; Davis, L.G.; Cohen, R.K.; Nuttall, E.A. 1981. Lecithin administration in tardive dyskinesia: Clinical and biomedical correlates. *Biol Psychiatry* 16(1):85-90.
- JECFA. 1974. Lecithin. *In: Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents. 17th JECFA Session, June 25-July 4, 1973, Geneva. Food and Agriculture Organization of the United Nations (FAO); Rome. FAO Nutrition Meetings Report Series, No. 53A / WHO Technical Report Series, No. 539 / WHO Food Additives Series, No. 5, pp. 234-235. Available from: <http://www.inchem.org/documents/jecfa/jecmono/v05je42.htm>.*
- JECFA. 1987. Lead (Evaluation of health risk to infants and children). *In: Toxicological Evaluation of Certain Food Additives and Contaminants, 30th JECFA Session, June 2-11, 1986, Rome. Food and Agriculture Organization of the United Nations (FAO). Cambridge University Press, Cambridge, Eng.; New York, WHO Food Additives Series, No. 21, pp. 223-255 & 281. Available from: <http://www.inchem.org/documents/jecfa/jecmono/v21je16.htm>.*
- JECFA. 1989. Contaminants: [Arsenic, Cadmium, Methylmercury]. *In: Toxicological Evaluation of Certain Food Additives and Contaminants. 33rd JECFA Session, Mar. 21-30, 1989, Geneva. Food and Agriculture Organization of the United Nations (FAO). Cambridge University Press; Cambridge, Engl./New York. WHO Food Additives Series, No. 24, pp. 154-163, 163-219, 295-328. Available from: <http://www.inchem.org/documents/jecfa/jecmono/v024je01.htm>.*
- JECFA. 2002. Polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls. *In: Safety Evaluation of Certain Food Additives and Contaminants – 57th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), June 5-14, 2001, Rome. World Health Organization (WHO); Geneva. International Programme on Chemical Safety (IPCS), Joint FAO/WHO Expert Committee on Food Additives (JECFA), Food and Agriculture Organization of the United States (FAO). WHO Food Additives Series, No. 48, pp. 451-664 & 692. Available from: <http://www.inchem.org/documents/jecfa/jecmono/v48je20.htm>.*
- Jensen, R.G. 1989. *The Lipids of Human Milk. CRC Press; Boca Raton, Florida, pp. 65-92. Cited In: Gorbunov et al., 2001.*
- Jónsson, A.; Pálmadóttir, H.; Kristbergson, K. 1997. Fatty acid composition in ocean-ranched Atlantic salmon (*Salmo salar*). *Int J Food Sci Technol* 32(6):547-551.
- Kragballe, K.; Fogh, K. 1989. A low-fat diet supplemented with dietary fish oil (Max-EPA) results in improvement of psoriasis and in formation of leukotriene B5. *Acta Derm Venereol* 69(1):23-28.

- Krokan, H.E.; Bjerve, K.S.; 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. *Biochim Biophys Acta* 1168(1):59-67.
- Kruger, M.C.; Coetzer, H.; de Winter, R.; Gericke, G.; van Papendorp, D.H. 1998. Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis. *Aging (Milano)* 10(5):385-394.
- Kurlandsky, L.E.; Bennink, M.R.; Webb, P.M.; Ulrich, P.J.; Baer, L.J. 1994. The absorption and effect of dietary supplementation with omega-3 fatty acids on serum leukotriene B4 in patients with cystic fibrosis. *Pediatr Pulmonol* 18(4):211-217.
- Leaf, A.; Jorgensen, M.B.; Jacobs, A.K.; Cote, G.; Schoenfeld, D.A.; Scheer, J.; Weiner, B.H.; Slack, J.D.; Kellett, M.A.; Raizner, A.E.; Weber, P.C.; Mahrer, P.R.; Rossouw, J.E. 1994. Do fish oils prevent restenosis after coronary angioplasty? *Circulation* 90(5):2248-2257.
- Lechowski, R.; Bielecki, W.; Sawosz, E.; Krawiec, M.; Klucinski, W. 1999. The effect of lecithin supplementation on the biochemical profile and morphological changes in the liver of rats fed different animal fats. *Vet Res Commun* 23(1):1-14.
- Leigh-Firbank, E.C.; Minihane, A.M.; Leake, D.S.; Wright, J.W.; Murphy, M.C.; Griffin, B.A.; Williams, C.M. 2002. Eicosapentaenoic acid and docosahexaenoic acid from fish oils: Differential associations with lipid responses. *Br J Nutr* 87(5):435-445.
- Lemaitre-Delaunay, D.; Pachiardi, C.; Laville, M.; Pousin, J.; Armstrong, M.; Lagarde, M. 1999. Blood compartmental metabolism of docosahexaenoic acid (DHA) in humans after ingestion of a single dose of [¹³C]DHA in phosphatidylcholine. *J Lipid Res* 40(10):1867-1874.
- Levy, E.; Roy, C.C. 1989. Developmental aspects of intestinal lipoprotein synthesis and secretion. In: Leberthal, E. (Ed.). *Human Gastrointestinal Development*. Raven Press; New York, pp. 491-503. Cited In: Amate et al., 2001.
- Litton Bionetics, Inc. 1975. Mutagenic Evaluation of Compound FDA 71-88, Lecithin. Produced by: Litton Bionetics, Inc.; Kensington, Maryland [LBI-2468-323] for the Food and Drug Administration, U.S. (FDA); Washington, DC [FDABF-GRAS-323; PB-245 478/3/XAB]. Cited In: CIR, 2001.
- Maki, K.C.; Van Elswyk, M.E.; McCarthy, D.; Seeley, M.A.; Veith, P.E.; Hess, S.P.; Ingram, K.A.; Halvorson, J.J.; Calaguas, E.M.; Davidson, M.H. 2003. Lipid responses in mildly hypertriglyceridemic men and women to consumption of docosahexaenoic acid-enriched eggs. *Int J Vitam Nutr Res* 73(5):357-368.
- Maltby, N.; Broe, G.A.; Creasey, H.; Jorm, A.F.; Christensen, H.; Brooks, W.S. 1994. Efficacy of tacrine and lecithin in mild to moderate alzheimer's disease: Double blind trial. *BMJ* 308(6933):879-883.
- Mathews, S.A.; Oliver, W.T.; Phillips, O.T.; Odle, J.; Diersen-Schade, D.A.; Harrell, R.J. 2002. Comparison of triglycerides and PL as supplemental sources of dietary long-chain polyunsaturated fatty acids in piglets. *J Nutr* 132(10):3081-3089.

- McGrath, L.T.; Brennan, G.M.; Donnelly, J.P.; Johnston, G.D.; Hayes, J.R.; McVeigh, E.G. 1996. Effect of dietary fish oil supplementation on peroxidation of serum lipids in patients with non-insulin dependent diabetes mellitus. *Atherosclerosis* 121(2):275-283.
- McVeigh, G.E.; Brennan, G.M.; Cohn, J.N.; Finkelstein, S.M.; Hayes, R.J.; Johnston, G.D. 1994. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb* 14(9):1425-1429.
- Merritt, R.J.; Auestad, N.; Kruger, C.; Buchanan, S. 2003. Safety evaluation of sources of docosahexaenoic acid and arachidonic acid for use in infant formulas in newborn piglets. *Food Chem Toxicol* 41(6):897-904.
- Meyer, B.J.; Mann, N.J.; Lewis, J.L.; Milligan, G.C.; Sinclair, A.J.; Howe, P.R. 2003. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. *Lipids* 38(4):391-398.
- Minami, A.; Ishimura, N.; Sakamoto, S.; Takishita, E.; Mawatari, K.; Okada, K.; Nakaya, Y. 2002. Effect of eicosapentaenoic acid ethyl ester v. oleic acid-rich safflower oil on insulin resistance in type 2 diabetic model rats with hypertriacylglycerolaemia. *Br J Nutr* 87(2):157-162.
- Misso, N.L.A.; Thompson, P.J. 1995. Fish oil supplementation inhibits platelet aggregation and ATP release induced by platelet-activating factor and other agonists. *Platelets* 6(5):275-282.
- Morgan, D.R.; Dixon, L.J.; Hanratty, C.G.; El-Sherbeeny, N.; Hamilton, P.B.; McGrath, L.T.; Leahey, W.J.; Johnston, G.D.; McVeigh, G.E. 2006. Effects of dietary omega-3 fatty acid supplementation on endothelium-dependent vasodilation in patients with chronic heart failure. *Am J Cardiol* 97(4):547-551.
- Nagakura, T.; Matsuda, S.; Shichijyo, K.; Sugimoto, H.; Hata, K. 2000. Dietary supplementation with fish oil rich in ω -3 polyunsaturated fatty acids in children with bronchial asthma. *Eur Respir J* 16(5):861-865.
- Nakamura, M.T.; Nara, T.Y. 2003. Essential fatty acid synthesis and its regulation in mammals. *Prostaglandins Leukot Essent Fatty Acids* 68(2):145-150.
- National Marine Fisheries Service. UN Food and Agriculture Organization. 1996. Cited In: Abril and Barclay, 1998.
- Nordøy, A.; Hatcher, L.; Goodnight, S.; Fitzgerald, G.A.; Conner, W.E. 1994. Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid production and hemostatic parameters in normal men. *J Lab Clin Med* 123(6):914-920.
- Partos, L. 2004. Novozymes Enzyme Pierces Trans Fat Market. Decision News Media SAS; Montpellier, France. Available from: <http://www.foodnavigator.com/news/ng.asp?n=55356-novozymes-enzyme-pierces>.

- PDRNS. 2001. Flaxseed oil. In: PDR® for Nutritional Supplements (1st Ed.). Physicians' Desk Reference (PDR); Des Moines, Iowa/Medical Economics Data Production Company; Montvale, New Jersey, pp. 150-152. Available from: http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/fla_0107.shtml.
- Pomara, N.; Domino, E.F.; Yoon, H.; Brinkman, S.; Tamminga, C.A.; Gershon, S. 1983. Failure of single-dose lecithin to alter aspects of central cholinergic activity in Alzheimer's disease. *J Clin Psychiatry* 44(8):293-295.
- Poulsen, R.C.; Kruger, M.C. 2004. Detrimental effect of high dose eicosapentaenoic acid supplementation on bone density in ovariectomised sprague dawley rats. *Asia Pac J Clin Nutr* 13(Suppl.):S49 [Abstract].
- Prisco, D.; Paniccia, R.; Filippini, M.; Francalanci, I.; Bandinelli, B.; Comeglio, P.; Rostagno, C.; Abbate, R.; Neri Serneri, G.G. 1994. No changes in PAI-1 levels after four-month n-3 PUFA ethyl ester supplementation in healthy subjects. *Thromb Res* 76(3):237-244.
- Prisco, D.; Filippini, M.; Francalanci, I.; Paniccia, R.; Gensini, G.F.; Neri Serneri, G.G. 1995. Effect of n-3 fatty acid ethyl ester supplementation on fatty acid composition of the single platelet PL and on platelet functions. *Metabolism Clin Exp* 44(5):562-569.
- Randels, P.M.; Marco, L.A.; Ford, D.I.; Mitchell, R.; Scholl, M.; Plesnarski, J. 1984. Lithium and lecithin treatment in Alzheimer's disease: A pilot study. *Hillside J Clin Psychiatry* 6(2):139-147.
- Rhodes, L.E.; White, S.I. 1998. Dietary fish oil as a photoprotective agent in hydroa vacciniforme. *Br J Dermatol* 138(1):173-178.
- Romano, C.; Cucchiara, S.; Barabino, A.; Annese, V.; Sferlazzas, C. 2005. Usefulness of -3 fatty acid supplementation in addition to mesalazine in maintaining remission in pediatric Crohn's disease: A double-blind randomized, placebo-controlled study. *World J Gastroenterol* 11(45):7118-7121.
- Sacks, F.M.; Stone, P.H.; Gibson, C.M.; Silverman, D.I.; Rosner, B.; Pasternak, R.C. (For the HARP Research Group). 1995. Controlled trial of fish oil for regression of human coronary atherosclerosis. *J Am Coll Cardiol* 25(7):1492-1498.
- Sala-Vila, A.; Castellote-Bargallo, A.I.; Rodriguez-Palmero-Seuma, M.; Lopez-Sabater, M.C. 2003. High-performance liquid chromatography with evaporative light-scattering detection for the determination of phospholipid classes in human milk, infant formulas and phospholipid sources of long-chain polyunsaturated fatty acids. *J Chromatogr A* 1008(1):73-80.
- Sala-Vila, A.; Castellote, A.KI.; Campoy, C.; Rivero, M.; Rodriguez-Palmero, M.; López-Sabater, M.C. 2004. The source of long-chain PUFA in formula supplements does not affect the fatty acid composition of plasma lipids in full-term infants. *J Nutr* 134(4):868-873.
- Sampalis, F.; Bunea, R.; Pelland, M.F.; Kowalski, O.; Duguet, N.; Dupuis, S. 2003. Evaluation of the effects of Neptune Krill Oil on the management of premenstrual syndrome and dysmenorrhea. *Altern Med Rev* 8(2):171-179.

- Sanders, T.A.B.; Oakley, F.R.; Miller, G.J.; Mitropoulos, K.A.; Crook, D.; Oliver, M.F. 1997. Influence of *n-6 versus n-3* polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. *Arterioscler Thromb Vasc Biol* 17(12):3449-3460.
- Schechter, A.; Cramer, P.; Boggess, K.; Stanley, J.; Pöpke, O.; Olson, J.; Silver, A.; Schmitz, M. 2001. Intake of dioxins and related compounds from food in the U.S. population. *J Toxicol Environ Health A* 63(1):1-18.
- Shah, A.B.; Combes, R.D.; Rowland, I.R. 1991. Interaction with microsomal lipid as a major factor responsible for S9-mediated inhibition of 1,8-dinitropyrene mutagenicity. *Mutat Res* 249(1):93-104.
- Silva, J.M.; Souza, I.; Silva, R.; Tavares, P.; Teixeira, F.; Silva, P.S. 1996. The triglyceride lowering effect of fish oils is affected by fish consumption. *Int J Cardiol* 57(1):75-80.
- Smuts, C.M.; Huang, M.; Mundy, D.; Plasse, T.; Major, S.; Carlson, S.E. 2003. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. *Obstet Gynecol* 101(3):469-479.
- Swahn, E.; von Schenck, H.; Olsson, A.G. 1998. Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients. *Clin Drug Invest* 15(6):473-482.
- Takagi, T.; Eaton, C.A.; Ackman, R.G. 1980. Distribution of fatty-acids in lipids of the common Atlantic sea-urchin *Strongylocentrotus droebachiensis*. *Can J Fish Aquat Sci* 37(2):195-202.
- Thies, N.H. 1997. The effect of 12 months' treatment with eicosapentaenoic acid in five children with cystic fibrosis. *J Paediatr Child Health* 33(4):349-351.
- U.S. EPA. 2002. 2. Breast milk intake. In: *Child-Specific Exposure Factors Handbook (Interim Report)*. U.S. Environmental Protection Agency (U.S. EPA), Office of Research and Development, National Center for Environmental Assessment; Washington, DC. [EPA-600-P-00-002B], pp. 2-1 to 2-20. Available from: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?PrintVersion=True&deid=55145>.
- USDA. 2005. Composition of Food: Raw, Processed, Prepared [Results on: "Mollusks, mussel, blue, cooked, moist heat" ; "Fish, herring, Atlantic, cooked, dry heat" ; "Milk, human, mature, fluid" ; and "Oil, peanut, salad or cooking"]. In: *USDA National Nutrient Database for Standard Reference, Release 18*. U.S. Department of Agriculture (USDA), Agricultural Research Service (ARS), Beltsville Human Nutrition Research Center Nutrient Data Laboratory; Beltsville, Maryland. Available from: <http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/sr18.html>.
- Vickar, G.M. 1982. A case study: Idiopathic dyskinesia treated with choline and lecithin. *J Orthomol Psychiatry* 11(2):77-80.
- Volavka, J.; O'Donnell, J.; Muragali, R.; Anderson, B.G.; Gaztanaga, P.; Boggiano, W.; Whittaker, R.; Sta. Maria, T. 1986. Lithium and lecithin in tardive dyskinesia: An update. *Psychiatry Res* 19(2):101-104.

- von Schacky, C.; Angerer, P.; Kothny, W.; Theisen, K.; Mudra, H. 1999. The effect of dietary ω -3 fatty acids on coronary atherosclerosis: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 130(7):554-562.
- Wang, L.; Shimizu, Y.; Kaneko, S.; Hanaka, S.; Abe, T.; Shimasaki, H.; Hisaki, H.; Nakajima, H. 2000. Comparison of the fatty acid composition of total lipids and phospholipids in breast milk from Japanese women. *Pediatr Int* 42(1):14-20.
- Weinstock-Guttman, B.; Baier, M.; Park, Y.; Feichter, J.; Lee-Kwen, P.; Gallagher, E.; Venkatraman, J.; Meksawan, K.; Deinehert, S.; Pendergast, D.; Awad, A.B.; Ramanathan, M.; Munschauer, F.; Rudick, R. 2005. Low fat dietary intervention with -3 fatty acid supplementation in multiple sclerosis patients. *Prostaglandins* 73(5):397-404.
- Wigmore, S.J.; Ross, J.A.; Falconer, J.S.; Plester, C.E.; Tisdale, M.J.; Carter, D.C.; Fearon, K.C. 1996. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. *Nutrition* 12(1):S27-S30.
- Wilbur, K.; Kulik, A.V.; Brecht, T.C. 1982. Lecithin for tardive dyskinesia. *Am J Psychiatry* 139(10):1375.
- Wohl, D.A.; Tien, H.C.; Busby M.; Cunningham, C.; Macintosh, B.; Napravnik, S.; Danan, E.; Donovan, K.; Hossenipour, M.; Simpson, R.J. (Jr.). 2005. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. *Clin Infect Dis* 41(10):1498-1504.
- Wood, J.L.; Allison, R.G. 1982. Effects of consumption of choline and lecithin on neurological and cardiovascular systems. *Fed Proc* 41(14):3015-3021.
- Wurtman, J.J. 1979. Sources of lecithin and choline in the diet. In: Barbeau, A.; Growdon, J.H.; Wurtman, R.J. (Eds.). *Choline and Lecithin in Brain Disorders*. Raven Press; New York, *Nutrition and the Brain*, Vol. 5, pp. 73-81.
- Yackulic, C.F.; Anderson, B.G.; Reker, D.; Webb, E.; Volavka, J. 1982. The safety of lecithin diet supplementation in schizophrenic patients. *Biol Psychiatry* 17(12):1445-1448.
- Zeisel, S.H.; Blusztajn, J.K.; Wurtman, R.J. 1979. Brain lecithin biosynthesis: Evidence that bovine brain can make choline molecules. In: Barbeau, A.; Growdon, J.H.; Wurtman, R.J. (Eds.). *Choline and Lecithin in Brain Disorders*. Raven Press; New York, *Nutrition and the Brain*, Vol. 5, pp. 47-55.
- Zeisel, S.H.; Gelenberg, A.J.; Growdon, J.H.; Wurtman, R.J. 1980. Use of choline and lecithin in the treatment of tardive dyskinesia. In: Cattabeni, F.; Racagni, G.; Spano, P.F.; Costa, E. (Eds.). *Long-Term Effects of Neuroleptics*. Raven Press; New York, *Advances in Biochemical Psychopharmacology*, Vol. 24, pp. 463-470.
- Zeisel, S.H.; Garry, P.J.; Brigida, M.; Magil, S.G.; Goodwin, J.S.; Alvarez, N. 1982. Serum choline concentrations in aged humans. In: Corkin, S.; Davis, K.; Growdon, J.; Usdin, E.; Wurtman, R. (Eds.). *Alzheimer's Disease: A Report of Progress in Research*. Raven Press; New York, *Aging*, Vol. 19, pp. 45-47.

Zubr, J.; Matthäus, B. 2002. Effects of growth conditions on fatty acids and tocopherols in *Camelina sativa* oil. *Ind Crops Prod* 15(2):155-162.