OCEAN NUTRITION CANADA
wellness through innovation

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Robert Pooler, Agricultural Marketing Specialist
National Organic Standards Board (NOSB)
USDA-AMS-TMP-NOP
1400 Independence Avenue, SW
Washington, DC 20250-0020

January 12, 2007

Resubmission of ONC's Petition for the Addition of Fish Oil to 205.606

Dear Mr. Pooler,

Please find attached the updated petition submission from Ocean Nutrition Canada, Limited (ONC). ONC is re-submitting this updated petition to the National Organic Standards Board (NOSB) to request the addition of fish oil to section 205.606 of the National Organic Program's National List. ONC believes that fish oil is a nonorganically produced agricultural product, as encompassed by Section 205.606 of the National List.

The attached petition updates and replaces the previous submission by ONC in August 2006. This petition submission has been updated according to the December 2006 revised National Organic Program guidelines on the submission for inclusion on or removal from the National List of Substances Allowed and Prohibited in Organic Production and Handling (National List.)

Please do not hesitate to contact us if you require any additional information in relation to this fish oil petition.

Sincerely,

Julianne Mayo
Regulatory Affairs Associate

PETITION FOR THE ADDITION OF FISH OIL TO 7 CFR 205.606

ITEM A

Category for which substance is being petitioned:

Ocean Nutrition Canada Limited (ONC) is petitioning for the inclusion of fish oil in the category of nonorganically produced agricultural products allowed as ingredients in or on processed products labeled as "organic" under Section 7 CFR 205.606.

The NOP defines an agricultural product as "any agricultural commodity or product, whether raw or processed, including any commodity or product derived from livestock..." The OFPA defines livestock as "any cattle, sheep, goats, swine, poultry, equine animals used for food or in the production of food, fish used for food, wild or domesticated game, or other nonplant life." This product is derived from fish, and is therefore an agricultural product.

ITEM B

1. The substance's common name.

Fish oil.

2. The producer or manufacturer's name, address and telephone number.

Ocean Nutrition Canada Limited (ONC)
101 Research Drive
Dartmouth, NS
B2& 4T6 Canada
Phone: 902-480-3200
Fax: 902-480-3199

3. A list of the types of product(s) (e.g., cereals, salad dressings) for which the substance will be used and a description of the substance's function in the product(s) (e.g., ingredient, flavoring agent, emulsifier, processing aid).

a) Products: Fish oil has been affirmed by the Food and Drug Administration (FDA) to be Generally Recognized as Safe (GRAS) for addition to a variety of foods (e.g. 21 CFR Part 184.1472, GRAS Notice No's. GRN 00109, GRN 00138). Examples of approved food categories include the following:

- Baked goods, baking mixes
- Cereals
- Cheese products
- Chewing gum
- Condiments
- Confections, frostings

- Dairy product analogs
- Egg products
- Fats, oils
- Fish products
- Frozen dairy desserts
- Gelatins, puddings
- Gravies, sauces,
- Hard candy
- Jams, jellies
- Meat products
- Milk products
- Nonalcoholic beverages
- Nut products
- Pastas
- Plant protein products
- Poultry products
- Processed fruit juices
- Processed vegetables juices
- Snack foods
- Soft candy
- Soup mixes
- Sugar substitutes
- Sweet sauces, toppings, syrups

b) Function: Fish oil is an ingredient typically used to increase the omega-3 fatty acid content of foodstuffs. The primary omega-3 polyunsaturated fatty acids present in fish oil are the long chain fatty acids, EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid).

4. A list of the crop, livestock or handling activities for which the substance will be used. If used for handling (including processing), the substance's mode of action must be described.

This product is used in handling organic agricultural products. Its mode of action is as an ingredient.

5. The source of the substance and a detailed description of its manufacturing or processing procedures from the basic component(s) to the final product.

a) Source: Fish oils are derived from high fat containing fish, such as salmon, tuna, anchovy and sardines. The primary fish oil currently used by ONC is a by-product of the Peruvian fishmeal industry, extracted from wild fish caught off the coast of Peru. The fish species from which the oil is extracted is predominantly anchovy (95-99%) with some sardine (1-5%). Anchovy and sardine are naturally fatty fish that feed on algae in the ocean.

b) Manufacturing and Processing: Manufacturing of fish oil typically involves alkali refining, filtration, bleaching and deodorization. The details of ONC's specific

manufacturing and processing of fish oil are provided below.

ONC's starting material is extracted from marine fish species (e.g. anchovy and sardine) caught off the coast of Peru. The fish are ground and processed in hot water. The solids are removed and used for fishmeal production. The remaining oil and water are passed through a filter to remove any residual solids. The remaining liquid is centrifuged in order to separate the oil from the water and the fish oil is further refined.

During refining, the crude oil is heated again and an alkali (sodium hydroxide) is added to neutralize the oil. The oil undergoes two stages of centrifugation including the addition of water to wash out and eliminate any remaining alkali, ensuring that none is present in the finished product. Following centrifugation, the oil is dried using evaporation to reduce the moisture content.

Production of the food grade fish oil involves steam deodorization and bleaching of the fish oil using clay and carbon. These steps are carried out for the purpose of purifying the fish oil; there is no chemical change in the fish oil during processing.

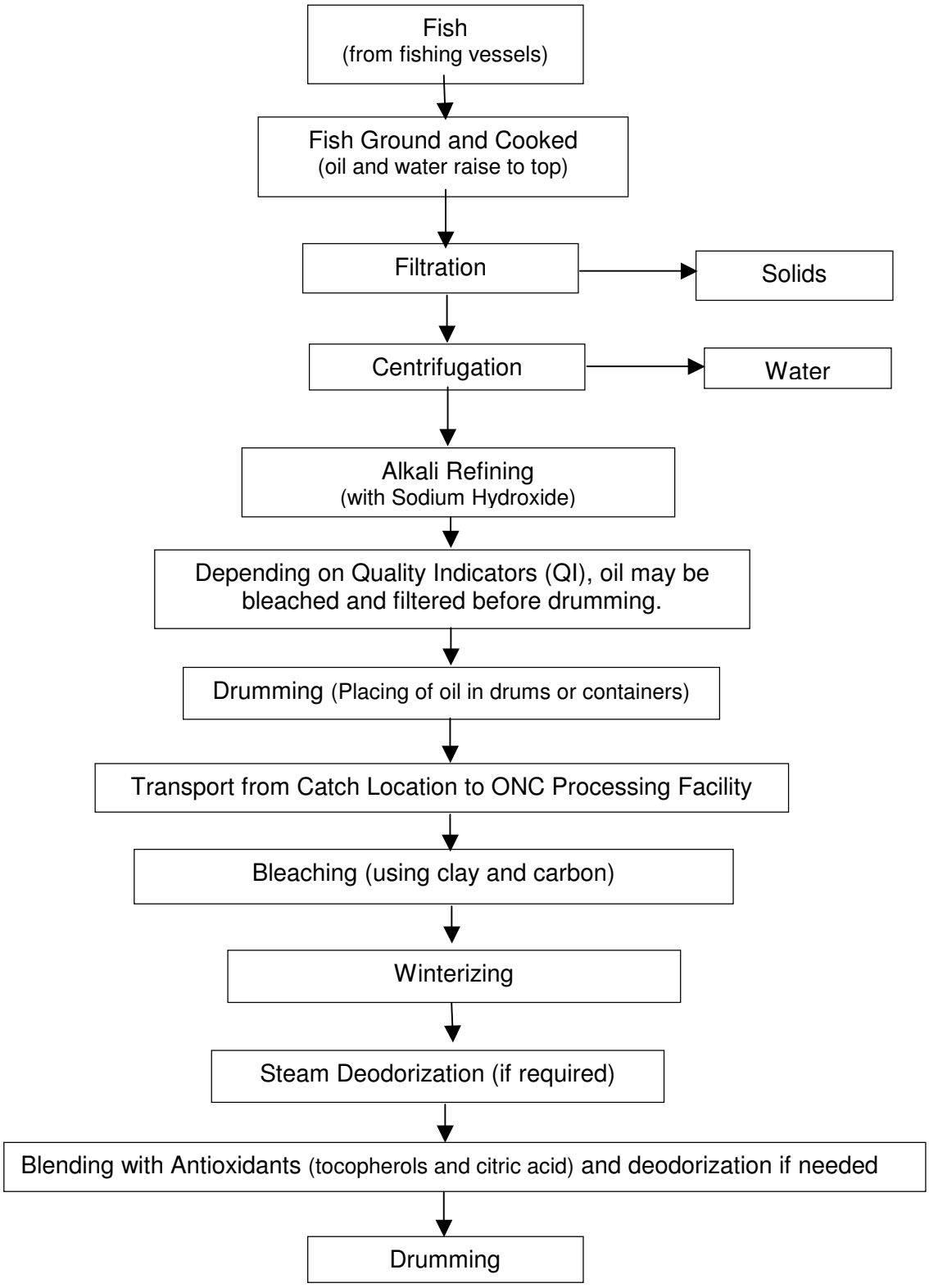
During steam deodorization, the temperature of the oil is raised under full vacuum and steam is injected into the oil. This substantially reduces most naturally occurring undesirable compounds (e.g. aldehydes, ketones – taste, smell).

The bleaching step helps to remove the remaining naturally occurring impurities in the fish oil. Bleaching clay and plant-derived natural carbon are added to the fish oil, then agitated, heated, cooled and filtered until there is no clay or carbon left in the mixture, and therefore none left in the finished product

This is the final stage of processing of the fish oil ingredient. This fish oil ingredient is then blended with antioxidants and used in various applications, including the production of a fish oil powder. ONC uses an antioxidant blend, with the antioxidant function being provided by tocopherols and citric acid.

The fish oil manufacturing process is outlined in the flow chart on the following page.

Fish Processing, Transportation, and Refinement Flow Chart



6. A summary of any available previous reviews by State or private certification programs or other organizations of the petitioned substance.

Reviews of the petitioned substance have been undertaken by the following organizations:

QAI: ONC Fish Oil and Fish Powder were determined to be commercially unavailable in organic form by Quality Assurance International.

The Council of Responsible Nutrition (CRN): CRN developed a Voluntary Monograph for Long Chain Omega-3 EPA & DHA Products. This monograph specifies a uniform standard of analysis, quality, stability, and purity criteria for these fatty acids. The specifications outlined in the CRN Voluntary Monograph are consistent with current, and emerging standards including stringent limits on environmental contaminants such as dioxins, PCB's and heavy metals. Ocean Nutrition Canada has adopted the requirements of the CRN Voluntary Monograph.

Exponent: Ocean Nutrition Canada also commissioned a safety review of EPA and DHA, the polyunsaturated fatty acids found in fish oil. *Exponent*, a multidisciplinary scientific and engineering consulting firm that performs in-depth scientific research and analysis, carried out the safety assessment. They completed a summary of previous literature reviews and safety evaluations (Exponent 2003). The following conclusion is from the Executive Summary of the *Exponent* report:

> *There have been four major independent compilations and evaluations of scientific data in connection with the human safety of fish oil and/or the omega-3 fatty acids (Omega-3 PUFAs) EPA and DHA since 1986, covering more than 650 studies published in peer reviewed scientific journals. The preponderance of these studies has been human data. …To date, there has been no evidence that contradicts the FDA's original 1997 determination that intake of 3 g/day EPA+DHA is safe."*

7. Information regarding EPA, FDA, and State regulatory authority registrations, including registration numbers.

Fish oil has been approved as Generally Recognized As Safe from various sources including tuna oil (GRN 000109), and predominantly anchovy oil (GRN 000138).

The 18/12TG fish oil that is the subject of this petition is a mixture of fatty acids; therefore, no Chemical Abstracts Service (CAS) Registry Number exists for this substance. The CAS Registry Numbers for EPA and DHA, the primary components of this product, are 10417-94-4 and 25167-62-8, respectively

8. The Chemical Abstract Service (CAS) number or other product numbers of the substance and labels of products that contain the petitioned substance.

The 18/12TG fish oil that is the subject of this petition is a mixture of fatty acids; therefore, no Chemical Abstracts Service (CAS) Registry Number exists for this substance. The CAS Registry Numbers for EPA and DHA, the primary components of

this product, are 10417-94-4 and 25167-62-8, respectively.

A copy of the label for a product containing fish oil is attached.

9. The substance's physical properties and chemical mode of action, including:

The attached MSDS for ONC Fish Oil describe its physical properties.

(a) chemical interactions with other substances, especially substances used in organic production;

No distinct chemical interactions are known to occur.

(b) toxicity and environmental persistence;

Please see the *Exponent* safety assessment described above (Section 6) as evidence of fish oil non-toxicity. Fish oil is fully biodegradable, and does not persist in the environment.

(c) environmental impacts from its use or manufacture;

Fish oil is sourced from fish and is typically a by-product of commercially harvested species for the food and fishmeal industries. ONC's fish oil is derived from species harvested using environmentally responsible methods. The anchovies and sardines that are the source of ONC's fish oil come from Peru, where fish harvesting is tightly regulated and monitored. The fishery is open for only short periods of time each year, and access to the fishery is restricted to a limited number of licensed applicants. The prohibition on by-catch of marine mammals is also strictly enforced. See "Eco-friendly Peruvian Fishing Practices," attached.

Oil wastes from the manufacturing process are also recycled to power the ONC processing plant, and excess waste oil is distributed in the form of biodiesel. The biodiesel product is also tested for sulphur content, to ensure that it remains below Canadian regulatory limits. See "Biodiesel Fuel from Ocean Nutrition Canada Fish Oil," attached.

(d) effects on human health;

The safety of fish oil consumption in relation to human health has been assessed and summarized by *Exponent* (see Section 6 above). *Exponent* concluded that there was no evidence that contradicted the FDA's original 1997 determination that EPA+DHA intake is safe up to a level of 3 g/day. The addition of fish oil (in liquid and powder forms) to food products is typically substantially less than this level.

Further, there is considerable evidence for the beneficial effects of fish oil on human health, specifically the EPA+DHA fatty acids found in fish oil. Health authorities and government recommendations often distinguish between the short chain ALA and the long chain Omega-3 fatty acids, EPA and DHA. The evidence for a cardio-protective

effect for EPA+DHA is far stronger than the evidence for a beneficial effect of ALA. While ALA is converted to the longer chain fatty acids, the conversion rate is low. Research has shown that the conversion in adult humans is only approximately 6% to EPA and 3.8% to DHA when the background diet is high in saturated fats (Gester 1998). Also, the conversion is reduced 40-50% when the diet is rich in omega-6 fatty acids (Gester 1998). Typical diet in North America is high in omega-6 PUFAs (e.g. linolenic acid (LA) obtained through consumption of vegetable oils including sunflower, safflower, corn, sesame, and soybean); the level of EPA and DHA that can be obtained from ALA-rich vegetable oils (e.g. flaxseed) through conversion in humans is insufficient. A diet low in omega-6 fatty acids reduces competition on ALA metabolism to its longer chain products (*i.e.* EPA and DHA). Additionally, a balanced n-6/n-3 ratio (optimal recommended ratio is 2:1) in the diet is essential for normal growth and development and should lead to decreases in cardiovascular disease (Engler and Engler 2006).

ONC has a rigorous testing program for potential contaminants in the fish oil. Stringent limits on environmental contaminants such as dioxins, PCB's and heavy metals are monitored according to the requirements of the Council of Responsible Nutrition (CRN) Voluntary Monograph for Long Chain Omega-3 EPA and DHA Products. This monograph specifies a uniform standard of analysis, quality, stability and purity criteria. Every lot of raw fish oil used in the process is tested for heavy metals, PCBs, and dioxins/furans. Incoming oils are tested for pesticides and PAHs three times a year. One in twenty batches of finished products are also tested.

(e) effects on soil organisms, crops, or livestock.

Not applicable. Fish oil is an ingredient and is not applied to the soil, crops or livestock.

10. Safety information about the substance including a Material Safety Data Sheet (MSDS) and a substance report from the National Institute of Environmental Health Studies.

Example of Fish Oil MSDS is attached.

11. Research information about the substance which includes comprehensive substance research reviews and research bibliographies, including reviews and bibliographies which present contrasting positions to those presented by the petitioner in supporting the substance's inclusion on or removal from the National List.

Balk, E., M. Chung, A. Lichtenstein, P. Chew, B. Kupelnick, A. Lawrence, D. DeVine, and J. Lau. 2004. *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease*. Evidence Report/Technology Assessment No.93. AHRQ Publication No. 04-E010-2. Agency for Healthcare Research and Quality, Maryland.

Council for Responsible Nutrition (CRN). 2005. *White Paper – Long Chain Omega-3 Fatty Acids in Human Health. Heart Health: The Role of Eicosapentaenoic, Docosahexaenoic, & Alpha-Linolenic Acids (EPA, DHA, and ALA).* CRN,

Washington.

Engler, M.M. and M.B. Engler. 2006. Omega-3 Fatty Acids: Role in Cardiovascular Health and Disease. *Journal of Cardiovascular Nursing*, 21(1):17-24.

Exponent. 2003. *Safety of EPA+DHA: Summary of Previous Literature Reviews and Safety Evaluations*. Exponent, Washington.

Gester, H. 1998. Can adults adequately convert *a*-linolenic acid to eicosapentaenoic acid and docosahexaenoic acid? *International Journal for Vitamin and Nutrition Research*, 68:159-173.

Harper, C.R., M.J. Edwards, A.P. DeFilipis, and T.A. Jacobson. 2006. Flaxseed Oil Increases the Plasma Concentrations of Cardioprotective (n-3) Fatty Acids in Humans. *Journal of Nutrition*, 136:83-87.

Harper, C.R., and T.A. Jacobsen. 2005. Usefulness of Omega-3 Fatty Acids and the Prevention of Coronary Heart Disease. *The American Journal of Cardiology*, 96:1521-1529.

Kris-Etherton, P.M., W.S. Harris, and L.J. Appel. 2002. AHA Scientific Statement: Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease. *Circulation*, 106:2747-2757.

Lewis, C.J. 2000. *Letter Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease, Docket No. 91N-0103.* U.S. Food and Drug Administration, Maryland.

Natural Standard. 2005. *Omega-3 fatty acids, fish oil, alpha-linolenic acid.* from Medline Plus Web site: http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html

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

12. Petition Justification Statement:

ONC is petitioning for the inclusion of Fish Oil on the National List under Section 7 CFR 205.606, as a nonorganically produced agricultural product allowed as an ingredient in or on agricultural products labeled as “organic.”

Fish oil is an ingredient that can be made into a fine powder or used in the oil form. Unlike its vegetable oil counterparts, fish oil is high in long-chain polyunsaturated omega-3 fatty acids, specifically EPA and DHA (unlike its algal oil counterparts, which are high in DHA, specifically). Fish oil powder can be easily added to foodstuffs to serve the function of increasing the amount of EPA and DHA in the product, without adding a

fishy taste or smell.

Food developers and manufacturers are recognizing the need to deliver products containing Omega-3 to their customers. This need stems from customer demand as well as from the genuine desire of food manufacturers to provide value-added products to their customers. ONC's fish oil powder can currently be found in many food applications in the US and worldwide, including yogurt, bread, pizza, wraps, cookies and juice, just to name a few. In the organic industry, Stonyfield Farm, Inc. uses ONC's fish oil powder in their organic *YoBaby Plus* products. Other organic applications of fish oil may include any of the conventional applications already seen on the market, particularly in the dairy and bakery sectors.

Many international health authorities have agreed on the beneficial effects of fish oil containing omega-3 fatty acids, particularly the long chain omega-3s that are found in fish and fish oil (i.e. EPA and DHA). Several health authorities have also made recommendations for dietary consumption. For example, the American Heart Association (AHA) and the Council for Responsible Nutrition (CRN) have recognized that omega-3s are important to overall health and have a special role to play in promoting heart health, especially the very long chain fatty acids, EPA and DHA (CRN 2005; Kris-Etherton *et al.* 2002).

DHA has been found to be physiologically essential for healthy functioning of the brain, eyes, nervous system, liver and kidneys and is recognized as particularly important in the diet of infants and toddlers. The attached document entitled "The Truth About Omega-3:" summarizes the benefits of fish oil in comparison to alternative Omega-3 sources.

The use of this ingredient in organic products is necessary in order to deliver the health benefits provided by fish oil to organic consumers. Further, the addition of fish oil to 205.606 in order to allow its continued use in organic products is required in order to maintain a competitive position with similar conventional products, many of which are fortified with fish oil omega-3 ingredients.

Statement of need for the non-organic form of the ingredient for use in organic handling:

There are no alternative EPA+DHA sources to fish oil. While it is possible to obtain omega-3's from vegetable sources such as flax seed, this is mainly in the form of ALA (alpha linoleic acid), a shorter chain fatty acid than those obtained from fish oil (EPA+DHA). More dramatic benefits for preventing cardiovascular disease are indicated when the long chain omega-3's found in fish oil are included in the diet (see additional information attached, "Omega-3 Fatty Acids and Cardiovascular Health"). However, there is no organic source of fish oil until such time as standards for organic wild caught fish are implemented. As such, the non-organic form of fish oil is necessary for use in organic handling as no other form exists.

Information concerning how or why the ingredient/substance cannot be obtained organically in the appropriate form to fulfill an essential function in a system of

organic handling:

There are currently no NOP standards for organic aquaculture or wild caught fish or their derivatives, and therefore no possibility of obtaining fish oil in any form, quantity or quality from a certified organic source. ONC intends to pursue the suitability of a potential supply of organic fish oil at such time that the NOP implements standards for organic fish.

Information concerning how or why the ingredient/substance cannot be obtained organically in the appropriate quality to fulfill an essential function in a system of organic handling:

There are currently no NOP standards for organic aquaculture or wild caught fish or their derivatives, and therefore no possibility of obtaining fish oil in any form, quantity or quality from a certified organic source. ONC intends to pursue the suitability of a potential supply of organic fish oil at such time that the NOP implements standards for organic fish.

Information concerning how or why the ingredient/substance cannot be obtained organically in the appropriate quantity to fulfill an essential function in a system of organic handling:

There are currently no NOP standards for organic aquaculture or wild caught fish or their derivatives, and therefore no possibility of obtaining fish oil in any form, quantity or quality from a certified organic source. ONC intends to pursue the suitability of a potential supply of organic fish oil at such time that the NOP implements standards for organic fish.

Information on ingredient/substance non-availability of organic sources:

There are currently no NOP standards for organic aquaculture or wild caught fish or their derivatives, and therefore no possibility of obtaining fish oil in any form, quantity or quality from a certified organic source. ONC intends to pursue the suitability of a potential supply of organic fish oil at such time that the NOP implements standards for organic fish.

List of Attachments:

"Eco-friendly Peruvian Fishing Practices", ONC document.

"Biodiesel Fuel from Ocean Nutrition Canada's Fish Oil", ONC document.

Fish Oil MSDS (XOFG30TGNH-K), ONC document.

"The Truth about Omega-3", ONC document.

Stonyfield Farm *YoBaby Plus* Yogurt label ingredient panel, Stonyfield Farm.

"Omega-3 Fatty Acids and Cardiovascular Health", ONC document.

Commercial Unavailability Determination, Quality Assurance International.

Exponent. 2003. *Safety of EPA+DHA: Summary of Previous Literature Reviews and Safety Evaluations*. Exponent, Washington. (Separate document, CBI)

The following chart may be used by the NOSB as Evaluation Criteria for Substances to be Added to the National List Section 205.606.

Please include the following information:

Is the Substance Essential for Organic Production? Substance __Fish Oil

Question	Yes	No	N/A	Documentation Source
1. Is the substance an agricultural product?	X			
2. Is the substance formulated or manufactured by a process that chemically changes a substance extracted from a nonorganic agricultural substance?		X		
3. Is the substance created by naturally occurring biological processes?	X			
4. Is there an organic source of the substance? [1]		X		
5. Is the substance essential for handling of organically produced agricultural products? [2]	X			
6. Are there any commercially available alternative organic substances? [3]		X		
7. Is there another practice that would make the substance unnecessary?		X		

[1] Documentation should specify details of efforts made to obtain an organic source and the outcome of that effort.

[2] Documentation should specify the essential qualities required for the product to be suitable, e.g., liquid vs. powder, viscosity, color, flavor profile, etc.

[3] Documentation should specify organic alternatives that have been evaluated and reasons for unacceptability.

101 Research Drive
Dartmouth, Nova Scotia
B2Y 4T6 Canada

1 902 480 3200
ocean-nutrition.com

Biodiesel Fuel from Ocean Nutrition Canada Fish Oil

Ocean Nutrition Canada Limited (ONC) is a marine natural products ingredient supplier and has been supplying customers worldwide with dietary supplement and functional food ingredients since 1997. In 1999, ONC began manufacturing concentrated Omega-3 EPA/DHA ingredients through its proprietary manufacturing process, producing novel and innovative EPA/DHA mixtures for its customers.

Omega-3s are extracted from fish oil; during the processing of Omega-3 fish oil, the unwanted saturated fat portion of the fish oil becomes a waste by-product. This waste by-product can function as a potential fuel source, a form of biodiesel. Therefore, ONC tested the use of this by-product biodiesel in the main boiler of the fish oil manufacturing facility as a means of recycling the waste by-product produced by our own manufacturing. Short-term and long-term testing showed successful burning of the biodiesel. Therefore, additional boilers in the manufacturing process were gradually converted to biodiesel originating from fish oil by-product.

Since 2003, ONC has been fully self-sufficient, burning its own Biodiesel in all five boilers, without any excessive hydrocarbon creation and without any modifications to the equipment. Currently, ONC's boilers consume anywhere from two to three million litres of Biodiesel fuel annually. Essentially, the fish oil manufacturing facility runs off the by-product of the fish oil manufacturing itself; an effective recycling of energy and material which reduces waste and pollution.

The fish oil manufacturing facility produces fish oil biodiesel in amounts that exceed the company's internal consumption requirements considerably. Therefore, ONC has an agreement with a local fuel company who distributes biodiesel produced from fish oil in the Atlantic Canadian marketplace for home heating oil and general biodiesel fuel purposes.

Further, as part of the Federal Fuels Regulations, Canada has implemented new sulphur testing requirements for biodiesel. As such, ONC regularly tests the sulphur content in our fish oil biodiesel. Test results indicate that the sulphur level in ONC's biodiesel is well below regulated limits in Canada.

OCEAN NUTRITION CANADA
wellness through innovation

MATERIAL SAFETY DATA SHEET

SECTION 1 – PRODUCT IDENTIFICATION, COMPANY INFORMATION AND USE

Product Identifier: Fish Oil Triglyceride (TG)

Production Identification Number (PIN): XOEU0525TG-IP, XOE0860TG-IP,XOEU1812TGSD-IP
XOEU0560TG-IP, XOEU1050TG-1P, XOEU2050TG-IP, XOEU1812TG-IP, XOEU180120TG-IP,
XOEU1812TGSAL-IP,XO3020TG-IP, XOEU3222TG-IP, XOEU4020TG-IP, XOEU4510TG-IP,
XOEU6003TG-IP,XOEU30TG-K-IP, XOEU1812TG.01,XOEU1812TGFSD-NG
XO0558TG, XO0655TG, XO180120TG, XO180120TG-RPS, XO180120TG, XO180130TGT,
XO1812TG, XO1812TGDAT, XO1812TGE, XO1812TG-IP, XO1812TGOX, XO1812TGAL, XO1812TGFGSD
XO3322TG, XO2050TG, XO300200TG, XO3020TG, XO3030TG, XO3030TGJ, XO30TG-K,XOFG30TG
XO320230TG, XO3222TG, XO3525TG, XO4020TG, XO4825TG, XO6003TG, XO9107, XO9109N,
XODHA, XOEVB, XOFG30TG, XOFG30TG-K, XOGCN1, XOOMB, XOT01, XO290235TG-IP,
XO0355TG, XO0355TGJ, XO0525TG, XO0525TGSD,XOEU3322TG-IP, XOFG30TGNH-K

Product Use: Dietary Supplement, Food Ingredient
Manufacturers Name : Ocean Nutrition Canada Ltd.
Street Address: 39 England Drive
City: Mulgrave, Nova Scotia
Postal Code: B0E 2G0
Emergency Phone Number: 1-888-980-8889

SECTION 2 – COMPOSITION/ INFORMATION ON INGREDIENTS

Hazardous	%	CAS	LD_{50} of Ingredient	LC_{50} of Ingredient
Fish Oil	100	N/AP	N/AP	N/AP

SECTION 3 – HAZARDOUS IDENTIFICATION

N/AP

SECTION 4 - FIRST AID MEASURES

Specific Measures:
For eye contact, flush eyes with copious amounts of tempered water.
For contact with clothing, wet down clothing, seal the clothing from air and wash as soon as possible. For skin contact, wipe skin dry. For ingestion of 10g+, nausea may occur.

SECTION 5 - FIRE AND EXPLOSION DATA

Flammability: X YES __ NO
If yes, under which condition?
High temperatures or with an absorbent (i.e. paper) exposed to air for 6-8+ hours
Flashpoint (Celsius) and method: > 180° C
Upper Flammable Limit(% by volume): --
Lower Flammable Limit (% by volume): 180° C
Auto ignition Temperature (Celsius):
May auto ignite with high surface compounds for long periods of time, exposed to air
Hazardous Combustion Products: Carbon monoxide, carbon dioxide, hydrocarbon, water
Explosion Data: N/A
Sensitivity to impact: N/A
Sensitivity to static discharge: N/A

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Leak and Spill Procedure: Collect major quantity; never use porous material as absorbent, clean with water and detergent. (If absorbent is used, immediately after clean up, wet absorbent with water and seal in garbage bag.) Dispose of according to local laws.

SECTION 7 - HANDLING AND STORAGE

Handling Procedures and Equipment: No special requirements except for latex gloves and protective eyeglasses. Minimize exposure to air

SECTION 8 - EXPOSURE CONTROLS/ PERSONAL PROTECTION

Personal Protective Equipment:
Gloves (specify) - Latex, Rubber, Respirator (specify) - N/AP Eye (specify) - Eyewear
Clothing (specify) - N/AP, Footwear (Specify) - N/AP, Other specify - N/AP
Engineering Controls (Specify: e.g. ventilation, enclosed process): Not required

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Physical State: Liquid	Odor and Appearance: Pale Yellow Liquid, Fishy Odor		Odor Threshold (ppm): N/A
Vapor Pressure (mm Hg): N/A	Vapor Density (Air-1):N/A	Evaporation Rate: N/A	Boiling Point: 400° C
Freezing Point: -5° C	pH: 5- 6	Specific Gravity: 0.9	COEFF Water/Oil Dist.: nil

SECTION 10 - STABILITY AND REACTIVITY

Chemical Stability: Stable when sealed from air conditions with nitrogen.
Incompatibility with other substances: Reacts with alkali to form free fatty acids.
Reactivity and under which conditions: As stated above.
Hazardous Decomposition Products: Peroxides. Combustion produces carbon monoxide and carbon dioxide along with thick smoke.

SECTION 11 - TOXICOLOGICAL PROPERTIES

Route of Entry: X Skin Contact __ Skin Absorption X Eye Contact
__ Inhalation X Ingestion

Effects of Acute Exposure to Product: 10g+ may cause nausea.
Effects of Chronic Exposure to Product: N/A

Exposure Limits: N/A	Irritancy of Product: N/A	Sensitization to Product: N/A	Carcinogenicity: N/A
Teratogenicity: N/A	Reproductive Toxicity: N/A	Mutagenicity: N/A	Synergistic Products: N/A

SECTION 12 - ECOLOGICAL INFORMATION

No data available.

SECTION 13 - DISPOSAL CONSIDERATIONS

Waste Disposal: Dispose of all wastes in accordance with all federal, provincial/state and local agency legislation

SECTION 14 - TRANSPORTATION INFORMATION

RID/ADR - Non-hazardous for road transport
IMDG - Non-hazardous for sea transport
IATA - Non-hazardous for air transport

SECTION 15 - REGULATORY INFORMATION

N/AP

SECTION 16 - OTHER INFORMATION

Warranty:
The above information is believed to be correct but does not propose to be all-inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Ocean Nutrition shall not be held liable for damage resulting from handling or from contact with the above product.

PREPARATION DATE OF MSDS

Ocean Nutrition Canada Limited
101 Research Drive
Dartmouth, Nova Scotia, Canada
B2Y 4T6

Phone Number:
1-902-480-3200

Date:
December 11, 2006

The Truth About Omega-3:

Get all the health benefits of EPA and DHA from fish oil ... the best source of Omega-3!

The Truth About Omega-3:

Get all the health benefits of EPA and DHA from fish oil…the best source of Omega-3!

Health researchers have shown increased interest in Omega-3 for decades. First, the dietary supplement industry and, now, the food industries have caught on to the idea that food products containing Omega-3 are a significant marketplace opportunity.

Elizabeth Mannie

And what an opportunity it is, as shown by a 2004 consumer research study conducted by an independent research firm. All 100% of participants indicated that they would be inclined to purchase a product enriched with Omega-3, if there was no impact on taste or price of the product. Additionally, 100% of participants indicated an interest in educating their families about the many health benefits of Omega-3. When asked about the primary health benefits associated with Omega-3, 40% of the participants felt that it was "good for the heart," 18% felt that it was good for the skin, and 16% felt that it would help lower cholesterol. The bottom line is that consumer awareness of Omega-3, and fish oil as the primary source of Omega-3, is very high.

Omega-3 fatty acids are considered essential for normal growth and development; they are present in every cell in the human body. Important in cell membranes and human metabolism, low levels of Omega-3 in today's diet are a known risk factor for heart and inflammatory diseases. Other evidence points to fatty acid deficiencies contributing to psychiatric and neurologic disorders and childhood neurodevelopmental disorders including Attention Deficit Hyperactivity Disorder (ADHD), dyslexia, dyspraxia/developmental coordination disorder (DCD) and autistic spectrum disorders.[1,2] Omega-3 deficiencies are also thought to play a role in asthma, hypertriglyceridemia, high blood pressure and rheumatoid arthritis.[3,4,5,6]

Western Diets and Health Issues

While scientists and consumers are more educated about the vital role Omega-3 plays in preventing certain diseases, the beginning of this dietary deficiency can be traced to approximately 50 years ago, when food processing technologies allowed manufacturers to offer more packaged foods, and fish was not easily available everywhere. Today, 25% of Americans don't eat fish. The physiologically essential and biologically active forms of Omega-3 are EPA (eicosapentaenoic acid or 22:6n-3) and DHA (docosahexaenoic acid or 20:5n-3). ALA (alpha-linolenic acid or 18:3n-3) is also an Omega-3, but the body needs to con-

vert it to EPA and DHA to derive the health benefits, and this conversion is very inefficient (about a 5% conversion efficiency).[7]

Therefore, it is not surprising that the World Health Organization and others have identified a serious and pervasive deficiency in the Omega-3 fatty acids EPA and DHA, which are vital for heart and brain health as well as for normal growth and development.

In another effort to address the issue, the United States Department of Agriculture changed the food pyramid in 2005, adding the recommendation that people eat at least two, four-ounce meals of fatty fish per week. The American Heart Association (AHA) recommends that adults consume plant-derived sources of Omega-3 fatty acids in addition to eating fish at least twice per week. Because of the inconvenience of preparing fish, and its higher cost, this level of fish consumption is difficult for the average American to achieve.

Danone Danino Yogurt, co-branded with MEG-3®, is available in Canada and targeted to children. It contains 20mg DHA per serving and carries a Biological Role Claim: "DHA, an Omega-3 fatty acid, supports the normal development of the brain, the eyes and the nerves" on the front panel.

All Omega-3s are not Created Equal

It is important to remember that all Omega-3s are not created equal. Three common forms of Omega-3 fatty acids are found in foods. ALA is primarily from flax and a few other plant sources such as soy, walnuts, flaxseed and canola oil, while EPA and DHA are primarily from oily fish such as anchovies, sardines, salmon and mackerel. The highest sources of Omega-3 come from anchovies and sardines.

ALA is different bioactively than EPA and DHA. The Institute of Medicine states that ALA is not known to have any specific functions other than as a precursor to EPA and DHA. However, the conversion rate is very inefficient and will not produce the levels of EPA and DHA believed to offer heart health benefits.[4] The optimal approach for heart health with Omega-3 fatty acids is to consume EPA and DHA via fish consumption and/or supplementation.[8]

Health Benefits

Over 8,000 research publications support the health claims of EPA and DHA. Only calcium has as much scientific evidence for importance in human health. Here are some of the well-researched health benefits.

• Cardiovascular Disease

The FDA reviewed clinical data supporting EPA and DHA benefits to the heart when considering evidence for a qualified health claim. It was noted that four trials conducted in populations with coronary heart disease or high risk factors for CHD found substantial benefits.[8]

The AHA in its 2003 recommendations stated that 2g-4g of EPA and DHA taken daily can lower triglycerides by 20% to 40%. The effects appear to be synergistic with the HMG-CoA reductase inhibitor (statin) drugs such as simvastin (Zocor®), pravastatin (Pravachol®), and atorvastatin (Lipitor®). The AHA also recommended in 2003 that people with known coronary disease take approximately 1g of EPA and DHA combined each day, either by eating fish or taking fish oil supplements.[3]

High blood pressure also responds favorably to Omega-3 supplementation, and the effects appear to be dose sensitive. Higher doses seem to have greater effects on reducing blood pressure.[3]

• Rheumatoid Arthritis

Multiple randomized, controlled trials report improvements in morning stiffness and joint tenderness with regular intake of fish oil supplements over a three-month period. Clinical trials commonly have used doses of between 3g and 5g of EPA and DHA per day, but the effects beyond three months of treatment have not been well evaluated.[3]

• Fetal and Infant Benefits

Studies have shown that maternal intake of DHA during pregnancy and lactation may be favorable for later mental development of the child. It was also demonstrated that an early dietary supply of DHA was a major dietary determinant of improved performance on the Mental Development Index (MDI).[9,10] Human breast milk contains both DHA and EPA in a 4:1 ratio, indicating the importance of both nutrients in infant nutrition.[11]

• Developmental Coordination Disorder

Disturbances of perception, attention and behavior seen in DCD/dyspraxia show parallels to symptoms of Omega-3 fatty acid deficiency seen in animal studies.

Farmers Choice 1% low-fat Milk Beverage, available at Sobeys and Superstore in Canada, contains 40mg EPA and DHA per serving.

DCD affects 5% of school-aged children to a serious degree. It is characterized by deficits in motor function, difficulties in learning, behavior, and psychosocial adjustment that remain into adulthood. DCD shows substantial overlap with ADHD, dyslexia, and autistic spectrum disorders.[12,13]

A randomized, double-blind, placebo-controlled trial involving children aged five through 12 with suspected DCD-type difficulties featured treatment in parallel groups for three months. This was followed by a one-way crossover for an additional three months. Treatment consisted of supplements containing 80% fish oil (558mg EPA and 174mg DHA) and 20% primrose oil, along with Omega-6 (60mg γ-linoleic acid) and 9.6mg vitamin E. The placebo was olive oil.

There was significant improvement in reading, spelling, and behavior, when compared to the placebo group. Mean reading age increased by 9.5 months versus 3.3 months for the placebo group. Mean spelling age increased by 6.6 months versus 1.2 months for the placebo group. The author suggested that fatty acid supplementation might be a safe, tolerable and effective treatment for improving academic progress and behavior among children with DCD.[14]

• Asthma

A study of Australian school-aged children showed that consumption of one fish meal per week reduced asthma, when compared to control groups that rarely ate fish.[4] Another study, where children were evaluated for asthma at eight years of age and compared to healthy control groups of the same age, showed that asthmatics were more likely to have a diet with a higher ratio of Omega-6 to Omega-3 than their control counterparts.[5]

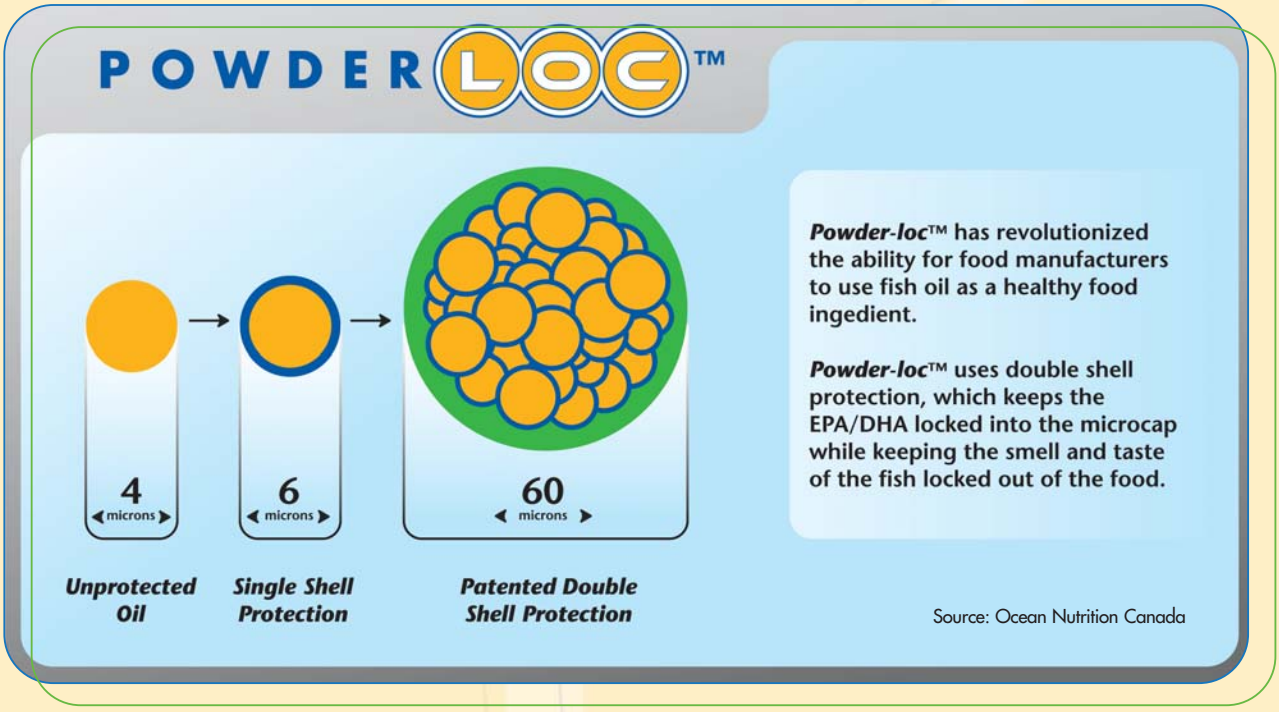
The Omega-3 to Omega-6 ratio, in fact, is the foundation of why Omega-3 is so critical. In another study, involving 616 women at risk for having children with asthma, mothers who received fish oil concentrate and gave fish oil concentrate to their infants after birth had fewer doctor visits for their children for wheezing, nocturnal cough, and bronchodilator use compared with control participants at 18 months old.[6]

Considering that EPA has anti-inflammatory characteristics, it is not surprising that fish oil could lessen asthmatic symptoms. Since asthma, atopy, and atopic dermatitis are closely related, it is possible that Omega-3 could help treat all of these. Although research on Omega-3 supplementation in asthmatics is in its early stages, there are some very encouraging results.

The Challenge of Providing Omega-3

Polyunsaturated fatty acids fall into two classes, Omega-3 and Omega-6. Over the past half century, a disproportionate increase in

Stonyfield Farm Organic Yo-Baby Yogurt with DHA for babies and toddlers. This is a U.S. product containing 17mg DHA per serving.



Omega-6 relative to Omega-3 consumption has occurred. Vegetable oil consumption soared while fish consumption declined, accounting for the current Omega-6 to Omega-3 intake ratio of approximately 15 to 1 in Western diets. Previously, the ratio was closer to 3 to 1.

The increased intake of Omega-6 fatty acids is due to consumption of vegetable oils containing linolaic acid such as corn, safflower, soybean and sunflower oils, as well as less ordinary oils like evening primrose, pumpkin, sesame, walnut and wheat germ. The increased Omega-6 to Omega-3 ratio creates a health issue, since the two types of lipids compete with each other to be converted to active metabolites in the body. Currently, at this reduced intake ratio, Omega-3 is not converted in the quantities needed for health. When more Omega-6 is converted, arachidonic acid is made more prevalent; this is a precursor of the inflammatory cascade and research suggests that this leads to inflammation, the first phase of many disease conditions. Thus, by either decreasing Omega-6 intake or increasing Omega-3 intake, health benefits can be achieved.[15]

One way to increase Omega-3 in the diet is to put fish oil into foods. Previously, many companies have tried this with limited success because the oil is prone to oxidation, causing flavor and odor issues. However, one company, Ocean Nutrition Canada Limited (ONC), has invested in an intensive research and development program to create a solution for the problem of adding fish oil into food products.

The traditional approach to preventing oxidation was microencapsulation, where spray-dry emulsion technology was used to create a sponge-like gelatin matrix of oil. However, this provided limited protection because when the encapsulated oil was exposed to the stresses of food processing, the oil would leak into the food. Also, the older technology allowed large amounts of free oil on the outside of the microencapsulated droplet, resulting in a fishy taste or smell.

Ocean Nutrition's solution is a new, patented process of microencapsulation called Powder-loc™, which enables foods to be enhanced with Omega-3 without any fishy taste or smell. In essence, Powder-loc™ uses double shell protection, which means that each oil droplet not only has its own protective shell, but all the single shells are then grouped together and protected in a second shell. This process keeps the EPA and DHA locked into the microcap, while keeping the taste and the smell of the fish locked out of the food.

In 2005, Ocean Nutrition's MEG-3® brand food ingredient, which uses the unique Powder-loc™ micro-encapsulation technology, has become the world's leading fish oil ingredient in food products. MEG-3® is the breakthrough Omega-3 product that finally enables food companies to create nutritionally dense foods containing EPA and DHA from fish oil, without affecting the taste or smell of the foods.

Micro Spheres of Fish Oil

A cross-section of one grain of MEG-3® powdered fish oil, using Powder-loc™ technology, looks like many little balls inside one large ball. Each of these smaller balls is a mini-

microcapsule that contains fish oil and protects the oil from both oxidation and the rigorous stresses of food processing. Even if the outer shell were to break, which is unlikely, the oil still has the protection of the inner mini-microcapsules that surround it. Thus, the whole cluster of mini-microcapsules is protected by a tough outer shell, resulting in virtually no free oil on the outside.

MEG-3® food ingredient, made with Powder-loc™ technology, enables food companies to put fish oil in their products, without the taste or smell of fish, allowing for the development of a wide variety of new products. With the technology's superior processing tolerance characteristics, the ingredient can withstand the high stress of being kneaded in bread, for example. It can also be heated to high temperatures, surviving milk pasteurization or hot candy processing. Having double the nutritional density of Omega-3 compared with many competitive products, it is also the most cost effective form of microencapsulated fish oil on the market.

The MEG-3® ingredient is commercially available for a broad range of food applications around the globe. No other competitive product has demonstrated its ability to provide foods with added EPA and DHA from fish oil on this magnitude of scale. MEG-3® also demonstrates great flexibility in the range of foods it can be added to including bread, dairy, nutrition bars, orange juice, pizza crust and confections.

Cali Wraps with MEG-3® include four types: original, whole wheat, whole grain and Mediterranean Herb. A Canadian product containing 50mg EPA/DHA per serving, the front panel states: "Source of Omega-3 polyunsaturates from the sea. 0.05g EPA+DHA per tortilla." The company also uses the Biological Role Claim: "Cali-Wraps with MEG-3® contain DHA, an Omega-3 polyunsaturate, which supports the normal development of the brain, eyes and nerves."

Regulatory Benefits

In the U.S., MEG-3® ingredients are FDA-notified Generally Recognized as Safe (GRAS) and a copy of their letter from the FDA can be found on the FDA's website (www.cfsan.fda.gov/~rdb/opag138.html). This letter summarizes the maximum levels and the food categories which are allowed to have MEG-3® added to them.

Based on a large amount of scientific evidence demonstrating the efficacy of EPA and DHA, the Food and Drug Administration has allowed a Qualified Health Claim for heart benefits in supplements and foods containing these Omega-3. This allows manufacturers of nutritional products to better position their products as healthy because EPA and DHA may play significant roles in heart health.

Recently, the U.S. has approved a prescription form of concentrated fish oil for reduction of hypertriglyceridemia, an independent risk factor for coronary artery disease. In Italy, concentrated fish oil is also prescribed by physicians to prevent secondary myocardial infarctions based on the results of a major clinical trial called the GISSI study. These examples demonstrate that there is a positive regulatory environment supporting the efficacy and value of fish oil as a food ingredient.

In Canada, Ocean Nutrition obtained Novel Food approval for the ingredient to be added to food products. Currently, Ocean Nutrition customers are allowed to add a maximum of 50mg EPA and DHA per serving in a limited list of foods. Specifically, they are: unstandardized loaves (not including bagels, flat breads and rolls), granola and cereal bars, meal replacement bars, unstandardized frozen dairy desserts, unstandardized milk-based beverages, yogurt and nutritional supplements in liquid form and chicken nuggets.

Under U.S. labeling regulations, Omega-3, EPA or DHA cannot currently be listed as voluntary nutrients on the Nutrition Facts panel. However, the amounts per serving of Omega-3 or DHA/EPA can be listed on the front panel of a food package. An example statement would be: "A serving contains 90mg of DHA and EPA Omega-3 fats."

In Canada, Omega-3 content may be listed on nutrition facts while EPA and DHA (separately) are not allowed. However, EPA/DHA can be listed separately on the front panel. In the U.K., Omega-3 (DHA/EPA) is represented on the Nutrition Panel, expressed as mg per serving as well as % RDA (Recommended Dietary Allowances) per serving.

Consumer Awareness of Omega-3

Ocean Nutrition has been working diligently to better understand consumers and it has found that adequate access to accurate information about Omega-3 has not been available up until now. Data has shown that consumers who are well informed about Omega-3 are substantially more likely to purchase Omega-3 supplements and Omega-3-enriched foods.

Through extensive research, Ocean Nutrition has developed many insights to customize consumer messaging for specific products. Their dynamic website (www.meg-3.com) helps food manufacturers educate consumers about the benefits of Omega-3 effectively. Their Point of Purchase program helps attract and educate consumers, while highly interactive training programs help educate employees, key stakeholders and health professionals. A public awareness campaign to keep Omega-3 in the public eye is currently being rolled out by Ocean Nutrition in both the U.S. and Canada.

The MEG-3® brand creates a positive emotional relationship with consumers. The product positioning is "Trust the Source" of MEG-3® Omega-3 ingredients. The phrases," A little fish your heart will love™," for MEG-3® and "A little fish your brain will love™," for MEG-3®DHA, educate people to appreciate the health benefits and consume products containing MEG-3® ingredients because they feel confident about the idea of consuming fish oil.

MEG-3® ingredients are available around the globe for use in dietary supplements and food ingredient applications, and many products containing the ingredients have recently been launched. Several examples appear throughout this publication. These and more product launches have been occurring in the last 12 months and many more are in development planning for 2006 and beyond. A new consumer market is converging to make EPA and DHA from fish oil the next mass consumer ingredient, following in the success of soy and calcium.

A New Kind of Fish Market

The food ingredient market for fish oil historically has been a small niche market at best. At that time, product applications were limited to foods where masking agents were used to cover up fish flavor and odor. But now, because of the large-scale ability of MEG-3® ingredients to fortify foods with Omega-3 without the fishy taste or smell, a completely new segment of the food industry (which did not exist even 18 months ago) is being created.

People can now get the essential nutrients EPA and DHA from fish oil in foods they love to eat. This improves human health by providing nutritionally dense foods and creating convenience. Now, large groups of people who have been lacking these nutrients in their diets have the opportunity to improve their nutrition by eating foods they like in brands they love. This will have spillover effects on all levels of the value chain, creating new products, new wealth and new exciting commercialization opportunities for our industry as a whole. Pf

A.C. LaRocco Pizza in the U.S. has added 50mg EPA/DHA per slice to its Tomato & Feta, and Greek Sesame frozen pizza crusts, which are distributed and promoted nationally.

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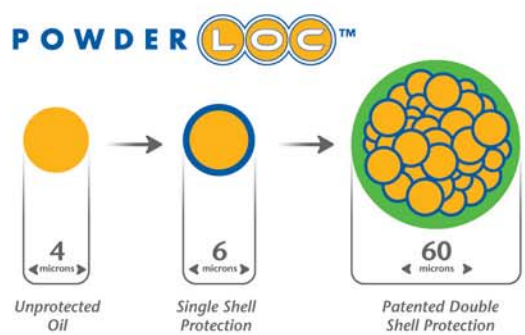
We just built a better
FISH TRAP

Everyone knows that the best source of Omega-3 is EPA and DHA from fish oil. Scientists know it. And so do increasing numbers of consumers. But using fish oil in food processes has been problematic because of well, the fish. You always noticed it. The taste. The smell. That is... until now!



Introducing MEG-3®, a healthy food ingredient, derived from fish oil. MEG-3® is manufactured using our exclusive Powder-loc™ technology. Powder-loc™ is changing the market. Its patented, double shell protection produces a free flowing, dry powder with a unique molecular construction that locks in the health benefits of Omega-3, and locks out even the slightest hint of fishiness. This new powder can be easily incorporated into any production facility without the mess or smell of working with conventional fish oil products.

MEG-3® is proven and versatile. It has already been successfully commercialized in over ten food categories, to date, including everything from milk and yogurt to breads and frozen pizza. This year, food manufacturers, in over a dozen countries, will produce over two billion food servings that include MEG-3®.

With the better fish trap there's no instability. So, there's no need to compromise your Omega-3 food products with inferior flax derived ingredients anymore. Should you beat a path to our door? Absolutely. But, it might be easier to just pick up the phone! We'll be happy to answer all of your questions about MEG-3® and our revolutionary Powder-loc™ process.

Well go on. "Snap" to it!

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Omega-3 Fatty Acids and Cardiovascular Health

Reviews by Health Authorities (North America) and the Scientific Community

Attention on Omega-3 fatty acids and their impact on cardiovascular function has increased substantially over the last several years. This attention has come from the scientific community, health authorities and from the public. Well recognized institutions such as the American Heart Association have been reviewing available data and drawing conclusions about the effectiveness of Omega-3s in relation to coronary heart disease (CHD) and cardiovascular disease (CVD). In 2002 the AHA issued a scientific statement, which concluded that epidemiological and clinical trials with Omega-3 fatty acids showed a reduction in the incidence of CVD. Large-scale epidemiological studies suggested that individuals at risk for CHD benefited from consuming both plant- and marine-derived omega-3 fatty acids. However, the AHA further stated that evidence from prospective secondary prevention studies suggested EPA+DHA supplementation specifically produced a significant reduction in subsequent cardiac and all-cause mortality (Kris-Etherton *et al*. 2002).

The AHA scientific statement supported the cardiovascular-related benefits of plant-derived omega-3s (ALA) as well as marine-derived omega-3s (EPA+DHA). However, many health authority reports and scientific reviews since then have differentiated between the strength of evidence available for EPA+DHA and that available for ALA, suggesting that ALA has a much weaker body of evidence to support cardiovascular claims.

In March 2004 the Agency for Healthcare Research and Quality (AHRQ), a division of the U.S. Department of Health and Human Services, issued two evidence-based reports on the cardiovascular health effects of polyunsaturated Omega-3 fatty acids (Balk *et al*. 2004; Wang *et al.* 2004). The reports were in response to a request from the National Institute of Health (NIH) Office of Dietary Supplements (ODS). Three Evidence-based Practice Centers (Tufts-New England Medical Center, University of Ottawa and Southern California-RAND) were selected to conduct systematic reviews of the existing scientific and medical literature for Omega-3 fatty acid influence on certain medical conditions, including cardiovascular disease. They were also asked to make recommendations to the ODS and report existing research gaps which could be used to assist the NIH in developing future clinical guidelines and performance measures.

The Tufts group that prepared the cardiovascular-related reports had several recommendations for future research, including the identification of research gaps. Both reports concluded that the potential effect of ALA was unknown and that the existing data sets were of poor quality, too limited for adequate assessment. They proposed that more multi-center trials are needed to assess the effect of ALA, separate from the effect of EPA+DHA, on CVD risk factors and outcomes (Balk *et al*. 2004; Wang *et al.* 2004).

However, the AHRQ reports did present conclusions related to fish and fish oil. Omega-3 fatty acids derived from fish oil were found to have a beneficial effect on problems associated with

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heart and blood vessel disease in persons with existing conditions. There was strong evidence that fish oil lowers levels of circulating triglycerides (TGs) in blood; high TGs are considered a serious risk factor for CVD. They concluded that "overall, the evidence supports the hypothesis that consumption of omega-3 fatty acids (EPA, DHA or ALA) from fish or from supplements of fish oil reduces all-cause mortality and various CVD events, although the evidence is strongest for fish and fish oil supplements" (Wang *et al.* 2004).

In 2000, the FDA published a letter regarding a health claim specific to dietary supplements for omega-3 fatty acids and coronary heart disease; they concluded "that the weight of the scientific evidence for a claim relating to EPA and DHA omega-3 fatty acids and reduced risk of CHD outweighs the scientific evidence against the claim". The FDA came to this conclusion because evidence from intervention trials with CHD as an endpoint was "strongly favorable in a diseased population showing that omega-3 fatty acid intake is related to reduced risk of CHD". Further, they found that suggestive evidence supported this benefit would carry over to the general population "because omega-3 fatty acids have similar physiological effects in both diseased and general populations". Overall, they felt the scientific evidence was "suggestive of a relationship between omega-3 fatty acids and reduce risk of CHD" and that use of EPA and DHA as a dietary supplement was safe and lawful provided that daily intakes of EPA and DHA do not exceed 3 g per day (from conventional food and dietary supplement sources) (Lewis 2000). In 2004, the US Food and Drug Administration (FDA) also approved a qualified health claim specific to EPA and DHA for food. Their claim states "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease". This claim is currently in use on food products in the US containing EPA and DHA. The claim must include a statement specifying the name of the food and the amount (g) of EPA and DHA omega-3 fatty acids in one serving.

Recently published reviews of scientific literature continue to confirm that the body of literature supporting the positive cardiovascular effects of EPA+DHA is stronger than the literature and clinical studies focusing on ALA. For example, Harper and Jacobson (2005) systematically reviewed previously published reports (published between 1966 and June 2004) that had assessed different types of omega-3 PUFA interventions and cardiovascular outcomes. They concluded that the evidence suggested a role for fish or fish oil (specifically, EPA and DHA) in secondary prevention because recent clinical trial data has demonstrated significant reduction in total mortality, CHD death, and sudden death. They further concluded that the data on plant-based ALA was promising but restricted by studies of smaller sample size and limited quality. They identified the need for more clinical trials and specifically, a large randomized controlled trial on ALA before recommendations can be made for CHD prevention.

Harper *et al.* (2006) recently published an Omega-3 paper that focused on flaxseed oil. Harper *et al*. recognized that the conversion of ALA to EPA in the body is limited but believed that the conversion might still be physiologically and clinically important. They further recognized that earlier trials with ALA yielded mixed results. Their FORCE trial demonstrated increased plasma EPA levels in subjects that were provided its precursor, ALA. However, it is very important to note that Harper *et al*. also recognized key limitations with their trial. They

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concluded that broad-based dietary recommendations and governmental guidelines concerning ALA consumption should not be established in a heterogeneous population until more studies are conducted on ALA metabolism, including clinical studies in patients with a variety of ethnic and medical backgrounds. The final conclusion of the FORCE trial was that the trial demonstrated the ability to increase EPA levels by supplementing the diet with ALA in a high risk population, but that ultimately, their flaxseed oil trial underscored "the need for a larger more definitive trial with coronary endpoints to determine whether ALA is indeed cardioprotective" (Harper *et al*., 2006).

A further example of continued support for EPA+DHA versus ALA in terms of heart health is the Natural Standard database. Natural Standard is an international research collaboration that aggregates and synthesizes data on complementary and alternative therapies. Using a comprehensive methodology and reproducible grading scales, information is created that is evidence-based, consensus-based, and peer-reviewed, tapping into the collective expertise of a multidisciplinary Editorial Board. In August of 2005, Natural Standard updated its evaluation of the existing scientific evidence supporting various uses of omega-3 fatty acids. It graded the various uses, including heart health, based on the strength of scientific evidence for each use. For secondary cardiovascular disease protection, fish oil/EPA+DHA received an 'A' for 'strong scientific evidence' in support of the use. However, ALA received a 'C' for 'unclear scientific evidence' in relation to the same use. They conclude that while similar cardiovascular benefits are proposed for EPA+DHA and ALA, the scientific evidence for ALA is less compelling and beneficial effects may be less pronounced (Natural Standard 2005).

Health authorities in North America as well as internationally are increasingly supportive of the cardiovascular benefits of EPA+DHA, specifically.

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January 11, 2007

Ms. Julianne Mayo
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Canada B2Y 4T6

RE: Use of Microencapsulated Fish Oil in Organic Products

Dear Julianne,

I am writing to confirm that, for at least one of our certified clients, QAI approved the use of non-organic microencapsulated fish oil powder in an organic product. Our approval was based on the following:

1. QAI's interpretation that fish and fish products are "agricultural" materials; and
2. Microencapsulated fish oil powder is not commercially available in organic form. Currently there is no US organic standard for fish and fish products. As such, fish and fish products cannot be organically certified to the National Organic Program (NOP) and cannot be organically sourced.

Please let me know if I can be of any further assistance.

Sincerely,

Jessica Walden
Technical Specialist

YoBaby Plus Fruit & Cereal With DHA

Serving Size 1 CONTAINER	
Amount Per Serving	
Calories 120	
Total Fat	4g
Trans Fat	0g
Sodium	55mg
Total Carbohydrate	19g
Dietary Fiber	2g
Sugars	16g
Protein	4g
Protein 25%	Vitamin A 4%
Vitamin C 0%	Calcium 15%
Iron 0%	
Based on the RDI for children 1-4 years.	

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ONC Fish Oil Petition
CONFIDENTIAL BUSINESS INFORMATION (CBI) Justification Statement

Please find attached the complete copy of *Exponent*'s safety assessment, entitled "Safety of EPA+DHA: Summary of Previous Literature and Reviews and Safety Evaluations." The report text that ONC considers to be confidential business information (CBI) has been marked as such (following NOP guidelines for CBI). This information is confidential and proprietary because it is a result of employed expertise to extract and summarize relevant safety information, and to draw expert safety conclusions based on published reviews and evaluations. The appendices of the report contain published information therefore they are not CBI. Thank you for your consideration of this CBI material.

Food and Chemicals Division

Safety of EPA+DHA: Summary of Previous Literature Reviews and Safety Evaluations

Safety of EPA+DHA: Summary of Previous Literature Reviews and Safety Evaluations

Prepared for

Ocean Nutrition Canada
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Bedford, Nova Scotia
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1730 Rhode Island Avenue, NW
Washington, DC 20036

October 31, 2003

WD00789.000 C0T0 1003 0003

Contents

Appendix A Mitre Report, Summary Sections and Bibliography

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. Recipient's Accession No. PB89 182398/AS
4. Title and Subtitle: Health Effects of Refined Menhaden Oil			5. Report Date: April 89 6.
7. Author(s): M.T. Stephen Hsia, Richard D. Marvis and John M. DeSesso			8. Performing Organization Rept. No. MTR-89W35
9. Performing Organization Name and Address: Civil Systems Division, The MITRE Corporation, 7525 Colshire Drive, McLean, VA 22102			10. Project/Task/Work Unit No. 3020B 11. Contract(C) or Grant(G) No. (C) 223-86-2104 (G)
12. Sponsoring Organization Name and Address: Food and Drug Administration, 200 C Street, S.W., Washington, DC 20204			13. Type of Report & Period Covered 9/87 - 3/89 14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This report assesses the potential adverse health effects of refined menhaden oil (MO). The report presents a brief overview of the chemistry and general history of use of MO as well as a brief discussion of the biochemistry of polyunsaturated fatty acids. An analysis of pertinent studies conducted in humans and laboratory animals on fish oils and related omega-3 fatty acids that may contain data indicative of potential adverse health effects, is presented. The specific topics covered in this analysis include: absorption and distribution, biochemical effects, effects on hemostasis and serum lipids, immunological effects, carcinogenicity, reproductive effects, effects on vision, neurological effects, cardiac lipidosis and related cardiotoxic effects, and other effects. It also includes a discussion of the toxicity of oxidized or heated MO and related fish oils. Finally, implication of the findings relevant to human health concern is discussed.

17. Document Analysis a. Descriptors

Menhaden oil
Fish oils
omega-3 fatty acids
Health effects

b. Identifiers/Open-Ended Terms

MITRE Corporation

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
No restriction on distribution Available from National Technical Information Service, Springfield, VA 22161	Unclassified	175
	20. Security Class (This Page) Unclassified	22. Price

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tment of Commerce

Health Effects of Refined Menhaden Oil

M. T. Stephen Hsia
Richard D. Mavis
John M. DeSesso

April 1989

MTR-89W35

SPONSOR:
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CONTRACT NO.:
223-86-2104
PROJECT:
3020B
DEPT.:
W-56

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MITRE Department
and Project Approval: Pamela Waldron

ABSTRACT

This report, which assesses the potential adverse health effects of refined menhaden oil (MO), was prepared for the Center for Food Safety and Applied Nutrition of the U.S. Food and Drug Administration (FDA). Since refined MO will most likely be marketed to consumers as dietary supplements, the FDA felt that the potential adverse health consequences of MO ingestion need to be evaluated in depth by independent, objective reviewers outside the agency as a part of the Agency's assessment. Therefore, MITRE was requested to perform the analysis and to prepare this report. The report presents a brief overview of the chemistry and general history of use of MO as well as a brief discussion of the biochemistry of polyunsaturated fatty acids. An analysis of pertinent studies conducted in humans and laboratory animals on fish oils and related ω-3 fatty acids that may contain data indicative of potential adverse health effects, is presented. The specific topics covered in this analysis include: absorption and distribution, biochemical effects, effects on hemostasis and serum lipids, immunological effects, carcinogenicity, reproductive effects, effects on vision, neurological effects, cardiac lipidosis and related cardiotoxic effects, and other effects. It also includes a discussion of the toxicity of oxidized or heated MO and related fish oils. Finally, implication of the findings relevant to human health concern is discussed.

Suggested Keywords: Menhaden oil, Fish oils, ω-3 fatty acids, Eicosapentaenoic acid, Docosahexaenoic acid, Toxicity.

SECTION 7

CONCLUSIONS

Partially hydrogenated MO has been used in shortening and margarine for over half a century. However, available evidence does not demonstrate the use of refined MO as a dietary food component in the United States prior to 1958.

In order to infer the potential adverse health effects of refined MO, a large amount of information on the effects of the various fish oils on both humans and laboratory animals has been evaluated. Information is lacking on the safety of long-term use of MO as a dietary component. Because ω-3 fatty acids are normal dietary components, present in foods of marine origin, these components of MO would not be expected to exhibit a high level of toxicity. The possibility of adverse health effects from MO consumption increases as MO increasingly replaces other fat sources of the ω-6 fatty acids. The presence of small amounts of ω-6 fatty acids in fish oils (3 to 5 percent) precludes the absolute exclusion of these fatty acids from diet even in the case of the total exclusion of other fat sources. The Greenland Eskimos are the best example of a population experiencing the long-term consumption of fish oil as the major source of fat. In light of the lack of convincing evidence for adverse health effects from animal studies and other more limited epidemiological and clinical studies, the lack of definitive adverse health effects in the Eskimo population remains the most relevant evidence that human consumption of fish oil as the exclusive source of fat is unlikely to produce effects on health other than the increase in bleeding time.

An increase in bleeding time is the only prominent health effect observed in humans that has been firmly established as a consequence of fish oil ingestion. This effect has been reported anecdotally in the Eskimo population and consistently observed in studies of healthy human subjects with a daily intake of 3 g of ω-3 fatty acids. The magnitude of

the effect at this low dose is not a cause for alarm, but a lack of systematic dose-response data precludes prediction of the severity of the effect at higher daily intakes. The consequences of increased bleeding times in the Greenland Eskimo population have not been systematically studied, but it seems clear that a combination of this effect with other conditions that cause bleeding could present a problem. The reported higher incidence of stroke in the Eskimo population compared to Danes is a possible manifestation of hemostatic changes, but a causal relationship between this observation and diet has not been corroborated, and the effect of confounding factors such as genetics or lifestyle cannot be ruled out.

A biochemical effect that is well established as a result of fish oil consumption is a change in the synthesis of eicosanoids. While no health effects of major concern have been consistently demonstrated as a consequence of these changes, they present the possibility of an adverse complication of the combination of these changes with other factors. Perturbations in eicosanoid synthesis could theoretically compromise the normal functioning of the immune system. The currently available human data, however, are insufficient to address this possibility.

Strong evidence for an essential role of DHA in the functioning of the reproductive, visual, and neurological systems, and for biochemical regulation of the amount of this ω-3 fatty acid in the membranes of these systems argues against any adverse effects of this component of fish oil. Available feeding studies confirm the safety of fish oil with respect to these three systems.

The evidence regarding carcinogenicity of MO, while predominantly negative, is limited in scope. Additional data, from well-designed animal and epidemiological studies, would be most helpful in a conclusive evaluation of the carcinogenicity of MO.

The possibility of contamination of MO with environmental contaminants such as halogenated hydrocarbons and toxic metals is one that must be

considered. Analytical data on the quantities of these contaminants is a necessary component of the overall assessment of the safety of refined MO as a dietary supplement.

SECTION 8

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Appendix B FDA Final Rule on Menhaden Oil

Regulatory Flexibility Act

We certify that these rules will not have a significant economic impact on a substantial number of small entities. Therefore, a regulatory flexibility analysis as provided in Pub. L. 96–354, the Regulatory Flexibility Act, is not required.

(Catalog of Federal Domestic Assistance Program No. 96.006, Supplemental Security Income)

List of Subjects in 20 CFR Part 416

Administrative practice and procedure, Aged, Blind, Disability benefits, Public assistance programs, Reporting and recordkeeping requirements, Supplemental Security Income (SSI).

Dated: May 27, 1997.

John J. Callahan,

Acting Commissioner of Social Security.

Subpart D of part 416 of chapter III of title 20 of the Code of Federal Regulations is amended as follows:

PART 416—[AMENDED]

1. The authority citation for subpart D of part 416 continues to read as follows:

Authority: Secs. 702(a)(5), 1611(e), (b), (c), and (e), 1612, 1617, and 1631 of the Social Security Act (42 U.S.C. 902(a)(5), 1382(e), (b), (c), and (e), 1382a, 1382f, and 1383).

2. Section 416.420 is amended by revising paragraph (a) and redesignating paragraph (c) as paragraph (d) and adding a new paragraph (c) to read as follows:

§ 416.420 Determination of benefits; general.

* * * * *

(a) *General rule.* We use the amount of your countable income in the second month prior to the current month to determine how much your benefit amount will be for the current month. We have determined that no reliable information exists which is currently available to compute benefits on a current basis as is explained in paragraph (c) of this section. However, if you have been receiving an SSI benefit and receiving a Social Security insurance benefit and the latter is increased on the basis of the cost-of-living adjustment or because your benefit is recomputed, we will compute the amount of your SSI benefit for January, the month of an SSI benefit increase, by including in your income the amount by which your Social Security benefit in January exceeds the amount of your Social Security benefit in November. Similarly, we will compute the amount of your SSI benefit for February by including in your income the amount by which your Social Security benefit in February exceeds the amount of your Social Security benefit in December.

Example 1. Mrs. X's benefit amount is being determined for September (the current month). Mrs. X's countable income in July is used to determine the benefit amount for September.

Example 2. Mr. Y's SSI benefit amount is being determined for January (the current month). Mr. Y has Social Security income of $100 in November, $100 in December, and $105 in January. We find the amount by which his Social Security income in January exceeds his Social Security income in November ($5) and add that to his income in November to determine the SSI benefit amount for January.

* * * * *

(c) *Reliable information which is currently available for determining benefits.* The Commissioner has determined that no reliable information exists which is currently available to use in determining benefit amounts.

(1) *Reliable information.* For purposes of this section "reliable information" means payment information that is maintained on a computer system of records by the government agency determining the payments (e.g., Department of Veterans Affairs, Office of Personnel Management for Federal civil service information and the Railroad Retirement Board).

(2) *Currently available information.* For purposes of this section "currently available information" means information that is available at such time that it permits us to compute and issue a correct benefit for the month the information is pertinent.

* * * * *

[FR Doc. 97–14614 Filed 6–4–97; 8:45 am]

BILLING CODE 4190–29–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 184

[Docket No. 86G–0280]

Substances Affirmed as Generally Recognized as Safe: Menhaden Oil

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is affirming that menhaden oil is generally recognized as safe (GRAS) as a direct human food ingredient with specific limitations. The agency is also affirming that partially hydrogenated menhaden oil with an iodine number between 86 and 119 is GRAS as a direct human food ingredient with no limitation other than current good manufacturing practice. These actions complete the agency's response to a petition filed by the National Fish Meal and Oil Association.

DATES: Effective June 5, 1997. The Director of the Office of the Federal Register approves the incorporation by reference, in accordance with 5 U.S.C. 552(a) and 1 CFR part 51, of certain publications in 21 CFR 184.1472(a)(2), effective June 5, 1997.

FOR FURTHER INFORMATION CONTACT: Lawrence J. Lin, Center for Food Safety and Applied Nutrition (HFS–206), 200 C St. SW., Washington, DC 20204, 202–418–3103.

SUPPLEMENTARY INFORMATION: In accordance with 21 CFR 170.35, the National Fish Meal and Oil Association, 2000 M St. NW., suite 580, Washington, DC 20036 (current address: 1525 Wilson Blvd., suite 500, Arlington, VA 22209), submitted a petition (GRASP 6G0316) seeking affirmation that menhaden oil and partially hydrogenated menhaden oil are GRAS for use as direct human food ingredients. The petition included information about the identity of, and manufacturing processes for, menhaden oil and partially hydrogenated menhaden oil; final reports and published articles of long-term animal feeding studies with partially hydrogenated menhaden oil; information about the history of human food use of partially hydrogenated menhaden oil; and the results of an extensive search of the published scientific literature (encompassing over 2,600 articles) with respect to the safety of fish oils in general.

FDA published a notice of filing of this petition in the **Federal Register** of July 31, 1986 (51 FR 27461), and gave interested persons an opportunity to submit comments to FDA's Dockets Management Branch. FDA received three comments, two from manufacturers and one from a government agency. All of the comments supported the affirmation of GRAS status for use of the oils in food.

FDA affirmed that partially hydrogenated menhaden oil (with an iodine number not more than 85) and fully hydrogenated menhaden oil are GRAS in the **Federal Register** of September 15, 1989 (54 FR 38219). These oils were affirmed as GRAS based on the chemical similarity between these oils and partially hydrogenated common edible vegetable oils, and on the established history of use in Europe

of these oils in margarine and shortening (54 FR 38219 at 38222).

Pending further evaluation, the agency deferred its decision on menhaden oil that has not been hydrogenated, because this oil contains high levels of the *omega*-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are known to have physiologic effects, for example, effects on blood clotting (54 FR 38219). The agency's evaluation is now complete.

I. Basis for GRAS Status

Under section 201(s) of the act (21 U.S.C. 321(s)) and § 170.30 (21 CFR 170.30), general recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances added to food. The basis of such views may be either: (1) Scientific procedures or, (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food. General recognition of safety based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of a food additive and ordinarily is to be based upon published studies, which may be corroborated by unpublished studies and other data and information (§ 170.30(b)). The petitioner relies upon scientific procedures to establish that menhaden oil is GRAS, because the oil has no history of common use as a food ingredient prior to 1958.

II. Identity

Menhaden oil is a refined marine oil that is derived from menhaden fish (*Brevoortia* species). It consists primarily of triglycerides, with small amounts of monoglycerides and diglycerides. The triglycerides are esters of glycerol and fatty acids with chains of 14 to 22 carbon atoms. Menhaden oil differs from edible vegetable oils and animal fats in its high proportion of polyunsaturated fatty acids with 4, 5 and 6 double bonds (about 25 percent). The mean percentages for these polyunsaturated fatty acids in menhaden oil are C18:4 (2.3 percent), C20:4 (2.0 percent), C20:5 (13.1 percent), C22:5 (2.5 percent) and C22:6 (6.7 percent).[1] C20:5 and C22:6 are EPA and DHA, respectively, and are the major source of *omega*-3 fatty acids from fish oil. (*Omega*-3 fatty acids refer to fatty acids with the first double bond occurring at the third carbon from the methyl (or omega) end of the fatty acid.) Menhaden oil also contains about 33 percent saturated fatty acids and about 31 percent monounsaturated fatty acids.

[1] The first number refers to the total number of carbon atoms in the fatty acid; the second number refers to the total number of double bonds.

III. Manufacturing Process

Menhaden, a plankton-feeding fish, is harvested commercially from the Gulf of Mexico and northward along the Atlantic coast of the United States. The fish is less than 12 inches long and less than a pound in weight. To produce menhaden oil, the fish is cooked whole at about 96 °C for 8 to 10 minutes to coagulate the protein and rupture the fat cells. The cooked fish is then pressed and the liquid is centrifuged to separate the oil and aqueous phases. Crude oil is then shipped to food companies for further processing, which may include storage (winterization), degumming, neutralization, bleaching, deodorization, and hydrogenation.

IV. Previous Evaluations

Data in the petition indicate that ingestion of EPA and DHA from fish oils can have a significant effect on bleeding time (the time taken for bleeding from a standardized skin wound to cease) and other physiological effects, as discussed below. Because of the potential safety concerns raised by these effects, and because there are no food oils in the food supply containing significant amounts of EPA and DHA, the agency contracted with the Mitre Corp. to perform an independent analysis of the scientific literature on the safety of menhaden oil. The Mitre Corp. issued, in April 1989, a report entitled, "Health Effects of Refined Menhaden Oil." (Copies are available from the National Technical Information Service, Order No. PB89–182398, price code A08.)

The report stated that:

[a]n increase in bleeding time is the only prominent health effect observed in humans that has been firmly established as a consequence of fish oil ingestion. This effect has been reported anecdotally in the Eskimo population and consistently observed in studies of healthy human subjects with a daily intake of 3 g [grams] of omega-3 fatty acids. The magnitude of the effect at this low dose is not a cause for alarm, but a lack of systematic dose-response data precludes prediction of the severity of the effect at higher daily intakes.

(Pages 7–1 and 7–2 of the report.)

In addition, the Nutrition Labeling and Education Act of 1990 required FDA to evaluate health claims for 10 nutrient-disease relationships, including the relationship of *omega*-3 fatty acids and heart disease. The agency evaluated the claim that consumption of *omega*-3 fatty acids is associated with a decreased risk of coronary heart disease under the standard set forth in section 403(r)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(r)(3)): Whether, based on the totality of publicly available scientific evidence, there is significant scientific agreement, among experts qualified by scientific training and experience, that the claim for the diet-disease relationship is supported by the evidence. In the **Federal Register** of January 6, 1993 (58 FR 2682), FDA issued a final rule announcing its decision not to authorize a health claim relating to an association between *omega*-3 fatty acids and a decreased risk of coronary heart disease because it had concluded that there was not significant scientific agreement among experts that the totality of the scientific evidence supported the claim. Because the focus of that evaluation was a review of evidence concerning a possible beneficial effect of *omega*-3 fatty acids on the heart, a comprehensive review of the safety of *omega*-3 fatty acids from fish oils or other sources was not conducted. However, in the health claim final rule the agency did discuss, in addition to the potential health benefit, concerns over possible adverse effects of fish oils on bleeding time, glycemic control, and low-density lipoprotein (LDL) cholesterol. These issues are discussed below.

V. Safety Information

A. Bleeding Time

Increased bleeding time has been reported in many studies with humans whose diets were supplemented with fish oils. FDA stated in the health claim final rule that the importance of the increase in bleeding time reported in many studies with supplemental fish oils or with increased fish consumption is not clear (58 FR 2682 at 2699). Further, increases in bleeding time do not correlate with clinically significant bleeding, and there are debates regarding the clinical significance of the increase in bleeding time (Ref. 1). However, FDA considers excessive bleeding to be a safety concern, and has examined the scientific literature for evidence that consumption of fish oils may contribute to excessive bleeding.

There are more than 50 reports in the scientific literature on fish oils that include data on bleeding time. Several reports described the absence of changes in bleeding time, but did not provide data. A few studies involving substantial numbers of healthy human subjects indicated that there was no statistically significant increase in bleeding time after supplemental intakes of EPA and DHA from fish oils

in daily amounts of 3.0 g or less (Refs. 3 through 6). Other studies with fewer human subjects, but in which the total diet was carefully controlled, also revealed that daily intakes of 3.0 g or less of EPA and DHA in fish oils did not increase bleeding time (Refs. 7 and 8).

However, two studies described increases in bleeding time that were reported to be statistically significant. Subjects in the studies consumed about 3.0 g per person per day (/p/d) EPA and DHA from fish oils. Mortensen et al. (Ref. 9), in a crossover, double-blind, placebo-controlled study among 20 normal, healthy males, showed that consumption of slightly more than 3.0 g/d of EPA and DHA in fish oil capsules for 4 weeks produced a small but statistically significant increase (16 percent) in median bleeding time; however, both the mean and 75th percentile bleeding times were well within the normal range. Harris and Windsor (Ref. 10) reported that consumption of fish oil containing 2.2 g/d of EPA and DHA also produced a small (15 percent) but statistically significant increase in bleeding time, but this increase was also within the normal range.

Studies in which greater daily amounts (higher than 3.0 g/p/d) of fish oils were fed often reported statistically significant increases in bleeding time (Refs. 11 through 22). In some of those studies, use of fish oils resulted in substantial prolongation of bleeding time outside the normal range, as indicated by the standard deviations reported (Refs. 8, 12, 18, 21, and 22). However, the pre-treatment bleeding times in those studies were also beyond the normal range, making it difficult to evaluate the effect of fish oils on bleeding time. In other studies, the increase in bleeding time after daily intakes of more than 3.0 g of EPA and DHA is difficult to interpret meaningfully because of the small number of subjects tested (Refs. 23 through 27).

Studies have also been carried out with subjects who had evidence of coronary heart disease or risk factors for coronary heart disease. After intake of 3.2–6.0 g/p/d of EPA and DHA in fish oils, many of these subjects showed increased bleeding time (Refs. 20, and 28 through 33). However, none of the studies reported evidence that the prolonged bleeding time was clinically significant. In those cases where the effect of fish oils in angioplasty or bypass surgery patients (a total of 520 patients fed supplemental fish oil) was studied, excessive bleeding was not reported even though acetylsalicylic acid (aspirin), which itself greatly prolongs bleeding time, was used concurrently (Refs. 34 through 40). One large study that used a dose of 6 g/p/d EPA and DHA in fish oils did report four cases of increased bleeding in the fish oil group (of 124 treated) versus none in the placebo group, but the difference in rates of occurrences between the two groups was not statistically significant (Ref. 40).

In summary, the totality of the scientific evidence demonstrates that when consumption of fish oils is limited to 3 g/p/d or less of EPA and DHA, there is no significant risk for increased bleeding time beyond the normal range. A report from an industry-sponsored roundtable discussion on the topic of fish oils and bleeding time (Ref. 2) also supports the conclusion that EPA and DHA are safe at intake levels at or below 3 g/p/d. On the other hand, amounts of fish oils providing more than 3 g/d of EPA and DHA have generally been found to produce increases in bleeding time that are statistically significant. At this time, there are insufficient data to evaluate the clinical significance of this finding. Because of the lack of data and because of the potential risk of excessive bleeding in some individuals with intakes at higher levels, FDA concludes that the safety of menhaden oil is generally recognized only at levels that limit intake of EPA and DHA to 3 g/p/d.

B. Glycemic Control

Some studies on non-insulin-dependent diabetics have reported increased glucose levels when large amounts of fish oils (4.5 to 8.0 g/p/d) were used in the diet. In the health claim final rule, FDA discussed the possible adverse effects of fish oil consumption on glycemic control among diabetics and stated that such effects were a safety concern (58 FR 2682 at 2704 through 2705). FDA concluded in that document that the effects of fish oils on blood glucose appear to depend on the amount of fish oils fed, based on review of a number of studies (58 FR 2682 at 2705). One study found no change in fasting blood glucose levels among type-II [non-insulin-dependent] diabetics treated with 3.0 g/d EPA plus DHA for 2 weeks (Ref. 41). Two other studies that used 3 g/d EPA plus DHA for 6 weeks (Ref. 42) and 2.7 g/d EPA plus DHA for 8 weeks (Ref. 43) found only transient increases in blood glucose halfway through their respective supplementation periods. Another study (Ref. 44) that used 3.0 g/d EPA plus DHA for 3 weeks found comparable increases in fasting blood glucose when either fish oil or safflower oil was fed, so the increase cannot be attributed specifically to *omega*-3 fatty acids. A study that compared the effects of fish oil and olive oil (Ref. 45) fed 3 g/d of EPA plus DHA and did not find a difference in fasting glucose or glycosylated hemoglobin after fish oil supplementation compared to baseline; they did find a significant difference compared to the olive oil treatment, which produced changes in the opposite direction from fish oil. Studies on type II diabetics that reported increased glucose used higher amounts (4.5 to 8 g/d) of *omega*-3 fatty acids (Refs. 46 through 49).

Based on the available information, FDA concludes that consumption of EPA and DHA in fish oils at 3 g/p/d by diabetics has no clinically significant effect on glycemic control, although higher amounts of EPA and DHA (4.5 g/p/d and above) remain of concern. Therefore, FDA concludes that 3 g/p/d of EPA and DHA is a safe level with respect to glycemic control.

C. LDL Cholesterol

In the health claim final rule, FDA noted that many studies on hypertriglyceridemic or hypercholesterolemic subjects, and some studies on normal subjects, reported an increase in LDL cholesterol or apo B (apolipoprotein B, a principal component of LDL) following fish oil supplementation (58 FR 2682 at 2705). Because increases in LDL cholesterol predict increased risk of coronary heart disease, FDA recently reevaluated those studies, as well as newer studies published since the health claim final rule, to address the question of whether 3 g/p/d of EPA and DHA derived from menhaden oil is generally recognized as a safe level with respect to its effect on LDL cholesterol. The agency considered the reported effects of fish oil on LDL cholesterol levels in healthy persons with normal cholesterol levels, as well as in persons with diabetes mellitus, hypertension, abnormal blood lipid levels, and cardiovascular disease.

As a result of its reevaluation, FDA found that although reported study results are variable, there appears to be a trend toward increased LDL cholesterol values with increased fish oil consumption in all population subgroups, with the magnitude of the increase appearing greater and more consistent in populations with abnormal blood lipid levels, hypertension, diabetes, and cardiovascular disease.

In the health claims final rule, FDA noted that because most reports of increased LDL were in studies where large amounts of fish oils were given (i.e., 5 g or more per day of EPA plus DHA), any safety concern relating to

changes in LDL cholesterol might be suitably addressed by restricting the intake of DHA and EPA (58 FR 2682 at 2705). As discussed below, the petitioner has suggested maximum use levels of menhaden oil for each food category in which menhaden oil can be used. Based on these levels, FDA has determined that the mean intake of menhaden oil, if menhaden oil were to be used at the maximum allowable level in all permitted food categories, would be less than 3 g of DHA and EPA per day. Further, menhaden oil would substitute for other dietary fats, some of which have similar effects on LDL cholesterol. Based on its evaluation, the agency concludes that the petitioned levels of menhaden oil are safe with respect to the effect on LDL cholesterol.

VI. Consumer Exposure

In September 1993, the petitioner amended the petition to include maximum use levels for menhaden oil in various food categories. Based on these levels, FDA estimated that the mean exposure to EPA and DHA from the use of menhaden oil in all food categories would be 2.8 g/p/d (Ref. 50). Although the petition originally included all potential food uses of menhaden oil, the petitioner subsequently requested that the use of menhaden oil in infant formula be withdrawn from consideration. Therefore, the exposure estimate does not include this potential use of menhaden oil.

VII. Iodine Numbers of Oils from Menhaden

When FDA affirmed hydrogenated and partially hydrogenated menhaden oils as GRAS based on their pre-1958 history of safe use in food, the agency included in the regulation a specification that the iodine number for partially hydrogenated menhaden oil be no more than 85. (Iodine number is a measure of the unsaturation of fats and oils, expressed in terms of centigrams of iodine absorbed per gram of sample.) The iodine number limit of 85 was chosen then because menhaden oil with an iodine number greater than 85 is not considered hardened, and only hardened oil had a documented history of common use in food before 1958 (54 FR 38219 at 38222). Moreover, corroborative toxicological studies submitted in the petition used oil with an iodine number no more than 85 (54 FR 38219 at 38222). The iodine number limit of 85 also ensured that the partially hydrogenated menhaden oil affirmed as GRAS at that time would contain no more than traces of EPA and DHA, and thus would not significantly increase the dietary intake of these substances, pending completion of the agency's evaluation of the safety of DHA and EPA as part of its review of the GRAS status of menhaden oil. By specifying this upper limit, the agency deferred its decision on the GRAS status of partially hydrogenated menhaden oil with an iodine number above 85.

The agency now concludes (as stated below), based on scientific procedures, that menhaden oil is GRAS, provided that daily intakes of EPA and DHA from menhaden oil do not exceed 3 g/p/d. The petitioner has provided information demonstrating that partially hydrogenated menhaden oil may have an iodine number up to 119. The agency finds that the use of partially hydrogenated menhaden oil with an iodine number up to 119 under conditions specified in current 21 CFR 184.1472 will not cause the total exposure to EPA and DHA from all types of menhaden oil to exceed 3 g/p/d (Ref. 50). Therefore, FDA concludes that partially hydrogenated menhaden oil with an iodine number between 86 and 119 is GRAS based on scientific procedures, and is raising the iodine number limit in the regulation for partially hydrogenated menhaden oil to 119. With this change, the iodine number range for partially hydrogenated menhaden oil will be 11 through 119 instead of 11 through 85.

The effect of the change in the iodine number range for partially hydrogenated menhaden oil will be to affirm as GRAS a substance that was not previously affirmed as GRAS (i.e., partially hydrogenated menhaden oil with an iodine number between 86 and 119), rather than to amend the specifications for a substance already affirmed as GRAS. Even if the change in the iodine number range is characterized as an amendment, however, the Administrative Procedure Act (5 U.S.C. 553(b)(3)(B)) permits an agency to amend a regulation without notice and comment procedures when the agency for good cause finds that such procedures are impracticable, unnecessary, or contrary to the public interest. Because notice of the filing of a petition seeking GRAS affirmation of menhaden oil and partially hydrogenated menhaden oil was given (51 FR 27461), and an opportunity for public comment on all issues relating to the petition, including iodine number ranges, was provided at that time, FDA finds that separate, additional notice and comment procedures on the specific issue of the iodine number range for partially hydrogenated menhaden oil are unnecessary. Therefore, the agency finds that there is good cause to proceed to final action without an opportunity for additional public comment on this issue.

VIII. Conclusions

FDA has evaluated the information in the petition and many published articles in scientific journals, along with other relevant information. Based on this evaluation, the agency finds that the use of menhaden oil as a direct food ingredient is safe, provided that daily intakes of EPA and DHA from menhaden oil do not exceed 3 g/p/d. As noted in section VI of this document, the petitioned uses of menhaden oil incorporate maximum use levels for menhaden oil in specific food categories to ensure that daily intakes of EPA and DHA from menhaden oil do not exceed 3 g/p/d. FDA has further determined that the many pertinent published human clinical studies provide an adequate basis to conclude that the safety of the petitioned uses of menhaden oil is generally recognized among the community of experts qualified by scientific training and experience to evaluate the safety of food ingredients. Therefore, the agency is affirming that the use of menhaden oil as a direct human food ingredient is GRAS with specific limitations (21 CFR 184.1(b)(2)). This GRAS affirmation is based on scientific procedures (21 CFR 170.30(b)). To ensure that only food-grade menhaden oil is used in food, FDA is including appropriate specifications in the regulation.

FDA further concludes, based on scientific procedures, that partially hydrogenated menhaden oil with an iodine number between 86 and 119 is GRAS with no limitation other than current good manufacturing practice. Therefore, the agency is increasing the iodine number limit for partially hydrogenated menhaden oil to 119.

IX. Environmental Impact

The agency is affirming that menhaden oil is generally recognized as safe (GRAS) as a direct human food ingredient with specific limitations. The agency is also affirming that partially hydrogenated menhaden oil with an iodine number between 86 and 119 is GRAS as a direct human food ingredient with no limitation other than current good manufacturing practice.

The agency has carefully considered the potential environmental effects of these actions. FDA has concluded that these actions will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an

environmental assessment, may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

X. Analysis of Impacts

FDA has examined the economic implications of the final rule as required by Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select the regulatory approach that maximizes net benefits (including potential economic, environmental, public health and safety effects; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize the economic impact of that rule on small entities.

FDA finds that this final rule is not a significant rule as defined by Executive Order 12866. This final rule recognizes the applicability of a statutory exemption. The impact of the rule is to remove uncertainty about the regulatory status of the petitioned substance. Accordingly, under the Regulatory Flexibility Act, 5 U.S.C. 605(b), the Commissioner of Food and Drugs certifies that this final rule will not have a significant economic impact on a substantial number of small entities (Ref. 51).

XI. Effective Date

As this rule recognizes an exemption from the food additive definition in the Federal Food, Drug, and Cosmetic Act, and from the approval requirements applicable to food additives, no delay in effective date is required by the Administrative Procedure Act (5 U.S.C. 553(d)). The rule will therefore be effective immediately (5 U.S.C. 553(d)(1)).

XII. References

The following information has been placed on display with the Dockets Management Branch (address above), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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51. Memorandum, May 16, 1997, William Hubbard, Associate Commissioner for Policy Coordination, FDA, Rockville, MD to Lawrence Lin, FDA, Washington, DC.

List of Subjects in 21 CFR Part 184

Food additives, Food ingredients, Incorporation by reference.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 184 is amended as follows:

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

1. The authority citation for 21 CFR part 184 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 371).

2. Section 184.1472 is revised to read as follows:

§ 184.1472 Menhaden oil.

(a) *Menhaden oil.* (1) Menhaden oil is prepared from fish of the genus *Brevoortia*, commonly known as menhaden, by cooking and pressing. The resulting crude oil is then refined using the following steps: Storage (winterization), degumming (optional), neutralization, bleaching, and deodorization. Winterization may separate the oil and produce a solid fraction.

(2) Menhaden oil meets the following specifications:

(i) *Color and state.* Yellow liquid to white solid.

(ii) *Odor.* Odorless to slightly fishy.

(iii) *Saponification value.* Between 180 and 200 as determined by the American Oil Chemists' Society Official Method Cd 3–25—"Saponification Value" (reapproved 1989), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies of this publication are available from the Office of Premarket Approval, Center for Food Safety and Applied Nutrition (HFS–200), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, or available for inspection at the Center for Food Safety and Applied Nutrition's Library, Food and Drug Administration, 200 C St. SW., rm. 3321, Washington DC, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

(iv) *Iodine number.* Not less than 120 as determined by the American Oil Chemists' Society Recommended Practice Cd 1d–92—"Iodine Value of Fats and Oils, Cyclohexane—Acetic Acid Method," which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. The availability of this incorporation by reference is given in paragraph (a) (2) (iii) of this section.

(v) *Unsaponifiable matter.* Not more than 1.5 percent as determined by the American Oil Chemists' Society Official Method Ca 6b–53—"Unsaponifiable Matter" (reapproved 1989), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. The availability of this incorporation by reference is given in paragraph (a) (2) (iii) of this section.

(vi) *Free fatty acids.* Not more than 0.1 percent as determined by the American Oil Chemists' Society Official Method Ca 5a–40—"Free Fatty Acids"

(reapproved 1989), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. The availability of this incorporation by reference is given in paragraph (a) (2)(iii) of this section.

(vii) *Peroxide value.* Not more than 5 milliequivalents per kilogram of oil as determined by the American Oil Chemists' Society Official Method Cd 8–53—"Peroxide Value, Acetic Acid—Chloroform Method" (updated 1992) or Recommended Practice Cd 8b–90—"Peroxide Value, Acetic Acid—Isooctane Method" (updated 1992), which are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. The availability of this incorporation by reference is given in paragraph (a)(2)(iii) of this section.

(viii) *Lead.* Not more than 0.1 part per million as determined by the American Oil Chemists' Society Official Method Ca 18c–91—"Determination of Lead by Direct Graphite Furnace Atomic Absorption Spectrometry" (revised 1992), which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. The availability of this incorporation by reference is given in paragraph (a)(2)(iii) of this section.

(ix) *Mercury.* Not more than 0.5 part per million as determined by the method entitled "Biomedical Test Materials Program: Analytical Methods for the Quality Assurance of Fish Oil," published in the "NOAA Technical Memorandum NMFS–SEFC–211," F. M. Van Dolah and S. B. Galloway, editors, National Marine Fisheries Service, U. S. Department of Commerce, pages 71–88, November, 1988, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. The availability of this incorporation by reference is given in paragraph (a)(2)(iii) of this section.

(3) In accordance with § 184.1(b)(2), the ingredient may be used in food only within the following specific limitations:

Category of food	Maximum level of use in food (as served)
Cookies, crackers, § 170.3(n)(1) of this chapter.	5.0 percent
Breads, rolls (white & dark), § 170.3(n)(1) of this chapter.	1.0 percent
Fruit pies, custard pies, § 170.3(n)(1) of this chapter.	7.0 percent
Cakes, § 170.3(n)(1) of this chapter.	10.0 percent
Cereals, § 170.3(n)(4) of this chapter.	4.0 percent
Fats, oils, § 170.3(n)(12) of this chapter, but not in infant formula.	20.0 percent
Yogurt, § 170.3(n)(31) of this chapter.	4.0 percent
Cheese products, § 170.3(n)(5) of this chapter.	5.0 percent
Frozen dairy products, § 170.3(n)(20) of this chapter.	5.0 percent
Meat products, § 170.3(n)(29) of this chapter.	10.0 percent
Egg products, § 170.3(n)(11) of this chapter.	5.0 percent
Fish products, § 170.3(n)(13) of this chapter.	20.0 percent
Condiments, § 170.3(n)(8) of this chapter.	5.0 percent
Soup mixes, § 170.3(n)(40) of this chapter.	3.0 percent
Snack foods, § 170.3(n)(37) of this chapter.	5.0 percent
Fruit products, § 170.3(n)(32) of this chapter.	5.0 percent
Gravies, sauces, § 170.3(n)(24) of this chapter.	5.0 percent

(b) *Hydrogenated and partially hydrogenated menhaden oils.* (1) Partially hydrogenated and hydrogenated menhaden oils are prepared by feeding hydrogen gas under pressure to a converter containing crude menhaden oil and a nickel catalyst. The reaction is begun at 150 to 160 °C and after 1 hour the temperature is raised to 180 °C until the desired degree of hydrogenation is reached. Hydrogenated menhaden oil is fully hydrogenated.

(2) Partially hydrogenated and hydrogenated menhaden oils meet the following specifications:

(i) *Color.* Opaque white solid.

(ii) *Odor.* Odorless.

(iii) *Saponification value.* Between 180 and 200.

(iv) *Iodine number.* Not more than 119 for partially hydrogenated menhaden oil and not more than 10 for fully hydrogenated menhaden oil.

(v) *Unsaponifiable matter.* Not more than 1.5 percent.

(vi) *Free fatty acids.* Not more than 0.1 percent.

(vii) *Peroxide value.* Not more than 5 milliequivalents per kilogram of oil.

(viii) *Nickel.* Not more than 0.5 part per million.

(ix) *Mercury.* Not more than 0.5 part per million.

(x) *Arsenic (as As).* Not more than 0.1 part per million.

(xi) *Lead.* Not more than 0.1 part per million.

(3) Partially hydrogenated and hydrogenated menhaden oils are used as edible fats or oils, as defined in § 170.3(n)(12) of this chapter, in food at levels not to exceed current good manufacturing practice.

(4) If the fat or oil is fully hydrogenated, the name to be used on the label of a product containing it shall include the term "hydrogenated," or if it is partially hydrogenated, the name shall include the term "partially hydrogenated," in accordance with § 101.4(b)(14) of this chapter.

Dated: May 22, 1997.

Fred R. Shank,

Director, Center for Food Safety and Applied Nutrition.

[FR Doc. 97–14683 Filed 6–4–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF TRANSPORTATION

Federal Highway Administration

23 CFR Part 658

[FHWA Docket No. 96–12]

RIN 2125–AE04

Truck Size and Weight; National Network; North Carolina

AGENCY: Federal Highway Administration (FHWA), DOT.

ACTION: Final rule.

SUMMARY: The FHWA has modified the National Network for commercial motor vehicles by adding a route in North Carolina. The National Network was

Table 8
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Examining Bleeding Time
(Shaded rows represent an effect of Omega-3 on Bleeding Time)
Only bleeding parameters are summarized

Reference	Study design	Duration	Intake	Subjects	Results
Badalamenti et al. 1997 *Hepatology* 1997. 25:313-316. [Spain]	Non-randomized, parallel, controlled	4 weeks	6 g/day EPA + DHA (3.24 g/day EPA (27%), 2.76 g/day DHA (23%)) from 12 g/day fish oil All subjects received fish oil supplementation. Compliance: plasma fatty acid chromatography	23 subjects 17 cirrhosis patients with ascites (10 male/7 female). Nine cirrhotic patients with normal renal function. Eight cirrhotic patients with renal failure 6 healthy subjects (sex- and age-matched) served as controls.	Bleeding time: slight NS ↑ in cirrhotic patients with normal renal function (819 seconds to 983 seconds (+20%), NS) and patient with renal failure (633 seconds to 777 seconds (+22.7%), NS) after fish oil supplementation. ↑ reached significance when patients were considered collectively (from 744 seconds to 872 seconds (+17.2%, p=0.0068)
Cirillo et al. 1994 *World Rev. Nutr. Diet.* 1994. 76:60-63. [Italy]	Not controlled	4 weeks	5.1 g/day n-3 FA ethyl esters (2.55 g twice daily) EPA/DHA ratio: 1:4 Compliance: Not reported	10 healthy subjects (8 male/2 female) age range: 24-30 years	Skin bleeding time: slightly prolonged (NS) at end of 4-wk supplementation; no change after 3 months following cessation of supplementation. Platelet adhesion to glass: no change Platelet aggregation in response to collagen: ↓ significantly after a prolonged lag phase (p<0.01, 1-2 months after supplementation) Platelet aggregation in response to ADP: ↓ significantly (similarly to response to collagen) Platelet aggregation in response to AA: no change Platelet secretion of ATP: normal Platelet levels of cAMP: normal Platelet binding to fibrinogen: no change Membrane glycoproteins: no change

Ex

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Only bleeding parameters are summarized

Reference	Study design	Duration	Intake	Subjects	Results
Eritsland et al. 1995c *Blood Coagulation and Fibrin*. 1995. 6:17-22 [Norway]	Randomized, controlled	9 months (starting on the second postoperative day)	3.32 g/day EPA + DHA from 4 g/day fish oil (1 g fish oil capsules contained 51% EPA, 32% DHA, and 3.7 mg vitamin E) ± antithrombotic treatment with aspirin or warfarin Compliance: serum phospholipid fatty acids	511 patients undergoing coronary artery bypass surgery mean age: 59.9 years (fish oil group); 59.4 years (control group) % male: 85.8% (fish oil group); 87.6% (control group) Aspirin + n-3 FA: 143 Aspirin alone: 148 Warfarin + n-3 FA: 174 Warfarin alone: 145 99 patients withdrawn due to: deviation from assigned treatment (66), death (12), started anti-diabetic or lipid-lowering drug therapy during study (11), angiography before 9 months (9), and absence at 9 months visit (1).	Bleeding episodes: NS differences in frequency of bleeding episodes between the fish oil and control group, and for patients who received aspirin compared to those who received warfarin (total number of bleeding episodes were 8, 10, 14, and 17 for patients who received aspirin, aspirin + fish oil, warfarin, and warfarin + fish oil, respectively). Bleeding time: ↑ NS for both fish oil and control patients; NS difference between groups Platelet count: ↑ in both fish oil and control group, but fish oil group had less of an increase (group difference was of borderline significance, p=0.054). Beta-thromboglobulin: NS difference between groups. Fibrinogen: NS change Factor VII: NS change Fibrinopeptide A: NS change D-Dimer: NS change PAI-1 activity: NS change PAI-1 antigen: small ↑ in fish oil group; small ↓ in control group (group difference of borderline significance, p = 0.077) Thrombin-antithrombin III complexes: NS ↓ compared to control (p=0.37)

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Only bleeding parameters are summarized

Reference	Study design	Duration	Intake	Subjects	Results
Freese and Mutanen 1997a *Am. J. Clin. Nutr.* 1997. 66:591-596 [Finland]	Randomized, double-blind, parallel trial.	4 weeks there was a pretreatment period and a 12 week follow-up period	5.2 g/day EPA + DHA (mean intake); range: 4-7.6 g/day, from 9-17 g/day fish oil (mean: 11.5) + sunflower oil Control: linseed oil (5.9 g/day ALA) Compliance: Platelet lipid FA analysis; diaries	46 healthy subjects age range: 20-44 years 17 male/19 female n-3 FA: n=24 Control: n=22 4 dropouts due to large changes in smoking habits, abnormally long bleeding times, or difficulties in blood sampling.	Bleeding time: ↑ from 5.4 to 6.4 minutes (+18.5%) in fish oil group but returned to baseline during follow-up; also ↑ in linseed oil group (from 5.7 to 6.9 minutes, +21%), but did not return to baseline during follow-up (NS between groups) Factor VIIc: ↑ in both groups PAI-1 activity: ↑ in both groups, but returned to baseline during follow-up period (NS between groups) Platelet aggregation to collagen: NS between groups Thromboxane B_2: NS between groups Platelet aggregation to I-BOP: NS between groups Urinary excretion of 1,1-dehydrothromboxane B_2: NS between groups β-thromboglobulin: NS between groups Plasma fibrinogen concentration: NS between groups Antithrombin III activity: NS between groups Factor VII coagulant activity: NS between groups

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Reference	Study design	Duration	Intake	Subjects	Results
Grundt et al. 1999 *Thromb. Haemost.* 1999. 81:561-565 [Norway]	Randomized, double-blind, controlled	12 weeks 10 week run-in period prior to intervention	3.4 g/day EPA/DHA from 4 g/day of a concentrated compound of 85% EPA/DHA Control: 4 g/day corn oil Compliance: fish intake, body weight, capsule count, phospholipid analysis (mean compliance: 90%)	56 subjects with combined (type IIb) hyperlipidemia 51 male/6 female age range: 18-70 years EPA/DHA: n=28 Control: n=28 Inclusion criteria: serum TG: ≥2.0 mmol/l and ≤15.0 mmol/l; serum TC ≥ 6.0 mmol/l.	Bleeding time: NS ↑ at week 12 compared to baseline (from 358 seconds to 390 seconds, +9%) (NS ↓ occurred in control group) Platelet count: ↓ by 3.3% ($p<0.05$) (NS decrease in control group) PAI-1: ↑ significantly ($p<0.05$) (no change in control group) Fibrinogen: NS changes Coagulation factor FVIIc: NS changes Tissue factor pathway inhibitor (TFPI): no significant changes
Henderson et al. 1994 *J. Pediatr.* 1994. 124:400-408 [U.S.]	Randomized double-blind, placebo-controlled	6 weeks	5.4 g/day EPA + DHA from 8 g/day encapsulated fish oil Control: olive oil esters (flavored with 0.4% processed menhaden oil to give slight fish taste and contained 0.002 g/day EPA+DHA) Compliance: capsule count, diary, phone calls, plasma and erythrocyte FA analysis	24 subjects 12 patients with cystic fibrosis; (mean age: 12 years; 7 male/5 female) received fish oil treatment. Control: 12 healthy subjects (without cystic fibrosis; mean age: 13 years; 7 male/6 female) received olive oil.	Bleeding incidence: no change Prothrombin time: no change Platelet aggregation to ADP: no change Platelet aggregation to collagen: no change

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Reference	Study design	Duration	Intake	Subjects	Results
Lenzi et al. 1996 *Nephron* 1996. 72:383-390 [Italy]	Not randomized, open, prospective	6 weeks	7.7 g/day EPA + DHA (9 capsules per day of ethyl esters of n-3 FA (K-85), each capsule containing 1,000 mg fish oil yielding 85% EPA + DHA) - Study B 3 g/day EPA + DHA (12 capsules per day of n-3 FA, each capsule containing 750 mg fish oil (MaxEPA) yielding 33% EPA+DHA) - Study A Compliance: measured by pill count, n-3 FA in plasma lipids, bleeding time, and serum thromboxane	8 patients with chronic glomerular diseases (age range: 19-70 years 6 male/2 female). One pt had NIDDM; two pts were hypertensive; five pts were hyper-cholesterolemic 3 subjects were studied twice (studies A and B) and 1 subject was studied 3 times (once on study A and twice on study B) Study A: n=9 subjects (1 subject studied twice) Study B: n=4 subjects (all participated in Study A also)	Bleeding time: ↑ significantly with both doses: +21.4% with 3 g/day, +33% with 7.7 g/day ($p<0.05$) Serum thromboxane: ↓ significantly with both doses: -22.5% with 3 g/day, -33.8% with 7.7 g/day ($p<0.05$)

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Reference	Study design	Duration	Intake	Subjects	Results
Mundal, et. al. 1993 *Thrombosis Res.* 1993; 72:257-62 [Norway]	Randomized, double-blind, cross-over study design.	4 weeks on EPA + DHA or placebo followed by a 4 week washout. Tx were then reversed for 8 weeks, with the last 4 weeks EPA + DHA + nifedipine or placebo + nifedipine. A 4-week placebo run-in period preceded trial	4.6 g/d EPA + DHA (EPA = 1.8 g/d and DHA = 2.8 g/d). Group 1: fish oil (4 weeks), wash-out (4 weeks), placebo (4 weeks), placebo + nifedipine (4 weeks). Group 2: placebo (4 weeks), washout (4 weeks), fish oil (4 weeks), fish oil + nifedipine (4 weeks). Compliance: Pill count.	18 healthy, hypertensive males with elevated blood lipids taking no medications. BP was >145/95. All had TC >6.0 mmol/l and TG > 1.4 mmol/l or TG >1.8 mmol/l if TC was <6.0 mmol/l. Group 1: n = 8 Group 2: n = 10	Bleeding time: No effects seen compared to controls when comparing EPA-DHA vs. placebo tx. with and without (p>0.60) nifedipine. Platelet count: No effects after EPA+ DHA tx vs. placebo (p=0.65) nor after EPA + DHA + nifedipine tx vs. placebo controls (p values not specified). Platelet volume: no effects after EPA+ DHA tx vs. placebo (p=0.96) nor after EPA + DHA + nifedipine tx vs. placebo + nifedipine controls (p values not specified).

Table 8
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Examining Bleeding Time
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Reference	Study design	Duration	Intake	Subjects	Results
Nelson et al. 1997b *Lipids* 1997. 32(11):1129-1136 [U.S.]	Randomized, Parallel single-blind	13 weeks (90 days) with a 30- day stabilization period prior to intervention	6 g/day DHA from 15 g of DHASCO oil (high-DHA diet) (Group A) Group B: <0.05 g/day DHA (low-DHA diet) both groups received the low-DHA diet during the 30-day stabilization period Compliance: Platelet lipid FA analysis	10 healthy male subjects; mean age: 33 years Group A: n=6 Group B: n=4 No significant difference in body weight, blood pressure, or bleeding time between subjects at study entry 2 subjects were unable to complete the protocol.	Bleeding time: NS ↓in bleeding (from a mean of 9.4 minutes observed after the 30-day low-DHA diet to 8 minutes after the high-DHA diet, p=0.06). NS ↑ in control group (5.9 minutes to 6.4). Erythrocyte count: no significant changes Hemoglobin levels: no significant changes Average hematocrit: no significant changes Blood pressure: no significant changes Platelet counts (whole blood): NS □ in both groups. ADP-induced platelet aggregation: NS ↑ with high-DHA diet; NS ↑ with control diet Collagen-induced platelet aggregation: NS □□in both groups. Prothrombin time: no significant changes Activated partial thromboplastin time: no significant changes Antithrombin-III: NS ↑ with high-DHA diet (p=0.11); NS ↑ with control diet (p=0.13)

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Only bleeding parameters are summarized

Reference	Study design	Duration	Intake	Subjects	Results
Nordoy et al. 1994 *J. Lab. Clin. Med.* 1994. 123:914-920 [U.S.]	Randomized, double-blind, crossover	3 weeks per treatment period, with a 6-week washout between periods	1.7 g/day EPA + DHA (6.1 g/day n-3 FA from encapsulated fish oil concentrate (EPAX) containing 68% n-3 content (35% EPA, 19% DHA) Subjects fed: (1) a high-fat diet (39% of energy), (2) a high-fat diet + n-3 FA, (3) a low fat diet (25% of energy), or (4) a low fat diet + n-3 FA Compliance: plasma fatty acid composition, participant interviews, and leftover meals	6 normolipidemic males age range: 27-58 years (mean: 39.7 years)	Skin bleeding time: ↑ significantly for n-3 FA + low saturated-fat diet compared to n-3 FA + high saturated-fat diet ($p<0.02$). Platelet count: NS change Mean platelet volume: NS change Fibrinogen: NS change Factor VII activity: NS change Phospholipase C-sensitive component of factor VII: NS change Antithrombin III: NS change Protein S antigen: NS change Protein C activity: NS change Thromboxane A_2: ↓ significantly with n-3 FA + low saturated-fat diet (as assessed by urinary metabolites *in vivo*) Thromboxane A_3: slightly ↑ synthesis with both diets Prostacyclin production: ↓ for low-fat diet compared to high-fat diet Prostacyclin I_3: slightly ↑ synthesis with both diets

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Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Examining Bleeding Time
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Reference	Study design	Duration	Intake	Subjects	Results
Parkinson et al. 1994 *Am J Clin. Nutr* 1994;59:384-388 [U.S.]	Cross-sectional		Not quantified Dietary information collected using 2-month dietary recall (July and August 1985) to capture the frequency of foods consumed, but not portion size. Included questions about specific types of fish, marine and land mammals, fowl, and types of cooking oils used. Coastal residents reported consuming significantly ($p<0.01$) more marine fish, marine mammals, birds, and consuming items with seal oil.	80 residents of two Eskimo villages, randomly selected by age and gender category: 40 residents of a river village 39 residents of a coastal village. Excluded subjects were receiving anticoagulant therapy or had used aspirin-containing substances 2 weeks prior to blood draw. Plasma fatty acid analyses were compared with selected age-specific volunteers from the University of Oregon Family Heart Study and Lipid Clinic.	Bleeding time: 88% of river-village (mean of 5.5 min) and 98% of coastal village (mean of 5.2 minutes) subjects had normal bleeding times. 3 subjects had bleeding times longer than normal range, but bleeding time did not correlate to high EPA or n-3 FA concentrations. Platelet counts: at or above normal range for subjects in both villages, but were not association with dietary intakes of n-3 fatty acids.

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Reference	Study design	Duration	Intake	Subjects	Results
Uauy et al. 1994 *J. Pediatr.* 124:612-620 [U.S.]	Randomized, controlled	57 weeks (follow-up from 40 to 57 weeks)	Not quantified. Infants were fed human milk (not randomized) or randomized to receive infant formula with varying amounts of n-3 FA: Formula A: corn oil (24.2% linoleic acid and 0.5% α-linolenic acid). Formula B: soy oil (20.8% linoleic acid and 2.7% α-linolenic acid). Formula C: soy oil + marine oil (0.3% DHA -similar to amount in human milk)	52 infants with low birth weights (between 1,000-1,500 g) and no major neonatal morbidity by the tenth day of life. Human milk: n=9 Formula A: n=13 Formula B: n=16 Formula: C: n=14 Reference group for infants fed human milk were birth-weight matched infants fed mother's milk since birth. 18 infants discharged early were not included in study.	Bleeding time: ↑ in infants fed formula C at 37 weeks, but values did not exceed the normal upper limit (7 minutes); increased +26.7% and +28% compared to corn oil and soil oil, respectively ($p<0.05$). Platelet counts: NS change; all were within normal limits. Rotational membrane fluidity of intact RBCs: NS changes in any group.

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) Including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Ågren et al. 1997 *Prostaglandin-Ins, Leukotrienes and Essen. Fatty Acids* 1997. 57 (4/5):419-421 [Finland]	Randomized, Parallel Controlled	15 weeks	2.28 g/day DHA + EPA (1.3 g/day EPA and 0.95 g/day DHA from 4 g/day fish oil (Bio-Marin)) 1.05 g/day EPA+DHA (0.38 g/day EPA and 0.67 g/day DHA from fish diet - 4.3 meals/ wk) 1.66 g/day DHA (from 4 g/day DHA oil (Martek)) Control: not reported if control group received placebo or no supplementation/food Compliance: not reported	55 healthy male subjects	Factor X: ↓ in fish diet group vs. baseline ($p<0.05$); no significant changes in any other group. Collagen-induced platelet aggregation: ↓ in fish diet and fish oil groups vs. baseline ($p<0.05$); tendency for ↑ in DHA oil group (NS) that was inversely correlated with change in fasting triglyceride levels. Prothrombin time: NS change Activated partial thromboplastin time: NS change Fibrinogen: NS change Factor VII: NS change Prothrombin fragment 1+2: NS change Tissue factor pathway inhibitor: NS change ADP-induced platelet aggregation: NS change
Axelrod et al. 1994 *Diabetes Care* 1994;17(1):37-44 [U.S.]	Randomized, double-blind, controlled trial	6 weeks 6 week washout after cessation of supplementation	2.5 g/day EPA + DHA 1.5g/day EPA 1 g/day DHA (SuperEPA capsules) Control: Safflower oil Compliance: interviews mid-study	18 patients w/NIDDM and meeting HbA_{1c} and hemoglobin criteria; age range: 21-65 years Fish oil: n=9 Control: n=9 2 subjects excluded: 1 due to noncompliance; 1 due to small bowel obstruction caused by metastatic colon cancer	Collagen-induced platelet aggregation: ↓ dose/response curve vs. safflower ($p=0.035$) and vs. baseline ($p=0.022$). ADP-induced platelet aggregation: NS TXB_2 platelet generation induced by collagen: NS TXB_2 platelet generation induced by ADP: NS TXB_2 serum concentration: NS
Berstad et al. 1995 *Blood Coagulation and Fibrinolysis* 1995;6:374-381	Open study (not randomized, not blinded, not controlled)	12 weeks	1.2 g/day EPA + DHA from 2.4 g/day n-3 FA (Triomar capsules containing 60% n-3, 30% EPA, 20% DHA)	15 healthy males mean age: 34 years (range: 22-45 years)	Plasma EPA & Beta TG: NS Plasma fibrinogen: ↓ vs. baseline (-19%) ($p<0.0006$). Collagen-induced thrombus formation (%

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
[Norway]			Control: none Compliance: serum FA analysis	Data from 1 subject excluded; the subject was diagnosed with celiac disease shortly after finishing the study	surface coverage with platelets): NS Platelet aggregation formation (thrombus volume per unit area): NS Fibrin deposition (% surface coverage with fibrin): ↓ significantly (-34%) at apex of stenosis vs. baseline ($p<0.03$)
Berrettini et al. 1996 *Thrombosis & Haemostasis* 1996;75(3):395-400 [Italy]	Randomized double-blind, controlled trial.	16 weeks	3 g/d EPA + DHA ethyl esters EPA:DHA = 1.46 (Seacor capsules) Control: corn oil Compliance: capsule count	39 with chronic vascular atherosclerotic diseases n-3 FA: n=20 Control: n=19	Factor VII clotting activity: NS Tissue factor pathway inhibitor (TFPI) activity: ↑ with time effect ($p=0.029$), time to treatment interaction ($p=0.003$), linear trend over time ($p=0.0001$). Plasma F1+2: ↓, treatment effect ($p=0.016$), linear trend over time ($p=0.07$) with ↓ after 16 weeks NS ($p=0.06$).
Cirillo et al. 1994 *World Rev. Nutr. Diet*. 1994, 76:60-63. [Italy]	Not controlled	4 weeks	5.1 g/day n-3 FA ethyl esters (2.55 g twice daily) EPA/DHA ratio: 1:4 Compliance: Not reported	10 healthy subjects (8 male/2 female) age range: 24-30 years	Skin bleeding time: slightly prolonged (NS) at end of 4-wk supplementation; no change after 3 months following cessation of supplementation. Platelet adhesion to glass: no change Platelet aggregation in response to collagen: ↓ significantly after a prolonged lag phase ($p<0.01$, 1-2 months after supplementation) Platelet aggregation in response to ADP: ↓ significantly (similarly to response to collagen) Platelet aggregation in response to AA: no change Platelet secretion of ATP: normal Platelet levels of cAMP: normal Platelet binding to fibrinogen: no change Membrane glycoproteins: no change
De Maat et al. 1994 *Fibrinolysis* 1994, 8 (Suppl.2):50-52	Not controlled	1 week	9.0 g/day EPA + DHA from 30 g/day fish oil (Maxepa) containing 5.4 g EPA, 3.6 g DHA, 60 mg vitamin E	11 healthy volunteers age range: 18-22 years	Fibrinogen: NS change C-reactive protein: NS change

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
[The Netherlands]			Compliance: Not reported		
De Marchi et al. 1995 *Nephr. Dialysis Transplant.* 1995. 10:1007 (ABSTRACT) [Italy]	Double-blind, cross-sectional, placebo-controlled	8 weeks per treatment period	3 g/day EPA + DHA or placebo (no other information provided) Compliance: Not reported	80 subjects 30 nondiabetic, hemodialysis patients served as treatment group. 50 healthy subjects served as the control group.	Fibrinogen: no change Factor VII: no change Prothrombin fragment 1 & 2: no change D-dimer: no change
Eritsland et al. 1994a *Fibrinolysis* 1994;8:120-125 [Norway]	Randomized controlled trial, (no placebo)	26 weeks (6 months)	3.4 g/day EPA + DHA ethyl esters (4 g K85 highly concentrated fish oil) Control: medication alone (ASA or warfarin) Study groups: ASA only; ASA + n-3 FA; warfarin only; warfarin + n-3 FA Compliance: serum phospholipid FA analysis	58 subjects with coronary artery disease who underwent bypass grafting. TG ≥ 1.5 mmol/l. 54 male/4 female n-3 FA: n=29 Control: n=29	Fibrinogen: NS between groups PAI-1 activity: NS between groups PAI-1 antigen: ↑ test,↓ control (p=0.039 between groups) Serum D-dimer after venous occlusion: NS between groups. Minor changes in t-PA activity and antigen both before and after venous occlusion. In groups, inverse correlation between change in serum FAs and change in TG (r=0.35, p=0.008). Correlation between changes in serum FAs and PAI-1 antigen (r=0.28, p=0.036).
Eritsland et al. 1995c *Blood Coagulation and Fibrin.* 1995. 6:17-22 [Norway]	Randomized, controlled	9 months (starting on the second postoperative day)	3.32 g/day EPA + DHA from 4 g/day fish oil (1 g fish oil capsules contained 51% EPA, 32% DHA, and 3.7 mg vitamin E) ± antithrombotic treatment with aspirin or warfarin Compliance: serum phospholipid fatty acids	511 patients undergoing coronary artery bypass surgery mean age: 59.9 years (fish oil group); 59.4 years (control group) % male: 85.6% (fish oil group); 87.6% (control group) Aspirin + n-3 FA: 143	Bleeding episodes: NS differences in frequency of bleeding episodes between the fish oil and control group, and for patients who received aspirin compared to those who received warfarin (total number of bleeding episodes were 8, 10, 14, and 17 for patients who received aspirin, aspirin + fish oil, warfarin, and warfarin + fish oil, respectively). Bleeding time: ↑ NS for both fish oil and control patients; NS difference between

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Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) Including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
				Aspirin alone: 148 Warfarin + n-3 FA: 174 Warfarin alone: 145 99 patients withdrawn due to: deviation from assigned treatment (66), death (12), started anti-diabetic or lipid-lowering drug therapy during study (11), angiography before 9 months (9), and absence at 9 months visit (1).	groups Platelet count: ↑ in both fish oil and control group, but fish oil group had less of an increase (group difference was of borderline significance, p=0.054). Beta-thromboglobulin: NS difference between groups. Fibrinogen: NS change Factor VII: NS change Fibrinopeptide A: NS change D-Dimer: NS change PAI-1 activity: NS change PAI-1 antigen: small ↑ in fish oil group; small ↓ in control group (group difference of borderline significance, p = 0.077) Thrombin-antithrombin III complexes: NS ↓ compared to control (p=0.37)
Freese and Mutanen 1997a *Am. J. Clin. Nutr.* 1997. 66:591-598 [Finland]	Randomized, double-blind, parallel trial.	4 weeks there was a pretreatment period and a 12 week follow-up period	5.2 g/day EPA + DHA (mean intake); range: 4-7.6 g/day, from 9-17 g/day fish oil (mean: 11.5) + sunflower oil Control: linseed oil (5.9 g/day ALA) Compliance: Platelet lipid FA analysis; diaries	46 healthy subjects age range: 20-44 years 17 male/19 female n-3 FA: n=24 Control: n=22 4 dropouts due to large changes in smoking habits, abnormally long bleeding times, or difficulties in blood sampling.	Bleeding time: ↑ from 5.4 to 6.4 minutes (+18.5%) in fish oil group but returned to baseline during follow-up; also ↑ in linseed oil group (from 5.7 to 6.9 minutes, +21%), but did not return to baseline during follow-up (NS between groups) Factor VIIc: ↑ in both groups PAI-1 activity: ↑ in both groups, but returned to baseline during follow-up period (NS between groups) Platelet aggregation to collagen: NS between groups Thromboxane B_2: NS between groups Platelet aggregation to I-BOP: NS between groups Urinary excretion of 1,1-dehydrothromboxane B_2: NS between groups ß-thromboglobulin: NS between groups Plasma fibrinogen concentration: NS between groups

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Reference	Study design	Duration	Intake	Subjects	Results
					Antithrombin III activity: NS between groups Factor VII coagulant activity: NS between groups
Freese and Mutanen 1997b *Thrombosis Res.* 1997. 85(2):147-152 [Finland]	Randomized, controlled trial.	4 weeks with a 12-week follow-up period	5.49 g/day EPA + DHA (3.04 g/day EPA, 2.45 g/day DHA); 12.2 g/day fish oil (Pikasol) + sunflower oil Control: 11.9 g/day linseed oil (6.21 g/day ALA) Compliance: Platelet lipid FA analysis	30 healthy normolipidemic subjects; 15 male, 15 female Fish oil: n=16 Control: n=14	*Fasting values:* Factor VII coagulant activity (FVIIc): ↑ in fish oil group, p<0.05 PAI-1 activity: ↑ in fish group, p<0.05 ADP-induced platelet aggregation: significant ↑ at 2 µmol/l ADP, p<0.05 (no significant change for other doses - 1 and 3 µmol/l) Collagen induced platelet aggregation: significantly ↑ at 0.5 µg/ml collagen, p<0.05 (NS changes for other dose levels - 1 and 3 µg/ml) Thromboxane B_2: NS change *Postprandial values:* Factor VII coagulant activity (FVIIc): significantly ↑ before and after supplementation (p<0.05) PAI-1 activity: ↓ after supplementation (p<0.05) ADP-induced platelet aggregation: significantly ↓ (p<0.05) Collagen induced platelet aggregation: significantly ↓ (p<0.05) Thromboxane B_2: NS change All levels returned to normal during the 12-week follow-up period except for collagen-induced aggregation and Factor VII coagulant activity. No significant change in any parameter in the control group.
Grundt et al. 1999	Randomized,	12 weeks	3.4 g/day EPA/DHA	56 subjects with combined	Bleeding time: NS ↑ at week 12

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Reference	Study design	Duration	Intake	Subjects	Results
Thromb. Haemost. 1999. 81:561-565 [Norway]	double-blind, controlled	10 week run-in period prior to intervention	from 4 g/day of a concentrated compound of 85% EPA/DHA Control: 4 g/day corn oil Compliance: fish intake, body weight, capsule count, phospholipid analysis (mean compliance: 90%)	(type IIb) hyperlipidemia 51 male/9 female age range: 18-70 years EPA/DHA: n=28 Control: n=28 Inclusion criteria: serum TG: ≥2.0 mmol/l and ≤15.0 mmol/l; serum TC ≥ 6.0 mmol/l.	compared to baseline (from 358 seconds to 390 seconds, +9%) (NS ↓ occurred in control group) Platelet count: ↓ by 3.3% ($p<0.05$) (NS decrease in control group) PAI-1: ↑ significantly ($p<0.05$) (no change in control group) Fibrinogen: NS changes Coagulation factor FVIIc: NS changes Tissue factor pathway inhibitor (TFPI): no significant changes
Haglund et al. 1994 *Am. J. Cardiol.* 1994. 74:189-192 [Sweden]	Not controlled (Study A) Double-blind, crossover (Study B)	48 weeks (12 months) Study A 3 weeks per treatment, with a 2-week washout in-between Study B	9 g/day n-3 fatty acids (Study B) 4.5 g/day n-3 fatty acids, mainly EPA + DHA [from 15 ml fish oil, (ESKIMO-3)] -Study A Study B subjects received fish oil plus a high dose of vitamin E (1.5 IU/g) or fish oil plus a low dose of vitamin E (0.3 IU/g) - Study B The fish oil used contained 40% n-3 fatty acids (19% EPA and 13% DHA)	15 healthy subjects with normal or slightly increased serum lipids; mean age: 41 years; 11 male/4 female (Study A) 12 healthy subjects; mean age: 51 years; 10 male/2 female (Study B)	Study A: PAI-1 antigen: ↑ significantly (+90%) compared to baseline values ($p<0.01$) PAI-1 activity: ↑ significantly (+75%) compared to baseline values ($p<0.01$) t-PA antigen: ↓ significantly (-33%) compared to baseline values ($p<0.05$) Plasma fibrinogen: ↓ significantly (-17%) compared to baseline values ($p<0.05$) Study B: PAI-1 antigen: ↑ significantly (+63%) with fish oil + 0.3 IU/g vitamin E ($p<0.01$); slight, NS ↑ with vitamin E-rich fish oil. PAI-1 activity: ↑ significantly (+25%) with fish oil + 0.3 IU/g vitamin E ($p<0.01$); slight, NS ↑ with vitamin E-rich fish oil. t-PA antigen: no change Fibrinogen: ↓ significantly (-11%) with vitamin E-rich fish oil; no change with fish oil + 3 IU/g
Haglund et al. 1998 *Nutr Biochem* 1998;9:629-635	Double-blind, crossover trial.	4 weeks per treatment, with a 5- week washout in between	Not quantified 32% EPA + DHA mixture (30 ml fish oil (ESKIMO-3®)	12 healthy subjects with moderately increased blood lipids (10 men, 2 post menopausal women)	Plasma fibrinogen: ↓ by 10% ($p<0.05$) and 8% ($p<0.05$) with fish oil and FO+EPO treatments, respectively. tPA antigen: NS change

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[Sweden]			19% EPA 13% DHA (fish oil) Control: FO + EPO (30 ml) Compliance: interview, capsule counts, plasma phospholipids fatty acids analyses.		PAI-1 activity: ↑ by 50 ($p<0.05$) and 23%, respectively with fish oil and FO+EPO treatments. PAI-1 antigen: ↑ by 49% ($p<0.05$) with fish oil, but no change with FO+EPO treatment. Significant difference between the two groups ($p<0.05$).
Hayashi et al. 1995 *Curr. Ther. Res.* 1995. 56:24-31 [Japan]	Not controlled	8 weeks	1.8 g/day ethyl icosapentate Compliance: Not reported	28 subjects with familial combined hyperlipidemia showing phenotype IIa, IIb, or IV; age range: 20-69 years	PAI-1: ↓ significantly (-40%), $p<0.01$ Coagulation factor VII: ↓ significantly (-9%), $p<0.01$ Coagulation factor X: ↓ significantly (-10%), $p<0.01$
Henderson et al. 1994 *J. Pediatr.* 1994. 124:400-408 [U.S.]	Randomized double-blind, placebo-controlled	6 weeks	5.4 g/day EPA + DHA from 8 g/day encapsulated fish oil Control: olive oil esters (flavored with 0.4% processed menhaden oil to give slight fish taste and contained 0.002 g/day EPA+DHA) Compliance: capsule count, diary, phone calls, plasma and erythrocyte FA analysis	24 subjects 12 patients with cystic fibrosis; (mean age: 12 years; 7 male/5 female) received fish oil treatment. Control: 12 healthy subjects (without cystic fibrosis; mean age: 13 years; 7 male/6 female) received olive oil.	Bleeding incidence: no change Prothrombin time: no change Platelet aggregation to ADP: no change Platelet aggregation to collagen: no change
Herrmann et al. 1995 *Am J Cardiol* 1995;76:459-462 [Germany]	Randomized, double-blind, controlled trial.	4 weeks	8.5 g/day n-3 FA (EPA + DHA and other FA) 12 g/d of fish oil (fish oil group) Control: Rapeseed oil capsules Compliance: serum n-3 FA analyses	53 male subjects with ischemic heart disease, hospitalized in a rehabilitation sanatorium mean age: 53.9 years n-3 FA: n=35 Control: n=18	Platelet count: NS Platelet aggregation: NS tPA: ↓ significantly in both groups (approx. -16%)

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Reference	Study design	Duration	Intake	Subjects	Results
Johansen et al. 1999b *Arterioscler. Thromb. Vasc. Biol.* 1999 19:1681-1686 [Norway]	Randomized, Parallel	4 weeks with a 6 month pretreatment period	5 g/day EPA + DHA (2.7 g/day EPA, 2.3 g/day DHA) Group I subjects were pretreated with 5.1 g/day n-3 FA for 6 months Group II subjects were pretreated with placebo (corn oil) for 6 months Compliance: serum phospholipid fatty acids	54 male patients with heart disease; age range: 40-74 years Group I: n=23 Group II: n=31 All subjects (group I and II) received n-3 supplementation during 4 week test period.	Tissue plasminogen activator antigen (tPA): slight ↑ (group I); NS ↓ (group II); change significantly different in group II vs. group I ($p<0.01$) von Willebrand factor: NS ↓ (group I & II) serum thrombomodulin: slight ↓ (group I); NS ↓ (group II); significantly higher at baseline (before 4 week treatment period) in group II ($p<0.01$), but NS after 4 weeks serum P-selectin: slight ↓ (group I & II) serum E-selectin: NS ↑ (group I & II); change significantly higher in group I vs. group II ($p<0.01$) serum vascular cell adhesion molecule-1 (VCAM-1): NS ↑ (group I & II); change significantly higher in group I vs. group II ($p<0.01$)
Katz et al. 1996 *Nutr.* 1996. 12:334-339 [U.S.]	Randomized, double-blind, controlled	4 weeks	Not quantified 150 mg/kg of 10% n-3 FA-containing lipid emulsion (Omegavenous, which contained 18.3% EPA and 27.6% DHA) Control: 10% Liposyn III lipid emulsion (contained no EPA or DHA) via intravenous infusion Compliance: plasma phospholipid FA analysis	18 subjects with cystic fibrosis age range: 10-37 years; 9 male/9 female n-3 FA: n=9 Control: n=9 The treatments were administered iv.	Fish oil administration had no effect on coagulation parameters (actual parameters not reported in paper).
Lau et al. 1995 *Clin. Exp. Rheumatol.* 1995. 13:87-90	Randomized, double-blind, controlled	6 months	2.8 g/day (EPA + DHA) from fish oil (Maxepa) capsules or placebo (air-filled capsules)	45 patients with rheumatoid arthritis as defined by the Am. Rheum. Assoc. age range: 27-69 years; 32 male/13 female	Fibrinogen: ↓ significantly (-17.7%) compared to baseline and month 3 level ($p<0.02$) and control ($p<0.01$) t-PA activity: ↓ significantly (-27.6%) compared to baseline ($p<0.001$) and

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Reference	Study design	Duration	Intake	Subjects	Results
[Hong Kong]			Compliance: pill count and measurement of RBC membrane FA analysis	n-3 FA: n=25 Control: n=20	control ($p<0.01$) PAI-1 activity: NS change NS change in any of the above parameters for the group receiving placebo.
Lenzi et al. 1996 *Nephron* 1996. 72:383-390 [Italy]	Not randomized, open, prospective	6 weeks	7.7 g/day EPA + DHA (9 capsules per day of ethyl esters of n-3 FA (K-85), each capsule containing 1,000 mg fish oil yielding 85% EPA + DHA) - Study B 3 g/day EPA + DHA (12 capsules per day of n-3 FA, each capsule containing 750 mg fish oil (MaxEPA) yielding 33% EPA+DHA) - Study A Compliance: measured by pill count, n-3 FA in plasma lipids, bleeding time, and serum thromboxane	8 patients with chronic glomerular diseases (age range: 19-70 years 6 male/2 female). One pt had NIDDM; two pts were hypertensive; five pts were hyper-cholesterolemic 3 subjects were studied twice (studies A and B) and 1 subject was studied 3 times (once on study A and twice on study B) Study A: n=9 subjects (1 subject studied twice) Study B: n=4 subjects (all participated in Study A also)	Bleeding time: ↑ significantly with both doses: +21.4% with 3 g/day, +33% with 7.7 g/day ($p<0.05$) Serum thromboxane: ↓ significantly with both doses: -22.5% with 3 g/day, -33.8% with 7.7 g/day ($p<0.05$)
Matyszko et al. 1996 *Przegl.Lek.* 1996. 53:600-603 (ABSTRACT, foreign) [Poland]	Not controlled	6 months	Not quantified Trienyl (fish oil/ omega-3 FA treatment) Compliance: not reported.	7 pts with glomerulo-nephritis	Fibrinogen: ↓ significantly at 6 months (-18%) tPA activity: ↓ at 6 months (-7.3%) tPA antigen: NS change PAI antigen: NS change PAI activity: ↓ at 6 months (-15%) Euglobulin: ↑ at 6 mos (+14.2%) Thrombin-antithrombin complexes: NS change Plasmin-antiplasmin complexes: ↑ at 6 mos (+8.9%)

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Reference	Study design	Duration	Intake	Subjects	Results
					Fibrinogen 1&2: NS change Platelet aggregation in whole blood in response to collagen: ↓ significantly at 6 mos (-34.6%) Platelet aggregation in whole blood in response to ADP: ↓ significantly at 6 mos (-24.3%) Platelet aggregation in platelet-rich plasma in response to collagen: NS change Platelet aggregation in platelet-rich plasma in response to ADP: NS change
Misso and Thompson 1995 *Platelets* 1995. 6:275-282 [Australia]	Double-blind, crossover	4 weeks per treatment period with a 4-week washout period between treatments and at the end of study	3.6 g/day EPA + DHA from fish oil capsules (MaxEPA) Control: 12 g/day olive oil	12 normal, healthy subjects age range: 23-40 years 6 males/6 female	Platelet aggregation to PAF: NS ↓ in fish oil group; no change in olive oil group Platelet aggregation to collagen: NS ↓ in fish oil group; no change in olive oil group Platelet aggregation to ADP: NS change Platelet aggregation to adrenalin: NS change Platelet aggregation to AA: NS change Platelet ATP release induced by PAF: ↓ significantly in fish oil group (p<0.0005); no change in olive oil group Platelet ATP release induced by collagen: ↓ significantly in fish oil group (p<0.0005); ↓ in olive oil group at higher collagen doses Platelet ATP release induced by ADP: ↓ significantly in fish oil group (p<0.02-0.05); no change in olive oil group Platelet ATP release induced by AA: NS change Platelet ATP release induced by ionophor: NS change Fibrinogen: NS ↓ with fish oil; ↓ significantly with olive oil Prothrombin time: ↓ significantly (-8.4%) with fish oil (p<0.001) and olive oil (-7.8,

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Reference	Study design	Duration	Intake	Subjects	Results
					p<0.0025) Partial thromboplastin time with kaolin: NS change Thrombin clotting time: NS change
Mori et al. 1997 *Arterioscler. Thromb. Vasc. Biol* 1997. 17(2):279-286 [Australia]	Randomized, parallel, controlled	12 weeks (following a 3-week screening period and a 1-week baseline measurement period)	2.6-3.7 g/day EPA + DHA (1.5-2.4 g/day DHA and 1.3 g/day EPA provided by fish 2.1 g/day EPA + DHA (0.8 g/day DHA and 1.3 g/day EPA) provided by fish oil capsules high-fat diets: 1. placebo capsules 2. 90-160 g/day fish 3. 6 g/day fish oil capsules 4. 90-160 g/day fish + 6 g/day fish oil capsules, 5. 12 g/day fish oil capsules low-fat diets: 1. placebo capsules 2. 90-160 g/day fish Compliance: platelet phospholipid FA analysis	120 nonsmoking, healthy males, 30-60 years of age 16 withdrawals due to reasons unrelated to treatment	Platelet aggregation to collagen: ↓ in all fish or fish oil groups (p=0.0487 - low-fat diet and p<0.0001 - high fat diet), no difference seen between fish and fish oil diets Platelet aggregation to PAF: ↓ in all groups (p<0.05), ↓ more pronounced in fish oil high-fat diet compared to fish high-fat diet, greatest effect seen with fish oil + fish; fish had a greater effect as part of a low-fat diet Platelet-derived TXB_2 responses to collagen-induced aggregation: ↓ in all groups (p<0.05)
Mundal, et. al. 1993 *Thrombosis Res.* 1993; 72:257-62 [Norway]	Randomized, double-blind, cross-over study design.	4 weeks on EPA + DHA or placebo followed by a 4 week washout. Tx were then reversed for 8 weeks, with the last 4 weeks EPA + DHA + nifedipine or placebo + nifedipine.	4.6 g/d EPA + DHA (EPA = 1.8 g/d and DHA = 2.8 g/d). Group 1: fish oil (4 weeks), wash-out (4 weeks), placebo (4 weeks), placebo + nifedipine (4 weeks). Group 2: placebo (4 weeks),	18 healthy, hypertensive males with elevated blood lipids taking no medications. BP was >145/95. All had TC >6.0 mmol/l and TG > 1.4 mmol/l or TG >1.8 mmol/l if TC was <6.0 mmol/l.	Bleeding time: No effects seen compared to controls when comparing EPA-DHA vs. placebo tx. with and without (p>0.60) nifedipine. Plasma b-thrombo-globulin: There were no effects seen in the median plasma b-thrombo-globulin (p>0.12) after EPA + DHA tx vs. placebo controls (and without nifedipine tx). Plasma β-thrombo-

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Reference	Study design	Duration	Intake	Subjects	Results
		A 4-week placebo run-in period preceded trial	washout (4 weeks), fish oil (4 weeks), fish oil + nifedipine (4 weeks). Compliance: Pill count.	Group 1: n = 8 Group 2: n = 10	globulin ↑ significantly (p=0.003, n = 18) after nifedipine tx in all subjects studied, although there was no difference between the EPA-DHA-nifedipine vs. placebo-nifedipine groups (p = 0.33). Platelet count: No effects after EPA+ DHA tx vs. placebo (p=0.65) nor after EPA + DHA + nifedipine tx vs. placebo controls (p values not specified). Platelet volume: no effects after EPA+ DHA tx vs. placebo (p=0.96) nor after EPA + DHA + nifedipine tx vs. placebo + nifedipine controls (p values not specified).
Nelson et al. 1997b *Lipids* 1997. 32(11):1129-1136 [U.S.]	Randomized, Parallel single-blind	13 weeks (90 days) with a 30- day stabilization period prior to intervention	6 g/day DHA from 15 g of DHASCO oil (high-DHA diet) (Group A) Group B: <0.05 g/day DHA (low-DHA diet) both groups received the low-DHA diet during the 30-day stabilization period Compliance: Platelet lipid FA analysis	10 healthy male subjects; mean age: 33 years Group A: n=6 Group B: n=4 no significant difference in body weight, blood pressure, or bleeding time between subjects at study entry 2 subjects were unable to complete the protocol.	Bleeding time: NS ↓in bleeding (from a mean of 9.4 minutes observed after the 30-day low-DHA diet to 8 minutes after the high-DHA diet, p=0.06). NS ↑ in control group (5.9 minutes to 6.4). Erythrocyte count: no significant changes Hemoglobin levels: no significant changes Average hematocrit: no significant changes Blood pressure: no significant changes Platelet counts (whole blood): NS ↑ in both groups. ADP-induced platelet aggregation: NS ↑ with high-DHA diet; NS ↓ with control diet Collagen-induced platelet aggregation: NS ↑in both groups. Prothrombin time: no significant changes Activated partial thromboplastin time: no significant changes Antithrombin-III: NS ↑ with high-DHA diet

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Reference	Study design	Duration	Intake	Subjects	Results
					(p=0.11); NS ↑ with control diet (p=0.13)
Nordoy et al. 1994 *J. Lab. Clin. Med.* 1994. 123:914-920 [U.S.]	Randomized, double-blind, crossover	3 weeks per treatment period, with a 6-week washout between periods	1.7 g/day EPA + DHA (6.1 g/day n-3 FA from encapsulated fish oil concentrate (EPAX) containing 68% n-3 content (35% EPA, 19% DHA) Subjects fed: (5) a high-fat diet (39% of energy), (6) a high-fat diet + n-3 FA, (7) a low fat diet (25% of energy), or (8) a low fat diet + n-3 FA Compliance: plasma fatty acid composition, participant interviews, and leftover meals	6 normolipidemic males age range: 27-58 years (mean: 39.7 years)	Skin bleeding time: ↑ significantly for n-3 FA + low saturated-fat diet compared to n-3 FA + high saturated-fat diet (p<0.02). Platelet count: NS change Mean platelet volume: NS change Fibrinogen: NS change Factor VII activity: NS change Phospholipase C-sensitive component of factor VII: NS change Antithrombin III: NS change Protein S antigen: NS change Protein C activity: NS change Thromboxane A_2: ↓ significantly with n-3 FA + low saturated-fat diet (as assessed by urinary metabolites *in vivo*) Thromboxane A_3: slightly ↑ synthesis with both diets Prostacyclin production: ↓ for low-fat diet compared to high-fat diet Prostacyclin I_3: slightly ↑ synthesis with both diets
Oosthuizen et al. 1994 *Thrombosis & Haemostasis* 1994;72(4):557-562 [South Africa]	Randomized, double-blind, placebo-controlled, crossover	6 weeks per treatment period, with a 3-week washout in between	1.58 g/day EPA + DHA 1.14 g/day EPA 0.44 g/day DHA 6 g/day n-3 (12 capsules/day Efamed) Control: olive oil Compliance: FA analysis	20 healthy normolipidemic subjects 10 male/10 female	Plasma fibrinogen: ↓ (p<0.05) with test and olive oil vs. baseline in women, who had higher baseline values than the men. Plasma factors Vc, VIIc, Xc: ↓ in women during fish oil intake vs. baseline. Xc also lower for women during olive oil intake. Factor VIIc: NS PAI-1 activity: ↑ during test period for males and females (p<0.05) vs. baseline. ↑ for females only during olive oil intake. . tPA activity: NS tPA antigen: NS

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Reference	Study design	Duration	Intake	Subjects	Results
Osterud et al. 1995 *Lipids* 1995. 30:1111-1118 [Norway]	Randomized, parallel, controlled	10 weeks	Not quantified. 15 ml/day Harp seal blubber oil, cod liver oil, oil from blubber of Minke whales, seal blubber oil/ cod liver oil (Minke whale oil: 12.2 % w/w EPA + DHA Harp seal oil: 17.9 % w/w EPA + DHA Cod liver oil: 22.6 % w/w EPA + DHA) Control: no oil Compliance: Serum phospholipid FA analysis	134 healthy subjects age range: 18-60 years (mean age: 29 years) 72 male/62 female Seal oil: n=27 Cod liver oil: n=26 Seal/Cod liver oil: n=27 Whale oil: n=26 Control: n=28	Fibrinogen: no change FVIIc: no change Prothrombin fragment 1+2 (F1+2): ↓ significantly (-25%) in whale oil group; NS change in other groups LPS-induced TNF-α activity in monocytes of whole blood: ↓ significantly in whale oil group; NS ↓ in seal/cod liver oil group LPS-induced TF activity in monocytes of whole blood: ↓ significantly in seal/cod liver oil and whale oil groups; NS ↓ in all other groups Thromboxane B_2: ↓ significantly (-43.7%) in whale oil group ($p<0.01$); NS ↓ in all other fish oil groups
Otto et al. 1996 *Metabolism* 1996. 45:1305-1311 [Germany]	Not controlled	8 weeks of fish oil (2-week acclimation period with low dose n-3 FA followed by 6-week test period with high dose n-3 FA) 1 week baseline period prior to study 1 week washout period between n-3 FA and fenofibrate treatment (week 12) 6 weeks of therapy with fenofibrate (starting with week 12)	3 g/day EPA + DHA from 6 g/day fish oil capsules containing 3.6 g ethyl esters (test period) 1.5 g/day EPA + DHA from 3 g/day fish oil capsules containing 1.8 g n-3 FA ethyl esters (50% EPA, 33% DHA) (acclimation period) Subjects administered 250 mg slow-release fenofibrate starting after 12 weeks Compliance: plasma EPA and DHA concentrations	23 subjects with primary hypertri-glyceridemia (plasma triglycerides > 2.85 mmol/l; mean age: 45.7 years; 22 male/1female). Fifteen subjects had familial hypertriglyceride-mia (FHTG); 8 subjects had familial dysbetalipo-proteinemia (FDL) 2 withdrawals: 1 due to pregnancy, the other due to gastrointestinal effects	Fibrinogen: NS change in FHTG subjects; ↓ by 20% at wk 20 with fenofibrate in FDL subjects vs. washout ($p<0.05$). Plasma viscosity: NS change in FHTG subjects; ↓ by 6% at wk 20 with fenofibrate in FDL subjects vs. washout ($p<0.05$). Standard blood viscosity: NS change in FHTG subjects; ↓ at all shear rates at wk 20 with fenofibrate in FDL subjects vs. washout period ($p<0.05$). RBC filterability (as measured by clogging and transit time): NS change RBC aggregation: ↓ significantly for stasis in FHTG subjects at weeks 4 and 8 of n-3 FA oil intake and week 12 (washout) vs. baseline; ↓ for shear rate 3/s in FHTG subjects at weeks 4-8 of n-3 FA intake vs. baseline ($p<0.05$).

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(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Parkinson et al. 1994 *Am J Clin. Nutr* 1994;59:384-388 [U.S.]	Cross-sectional		Not quantified Dietary information collected using 2-month dietary recall (July and August 1985) to capture the frequency of foods consumed, but not portion size. Included questions about specific types of fish, marine and land mammals, fowl, and types of cooking oils used. Coastal residents reported consuming significantly ($p<0.01$) more marine fish, marine mammals, birds, and consuming items with seal oil.	80 residents of two Eskimo villages, randomly selected by age and gender category: 40 residents of a river village 39 residents of a coastal village. Excluded subjects were receiving anticoagulant therapy or had used aspirin-containing substances 2 weeks prior to blood draw. Plasma fatty acid analyses were compared with selected age-specific volunteers from the University of Oregon Family Heart Study and Lipid Clinic.	Bleeding time: 86% of river-village (mean of 5.5 min) and 98% of coastal village (mean of 5.2 minutes) subjects had normal bleeding times. 3 subjects had bleeding times longer than normal range, but bleeding time did not correlate to high EPA or n-3 FA concentrations. Platelet counts: at or above normal range for subjects in both villages, but were not association with dietary intakes of n-3 fatty acids.
Prisco et al. 1994; 1995 *Thrombosis Res.* 1994. 76:237-244 *Metabolism* 1995. 44:562-569 [Italy]	Randomized, double-blind, parallel, controlled	16 weeks (4 months)	3.44 g/day EPA + DHA from 4 g capsules of EPA and DHA ethyl esters (ESAPENT) Control: 4 g/day olive oil Compliance: capsule count, platelet phospholipid FA analysis	20 healthy male subjects with normal physical exam, hemetology analyses, blood pressure, and cholesterol levels mean age: 32 years (age range: 27-41 years) n-3 FA: n=10 Control: n=10	Plasminogen: NS change Alpha 2-antiplasmin: NS change PAI-1 activity: NS change PAI-1 antigen: NS change Fibrinogen: NS ↓ Prothrombin fragment 1+2: NS change Serum thromboxane B_2: ↓ significantly; no change with placebo Collagen aggregation threshold: ↑ significantly; no change with placebo
Roche and Gibney 1995 *Proc. Nutr. Soc.* 1994. 54:69A	Not a randomized, controlled trial.	16 weeks	0.9 g/day n-3 PUFA from fish oil Subjects consumed either a: 1) low-fat diet + fish oil, 2) low-fat w/o fish oil,	32 healthy subjects 3 male/5 female Low fat + fish oil: n=8	FVIIc: both fasting and postprandial levels ↓ significantly in low-fat diet + fish oil and low-fat diet w/o fish oil

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
(ABSTRACT) [Ireland]			3) full-fat diet (normal diet) + fish oil, or 4) full-fat diet w/o fish oil Compliance: not reported.	Low fat, no fish oil: n=8 Full fat + fish oil: n=8 Full fat, no fish oil: n=8	
Roulet et al. 1997 *J. Parenteral and Enteral Nutr.* 1997 21(6):296-301 [Switzerland]	Randomized, controlled	1 week (7 days)	4 g/day EPA+ DHA (by iv administration), soybean fat emulsion + 10% marine fish oil emulsion (Omegavenos, Fresenius AG) 28.45 mg/kg/day DHA (2 g/day), 28.16 mg/kg/day EPA (2 g/day) (fish oil group) Control group: soybean fat emulsion Compliance: Platelet lipid FA analysis	19 patients with esophageal epidermoid carcinoma undergoing elective total esophagectomy Fish oil: n=10 Control: n=9	Bleeding time: NS change in either group, but tended to ↓ in fish oil group (from 4.3 to 3.3 minutes, -23%); bleeding time was higher at baseline for fish oil group compared to the control group (4.3 vs. 2.9 minutes) Maximum reaction speed with collagen-induced aggregation factor: decreased ($p<0.02$) (no change in control group) Latency with collagen-induced aggregation factor: increased ($p<0.002$) No change in maximum reaction speed, latency, or maximal aggregation with ADP-induced aggregation factor or maximal aggregation with collagen-induced aggregation factor.
Salachas et al. 1994b *J Vascular Disease* 1994;45(12): 1023-1031 [Greece, England]	Randomized, double-blind, placebo-controlled trial	12 weeks (with a 2-week run-in period)	3 g/day EPA + DHA (1.8 g/day EPA and 1.2 g/day DHA from five 1-g capsules (Seven Seas) twice daily) (fish oil) Control: olive oil Compliance: Capsule count.	39 patients w/ CAD & 1-yr history of stable angina pectoris Fish oil: n=20 Control: n=19 11 withdrawals due to coronary angiography (n=6) or poor compliance (n=5)	Platelet aggregation ratio: NS Beta thromboglobulin: NS
Sanders et al. 1997 *Arterioscler. Thromb. Vasc. Biol.* 1997,	Randomized, crossover	3 weeks (21 days per treatment period), with a 8-week washout in between	5 g/day (1.5% of energy) EPA + DHA from fish oil - (Max EPA, Seven Seas) (the n-3 diet)	26 healthy, normolipidemic, non-obese males; age range: 18-34 years (mean: 23 years)	Factor VII antigen: NS change Factor VIIc activity: ↑ by 7% for n-3 diet compared to saturated fat diet ($p\leq0.01$) and by 5% compared to n-6 diet

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting (Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
17:3449-3460 [London]		all subjects fed a saturated fat diet for 3 weeks prior to study	n-6 diet: 5 g/day linoleic acid the saturated diet: 4% of total energy provided by PUFAs, trace amounts of DHA and EPA Compliance: not reported.		(p=0.19). Fibrinogen: ↑ by 10% for the n-6 diet compared to the n-3 diet (p=0.004) and saturated fat diet (p=0.02). Prothrombin fragment 1 + 2: NS change PAI-1 activity: NS change tPA activity: NS change von Willebrand factor: similar for n-3 and n-6 diets; lower for saturated diet compared to other diets (p≤0.01). β-thromboglobulin: similar for n-3 and n-6 diets; lower for saturated diet compared to other diets (p≤0.01). Platelet count: similar for n-3 and n-6 diets; higher for saturated diet compared to other (p≤0.05).
Schmidt et al., 1992b Scand J. Clin. Lab. Invest. 1992;52:221-228 [Denmark]	Clinical trial	36 weeks (9 months)	3.2 g/d EPA+DHA (4 g/d n-3 FAs, Pikasol fish oil capsules) (2.04 g/day EPA 1.14 g/day DHA) Compliance: EPA and DHA platelet fatty acid composition, interview.	24 healthy volunteers (14 female, 10 males) All subjects were free of medication, including aspirin, and non-steroidal anti-inflammatory drugs for at least two weeks prior to the study. Participants maintained normal dietary and life-style patterns.	Bleeding time: Significant ↑ with fish oil after 6 weeks and 9 months and remained higher 3 months post treatment (median values, before 5.3, 6 weeks 6.0, 9 months 6.0, 3 months post 6.0 min; p<0.001 for before and 9 months, p<0.05 9 months and 3 months post, p<0.001 for time dependent trend). Platelet umber: NS changes with fish oil Platelet volume: NS changes with fish oil Platelet aggregability: NS changes with fish oil β-thromboglobulin: NS changes with fish oil Fibrinogen: Significant ↑ with fish oil in the period between 6 weeks and 9 months (p<0.001) t-PAag: Significant ↑ after 9 months with fish oil before venous occlusion (p<0.05). t-PA activity: Significant ↓ after 9 months with fish oil after venous occlusion

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
					(p<0.001). PAI: Significant ↑ after 9 months with fish oil (p<0.05). Fibronectin antigen: No change VWF: Significant ↓ after 9 months with fish oil (p<0.05). Both EPA and DHA levels ↑ significantly with n-3 supplementation for 9 months (both p<0.001)
Seljeflot et al. 1999 *Thrombosis and Hemostasis* 1999. 81:566-570 [Norway]	Randomized, double-blind, controlled	4 weeks 6 month pre- study period baseline measurements taken after 6 month pre-study period	5.1 g/day of highly concentrated ethyl esters of fatty acids (ratio of EPA to DHA was 2:1) Prior to this study, subjects in the fish oil group received fish oil (same dose as above) and subjects in placebo group received placebo for 6 months. In this study, subjects from both groups (11 from fish oil, 12 from placebo group) received fish oil for 4 weeks. Compliance: serum phospholipids	23 subjects with atherosclerosis but without clinical symptoms 7 male/16 female age range: 43-75 years All subjects received fish oil.	LPS-induced production of procoagulant activity (measured as): Prothrombin fragment 1+2: ↓ in group 1 compared to group II at baseline (p=0.010); NS difference between groups at 4 weeks; change from baseline between groups significant (p<0.001). Fibrinopeptide A: ↓ in group I at baseline (p=0.049); NS difference between groups at 4 weeks.
Sorensen et al. 1994 *Fibrinolysis* 1994. 8:54-60 [Denmark]	Randomized, double-blind, parallel, controlled	7 weeks (from 30th to 37th week of gestation)	2.7 g/day n-3 FA from four 1 g capsules of fish oil (Pikasol) containing 32% EPA and 23% DHA) (fish oil group) olive oil group: 4 g/day olive oil Control group: no supplementation Compliance: capsule count and interview; in subset of subjects, the level of EPA-derived prostaglandins,	84 women in third trimester (30th week) of pregnancy, otherwise healthy mean age: 29.5 years (range: 23-41 years) n-3 FA: n=44 Control: n=40 (olive oil and no supplementation group combined)	FVII activity: NS change FVII antigen: NS change Thrombin-antithrombin III complexes: NS change F1+2: NS change Fibrinogen activity: NS change Fibrinogen concentration: NS change Fibrin degradation products (FbDP): ↑ significantly compared to controls (p <0.05) tPA antigen: NS change PAI-1 antigen: NS change tPA/PAI-1 antigen ratio: NS change

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
			thromboxane A_3, and prostanglandin I_3 also measured		PAI-1 activity: NS change Euglobulin: NS change t-PA activity: NS change Total HRG: NS change Total plasminogen: NS change Free plasminogen: NS change Plasma of α_2-antiplasmin: NS change Serum of α_2-antiplasmin: NS change Plasmin-antiplasmin complexes: NS change Dextran sulfate euglobulin fraction: NS change FXII-dependent fibrinolytic activity: NS change Urokinase-type fibrinolytic activity: NS change
Swahn et al. 1998 *Clin Drug Invest* 1998;15(6):473-482. [Sweden]	Randomized, double-blind, placebo-controlled trial.	12 weeks following an 8-w dietary run-in period.	1.4 g/day EPA + DHA ethyl esters (4 1-g capsules n-3/day provided by Norsk Hydro AS.) Control: corn oil Compliance: capsule counts, serum FA analysis	53 with a history of MI more than 3 months prior to enrollment and TG ≥ 2 mmol/l & TC ≤ 10 mmol/l. 80% subjects male 22 subjects not included in study (did not meet inclusion criteria.	Antithrombin III: ↑ vs. baseline (P<0.05) but NS between groups PAI-1 activity: NS PAI-1 antigen: NS t-PA antigen: NS
Terano et al. 1994 *Jpn. J. Geriatrics* 1994. 31:596-603 (ABSTRACT; foreign) [Japan]	Parallel	4 weeks (1 month)	0.25-0.5 g/day EPA from 3-6 capsules of fish oil concentrate Compliance: plasma phospholipid FA analysis	36 elderly subjects with no signs or symptoms of cerebrovascular disease; mean age of 78 years) Controls were younger subjects (number and mean age not reported)	Platelet aggregation to collagen: ↓ significantly at all fish oil doses and at the low and threshold dose of collagen (p<0.05 or p<0.01) Platelet aggregation to ADP: ↓ significantly at all fish oil doses and ADP concentrations (p<0.05 or p<0.01)
Toft et al. 1997 *Arterioscler. Thromb. Vasc. Biol.* 1997.	Randomized, double-blind, controlled	16 weeks	4 g/day EPA + DHA as ethyl esters (Omacor) Control: 4 g/day corn oil with 56%	78 hypertensive persons; mean age 53 years; 50 male, 28 female	PAI-1: NS ↑ (p=0.15) (significant ↑ in control group, p=0.009) tPA activity: NS ↓ (p=0.24) (significant ↓ in control group, p=0.0005)

Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
17:814-819 [Norway]			linoleic and 26% oleic acid Compliance: capsule count	Subjects taking cod liver oil supplements discontinued use 12 months before the study n-3 FA: n=38 Control: n=40	Fibrinogen level: ↑ (p=0.0001) (↑ also in control group, p=0.002) Coagulation factor VII: NS change (both groups) Platelet count: NS change (both groups)
Tomer et al. 1995 *Blood* 1995. 86:299a (ABSTRACT) [U.S.]	Randomized, double-blind, parallel	6 months	0.25 g/kg/day n-3 FA Compliance: not reported.	13 subjects with sickle cell disease and frequent painful episodes Controls: 10 normal African American subjects	Platelet procoagulant activity: ↑ compared to controls (as measured by increased binding of certain platelet receptors) RBC procoagulant activity: ↑ compared to controls (as measured by increased binding of certain receptors) Circulating platelet release products (Factor 4 and ß-thromboglobulin): ↑ significantly compared to controls Thrombin-antithrombin complexes: ↑ significantly compared to controls D-dimers: ↑ significantly compared to controls Prothrombin fragment: ↑ significantly compared to controls Plasmin-antiplasmin complexes: ↑ significantly compared to controls
Tremoli et al. 1995 *Am. J. Clin. Nutr.* 1995. 61:607-613 [Italy]	Randomized, double-blind, parallel	18 weeks (Group A) 18 weeks, 6 weeks at high dose followed by 12 weeks at the low dose (Group B) Subjects followed for an additional 24 weeks	4.5 g EPA + DHA (from 6 g n-3 FA capsules (Esapent) for 6 weeks followed by 2.25 g EPA + DHA (from 3 g n-3 FA capsules) for 12 weeks (Group B) 2.25 g EPA + DHA (from 3 g n-3 FA capsules (Esapent); each 1-g capsule contained 430 mg EPA and 320 mg DHA) plus 3 g/day	16 healthy volunteers 8 male/8 female Group A: n=8 Group B: n=8	Platelet aggregation to collagen: NS at 6 weeks for both groups; ↑ at 12 and 18 weeks compared to baseline values (p<0.001). Levels remained ↑ for 14 weeks after treatment ended. Platelet thromboxane B_2: NS at 6 weeks for both groups; ↓ at 12 and 18 weeks; significant only for group B at 12 weeks (p<0.05); levels returned to baseline within 4 weeks after treatment ended.

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Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
			olive oil (Group A)		Urinary excretion of thromboxane metabolites: NS at 6 weeks; ↓ after 12 weeks (-15% for group A and -19% for group B, p<0.001) compared to baseline values; ↓ maintained after 18 weeks and returned to baseline 4 weeks after treatment ended.
Turini et al. 1994 *Am. J. Clin. Nutr.* 1994. 60:717-724 [Canada]	Randomized, parallel, controlled	6 weeks	4.5 g/day EPA + DHA from 6 oz bottled liquid formula of fish oil (sardine oil) Control: 13.6 g/day vegetable oil (mixture of high oleic acid (6.3 g) safflower and soy oil) Compliance: phospholipid FA analysis	20 healthy male subjects average age: 26 years for controls; 27 years for fish oil subjects Fish oil: n=10 Control: n=10	Platelet aggregation to collagen: ↓ significantly in fish oil and control groups compared to baseline values (p<0.05)
Uauy et al. 1994 *J. Pediatr.* 124:612-620 [U.S.]	Randomized, controlled	57 weeks (follow-up from 40 to 57 weeks)	Not quantified. Infants were fed human milk (not randomized) or randomized to receive infant formula with varying amounts of n-3 FA: Formula A: corn oil (24.2% linoleic acid and 0.5% α-linolenic acid). Formula B: soy oil (20.8% linoleic acid and 2.7% α-linolenic acid). Formula C: soy oil + marine oil (0.3% DHA -similar to amount in human milk)	52 infants with low birth weights (between 1,000-1,500 g) and no major neonatal morbidity by the tenth day of life. Human milk: n=9 Formula A: n=13 Formula B: n=16 Formula: C: n=14 Reference group for infants fed human milk were birth-weight matched infants fed mother's milk since birth.	Bleeding time: ↑ in infants fed formula C at 37 weeks, but values did not exceed the normal upper limit (7 minutes); increased +28.7% and +28% compared to corn oil and soil oil, respectively (p<0.05). Platelet counts: NS change; all were within normal limits. Rotational membrane fluidity of intact RBCs: NS changes in any group.

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Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) Including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA))

Reference	Study design	Duration	Intake	Subjects	Results
				18 infants discharged early were not included in study.	
Valagussa et al. 1999 *Lancet* 1999;354:447-55 [Italy]	Randomized, control trial. Open label design. Multicenter (172)	189 weeks (3.5 years).	0.850-0.882 g/d (850-882 mg) of EPA + DHA as ethyl esters (n-3 group) (n-3 PUFAs group) 300 mg/d vitamin E (vitamin E group) n-3 + vitamin E group Control group Compliance: capsule counts	11,324 subjects. Patients surviving recent (≤ 3 months) MI were recruited from October 1993 through September 1998 from 172 centers (cardiology department and rehabilitation center). n-3 group: n=2836 patients vitamin E group: n=2830 patients n-3 + vit E group: n=2830 patients control group: n=2828 patients	Fibrinogen: NS change with n-3 or any other treatment.
Walker et al. 1999 *J. Obstr. Gynecol.* 19(1):56-58 [UK]	Randomized, parallel, single-blind	4 weeks	4 g/day fish oil (19% EPA, 12.8% DHA) (fish oil group) 4 g/day evening primrose oil (66-85% linoleic acid) aspirin aspirin + fish oil aspirin + evening primrose oil Control: no supplementation	80 healthy, non-pregnant females Aspirin: n=10 Evening primrose oil: n=10 Fish oil: n=10 Evening primrose + aspirin: n=10 Fish oil + aspirin: n=10 Control: n=10	Platelet AU binding: ↓ in fish oil only (NS), evening primrose only (NS), evening primrose + aspirin (NS), and fish oil + aspirin (p=0.04) groups; NS increase in aspirin only group

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Table 9
Clinical Trials Published 1992-2000 with Omega-3 fatty acids (EPA and DHA) including a Measurement of Factors Associated with Blood Clotting
(Shaded rows demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Yosefy et al. 1998 . *Human Hypertension* 1998. 0:S135-S139 Israel]	Crossover	1.9 weeks (13 days per treatment period), with a 3-week washout interval in between each treatment period Day 1, 5, 9, and 13 were fasting day (20 hrs/day) followed by refeeding	4.5 g/day EPA + DHA from 15 1-g capsules of Alsepa deep sea fish oil containing 180 mg EPA and 120 mg DHA); administered after fasting and followed by refeeding (Period I) Subjects fasted and then refeeded w/o fish oil ingestion (Period II) Subjects given fish oil as in period I but without fasting and refeeding (Period III) Compliance: plasma phospholipid FA analysis	20 hypertensive, mildly obese, dyslipidemic subjects mean age: 61.7 years (range: 40-71 years) 8 male/12 female	Platelet adhesion and aggregation on extracellular matrix (as a % of surface coverage): ↓ significantly during period I (p=0.0001); NS change in periods II and III. Platelet function: NS change Alpha-2-anti-plasmin: ↓ significantly during period I (-8.8%, p=0.01) Fibrinogen: NS change

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Axelrod et al. 1994 *Diabetes Care* 1994;17(1):37-44 [U.S.]	Randomized, Double-blind, Controlled trial.	6 weeks 6 week washout	2.5 g/d EPA+DHA 1.5g/d EPA 1 g/d DHA (SuperEPA capsules) Control: Safflower oil Compliance: Interviews mid-study	18 patients w/NIDDM and meeting HbA_{1c} and hemoglobin criteria. 9 test 9 control 2 dropouts Male:female ratio not given.	Fasting glucose: NS vs. safflower HbA_{1c}: ↑ with fish oil (4 weeks 0.56%, p=0.009; 6 weeks 0.72%,p=0.006) compared to safflower. At the end of washout period the differences were not significant between the groups.
Bagdade et al. 1996 *Diabetologia* 1996;39:487-491 [U.S]	Uncontrolled clinical study	8 weeks (2 months)	4.6 g/d of EPA and DHA as methyl esters (3.6 g/d of EPA and 1 g/d of DHA) (4.6 g/d of fish oil, Super-EPA) Compliance: Capsule count	9 IDDM subjects (6 females and 3 males) were recruited. Both IDDM and normal subjects were treated with fish oil. Fish oil: n=9	Fasting glucose: No significant change in plasma glucose levels after fish oil treatment (baseline 7.66 ± 5.22 mmol/l, fish oil 9.49 ± 5.44 mmol/l). Plasma fructosamine: No significant change in plasma glucose levels after fish oil treatment.
Bonnema et al. 1995 *Diab Nutr Metab* 1995;8:81-87 [Denmark]	Randomized, double-blind parallel trial.	24 weeks (6 months)	2.331 g/d EPA + DHA (1.407 g/d of EPA and 0.924 g/d of DHA, 6 Pikasol® capsules per day) (fish oil group) Olive oil group Compliance: Capsule count	27 type I and type II diabetic patients (15 men, 13 women) (insulin treated) without hypertension or hyperlipidemia were recruited. Fish oil group: n=14 Olive oil group: n=13	Fasting glucose: ↑ significantly ($p<0.05$) with fish oil (9.2 ± 4.1 mmol/l) compared to olive oil (8.6 ± 4.9 mmol/l). Glycated hemoglobin: NS ↓ in both groups.

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Fasching et al. 1996 *Horm Metab Res* 1996;28:230-236 [Austria]	Randomized, open, crossover trial.	2 weeks The subjects underwent a 2-month run-in phase. Then they were randomly assigned to either fish oil or Gemfibrozil for 2 weeks. After 2 weeks the treatments were reversed with a 6-week washout period between the treatments.	4.674 g/d EPA + DHA as triacylglycerols (2.890 g/d EPA and 1.764 g/d DHA, EPAX5000TG) (fish oil) Gemfibrozil 900 mg and equaled 25% of the ingested molar amount of n-3 FAs. Compliance: Plasma EPA and DHA levels.	10 hyperlipidemic subjects with NIDDM were recruited in the diabetes outpatient clinic.	Fasting glucose: NS ↑ during fish oil treatment (9.83 ± 3.50 mmol/l) compared to baseline (9.05 ± 3.44 mmol/l), but no change with Gemfibrozil. Insulin: NS ↑ with fish oil and Gemfibrozil treatment compared to baseline. C-peptide: NS ↑ with fish oil and Gemfibrozil treatment compared to baseline. AUC-glucose: No change with fish oil and Gemfibrozil treatment after ivGTT. AUC-insulin: NS ↓ with fish oil and Gemfibrozil treatment after ivGTT. AUC-C-peptide: NS ↓ with fish oil and Gemfibrozil treatment after ivGTT. Glycated hemoglobin: No change with fish oil or Gemfibrozil treatment on basal concentrations (baseline 7.4 ± 1.9, fish oil 7.5 ± 2.0 %).
Goh et al. 1997 *Diabetologia* 1997;40:42-52 [Canada]	Randomized, double-blind, crossover trial.	12 weeks (3 months) on each treatment (fish oil or linseed oil) with an initial 3-month olive oil placebo period.	35 mg/kg/d of EPA+DHA (fish oil group) 35 mg/kg/d of linolenic acid: Linseed oil group Olive oil: placebo Compliance: EPA and DHA levels in lipoproteins, pill counts, telephone or personal interview	28 NIDDM patients were recruited from the outpatient Metabolic Clinic at the University of Alberta Hospital.	Fasting glucose: Not influenced by the type of n-3 fatty acids consumed. Insulin: Not influenced by the type of n-3 fatty acids consumed. Glucagon: Not influenced by the type of n-3 fatty acids consumed.

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Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Haban et al. 1998 *Bratisl Lek Listy* 1998;99(1):37-42 (ABSTRACT, foreign) [Slovakia]	Clinical trial.	4 weeks (28 days)	2.85 g/d of EPA+DHA (10 capsules of MAXEPA®) (1.7 g/d of EPA and 1.15 g/d of DHA) Compliance: Serum EPA and DHA levels	21 NIDDM patients with dyslipoproteinemia type IV were treated with n-3 PUFA.	Fasting glucose: No significant change (baseline 8.906 ± 0.893 mmol/l, after treatment 9.324 ± 0.750 mmol/l) Glycated hemoglobin: No significant change (baseline 7.092 ± 0.675 mmol/l, after treatment 8.264 ± 0.528 mmol/l).
Luo et al. 1998 *Diabetes Care* 1998;21(5):717-724 [France]	Randomized, double-blind, crossover trial.	8 weeks (2 months) The subjects first underwent a 2-month dietary run-in period. Then they were randomly assigned to either fish oil of sunflower oil treatment for 2 months. After 2 month period the treatments were switched for another 2 months with a 2-month washout period between the treatments.	1.8 g/d n-3 PUFA from 6 g/d of fish oil (fish oil group) 6 g/d of sunflower oil (sunflower oil group) Compliance: FAs composition in plasma and erythrocyte membrane phospholipids.	10 men with NIDDM were recruited from the outpatient clinic of the Department of Diabetes.	Fasting glucose: NS ↑ with fish oil (baseline 10.86 ± 1.0 mmol/l, fish oil 11.06 ± 1.0 mmol/l) and a ↓ with sunflower oil treatment (baseline 11.50 ± 0.90 mmol/l, sunflower oil 11.23 ± 1.20 mmol/l). Fasting insulin: A ↓ with fish oil (baseline 84 pmol/l, fish oil 63 pmol/l) and with sunflower oil treatment (baseline 91 pmol/l, sunflower oil 76 pmol/l). Glycated hemoglobin: A ↓ with fish oil (baseline 8.8 ± 0.6%, fish oil 8.7 ± 0.5%) and an ↑ with sunflower oil treatment (baseline 8.6 ± 0.5%, sunflower oil 8.9 ± 0.6%). Basal plasma glucose and insulin were similar after 2 months of treatment with fish oil and sunflower oil. Basal hepatic glucose production was similar after both treatments.

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
McGrath et al. 1996 *Atherosclerosis* 1996;121:275-283 [UK]	Randomized, double-blind, placebo controlled crossover trial.	6 weeks on each treatment with a 6 week washout period between the treatment.	3 g/d of EPA + DHA (10 capsules of Maxeps; 1.8 g/d EPA, 1.2 g/d (DHA) (fish oil group) Olive oil: placebo group Compliance: Pill count, platelet membrane FA analysis.	23 NIDDM subjects (20 males and 3 females) were recruited. Diabetes was controlled by either diet alone or diet + hypoglycemic drugs.	Fasting glucose: NS ↑ (p=0.06) with fish oil (11.4 (CI 9.7-13.3) mmol/l), when compared to baseline (10.2 (CI 8.9-11.4) mmol/l). No changes with olive oil. No differences between the groups. Glycated hemoglobin: No effect of fish oil or olive oil. (baseline 9.6% (CI 8.8-10.4%); fish oil 9.9% (CI 8.5-11.3%). Glycosylated LDL: No effect of fish oil or olive oil.
McManus et al. 1996 *Diabetes Care* 1996;19(5):463-466 [Canada]	Randomized, double-blind, placebo-controlled crossover trial.	12 weeks (3 months) on each treatment Total 9-month: the subjects underwent a 3-month run-in period with olive oil. Then they were randomly assigned to either FO or LO for 3 months. After 3 months the treatments were reversed.	35 mg/kg of EPA + DHA combined (FO group) 35 mg/kg of olive oil (placebo run-in period) 35 mg/kg of LO Compliance: Capsule count	11 NIDDM patients (3 women and 8 men) were from a tertiary care diabetic center. None of the subjects were taking hypoglycemic drugs.	Fasting glucose: No significant difference between the three treatments (baseline 8.0 ± 0.7; placebo 7.6 ± 0.6; LO 7.9 ± 0.8; FO 8.2 ± 0.9 mmol/l). Glycated hemoglobin: ↑ significantly with placebo compared to baseline, although the mean was within the normal range. No significant difference between the three treatments (baseline 0.058 ± 0.004; placebo 0.061 ± 0.004; LO 0.066 ± 0.006; FO 0.065 ± 0.006). Units not reported. Fasting insulin: No significant difference between the three treatments, but a trend towards lowering the fasting insulin was observed in the LO and FO group. Insulin sensitivity: A non-significant ↓ (p=0.06) with FO. No change with LO. Glucose effectiveness: No significant change with LO or FO. Acute insulin response to glucose: No effect of LO or FO. Glucose tolerance: No significant change with LO or FO.

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
McVeigh et al. 1994 *Arterioscler Thromb* 1994;14:1425-1429 [Ireland]	Randomized, double-blind, placebo-controlled, crossover trial.	6 weeks on fish oil or placebo followed by 6 weeks of washout period. After the washout period the treatments were switched for 6 weeks.	3 g/d EPA + DHA (1.8 g/d EPA, 1.2 g/d DHA; MAXEPA) (fish oil) Placebo: olive oil. Compliance: Capsule count, platelet membrane FA analysis.	20 (16 men, 4 females) subjects with NIDDM were recruited from diabetic clinic in Belfast. Diabetes was controlled with diet alone or diet + hypoglycemic drugs. Subjects were not taking any cardiovascular drugs.	Fasting glucose: NS ↑ with fish oil (11.4 (CI 9.7- 13.3) mmol/l, p=0.07) compared to baseline (10.2 (CI 8.9-11.4) mmol/l).
Morgan et al. 1995 *Diabetes Care* 1995;18(1):83-86 [U.S.]	Randomized, double-blind, trial.	12 weeks of treatment Initial baseline period 4 week post-treatment phase	10.098 g/d EPA + DHA (5.184 EPA, 4.914 DHA, from 18 g of fish oil) 5.049 g/d EPA + DHA (2.592 g/d EPA, 2.457 g/d DHA, from 9 g of fish oil) 9 g/d corn oil 18 g/d corn oil Compliance: Capsule count	40 (18 men, 22 women) hyperlipidemic patients with NIDDM were recruited. 18 g/d fish oil group: n=10 9 g/d fish oil group: n=10 18 g/d corn oil group: n=10 9 g/d corn oil group: n=10	Fasting glucose: No significant differences between the groups or over time within the group (fish oil: 0 week 10.4 ± 3.4, 6 weeks 12.2 ± 3.5, 12 weeks 11.6 ± 3.4 mmol/l; corn oil: 0 week 11.6 ± 3.5, 6 weeks 12.1 ± 3.3, 12 weeks 12.4 ± 3.5 mmol/l). Glycated hemoglobin: No significant differences between the groups or over time within the group No significant differences between the groups or over time within the group (fish oil: 0 week 7.3 ± 1.5, 6 weeks 7.6 ±1.5, 12 weeks 7.7 ± 1.7 mmol/l; corn oil: 0 week 7.6 ± 1.7, 6 weeks 7.7 ± 1.9, 12 weeks 7.8 ± 2.0 mmol/l).
Nakamura et al. 1998 *In vivo* 1998;12:311-314 [Japan]	Clinical trial.	12 weeks (3 months)	1.8 g/d EPA (1800 mg/d of EPA ethyl esters) 0.9 g/d EPA (900 mg/d of EPA ethyl esters) Compliance: Plasma EPA concentration	10 subjects with NIDDM. Some subjects were treated for hyperlipidemia. EPA 1800 mg/d: n=4 EPA 900 mg/d: n=6	Glycated hemoglobin: No significant ↓ was observed with EPA supplementation.

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Rivellese et al. 1996 *Diabetes Care* 1996;19(11):1207-1213 [Italy]	Randomized, double-blind, placebo controlled with a parallel group sequence.	24 weeks (6 months) The subjects underwent a 4-week washout period during which they were stabilized on isoenergetic diet and hypoglycemic treatment and all hypolipidemic drugs were withdrawn. After the washout period all subjects consumed placebo capsules for 3 weeks during the run-in period. After the run-in period treatments were assigned to the subjects	2.5 g/d EPA + DHA (0.96 g/d EPA and 1.59 g/d DHA) for the first 2 months. The dose was reduced to 1.7 g/d EPA + DHA (0.64 g/d EPA and 1.06 g/d DHA) for the remaining 4 months) (fish oil group) Placebo: olive oil (the olive oil dose was also reduced after 2 months0. Compliance: RBC phospholipid FA analysis.	16 hypertriglyceridemic patients with NIDDM were recruited from diabetic clinic. Some patients had moderate arterial hypertension. Multicenter trial. Fish oil: n=8 Placebo: n=8	Fasting glucose: No significant change with fish oil (baseline 10.2 ± 1.2 mmol/l, 6 months 10.9 ± 0.5 mmol/l) Postprandial glucose: No significant change with fish oil (baseline 12.9 ± 1.6 mmol/l, 6 months 12.1 ± 1.7 mmol/l) Fasting insulin: Significant ↑ ($p<0.01$) with fish oil (105.6 ± 15.6 pmol/l) compared to baseline (75 ± 9 pmol/l). The net change after fish oil supplementation was not significantly different from the net change after placebo. Postprandial insulin: No significant change with fish oil or placebo and no significant differences between the groups. Glycated hemoglobin: Slight but non-significant ↑ in both groups (fish oil 1%, placebo 0.7%). No group differences in the net change.
Rossing et al. 1996 *Diabetes Care* 1996;19(11):1214-1219. [Denmark]	Randomized, double-blind parallel placebo controlled trial.	52 weeks (1 year)	4.6 g/d of EPA + DHA (2 g/d EPA and 2.6 g/d DHA from 21 ml of cod-liver oil given as Eskisol Fish oil Emulsion) (cod-liver oil group) 21 ml of olive oil (olive oil group) Compliance: Fatty acids in platelets.	29 IDDM patients with persistent albuminuria were recruited from outpatient clinic at Steno Diabetes Center during 1992. Cod-live oil: n=14 Olive oil: n=15	Glycated hemoglobin: NS change in both groups. Data on endpoints assessing kidney function is not reported in this summary.

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Sheehan et al. 1997 *Am J Clin Nutr* 1997;66:1183-1187 [U.S.]	Controlled sequential study	4 weeks on fish oil treatment followed by 4 weeks on fish oil + pectin followed by 4 weeks of follow-up control period. The fish oil treatment period was considered a run-in period for fiber treatment period.	8 g/d n-3 FAs from 20 g/d of fish oil (MaxEPA) 15 g/d pectin Compliance: FA analysis	15 (12 men, 3 women) nonobese subjects with NIDDM were recruited. Diet or diet + oral agents or diet + insulin was used to control diabetes. All subjects were treated with fish oil for 4 weeks followed by fish oil + pectin followed by control period. During the control period the subjects did not receive fish oil or pectin treatment and followed their diabetic diet.	Fasting glucose: NS change with fish oil (7.88 ± 2.6 mmol/l), fish oil + fiber (7.72 ± 2.8 mmol/l) compared to baseline (7.72 ± 2.7 mmol/l). Postprandial glucose: NS change with fish oil (10.77 ± 4.9 mmol/l), fish oil + fiber (10.44 ± 5.1 mmol/l) compared to baseline (10.38 ± 5.3 mmol/l). Fasting insulin: NS change with fish oil (159 ± 102 pmol/l), fish oil + fiber (131 ± 71 pmol/l) compared to baseline (140 ± 81 pmol/l). Glycated hemoglobin: NS change with fish oil (6.5 ± 2.0%), fish oil + fiber (6.7 ± 2.6%) compared to baseline (7.0 ± 2.7%). Glycated albumin: NS change with fish oil (2.2 ± 1.0%), fish oil + fiber (2.7 ± 1.8%) compared to baseline (2.3 ± 1.7%).
Sirtori et al. 1997 *Am J Clin Nutr* 1997;65:1874-81 [Italy]	Randomized, double-blind, placebo-controlled trial. Multicenter.	24 weeks (6 months) Run-in period was ≥ 4 weeks. 2 months on high dose of EPA+DHA 4 months on low-dose of EPA+DHA	2.580 g/d (2580 mg/d) of EPA+DHA as ethyl esters for 2 months (high dose). (Eskapent capsules) 1530 mg/d EPA 1050 mg/d DHA 1.720 g/d (1720 mg/d) of EPA+DHA as ethyl esters for 4 months (low dose) 1020 mg/d EPA 700 mg/d DHA Compliance: capsule counts	935 subjects Treatment: 470 subjects Placebo: 465 subjects Subjects with either type IIB or IV hyperlipoproteinemias with at least one additional risk factor such as NIDDM, arterial hypertension or impaired glucose tolerance were recruited from 83 clinical groups.	Fasting glucose: No significant change with n-3 (baseline 8.28 ± 2.17; 8 months 8.16 ± 2.05 mmol/l) or with placebo (baseline 8.14 ± 2.06; 8 months 7.83 ± 2.05 mmol/l). Glycated hemoglobin: No significant change with n-3 (baseline 7.25 ± 1.56; 8 months 7.05 ± 1.64 mmol/l) or with placebo (baseline 7.14 ± 1.63; 8 months 6.89 ± 1.42 mmol/l). Insulinemia: No significant change with n-3 (baseline 115.9 ± 64.0; 8 months 112.0 ± 50.7 mmol/l) or with placebo (baseline 111.6 ± 57.2; 8 months 119.7 ± 84.5 mmol/l). Oral glucose tolerance: No effect of n-3 FAs.

Table 10
Safety of Omega-3 Fatty Acids (EPA and DHA) - Clinical Trials Published 1992-2000 Examining Glycemic Control
Shaded Rows Demonstrate an effect of Omega-3 Fatty Acids (EPA and DHA)

Reference	Study design	Duration	Intake	Subjects	Results
Sirtori et al. 1998 *Atherosclerosis* 1998;137:419-427 [Italy]	Open phase. Multicenter.	24 weeks (6 months)	1.720 g/d (1720 mg/d) of EPA+DHA as ethyl esters for 6 months; 1020 mg/d EPA 700 mg/d DHA; ESAPENT®) Compliance: EPA and DHA levels in plasma and RBCs	863 subjects were given fish oil treatment. Subjects with either type IIB or IV hyperlipoproteinemia with at least one additional risk factor such as NIDDM, arterial hypertension or impaired glucose tolerance were recruited from 63 clinical groups. 5 subjects (total 868) withdrew because of worsening of NIDDM.	Fasting glucose: No difference in fasting glucose at the end of 12 months of the study in patients from either the n-3 or placebo group in phase I. NIDDM patients showed no changes after 1 year of n-3 treatment or 6 months for those who got placebo for the first 6 months. Glycated hemoglobin: NIDDM patients showed no changes after 1 year of n-3 treatment or 6 months for those who got placebo for the first 6 months. Insulinemia: NIDDM patients showed no changes after 1 year or n-3 treatment or 6 months for those who got placebo for the first 6 months.

Summary of LDL Cholesterol Concentrations at Baseline, Interim Time Periods, and Study Completion For EPA/DHA Supplementation Studies of 12 Weeks Duration

Reference (no. of subjects)	Intake (g/day)	LDL Cholesterol (mmol/L) at WEEKS:							% change from baseline
		Baseline	3	4	6	8	9	12	
Baker and Najadah (1996) (n=20)	0.285 g pre-men[1]	4.11		4.25		3.75		3.65	-11%
	0.285 g post-men[1]	4.25		4.21		4.44		4.17	-1.9%
Adler and Holub (1997) (n=10)	3.6 g	4.42	4.75		4.78		4.94	4.81	8.8%
Morgan et al. (1995) (n=20)	7.5 g[2]	3.71			4.04			4.08	10%

NOTE: Blank cells indicate that data were not provided at that timepoint.
[1]Pre-menopausal (premen) and post-menopausal (postmen)
[2]Mean intake of the two study groups, 5 g/day and 10 g/day, whose results were combined by the authors

Summary of LDL Cholesterol Concentrations at Baseline, Interim Time Periods, and Study Completion For EPA/DHA Supplementation Studies of at Least 12 Months Duration

Reference	Intake (g/day)	LDL Cholesterol (mmol/L) at MONTHS:						% change from baseline
		Baseline	1	6	12	18	24	
Von Schacky et al. (1999) (n=111)	3.4 g (months 1-3) 1.7 g (months 4-24)	4.10	4.05	4.30	4.20	4.10	3.85	- 6.1%
Rossing et al. (1996) (n=14)	4.6 g	2.93		3.41	3.52			20%

NOTE: Blank cells indicate that data were not provided.

Figure 5

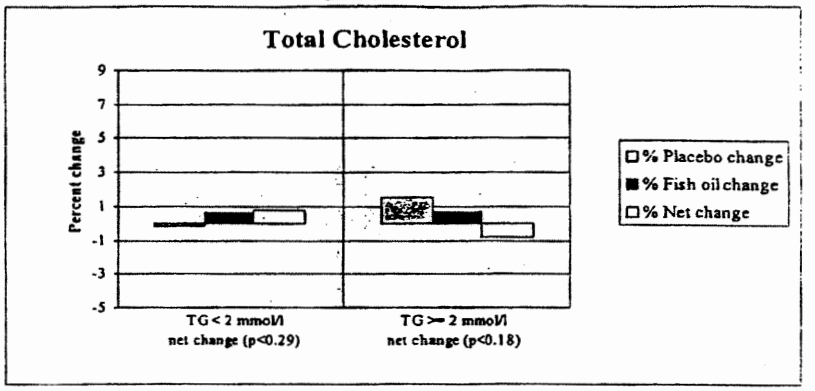

Figure 6

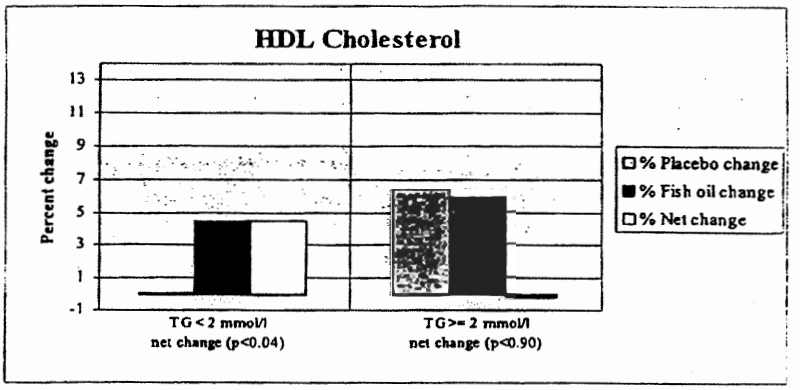

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Adler and Holub 1997 *Am J Clin Nutr* 1997;65:445-50 [Canada]	Randomized, single-blind, placebo-controlled, trial.	12 weeks 3 weeks run-in period before 12 week treatment period.	3.6 g/d of EPA+DHA (Nupulse, fish oil capsules) 2.160 g/d EPA, 1.440 g/d DHA. Four groups: 5) Fish oil + garlic placebo 6) garlic + fish oil placebo 7) fish oil + garlic 8) garlic placebo + fish oil placebo Compliance: serum phospholipid fatty acid analyses, capsule count.	46 hypercholesterolemic men. Fish oil: 10 subjects Garlic: 12 subjects Fish oil + garlic: 13 subjects Placebo: 11 The inclusion criteria was total cholesterol > 200 mg/dl.	LDL: increased significantly with fish oil at 3 weeks and persisted until 12 weeks. At 3 weeks, significant † (4.75 ± 0.32 mmol/l, +8.5%) compared to baseline (4.42 ± 0.88 mmol/l p < 0.05) and placebo (4.19 ± 0.25 mmol/l). At 6 weeks, significant † (4.78 ± 0.41 mmol/l) compared to baseline (4.42 ± 0.88 mmol/l, p < 0.05) and placebo (4.18 ± 0.27 mmol/l, p<0.05). At 9 weeks, significant † (4.84 ± 0.43 mmol/l) compared to baseline (4.42 ± 0.88 mmol/l, p < 0.001) and placebo (4.19 ± 0.28 mmol/l, p<0.05). At 12 weeks, significant † (4.61 ± 0.40 mmol/l) compared to baseline (4.42 ± 0.88 mmol/l, p < 0.05) and placebo (4.26 ± 0.31 mmol/l, p<0.05). Insignificant changes in the placebo group during the study.

Ex

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Axelrod et al. 1994 *Diabetes Care* 1994;17(1):37-44 [U.S.]	Randomized, Double-blind, Controlled trial.	6 weeks 6 week washout	2.5 g/d EPA+DHA 1.5g/d EPA 1 g/d DHA (SuperEPA capsules) Control: Safflower oil Compliance: interviews mid-study	18 patients w/NIDDM and meeting HbA1c and hemoglobin criteria. 9 test; 9 control	LDL: NS effect of fish oil (data not given).

Ex

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Baker and Najadah 1996 *Sports Med Training and Rehab* 1996;6:287-297 [Kuwait]	Randomized, controlled trial	12 weeks	0.285 g/d of EPA+DHA (Maxepa, 171 mg/d EPA and 114 mg/d DHA) (Fish oil group) Exercise group Exercise + fish oil group Control group (daily lifestyle) Compliance: Not measured	70 women selected from a larger voluntary cohort. The subjects did not have CHD and were sedentary. Premenopausal group: 35 women Postmenopausal group: 35 women The pre and postmenopausal women were divided into 4 groups Exercise group: 20 women (pre + postmenopausal) Exercise + fish oil group: 20 women (pre + postmenopausal) Fish oil group: 20 women (pre + postmenopausal) Control group: 10 women (pre + postmenopausal)	LDL: premenopausal: NS ↓ at 4 (4.25 ± 0.71 mmol/l) and 8 weeks (3.75 ± 1.06 mmol/l) but significantly at 12 weeks (3.65 ± 0.87 mmol/l, p≤0.05) with fish oil compared to baseline (4.11 ± 0.95 mmol/l). postmenopausal: NS ↓ at 4 (4.21 ± 0.76 mmol/l) and 8 weeks (4.44 ± 0.74 mmol/l) but significantly at 12 weeks (4.17 ± 0.74 mmol/l, p≤0.05) with fish oil compared to baseline (4.25 ± 0.58). In the control group insignificant ↑ in premenopausal women compared to baseline (baseline 3.17 ± 0.53, 4 weeks 3.23 ± 1.03, 8 weeks 3.25 ± 0.37, 12 weeks 3.60 ± 0.18 mmol/l). In the control group NS change in postmenopausal women compared to baseline (baseline 4.12 ± 0.92, 4 weeks 4.15 ± 1.06, 8 weeks 4.06 ± 1.08, 12 weeks 4.12 ± 1.00 mmol/l).

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Balestrieri et al. 1996 *Recenti Progressi in Medicina* 1996;87(3):102-105 [Italy]	Randomized, double-blind, controlled, cross over.	4 weeks of each treatment separated by a 4 week washout	5.1 g/d of EPA+DHA (Esapent fish oil capsules, 6g fish oil) 2.55 g/d EPA 2.55 g/d DHA 6 g/d of olive oil in control group Compliance: Not reported	14 patients with familial hypercholesterolemia (FH). Three had established CHD. All maintained Step 1 AHA diet and treatment with simvastatin throughout the trial. Fish Oil : 7 subjects Olive Oil: 7 subjects	LDL: no significant variation (228 ± 46 vs. 228 ± 50 mg/dl) compared to baseline.
Barstad et al. 1995 *Blood Coagulation and Fibrinolysis* 1995;6:374-381 [Norway]	Open study (Not randomized, not blinded, not controlled)	12 weeks	2.4 g/d n-3 FAs (Triomar capsules containing 60% n-3, 30% EPA, 20% DHA) Control: none Compliance: method not reported.	15 healthy males	LDL: NS effect of n-3 FAs
Berrettini et al. 1996 *Thrombosis & Haemostasis* 1996;75(3):395-400 [Italy]	Randomized Double-blind, controlled trial.	16 weeks	3 g/d EPA+DHA ethyl esters EPA:DHA = 1.46 (Seacor capsules) Control: corn oil	39 w/ chronic vascular atherosclerotic diseases. Test: 20; Control: 19 1 dropout placebo group Compliance: Capsule count	LDL: ↑ (+33%, p=0.0013) after 2 weeks; slow ↓ thereafter (+27%, p=0.0013 after 16 weeks). Over all significant ↑ (p=0.0089) with fish oil.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Chin and Dart 1994 Clin Exp Pharma Physiol 1994;21:749-55 [Australia]	Randomized, patient-blind, placebo controlled study design.	4 weeks (28 days)	5.88 g/d EPA + DHA (3.56 g EPA and 2.32 g DHA, given as 20 g/d maxEPA capsules, which is equivalent to approximately 340 g of mackerel or 500 g salmon). Placebo was a mixture of celestial, safflower and olive oils given in capsules at 20 g/d. This mixture has previously been shown to have no effect on forearm vascular reactivity.	23 subjects 7 normal TC controls (males, mean age 52.3 ± 3.3 years). 9 high-TC controls (7 males and 2 females, mean age 49.6 ± 4.2 years); 5 were previously untreated and 4 had tx (simvastin and/or questran) withdrawn from a minimum of 4 weeks prior to study. 6 hypercholesterolemic subjects (6 males and 1 female; mean age 44.3 ± 4.9 years) given fish oil. These subjects were either previously untx, or their lipid-lowering therapy was withdrawn for a minimum of 4 weeks, during which time they consumed mixed oil placebo capsules before switching to fish oil capsules. 6 (4 males, 2 females) untreated subjects were treated with lipid lowering drugs for 4 weeks.	LDL: Mean LDL levels were higher (89%) at the time of the study in hypercholesterolemic subjects compared to the control subjects. Dietary fish oil (6.97 ± 0.73 mmol/l) had no effect on LDL levels in hypercholesterolemic subjects compared to baseline (6.29 ± 0.38 mmol/l). ↓ significantly with lipid-lowering therapy.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Christensen et al. 1995 *Nutr Res* 1995;15(1):1-8 [Denmark]	Randomized, Double-blind, Placebo-controlled trial.	16 weeks	4.3 g/d EPA+DHA (Pikasol triglyceride capsules) (fish oil group) Control: corn oil Compliance: Plasma FAs analysis	19 patients discharged from Aalborg Hospital Dept Cardiology with diagnosis of ventricular tachyarrhythmia. Test: 9; Control: 10	LDL: NS ↑ with fish oil (4.9 mmol/l) compared to baseline (4.5 mmol/l). Significant ↓ with control (5.4 mmol/l) compared to baseline (6.1, p<0.05)
Clandinin et al. 1997 *Biochimica et Biophysica Acta* 1997;1346:247-252 [Canada]	Randomized, double-blind, placebo-controlled, crossover trial. All subjects were first asked to consume placebo (olive oil) for 3 months and then randomized to either n-3 from fish oil or n-3 from flaxseed oil for 3 months. The treatments were then switched for the next 3 months.	12 weeks (3 months) on fish oil 3 months on flaxseed oil 3 months on olive oil (placebo)	35 mg/kg bw/d of EPA+DHA (fish oil group) 35 mg/kg bw/d of 18:3n-3 from flaxseed (flaxseed oil group) Olive oil (placebo group) Compliance: phone call	26 healthy, normal, free-living, non-smoking subjects.	LDL: NS ↑ with fish oil (2.73 ± 0.15 mmol/l), flaxseed oil (2.64 ± 0.13 mmol/l) and olive oil (2.57 ± 0.15 mmol/l) compared to baseline (2.22 ± 0.15 mmol/l).
Conquer and Holub 1996 *J Nutr* 1996;126:3032-3039 [Canada]	Randomized, double-blind, controlled study.	6 weeks (treatment) 3 week washout period.	1.62 g/d DHA (from algae, encapsulated triglyceride oil, DHASCO®) Control group: vegetable oil Compliance: capsule count, serum and platelet phospholipid FA levels.	24 young healthy vegetarians (12 males, 12 females) from the Guelph community who reported no intake of meat for the past 6 months were recruited. DHA group: 12 subjects (6 males and 6 females) Control group: 12 subjects (6 males and 6 females)	LDL: NS ↓ at 3 (1.97 ± 0.21 mmol/l) and 6 weeks (1.86 ± 0.17 mmol/l) compared to baseline (1.99 ± 0.18 mmol/l) with DHASCO. NS ↓ at 3 weeks (2.02 ± 0.18 mmol/l), but significant ↑ at 6 weeks (2.29 ± 0.18 mmol/l) compared to baseline (2.10 ± 0.18 mmol/l) in the control group.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Davidson et al. 1997a *Journal of American College of Nutrition* 1997;16(3):236-243 [U.S.]	Randomized, double-blind, placebo-controlled study with 3 parallel groups.	6 weeks 6 week dietary run-in period 4 weeks placebo run-in period followed by 6 weeks on treatment with placebo or DHA.	2.5 g/d of DHA as triglyceride (6 g/d of DHASCO®, produced from microalgae) 1.25 g/d of DHA + placebo (3 g/d of DHASCO) 6 g/d of placebo (mixture of corn and soybean oil) Compliance: Measured (method not specified)	26 subjects with CHL (LDL 130-220 mg/dl; TG 150-400 mg/dl) were recruited from Chicago. 2.5 g/d DHA group: 9 subjects 1.25 g/d group: 9 subjects Placebo group: 8 subjects (1 subjects dropped out due to personal reasons)	LDL: ↑ significantly (13.6 ± 2.3%, p<0.001) in the 2.5 g/d DHA group. NS changes from baseline in the placebo (-2.4 ± 4.7%) and in 1.25 g/d DHA groups (+9.3 ± 5.6%). A dose-dependent ↑ in LDL was observed with increasing doses of DHA (r=0.35, p<0.09).
Eritsland et al. 1994a *Fibrinolysis* 1994;8:120-125 [Norway]	Randomized Controlled trial, but no placebo	26 weeks (6 months)	4.4 g EPA+DHA ethyl esters (4 g K85 highly concentrated fish oil) Control: Medication alone (ASA or Warfarin) 2X2 factorial design: 1. ASA (16) 2. ASA + n-3 (15) 3. Warfarin (13) 4. Warfarin+n-3 (14) Compliance: Not reported	58 w/ coronary artery disease that underwent bypass grafting. TG ≥ 1.5 mmol/l. Test: 29 Control: 29 90+% males each group.	LDL: An average, ↓ (-0.41 mmol/l) with fish oil compared to baseline (5.38 (range 4.39-7.67) mmol/l). In control group an average ↓ (- 0.37 mmol/l) compared to baseline (5.23 (range 2.36-8.96) mmol/l). No significant differences between the groups.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Eritsland et al. 1994b Scand J Clin Lab Invest 1994;54:273-280 [Norway]	Randomized controlled trial	24 weeks (6 months)	3.4 g/day EPA+DHA (K 85 fish oil concentrate, 4 g of fish oil) 2.07 g/day EPA 1.28 g/day DHA Control group Compliance: FA analysis	57 patients suffering from stenosing coronary artery disease who had undergone coronary artery bypass grafting (CABG) with elevated serum TG levels, but not defined to have diabetes All patients received either aspirin or warfarin Fish oil group: 28 patients Control group 29 patients	LDL: no significant differences compared to control.
Eritsland et al. 1995a *Am J Clin Nutr* 1995;61:831-6 [Norway]	Randomized Controlled trial, no placebo (Not blinded)	36 weeks (9 months)	3.4g/d EPA+DHA 2.1 g/d EPA 1.3 g/d DHA (4 g/d Omacor fish oil) Control: Unsupplemented Compliance: Serum FAs	511 patients whstenosing coronary artery disease who were undergoing bypass surgery. 260 test 251 control (99 drop outs) @85% males	LDL: NS ↑ with fish oil (5.11 ± 1.18 mmol/l) compared to baseline 4.59 ± 0.97 mmol/l). NS ↑ (5.03 ± 1.25 mmol/l) in the control group compared to baseline 4.61 ± 1.09 mmol/l). No significant differences between groups

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Eritsland et al. 1996 *Am J Cardiol* 1996;77:31-36 [Norway]	Randomized, controlled trial.	52 weeks (1 year)	3.32 g/d of EPA+DHA (Omacor® fish oil capsules as ethyl esters) EPA=2.04 g/d DHA=1.28 g/d Treatment: fish oil capsules + either warfarin or aspirin Control: warfarin or aspirin Compliance: serum phospholipid fatty acid analyses, capsule count.	556 patients admitted for coronary artery bypass grafting. Treatment: 289 subjects Control: 267 subjects	LDL: Significant ↑ with fish oil (198 ± 45 mg/dl) compared to baseline (180 ± 41 mg/dl, $p < 0.001$). Significant ↑ in the control group (195 ± 48 mg/dl) compared to the baseline (181 ± 44 mg/dl, $p < 0.001$). No significant difference between groups
Fasching et al. 1996 *Horm Metab Res* 1996;28:230-236 [Austria]	Randomized, open, crossover trial.	2 weeks The subjects underwent a 2-month run-in phase. Then they were randomly assigned to either fish oil or Gemfibrozil for 2 weeks. After 2 weeks the treatments were reversed with a 8-week washout period between the treatments.	4.674 g/d EPA + DHA as triacylglycerols (2.890 g/d EPA and 1.784 g/d DHA, EPAX5000TG) (fish oil) Gemfibrozil 900 mg and equaled 25% of the ingested molar amount of n-3 FAs. Compliance: Plasma EPA and DHA levels.	10 hyperlipidemic subjects with NIDDM were recruited in the diabetes outpatient clinic. Initially 13 subjects were recruited but 3 subjects were excluded for the following reasons: one subject developed acute pancreatitis, one subject had problems with venous blood sampling and one patient left the country.	LDL: No significant ↓ with fish oil (baseline 4.86 ± 1.22 mmol/l, fish oil 4.78 ± 1.24 mmol/l), but a 15% ↓ ($p<0.01$) with Gemfibrozil treatment.
Fisher et al. 1998 *J Lipid Res* 1998;39:388-401 [U.S.]		3 weeks (21 days) The subjects were fed safflower oil for 21 days and then fish oil for 21 days with a 1-month washout period between the two diets.	0.249 g/d (249 mg/g of EPA +DHA (1 g menhaden oil capsules)) (fish oil group) <1 mg/g of n-3 oils from safflower (safflower group) Compliance: Not reported	5 NIDDM subjects (1 female and 4 males) were recruited and admitted to the Clinical Research Center. The subjects received a weight maintenance diet for the duration of the study.	LDL: No significant ↕ with fish oil (average: safflower 77 mg/dl, fish oil 107 mg/dl, $p<0.08$)

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
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Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Goh et al. 1997 *Diabetologia* 1997;40:42-52 [Canada]	Randomized, double-blind, crossover trial.	12 weeks (3 months) on each treatment (fish oil or linseed oil) with an initial 3-month olive oil placebo period. The subjects were assigned to a high polyunsaturated/saturated group (high P/S, n=10) or a low polyunsaturated/saturated group (low P/S, n=18) based on 7 day diet analysis. They were then given olive oil for 3 months. After the placebo period the treatments were started in each group.	35 mg/kg/d of EPA+DHA (fish oil group) 35 mg/kg/d of linolenic acid: Linseed oil group Olive oil: placebo Compliance: EPA and DHA levels in lipoproteins, pill counts, telephone or personal interview	28 NIDDM patients were recruited from the outpatient Metabolic Clinic at the University of Alberta Hospital.	LDL: Fish oil and linseed oil did not affect the plasma LDL levels. Low P/S group: fish oil 4.08 ± 0.23, linseed oil 3.98 ± 0.31, olive oil 3.79 ± 0.19 mmol/l. High P/S group: fish oil 3.35 ± 0.23, linseed oil 3.20 ± 0.20, olive oil 3.33 ± 0.21 mmol/l.
Goode et al. 1997 Circulation 1997;96:2802-2807 [UK]	Randomized, double-blind, placebo controlled trial	12 weeks (3 months)	3 g/day EPA+DHA (Maxepa fish oil capsules, assumed 1 g capsules for a total of 10 g/day oil) 1.8 g/day EPA, 1.2 g/day DHA Control group: olive oil (assume 1 g capsules for 10 g/day oil) Compliance: Pill count	28 subjects recruited either through the hospital (treatment) or by advertisement (control) Study group: 8 hypercholesterolemic (HC) patients and 6 healthy age-sex matched control individuals Control group: 8 hypercholesterolemic (HC) patients and 6 healthy age-sex matched control individuals	LDL: NS ↓ with fish oil in HC patients (5.96 ± 0.16 5.77 ± 0.15 mmol/l) and control patients (3.13 ± 0.34 – 3.06 ± 0.29 mmol/l) compared to baseline.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Gray et al. 1996 *Pharmacotherapy* 1996;16(2):295-300 [U.S.]	Randomized, double-blind controlled trial	8 weeks	3.4 g/day EPA + DHA (menhaden oil produced by NMFS and provided by NIH, 18 g of total oil) 2.16 g/day EPA 1.28 g/day DHA Control group: 18 g/day corn oil Compliance: Pill count	19 subjects (all male) with essential hypertension which was not optimally controlled with one or more antihypertensive drugs fish oil group: 9 subjects control group: 10 subjects All subjects continued to take antihypertensive drugs and maintain their normal dietary habits.	LDL: significant ↑ at 4 weeks (13.5%) and at 8 weeks (19.1%) compared to baseline (both ps<0.05).
Haban et al. 1998 *Bratisl Lek Listy* 1998;99(1):37-42 (ABSTRACT, foreign) [Slovakia]	Clinical trial.	4 weeks (28 days)	2.85 g/d of EPA+DHA (10 capsules of MAXEPA®) (1.7 g/d of EPA and 1.15 g/d of DHA) Compliance: Serum EPA and DHA levels	21 NIDDM patients with dyslipoproteinemia type IV were treated with n-3 PUFA.	LDL: Small but significant ↑ (p<0.05) with n-3 PUFA. The LDL values increased from 3.625 ± 0.137 mmol/l at baseline to 4.365 ± 0.199 mmol/l after n-3 PUFA treatment.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
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Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Haglund et al. 1994 *Am. J. Cardiol.* 1994, 74:189-192 (Sweden)	Not controlled (Study A) Double-blind, crossover (Study B)	48 weeks (12 months) Study A 3 weeks per treatment, with a 2- week washout in- between Study B	9 g/day n-3 fatty acids (Study B) 4.5 g/day n-3 fatty acids, mainly EPA + DHA [from 15 ml fish oil, (ESKIMO-3)] -Study A Study B subjects received fish oil plus a high dose of vitamin E (1.5 IU/g) or fish oil plus a low dose of vitamin E (0.3 IU/g) - The fish oil used contained 40% n-3 fatty acids (19% EPA and 13% DHA)	15 healthy subjects with normal or slightly increased serum lipids; mean age: 41 years; 11 male/4 female (Study A) 12 healthy subjects; mean age: 51 years; 10 male/2 female (Study B)	LDL: no change
Haglund et al. 1998 *Nutr Biochem* 1998;9:629-635 (Sweden)	Double-blind, crossover trial.	8 weeks 4 weeks on fish oil 5 weeks wash out period 4 weeks on FO+PEO.	32% EPA+DHA mixture (30 ml fish oil (ESKIMO-3®) 19% EPA 13% DHA (fish oil group) FO+EPO (30 ml) Compliance: interview, capsule counts, plasma phospholipids FAs analyses.	12 healthy subjects or with moderately increased blood lipids (10 men, 2 post menopausal women)	LDL: NS ↓ with fish oil (5%) and with the oil mixture (1%) compared to the baseline.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
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Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Hamazaki et al. 1996 *J Nutr* 1996;126:2784-2769 [Japan]	Randomized, double-blind, placebo-controlled trial.	13 weeks	3.6 g/d of DHA-rich fish oil 10-12 capsules of DHA rich fish oil each containing 300 mg oil (49.3% DHA/100 g DHA-rich fish oil). The number of capsules taken depended on the body weight (10 capsules for ≤ 50 kg; 11 capsules for > 50 kg but ≤ 55 kg; 12 capsules for >55 kg) Control oil: 97% soybean oil and 3% fish oil (fish oil was added so that the control oil had same smell as DHA oil capsules). Compliance: capsule count	24 (age 21-30 years) healthy non-smoking students (males and females) were recruited from Toyama Medical and Pharmaceutical University. DHA group: 13 subjects Control group: 11 subjects	LDL: NS ↓ with DHA (2.57 ± 0.58 mmol/l) compared to the baseline (2.60 ± 0.61 mmol/l). NS ↓ in the control group (2.25 ± 0.48 mmol/l) compared to the baseline (2.29 ± 0.38 mmol/l).
Harris et al. 1997 *Journal of Cardiovascular Risk* 1997;4:385-391 [U.S.]	Randomized, double-blind, prospective parallel-group placebo controlled study	16 weeks following a 4 week dietary run-in period	3.4 g/day EPA+DHA (Omacor concentrated EPA & DHA as ethyl esters, 4 g total supplement) 1.92 g/day EPA 1.52 g/day DHA placebo group: corn oil Compliance: Study reports compliance rate, but does not state the nature of the measure.	42 patients with elevated serum triglycerides study group: 22 patients control group 20 patients	LDL: significant ↑ with Omacor from baseline (32%) compared to the placebo (2.05 ± 0.93 vs. 2.89 ± 0.96 mmol/l). Significant difference in the changes from baseline between the groups (p=0.0014).

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Hayashi et al. 1995 *Curr. Ther. Res.* 1995. 56:24-31 [Japan]	Not controlled	8 weeks	1.8 g/day ethyl icosapentate Compliance: Not reported	28 subjects with familial combined hyperlipidemia showing phenotype IIa, IIb, or IV; age range: 20-69 years	LDL: NS change
Herrmann et al. 1995 *Am J Cardiol* 1995;76:459-462 [Germany]	Randomized, double-blind, controlled trial.	4 weeks	8.5 g/d of n-3 FAs (EPA+DHA and other FAs) 12 g/d of fish oil (fish oil group) Rapeseed oil capsules rapeseed oil group). Compliance: serum n-3 FAs analyses	53 male subjects Treatment: 35 Control: 18 The subjects were ischemic heart disease patients, hospitalized in a rehabilitation sanatorium.	LDL: ↓ significantly with fish oil (-16%, p<-0.01) or rapeseed oil (-20.3%, p<0.01) compared to baseline
Horrocks and Yea 1999 *Lipids* 1999;34:S313 [Korea]	Controlled trial.	4 weeks	0.2 % each of EPA and DHA in 585 ml/d of Einstein milk (DHA group) Generic milk control group (study 1) Study 2: 3 Edison eggs containing DHA (DHA group) 3 generic eggs: control group Study 3: Chicken group: 200 g/d of chicken pork group: 200 g/d of pork Both chicken and pork were enriched with DHA (DHA group)	500 boys (14 years) were recruited (study 1) DHA group: 250 boys Control group:250 boys Study 2: DHA group: 100 women (20 years) Control group: 100 women Study 3: Chicken group: 20 women Pork group: 20 women	LDL: ↓ from 85.2 ± 6.4 to 68.1 ± 4.4 mg/dl in women consuming chicken enriched with DHA after 4 weeks. ↓ from 110.0 ± 8.0 to 91.8 ± 7.3 mg/dl in women consuming pork enriched with DHA after 4 weeks.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Hsu et al. 2000 Am J Clin Nutr 2000;71:26-35 [Taiwan]	Clinical trial.	4 weeks	3 g/day EPA+DHA (TAMA fish oil capsules, 10 g fish oil) 1.45 g/d EPA, 1.55 g/d DHA Control group Compliance: Fatty acid analysis	14 patients (11 men, 3 women) with hypertriglyceridemia, recruited from outpatients at the hospital. Each patient followed the AHA step 1 diet, but with traditional Chinese composition. Patients were instructed to discontinue any lipid lowering agents at least 8 weeks before the trial. Control group: 11 healthy (8 men, 3 women) normolipidemic subjects with height and weight similar to study group.	LDL: ↑ significantly with fish oil (3.33 ± 0.49 vs. 3.51 ± 0.25 mmol/l, p<0.05) compared to baseline.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA) Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Hwang et al. 1997 Am J. Clin Nutr 1997;66:89-96 [U.S.]	Randomized, double-blind, placebo-controlled, parallel study	8 weeks for study 1 4 weeks for study 2 Study 1 had a 4 week run-in, while study 2 had a 2 week run in	9 g/day n-3 PUFAs 9 g/day menhaden fish oil capsules) (study 1) 15 g/day n-3 PUFAs (NIH/NOAA Biomedical Test material, 15 g/day menhaden fish oil capsules) (study 2) Control group (study 1): 9 g/day olive oil as placebo + 16 g/day olive oil incorporated into the diet Treatment 1 (study 1): 9 g/day fish oil + 16 g/day safflower oil incorporated into the diet Treatment 2 (study 1): 9 g/day fish oil + 8 g/day safflower oil and 8 g/day olive oil incorporated into the diet Treatment 3 (study 1) 9 g/day fish oil + 16 g/day olive oil incorporated into the diet Control group (study 2): 15 g/day olive oil Treatment 1 (study 2): 6 g/day fish oil+9 g/day olive oil Treatment 2 (study 2): 15 g/day fish oil Study 1: baseline diet included 8 g/day of n-6 fatty acids. Study 2: baseline diet included 16 g/day of n-6 fatty acids	28 subjects for study 1 (16 male, 16 female) 34 subjects for study 2 (18 male, 16 female) Subjects for both studies were healthy individuals with BMI between 19 and 27 , with normal BP, recruited by newspaper advertising. Control group (study 1): 8 subjects Treatment 1 (study 1): 8-8 subjects Treatment 2 (study 1): 8-8 subjects Treatment 3 (study 1): 8-8 subjects Control group (study 2): 11-12 subjects Treatment 1 (study 2): 11-12 subjects Treatment 2 (study 2): 11-12 subjects	LDL: no significant changes were seen in any of the treatment groups from either study.

Ex

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Layne et al. 1996 *J. Nutr.* 1996;126:2130-2140 [Canada]	Randomized, Double-blind, Controlled Cross-over	12 weeks (3 mo. olive oil, 3 mo. test or control, crossover 3 mo.)	7 g/d fish oil (example for 70 kg person) = 35 mg/kg bw/d of olive oil, flaxseed oil, or EPA+DHA. Compliance: Pill counts, interviews, serum FAs analysis	26 normolipidemics recruited at a university campus. Low P/S: n=15 with P/S ≤0.74 High P/S: n=11 with min. P/S 0.43 6 drop outs due to protocol exclusion criteria (altering of fat intake & P/S group)	LDL: Low P/S: NS ↑ with fish oil (3.01 ± 0.20 mmol/l) flaxseed oil (2.87 ± 0.15 mmol/l) and olive oil (2.83 ± 0.18 mmol/l) compared to baseline. High P/S: NS ↑ with fish oil (2.35 ± 0.17 mmol/l), flaxseed oil (2.31 ± 0.19 mmol/l) and olive oil (2.20 ± 0.19 mmol/l) compared to baseline.
Lenzi et al. 1996 *Nephron* 1996. 72:383-390 [Italy]	Not randomized, open, prospective	6 weeks	7.7 g/day EPA + DHA (9 capsules per day of ethyl esters of n-3 FA (K-85), each capsule containing 1,000 mg fish oil yielding 85% EPA + DHA) - Study B 3 g/day EPA + DHA (12 capsules per day of n-3 FA, each capsule containing 750 mg fish oil (MaxEPA) yielding 33% EPA+DHA) - Study A Compliance: measured by pill count, n-3 FA in plasma lipids, bleeding time, and serum thromboxane	8 patients with chronic glomerular diseases (age range: 19-70 years 6 male/2 female). One pt had NIDDM; two pts were hypertensive; five pts were hyper-cholesterolemic 3 subjects were studied twice (studies A and B) and 1 subject was studied 3 times (once on study A and twice on study B) Study A: n=9 subjects (1 subject studied twice) Study B: n=4 subjects (all participated in Study A also)	LDL: NS change

Table 13
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Reference	Study design	Duration	Intake	Subjects	Results
Lungershausen et al. 1994 *J. Hyperten* 1994;12(9):1041-1045 [Australia]	Randomized, Double-blind, Placebo-controlled, Crossover trial.	6 weeks n-3 (6 weeks control run-in)	3.4 g/d EPA+DHA (1.9 g/d EPA 1.5 g/d DHA) (Omacor capsules) Control: corn oil Compliance: interview, capsule counts	42 patients recruited by collaborating general practitioners in Adelaide Australia. Patients w/ uncomplicated essential hypertension controlled with beta-blockers or diuretic or combo. @30% male 1 drop out	LDL: NS ↑ with fish oil (4.21 ± 0.19 mmol/l) compared to baseline (4.04 ± 0.19 mmol/l) or control (4.04 ± 0.18 mmol/l).
Luo et al. 1998 *Diabetes Care* 1998;21(5):717-724 [France]	Randomized, double-blind, crossover trial.	8 weeks (2 months) The subjects first underwent a 2-month dietary run- in period. Then they were randomly assigned to either fish oil of sunflower oil treatment for 2 months. After 2 month period the treatments were switched for another 2 months with a 2-month washout period between the treatments.	1.8 g/d n-3 PUFA from 6 g/d of fish oil (fish oil group) 6 g/d of sunflower oil (sunflower oil group) Compliance: FAs composition in plasma and erythrocyte membrane phospholipids.	10 men with NIDDM were recruited from the outpatient clinic of the Department of Diabetes. 12 patients were initially recruited but two were excluded for the following reasons: one patient was excluded because he misunderstood the experimental design and the second patient stopped the antidiabetic drug therapy which affected his results.	LDL: An ↑ with fish oil (2.59 ± 0.21 mmol/l) compared to baseline (2.22 ± 0.20 mmol/l) and sunflower oil treatment (2.49 ± 0.23 mmol/l).

Table 13
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Reference	Study design	Duration	Intake	Subjects	Results
Mackness et al. 1994 *Eur J Clin Nutr* 1994;48:859-865 [U.K.]	Randomized, Double-blind, Placebo- controlled Multi-center (7)	14 weeks	3.4 g/d EPA or DHA in 4 g K-85 containing 92% n-3. Control: corn oil Compliance: Not reported.	79 patients with primary Type IIB or IV hyperlipidemia. Test: 41 K-85 Control: 38 corn oil 95 patients began trial, 16 drop outs Males: 63% test, 74% control	LDL: NS effect of K-85 for the group. When the subjects were divided into type IV and type IIB then a NS ↑ was observed with K-85 (3.93 ± 1.12 mmol/l) compared to baseline (3.60 ± 0.66 mmol/l) in type IV, and a NS ↓ was observed with K-84 (5.53 ± 1.33 mmol/l) compared to baseline (5.63 ± 0.69 mmol/l) in type IIB. Corn oil placebo did not affect any parameters
Małyszko et al. 1996 *Przegl.Lek.* 1996. 53:600-603 (ABSTRACT, foreign) [Poland]	Not controlled	6 months	Not quantified Trienyl (fish oil/ omega-3 FA treatment) Compliance: not reported.	7 pts with glomerulo-nephritis	LDL: NS ↑
McGrath et al. 1996 *Atherosclerosis* 1996;121:275-283 [UK]	Randomized, double-blind, placebo controlled crossover trial.	6 weeks on each treatment with a 6 week washout period between the treatment.	3 g/d of EPA + DHA (10 capsules of Maxepa; 1.8 g/d EPA, 1.2 g/d (DHA) (fish oil group) Olive oil: placebo group Compliance: Pill count, platelet membrane FA analysis.	23 NIDDM subjects (20 males and 3 females) were recruited. Diabetes was controlled by either diet alone or diet + hypoglycemic drugs.	LDL: No changes in the amount or composition of LDL with fish oil compared to baseline or olive oil.

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Reference	Study design	Duration	Intake	Subjects	Results
McManus et al. 1996 *Diabetes Care* 1996;19(5):463-466 [Canada]	Randomized, double-blind, placebo-controlled crossover trial.	12 weeks (3 months) on each treatment Total 9-month: the subjects underwent a 3-month run-in period with olive oil. Then they were randomly assigned to either FO or LO for 3 months. After 3 months the treatments were reversed.	35 mg/kg of EPA + DHA combined (FO group) 35 mg/kg of olive oil (placebo run-in period) 35 mg/kg of LO Compliance: Capsule count	11 NIDDM patients (3 women and 8 men) were from a tertiary care diabetic center. None of the subjects were taking hypoglycemic drugs.	LDL: No significant difference between the three treatments (baseline 3.79 ± 0.37; placebo 3.42 ± 0.26; LO 3.41 ± 0.26; FO 3.39 ± 0.25 mmol/l).
Morgan et al. 1995 *Diabetes Care* 1995;18(1):83-86 [U.S.]	Randomized, double-blind, trial.	12 weeks of treatment Initial baseline period 4 week post-treatment phase	10.098 g/d EPA + DHA (2.582 g/d EPA, 2.457 g/d DHA, from 18 g of fish oil) 5.049 g/d EPA + DHA (5.164 EPA, 4.914 DHA, from 9 g of fish oil) 9 g/d corn oil 18 g/d corn oil Compliance: Capsule count	40 (18 men, 22 women) hyperlipidemic patients with NIDDM were recruited. 18 g/d fish oil group: n=10 9 g/d fish oil group: n=10 18 g/d corn oil group: n=10 9 g/d corn oil group: n=10	LDL: Significantly ↑ with fish oil (baseline 3.71 ± 0.78 mmol/l, fish oil 4.04 ± 0.92 mmol/l) compared to corn oil (baseline 3.87 ± 1.30 mmol/l, corn oil 3.62 ± 1.30 mmol/l) at 6 weeks, but this difference was not observed at 12 weeks (fish oil 4.06 ± 0.76; corn oil 3.67 ± 1.43).

Table 13
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Reference	Study design	Duration	Intake	Subjects	Results
Mori et al. 1994 *Am J Clin Nutr* 1994;59:1060-8 [Australia]	Randomized, placebo-controlled trial.	12 weeks	2.12 g/d EPA+DHA from fish oil (Lipitac, ≈1.3 g/d EPA and ≈0.8 g/d DHA) 2.6 g/d of n-3 from fish oil 3.2 – 4.1 g/d of n-3 FAs from fish. 1.3 g/d EPA approximate amount from fish oil or fish Placebo contained palm, olive and sunflower oil. 7 treatments were assigned Group 1: 40% fat diet + placebo Group 2: 40% fat diet + fatty fish (1 fish meal) + placebo Group 3: 40% fat diet + 6 fish oil capsules (1 g each) Group 4: 40% fat diet + fatty fish (1 fish meal) + 6 fish oil capsules Group 5: 40% fat diet + 12 fish oil capsules Group 6: 30% fat diet alone + placebo Group 7: 30% fat diet + fatty fish (1 fish meal) + placebo	120 healthy nonsmoking males were recruited by media publicity. The entry criteria was BMI of <30 kg/m^3, SBP 130-159 mmHg, DBP 80-90 mmHg, serum TC of 5.2-6.9 mmol/l.	LDL: Significant group effects ($p<0.001$). LDL ↑ in groups 2-5 by 8-12% and group 5 showed an ↑ by 16%. The 30% fat diet alone ↓ LDL by 10%. The fall in LDL with addition of fish to the 30% fat diet was attenuated (3%).

Table 13
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Reference	Study design	Duration	Intake	Subjects	Results
Nordoy et al. 1998 *J. Intern Med* 1996;243:163-170 [Norway]	Randomized, Double-blind, Placebo-controlled trial.	5 weeks EPA+DHA intervention 1. 16 weeks dietary run-in 2. 5 weeks S 3. 5 weeks S+n-3	3.4 g/d EPA+DHA 1.8 g/d EPA & 1.6 g/d DHA (4 1-g capsules Omacor fish oil) Control: corn oil Compliance: Capsule counting, Serum FAs analysis.	41 patients with combined hyperlipidemia, TG 2-15 mmol/l & TC >5.3 mmol/l after run-in. Recruited from the Lipid Clinic Dept of Medicine. Test: 21 Control: 20 @70% men.	LDL: Significant ↓ (0.62 ± 0.18 mmol/l, $p < 0.01$) compared to baseline. NS ↓ with corn oil compared to baseline. NS differences between the groups.
Oosthuizen et al. 1994 *Thrombosis & Haemostasis* 1994;72(4):557-562 [South Africa]	Randomized Double blind Placebo controlled Crossover	6 weeks 3 weeks washout 6 weeks crossover	1.58 g/d EPA+DHA 1.14 g/d EPA 0.44 g/d DHA 6 g/d n-3 (12 capsules/d Efamed) Control: olive oil Compliance: FAs analysis, other methods not reported, but compliance was evaluated.	20 healthy normolipidaemic subjects 10 male, 10 female	LDL: NS ↓ in men (3.04 ± 0.41 mmol/l) and women (3.26 ± 1.01 mmol/l) with fish oil compared to baseline (men 3.36 ± 0.99, women 3.42 ± 1.03 mmol/l). NS ↓ with olive oil in men (3.21 ± 0.73 mmol/l) and women (3.10 ± 0.79 mmol/l) compared to baseline (men 3.60 ± 0.88, women 3.35 ± 0.99 mmol/l).

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Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Otto et al. 1996 *Metabolism* 1996. 45:1305-1311 [Germany]	Not controlled	8 weeks of fish oil (2-week acclimation period with low dose n-3 FA followed by 6-week test period with high dose n-3 FA) 1 week baseline period prior to study 1 week washout period between n-3 FA and fenofibrate treatment (week 12) 8 weeks of therapy with fenofibrate (starting with week 12)	3 g/day EPA + DHA from 6 g/day fish oil capsules containing 3.6 g ethyl esters (test period) 1.5 g/day EPA + DHA from 3 g/day fish oil capsules containing 1.8 g n-3 FA ethyl esters (50% EPA, 33% DHA) (acclimation period) Subjects administered 250 mg slow-release fenofibrate starting after 12 weeks Compliance: plasma EPA and DHA concentrations	23 subjects with primary hypertriglyceridemia (plasma triglycerides > 2.85 mmol/l; mean age: 45.7 years; 22 male/1female). Fifteen subjects had familial hypertriglyceridemia (FHTG); 8 subjects had familial dysbetalipoproteinemia (FDL) 2 withdrawals: 1 due to pregnancy, the other due to gastrointestinal effects	LDL: ↑ by 44% and 27% in FHTG subjects during n-3 FA and fenofibrate intake, respectively ($p<0.01$); NS change in FDL subjects.
Pertsichetti et al. 1996 *Minerva Urol. Nefrol.* 48:137-138 [Italy]	Not controlled	24 weeks (6 months)	3 g/day n-3 FA in capsules, each capsule contained 1,000 mg n-3 FA (with EPA and DHA in a reciprocal ratio of 0.9-1.5) Compliance: not reported.	18 hypertriglyceridemic and hyperfibrinogenemic maintenance dialysis patients; none were diabetic	LDL: ↓ (-19%)

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Rambjør et al. 1996 *Lipids* 1996;31:S-45-S-49 [U.S.]	Randomized, single-blinded, placebo-controlled trial.	3 weeks Placebo for 2 weeks Treatment for 3 weeks	5 g/d of n-3 FAs as ethyl esters (FOC group) 3g/d DHA ethyl esters (DHA group) 3 g/d EPA ethyl esters (EPA group) Olive oil group (placebo) Compliance: capsule counts	49 normolipidemics were recruited from the University of Kansas medical center staff and student population. The TG levels were in the higher end of (50-90th percentile for age and sex) normal range. EPA group: 25 subjects DHA group: 9 subjects FOC: 35 subjects Placebo: Olive oil	LDL: ↑ by 10% ($p<0.05$) with FOC. EPA ↑ LDL by 8% ($p<0.01$) while DHA had no effect.
Ramirez-Tortosa et al. 1999 *British Journal of Nutrition* 1999;82:31-39 [Spain]	Longitudinal crossover trial 24 subjects were assigned olive oil for 3 months followed by 3 month washout period and then assigned to olive oil + fish oil for 3 months.	16 g/d fish oil (as maltodextrin-starch microcapsules). The powder was consumed mixed with either water or fruit juice. Olive oil used in cooking (O) Olive oil + fish oil (OF) Control (C)	12 weeks (3 months) on olive oil + fish oil 12 weeks olive oil 12 weeks washout period Compliance: interview	37 subjects diagnosed with PVD were recruited from a group of cardiovascular outpatients followed-up by the Department of Vascular Surgery. Olive oil, olive oil + fish oil: 24 subjects Control group: 13 subjects Reference group: 20 healthy individuals	LDL: Significant ↑ with OF group (5.03 ± 0.21 mmol/l) compared to the reference group (4.34 ± 0.21 mmol/l, $p<0.05$). NS changes in the O group compared to the control or reference groups.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Rivellese et al. 1996 *Diabetes Care* 1996;19(11):1207-1213 [Italy]	Randomized, double-blind, placebo controlled with a parallel group sequence.	24 weeks (6 months) The subjects underwent a 4-week washout period during which they were stabilized on isoenergetic diet and hypoglycemic treatment and all hypolipidemic drugs were withdrawn. After the washout period all subjects consumed placebo capsules for 3 weeks during the run-in period. After the run-in period treatments were assigned to the subjects	2.5 g/d EPA + DHA (0.96 g/d EPA and 1.59 g/d DHA) for the first 2 months. The dose was reduced to 1.7 g/d EPA + DHA (0.64 g/d EPA and 1.06 g/d DHA) for the remaining 4 months) (fish oil group) Placebo: olive oil (the olive oil dose was also reduced after 2 months). Compliance: RBC phospholipid FA analysis.	16 hypertriglyceridemic patients with NIDDM were recruited from diabetic clinic. Some patients had moderate arterial hypertension. Multicenter trial. Fish oil: n=8 Placebo: n=8	LDL: Significant ↑ ($p<0.01$) with fish oil (3.29 ± 0.49 mmol/l) compared to baseline (2.88 ± 0.20 mmol/l). No effect of placebo.
Rossing et al. 1996 *Diabetes Care* 1996;19(11):1214-1219. [Denmark]	Randomized, double-blind parallel placebo controlled trial.	52 weeks (1 year)	4.6 g/d of EPA + DHA (2 g/d EPA and 2.6 g/d DHA from 21 ml of cod-liver oil given as Eskdol Fish oil Emulsion) (cod-liver oil group) 21 ml of olive oil (olive oil group) Compliance: Fatty acids in platelets.	29 IDDM patients with persistent albuminuria were recruited from outpatient clinic at Steno Diabetes Center during 1992. Cod-live oil: n=14 Olive oil: n=15	LDL: ↑ significantly from 2.93 ± 0.2 mmol at baseline to 3.41 ± 0.22 mmol/l and 3.52 ± 0.24 mmol/l at 6 ($p\leq0.01$) and 12 ($p<0.05$) months, respectively with cod-liver oil when compared to the baseline. The increase with cod-liver oil at 6 months was significantly ($p<0.05$) different from olive oil.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Sacks et al. 1995 *J Am Coll Cardiol* 1995;25(7):1492-8 [U.S.]	Randomized, Partially-blinded, Placebo-controlled	121 weeks (28 mo.)	4.8 g/d EPA+DHA 2.9g/d EPA 1.9 g DHA 6 g/d n-3 (Promega capsules) Control: Olive oil Compliance: pill counts.	59 patients w/ narrowing lumen diameter and TC<250mg/dl TG<350 mg/dl. 31 test 28 control 55 males, 4 females	LDL: Significant ↑ (p<0.01) with fish oil (132 ± 30 mg/dl) compared to baseline (122 ± 29 mg/dl). NS ↑ in the control group (122 ± 24 mg/dl) compared to baseline (117 ± 27 mg/dl). No differences between the groups.
Sanders et al. 1997 *Arterioscler. Thromb. Vasc. Biol.* 1997. 17:3449-3460 [London]	Randomized, cross-over-design	two 3-week (21 days) periods with a 8-week washout period in between all subjects fed a saturated fat diet for 3 weeks prior to study	5 g/day (1.5% of energy) EPA + DHA (olive oil and fish oil - Max EPA, Seven Seas) (n-3 diet) the saturated diet: 4% of total energy provided by PUFAs, trace amounts of DHA and EPA n-6 diet: 5 g/day linoleic acid	26 healthy, normolipidemic, non-obese males; age range: 18-34 years (mean: 23 years)	LDL: The saturated diet ↑ fasting LDL significantly (p<0.0001). Fasting LDL ↓ from 2.60 ± 0.71 mmol/l (saturated fat diet, baseline) (p<0.0001) to 2.29 ± 0.75 and 2.30 ± 0.67 (p<0.0001) with n-6 and n-3 diets, respectively.
Schindler and Rost 1996 *Z Ernahrungswiss* 1996;35:191-196 (ABSTRACT, foreign)	Clinical study	8 weeks	0.18-1.1 g/d of n-3 FAs in form of fish oil capsules.	20 subjects with primary hyperlipoproteinemia of phenotypes IIa, IIb and IV and with proven coronary sclerosis.	LDL: NS ↓ in type IIa and IIb patients with n-3 FAs. Significant ↑ (+6.7%, p<0.05) at 1.1 g/d n-3 FAs in type IV patients.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Sheehan et al. 1997 *Am J Clin Nutr* 1997;66:1183-1187 [U.S.]	Controlled sequential study	4 weeks on fish oil treatment followed by 4 weeks on fish oil + pectin followed by 4 weeks of follow-up control period. The fish oil treatment period was considered a run-in period for fiber treatment period.	6 g/d n-3 FAs from 20 g/d of fish oil (MaxEPA) 15 g/d pectin Compliance: FA analysis	15 (12 men, 3 women) nonobese subjects with NIDDM were recruited. Diet or diet + oral agents or diet + insulin was used to control diabetes. All subjects were treated with fish oil for 4 weeks followed by fish oil + pectin followed by control period. During the control period the subjects did not receive fish oil or pectin treatment and followed their diabetic diet.	LDL: NS ↑ with fish oil (4.40 ± 0.93 mmol/l) compared to baseline (4.32 ± 1.58 mmol/l). Significant ↓ after addition of fiber compared to baseline ($p<0.05$) and fish oil ($p<0.05$).
Silva et al. 1996 *International Journal of Cardiology* 1996;57:75-80 [Portugese]	Randomized, double-blind trial	8 weeks (2 months) of treatment 4 weeks of washout or diet period	3.6 g/d EPA+DHA (12 g/d of fish oil) 2.16 g/d EPA 1.44 g/d DHA (fish oil group) Soy oil Compliance: capsule counts	35 subjects (25 females and 10 males) with hypertriglyceridaemia were recruited from the Atherosclerosis Out-patient Clinic of the University Hospital of Coimbra.	LDL: NS ↑ (7.7%) with fish oil (126 ± 9 mg/dl) compared to baseline (117 ± 11 mg/dl). NS ↓ (10.0%) with soya oil (137 ± 14 mg/dl) compared to baseline (151 ± 17 mg/dl). NS difference between groups ($p=0.0672$).

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Sirtori et al. 1997 *Am J Clin Nutr* 1997;65:1874-81 [Italy]	Randomized, double-blind, placebo-controlled trial. Multicenter.	24 weeks (6 months) Run-in period was ≥ 4 weeks. 2 months on high dose of EPA+DHA 4 months on low-dose of EPA+DHA	2.560 g/d (2560 mg/d) of EPA+DHA as ethyl esters for 2 months (high dose). (Esapent capsules) 1530 mg/d EPA 1050 mg/d DHA 1.720 g/d (1720 mg/d) of EPA+DHA as ethyl esters for 4 months (low dose) 1020 mg/d EPA 700 mg/d DHA Placebo: Olive oil The dose of olive oil was reduced during the last 4 months. Compliance: capsule counts	935 subjects Treatment: 470 subjects Placebo: 465 subjects Subjects with either type IIB or IV hyperlipoproteinemias with at least one additional risk factor such as NIDDM, arterial hypertension or impaired glucose tolerance were recruited from 63 clinical groups.	LDL: ↑ with fish oil (6.0%) and placebo (3%) compared to the baseline values. Significant ↑ (p=0.048) in LDL at the end of six months in the n-3 group compared to the placebo group
Sirtori et al. 1998 *Atherosclerosis* 1998;137:419-427 [Italy]	Open phase. Multicenter.	24 weeks (6 months)	1.720 g/d (1720 mg/d) of EPA+DHA as ethyl esters for 6 months; 1020 mg/d EPA 700 mg/d DHA; ESAPENT®) Compliance: EPA and DHA levels in plasma and RBCs	863 subjects were given fish oil treatment. Subjects with either type IIB or IV hyperlipoproteinemia with at least one additional risk factor such as NIDDM, arterial hypertension or impaired glucose tolerance were recruited from 63 clinical groups. 5 subjects (total 868) withdrew because of worsening of NIDDM.	LDL: Minimal ↑ was observed in patients treated with fish oil for 12 months vs. the 6 month average value. In patients with type IV and IIB hyperlipoproteinemia with NIDDM, no change was observed, although type IIB experienced a non-significant ↓ (2.8%). Conversely, type IV patients had a non-significant ↑ (6.9%) in LDL in the open treatment phase. In type IV patients without NIDDM a significant ↑ (15.9%, p<0.002) in LDL was observed.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Suzukawa et al. 1995 Journal of Lipid Research 1995;36:473-484 [Australia]	Randomized, double-blind, placebo controlled crossover study	6 week treatment with either corn oil or fish oil, at which point patients crossed over 4 week run in period No washout period	2.9 g/d of EPA+ DHA (Omacor fish oil capsules) 1.64 g/d EPA 1.21 g/d DHA 4 g/d corn oil in control group Compliance: By interview	20 hypertensive patients (14 men and 6 women) managed with either atenolol or antenolol + diuretic.	LDL: 7.6% ↑ (p <0.01) compared to corn oil.
Swahn et al. 1998 *Clin Drug Invest* 1998;15(6):473-462. [Sweden]	Randomized, Double-blind, Placebo-controlled trial.	12 weeks following an 8-w dietary run-in period.	4.5 g/d EPA+DHA ethyl esters (4 1-g capsules n-3/day provided by Norsk Hydro AS.) Control: corn oil Compliance: Capsule counts, Serum FAs analysis	53 with a history of MI more than 3 mo. prior to enrollment and TG ≥ 2 mmol/l & TC ≤ 10 mmol/l. @ 80% male Test: 26 Control: 27	LDL cholesterol: ↑ with n-3 FAs (7%, p<0.001) compared to baseline. NS ↓ in the control group. Significant difference between the groups (p<0.05) (n-3 FAs 4.13 ± 0.76, placebo 3.87 ± 0.82 mmol/l).

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Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Szostak-Weglerek et al. 1994 *Pol Arch Med Wewn* 1994;92:178-183 (ABSTRACT, foreign)	Crossover study. Subjects were divided in group I and II and received the treatments in reversed order.	3 weeks 3 weeks fish oil 3 weeks olive oil. In 9 patients fish oil was given for 6 weeks	3.6 g/d EPA+DHA (12/d fish oil) Olive oil	29 hypertriglyceridemic men. 20 subjects were given fish oil for 3 weeks and olive oil for 3 weeks. Nine subjects were given fish oil for 6 weeks.	LDL: NS ↑ (14%) with fish oil compared to baseline in the group that received fish oil first. Significant ↓ (-9%, p<0.05) with olive oil in the group that received olive oil after fish oil compared to fish oil. NS ↓ (-5%) with olive oil compared to baseline in the group that received olive oil first. Significant ↑ (+31%, p<0.01) with fish oil in the group that received olive oil first compared to olive oil. Significant ↑ at 3 weeks (3.31 ± 1.14 mmol/l, 15%, p<0.01) compared to baseline (2.87 ± 1.27 mmol/l), but NS ↑ at 6 weeks (3.67 ± 1.55 mmol/l, 11%) compared to 3 weeks in the group that received fish oil first for 3 weeks.
Toft et al. 1995 *Ann Intern Med* 1995;123:911-918 (Norway)	Randomized, double-blind, placebo-controlled.	16 weeks	4 g/d fish oil as ethyl esters (Omacor) (fish oil group) Placebo group: 4 g/d corn oil. Compliance: Capsule count, plasma phospholipid FA analysis, and interview.	78 subjects with untreated stable hypertension. 58 subjects who had participated in a health survey and 26 subjects from primary health care services were recruited. Fish oil group: n=38 Placebo: n=40	The corn group had higher BMI, waist-to-hip ratio, fasting plasma glucose and insulin compared to the fish oil group. LDL: NS ↓ with fish oil (-0.01 ± 0.10 mmol/l, p=0.94) and corn oil (-0.13 ± 0.11 mmol/l, p=0.22).

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Tsai and Lu 1997 *J Forums Med Assoc* 1997;96(9):718-726 [Taiwan]	Randomized trial. Subjects were randomly assigned to two groups of 8 subjects. One group received low dose of cholesterol (low cholesterol group) and the other received high dose of cholesterol (high cholesterol group). Both groups were given soybean enriched diet for 3 weeks followed by fish oil rich diet for 3 weeks.	3 weeks on n-3 FAs 3 weeks on soybean oil	8.6 g/d EPA+DHA 7.2 g/d EPA 1.6 g/d DHA (20 g/d fish oil capsules) (n-3 group) 20 g/d soybean oil (n-6 group) Compliance: Not measured	16 healthy normolipidemic male subjects were recruited form the medical students population of National Taiwan University. 8 subjects in each cholesterol groups.	LDL: Low cholesterol group: NS ↓ with soybean oil at the end of 3 weeks (-18.7%) and fish oil at the end of 6 weeks (-29.5%) compared to the baseline values. High cholesterol group: NS ↓ with soybean oil at the end of 3 weeks (-16.2%) and fish oil at the end of 6 weeks (-22.1%) compared to the baseline values.
Valagussa et al. 1999 *Lancet* 1999;354:447-55 [Italy]	Randomized, control trial. Open label design. Multicenter (172)	189 weeks (3.5 years).	0.850-0.882 g/d (850-882 mg) of EPA + DHA as ethyl esters (n-3 group) (n-3 PUFAs group) 300 mg/d vitamin E (vitamin E group) n-3 + vitamin E group Control group Compliance: capsule counts	11324 subjects. Patients surviving recent (≤ 3 months) MI were recruited from October 1993 through September 1995 from 172 centers (cardiology department and rehabilitation center). n-3 group: 2836 patients vitamin E group: 2830 patients n-3 + vit E group: 2830 patients control group: 2828 patients	LDL: ↑ with n-3 PUFA (9.9%), vitamin E (7.2%), n-3 + vitamin E (10.8%) and in the control group (7.4%) compared to the baseline.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
von Schacky et al. 1999 *Ann Intern Med* 1999;130:554-562 [Germany]	Randomized, Double-blind, Placebo-controlled	112 weeks (2 years)	3.4 g/d EPA+DHA 2.1 g/d EPA, 1.3 g/d DHA) Months 1-3 Next 21 months: 1.71 g/d EPA+DHA Control: FAs mixture reflecting composition of avg. European diet. Compliance: Interview, capsule counts, FAs analysis.	233 patients w/ angiographically proven coronary artery disease. 111 test 112 control Ratio Males:Females not given.	LDL: NS ↑ with fish oil (4.05 ± 0.96 mmol/l) compared to placebo (3.95 ± 1.08 mmol/l) after 1 month. Significant ↑ with fish oil (4.30 ± 1.21 mmol/l, $p<0.05$) compared to placebo (3.85 ± 1.09 mmol/l) after 6 months. NS ↑ with fish oil (4.20 ± 1.09 mmol/l) compared to placebo (3.95 ± 1.13 mmol/l) after 12 months. Significant ↑ with fish oil (4.10 ± 1.00 mmol/l, $p<0.05$) compared to placebo (3.75 ± 1.06 mmol/l) after 18 months. Significant ↑ with fish oil (3.85 ± 0.85 mmol/l, $p<0.05$) compared to placebo (3.50 ± 1.04 mmol/l) after 24 months. There was a slight ↑ in LDL at 6, and 12 months, but the levels ↓ by 24 months with fish oil compared to the baseline values (4.10 ± 1.06 mmol/l).
Yamamoto et al. 1995 *Jpn Circ J* 1995;59:608-616 [Japan]	Randomized, controlled trial.	16 weeks (4 months)	1.8 g/d EPA (Epadel capsules) Fish oil group: fish oil + Ca channel blocker Control group: Ca channel blocker. EPA treatment was started after the first coronary angiography examination. Compliance: Fatty acid analysis.	22 (17 males and 5 females) patients with variant angina were recruited from the Kyushu Kosei Nenkin Hospital. Fish oil group: n=12 (9 males and 3 females) Control group: n=10 (8 males and 2 females)	LDL: NS difference between the groups.

Table 13
Safety of Omega-3 Fatty Acids (EPA and DHA) Clinical Trials Published 1992-2000 Including an LDL Measure in the Protocol
Shaded rows represent an effect of Omega-3 Fatty Acids (EPA and DHA)
Only LDL measures summarized here

Reference	Study design	Duration	Intake	Subjects	Results
Yosefy et al. 1996 *J. Human Hypertension* 1996. 10:S135-S139 [Israel]	Crossover	1.9 weeks (13 days per treatment period), with a 3-week washout interval in between each treatment period Day 1, 5, 9, and 13 were fasting day (20 hrs/day) followed by refeeding	4.5 g/day EPA + DHA from 15 1-g capsules of Alsepa deep sea fish oil containing 180 mg EPA and 120 mg DHA); administered after fasting and followed by refeeding (Period I) Subjects fasted and then refeeded w/o fish oil ingestion (Period II) Subjects given fish oil as in period I but without fasting and refeeding (Period III) Compliance: plasma phospholipid FA analysis	20 hypertensive, mildly obese, dyslipidemic subjects mean age: 61.7 years (range: 40-71 years) 8 male/12 female	LDL: NS change
Zak et al. 1997 *Sbornik Lékařský* 1997;98:213-224 (ABSRACT, foreign) [Czech Republic]	Clinical trial	3 weeks	3.5 g/d n-3 FAs Compliance: Not reported	82 subjects (61 men and 21 women) with primary hyperlipoproteinemia. HLP IIA: n=9 HLP IIB: n=29 HLP IV: n=35 HLP V: n=7 HLP III: n=2	LDL: NS changes with fish oil.

TABLE 8-8 Effects of *n*-3 Fatty Acid Intake on Immune Function

Reference	Study Design	*n*-3 Fatty Acid Dose (Daily)[a]	Results[b]
Lee et al., 1985	7 men 6 wk	MaxEPA (3.2 g EPA, 2.2 g DHA)	Depressed neutrophil LTB_4, 6-*trans*-LTB_4, 5-HETE, and endothelial adherence, monocyte LTB_4 and 5-HETE, neutrophil chemotaxis
Endres et al., 1989	9 men 6 wk	MaxEPA (2.75 g EPA, 1.85 g DHA)	Depressed PBMC IL-1β, IL-1α, TNF, PGE_2, and neutrophil chemotaxis
Schmidt et al., 1989	12 men 6 wk	Cod liver oil (2.5 g EPA)	Depressed neutrophil migration, monocyte cell density (marker of monocyte migration)
Kelley et al., 1991	10 men 56 d crossover	Basal diet Flaxseed oil-supplemented diet (20 g 18:3*n*-3)	Depressed PBMC proliferation in response to T-cell mitogen but not to B-cell mitogen with flax seed oil-supplemented diet
Meydani et al., 1991	6 young women, 6 older women 12 wk	ProMega (1.68 g EPA, 0.72 g DHA)	Depressed PBMC IL-1β and IL-6 (greater in older women), TNF and IL-2 (older women only)
Malvig et al., 1991	8 men 9 men 8 men 7 wk	Placebo oil Fish oil (1 g EPA, 0.5 g DHA) Fish oil (2 g EPA, 1 g DHA)	Depressed PBMC proliferation, IL-1β in PBMCs and monocytes with *n*-3 fatty acids PBMC secretion of IL-1β, TNF-α, PGE_2 or LTB_4 not affected by *n*-3 fatty acids
Thompson et al., 1991	6 men, 6 women 4 wk crossover	MaxEPA (2.16 g EPA) 12 g olive oil	Depressed neutrophil chemiluminescence (marker of neutrophil function) with MaxEPA diet
Virella et al., 1991	4 men fed fish oil, 2 men fed olive oil 6 wk	Fish oil (2.4 g EPA)	Depressed PBMC IL-2
Yamashita et al., 1991	3 adults 1 d	3 g EPA, infused	Depressed NK cell activity of PBMCs
Cooper et al., 1993	8 men and women 6–8 wk	Fish oil (0.9 g EPA, 0.6 g DHA)	Typhoid vaccine injection site less inflamed, post-vaccination tachycardia inhibited, depressed blood IL-1 and IL-6 concentrations

Endres et al., 1993	9 men 6 wk	MaxEPA (2.75 g EPA, 1.85 g DHA)	Depressed PBMC IL-2 and proliferation
Meydani et al., 1993	7 women, 3 men 24 wk after 6 wk on typical U.S. diet (baseline)	Low fat, high fish diet (1.23 g EPA + DHA)	Depressed PBMC IL-1β, TNF, IL-6, PGE_2, CD_4+ lymphocytes, and lymphocyte proliferation, delayed-type hypersensitivity
Sperling et al., 1993	5 women and 3 men with rheumatoid arthritis 10 wk	SuperEPA (9.4 g EPA, 5.0 g DHA)	Depressed neutrophil chemotaxis, inositol tris-phosphate formation, and LTB_4, monocyte LTB_4
Gallai et al., 1995	20 patients with relapsing/remitting multiple sclerosis and 15 controls 6 mo	Fish oil (3.06 g EPA, 1.86 g DHA)	Depressed PBMC IL-1β, TNF-α, IL-2 and IFN-γ, PGE_2, and LTB_4, serum-soluble IL-2 receptors
Caughey et al., 1996	30 men 4 wk diet + 4 wk diet with fish oil	Flaxseed oil-enriched diet and fish oil (EPA 1.62 g, DHA 1.08 g) Sunflower oil diet and fish oil (EPA 1.62 g, DHA 1.08 g)	Depressed PBMC TNF-α, IL-1β, TXB_2, and PGE_2 with flaxseed oil-enriched diet Greater decreases in PBMC TNF-α, IL-1β, and TXB_2 in both groups after fish oil supplementation
Hughes et al., 1996	3 men, 3 women 3 wk	EPA Forte (0.93 g EPA, 0.63 g DHA)	Depressed monocyte surface proteins: HLA-DR, HLA-DP, HLA-DQ, ICAM-1, LFA-1
Blok et al., 1997	58 men 1 y	0, 3, 6, or 9 g fish oil (0, 0.81, 1.62, or 2.43 g EPA, 0, 0.16, 0.33, or 0.49 g DHA)	No effect on whole blood IL-1β, TNF-α, or IL-1 receptor antagonist
Kelley et al., 1998	4 men 7 men 120 d	Basal diet DHA-enriched oil (6 g DHA)	Decreased white blood cells PBMC proliferation and delayed-type hypersensitivity not different between groups
Kelley et al., 1999	4 men 7 men 120 d	Basal diet DHA-enriched oil (6 g DHA)	Depressed PBMC IL-1β and TNF-α production, in vitro PBMC PGE_2 and LTB_4 secretion

continues

TABLE 8-8 Continued

Reference	Study Design	*n*-3 Fatty Acid Dose (Daily)[a]	Results[b]
Yaqoob et al., 2000	5 men, 3 women 7 men, 1 woman 3 other groups of 8 fed other oils, but all comparable to placebo 12-wk parallel	Placebo oil (3:1 coconut and soybean oils) Fish oil (2.1 g EPA, 1.1 g DHA)	No effect of fish oil on PBMC NK cell activity, proliferation, types of blood lymphocytes, IL-1α, IL-1β, TNF-α, IL-2, IL-10, and IFN-γ

[a] EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.

[b] LTB_4 = leukotriene B_4; 5-HETE = 5-hydroxyeicosatetraenoic acid; PBMC = peripheral blood mononuclear cell; IL-1β = interleukin-1β, IL-1α = interleukin -1α, TNF = tumor necrosis factor, PGE_2 = prostaglandin E_2; IL-6 = interleukin-6; IL-2 = interleukin 2; NK cell – natural killer cell; IFN-γ = interferon-γ; HLA-DR = human leukocytes antigen-DR; HLA-DP = human leukocyte antigen-DP; HLA-DQ = human leukocyte antigen-DQ; ICAM-1 = Intercellular Adhesion Molecule-1; LFA-1 = Leukocyte Function-Associated Antigen-1.

TABLE 11-10 *n*-3 Fatty Acid (EPA and DHA)[a] Intake and Blood Lipid Concentrations

Reference	Study Design		Post-Intervention Blood Lipid Concentrations (mmol/L)[b]		
			LDL-C	HDL-C	Triacylglycerol
Flaten et al., 1990	64 men	Control diet (0% *n*-3)		1.28[c]	1.71[c]
	6-wk parallel	Control diet + 2.2%EPA/DHA		1.15[c]	1.23[d]
Kestin et al., 1990	33 men	0.6% 18:3*n*-3	4.44[c]	1.26[c]	1.62[c]
	6-wk parallel	2.7% 18:3*n*-3	4.55[c]	1.16[c]	1.85[c]
		1.1% EPA/DHA	4.62[d]	1.28[c]	1.24[d]
Bhathena et al., 1991	40 men	0% EPA/DHA			1.62[c]
	10-wk crossover	2.2% EPA/DHA			1.17[d]
Bønaa et al., 1992	144 men and women	0.28% EPA/DHA/22:5	4.65	1.32	1.95
	Cross-sectional	0.30% EPA/DHA/22:5	4.71	1.31	1.49
		0.52% EPA/DHA/22:5	4.43	1.36	1.32
		0.72% EPA/DHA/22:5	4.47	1.36	1.34
Eritsland et al., 1994a	511 men and women	Control diet	5.03[c]	1.08[c]	2.08[c]
	9-mo parallel	Control diet + 1.46% EPA/DHA	5.11[c]	1.16[c]	1.57[d]
Eritsland et al., 1994b	57 men and women	Control diet	4.84[c]	1.01[c]	1.80[c]
	6-mo parallel	Control diet + 1.4% EPA/DHA	5.03[c]	0.97[c]	1.71[c]
Ågren et al., 1996	55 men	0% *n*-3	2.60[c]		1.42[c]
	15-wk parallel	0.36% *n*-3 (fish)	2.56[c]		1.16[d]
		0.60% *n*-3 (DHA oil)	2.42[c]		0.97[d]
		0.76% *n*-3 (fish oil)	2.51[c]		0.89[d]
Grimsgaard et al., 1997	224 men	0.19% *n*-3 (corn oil)	4.10[c]	1.40[c]	1.33[c]
	7-wk parallel	0.52% *n*-3 (DHA oil)	4.13[c]	1.42[d]	1.02[d]
		0.55% *n*-3 (EPA oil)	3.98[c]	1.34[c]	1.08[d]
Sanders et al., 1997	26 men	0% EPA/DHA (saturated fat diet)	2.60[c]	1.18[c]	0.93[c]
	3-wk crossover	0% EPA/DHA (*n*-6 diet)	2.29[d]	1.19[c]	0.92[c]
		1.5% EPA/DHA (*n*-3 diet)	2.30[d]	1.22[c]	0.68[d]

[a] EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.
[b] LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol.
[c, d, e] Within each study, the blood lipid concentrations that are significantly different between treatment groups have a different superscript.

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Appendix E J Heimbach LLC

IX. LITERATURE CITED

The literature cited in this notification does not form part of the document but copies of any or all published literature is available upon request*

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Appendix F Exponent Literature Update

Fish Oil/EPA+DHA Safety Update – Articles to be Reviewed

LDL & Glucose

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