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nutrinova

Nutrinova · Industriepark Hochst · D-65926 Frankfurt am Main

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

United States of America

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NOV 17 2004
OFFICE OF
FOOD ADDITIVE SAFETY

Scientific & Regulatory Affairs

Nutrinova
Nutrition Specialties &
Food Ingredients GmbH
Industriepark Höchst
D-65926 Frankfurt am Main

Date: 11. November 2004
From: Dr. Bernd Haber
Phone: +49 (0)69 305 - 15423
Fax: +49 (0)69 305 - 84682
E-Mail: b.haber@nutrinova.com

Re: GRAS Notification

Dear Sir or Madam,

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination] published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the notifier, Nutrinova Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, D 706, 65926 Frankfurt, Germany, i) a GRAS notification of DHA-Rich Oil for use as a food ingredient to provide a dietary source of ω-3 polyunsaturated fatty acids, notably docosahexaenoic acid (DHA), ii) a GRAS panel report setting forth the basis for the GRAS determination, and iii) curricula vitae of the members of the GRAS panel for review by the agency.

You received on Monday the 8th of November a notification letter (dated on October 29th, 2004) that contained no further enclosures. That was a human mistake from our consultant. We want to apologize for that. This time enclosed to this letter you will find the necessary documentation in triplicate.

Yours sincerely,

Nutrinova Nutrition Specialties & Food Ingredients GmbH

Dr. Bernd Haber
Head Scientific & Regulatory Affairs

Enclosures

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Celanese
Nutrinova
A business of Celanese AG

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OFFICE OF
FOOD ADDITIVE SAFETY

I GENERALLY RECOGNIZED AS SAFE (GRAS) EXEMPTION CLAIM FOR DHA-RICH OIL

I.A Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

DHA-rich oil, as defined in the report in Appendix I entitled, "**EXPERT PANEL CONSENSUS STATEMENT: THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF DHA-RICH OIL UNDER THE CONDITIONS OF INTENDED USE IN TRADITIONAL FOODS**", dated September 15, 2004, has been determined to be Generally Recognized As Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by their relevant national and international experience and scientific training and expertise to evaluate the safety of food ingredients. Therefore, the use of DHA-rich oil in food as described below is exempt from the requirement of premarket approval.

Signed,

October 29, 2004

Dr. Bernd Haber
Head Scientific and Regulatory Affairs
Nutrinova
Nutrition Specialties & Food Ingredients GmbH
Industriepark Höchst, D 706
65926 Frankfurt, Germany

Date

I.B Name and Address of Notifier

Dr. Bernd Haber
Head Scientific and Regulatory Affairs
Nutrinova Nutrition Specialties & Food Ingredients GmbH
Industriepark Höchst, D 706
65926 Frankfurt, Germany

I.C Common Name of the Notified Substance

DHA-rich oil

I.D Conditions of Intended Use in Food

DHA-rich oil is intended for use as a food ingredient to increase the intake of dietary ω-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA), a critical component of most cell membranes and tissues.

The individual intended food use levels of DHA-rich oil in food are consistent with the current GRAS use of menhaden oil specified in 21 CFR §184.1472 and the revised uses outlined in the FDA's tentative final rule regarding GRAS-affirmed food uses for menhaden oil (FDA, 2004a), respectively. The intended food uses and maximum levels for DHA-rich oil are presented in Table 1.

Table 1 Intended Uses and Maximum Use Levels of DHA-rich oil in Food

Food Category	Initial[a] Intended Use Levels (% by weight)	Future[b] Intended Use Levels (% by weight)
Cookies, crackers (1)[1,2]	3.3	-
Breads, rolls (white and dark) (1)[2]	0.7	-
Fruit pies, custard pies (1)[2]	4.7	-
Cakes (1)[2]	6.7	-
Cereals (4)	2.7	2.7
Baked Goods and baking mixes	-	3.3
Fats and oils (12)[3]	13.4	8 0
Yogurt (31)[4]	2.7	-
Milk Products (31)	-	3.3
Cheese products (31)	-	3.3
Frozen dairy products (20)	3.3	3.3
Meat products (29)	6.7	3.3
Egg products (11)	3.3	3.3
Fish products (13)	13.4	3.3
Condiments (8)	3.3	3.3
Soup mixes (40)	2.0	3.3
Snack foods (37)	3.3	3.3
Nut products (32)	3.3	3.3
Gravies and sauces (24)	3.3	3.3
Plant protein products (33)	-	3.3
Processed vegetable juices (36)	-	0.7
Hard candy (25)	-	6.7
Soft candy (38)	-	2 7
Jams and jellies (28)	-	4.7
Dairy product analogs (10)	-	3.3

Docket No. 03–ASO–21." The postcard will be date/time stamped and returned to the commenter. All communications received before the specified closing date for comments will be considered before taking action on the proposed rule. The proposal contained in this notice may be changed in light of the comments received. A report summarizing each substantive public contact with FAA personnel concerned with this rulemaking will be filed in the docket.

Availability of NPRMs

An electronic copy of this document may be downloaded through the Internet at *http://www.dms.dot.gov.* Recently published rulemaking documents can also be accessed through the FAA's web page at *http://www.faa.gov* or the Superintendent of Document's web page at *http://www.access.gpo.gov/nara.* Additionally, any person may obtain a copy of this notice by submitting a request to the Federal Aviation Administration, Office of Air Traffic Airspace Management, ATA–400, 800 Independence Avenue, SW., Washington, DC 20591, or by calling (202) 267–8783. Communications must identify both docket numbers for this notice. Persons interested in being placed on a mailing list for future NPRM's should contact the FAA's Office of Rulemaking, (202) 267–9677, to request a copy of Advisory Circular No. 11–2A, Notice of Proposed Rulemaking Distribution System, which describes the application procedure.

The Proposal

The FAA is considering an amendment to part 71 of the Federal Aviation Regulations (14 CFR part 71) to amend Class E5 airspace at Lexington, TN. Class E airspace designations for airspace areas extending upward from 700 feet or more above the surface of the earth are published in Paragraph 6005 of FAA Order 7400.9L, dated September 2, 2003, and effective September 16, 2003, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designations listed in this document would be published subsequently in the Order.

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. It, therefore, (1) is not a "significant regulatory action" under Executive Order 12866; (2) is not a "significant rule" under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a Regulatory Evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this rule, when promulgated, will not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

List of Subjects in 14 CFR Part 71.

Airspace, Incorporation by reference, Navigation (Air).

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, CLASS B, CLASS C, CLASS D, AND CLASS E AIRSPACE AREAS; AIRWAYS; ROUTES; AND REPORTING POINTS

1. The authority citation for part 71 continues to read as follows:

Authority: 49 U.S.C. 106(g); 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

2. The incorporation by reference in 14 CFR 71.1 of Federal Aviation Administration Order 7400.9L, Airspace Designations and Reporting Points, dated September 2, 2003, and effective September 16, 2003, is amended as follows: Paragraph 6005 Class E Airspace Areas Extending Upward from 700 feet or More Above the Surface of the Earth.

* * * * *

ASO TN E5 Lexington, TN [Revised]

Lexington, Franklin Wilkins Airport, TN
(Lat. 35°39′05″ N, long. 88°22′44″ W)
Jacks Creek VORTAC
(Lat. 35°35′56″ N, long. 88°21′32″ W)

That airspace extending upward from 700 feet above the surface within a 6.6-mile radius of Franklin Wilkins Airport, and within 8 miles east and 4 miles west of the Jacks Creek VORTAC 166° radial extending from the 6.6-mile radius to 16 miles southeast of the VORTAC.

* * * * *

Issued in College Park, Georgia on January 7, 2004.

Jeffrey U. Vincent,

Acting Manager, Air Traffic Division, Southern Region.

[FR Doc. 04–919 Filed 1–14–04; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 184

[Docket No. 1999P–5332]

Substances Affirmed as Generally Recognized as Safe: Menhaden Oil

AGENCY: Food and Drug Administration, HHS.

ACTION: Tentative final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a tentative final rule to amend its regulations by reallocating the uses of menhaden oil in food that currently are established in § 184.1472 (21 CFR 184.1472). FDA has tentatively concluded that these uses of menhaden oil are generally recognized as safe (GRAS), but only when the menhaden oil is not used in combination with other added oils that are significant sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Because FDA's proposed rule of February 26, 2002, did not include a condition of use for other added oils, FDA is issuing this tentative final rule to give interested persons an opportunity to comment on this use limitation.

DATES: Submit written or electronic comments by March 30, 2004.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Andrew J. Zajac, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740–3835, 202–418–3095.

SUPPLEMENTARY INFORMATION:

I. Background

Menhaden oil is a refined marine oil that is derived from menhaden fish (*Brevoortia* species). Menhaden oil differs from edible vegetable oils and animal fats in its high proportion of polyunsaturated fatty acids, including omega-3 fatty acids. EPA and DHA are the major source of omega-3 fatty acids from fish oil and together comprise approximately 20 percent by weight of menhaden oil. In response to a petition (GRASP 6G0316) from the National Fish Meal and Oil Association, FDA issued a final rule on June 5, 1997 (62 FR 30751)

(the June 1997 final rule), affirming menhaden oil as GRAS for use as a direct human food ingredient with limitations on the maximum use levels of menhaden oil in specific food categories. FDA concluded that these limitations are necessary to ensure that daily intakes of EPA and DHA from menhaden oil do not exceed 3.0 grams per person per day (g/p/d). As discussed in the following paragraphs, the maximum limit of 3.0 g/p/d on the total daily intake of EPA and DHA is a safeguard against the possible effects of these fatty acids on increased bleeding time (the time taken for bleeding from a standardized skin wound to cease), glycemic control in non-insulin-dependent diabetics, and increased levels of low-density lipoprotein (LDL) cholesterol. The concerns over possible adverse effects of fish oil consumption on bleeding time, glycemic control, and LDL cholesterol were discussed in the June 1997 final rule.

As part of FDA's evaluation of GRASP 6G0316, FDA examined the scientific literature for evidence that consumption of fish oils may contribute to excessive bleeding. In the June 1997 final rule, FDA concluded based on this examination of the scientific literature, including more than 50 reports on fish oils with data on bleeding time, that when consumption of fish oils is limited to 3.0 g/p/d or less of EPA and DHA, there is no significant risk for increased bleeding time beyond the normal range (62 FR 30751 at 30752 to 30753). FDA also concluded that amounts of fish oils providing more than 3.0 g/p/d of EPA and DHA have generally been found to produce increases in bleeding time that are statistically significant, but that there are insufficient data to evaluate the clinical significance of this finding. Therefore, because of the lack of data on clinical significance and because of the potential risk of excessive bleeding in some individuals with intakes at higher levels, FDA concluded that the safety of menhaden oil was generally recognized only at levels that limit intake of EPA and DHA to 3.0 g/p/d.

FDA also concluded in the June 1997 final rule that 3.0 g/p/d of EPA and DHA is a safe level with respect to glycemic control (62 FR 30751 at 30753). This conclusion was based on FDA's review of a series of studies on non-insulin-dependent diabetics. Studies on type-II diabetics that reported increased glucose used higher amounts (4.5 to 8 g/p/d) of omega-3 fatty acids. One study found no change in fasting blood glucose levels among type-II (non-insulin-dependent) diabetics treated with 3.0 g/p/d EPA plus DHA for 2 weeks. Two other studies that used 3.0 g/p/d EPA plus DHA for 6 weeks and 2.7 g/p/d EPA plus DHA for 8 weeks found only transient increases in blood glucose halfway through their respective supplementation periods. Another study that used 3.0 g/p/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 fed 3.0 g/p/d of EPA plus DHA 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. Based on its evaluation of the available information, FDA concluded in the June 1997 final rule that consumption of EPA and DHA in fish oils at 3.0 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.

The June 1997 final rule also 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 (62 FR 30751 at 30753 to 30754). As a result of its evaluation, FDA found that although reported study reports 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. Based on its evaluation, FDA concluded that 3.0 g/p/d of EPA and DHA is a safe level with respect to LDL cholesterol.

In the **Federal Register** of February 26, 2002 (67 FR 8744), FDA published a proposed rule to amend § 184.1472 by reallocating the uses of menhaden oil in food, while maintaining the total daily intake of EPA and DHA from menhaden oil at a level not exceeding 3.0 g/p/d. The proposal was based on a citizen petition from the National Fish Meal and Oil Association. The maximum limit of 3.0 g/p/d on the total daily intake of EPA and DHA is a safeguard against the possible adverse effects discussed in the June 1997 final rule and the February 2002 proposed rule. The reallocation is performed by the following three actions: (1) Reducing the maximum levels of use of menhaden oil in some of the currently listed food categories; (2) adding additional food categories along with assigning maximum levels of use in these new categories; and (3) eliminating the listing of subcategories, e.g., cookies and crackers, breads and rolls, fruit pies and custard pies, and cakes, and including them under broader food categories, e.g., baked goods and baking mixes.

The purpose of the maximum use levels of menhaden oil in the food categories is to ensure that the total daily intake of EPA and DHA does not exceed 3.0 g/p/d (67 FR 8744 to 8745). When the June 1997 final rule published affirming that menhaden oil is GRAS for use as a direct human food ingredient with specific limitations, FDA considered food sources of EPA and DHA likely to be in the diet at that time, but the agency did not take into account that other sources of EPA and DHA might be developed in the future. The implicit basis for the restrictions in the menhaden oil regulation was that while menhaden oil might be blended with other oils to make a particular food product, the sum of DHA and EPA would not exceed 3.0 g/p/d because other oils were not significant sources of DHA and EPA. However, since publication of the proposed rule, FDA has received notices from three companies that have concluded that fish oils, other than menhaden oil, are GRAS for use in the same food categories as those currently listed in § 184.1472(a)(3) at maximum use levels that are designed to assure that the combined daily intake of EPA and DHA would not exceed 3.0 g/p/d. These oils included small planktivorous pelagic fish body oil (oil derived primarily from sardine and anchovy fish) (Ref. 1), a fish oil concentrate (manufactured from oil extracted from edible marine fish species that normally include anchovy, sardine, jack mackerel, and mackerel) (Ref. 2), and tuna oil (Ref. 3). In each case, the company acknowledged the concerns raised by FDA in the June 1997 final rule and the proposed rule, about consumption of high levels of EPA and DHA. Furthermore, in each case the company stated that its determination of GRAS status related only to the circumstance where its fish oil product is used as the sole added source of EPA and DHA in any given food category and is not combined or augmented with any other EPA/DHA-rich oil.

Because of developing interest in food ingredients that are sources of EPA and DHA, FDA now believes that it is necessary to state explicitly in the regulation that when menhaden oil is added as an ingredient in foods, it may

not be used in combination with any other added oil that is a significant source of EPA and DHA. Without this restriction, the intake of DHA and EPA could exceed 3.0 g/p/d. Because this use restriction was not contained in the proposed rule, FDA is issuing this regulation as a tentative final rule under 21 CFR 10.40(f)(6). FDA will review any comments that are relevant to this condition of use and that are received within the 75-day comment period and will respond accordingly to these comments in the **Federal Register**.

FDA is also making an editorial update to § 184.1472(a)(2)(iii) to reflect that the name for the Office of Premarket Approval has been changed to the Office of Food Additive Safety.

II. Comments on the Proposed Rule

The agency provided 75 days for comments on the proposed rule. At the close of the comment period, the agency had received two comments that expressed concern regarding the environmental impact of the proposed rule. These two comments are addressed separately in section III of this document. The agency also received comments that were submitted from a fish oil company and a trade association that represents the fish oil industry that merely expressed general support for the agency's proposed rule. The other comments were from individual consumers who were opposed to the proposed rule.

Most of the comments FDA received expressing opposition to the proposed rule objected to declaring menhaden oil on food labels by the name "omega-3 fatty acids" or a variation of this name. Many of these comments asserted that "omega-3 fatty acids" is a misleading name for menhaden oil. Some comments were from vegetarians and vegans who stated that listing menhaden oil by the name "omega-3 fatty acids" will make it difficult for them to avoid this animal product in foods. There were also comments that stated that listing menhaden oil by the name "omega-3 fatty acids" will make it difficult for those with fish allergies to avoid this fish oil in foods.

The proposed rule did not address how menhaden oil is to be listed as an ingredient on food labels. Generally, under section 403(i)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(i)(2)), a food is misbranded unless its label bears the common or usual name of each ingredient. Although menhaden oil is a significant source of omega-3 fatty acids, FDA knows of no basis for considering omega-3 fatty acids to be its common or usual name. Any consideration of an alternative name for menhaden oil, such as "omega-3 fatty acids," is outside the scope of the proposed rule.

FDA also received comments from consumers asking the agency to consider the use of omega-3 fatty acids from sources other than menhaden fish, such as flax seed. FDA notes that although menhaden oil does contain omega-3 fatty acids (primarily EPA and DHA), omega-3 fatty acids are not the subject of the proposed rule. Therefore, the use of other oils is outside the scope of the proposed rule.

A few comments stated that the menhaden fish is unsuitable for human consumption and, therefore, oil from this fish should not be used as a food ingredient. As stated in the proposed rule, menhaden oil is already affirmed as generally recognized as safe as a direct human food ingredient (§ 184.1472). FDA has not received any new information or comments that would alter its previous determination that menhaden oil that meets the specifications in § 184.1472 is generally recognized as safe for use in food under the conditions specified.

Some of the comments FDA received expressing opposition to the proposed rule were against the addition of menhaden oil to foods because of a concern about the possibility of high levels of contaminants in the menhaden oil due to bioaccumulation of these contaminants in the menhaden fish. Bioaccumulation describes the process that results in an increase in the concentration of a chemical in a biological organism over time, compared to the chemical's concentration in the environment. FDA has evaluated data on levels of various chemical contaminants, such as pesticides, polychlorinated biphenyls and dioxins in menhaden oil. Based on these data, FDA finds no basis for a safety concern from food uses of menhaden oil due to possible bioaccumulation of lipophilic chemical contaminants in the source fish.

III. Environmental Impact

The agency received two comments expressing concern about the impact that the proposed rule will have on the menhaden fish population. One comment asked whether this action will result in the "near extinction" of menhaden, mackerel, and sardines, and further asked how near extinction, if it results, would effect ocean ecosystems. The other comment asserted that menhaden are being overfished to extinction, and that because of their population decline, larger game fish populations off the Atlantic coast are dropping proportionately. Neither comment cited supporting data or information.

To ensure that the maximum sustainable yield of menhaden is not exceeded and to provide long-term production, the menhaden fisheries are monitored by the Atlantic and Gulf States Marine Fisheries Commissions (which are under the jurisdiction of the National Marine Fisheries Service (NMFS)), as well as by State authorities. If there is a threat to the long-term yield of a fishery, generally, limits will be imposed by these organizations. At present, the Atlantic and Gulf menhaden fisheries are considered to be healthy and not overfished. With regard to the impact that the proposed rule will have on mackerel and sardines, the United Nation's Foreign Agricultural Organization reports that the primary practice used to catch menhaden has one of the lowest discard ratios of any method for general commercial fishing. (Less than 3 percent by weight of the total menhaden catch are other species of fish.) In addition, NMFS reports a numerical bycatch incidence (i.e., fish that are unintentionally caught) of less than 0.1 percent for the menhaden fishing industry. For these reasons, the agency does not believe that the proposed rule would result in overfishing of menhaden or have a significant impact on other species of fish. In summary, the comments do not provide a basis on which to change the conclusions of the environmental analysis that was prepared for the proposed rule, as discussed in the following paragraph.

The agency has previously considered the environmental effects of affirming menhaden oil as GRAS as a direct human food ingredient, provided that the combined daily intake of EPA and DHA from menhaden oil does not exceed 3.0 g/p/d (62 FR 30751 at 30754). The analysis assumed that the maximum use levels would be completely used for each food category and concluded that this action will not have a significant impact on the menhaden population. This rule will reallocate the maximum levels among food categories but will not increase the total maximum allowable level. Therefore, our previous analysis is applicable. No new information or comments have been received that would affect the agency's previous determination that there is no significant impact on the human environment, and that an environmental impact statement is not required.

IV. Analysis of Economic Impacts

A. Final Regulatory Impact Analysis

FDA has examined the economic implications of this tentative final rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; 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, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. FDA has determined that this tentative final rule is not a significant regulatory action as defined by Executive Order 12866.

In the economic analysis of the proposed rule, we stated that the main benefit of this rule would be the expansion of the potential uses of menhaden oil made possible by the new maximum levels. Firms choosing to use menhaden oil will bear labeling and other costs. Because these costs are voluntary, they will be borne only if doing so is anticipated to be advantageous to the firm. Although firms making products that now use menhaden oil at levels below the current maximum but above the new maximum could bear potential compliance costs, we noted in the proposed rule that FDA did not know of any products in that category. We received no comments on this conclusion, or on any other part of the preliminary regulatory impact analysis.

B. Final Regulatory Flexibility Analysis

FDA has examined the economic implications of this tentative final rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). 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 lessen the economic effect of the rule on small entities. FDA finds that this tentative final rule would not have a significant economic impact on a substantial number of small entities.

The use of the menhaden oil by any small business is voluntary and will be undertaken only if doing so is anticipated to be advantageous to the small business. Small businesses would only bear a compliance cost if, as stated previously, they make products that are below the current maximum but above the new maximum.

The agency specifically requested comments from small businesses on its assumption that no small businesses make products that will be affected by reducing the maximum levels of menhaden oil in pies, cakes, fats, oils, fish products, and meat products. We received no comments on that assumption or any other part of the initial regulatory flexibility analysis.

C. Unfunded Mandates

Title II of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires cost-benefit and other analyses before any rulemaking if the rule would include a "Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year." The current inflation-adjusted statutory threshold is $112 million. FDA has determined that this tentative final rule does not constitute a significant rule under the Unfunded Mandates Reform Act.

V. Paperwork Reduction Act

This tentative final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Federalism

FDA has analyzed this tentative final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the tentative final rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Because the agency concludes that this tentative final rule does not contain policies that have federalism implications as defined in the order, a federalism summary impact statement is not required.

VII. Comments

Interested person may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. GRAS notice GRN 000102, including the response letter to GRN 000102 dated September 3, 2002, from Alan M. Rulis of FDA to Edward Iorio of Jedwards International, available at *http://www.cfsan.fda.gov/~rdb/opa-gras.html.*

2. GRAS notice GRN 000105, including the response letter to GRN 000105 dated October 15, 2002, from Alan M. Rulis of FDA to Nancy L. Schnell of Unilever United States, Inc., available at *http://www.cfsan.fda.gov/~rdb/opa-gras.html.*

3. GRAS notice GRN 000109, including the response letter to GRN 000109 dated December 4, 2002, from Alan M. Rulis of FDA to Anthony Young of Piper Rudnick, LLP, available at *http://www.cfsan.fda.gov/~rdb/opa-gras.html.*

List of Subjects in 21 CFR Part 184

Food additives.

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, it is proposed that 21 CFR part 184 be 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: 21 U.S.C. 321, 342, 348, 371.

2. Section 184.1472 is amended by revising paragraph (a)(2)(iii) and (a)(3) and adding paragraph (a)(4) to read as follows:

§ 184.1472 Menhaden oil.

(a) * * *

(2)(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 Food Additive Safety, Center for Food Safety and Applied Nutrition (HFS–200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Center for Food Safety and Applied Nutrition's Library, Food and Drug Administration,

5100 Paint Branch Pkwy., College Park, MD 20740, or at the Office of the Federal Register, 800 North Capitol St. NW., suite 700, Washington, DC.

* * * * *

(3) In accordance with § 184.1(b)(2), the ingredient may be used in food only within the following specific limitations to ensure that total intake of eicosapentaenoic acid or docosahexaenoic acid does not exceed 3.0 grams/person/day:

Category of food	Maximum level of use in food (as served)
Baked goods, baking mixes, § 170.3(n)(1) of this chapter.	5.0 percent
Cereals, § 170.3(n)(4) of this chapter.	4.0 percent
Cheese products, § 170.3(n)(5) of this chapter.	5.0 percent
Chewing gum, § 170.3(n)(6) of this chapter.	3.0 percent
Condiments, § 170.3(n)(8) of this chapter.	5.0 percent
Confections, frostings, § 170.3(n)(9) of this chapter.	5.0 percent
Dairy product analogs, § 170.3(n)(10) of this chapter.	5.0 percent
Egg products, § 170.3(n)(11) of this chapter.	5.0 percent
Fats, oils, § 170.3(n)(12) of this chapter, but not in infant formula.	12.0 percent
Fish products, § 170.3(n)(13) of this chapter.	5.0 percent
Frozen dairy desserts, § 170.3(n)(20) of this chapter.	5.0 percent
Gelatins, puddings, § 170.3(n)(22) of this chapter.	1.0 percent
Gravies, sauces, § 170.3(n)(24) of this chapter.	5.0 percent
Hard candy, § 170.3(n)(25) of this chapter.	10.0 percent
Jams, jellies, § 170.3(n)(28) of this chapter.	7.0 percent
Meat products, § 170.3(n)(29) of this chapter.	5.0 percent
Milk products, § 170.3(n)(31) of this chapter.	5.0 percent
Nonalcoholic beverages, § 170.3(n)(3) of this chapter.	0.5 percent
Nut products, § 170.3(n)(32) of this chapter.	5.0 percent
Pastas, § 170.3(n)(23) of this chapter.	2.0 percent
Plant protein products, § 170.3(n)(33) of this chapter.	5.0 percent
Poultry products, § 170.3(n)(34) of this chapter.	3.0 percent
Processed fruit juices, § 170.3(n)(35) of this chapter.	1.0 percent
Processed vegetable juices, § 170.3(n)(36) of this chapter.	1.0 percent
Snack foods, § 170.3(n)(37) of this chapter.	5.0 percent
Soft candy, § 170.3(n)(38) of this chapter.	4.0 percent
Soup mixes, § 170.3(n)(40) of this chapter.	3.0 percent
Sugar substitutes, § 170.3(n)(42) of this chapter.	10.0 percent
Sweet sauces, toppings, syrups, § 170.3(n)(43) of this chapter.	5.0 percent
White granulated sugar, § 170.3(n)(41) of this chapter.	4.0 percent

(4) To ensure safe use of the substance, menhaden oil shall not be used in combination with any other added oil that is a significant source of eicosapentaenoic acid or docosahexaenoic acid.

* * * * *

Dated: January 6, 2004.

L. Robert Lake,

Director, Office of Regulations and Policy, Center for Food Safety and Applied Nutrition.

[FR Doc. 04–811 Filed 1–14–04; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE INTERIOR

Bureau of Indian Affairs

25 CFR Chapter 1

Meeting of the No Child Left Behind Negotiated Rulemaking Committee

AGENCY: Bureau of Indian Affairs, Interior.

ACTION: Announcement of negotiated rulemaking committee meeting.

SUMMARY: The Secretary of the Interior has established an advisory Committee to develop recommendations for proposed rules for Indian education under the No Child Left Behind Act of 2001. As required by the Federal Advisory Committee Act, we are announcing the date and location of the next meeting of the No Child Left Behind Negotiated Rulemaking committee.

DATES: The Committee's next meeting will be held February 2–7, 2004. The meeting will begin at 8:30 pm (PST) on Monday, February 2 and end at 5 pm (PST) on Saturday, February 7, 2004.

ADDRESSES: The meeting will be held at the San Diego Mission Bay Hilton, 901 Camino Del Rio South, San Diego, California 82108, telephone (619) 543–9000.

FOR FURTHER INFORMATION CONTACT: Shawna Smith, No Child Left Behind Negotiated Rulemaking Project Management Office, P.O. Box 1430, Albuquerque, NM 87103–1430; telephone (505) 248–7241/6569; fax (505) 248–7242; email *ssmith@bia.edu*. We will post additional information as it becomes available on the Office of Education Programs Web site under "Negotiated Rulemaking" at *http//www.oiep.bia.edu*.

SUPPLEMENTARY INFORMATION: The Secretary, after consultation with the tribes, has revised the charter of the negotiated rulemaking committee established to negotiate regulations to implement the No Child Left Behind Act of 2001 (Pub. Law 107–110). Under this revised charter, the committee will negotiate new regulations covering Closure or Consolidation of Schools (Section 1121(d)) and National Criteria for Home Living Situations (Section 1122). For more information on negotiated rulemaking under the No Child Left Behind Act, see the **Federal Register** notices published on December 10, 2002 (67 FR 75828) and May 5, 2003 (68 FR 23631) or the Web site at *http//www.oiep.bia.edu* under "Negotiated Rulemaking."

There is no requirement for advance registration for members of the public who wish to attend and observe the Committee meeting or any work group meetings. Members of the public may make written comments on the above-listed items to the Committee by sending them to the NCLB Negotiated Rulemaking Committee, Project Management Office, P.O. Box 1430, Albuquerque, New Mexico 87103. We will provide copies of the comments to the Committee.

The agenda for the February 2–7, 2004, meeting is as follows:

Table 1 Intended Uses and Maximum Use Levels of DHA-rich oil in Food

Food Category	Initial[a] Intended Use Levels (% by weight)	Future[b] Intended Use Levels (% by weight)
Nonalcoholic beverages (3)	-	0.3
Pastas (23)	-	1 3
Poultry products (34)	-	2.0
Processed fruit juices (35)	-	0.7
White grandulated sugar (41)	-	2.7
Sugar substitutes (42)	-	6.7
Chewing gum (6)	-	2.0
Gelatins and puddings (22)	-	0.7
Confections and frosting (9)	-	3.3
Sweet sauces, toppings, and syrups (43)	-	3.3

[a] Based on 21 CFR §184.1472
[b] Based on tentative final rule amending 21 CFR §184.1472 (69 FR 2313; January 15, 2004)
[1] The number in parenthesis following each food category refers to the paragraph listing of the particular food category in 21 CFR 170.3(n)
[2] Included in "Baked goods and baking mixes"
[3] Not including infant formula
[4] Included in "Milk products"

In a final rule affirming menhaden oil as GRAS for use as a direct human food ingredient (21 CFR §184.1472), the FDA concluded that 3.0 g EPA (eicosapentaenoic acid) and DHA/person/day is a safe intake level with respect to bleeding time, increased bleeding time, glycemic control and LDL cholesterol levels (FDA, 1997). In order to ensure that intake does not exceed 3.0 g/person/day the FDA introduced maximum use levels of menhaden oil in specific food categories. The specific food categories and use limitations for menhaden oil were published recently in a tentative final rule (FDA, 2004a). The use limitations of EPA and DHA were based on the content of EPA and DHA within menhaden oil, approximately 20%. Furthermore, the FDA stated that menhaden oil may not be used in combination with any other added oil that is a significant source of EPA and DHA, as to ensure compliance with the prescribed limitations.

Comparing the composition of menhaden oil (sum of approximately 20% of EPA and DHA) with DHA-rich oil (DHA content of 38 to 50% and no significant EPA content), it can reasonably be concluded that approximately twice as much menhaden oil as DHA-rich oil will have to be consumed for the same intake of ω-3 fatty acids. Inversely, any limitation of use levels from DHA-rich oil will therefore have to be less than 50% of the use levels of menhaden oil to ascertain compliance with the safe intake level. Consequently, the limitation of DHA-rich oil use levels to 40% of the use levels in all food categories considered by the US FDA for the GRAS use of menhaden oil would also ascertain compliance with the safe intake level of 3.0 g/person/day for the sum of EPA and DHA. To ensure safe use levels in the intended food

categories and levels of use, DHA-rich oil shall not be used in combination with any other added oil that is a significant source of EPA or DHA.

DHA is primarily consumed through the ingestion of fatty fish, which contain high amounts of PUFAs with concentrations of ω-3 fatty acids ranging from 0.1 to 5.3 g/100 g (Ascherio *et al.*, 1995; Sanders, 1989). The normal consumption of ω-3 fatty acids in the United States is approximately 1,600 mg/day, primarily as α-linolenic acid (18:3), as well as lesser amounts of EPA, DHA, and DPA. The total amount of DHA consumed per day in the United States has been estimated at 100 to 200 mg/day, while higher consumption of DHA has been reported in other populations such as Japan, Norway, South Africa, and the Portuguese island of Madeira whose diets include many DHA-containing foods with average DHA intakes of approximately 500 to 700 mg DHA/day (Dolecek and Granditis, 1991; Schloss *et al.*, 1997; Fluge *et al.*, 1998; Johansson *et al.*, 1998; Kris-Etherton *et al.*, 2000; Sugano and Hirahara, 2000; Torre *et al.*, 2000). Recommended intakes of ω-3 PUFAs have been published by a number of scientific authorities including Health Canada, which recommends an intake of 1,000 to 1,800 mg ω-3 PUFAs/day in a ratio of 1:4 to 1:10 with ω-6 PUFAs (Health and Welfare Canada, 1990). Furthermore, the International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommended adequate intakes (AI) of a minimum of 220 mg/day for both DHA and EHA separately, while a combined AI for both DHA and EPA was recommended at 650 mg/day. The British Nutrition Foundation also has recommended a desirable intake of DHA and EPA within females and males of the population of approximately 1,100 and 1,400 mg/day, respectively (BNF, 2000).

I.E Basis for the GRAS Determination

The determination that DHA-rich oil, as defined in Appendix I, is GRAS is on the basis of scientific procedures (see Appendix I entitled, "**EXPERT PANEL CONSENSUS STATEMENT: THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF DHA-RICH OIL UNDER THE CONDITIONS OF INTENDED USE IN TRADITIONAL FOODS**").

The safety of DHA-rich oil is based on animal studies using other DHA-containing oils, as well as studies performed specifically with DHA-rich oil (reported as DHA45-oil). The studies performed with DHA-rich oil included mutagenicity/genotoxicity, acute, subchronic, and a single generation reproductive toxicity study. Human clinical trials also are included in support of the safety of DHA-rich oil, whereby a number of toxicologically relevant endpoints are examined including bleeding times and other hemostatic parameters, glycemic control, LDL cholesterol and other plasma lipid fractions, as well as additional clinical studies with endpoints related to the safety of DHA.

I.F Availability of Information

The data and information that serve as the basis for this GRAS determination will be sent to the U.S. Food and Drug Administration upon request or will be available for FDA review and copying at reasonable times at the offices of:

Dr. Bernd Haber
Head of Scientific and Regulatory Affairs
Nutrinova Nutrition Specialties & Food Ingredients GmbH
Industriepark Höchst, D 706
65926 Frankfurt, Germany

Should the FDA have any questions or additional information requests regarding this notification, Nutrinova GmbH will supply these data and information.

II. Detailed Information About the Identity of the Substance

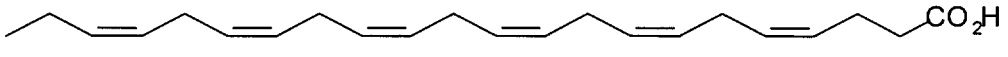
II.A Identity

DHA-rich oil is a refined triacylglycerol oil (>95% triacylglycerols), derived from a marine protist, with a total fatty acid composition of 38 to 50% DHA. The remaining fatty acids of DHA-rich oil are comprised mainly of saturated palmitic acid (16:0) (28 to 37%) and a lesser amount (8 to 14%) of the ω-6 fatty acid, docosapentaenoic acid (DPA) (22:5). In addition, DHA-rich oil contains safe and suitable antioxidants as permitted by the FDA for use in edible oils to ensure stability.

Common or Usual Name:	DHA-rich oil, containing 38 to 50% DHA; DHA oil 45; DHA45-TG; Nutrinova® DHA
Chemical Name:	All-cis-4,7,10,13,16,19-docosahexaenoic acid (22:6) esterified to glycerol
Chemical Abstracts Service	None assigned for DHA-rich oil; however, DHA assigned CAS No. 6217-54-5

The structural formula of DHA is provided below in Figure 1.

Figure 1 All-cis-4,7,10,13,16,19-docosahexaenoic acid (22:6)



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II.B Method of Manufacture

DHA-rich oil is produced in accordance with current good manufacturing practices through a multi-step fermentation and refining process using a genetically stable and pure culture of the marine protist, *Ulkenia sp*. DHA-rich oil is extracted *via* a solvent-based extraction process using food grade solvents and processing aids, and is further refined by processes standard to the edible oil industry, including degumming, deacidification, bleaching and deodorization, using materials appropriate for food processing. A schematic diagram of the proprietary manufacturing process for DHA-rich oil is presented in Figure 3. Product specifications are presented in Table 4.

Figure 3 – Proprietary Manufacturing Process for DHA-rich oil

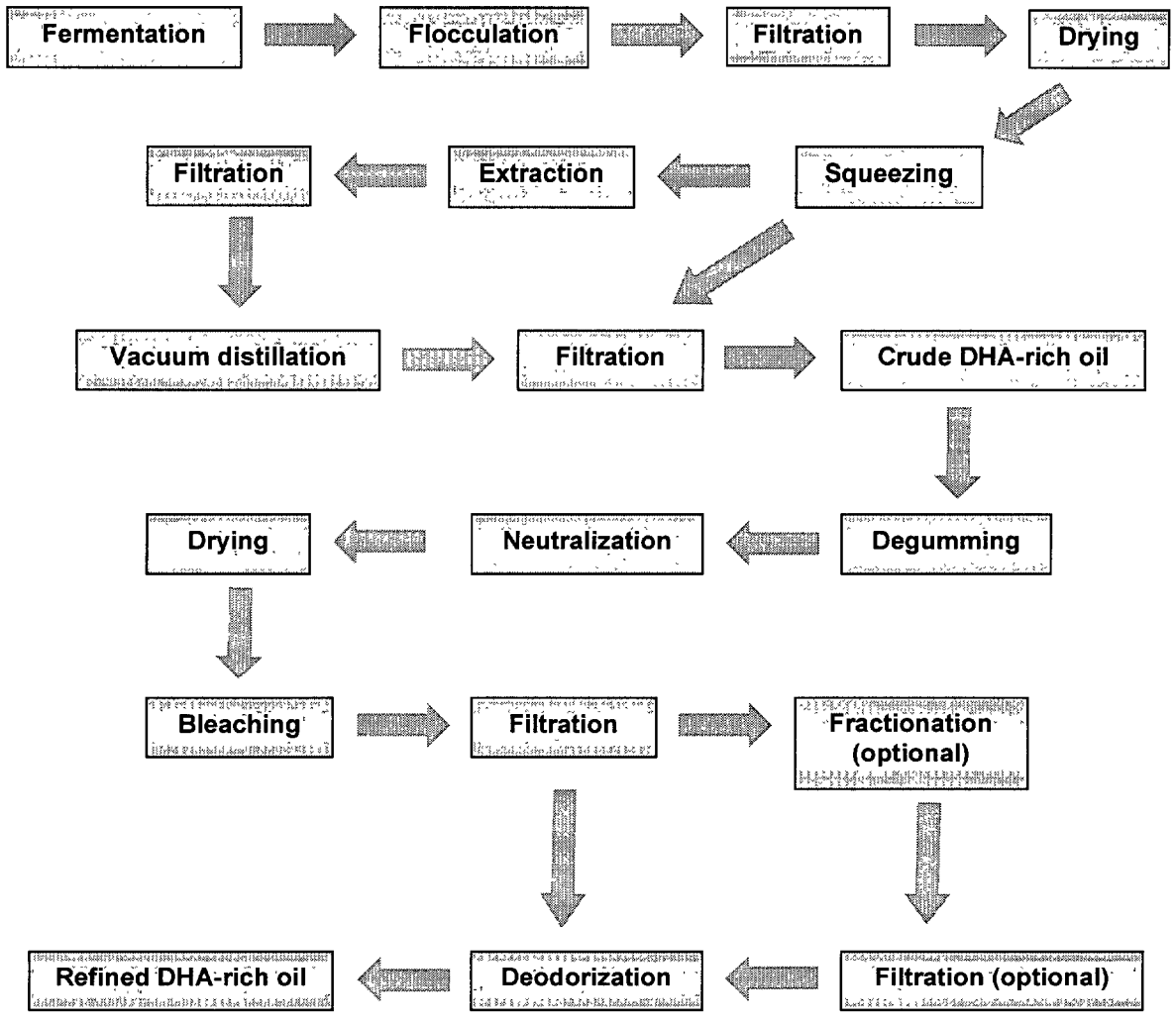

Table 4 Product Specifications for DHA-rich oil	
Parameter	**Specification**
DHA	38 to 50 (% by weight)
Trans Fatty Acids	≤ 2 %
Peroxide value	≤ 5 meq./kg
Acid value	≤ 0.5 mg KOH/g
Moisture and Volatiles	≤ 0.05 %
Unsaponifiables	≤ 4.5 %
Lead	≤ 0.1 ppm
Arsenic	≤ 0.5 ppm
Mercury	≤ 0.5 ppm

III. Basis for GRAS Determination

Pursuant to 21 CFR §170.30, the composition of DHA-rich oil intended for use in foods by Nutrinova GmbH, as defined in Appendix I, has been determined to be GRAS based on scientific procedures. This determination is based on the opinion of experts (the Expert Panel) who are qualified by their scientific training and experience to evaluate the safety of DHA-rich oil as a component of food. Further support for the safety of DHA-rich oil is well established based on the historical consumption of DHA from fatty fish (*e.g.*, haddock, tuna, salmon, mackerel) and other food sources.

The safety of DHA-rich oil is supported by a number of toxicological studies conducted in mice and rats, specifically acute, subchronic and single generation reproduction studies, as well as, with mutagenicity studies conducted using *Salmonella typhimurium*, *Escherichia coli* WP2 *uvrA* (with or without metabolic activation), or using a chromosomal aberration assay in Chinese hamster fibroblast cells (Fujii and Suwa, 1998; Kashima and Sarwar, 2000; Neda, 2000; Bruijntjes-Rozier and van Ommen, 2001; Kuilman and Waalkens-Berendsen, 2001; Kroes *et al.*, 2003). The results of these studies indicate that DHA-rich oil, is not genotoxic or mutagenic, and is of low toxicity. When administered to rats *via* the diet at levels providing up to 2,000 mg/kg body weight/day (equivalent to 900 mg DHA/kg body weight/day) in the subchronic study, and as high as 11,200 mg DHA-rich oil/kg body weight/day (equivalent to 5,040 mg DHA/kg body weight/day) in female rats during gestation and lactation (days 1 to 14), DHA-rich oil did not produce any compound-related adverse effects (aside from effects attributed to the extremely high levels of PUFAs added in the diet of the experimental animals).

The safety of DHA-containing fish and microalgal-derived oils has been studied extensively in toxicological studies, and these studies further support the safety of DHA-rich oil. Overall, the data from these studies indicate that gavage or dietary administration of fish or microalgal-derived oils does not produce significant adverse effects on mortality, body weight gains, food consumption, or clinical observations in laboratory animals including mice, rats, and pigs (Danse and Verschuren, 1978a; Ruiter *et al.,* 1978; Willumsen *et al.*, 1993; Boswell *et al.*, 1996; Hempenius *et al.*, 1997, 2000; Wibert *et al.,* 1997; Rabbani *et al.,* 1999; Arterburn *et al.,* 2000a,b; Oarada *et al.*, 2000; Hammond *et al.*, 2001a,b,c). Yellow fat disease, which is characterized by accretion of lipofuscin pigment, degeneration of adipose cells (steatosis), and inflammation of adipose tissue (steatitis) (Danse and Steenbergen-Botterweg, 1976; Danse and Verschuren, 1978a; Danse *et al.*, 1979), has been reported to occur naturally in wildlife species and was reported in rats, rabbits, mink, and pigs in various toxicological studies following the consumption of diets rich in ω-3 PUFAs (*i.e.*, ω-3 PUFA-containing oils at dietary concentrations ranging from as high as 12 to 19% for periods of 8 weeks to 12 months in length) in combination with a vitamin E deficient state (Jones *et al.,* 1969; Helgebostad and Ender, 1973; Danse and Steenbergen-Botterweg, 1976, 1978; Danse and Verschuren, 1978a,b; Ruiter *et al.*, 1978; Danse *et al.,* 1979; Charnock *et al.,* 1987; Verschuren et al., 1990; Farwer et al., 1994; Hempenius *et al.*, 1997, 2000). This effect is considered a normal response to a large load of dietary lipids, and may be prevented by concurrently administering vitamin E with high-PUFA diets (Helgebostad and Ender, 1973; Verschuren *et al.,* 1990; Farwer *et al.*, 1994; Muggli, 1994; Ando *et al.*, 2000). Some study authors reported increased liver and spleen weights in mice and rats administered high PUFA diets at daily intakes ranging from 25 to 9,500 mg/kg body weight and varying durations of 4 to 13 weeks (Danse and Verschuren, 1978a,b; Boswell et al., 1996; Hempenius *et al.*, 1997; McGuire *et al.*, 1997; Burns *et al.*, 1999a; Rabbani *et al.*, 1999; Oarada *et al.*, 2000); however, no histopathological effects were observed in these organs and the increased organ weights were reported to be adaptations to accommodate the large lipid load.

The safety of DHA-rich oil is further corroborated by an extensive number of human clinical studies with endpoints relevant to determining the safety and metabolism of DHA (von Schacky *et al.*, 1985; Hostmark *et al.*, 1988; Mehta *et al.*, 1988; Radack *et al.*, 1989; Bønaa *et al.*, 1992; Deslypere, 1992; Haglund *et al.,* 1992, 1998; Kenny *et al.*, 1992; Mori *et al.*, 1992, 1997, 2000; Saynor and Gillott, 1992; Schmidt *et al.*, 1992; Almdahl *et al.*, 1993; Clark *et al.,* 1993; Connor *et al.*, 1993; Hansen *et al.*, 1993a,b, 1998a,b; Harris *et al.,* 1993, 1997; Krokan *et al.*, 1993; Mundal *et al.*, 1993; Nilsen *et al.*, 1993; Swails *et al.*, 1993; Axelrod *et al.*, 1994; Chin and Dart, 1994; Cirillo *et al.*, 1994; de Maat *et al.*, 1994; Eritsland *et al.*, 1994a,b, 1995a,b, 1996; Henderson *et al.*, 1994; Leaf *et al.*, 1994; Lungershausen *et al.*, 1994; Mackness *et al.*, 1994; McVeigh *et al.*, 1994; Mundal *et al.*, 1994; Nordøy *et al.,* 1994, 1998; Prisco *et al.*, 1994, 1995; Turini *et al.*, 1994; Bonnema *et al.*, 1995; Christensen *et al.*, 1995; Luostarinen *et al.*, 1995; Misso and Thompson, 1995; Morgan *et al.*, 1995; Sacks *et al.*, 1995; Toft *et al.*, 1995, 1997; Tremoli *et al.*, 1995; Ågren *et al.*, 1996, 1997; Bagdade *et al.*, 1996; Balestrieri *et al.*, 1996; Conquer and Holub, 1996, 1998; Engström *et al.*, 1996; Fasching *et al.,* 1996; Gray *et al.*, 1996; Hamazaki *et*

al., 1996; Innis and Hansen, 1996; Lenzi *et al.*, 1996; McGrath *et al.*, 1996; McManus *et al.*, 1996; Otto *et al.*, 1996; Palozza *et al.*, 1996; Rivellese *et al.*, 1996; Rossing *et al.*, 1996; Silva *et al.*, 1996; Wigmore *et al.*, 1996; Yosefy *et al.*, 1996; Adler and Holub, 1997; Badalamenti *et al.*, 1997; Brister and Buchanan, 1997; Freese and Mutanen, 1997a,b; Goh *et al.*, 1997; Grimsgaard *et al.*, 1997, 1998; Nelson *et al.*, 1997; Roulet *et al.*, 1997; Sanders *et al.*, 1997; Tsai and Lu, 1997; Gogos *et al.*, 1998; Kelley *et al.*, 1998, 1999; Swahn *et al.*, 1998; Burns *et al.*, 1999b; Conquer *et al.*, 1999; Grundt *et al.*, 1999; Pirich *et al.*, 1999; Seljeflot *et al.*, 1999; Véricel *et al.*, 1999; Wensing *et al.*, 1999; Almallah *et al.*, 2000; Wallace *et al.*, 2000; Yaqoob *et al.*, 2000; Woodman *et al.*, 2003). As reviewed by Kroes *et al.* (2003) and as reported by the Expert Panel, clinical studies include metabolic studies indicating that the absorption, distribution, and metabolism of DHA is similar to other fatty acids, as well as, studies examining the effect of DHA-containing oils on bleeding times and other hemostatic parameters, glycemic control, low density lipoprotein (LDL) cholesterol and other plasma lipid fractions, as well as, additional measured endpoints (*e.g.*, immune function, liver and kidney function) related to the safety of DHA. Overall, the results of these studies provide evidence that DHA, at estimated exposures provided through the intended use of DHA-rich oil, would not have an adverse effect on human health. The available data further indicates other components of DHA-rich oil, namely palmitic acid, docosapentaenoic acid, and sterols, would not have adverse effects on human health (Kroes *et al.*, 2003) under the intended conditions of use of DHA-rich oil.

The consumption of DHA-containing oils providing up to 6 g DHA/day, alone or in combination with DPA and/or EPA, has been reported to result in alterations of platelet and total serum phospholipid and nonesterified fatty acid compositions, with increases in the levels of ω-3 PUFAs, including DHA, and concomitant decreases in levels of arachidonic acid (AA) (20:4; ω-6) of up to 26% (Mori *et al.*, 1992, 1997; Schmidt *et al.*, 1992; Mundal *et al.*, 1993; Eritsland *et al.*, 1994a; Henderson *et al.*, 1994; Leaf *et al.*, 1994; Turini *et al.*, 1994; Luostarinen *et al.*, 1995; Tremoli *et al.*, 1995; Conquer and Holub, 1996; Engström *et al.*, 1996; Parkinson *et al.*, 1996; Nelson *et al.*, 1997; Conquer and Holub, 1998; Haglund *et al.*, 1998; Conquer *et al.*, 1999; Yaqoob *et al.*, 2000). Arachidonic acid, either obtained in the diet or as a biosynthetic product of linoleic acid (18:2; ω-6), occurs as a fatty acid component of platelet membranes and most tissue phospholipids functioning as the main precursor of eicosanoids, which are involved in mediation of hemostatic parameters and immune cell function and response (Linder, 1991; Foegh *et al.*, 1998; Kelley and Rudolph, 2000). Critical review of the scientific literature indicates that while AA levels may decrease following consumption of ω-3 PUFAs, the concentration of AA generally remains within normal physiological concentrations of 5 to 15% of total fatty acids of platelet membranes and tissue phospholipids (Kroes *et al.*, 2003). There is no indication that DHA, at exposures estimated through the proposed uses of DHA-rich oil, would adversely affect hemostatic parameters or immune function or response as a result of possible concomitant decreases in platelet and total serum phospholipid and nonesterified fatty acid levels of AA (Haglund *et al.*, 1992, 1998; Mori *et al.*, 1992, 1997; Schmidt *et al.*, 1992; Eritsland *et al.*, 1994a; Henderson *et al.*, 1994; Leaf *et al.*, 1994; Parkinson *et al.*, 1994; Turini *et al.*, 1994; Luostarinen

et al., 1995; Tremoli *et al.*, 1995; Conquer and Holub, 1996; Engström *et al.*, 1996; Nelson *et al.*, 1997; Gogos *et al.*, 1998; Kelley *et al.*, 1998, 1999; Conquer *et al.*, 1999; Almallah *et al.*, 2000; Yaqoob *et al.*, 2000).

The safety of DHA-rich oil is further substantiated given that the source organism, *Ulkenia sp.*, a thraustochytrid and a member of the Chromista kingdom (Bahnweg, 1979; Cavalier-Smith *et al.*, 1994; Honda *et al.*, 1999; European Register of Marine Species, 2001), has not been reported to produce toxins or to demonstrate pathogenicity (OmegaTech GmbH, 1997; Van Dolah, 2001). Thraustochytrids are known to exhibit worldwide distribution, having been identified in plankton and other marine detritus, as well as comprising a portion of the diet of filter-feeding invertebrates in the marine ecosytem (Ulken *et al.*, 1990; Sathe-Pathak *et al.*, 1993; Azevedo and Corral, 1997; Naganuma *et al.*, 1998). Due to their wide distribution throughout the marine ecosystem, thraustochytrids constitute an indirect component of the human diet through the consumption of marine creatures (*e.g.*, clams or mussels). The source organism has been demonstrated to be nonmutagenic in the Ames assay using *Salmonella typhimurium* strains TA97, TA98, TA100, and TA102 with or without metabolic activation (Fujii and Suwa, 1999). Furthermore, the source organism, *Ulkenia sp.* is taxonomically distinct from known toxin-producing organisms and no known species of thraustochytrids have been identified as producers of microalgal toxins (OmegaTech GmbH, 1997; Van Dolah, 2001). The absence of microalgal toxins has been confirmed in lot analyses of DHA-rich oil, thus demonstrating the absence of common algal and cyanobacterial toxins. Furthermore, independent evaluation by scientific experts (Melkonian, 2003; Schaumann, 2003), using data pertinent to safety, has concluded *Ulkenia sp.* to be both nontoxigenic and nonpathogenic to man.

Evaluation of the totality of the scientific data by the Expert Panel pertaining to the safety of DHA-rich oil under the intended conditions of use in foods resulted in the conclusion that DHA-rich oil, "meeting appropriate food grade specifications, and manufactured and used in accordance with current good manufacturing practice, under the conditions of intended use specified herein, is "generally recognized as safe" (GRAS)" (see Appendix I).

The intended intake of DHA through the intended food uses of DHA-rich oil will not exceed the limits assigned by the FDA through the menhaden oil GRAS, and is consistent with other ω-3, DHA-containing oils that have notified the FDA as GRAS for similar uses (FDA, 2002a,b; 2004b,c). Since the DHA level in DHA-rich oil is approximately 2 to 2.5 times higher than the combined levels of DHA and EPA in menhaden oil, the proposed use levels for DHA-rich oil of 40% of those GRAS-affirmed for menhaden oil will ensure an intake within the limits considered safe by the FDA. Furthermore, DHA-rich oil is not intended for use in combination with other oils that are significant sources of ω-3 fatty acids, DHA and EPA.

There are no indications from the published literature, or from the published studies conducted with DHA-rich oil, that under the conditions of intended use in traditional foods, DHA-rich oil would result in any adverse health effects.

IV. References

Adler, A.J.; Holub, B.J. 1997. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. Am J Clin Nutr 65(2):445-450.

Ågren, J.J.; Hänninen, O.; Julkunen, A.; Fogelholm, L.; Maliranta, H.; Schwab, U.; Pynnönen, O.; Uusitupa, M. 1996. Fish diet, fish oil and docosahexaenoic acid rich oil lower fasting and postprandial plasma lipid levels. Eur J Clin Nutr 50(11):765-771.

Ågren, J.J.; Väisänen, S.; Hänninen, O.; Muller, A.; Hornstra, G. 1997. Hemostatic factors and platelet aggregation after a fish-enriched diet or fish oil or docosahexaenoic acid supplementation. Prostaglandins Leukot Essent Fatty Acids 57(4&5):419-421.

Akiba, S.; Murata, T.; Kitatani, K.; Sato, T. 2000. Involvement of lipoxygenase pathway in docosapentaenoic acid-induced inhibition of platelet aggregation. Biol Pharm Bull 23(11):1293-1297.

Almallah,Y.Z., Ewen, S.W., El-Tahir, A., Mowat, N.A., Brunt, P.W., Sinclair, T.S., Heys, S.D., Eremin, O. 2000. Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. J Clin Immunol 20(1):68-76.

Almdahl, S.M., Nilsen, D.W.T., Østerud, B., Sørlie, D.G.; Vaag, J. 1993. Thromboplastin activities and monocytes in the coronary circulation of reperfused human myocardium. Scand J Thorac Cardiovasc Surg 27(1):81-86.

Ando, K.; Nagata, K.; Yoshida, R.; Kigugawa, K.; Suzuki, M. 2000. Effect of n-3 polyunsaturated fatty acid supplementation on lipid peroxidation of rat organs. Lipids 35(4):401-407.

Arterburn, L.M.; Boswell, K.D.; Koskelo, E.; Kassner, S.L.; Kelly, C.; Kyle, D.J. 2000a. A combined subchronic (90-day) toxicity and neurotoxicity study of a single- cell source of docosahexaenoic acid triglyceride (DHASCO® oil). Food Chem Toxicol 38(1):35-49.

Arterburn, L.M.; Boswell, K D.; Henwood, S.M.; Kyle, D.J. 2000b. A development safety study in rats using DHA-and ARA-rich single-cell oils. Food Chem Toxicol 38(9):763-771.

Ascherio, A.; Rimm, E.B.; Stampfer, M.J.; Giovannucci, E.L.; Willett, W.C. 1995. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med 332(15):977-982.

Axelrod, L.; Camuso, J.; Williams, E.; Kleinman, K.; Briones, E.; Schoenfeld, D. 1994. Effects of a small quantity of -3 fatty acids on cardiovascular risk factors in NIDDM. Diabetes Care 17(1):37-44.

Azevedo, C.; Corral, L. 1997. Some ultrastructural observations of a thraustochytrid (Protoctista, Labyrinthulomycota) from the clam Ruditapes decussatus (Mollusca, Bivalvia). Dis Aquat Organ 31(1):73-78.

Badalamenti, S.; Salerno, F.; Sameron, J.M.; Lorenzano, E.; Rimola, A.; Gines, P.; Jimenez, W.; Graziani, G.; Arroyo, V.; Rodes, J.; Ponticelli, C. 1997. Lack of renal effects of fish oil administration in patients with advanced cirrhosis and impaired glomerular filtration. Hepatology 25(2):313-316.

Bagdade, J.D.; Ritter, M.; Subbaiah, P.V. 1996. Marine lipids normalize cholesteryl ester transfer in IDDM. Diabetologia 39(4):487-491.

Bahnweg, G. 1979. Studies on the physiology of thraustochytriales. I. Growth requirements and nitrogen nutrition of Thraustochytrium spp., Schizochytrium sp., Japonochytrium sp., Ulkenia spp., and Labyrinthuloides spp. Veroff Inst Meersforsch Bremerh 17:245-268.

Balestrieri, G.P.; Maffi, V.; Sleiman, I.; Spandrio, S.; Di Stefano, O.; Salvi, A.; Scalvini, T. 1996. Fish oil supplementation in patients with heterozygous familial hypercholesterolemia. Recenti Prog Med 87(3):102-105.

BNF. 2000. n-3 Fatty Acids and Health. British Nutrition Foundation (BNF); London, Engl.

Bønaa, K.H.; Bjerve, K.S.; Nordøy, A. 1992. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. Arterioscler Thromb 12(6):675-681.

Bonnema, S.J.; Jespersen, L.T.; Marving, J.; Gregersen, G. 1995. Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. Diabetes Nutr Metab 8(2):81-87.

Boswell, K.; Koskelo, E.K.; Carl, L.; Glaza, S.; Hensen, D.J.; Williams, K.D.; Kyle, D.J. 1996. *Preclinical evaluation of* single-cell oils that are highly enriched with arachidonic acid and docosahexaenoic acid. Food Chem Toxicol 34(7):585-593.

Brister, S.J.; Buchanan, M.R. 1997. Effects of linoleic acid and/or marine fish oil supplements on vessel wall thromboresistance in patients undergoing cardiac surgery. In: Sinzinger, H.; Samuelsson, B.; Vane, J.R.; Paoletti, R.; Ramwell, P.; Wong, P.Y.-K. (Eds.). Recent Advances in Prostaglandin, Thromboxane, and Leukotriene Research. 10th International Conference on Prostaglandins and Related Compounds - Proceedings, Sep. 22-27, 1996, Vienna, Austria. Plenum Press; New York. Advances in Experimental Medicine and Biology, Vol. 433, pp. 275-278.

Bruijntjes-Rozier, T.; van Ommen, B. 2001. Bacterial Reverse Mutation Test with DHA-Oil 45. Prepared by TNO Nutrition and Food Research; Zeist, The Netherlands at the request of Axiva GmbH Ventures; Frankfurt am Main, Germany. TNO-Report V2505/08.

Burns, R.A.; Wibert, G.J.; Diersen-Schade, D.A.; Kelly, C.M. 1999a. Evaluation of single-cell sources of docosahexaenoic acid and arachidonic acid: 3-month rat oral safety study with an in utero phase. Food Chem Toxicol 37(1):23-36.

Burns, C.P.; Halabi, S.; Clamon, G.H.; Hars, V.; Wagner, B.A.; Hohl, R.J.; Lester, E.; Kirshner, J.J.; Vinciguerra, V.; Paskett, E. 1999b. Phase I clinical study of fish oil fatty acid capsules for patients with cancer cachexia: cancer and leukemia group B study 9473. Clin Cancer Res 5(12):3942-3947.

Cavalier-Smith, T.; Allsopp, M.T.E.P.; Chao, E.E. 1994. Thraustochytrids are chromists, not fungi: 18s rRNA signatures of heterokanta. Philos Trans R Soc Lond B Biol Sci 346:387-397.

Charnock, J.S.; Turner, J.; McIntosh, G.H. 1987. The occurrence of cardiac lipidosis and necrotic lesions in the hearts of rats following long-term feeding of different lipid supplemented diets. J Nutr Sci Vitaminol 33(1):75-87.

Chin, J.P.; Dart, A.M. 1994. Therapeutic restoration of endothelial function in hypercholesterolaemic subjects: Effect of fish oils. Clin Exp Pharmacol Physiol 21(10):749-755.

Christensen, J.H.; Gustenhoff, P.; Ejlersen, E.; Jessen, T.; Korup, E.; Rasmussen, K.; Dyerberg, J.; Schmidt, E.B. 1995. n-3 Fatty acids and ventricular extrasystoles in patients with ventricular tachyarrhythmias. Nutr Res 15(1):1-8.

Cirillo, F.; Coppola, A.; Piemontinio, U.; Marottoli, V.; Amoriello, A.; Cerbone, A.M.; Stragliotto, E.; Tremoli, E.; Di Minno, G.; Mancini, M. 1994. Platelet effects of omega 3 fatty acid ethyl esters. In: Galli, C.; Simopoulos, A.P.; Tremoli, E. (Eds.). Effects of Fatty Acids and Lipids in Health and Disease. Karger; Basel, Switz./New York. World Review of Nutrition and Dietetics, Vol. 76, pp. 60-63.

Clark, W.F.; Parbtani, A.; Naylor, C.D.; Levinton, C.M.; Muirhead, N., Spanner, E.; Huff, M.W.; Philbrick, D.J.; Holub, B.J. 1993. Fish oil in lupus nephritis: Clinical findings and methodological implications. Kidney Int 44(1):75-86.

Connor, W.E., Prince, M.J., Ullmann, D., Riddle, M., Hatcher, L., Smith, F. E.; Wilson, D. 1993. The hypotriglyceridemic effect of fish oil in adult-onset diabetes with adverse glucose control. Ann N Y Acad Sci 683:337-340.

Conquer, J.A.; Holub, B.J. 1996. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. J Nutr 126(12):3032-3039.

Conquer, J.A.; Holub, B.J. 1998. Effect of supplementation with different doses of DHA on the levels of circulating DHA as non-esterified fatty acid in subjects of Asian Indian background. J Lipid Res 39(2):286-292.

Conquer, J.A.; Cheryk, L.A.; Chan, E.; Gentry, P.A.; Holub, B.J. 1999. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. Thromb Res 96(3):239-250.

Danse, L.H.; Steenbergen-Botterweg, W.A. 1976. Early changes of yellow fat disease in mink fed a vitamin-E deficient diet supplemented with fresh or oxidised fish oil. Zentralbl Veterinarmed 23(8):645-660.

Danse, L.H.; Steenbergen-Botterweg, W.A. 1978. Fish oil-induced yellow fat disease in rats. II. Enzyme histochemistry of adipose tissue. Vet Pathol 15(1):125-132.

Danse, L.H.; Verschuren, P.M. 1978a. Fish oil-induced yellow fat disease in rats. I. Histological changes. Vet Pathol 15(1):114-124.

Danse, L.H.; Verschuren, P.M. 1978b. Fish oil-induced yellow fat disease in rats. III. Lipolysis in affected adipose tissue. Vet Pathol 15(4):544-548.

Danse, L.H.; Stolwijk, J.; Verschuren, P.M. 1979. Fish oil-induced yellow fat disease in rats. *IV. Functional studies of the* reticuloendothelial system. Vet Pathol 16(5):593-603.

de Maat, M.P.M.; Princen, H.M.G.; Dagneli, P.C.; Kamerling, S.W.A.; Kluft, C. 1994. Effect of fish oil and vitamin E on the cardiovascular risk indicators fibrogen, C-reactive protein and PAI activity in healthy young volunteers. Fibrinolysis 8(Suppl. 2):50-52.

Deslypere, J.P. 1992. Influence of supplementation with N-3 fatty acids on different coronary risk factors in men: A placebo controlled study. Verh K Acad Geneeskd Belg 54(3):189-216.

Dolecek, T.A; Granditis, G. 1991. Dietary polyunsaturated fatty acids and mortality in Multiple Risk Factor Intervention Trial (MRFIT). World Rev Nutr Diet 66:205-216.European Register of Marine Species. 2001. [Labyrinthulids and Thaustrochytrids, etc.]. In: The European Register of Marine Species. European Union, MAST (Marine Science and Technology) Programme; Dublin, Ireland. [http://erms.biol.soton.ac.uk/].

Engström, K.; Luostarinen, R.; Saldeen, T. 1996. Whole blood production of thromboxane, prostacyclin and leukotriene B(4) after dietary fish oil supplementation in man: Effect on vitamin E. Prostaglandins Leukot Essent Fatty Acids 54(6):419-425.

Eritsland, J.; Seljeflot, M.; Abdelnoor, M.; Arnesen, H. 1994a. Long-term influence of omega-3 fatty acids on fibrinoylsis, fibrinogen, and serum lipids. Fibrinolysis 8:120-125.

Eritsland, J.; Seljeflot, M.; Abdelnoor, M.; Arnesen, H.; Torjesen, P.A. 1994b. Long-term effects on N-3 fatty acids on serum lipids and glycemic control. Scand J Clin Lab Invest 54:273-280.

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

Eritsland, J., Arnesen, H., Seljeflot, I.; Høstmark, A.T. 1995b. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. Am J Clin Nutr 61(4):831-836.

Eritsland, J., Arnesen, H., Grønseth, K., Fjeld, N.B.; Abdelnoor, M. 1996. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol 77(1):31-36.

Farwer, S.R.; Der Boer, B.C.; Haddeman, E.; Kivits, G.A.; Wiersma, A.; Danse, B.H. 1994. The vitamin E nutritional status of rats fed on diets high in fish oil, linseed oil or sunflower seed oil. Br J Nutr 72(1):127-145.

Fasching, P., Rohac, M., Liener, K., Schneider, B., Nowotny, P.; Waldhausl, W. 1996. Fish oil supplementation versus Gemfibrozil treatment in hyperlipidemic NIDDM. Horm Metab Res 28(5):230-236.

FDA. 1997. Substances affirmed as generally recognized as safe: Menhaden oil (Final rule) (21 CFR, Part 184, Docket No. 86G-0289). Fed Reg (U.S.) 62 (108):30751-30757.

FDA. 2002a. Agency Response Letter GRAS Notice No. GRN 000105. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

FDA. 2002b. Agency Response Letter GRAS Notice No. GRN 000109. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

FDA. 2004a. Substances affirmed as generally recognized as safe: Menhaden oil; Tentative final rule (21 CFR, Part 184, Docket No. 1999P-5332). Fed Reg (U.S.) 69 (10):2313-2317.

FDA. 2004b. Agency Response Letter GRAS Notice No. GRN 000137. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

FDA. 2004c. Agency Response Letter GRAS Notice No. GRN 000138. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

Fluge, Ø.; Omenaas, E.; Eide, G.E.; Gulsvik, A. 1998. Fish consumption and respiratory symptoms among young adults in a Norwegian community. Eur Respir J 12(2):336-340.

Foegh, M.L.; Hecker, M.; Ramwell, P.W. 1998. The eicosanoids: Prostaglandins, thromboxanes, leukotrienes, and related compounds. In: Katzung, B.G. (Ed.). Basic and Clinical Pharmacology (7th Ed.). Appleton & Lange; Stamford, Connecticut. pp. 304-318.

Freese, R.; Mutanen, M. 1997a. Small effects of linseed oil or fish oil supplementation on postprandial changes in hemostatic factors. Thromb Res 85 (2):147-152.

Freese, R.; Mutanen, M. 1997b. α-Linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. Am J Clin Nutr 66(3):591- 598.

Fujii, W.; Suwa, Y. 1998. [Unpublished] Final Report. 2) Mutagenicity Data. Prepared by Institute for Fundamental Research Suntory Ltd.

Gogos, C.A.; Ginopoulos, P.; Salsa, B.; Apostolidou, E.; Zoumbos, N.C.; Kalfarentzos, F. 1998. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severly ill patients with generalized malignancy: A randomized control trial. Cancer 82(2):395-402.

Goh, Y.K.; Jumpsen, J.A.; Ryan, E.A.; Clandinin, M.T. 1997. Effect of -3 fatty acid on plasma lipids, cholesterol and lipoprotein fatty acid content in NIDDM patients. Diabetologia 40(1).45-52.

Gray, D.R.; Gozzip, C.G.; Eastham, J.H.; Kashyap, M.L. 1996. Fish oil as an adjuvant in the treatment of hypertension. Pharmacotherapy 16(2):295-300.

Grimsgaard, S.; Bønaa, K.H.; Hansen, J.B.; Nordøy, A. 1997. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. Am J Clin Nutr 66(3):649-659.

Grimsgaard, S.; Bønaa, K.H.; Hansen, J.-B.; Myhre, E.S.P. 1998. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. Am J Clin Nutr 68 (1):52-59.

Grundt, H.; Nilsen, D.W.; Hetland, Ø.; Mansoor, M.A.; Aarsland, T.; Woie, L. 1999. Atherothrombogenic risk modulation by n-3 fatty acids was not associated with changes in homocysteine in subjects with combined hyperlipidaemia. Thromb Haemost 81(4):561-565.

Grundy, S.M.; Mok, H.Y.I. 1975. Effects of low dose phytosterols on cholesterol absorption in man. In: Greten, H. (Ed.). Lipoprotein Metabolism. Springer-Verlag; Berlin. pp. 112-118.

Haglund, O.; Luostarinen, R.; Wallin, R.; Saldeen, T. 1992. Effects of fish oil on triglycerides, cholesterol, lipoprotein(a), atherogenic index and fibrinogen. Influence of degree of purification of the oil. Nutr Res 12(4&5):455-468.

Haglund, O.; Wallin, R.; Wretling, S.; Hultberg, B.; Saldeen, T. 1998. Effects of fish oil alone and combined with long chain (n-6) fatty acids on some coronary risk factors in male subjects. J Nutr Biochem 9(11):629-635.

Hamazaki, T.; Sawazaki, S.; Asaoka, E.; Itomura, M.; Mizushima, Y.; Yazawa, K.; Kuwamori, T.; Kobayashi, M. 1996. Docosahexaenoic acid-rich fish oil does not affect serum lipid concentrations of normolipidemic young adults. J Nutr 126(11):2784- 2789.

Hammond, B.G.; Mayhew, D.A.; Naylor, M.W.; Ruecker, F.A.; Mast, R.W.; Sander, W.J. 2001a. Safety assessment of DHA-rich microalgae from Schizochytrium sp. I. Subchronic rat feeding study. Regul Toxicol Pharmacol 33(2):192-204.

Hammond, B.G.; Mayhew, D.A.; Holson, J.F.; Nemec, M.D.; Mast, R.W.; Sander, W.J. 2001b. Safety assessment of DHA-rich microalgae from Schizochytrium sp. II. Developmental toxicity evaluation in rats and rabbits. Regul Toxicol Pharmacol 33(2):205-217.

Hammond, B.G.; Mayhew, D.A.; Robinson, K.; Mast, R.W.; Sander, W.J. 2001c. Safety assessment of DHA-rich microalgae from Schizochytrium sp. III. Single-generation rat reproduction study. Regul Toxicol Pharmacol 33(3):356-362.

Hansen, J.B.; Olsen, J.O.; Wilsgard, L.; Lyngmo, V.; Svensson, B. 1993a. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. Eur J Clin Nutr 47(7):497-507.

Hansen, J.B.; Lyngmo, V.; Svensson, B.; Nordoy, A. 1993b. Inhibition of exercise-induced shortening of bleeding time by fish oil in familial hypercholesterolemia (Type IIa). Arterioscler Thromb 13(1):98-104.

Hansen, J.B.; Berge, R.K.; Nordøy, A.; Bønaa, K.H. 1998a. Lipid peroxidation of isolated chylomicrons and oxidative status in plasma after intake of highly purified eicosapentaenoic or docosahexaenoic acids. Lipids 33(11):1123-1129.

Hansen, J.B.; Grimsgaard, S.; Nilsen, H.; Nordøy, A.; Bønaa, K.H. 1998b. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on fatty acid absorption, incorporation into serum phospholipids and postprandial triglyceridemia. Lipids 33(2):131-138.

Harris, W.S.; Windsor, S.L.; Caspermeyer, J.J. 1993. Modification of lipid-related atherosclerosis risk factors by ω3 fatty acid ethyl esters in hypertriglyceridemic patients. J Nutr Biochem 4:706-712.

Harris, W.S.; Ginsberg, H.N.; Arunakul, N.; Shachter, N.S.; Windsor, S.L.; Adams, M.; Berglund, L.; Osmundsen, K. 1997. Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovasc Risk 4(5&6):385-391.

Helgebostad, A.; Ender, F. 1973. Vitamin E and its function in the health and disease of fur bearing animals. Acta Agric Scand Suppl (19):79-83.

Hempenius, R.A.; Van Delft, J.M.H.; Prinsen, M.; Lina, B.A.R. 1997. Preliminary safety assessment of an arachidonic acid-enriched oil derived from Mortierella alpina: Summary of toxicological data. Food Chem Toxicol 35(6):573-581.

Hempenius, R.A.; Lina, B.A.R.; Haggitt, R.C. 2000. Evaluation of a subchronic (13-week) oral toxicity study, preceded by an in utero exposure phase, with arachidonic acid oil derived from Mortierella alpina in rats. Food Chem Toxicol 38(2&3):127-139.

Henderson, W.R.; Astley, S.J.; McCready, M.M.; Kushmerick, P.; Casey, S.; Becker, J.W.; Ramsey, B.W. 1994. Oral absorption of omega-3 fatty acids in patients with cystic fibrosis who have pancreatic insufficiency and in healthy control subjects. J Pediatr 124(3):400-408.

Honda, D.; Yokochi, T.; Nakahara, T.; Raghukumar, S.; Nakagiri, A.; Schaumann, K.; Higashihara, T. 1999. Molecular phylogeny of labyrinthulids and thraustochytrids based on the sequencing of 18S ribosomal RNA gene. J Eukaryot Microbiol 46(6):637-647.

Hostmark, A.T.; Bjerkedal, T.; Kierulf, P.; Flaten H.; Ulshagen, K. 1988. Fish oil and plasma fibrinogen. BMJ 297(6642):180-181.

Innis, S.M.; Hansen, J.W. 1996. Plasma fatty acid responses, metabolic effects, and safety of microalgal and fungal oils rich in arachidonic and docosahexaenoic acids in healthy adults. Am J Clin Nutr 64(2):159-167.

Johansson, L.R.; Solvoll, K.; Bjorneboe, G.E.; Drevon, C.A. 1998. Intake of very- long-chain n-3 fatty acids related to social status and lifestyle. Eur J Clin Nutr 52(10):716-721.

Jones, D.; Howard, A.N.; Gresham, G.A. 1969. Aetiology of 'yellow fat' disease (pansteatitis) in the wild rabbit. J Comp Pathol 79(3):329-334.

Kashima, M.; Sarwar, G. 2000. [Unpublished] Final Report. Chromosomal Aberration Test of DHA-Oil in Cultured Chinese Hamster Cells. Prepared by Nippon Experimental Medical Research Institute Co., Ltd.; Gunma-ken, Japan. Project No. H-99144.

Kelley, D.S.; Rudolph, I.L. 2000. Effect of individual fatty acids of ω-6 and ω-3 type on human immune status and role of eicosanoids. Nutrition 16(2):143-145.

Kelley, D.S.; Taylor, P.C.; Nelson, G.J.; Mackey, B.E. 1998. Dietary docosahexaenoic acid and immunocompetence in young healthy men. Lipids 33(6):559-566.

Kelley, D.S.; Taylor, P.C.; Nelson, G.J.; Schmidt, P.C. Ferreti, A.; Erickson, K.L.; Yu, R.; Chandra, R.K.; Mackey, B.E. 1999. Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. Lipids 34(4):317-324.

Kenny, D.; Warltier, D.C.; Pleuss, J.A.; Hoffmann, R.G.; Goodfriend, T.L.; Egan, B.M. 1992. Effect of omega-3 fatty acids on the vascular response to angiotensin in normotensive men Am J Cardiol 70(15):1347-1352.

Kris-Etherton, P.M.; Taylor, D.S.; Yu-Poth, S.; Huth, P.; Moriarty, K.; Fishell, V.; Hargrove, R.L.; Zhao, G.; Etherton, T.D. 2000. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 71(1, Suppl.):179S-188S.250.

Kroes, R.; Schaefer, E.J.; Squire, R.A.; Williams, G.M. 2003. A review of the safety of DHA45-oil. Food Chem Toxicol 41:1433-1446.

Krokan, H.E.; Bjerve, K.S.; Mørk, E. 1993. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. Biochim Biophys Acta 1168(1):59-67.

Kuilman, M.E.M.; Waalkens-Berendsen, D.H. 2001. Oral One-Generation Reproduction Study with DHA Oil 45 in Rats. Prepared by TNO Nutrition and Food Research; The Netherlands for Celanese Ventures GmbH, Germany. Project No. 41089, TNO Study No. 2633.

Leaf, A.; Jorgensen, M.B.; Jacobs, A.K.; Cote, G.; Schoenfeld, D.A.; Scheer, J.; Weiner, B.H.; Slack, J.D.; Kellett, M.A.; Raizner, A.E.; Weber, P.C.; Mahrer, P.R.; Rossouw, J.E. 1994. Do fish oils prevent restinosis after coronary angioplasty? Circulation 90(5):2248-2257.

Lenzi, S.; Caprioli, R.; Rindi, P.; Lazzerini, G.; Bernini, W.; Pardini, E.; Lucchetti, A.; Galli, C.; Carr, L.; De Caterina, R. 1996. Omega-3 fatty acids supplementation and lipoprotein(a) concentrations in patients with chronic glomerular diseases. Nephron 72(3):383-390.

Linder, M.C. 1991. Nutrition and metabolism of fats. In: Linder, M.C. (Ed.). Nutritional Biochemistry and Metabolism With Clinical Applications (2nd Ed.). Elsevier Science Publishing Company, Inc.; New York, pp. 51-84.

Lungershausen, Y.K.; Abbey, M.; Nestel, P.J.; Howe, P.R.C. 1994. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. J Hypertens 12(9):1041-1045.

Luostarinen, R.; Wallin, R., Wibell, L.; Saldeen, T. 1995. Vitamin E supplementation counteracts the fish oil-induced increase of blood glucose in humans. Nutr Res 15(7):953-968.

Mackness, M.I.; Bhatnagar, D.; Durrington, P.N.; Prais, H.; Haynes, B.; Morgan, J.; Borthwick, L. 1994. Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. Eur J Clin Nutr 48(12):859-865.

McGrath, L.T.; Brennan, G.M.; Donnelly, J.P.; Johnston, G.D.; Hayes, J.R.; McVeigh, E.G. 1996. Effect of dietary fish oil supplementation on peroxidation of serum lipids in patients with non-insulin dependent diabetes mellitus. Atherosclerosis 121(2):275-283.

McGuire, S.O.; Alexander, D.W.; Fristche, K.L. 1997. Fish oil source differentially affects rat immune cell a-tocopherol concentration. J Nutr 127(7):1388-1394.

McManus, R.M.; Jumpson, J.; Finegood, D.T.; Clandinin, M.T.; Ryan, E.A. 1996. A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes. Diabetes Care 19(5):463-467.

McVeigh, G.E.; Brennan, G.M.; Cohn, J.N.; Finkelstein, S.M.; Hayes, R.J.; Johnston, G.D. 1994. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. Arterioscler Thromb 14(9):1425-1429.

Mehta, J.L.; Lopez, L.M.; Lawson, D.; Wargovich, T.J.; Williams, L.L. 1988. Dietary supplementation with omega-3 polyunsaturated fatty acids in patients with stable coronary heart disease. Effects on indices of platelet and neutrophil function and exercise performance. Am J Med 84(1):45-52.

Melkonian, M. 2003. Expert's Report on the Safety of Ulkenia (Thraustochytriales) in a Human-biological Context.

Misso, N.L.A.; Thompson, P.J. 1995. Fish oil supplementation inhibits platelet aggregation and ATP release induced by platelet-activating factor and other agonists. Platelets 6(5):275-282.

Morgan, W.A.; Raskin, P.; Rosenstock, J. 1995. A comparison of fish oil or corn oil supplements in hyperlipidemic subjects with NIDDM. Diabetes Care 18(1):83-86.

Mori, T.A.; Vandongen, R.; Mahanian, F.; Douglas, A. 1992. Plasma lipid levels and platelet and neutrophil function in patients with vascular disease following fish oil and olive oil supplementation. Metabolism 41(10):1059-1067.

Mori, T.A.; Beilin, L.J.; Burke, V.; Morris, J.; Ritchie, J. 1997. Interactions between dietary fat, fish and fish oils and their effects on platelet function in men at risk of cardiovascular disease. Arterioscler Thromb Vasc Biol 17(2):279-286.

Mori, T.A.; Burke, V.; Puddey, I.B.; Watts, G.F.; O'Neal, D.N.; Best, J. D.; Beilin, L.J. 2000. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. Am J Clin Nutr 71(5):1085-1094.

Muggli, R. 1994. Physiological requirements of vitamin E as a function of the amount and type of polyunsaturated fatty acid. In: Galli, C.; Simopoulos, A.P.; Tremoli, E. (Eds.). Fatty Acids and Lipids: Biological Aspects. Proceedings of the 1st International Congress of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). Karger; Basel, Switz./New York. World Review of Nutrition and Dietetics, Vol. 75, pp. 166-168.

Mundal, H.H.; Gjesdal, K.; Landmark, K. 1993. The effect of n-3 fatty acids and nifedipine on platelet function in hypertensive males. Thromb Res 72(3):257-262.

Mundal, H.; Meltzer, H.; Aursnes, I. 1994. Bleeding times related to serum triglyceride levels in healthy young adults. Thromb Res 75(3):285-291.

Naganuma, T.; Takasugi, H.; Kimura, H. 1998. Abundance of thraustochytrids in coastal plankton. Mar Ecol Progr Ser 162:105-110.

Nelson, G.J.; Schmidt, P.C.; Bartolini, G.L.; Kelly, D.S.; Kyle, D. 1997. The effect of dietary docosahexaenoic acid on plasma lipoproteins and tissue fatty acid composition in humans. Lipids 32(11):1137-1146.

Nilsen, D.W.T., Almdahl, S.M., Svensson, B., Vaage, J., Rasmussen, K.; Østerud, B. 1993. Lipopolysaccharide induced monocyte thromboplastin synthesis and coagulation responses in patients undergoing coronary bypass surgery after preoperative supplementation with n-3 fatty acids. Thromb Haemost 70(6):900-902.

Nordøy, A.; Hatcher, L.; Goodnight, S.; Fitzgerald, G.A.; Conner, W.E. 1994. Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid poduction and hemostatic parameters in normal men. J Lab Clin Med 123(6):914-920.

Nordøy, A., Bønaa, K.H., Nilsen, H., Berge, R.K., Hansen, J.B.; Ingebretsen, O.C. 1998. Effects of Simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 243(1):163-170.

Oarada, M.; Furukawa, H.; Majima, T.; Miyazawa, T. 2000. Fish oil diet affects on oxidative senescence of red blood cells linked to degeneration of spleen cells in mice. Biochim Biophys Acta 1487(1):1-14.

OmegaTech GmbH. 1997. Application for the Approval of DHA-rich Oil. Regulation (EC) No 258/97 of the European Parliament and of the Concil of 27th January 1997 concerning novel foods and novel food ingredients. [http://www.foodstandards.gov.uk/pdf_files/dha-rich_oil_novel_food_dossier.pdf]

Otto, C.; Ritter, M.M.; Soennichsen, A.C.; Schwandt, P.; Richter, W.O. 1996. Effects of n-3 fatty acids and fenofibrate on lipid and hemorrheological parameters in familial dysbetalipoproteinemia and familial hypertriglyceridemia. Metabolism 45(1):1305-1311.

Palozza, P.; Sgarlata, E.; Luberto, C.; Piccioni, E.; Anti, M.; Marra, G.; Armelao, F.; Franceschelli, P.; Bartoli, G.M. 1996. n-3 Fatty acids induce oxidative modifications in human erythrocytes depending on dose and duration of dietary supplementation. Am J Clin Nutr 64(3):297-304.

Parkinson, A.J.; Cruz, A.L.; Heyward, W.L.; Bulkow, L.R.; Hall, D.; Barstaed, L.; Connor, W.E. 1994. Elevated concentrations of plasma-3 polyunsaturated fatty acids among Alaskan eskimos. Am J Clin Nutr 59(2):384-388.

Pirich, C.; Gaszo, A.; Granegger, S.; Sinzinger, H. 1999. Effects of fish oil supplementation on platelet survival and ex vivo platelet function in hypercholesterolemic patients. Thromb Res 96(3):219-227.

Prisco, D.; Paniccia, R.; Filippini, M.; Francalanci, I.; Bandinelli, B.; Comeglio, P.; Rostagno, C.; Abbate, R.; Neri Serneri, G.G. 1994. No changes in PAI-1 levels after four-month n-3 PUFA ethyl ester supplementation in healthy subjects. Thromb Res 76(3):237-244.

Prisco, D.; Filippini, M.; Francalanci, I.; Paniccia, R.; Gensini, G.F.; Neri Serneri, G.G. 1995. Effect of n-3 fatty acid ethyl ester supplementation on fatty acid composition of the single platelet phospholipids and on platelet functions. Metabolism 44(5):562-569.

Rabbani, P.I.; Sheikh, N.M.; Chirtel, S.J.; Jackson, R.; Ruffin, G. 1999. Effects of long-term consumption of high doses of fish oil concentrates on clinical parameters in male and female rats. J Nutr Sci Vitaminol 45(5):553-565.

Radack, K.; Deck, C.; Huster, G. 1989. Dietary supplementation with low-dose fish oils lowers fibrinogen levels: A randomized, double- blind controlled study. Ann Intern Med 111(9):757-758.

Rivellese, A.A.; Maffettone, A.; Iovine, C.; Di Marino, L.; Annuzzi, G.; Mancini, M.; Riccardi, G. 1996. Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. Diabetes Care 19(11):1207-1213.

Rossing, P., Hansen, B.V., Nielsen, F.S., Myrup, B., Hølmer, G., Parving, H.H. 1996. Fish oil in diabetic nephropathy. Diabetes Care 19(11):1214-1219.

Roulet, M.; Frascarolo, P.; Pilet, M.; Chapuis, G. 1997. Effect of intraveneously infused fish oil on platelet fatty acid phosophlipid composiition and on platelet function in postoperative trauma. JPEN J Parenter Enteral Nutr 21(5):296-301.

Ruiter, A.; Jongbloed, A.W.; van Gent, C.M.; Danse, L.H.; Metz, S.H. 1978. The influence of dietary mackerel oil on the condition of organs and on blood lipid composition in the young growing pig. Am J Clin Nutr 31(12):2159-2166.

Sacks, F.M.; Stone, P.H.; Gibson, C.M.; Silverman, D.I.; Rosner, B.; Pasternak, R.C. (For the HARP Research Group). 1995. Controlled trial of fish oil for regression of human coronary atherosclerosis. J Am Coll Cardiol 25(7):1492-1498.

Sanders, T.A.B. 1989. Effects of fish oils on lipid metabolism. Nutrition 5(4):248-250.

Sanders, T.A.B.; Oakley, F.R.; Miller, G.J.; Mitropoulos, K.A.; Crook, D.; Oliver, M.F. 1997. Influence of n-6 versus n-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. Arterioscler Thromb Vasc Biol 17(12):3449-3460.

Sathe-Pathak, V.; Raghukumar, S.; Raghukumar, C.; Sharma, S. 1993. Thraustochytrid and fungal component of marine detritus. I -- Field studies on decomposition of the brown alga Sargassum cinereum J. Ag. Indian J Mar Sci 22:159-167.

Saynor, R.; Gillott, T. 1992. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. Lipids 27:533-538.

Schaumann, K. 2003. Extended Expert's Report on the "Safety" of Ulkenia Sp.

Schloss, I.; Kidd, M.S.; Tichelaar, H.Y.; Young, G.O.; O'Keefe, S.J. 1997. Dietary factors associated with a low risk of colon cancer in coloured west coast fishermen. S Afr Med J 87(2):152-158.

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

Seljeflot, I.; Johansen, O.; Arnesen, H.; Eggesbø, J.-B.; Westvik, A.-B.; Kierulf.; P. 1999. Procoagulant acitivity and cytokine expression in whole blood cultures from patients with atherosclerosis supplemented with omega-3 fatty acids Thromb Haemost 81(4):566-570.

Silva, J.M.; Souza, I.; Silva, R.; Tavares, P.; Teixeira, F.; Silva, P.S. 1996. The triglyceride lowering effect of fish oils is affected by fish consumption. Int J Cardiol 57(1):75-80.

Sugano, M.; Hirahara, F. 2000. Polyunsaturated fatty acids in the food chain in Japan. Am J Clin Nutr 71(1, Suppl.):189S-196S.

Swahn, E.; von Schenck, H.; Olsson, A.G. 1998. Omega-3 ethyl ester concentrate decreases total apoloprotein CIII and increases antithrombin III in postmyocardial infarction patients. Clin Drug Invest 15:473-482.

Swails, W.S., Bell, S.J., Bristrian, B.R., Lewis, E.J., Pfister, D., Forse, R.A., Kelly, S., Blackburn, G.L. 1993. Fish-oil containing diet and platelet aggression. Nutrition 9(3):211-217.

Tam, P.S.; Umeda-Sawada, R.; Yaguchi, T.; Akimoto, K.; Kiso, Y.; Igarashi, O. 2000. The metabolism and distribution of docosapentaenoic acid (n-6) in rats and rat hepatocytes. Lipids 35(1):71-75.

Toft, I.; Bønaa, K.H.; Ingebretsen, O.C.; Nordøy, A. ; Jenssen, T. 1995. Effects of n-3 polyunsaturated fatty acids on glucose homestasis and blood pressure in essential hypertension. A randomized, controlled trial. Ann Intern Med 123(12):911-918.

Toft, I.; Bønaa, K.H.; Ingebretsen, O.C.; Nordøy, A.; Jenssen, T. 1997. Fibrinolytic function after dietary supplementation with 3 polyunsaturated fatty acids. Arterioscler Thromb Vasc Biol 17(5):814-819.

Torres, I.C.; Mira, L.; Ornelas, C.P.; Melim, A. 2000. Study of the effects of dietary fish intake on serum lipids and lipoproteins in two populations with different dietary habits. Br J Nutr 83(4):371-379.

Tremoli, E.; Maderna, P.; Marangoni, F.; Colli, S.; Eligini, S.; Catalano, I.; Angeli, M.T.; Pazzucconi, F.; Gianfranceschi, G.; Davi, G.; Stragliotto, E.; Sirtori, C.R.; Galli, C. 1995. Prolonged inhibition of platelet aggregation after n-3 fatty acid ethyl ester ingestion by healthy volunteers. Am J Clin Nutr 61(3):607-613.

Tsai, P.-J.; Lu, S.-C. 1997. Fish oil lowers plasma lipid concentrations and increases the susceptibility of low density lipoprotein to oxidative modification in healthy men. J Formos Med Assoc 96(9):718-726.

Turini, M.E.; Powell, W.S.; Behr, S.R.; Holub, B.J. 1994. Effects of a fish-oil and vegetable-oil formula on aggregation and ethanolamine-containing lysophospholipid generation in activated human platelets and on leukotriene production in stimulated neutrophils. Am J Clin Nutr 60(5):717-724.

Ulken, A.; Víquez, R.; Valient, C.; Campos, M. 1990. Marine fungi (Chytridiomycetes and Thraustochytriales) from a mangrove area at Punta Morales, Golfo de Nicoya, Costa Rica. Rev Biol Trop 38(2A):243-250.

Van Dolah, F.M. 2001. Diversity of marine and freshwater algal toxins. In: Botana, M. (Ed.). Seafood and Freshwater Toxins: Pharmacology, Physiology, and Detection. Marcel Dekker; New York [as published at http://www chbr.noaa.gov/CoastalResearch/DiversityEssay.htm and including http://www.chbr.noaa.gov/CoastalResearch/MapAlgae.htm]

Véricel, E.; Calzada, C.; Chapuy, P.; Lagarde, M. 1999. The influence of low intake of n-3 fatty acids on platelets in elderly people. Atherosclerosis 147(1):187-192.

Verschuren, P.M.; Houtsmuller, U.M.; Zevenbergen, J.L. 1990. Evaluation of vitamin E requirement and food palatability in rabbits fed a purified diet with a high fish oil content. Lab Anim 24(2):164-171.

von Schacky, C.; Fischer, S.; Weber, P.C. 1985. Long-term effects of dietary marine ω-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest 76(4):1626-1631.

Wallace, J.M.W.; McCabe, A.J.; Roche, H.M.; Higgins, S.; Robson, P.J.; Gilmore, W.S.; McGlynn, H.; Strain, J.J. 2000. The effect of low-dose fish oil supplementation on serum growth factors in healthy humans. Eur J Clin Nutr 54(9):690-694.

Wensing, A.G.; Mensink, R.P.; Hornstra, G. 1999. Effects of dietary n-3 polyunsaturated fatty acids from plant and marine origin on platelet aggregation in healthy elderly subjects. Br J Nutr 82(3):183-191.

Wibert, G.J.; Burns, R.A.; Diersen-Schade, D.A.; Kelly, C.M. 1997. Evaluation of single cell sources of docosahexaenoic acid and arachidonic acid: A 4-week oral safety study in rats. Food Chem Toxicol 35(10&11):967-974.

Wigmore, S.J.; Ross, J.A.; Falconer, J.S.; Plester, C.E.; Tisdale, M.J.; Carter, D.C., Fearon, K.C. 1996. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. Nutrition 12(1):S27-S30.

Willumsen, N.; Hexeberg, S.; Skorve, J.; Lindquist, M.; Berge, R.K. 1993. Docosahexaenoic acid shows no triglyceride-lowering effects but increases the peroxisomal fatty acid oxidation in liver of rats. J Lipid Res 34(1):13-22.

Woodman, R.J.; Mori, T.A.; Burke, V.; Puddey, I.B.; Barden, A.; Watts, G.F.; Beilin, L.J. 2003. Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients. Atherosclerosis 166:85-93.

Yaqoob, P.; Pala, H.S.; Cortina-Borja, M.; Newsholme, E.A.; Calder, P.C. 2000. Encapsulated fish oil enriched in alpha-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. Eur J Clin Invest 30(3):260-274.

Yosefy, C.; Viskoper, J.R.; Varon, D.; Ilan, Z.; Pilpel, D.; Lugassy, G.; Schneider, R.; Adan, Y.; Raz, A. 1996. Repeated fasting and refeeding with 20:5, n-3 eicosapentaenoic acid (EPA): A novel approach for rapid fatty acid exchange and its effect on blood pressure, plasma lipids and hemostasis. J Hum Hypertens 10(Suppl. 3):S135-S139.

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APPENDIX I

EXPERT PANEL CONSENSUS STATEMENT: THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF DHA-RICH OIL UNDER THE CONDITIONS OF INTENDED USE IN TRADITIONAL FOODS

EXPERT PANEL CONSENSUS STATEMENT: THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF DHA-RICH OIL UNDER THE CONDITIONS OF INTENDED USE IN TRADITIONAL FOODS

September 15, 2004

INTRODUCTION

At the request of Nutrinova Nutrition Specialties & Food Ingredients GmbH (Nutrinova), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use as a nutrient in traditional foods, DHA-rich oil would be "generally recognized as safe" (GRAS), based on scientific procedures. DHA-rich oil is a docosahexaenoic acid (DHA)-rich triacylglycerol oil derived from *Ulkenia sp.* microalgae by Nutrinova. The Panel consisted of the below-signed qualified scientific experts: Robert Kroes, D.V.M., Ph.D. (Utrecht University), Ernst Schaefer, M.D. (Tufts University), and Gary Williams, M.D. (New York Medical College). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically evaluated a comprehensive package of scientific information and data compiled from the literature and other published sources through May 2004. The Panel also evaluated any other data and information, published or unpublished, that the Panel deemed appropriate or pertinent to safety of DHA-rich oil under the conditions of intended use. In addition, the Panel considered data and information provided by Nutrinova, including information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in specified food products, consumption estimates for all intended uses, data on the safety of similar DHA-containing fish and marine oils, and unpublished corroborating toxicological studies conducted on DHA-rich oil and the source microalgae.

Following independent, critical evaluation of such data and information, the Panel unanimously concludes that under the conditions of intended use in traditional foods described herein, DHA-rich oil, meeting appropriate food-grade specifications, and manufactured and used in accordance with current good manufacturing practice, is GRAS based on scientific procedures. A summary of the basis for the Panel's conclusion, excluding confidential data and information, is provided below.

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MANUFACTURING AND COMPOSITION

DHA-rich oil is produced in accordance with current good manufacturing practice following multi-step fermentation of a genetically stable and pure culture of the marine protist, *Ulkenia sp.* DHA-rich oil is extracted from the microalgae *via* a solvent-based extraction process using food grade solvents and processing aids, and is further refined by processes standard to the edible oil industry, including degumming, deacidification, bleaching and deodorization, using materials appropriate for food processing. Specifications for DHA-rich oil are presented in Table 1. Analysis of nonconsecutive representative lots demonstrated compliance with final product chemical, physical, and microbiological specifications, and stability under recommended storage conditions.

Table 1 Product Specifications for DHA-rich oil

Parameter	Specification
DHA	38 to 50 (% by weight)
Trans Fatty Acids	≤2 %
Peroxide value	≤5 meq./kg
Acid value	≤0.5 mg KOH/g
Moisture and Volatiles	≤0.05 %
Unsaponifiables	≤4.5 %
Lead	≤0.1 ppm
Arsenic	≤0.5 ppm
Mercury	≤0.5 ppm

DHA-rich oil is a refined, food grade oil of >95% triacylglycerols, with a total fatty acid composition of 38 to 50% DHA. The remaining fatty acids of DHA-rich oil are comprised mainly of saturated palmitic acid (16:0) (28 to 37%) and a lesser amount (8 to 14%) of the ω-6 fatty acid, docosapentaenoic acid (DPA) (22:5). In addition, the DHA-rich oil product will contain safe and suitable antioxidants permitted by the FDA for use in edible oils to ensure stability.

INTENDED USE AND ESTIMATED INTAKE

The main dietary source of polyunsaturated fatty acids (PUFAs), such as DHA, is fish, particularly fatty fish, in which concentrations of total ω-3 fatty acids range from 0.1 to 5.3 g/ 100 g (1, 2). In the U.S., the usual consumption of ω-3 fatty acids amounts to approximately 1,600 mg/day, predominantly as α-linolenic acid (18:3), but also including eicosapentaenoic acid (EPA), DHA, and DPA. Of the total amount of ω-3 fatty acids consumed per day in the U.S., an estimated 100 to 200 mg is consumed as DHA (3, 4). Other populations with a traditionally higher consumption of DHA-containing foods, such as Japan, Norway, South Africa, and the

Portuguese island of Madeira, have average DHA intakes of approximately 500 to 700 mg DHA/day (5-9).

Several international scientific authorities have published recommendations for daily intakes of ω-3 PUFAs. For example, although the nutrition recommendations of Health Canada do not distinguish the identities of individual ω-3 PUFAs, they provide a recommended daily intake of 1,000 to 1,800 mg ω-3 PUFAs/day, in a ratio of 1:4 to 1:10 with ω-6 PUFAs (10). A workshop convened by the International Society for the Study of Fatty Acids and Lipids (ISSFAL) concluded there was insufficient data to determine a Dietary Reference Intake (DRI) for ω-3 PUFAs; however, Adequate Intakes (AIs) of a minimum 220 mg/day each for DHA and EPA, and 650 mg/day for DHA and EPA combined were recommended (11). In Europe, the British Nutrition Foundation has recommended a desirable population intake of 1,100 mg (females) and 1,400 mg (males) of DHA and EPA/day (12).

Several ω-3 fatty acids, such as EPA (20:5) and DHA (including DHA from marine algae) also are sold as dietary supplements, and the U.S. Food and Drug Administration (FDA) currently allows a qualified health claim for ω-3 fatty acids and a reduced risk of coronary heart disease to appear in labeling for dietary supplement products (13). Additionally, under certain conditions of intended use in foods, similar oils, such as fully hydrogenated, partially hydrogenated, and refined menhaden oils, are affirmed as GRAS by FDA for use in several specified foods (21 CFR §184.1472) (14, 15). The recognized difference between menhaden oil, a refined oil derived from menhaden fish, and edible vegetable oils and animal fats is the higher percentage of PUFAs with 4 to 6 double bonds in menhaden oil, including EPA (13.7%), DHA (6.6%), and DPA (1.9%) (15). Furthermore, other DHA-containing oil ingredients are used in a number of traditional food products, as the FDA has responded with no objections against several GRAS notices submitted for other sources of ω-3 fatty acids for uses identical to those specified as GRAS for menhaden oil (16, 17, 203, 204).

The only notable differentiation regarding DHA-rich oil as compared to other DHA-containing products already on the market is the production source. DHA-rich oil is derived from a fermentation process using a nontoxigenic and nonpathogenic marine protist, which has not previously been used in the production of food products or ingredients; never the less, the fatty acids identified in DHA-rich oil are the same as those of fish and microalgal-derived oils already consumed by the human population.

Nutrinova intends to market DHA-rich oil as a food ingredient to increase the intake of dietary ω-3 PUFAs, particularly DHA, a critical component of most cell membranes and tissues.

In a final rule affirming menhaden oil as GRAS for use as a direct human food ingredient (21 CFR §184.1472) the FDA concluded that 3.0 g/person/day of EPA and DHA is a safe intake level with respect to bleeding time, increased bleeding, glycemic control and LDL cholesterol levels (15). To ascertain menhaden oil intake at a level not exceeding 3.0 g/person/day,

limitations on the maximum use levels in specific food categories were introduced. In a tentative final rule, the FDA published a revised list of food categories and use limitations for menhaden oil in these categories (202). The determination of use limitations was made on the basis of a content of EPA and DHA of approximately 20% in menhaden oil. To ensure compliance with the limitations, FDA stated that menhaden oil may not be used in combination with any other added oil that is a significant source of EPA and DHA.

The DHA content of DHA-rich oil is 38 to 50%, as shown in product specifications and product analyses. DHA-rich oil is a significant source of DHA, but contains only traces of EPA.

The individual intended food uses and use levels for DHA-rich oil are consistent with the current GRAS use of menhaden oil specified in 21 CFR §184.1472 and the revised uses outlined in FDA's tentative final rule regarding GRAS-affirmed food uses for menhaden oil. The food uses and maximum use levels for DHA-rich oil are summarized in Table 2.

Comparing the composition of menhaden oil (sum of approximately 20% of EPA and DHA) with DHA-rich oil (DHA content of 38 to 50% and no significant EPA content), it can reasonably be concluded that approximately twice as much menhaden oil as DHA-rich oil will have to be consumed for the same intake of ω-3 fatty acids. Inversely, any limitation of use levels from DHA-rich oil will therefore have to be less than 50% of the use levels of menhaden oil to ascertain compliance with the safe intake level. Consequently, the limitation of DHA-rich oil use levels to 40% of the use levels in all food categories considered by the US FDA for the GRAS use of menhaden oil would also ascertain compliance with the safe intake level of 3.0 g/person/day for the sum of EPA and DHA. To ensure safe use levels in the intended food categories and levels of use, DHA-rich oil shall not be used in combination with any other added oil that is a significant source of EPA or DHA.

Table 2 Intended Uses and Maximum Use Levels of DHA-rich oil in Food

Food Category	Initial[a] Intended Use Levels (% by weight)	Future[b] Intended Use Levels (% by weight)
Cookies, crackers (n = 1)[1,2]	3.3	-
Breads, rolls (white and dark) (1)[2]	0.7	-
Fruit pies, custard pies (1)[2]	4.7	-
Cakes (1)[2]	6.7	-
Cereals (4)	2.7	2.7
Baked Goods and baking mixes	-	3.3
Fats and oils (12)[3]	13.4	8.0
Yogurt (31)[4]	2.7	-
Milk Products (31)	-	3.3
Cheese products (31)	-	3.3
Frozen dairy products (20)	3.3	3.3

Table 2 Intended Uses and Maximum Use Levels of DHA-rich oil in Food		
Food Category	Initial[a] Intended Use Levels (% by weight)	Future[b] Intended Use Levels (% by weight)
Meat products (29)	6.7	3.3
Egg products (11)	3.3	3.3
Fish products (13)	13.4	3.3
Condiments (8)	3.3	3.3
Soup mixes (40)	2.0	3.3
Snack foods (37)	3.3	3.3
Nut products (32)	3.3	3.3
Gravies and sauces (24)	3.3	3.3
Plant protein products (33)	-	3.3
Processed vegetable juices (36)	-	0.7
Hard candy (25)	-	6.7
Soft candy (38)	-	2.7
Jams and jellies (28)	-	4.7
Dairy product analogs (10)	-	3.3
Nonalcoholic beverages (3)	-	0.3
Pastas (23)	-	1.3
Poultry products (34)	-	2.0
Processed fruit juices (35)	-	0.7
White grandulated sugar (41)	-	2.7
Sugar substitutes (42)	-	6.7
Chewing gum (6)	-	2.0
Gelatins and puddings (22)	-	0.7
Confections and frosting (9)	-	3.3
Sweet sauces, toppings, and syrups (43)	-	3.3

[a] Based on 21 CFR §184.1472
[b] Based on tentative final rule amending 21 CFR §184.1472 (69 FR 2313; January 15, 2004)
[1] The number in parenthesis following each food category refers to the paragraph listing of the particular food category in 21 CFR 170.3(n)
[2] Included in "Baked goods and baking mixes"
[3] Not including infant formula
[4] Included in "Milk products"

In its existing (21 CFR §184.1472) and tentative revised final rule affirming menhaden oil as generally recognized as safe, the FDA published maximum use levels for menhaden oil to ensure the total daily intake of combined DHA and EPA does not exceed 3 g/person/day. As the DHA level in DHA-rich oil is approximately 2 to 2.5 times higher than the combined levels of DHA and EPA in menhaden oil, the proposed use levels for DHA-rich oil of 40% of those GRAS-affirmed for menhaden oil, ascertain an intake within the limits considered safe by the FDA.

Furthermore, DHA-rich oil is not intended for use in combination with other oils that are significant sources of ω-3 fatty acids, DHA and EPA.

DATA PERTAINING TO SAFETY

Scientific evidence supporting the safety of DHA-rich oil includes a history of ω-3 fatty acid consumption as a result of their natural presence in food, an abundance of published metabolic, clinical, and toxicological data on DHA-containing fish and microalgal-derived oils, and unpublished corroborating toxicological and mutagenicity studies on DHA-rich oil, and mutagenicity and toxicity studies on the microalgal source, *Ulkenia sp.*

Studies of Absorption, Distribution, and Metabolism

DHA is an abundant cell membrane fatty acid (18-22), which is obtained directly in the diet or biosynthetically derived through desaturation and elongation of dietary precursor essential fatty acids (20, 23). The absorption, distribution, and metabolism of DHA are known to be similar to other dietary fatty acids. DHA is present in DHA-rich oil in triglyceride form. Following enzymatic hydrolysis of the triglyceride in the upper intestine, the free fatty acids and 2-monoglycerides are incorporated into bile acid micelles for diffusion into the enterocytes, where they are incorporated into new triglycerides (20, 21, 24). Reconstituted triglycerides enter the lymph in the form of chylomicrons and are transported to the blood for distribution and may rapidly be incorporated into plasma lipid fractions, erythrocyte membranes, platelets, and adipose tissue. In passing through the capillaries of adipose tissue and liver, the chylomicron-contained triglycerides and phospholipids are hydrolyzed with subsequent release of free fatty acids to the tissues for metabolism or reesterification into triglycerides and phospholipids for storage as energy (20, 22). Generally, free fatty acids are transported across the mitochondrial membrane in the form of acyl-carnitine (21), where they then undergo β-oxidation with removal of 2 carbons from the fatty acid chain and production of acetic acid, a shorter-chained fatty acid, and acetyl CoA, which combines with oxaloacetic acid and enters the citric acid cycle for energy production (22). As fatty acids of 20 carbons or more are not easily transported across the mitochondrial membrane, DHA also may be metabolized *via* peroxisomal β-oxidation (19, 21, 25-27). As a minor peroxisomal metabolic pathway, DHA may be retroconverted to EPA, which involves β-oxidation, auxiliary enzymes, and removal of 2 carbon units from the carboxyl end of the fatty acid (28-30).

Clinical Studies Relating to the Safety of DHA-Rich Oil

Human consumption of dietary DHA from traditional sources is considered safe based on the historical consumption of fish, and fish- and marine-based products. In 1993, the FDA identified 3 possible adverse effects associated with human consumption of ω-3 PUFAs: 1) reduced platelet aggregation; 2) increased low-density lipoprotein (LDL) cholesterol levels; and 3) reduced glycemic control among diabetics [58 FR 2682 (January 6, 1993)] (31).

In 1997, following a thorough evaluation of several published clinical trials, the FDA affirmed that menhaden oil is GRAS under certain specified conditions of intended use (21 CFR §184.1472), and concluded that consumption of up to 3 g DHA + EPA combined/person/day does not pose a "significant risk for increased bleeding time", has no "clinically significant effect on glycemic control", and is "safe with respect to the effect on LDL cholesterol" (15). Subsequently, in a public letter permitting a dietary supplement qualified health claim for ω-3 fatty acids and coronary heart disease, FDA stated that the use of EPA and DHA ω-3 fatty acids, including DHA from marine microalgae, as dietary supplements is safe (13).

Subsequent to FDA's 1997 GRAS affirmation of menhaden oil, a number of additional clinical studies of the potential effects of DHA-containing oils on hemostatic parameters, glycemic control, and LDL-C have been conducted. A comprehensive summary of greater than 90 published clinical trials was reviewed by the Panel (32-135). These clinical studies ranged in duration from 1 week to >1 year, and were conducted with DHA-containing fish and marine oils providing up to 6 g DHA/day, alone or in combination with DPA and/or EPA. The available clinical data do not provide evidence that DHA, at estimated exposures provided through the intended use of DHA-rich oil, would have an adverse effect on human health. The clinical data measured endpoints such as LDL-C levels, glycemic control, bleeding time, platelet aggregation, or other hemostatic parameters, as well as immune function or response, kidney or liver function, or lipid peroxidation. Overall, the results of these studies indicate that DHA, provided in fish or marine-derived oils alone or in combination with DPA and/or EPA, at levels up to 6 g DHA/person/day, would not produce significant adverse effects on these parameters. These results are consistent with the earlier conclusions of the FDA that consumption of up to 3 g DHA + EPA/day is safe.

The Panel noted that consumption of DHA-containing oils providing up to 6 g DHA/day, alone or in combination with DPA and/or EPA, has been reported to result in alterations of platelet and total serum phospholipid and nonesterified fatty acid compositions, with increases in the levels of ω-3 PUFAs, including DHA, and concomitant decreases in levels of arachidonic acid (AA) (20:4; ω-6) of up to 26% (42-45, 48, 56, 58-60, 72, 73, 77, 81, 82, 84, 113, 124, 136). Arachidonic acid (AA), either obtained in the diet or as a biosynthetic product of linoleic acid (18:2; ω-6), occurs as a fatty acid component of platelet membranes and most tissue phospholipids functioning as the main precursor of eicosanoids, which are involved in mediation of hemostatic parameters and immune cell function and response (20, 137, 138). Critical review of the scientific literature indicates that while AA levels may decrease following consumption of ω-3 PUFAs, the concentration of AA generally remains within normal physiological concentrations of 5 to 15% of total fatty acids of platelet membranes and tissue phospholipids. Additionally, the fatty acid composition of DHA-rich oil comprises up to 1.8% AA. There is no indication that DHA, at exposures estimated through the proposed uses of DHA-rich oil, would adversely affect hemostatic parameters or immune function or response as a result of possible

concomitant decreases in platelet and total serum phospholipid and nonesterified fatty acid levels of AA (42-44, 46, 48, 56, 58-60, 72, 73, 77, 81, 82, 84, 124-128, 136).

When viewed in its entirety, the scientific evidence from published clinical studies with DHA-containing oils indicates that the consumption of DHA-rich oil, under the conditions of intended use, would not be expected to produce adverse effects on human health.

Toxicological Studies

Safety of Other DHA-Containing Oils

The safety of DHA-containing fish and microalgal-derived oils has been studied extensively. Overall, the data from these toxicological studies indicate that gavage or dietary administration of fish or microalgal-derived oils does not produce significant adverse effects on mortality, body weight gains, food consumption, or clinical observations in laboratory animals including mice, rats, and pigs (25, 139-150). Yellow fat disease, which is characterized by accretion of lipofuscin pigment, degeneration of adipose cells (steatosis), and inflammation of adipose tissue (steatitis) (139, 151, 152), has been reported to occur naturally in wildlife species and was reported in rats, rabbits, mink, and pigs in various toxicological studies following the consumption of diets rich in ω-3 PUFAs (*i.e.*, ω-3 PUFA-containing oils at dietary concentrations ranging from as high as 12 to 19% for periods of 8 weeks to 12 months in length) in combination with a vitamin E deficient state (139, 140, 142, 147, 151-159). This effect is considered a normal response to a large load of dietary lipids, and may be prevented by concurrently administering vitamin E with high-PUFA diets (154, 158-161). Some study authors reported increased liver and spleen weights in mice and rats administered high PUFA diets at daily intakes ranging from 25 to 9,500 mg/kg body weight and varying durations of 4 to 13 weeks (139, 141, 142, 144, 147, 148, 162, 163); however, no histopathological effects were observed in these organs and the increased organ weights were reported to be adaptations to accommodate the large lipid load.

Studies of DHA-Rich Oil

In addition to a critical review of the available scientific data on the safety of DHA-containing fish and other microalgal-derived oils, the safety of DHA-rich oil (reported as DHA45-oil) derived from *Ulkenia sp.* was assessed in various genotoxicity and acute, subchronic, and reproductive toxicity studies. These studies were summarized and reported by Kroes *et al.* (201).

DHA-rich oil (reported as DHA45-oil) was not genotoxic in the Ames assay using *Salmonella typhimurium* and *Escherichia coli* WP2 *uvrA*, with or without metabolic activation (164, 165, 201), or in a chromosomal aberration assay in Chinese hamster fibroblast cells (166, 201). DHA-rich oil (reported as DHA45-oil) was reported to have low acute oral toxicity in mice and rats (*i.e.*, LD_{50} values >2,000 mg DHA-rich oil/kg body weight) (167, 168, 201).

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In a subchronic toxicity study of DHA-rich oil (reported as DHA45-oil), groups of 30 Sprague-Dawley Crj:CD (SD) IGS rats (15/sex/group) were administered distilled water or various combinations of DHA-rich oil and DHA27 (an oil containing 27% DHA) by daily oral gavage for a period of 90 days (169, 201). The combinations of DHA-rich oil/DHA27 tested included 0/2,000, 500/1,500, 1,000/1,000, and 2,000/0 mg/kg body weight/day. Based on total DHA oil content, these dosing regiments provided daily doses of 540, 630, 720, and 900 mg DHA/kg body weight/day, respectively. Additional groups of 5 rats/sex/dose receiving distilled water or 2,000 mg/kg body weight/day of DHA-rich oil or DHA27 were allowed a 4-week recovery period following the 90 days of dosing. Effects of treatment on mortality and clinical signs, neurologic responses, body weight gain, food and water consumption, hematology, clinical chemistry, urinalysis, and on the results of ophthalmology, gross pathological, and histopathological examinations were evaluated. There were no treatment-related differences between DHA27 and DHA-rich oil. Compared to the water controls, there were no biologically significant effects of treatment with DHA-rich oil alone or in combination with DHA27. At necropsy, increased relative liver weights were reported in animals fed DHA-rich oil alone or 1,000 mg/kg body weight/day of each oil, which were likely the result of the large lipid load, as reported for rats in several published feeding and gavage studies with fish and marine algal-derived oils providing daily intakes ranging from 25 to 9,500 mg/kg body weight for durations of 4 to 13 weeks. In the absence of histopathological lesions or changes in enzymes indicative of liver toxicity, the increased liver weights were considered to be not toxic in nature. Similarly, reported increases in the absolute weights, and in some cases, relative weights, of several organs including the spleen, kidneys, and adrenals were not considered to be of toxicological significance as there were no histopathological correlates to the organ weight findings and, in all cases, the magnitude of change was small. Thus, 90-day gavage treatment with DHA-rich oil, alone or in combination with DHA27 was reported to have no adverse effect on the findings of the ophthalmology, gross pathology, or histopathology examinations. Additionally, dose-dependent effects were not observed with increasing levels of DHA administration. Given the lack of histopathological effects, the NOAEL in this study was considered to be 2,000 mg DHA-rich oil/kg body weight/day (approximately 900 mg DHA/kg body weight/day), which was the highest dose tested.

The *in utero* toxicity of DHA-rich oil (reported as DHA45-oil) produced from *Ulkenia sp.* was evaluated in a one-generation study in rats (170, 201). Groups of 56 Wistar (Crl:(WI)WU BR) rats (28/sex/group) were administered DHA-rich oil in the diet at concentrations of 0 (control), 1.5, 3.0, or 7.5% for 10 weeks prior to mating. The total intake of test material (as DHA-rich oil) ranged throughout the different phases of the study period and is presented in Table 3. After successful mating, males were sacrificed and necropsied, while females continued to be exposed at their respective concentrations and were allowed to deliver. On post-natal Day (PND) 21, all pups were weaned and sacrificed after gross external evaluation. Evaluations were made of mortality, clinical signs, body weights, food consumption, fertility and reproductive performance, litter size, malformed pups, pup weights, and gross pathology and histology of

dead or stillborn pups and all F_0 animals. There was no effect of treatment with DHA-rich oil on mortality or clinical signs. Sporadic increases in body weight gains were reported for some of the treatment groups compared to corn oil controls; however, differences in food consumption also were detailed, which the authors indicated may have accounted for the observations of weight gains in these groups. With respect to reproductive parameters, treatment with DHA-rich oil was reported to have no effect on precoital time, mating index, fertility indices, fecundity, gestation index and duration, numbers of stillborn pups, or post-implantation losses. Similarly, there were no adverse effects of treatment on the numbers of pups, pups/litter, pup mortality, sex ratio, pup weight, or incidence of malformations. Absolute liver weights were increased in mid- and high-dose males, and in low- and high-dose females; however, these effects were considered by the study authors to be of no toxicological significance, as no gross or histopathological correlates were reported and similar effects have been reported in rats in several feeding and gavage studies of fish and marine algal-derived oils. Increased absolute and relative spleen weights were reported and were associated with an increased incidence and/or severity of extramedullary hematopoiesis observed histologically. The only significant gross pathology reported was the presence of "yellow spots" within the abdominal adipose tissue of the F_0 animals. These yellow spots were reportedly compatible with findings associated with yellow fat disease, and microscopic evaluation of these yellow spots yielded the diagnosis of lipogranuloma by the study authors. To address these reported effects, a panel of internationally recognized expert pathologists (Expert Pathology Panel) was convened to independently and collectively critically evaluate the scientific data of this study, as well as additional relevant data compiled from the published literature and any other data and information deemed by the pathology experts to be pertinent to the evaluation. The Expert Pathology Panel agreed that the reported effects were related to the administration of high levels of DHA-rich oil (reported as DHA45-oil), but, they concluded that the adipose tissue alteration was in fact steatitis, which occurs naturally and experimentally in many different species fed diets that are high in PUFAs, including DHA-containing oils, and are relatively low in antioxidants (171). The Expert Pathology Panel unanimously concluded that the steatitis was the "result of a nutritional imbalance... attributable to the extremely high levels of DHA45-oil administered", the increased spleen weights were due to extramedullary hematopoiesis "consistent with a response to steatitis," and the "findings reported in the one-generation reproduction study are those expected with high exposure to PUFAs and raise no concern for human safety of DHA45-oil under appropriate conditions of use." The findings of the Expert Panel were reported by Kroes *et al.* (201).

Safety of Other Components of DHA-Rich Oil

Palmitic Acid

The total fatty acid content of DHA-rich oil comprises approximately 33% palmitic acid (16:0) of total fatty acids. Palmitic acid is a natural component of the human diet and has been identified in meat, poultry, fish, grain products, and milk and milk products (172). Palmitic acid was

reported to have an estimated daily intake in the U.S. population in the range of 11 to 19 g/day (172).

The exposure to DHA from the intended food uses will be a maximum of 3 g/day under the conditions of intended use. On the basis of DHA-rich oil containing a minimum of 43% DHA of the total fatty acid content, the maximum intake of palmitic acid corresponds to approximately 2.3 g/day. This intake is at least 5 times less than the amount of palmitic acid already consumed as a natural constituent of the diet, and thus the estimated intake of palmitic acid through the intended use of DHA-rich oil would not have an impact on the relative amount of daily dietary palmitic acid. Therefore, the estimated intake of palmitic acid through the proposed uses of DHA-rich oil would not be expected to produce adverse effects on human health.

DPA

The fatty acid composition of DHA-rich oil includes up to 14 and 0.6%, respectively, of the ω-6 and ω-3 isomers of DPA. Similar to DHA, both forms of DPA are cell membrane fatty acids (23, 29, 173-175) which may be derived by biosynthesis through elongation, desaturation, or shortening of endogenous long chain fatty acids (20, 23, 27-29), or by the dietary intake of foods such as fish, seal, or fish or microalgal-derived oils (44, 176, 177). As both DPA isomers are component fatty acids of fish oil, the safety of ω-3 and ω-6 DPA is supported by the numerous non-clinical and clinical studies that have reported no adverse effects following dietary supplementation with fish or marine oil.

In a series of dietary studies in rats and rabbits that evaluated the subchronic, reproductive, and developmental toxicity of microalgal-derived DPA (ω-6)-containing oils (calculated to provide doses of up to 630 mg DPA/kg body weight/day) (149, 150, 178), no compound-related effects on survival, clinical observations, body weight gains, food consumption, urinalysis measurements, or gross necropsy findings, and no effect of treatment on hematological parameters, spleen weight, or on the gross and histopathological appearance of the spleen or adipose tissue were reported. Overall, there were no reported effects of treatment on reproductive performance, duration of gestation, mean litter size, or number of litters with live and/or dead pups, and no effects on postimplantation loss, mean fetal or pup body weight/litter, or morphological developments in either species.

In zinc deficient and non-deficient rats provided a dietary dose of up to 17 mg DPA/kg body weight for a period of 6 weeks, no differences between non-zinc deficient control or treatment groups with respect to final body weight, absolute liver and testes weight, plasma and testes zinc levels, or spermatid content of the testis parenchyma were reported (173).

Additionally, as described previously, subchronic toxicity and one-generation reproduction studies were performed in rats using DHA-rich oil (reported as DHA45-oil) (201). In the 90-day subchronic toxicity study, gavage administration of combinations of DHA-rich oil/DHA27 to

groups of 30 Sprague-Dawley Crj:CD (SD) IGS rats (15/sex/group) provided daily combined ω-3 and ω-6 DPA doses of at least 0, 41, 82, and 163 mg DPA/kg body weight/day (169, 201). As described previously, there were no biologically significant effects of treatment with DHA-rich oil at the highest dose evaluated in the study, 2,000 mg DHA-rich oil/kg body weight/day, providing 163 mg DPA/kg body weight/day. In the one-generation reproductive toxicity study in Wistar (Crl:(WI)WU BR) rats (28/sex/group), DPA intakes ranged from 65 to 913 mg DPA/kg body weight/day (see Table 3), without adverse toxicological effects attributable to DHA-rich oil, or components thereof (170, 201). As discussed above, lipogranuloma of the abdominal adipose tissue and increased absolute and relative spleen weights associated with an increased incidence and/or severity of extramedullary hematopoiesis were reported in some of the treatment animals compared to controls, and it was unanimously concluded by the Expert Pathology Panel that the "findings reported in the one-generation reproduction study are those expected with high exposure to PUFAs and raise no concern for human safety of DHA45-oil under appropriate conditions of use" (201).

Table 3 Estimated Daily Intake of DHA-rich oil, DHA, and DPA[1] by Rats in the One-Generation Reproduction Study

	Low-Dose Group (1.5% DHA-rich oil)	Mid-Dose Group (3.0% DHA-rich oil)	High-Dose Group (7.5% DHA-rich oil)
	Estimated Intake of DHA-rich oil (mg/kg body weight/day)		
Males	800 to 1,000	1,500 to 2,000	3,400 to 4,700
Females (pre-mating)	1,800 to 2,200	3,400 to 4,300	7,900 to 9,700
Females (gestation and lactation Days 1 to 14)	1,800 to 2,700	3,700 to 5,300	7,800 to 11,200
	Estimated Intake of DHA (mg/kg body weight/day)		
Males	360 to 450	675 to 900	1,530 to 2,115
Females (pre-mating)	810 to 990	1,530 to 1,935	3,555 to 4,365
Females (gestation and lactation Days 1 to 14)	810 to 1,215	1,665 to 2,385	3,510 to 5,040
	Estimated Intake of DPA (mg/kg body weight/day)		
Males	65 to 82	122 to 163	277 to 383
Females (pre-mating)	147 to 179	277 to 350	644 to 791
Females (gestation and lactation Days 1 to 14)	147 to 220	302 to 432	636 to 913

[1] Estimated DPA values were calculated using a minimum value of 8.15% as the DPA (ω-6 + ω-3) content of DHA-rich oil.

Although no clinical studies were identified that evaluated the possible effects of DPA alone, 6 studies of fish or marine-derived oils with reported DPA contents were reviewed and provide supporting evidence for the safety of dietary DPA. No significant effects on glycemic control or LDL-C levels were reported in healthy subjects or diabetic patients receiving supplemental fish oil providing up to 800 mg DPA/day for periods of 6 weeks to 9 months (approximately 13 mg

DPA/kg body weight/day for an average 60 kg individual) (54, 56, 84, 98, 99). Decreased collagen-induced platelet aggregation was reported in 18 diabetic patients receiving fish oil providing 200 mg DPA/day for 6 weeks; however, ADP-induced aggregation was not affected and therefore the Panel considered that the overall effect of the fish oil on platelet aggregation is not clear (54). Increased bleeding times and decreased von Willebrand factor were reported in 24 healthy subjects (10 males, 14 females) consuming fish oil providing approximately 210 mg DPA/person/day for a period of 9 months (84). Although bleeding times were increased, fibrinogen levels also were increased and there was no associated reduction in platelet aggregability; thus, the clinical significance of the increased bleeding times is not clear. Additionally, due to the various ω-3 and ω-6 fatty acids comprising the fatty acid content of fish oils, the effects reported by Schmidt *et al.* (84) and Axelrod *et al.* (54) cannot be attributed to a single PUFA, such as DPA. In 12 hyperlipidemic patients (10 males, 2 females) receiving 0.42 or 0.84 mL DPA/day (approximately 0.39 and 0.78 mg, respectively)[1] for a period of 4 weeks, LDL-C levels were decreased by 2% and no significant effects on glycemic control and were reported (44). Considering the totality of available evidence, the estimated intake of DPA (<1 g/day) through the proposed uses of DHA-rich oil would not be expected to produce adverse effects in humans.

Sterols

The unsaponifiable fraction of DHA-rich oil is low and consists primarily of sterols at a level around or even below 1%. Representative lot analyses of DHA-rich oil identified the main sterol components as cholesterol, 7-dehydrostigmasterol and 4-methyl-chondrillasterol.

The safety of dietary cholesterol and other sterols is well documented in the scientific literature. Cholesterol is a natural constituent of the human diet, and 4-methyl sterols have been identified in the normal metabolic pathway of cholesterol biosynthesis in man, and in several food sources, including fish, shellfish, and rice bran (180, 181). 7-Dehydrostigmasterol was quantified in phytosterols purified from the unsaponifiable fraction of soybean oil (182). Hence, although quantitatively minor constituents, the sterols in DHA-rich oil would be considered to already occur in the human diet.

With typical sterol levels below 1% in DHA-rich oil, the level of intake of sterols under the intended conditions of use of DHA-rich oil would be minimal. Typical cholesterol levels are around 30% of total sterols. Assuming a maximum intake of DHA-rich oil of 7.9 g/day (based on 38% DHA in DHA-rich oil contributing to 3 g/person/day), a total sterol content of 1% and 30% of sterols being cholesterol, the theoretical maximum daily cholesterol intake from DHA-rich oil would be approximately 24 mg. Similarly, the theoretical maximum intake for phytosterols

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[1]Calculated based on the density value for menhaden fish oil (179)

would be approximately 55 mg/day. The safety of dietary cholesterol and phytosterols is well documented in the scientific literature. Cholesterol and phytosterols are natural constituents of the diet and 4-methyl sterols occur in the endogenous metabolic pathway of cholesterol biosynthesis. These intakes well below the amounts of sterols already consumed as natural constituents of the diet (up to 400 mg/person/day) (183-187), and thus, the estimated intake of sterols through the proposed uses of DHA-rich oil would not have an impact on the relative amount of cholesterol and phytosterols already consumed in the diet. Therefore, the dietary exposure to cholesterol, 7-dehydrostigmasterol, and 4-methyl-chondrillasterol from the intended use of DHA-rich oil would not be expected to produce adverse effects on human health.

Studies Pertaining to the Safety of the Source Organism

The source organism (a thraustochytrid) is a member of the kingdom Chromista (188-191). Although there are no data demonstrating detailed human consumption of the source organism, thraustochytrids have been identified in plankton and other marine detritus and comprise a portion of the diet of filter-feeding invertebrates, and thus constitute an indirect component of the human diet through consumption of fish and other marine animals (192-195). There have been no identified reports of *Ulkenia sp.* producing toxic chemicals or pathogenicity (196, 197). Microalgal toxin analysis of representative lots of DHA-rich oil confirmed the absence of the common algal and cyanobacterial toxins, such as domoic acid, Paralytic Shellfish Poisons (PSP), Diarrhetic Shellfish Poisons (DSP), Neutrotoxic Shellfish Poisons (NSP), pectenotoxins, yessotoxins, azaspiracides, Prymnesium toxins, and microcystins and nodularin. Additionally, independent scientific expert evaluation of the available data pertinent to the safety of the microalgal source concluded *Ulkenia sp.* is both nontoxigenic and nonpathogenic to man (198, 205).

The conclusion that the microalgae is nontoxicogenic is supported by mutagenicity and classical rodent toxicity studies using the DHA-rich oil source organism. The microalgal source was reported to produce negative results in the Ames assay using *Salmonella typhimurium* strains TA97, TA98, TA100, and TA102, with or without metabolic activation (199). In a 14-day feeding study, the microalgal source suspended in distilled water was administered orally to ICR male mice (SPR) at a dose of 2 g source organism/kg body weight/day (200). A control group received distilled water only. No significant differences in clinical signs, body weight gains, or necropsy observations were reported for the microalgal source-treated mice.

Summary

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Overall, when viewed in its entirety, the scientific data summarized above support the safe intake of DHA-rich oil under the conditions of intended use in traditional foods. While the production of DHA-rich oil from the microalgae *Ulkenia sp.* for use as a food ingredient is unique, the source microorganism is nontoxigenic and nonpathogenic, and all components of DHA-rich oil have a history of occurrence in the diet. The safety of DHA-rich oil is established

by a wealth of historical information on populations consuming higher levels of DHA than those that would result from the conservative estimate of intake under the conditions of intended use. Clinical studies reveal no potential for toxicity of DHA under the conditions of intended use. The epidemiologic and clinical data are supported by animal toxicity studies, which are corroborated by studies on DHA-rich oil (reported as DHA45-oil). The Panel noted the growing body of evidence of cardiovascular risk reduction with the use of ω-3 fatty acids in randomized placebo-controlled clinical trials.

There are no indications from the published literature, or from the published studies conducted with DHA-rich oil, that under the conditions of intended use in traditional foods, DHA-rich oil would result in any adverse health effects.

CONCLUSION

Based on our independent and collective, critical review of the available pertinent scientific evidence, as members of an Expert Panel specially convened for this purpose, we unanimously conclude that DHA-rich oil, meeting appropriate food grade specifications, and manufactured and used in accordance with current good manufacturing practice, under the conditions of intended use specified herein, is "generally recognized as safe" (GRAS), based on scientific procedures.

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REFERENCES

1. Sanders, T.A.B. 1989. Effects of fish oils on lipid metabolism. Nutrition 5(4):248-250.

2. Ascherio, A.; Rimm, E.B.; Stampfer, M.J.; Giovannucci, E.L.; Willett, W.C. 1995. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med 332(15):977-982.

3. Dolecek, T.A; Granditis, G. 1991. Dietary polyunsaturated fatty acids and mortality in Multiple Risk Factor Intervention Trial (MRFIT). World Rev Nutr Diet 66:205-216.

4. Kris-Etherton, P.M.; Taylor, D.S.; Yu-Poth, S.; Huth, P.; Moriarty, K.; Fishell, V.; Hargrove, R.L.; Zhao, G.; Etherton, T.D. 2000. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 71(1, Suppl.):179S-188S.

5. Schloss, I.; Kidd, M.S.; Tichelaar, H.Y.; Young, G.O.; O'Keefe, S.J. 1997. Dietary factors associated with a low risk of colon cancer in coloured west coast fishermen. S Afr Med J 87(2):152-158.

6. Fluge, Ø.; Omenaas, E.; Eide, G.E.; Gulsvik, A. 1998. Fish consumption and respiratory symptoms among young adults in a Norwegian community. Eur Respir J 12(2):336-340.

7. Johansson, L.R.; Solvoll, K.; Bjorneboe, G.E.; Drevon, C.A. 1998. Intake of very- long-chain n-3 fatty acids related to social status and lifestyle. Eur J Clin Nutr 52(10):716-721.

8. Sugano, M.; Hirahara, F. 2000. Polyunsaturated fatty acids in the food chain in Japan. Am J Clin Nutr 71(1, Suppl.):189S-196S.

9. Torres, I.C.; Mira, L.; Ornelas, C.P.; Melim, A. 2000. Study of the effects of dietary fish intake on serum lipids and lipoproteins in two populations with different dietary habits. Br J Nutr 83(4):371-379.

10. Health and Welfare Canada. 1990. Table 19. Summary of examples of recommended nutrients based on energy expressed as daily rates. In: Nutrition Recommendations - The Report of the Scientific Review Committee. Health and Welfare Canada, Scientific Review Committee; Ottawa. H49-42/1990E, p. 203.

11. ISSFAL. 1999. Adequate Intakes. International Society for the Study of Fatty Acids and Lipids (ISSFAL); Tiverton,Devon, U.K. [http://www.issfal.org.uk/adequateintakes.htm].

12. BNF. 2000. n-3 Fatty Acids and Health. British Nutrition Foundation (BNF); London, Engl.

13. U.S. FDA. 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 (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Nutritional Products, Labeling, and Dietary Supplements.

14. U.S. FDA. 1989. Substances Affirmed as Generally Recognized as Safe: Hydrogenated and Partially Hydrogenated Menhaden Oils (Final rule) (21 CFR, Part 184, Docket No. 86G-0289). Fed Reg (U.S.) 54 (178):38219.

15. U.S. FDA. 1997. Substances affirmed as generally recognized as safe: Menhaden oil (Final rule) (21 CFR, Part 184, Docket No. 86G-0289). Fed Reg (U.S.) 62 (108):30751-30757.

16. U.S. FDA. 2002. Agency Response Letter GRAS Notice No. GRN 000105. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

17. U.S. FDA. 2002. Agency Response Letter GRAS Notice No. GRN 000109. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

18. Neuringer, M.; Anderson, G.J.; Connor, W.E. 1988. The essentiality of n-3 fatty acids for the development and function of the retina and brain. Annu Rev Nutr 8:517-541.

19. Hsia, M.T.S.; Marvis, R.D.; DeSesso, J.M. 1989. Health Effects of Refined Menhaden Oil. Prepared by Mitre Corp., Civil Systems Division; McLean, VA. For U.S. Food and Drug Administration (FDA); Washington, DC. [PB89-182398].

20. Linder, M.C. 1991. Nutrition and metabolism of fats. In: Linder, M.C. (Ed.). Nutritional Biochemistry and Metabolism With Clinical Applications (2nd Ed.). Elsevier Science Publishing Company, Inc.; New York, pp. 51-84.

21. Linscheer, W.G.; Vergroesen, A.J. 1994. Lipids. In: Shils, M.E.; Olson, J.A.; Shike, M. (Eds.). Modern Nutrition in Health and Disease, (8th Ed.). Lea & Febiger; Philadelphia. Vol. 1, pp. 47-88.

22. Krummel, D. 1996. Lipids [and] Polyunsaturated fatty acids. In: Mahan, L.K.; Escott-Stump, S. (Eds.). Krause's Food, Nutrition and Diet Therapy (9th Ed.). W.B. Saunders Company; Philadelphia, Penn./Toronto, pp. 49-62 & 528.

23. Alvarez, R.A.; Aguirre, G.D.; Acland, G.M.; Anderson, R.E. 1994. Docosapentaenoic acid is converted to docosahexaenoic acid in the retinas of normal and prcd-affected miniature poodle dogs. Invest Ophthalmol Vis Sci 35(2):402-408.

24. Guyton, A.C.; Hall, J.E. 1996. Digestion and absorption in the gastrointestinal tract. In: Guyton, A.C.; Hall, J.E. (Eds.). Textbook of Medical Physiology (9th Ed.). W.B. Saunders Company; Philadelphia, Penn., pp. 833-844.

25. Willumsen, N.; Hexeberg, S.; Skorve, J.; Lindquist, M.; Berge, R.K. 1993. Docosahexaenoic acid shows no triglyceride-lowering effects but increases the peroxisomal fatty acid oxidation in liver of rats. J Lipid Res 34(1):13-22.

26. Périchon, R.; Bourre, J.M. 1995. Peroxisomal ß-oxidation activity and catalase activity during development and aging in mouse liver. Biochimie 77:288-293.

27. Retterstøl, K.; Haugen, T.B.; Christophersen, B.O. 2000. The pathway from arachidonic to docosapentaenoic acid (20:4n-6 to 22:5n-6) and from eicosapentaenoic to docosahexaenoic acid (20:5n-3 to 22:6n-3) studied in testicular cells from immature rats. Biochim Biophys Acta 1483(1):119-131.

28. Rosenthal, M.D.; Garcia, M.C.; Jones, M.R.; Sprecher, H. 1991. Retroconversion and Δ4 desaturation of docosatetraenoate (22 : 4(n — 6)) and docosapentaenoate (22:5(n — 3)) by human cells in culture. Biochim Biophys Acta 1083(1):29-36.

29. Achard, F.; Bénistant, C.; Lagarde, M. 1995. Interconversions and distinct metabolic fate of eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in bovine aortic endothelial cells. Biochim Biophys Acta 1255(3):260-266.

30. Brossard, N.; Croset, M.; Pachiaudi, C.; Riou, J.P.; Tayot, J.L.; Lagarde, M. 1996. Retroconversion and metabolism of [13C]22:6n-3 in humans and rats after intake of a single dose of [13C]22:6n-3-triacylglycerols. Am J Clin Nutr 64(4):577-586.

31. U.S. FDA. 1993. Food Labeling: Health Claims and Label Statements: Omega-3 Fatty Acids and Coronary Heart Disease (Final rule) (21 CFR, Part 101, Docket No. 91N-0103 (RIN 0905-AB67). Fed Reg (U.S.) 58 (3):2682.

32. Kenny, D.; Warltier, D.C.; Pleuss, J.A.; Hoffmann, R.G.; Goodfriend, T.L.; Egan, B.M. 1992. Effect of omega-3 fatty acids on the vascular response to angiotensin in normotensive men. Am J Cardiol 70(15):1347-1352.

33. de Maat, M.P.M.; Princen, H.M.G.; Dagneli, P.C.; Kamerling, S.W.A.; Kluft, C. 1994. Effect of fish oil and vitamin E on the cardiovascular risk indicators fibrogen, C-reactive protein and PAI activity in healthy young volunteers. Fibrinolysis 8(Suppl. 2):50-52.

34. Swails, W.S., Bell, S.J., Bristrian, B.R., Lewis, E.J., Pfister, D., Forse, R.A., Kelly, S., Blackburn, G.L. 1993. Fish-oil containing diet and platelet aggression. Nutrition 9(3):211-217.

35. Roulet, M.; Frascarolo, P.; Pilet, M.; Chapuis, G. 1997. Effect of intraveneously infused fish oil on platelet fatty acid phosophlipid composiition and on platelet function in postoperative trauma. JPEN J Parenter Enteral Nutr 21(5):296-301.

36. Yosefy, C.; Viskoper, J.R.; Varon, D.; Ilan, Z.; Pilpel, D.; Lugassy, G.; Schneider, R.; Adan, Y.; Raz, A. 1996. Repeated fasting and refeeding with 20:5, n-3 eicosapentaenoic acid (EPA): A novel approach for rapid fatty acid exchange and its effect on blood pressure, plasma lipids and hemostasis. J Hum Hypertens 10(Suppl. 3):S135-S139.

37. Nordøy, A.; Hatcher, L.; Goodnight, S.; Fitzgerald, G.A.; Conner, W.E. 1994. Effects of dietary fat content, saturated fatty acids, and fish oil on eicosanoid poduction and hemostatic parameters in normal men. J Lab Clin Med 123(6):914-920.

38. Sanders, T.A.B.; Oakley, F.R.; Miller, G.J.; Mitropoulos, K.A.; Crook, D.; Oliver, M.F. 1997. Influence of n-6 versus n-3 polyunsaturated fatty acids in diets low in saturated fatty acids on plasma lipoproteins and hemostatic factors. Arterioscler Thromb Vasc Biol 17(12):3449-3460.

39. Harris, W.S.; Windsor, S.L.; Caspermeyer, J.J. 1993. Modification of lipid-related atherosclerosis risk factors by ω3 fatty acid ethyl esters in hypertriglyceridemic patients. J Nutr Biochem 4:706-712.

40. Cirillo, F.; Coppola, A.; Piemontinio, U.; Marottoli, V.; Amoriello, A.; Cerbone, A.M.; Stragliotto, E.; Tremoli, E.; Di Minno, G.; Mancini, M. 1994. Platelet effects of omega 3 fatty acid ethyl esters. In: Galli, C.; Simopoulos, A.P.; Tremoli, E. (Eds.). Effects of Fatty Acids and Lipids in Health and Disease. Karger; Basel, Switz./New York. World Review of Nutrition and Dietetics, Vol. 76, pp. 60-63.

41. Misso, N.L.A.; Thompson, P.J. 1995. Fish oil supplementation inhibits platelet aggregation and ATP release induced by platelet-activating factor and other agonists. Platelets 6(5):275-282.

42. Luostarinen, R.; Wallin, R.; Wibell, L.; Saldeen, T. 1995. Vitamin E supplementation counteracts the fish oil-induced increase of blood glucose in humans. Nutr Res 15(7):953-968.

43. Engström, K.; Luostarinen, R.; Saldeen, T. 1996. Whole blood production of thromboxane, prostacyclin and leukotriene B(4) after dietary fish oil supplementation in man: Effect on vitamin E. Prostaglandins Leukot Essent Fatty Acids 54(6):419-425.

44. Haglund, O.; Wallin, R.; Wretling, S.; Hultberg, B.; Saldeen, T. 1998. Effects of fish oil alone and combined with long chain (n-6) fatty acids on some coronary risk factors in male subjects. J Nutr Biochem 9(11):629-635.

45. Mundal, H.H.; Gjesdal, K.; Landmark, K. 1993. The effect of n-3 fatty acids and nifedipine on platelet function in hypertensive males. Thromb Res 72(3):257-262.

46. Haglund, O.; Luostarinen, R.; Wallin, R.; Saldeen, T. 1992. Effects of fish oil on triglycerides, cholesterol, lipoprotein(a), atherogenic index and fibrinogen. Influence of degree of purification of the oil. Nutr Res 12(4&5):455-468.

47. Freese, R.; Mutanen, M. 1997. Small effects of linseed oil or fish oil supplementation on postprandial changes in hemostatic factors. Thromb Res 85 (2):147-152.

48. Mori, T.A.; Vandongen, R.; Mahanian, F.; Douglas, A. 1992. Plasma lipid levels and platelet and neutrophil function in patients with vascular disease following fish oil and olive oil supplementation. Metabolism 41(10):1059-1067.

49. Freese, R.; Mutanen, M. 1997. α-Linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. Am J Clin Nutr 66(3):591- 598.

50. Brister, S.J.; Buchanan, M.R. 1997. Effects of linoleic acid and/or marine fish oil supplements on vessel wall thromboresistance in patients undergoing cardiac surgery. In: Sinzinger, H.; Samuelsson, B.; Vane, J.R.; Paoletti, R.; Ramwell, P.; Wong, P.Y.-K. (Eds.). Recent Advances in Prostaglandin, Thromboxane, and Leukotriene Research. 10th International Conference on Prostaglandins and Related Compounds - Proceedings, Sep. 22-27, 1996, Vienna, Austria. Plenum Press; New York. Advances in Experimental Medicine and Biology, Vol. 433, pp. 275-278.

51. Badalamenti, S.; Salerno, F.; Sameron, J.M.; Lorenzano, E.; Rimola, A.; Gines, P.; Jimenez, W.; Graziani, G.; Arroyo, V.; Rodes, J.; Ponticelli, C. 1997. Lack of renal effects of fish oil administration in patients with advanced cirrhosis and impaired glomerular filtration. Hepatology 25(2):313-316.

52. Lenzi, S.; Caprioli, R.; Rindi, P.; Lazzerini, G.; Bernini, W.; Pardini, E.; Lucchetti, A.; Galli, C.; Carr, L.; De Caterina, R. 1996. Omega-3 fatty acids supplementation and lipoprotein(a) concentrations in patients with chronic glomerular diseases. Nephron 72(3):383-390.

53. Hansen, J.B.; Berge, R.K.; Nordøy, A.; Bønaa, K.H. 1998. Lipid peroxidation of isolated chylomicrons and oxidative status in plasma after intake of highly purified eicosapentaenoic or docosahexaenoic acids. Lipids 33(11):1123-1129.

54. Axelrod, L.; Camuso, J.; Williams, E.; Kleinman, K.; Briones, E.; Schoenfeld, D. 1994. Effects of a small quantity of -3 fatty acids on cardiovascular risk factors in NIDDM. Diabetes Care 17(1):37-44.

55. Almdahl, S.M., Nilsen, D.W.T., Østerud, B., Sørlie, D.G.; Vaag, J. 1993. Thromboplastin activities and monocytes in the coronary circulation of reperfused human myocardium. Scand J Thorac Cardiovasc Surg 27(1):81-86.

56. Conquer, J.A.; Cheryk, L.A.; Chan, E.; Gentry, P.A.; Holub, B.J. 1999. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. Thromb Res 96(3):239-250.

57. Véricel, E.; Calzada, C.; Chapuy, P.; Lagarde, M. 1999. The influence of low intake of n-3 fatty acids on platelets in elderly people. Atherosclerosis 147(1):187-192.

58. Turini, M.E.; Powell, W.S.; Behr, S.R.; Holub, B.J. 1994. Effects of a fish-oil and vegetable-oil formula on aggregation and ethanolamine-containing lysophospholipid generation in activated human platelets and on leukotriene production in stimulated neutrophils. Am J Clin Nutr 60(5):717-724.

59. Henderson, W.R.; Astley, S.J.; McCready, M.M.; Kushmerick, P.; Casey, S.; Becker, J.W.; Ramsey, B.W. 1994. Oral absorption of omega-3 fatty acids in patients with cystic fibrosis who have pancreatic insufficiency and in healthy control subjects. J Pediatr 124(3):400-408.

60. Conquer, J.A.; Holub, B.J. 1996. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. J Nutr 126(12):3032-3039.

61. Pirich, C.; Gaszo, A.; Granegger, S.; Sinzinger, H. 1999. Effects of fish oil supplementation on platelet survival and ex vivo platelet function in hypercholesterolemic patients. Thromb Res 96(3):219-227.

62. Mundal, H.; Meltzer, H.; Aursnes, I. 1994. Bleeding times related to serum triglyceride levels in healthy young adults. Thromb Res 75(3):285-291.

63. Wensing, A.G.; Mensink, R.P.; Hornstra, G. 1999. Effects of dietary n-3 polyunsaturated fatty acids from plant and marine origin on platelet aggregation in healthy elderly subjects. Br J Nutr 82(3):183-191.

64. Hansen, J.B.; Olsen, J.O.; Wilsgard, L.; Lyngmo, V.; Svensson, B. 1993. Comparative effects of prolonged intake of highly purified fish oils as ethyl ester or triglyceride on lipids, haemostasis and platelet function in normolipaemic men. Eur J Clin Nutr 47(7):497-507.

65. Hostmark, A.T.; Bjerkedal, T.; Kierulf, P.; Flaten H.; Ulshagen, K. 1988. Fish oil and plasma fibrinogen. BMJ 297(6642):180-181.

66. Wallace, J.M.W.; McCabe, A.J.; Roche, H.M.; Higgins, S.; Robson, P.J.; Gilmore, W.S.; McGlynn, H.; Strain, J.J. 2000. The effect of low-dose fish oil supplementation on serum growth factors in healthy humans. Eur J Clin Nutr 54(9):690-694.

67. Otto, C.; Ritter, M.M.; Soennichsen, A.C.; Schwandt, P.; Richter, W.O. 1996. Effects of n-3 fatty acids and fenofibrate on lipid and hemorrheological parameters in familial dysbetalipoproteinemia and familial hypertriglyceridemia. Metabolism 45(1):1305-1311.

68. Nilsen, D.W.T., Almdahl, S.M., Svensson, B., Vaage, J., Rasmussen, K.; Østerud, B. 1993. Lipopolysaccharide induced monocyte thromboplastin synthesis and coagulation responses in patients undergoing coronary bypass surgery after preoperative supplementation with n-3 fatty acids. Thromb Haemost 70(6):900-902.

69. Mehta, J.L.; Lopez, L.M.; Lawson, D.; Wargovich, T.J.; Williams, L.L. 1988. Dietary supplementation with omega-3 polyunsaturated fatty acids in patients with stable coronary heart disease. Effects on indices of platelet and neutrophil function and exercise performance. Am J Med 84(1):45-52.

70. Swahn, E.; von Schenck, H.; Olsson, A.G. 1998. Omega-3 ethyl ester concentrate decreases total apoloprotein CIII and increases antithrombin III in postmyocardial infarction patients. Clin Drug Invest 15:473-482.

71. Grundt, H.; Nilsen, D.W.; Hetland, Ø.; Mansoor, M.A.; Aarsland, T.; Woie, L. 1999. Atherothrombogenic risk modulation by n-3 fatty acids was not associated with changes in homocysteine in subjects with combined hyperlipidaemia. Thromb Haemost 81(4):561-565.

72. Mori, T.A.; Beilin, L.J.; Burke, V.; Morris, J.; Ritchie, J. 1997. Interactions between dietary fat, fish and fish oils and their effects on platelet function in men at risk of cardiovascular disease. Arterioscler Thromb Vasc Biol 17(2):279-286.

73. Nelson, G.J.; Schmidt, P.C.; Bartolini, G.L.; Kelly, D.S.; Kyle, D. 1997. The effect of dietary docosahexaenoic acid on plasma lipoproteins and tissue fatty acid composition in humans. Lipids 32(11):1137-1146.

74. Ågren, J.J.; Väisänen, S.; Hänninen, O.; Muller, A.; Hornstra, G. 1997. Hemostatic factors and platelet aggregation after a fish-enriched diet or fish oil or docosahexaenoic acid supplementation. Prostaglandins Leukot Essent Fatty Acids 57(4&5):419-421.

75. Toft, I.; Bønaa, K.H.; Ingebretsen, O.C.; Nordøy, A. ; Jenssen, T. 1995. Effects of n-3 polyunsaturated fatty acids on glucose homestasis and blood pressure in essential hypertension. A randomized, controlled trial. Ann Intern Med 123(12):911-918.

76. Toft, I.; Bønaa, K.H.; Ingebretsen, O.C.; Nordøy, A.; Jenssen, T. 1997. Fibrinolytic function after dietary supplementation with 3 polyunsaturated fatty acids. Arterioscler Thromb Vasc Biol 17(5):814-819.

77. Tremoli, E.; Maderna, P.; Marangoni, F.; Colli, S.; Eligini, S.; Catalano, I.; Angeli, M.T.; Pazzucconi, F.; Gianfranceschi, G.; Davi, G.; Stragliotto, E.; Sirtori, C.R.; Galli, C. 1995. Prolonged inhibition of platelet aggregation after n-3 fatty acid ethyl ester ingestion by healthy volunteers. Am J Clin Nutr 61(3):607-613.

78. Prisco, D.; Paniccia, R.; Filippini, M.; Francalanci, I.; Bandinelli, B.; Comeglio, P.; Rostagno, C.; Abbate, R.; Neri Serneri, G.G. 1994. No changes in PAI-1 levels after four-month n-3 PUFA ethyl ester supplementation in healthy subjects. Thromb Res 76(3):237-244.

79. Prisco, D.; Filippini, M.; Francalanci, I.; Paniccia, R.; Gensini, G.F.; Neri Serneri, G.G. 1995. Effect of n-3 fatty acid ethyl ester supplementation on fatty acid composition of the single platelet phospholipids and on platelet functions. Metabolism 44(5):562-569.

80. Radack, K.; Deck, C.; Huster, G. 1989. Dietary supplementation with low-dose fish oils lowers fibrinogen levels: A randomized, double- blind controlled study. Ann Intern Med 111(9):757-758.

81. Eritsland, J.; Seljeflot, M.; Abdelnoor, M.; Arnesen, H. 1994. Long-term influence of omega-3 fatty acids on fibrinoylsis, fibrinogen, and serum lipids. Fibrinolysis 8:120-125.

82. Leaf, A.; Jorgensen, M.B.; Jacobs, A.K.; Cote, G.; Schoenfeld, D.A.; Scheer, J.; Weiner, B.H.; Slack, J.D.; Kellett, M.A.; Raizner, A.E.; Weber, P.C.; Mahrer, P.R.; Rossouw, J.E. 1994. Do fish oils prevent restinosis after coronary angioplasty? Circulation 90(5):2248-2257.

83. Seljeflot, I.; Johansen, O.; Arnesen, H.; Eggesbø, J.-B.; Westvik, A.-B.; Kierulf.; P. 1999. Procoagulant acitivity and cytokine expression in whole blood cultures from patients with atherosclerosis supplemented with omega-3 fatty acids. Thromb Haemost 81(4):566-570.

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

85. Clark, W.F.; Parbtani, A.; Naylor, C.D.; Levinton, C.M.; Muirhead, N.; Spanner, E.; Huff, M.W.; Philbrick, D.J.; Holub, B.J. 1993. Fish oil in lupus nephritis: Clinical findings and methodologial implications. Kidney Int 44(1):75-86.

86. Deslypere, J.P. 1992. Influence of supplementation with N-3 fatty acids on different coronary risk factors in men: A placebo controlled study. Verh K Acad Geneeskd Belg 54(3):189-216.

87. Saynor, R.; Gillott, T. 1992. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. Lipids 27:533-538.

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

89. Eritsland, J., Arnesen, H., Grønseth, K., Fjeld, N.B.; Abdelnoor, M. 1996. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol 77(1):31-36.

90. Fasching, P., Rohac, M., Liener, K., Schneider, B., Nowotny, P.; Waldhausl, W. 1996. Fish oil supplementation versus Gemfibrozil treatment in hyperlipidemic NIDDM. Horm Metab Res 28(5):230-236.

91. McVeigh, G.E.; Brennan, G.M.; Cohn, J.N.; Finkelstein, S.M.; Hayes, R.J.; Johnston, G.D. 1994. Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus. Arterioscler Thromb 14(9):1425-1429.

92. McGrath, L.T.; Brennan, G.M.; Donnelly, J.P.; Johnston, G.D.; Hayes, J.R.; McVeigh, E.G. 1996. Effect of dietary fish oil supplementation on peroxidation of serum lipids in patients with non-insulin dependent diabetes mellitus. Atherosclerosis 121(2):275-283.

93. Mori, T.A.; Burke, V.; Puddey, I.B.; Watts, G.F.; O'Neal, D.N.; Best, J. D.; Beilin, L.J. 2000. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. Am J Clin Nutr 71(5):1085-1094.

94. Gray, D.R.; Gozzip, C.G.; Eastham, J.H.; Kashyap, M.L. 1996. Fish oil as an adjuvant in the treatment of hypertension. Pharmacotherapy 16(2):295-300.

95. Bagdade, J.D.; Ritter, M.; Subbaiah, P.V. 1996. Marine lipids normalize cholesteryl ester transfer in IDDM. Diabetologia 39(4):487-491.

96. Silva, J.M.; Souza, I.; Silva, R.; Tavares, P.; Teixeira, F.; Silva, P.S. 1996. The triglyceride lowering effect of fish oils is affected by fish consumption. Int J Cardiol 57(1):75-80.

97. Morgan, W.A.; Raskin, P.; Rosenstock, J. 1995. A comparison of fish oil or corn oil supplements in hyperlipidemic subjects with NIDDM. Diabetes Care 18(1):83-86.

98. McManus, R.M.; Jumpson, J.; Finegood, D.T.; Clandinin, M.T.; Ryan, E.A. 1996. A comparison of the effects of n-3 fatty acids from linseed oil and fish oil in well-controlled type II diabetes. Diabetes Care 19(5):463-467.

99. Goh, Y.K.; Jumpsen, J.A.; Ryan, E.A.; Clandinin, M.T. 1997. Effect of -3 fatty acid on plasma lipids, cholesterol and lipoprotein fatty acid content in NIDDM patients. Diabetologia 40(1):45-52.

100. Mackness, M.I.; Bhatnagar, D.; Durrington, P.N.; Prais, H.; Haynes, B.; Morgan, J.; Borthwick, L. 1994. Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. Eur J Clin Nutr 48(12):859-865.

101. Harris, W.S.; Ginsberg, H.N.; Arunakul, N.; Shachter, N.S.; Windsor, S.L.; Adams, M.; Berglund, L.; Osmundsen, K. 1997. Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovasc Risk 4(5&6):385-391.

102. Rivellese, A.A.; Maffettone, A.; Iovine, C.; Di Marino, L.; Annuzzi, G.; Mancini, M.; Riccardi, G. 1996. Long-term effects of fish oil on insulin resistance and plasma lipoproteins in NIDDM patients with hypertriglyceridemia. Diabetes Care 19(11):1207-1213.

103. Connor, W.E., Prince, M.J., Ullmann, D., Riddle, M., Hatcher, L., Smith, F. E.; Wilson, D. 1993. The hypotriglyceridemic effect of fish oil in adult-onset diabetes with adverse glucose control. Ann N Y Acad Sci 683:337-340.

104. Bonnema, S.J.; Jespersen, L.T.; Marving, J.; Gregersen, G. 1995. Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. Diabetes Nutr Metab 8(2):81-87.

105. Eritsland, J.; Seljeflot, M.; Abdelnoor, M.; Arnesen, H.; Torjesen, P.A. 1994. Long-term effects on N-3 fatty acids on serum lipids and glycemic control. Scand J Clin Lab Invest 54:273-280.

106. Rossing, P., Hansen, B.V., Nielsen, F.S., Myrup, B., Hølmer, G.; Parving, H.H. 1996. Fish oil in diabetic nephropathy. Diabetes Care 19(11):1214-1219.

107. Eritsland, J., Arnesen, H., Seljeflot, I.; Høstmark, A.T. 1995. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. Am J Clin Nutr 61(4):831-836.

108. Innis, S.M.; Hansen, J.W. 1996. Plasma fatty acid responses, metabolic effects, and safety of microalgal and fungal oils rich in arachidonic and docosahexaenoic acids in healthy adults. Am J Clin Nutr 64(2):159-167.

109. Tsai, P.-J.; Lu, S.-C. 1997. Fish oil lowers plasma lipid concentrations and increases the susceptibility of low density lipoprotein to oxidative modification in healthy men. J Formos Med Assoc 96(9):718-726.

110. Chin, J.P.; Dart, A.M. 1994. Therapeutic restoration of endothelial function in hypercholesterolaemic subjects: Effect of fish oils. Clin Exp Pharmacol Physiol 21(10):749-755.

111. Balestrieri, G.P.; Maffi, V.; Sleiman, I.; Spandrio, S.; Di Stefano, O.; Salvi, A.; Scalvini, T. 1996. Fish oil supplementation in patients with heterozygous familial hypercholesterolemia. Recenti Prog Med 87(3):102-105.

112. Hansen, J.B.; Lyngmo, V.; Svensson, B.; Nordoy, A. 1993. Inhibition of exercise-induced shortening of bleeding time by fish oil in familial hypercholesterolemia (Type IIa). Arterioscler Thromb 13(1):98-104.

113. Conquer, J.A.; Holub, B.J. 1998. Effect of supplementation with different doses of DHA on the levels of circulating DHA as non-esterified fatty acid in subjects of Asian Indian background. J Lipid Res 39(2):286-292.

114. Lungershausen, Y.K.; Abbey, M.; Nestel, P.J.; Howe, P.R.C. 1994. Reduction of blood pressure and plasma triglycerides by omega-3 fatty acids in treated hypertensives. J Hypertens 12(9):1041-1045.

115. Grimsgaard, S.; Bønaa, K.H.; Hansen, J.B.; Nordøy, A. 1997. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. Am J Clin Nutr 66(3):649-659.

116. Grimsgaard, S.; Bønaa, K.H.; Hansen, J.-B.; Myhre, E.S.P. 1998. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on hemodynamics in humans. Am J Clin Nutr 68 (1):52-59.

117. Bønaa, K.H.; Bjerve, K.S.; Nordøy, A. 1992. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. Arterioscler Thromb 12(6):675-681.

118. Adler, A.J.; Holub, B.J. 1997. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. Am J Clin Nutr 65(2):445-450.

119. Hamazaki, T.; Sawazaki, S.; Asaoka, E.; Itomura, M.; Mizushima, Y.; Yazawa, K.; Kuwamori, T.; Kobayashi, M. 1996. Docosahexaenoic acid-rich fish oil does not affect serum lipid concentrations of normolipidemic young adults. J Nutr 126(11):2784- 2789.

120. Ågren, J.J.; Hänninen, O.; Julkunen, A.; Fogelholm, L.; Maliranta, H.; Schwab, U.; Pynnönen, O.; Uusitupa, M. 1996. Fish diet, fish oil and docosahexaenoic acid rich oil lower fasting and postprandial plasma lipid levels. Eur J Clin Nutr 50(11):765-771.

121. Christensen, J.H.; Gustenhoff, P.; Ejlersen, E.; Jessen, T.; Korup, E.; Rasmussen, K.; Dyerberg, J.; Schmidt, E.B. 1995. n-3 Fatty acids and ventricular extrasystoles in patients with ventricular tachyarrhythmias. Nutr Res 15(1):1-8.

122. von Schacky, C.; Fischer, S.; Weber, P.C. 1985. Long-term effects of dietary marine ω-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest 76(4):1626-1631.

123. Sacks, F.M.; Stone, P.H.; Gibson, C.M.; Silverman, D.I.; Rosner, B.; Pasternak, R.C. (For the HARP Research Group). 1995. Controlled trial of fish oil for regression of human coronary atherosclerosis. J Am Coll Cardiol 25(7):1492-1498.

124. Yaqoob, P.; Pala, H.S.; Cortina-Borja, M.; Newsholme, E.A.; Calder, P.C. 2000. Encapsulated fish oil enriched in alpha-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. Eur J Clin Invest 30(3):260-274.

125. Kelley, D.S.; Taylor, P.C.; Nelson, G.J.; Mackey, B.E. 1998. Dietary docosahexaenoic acid and immunocompetence in young healthy men. Lipids 33(6):559-566.

126. Kelley, D.S.; Taylor, P.C.; Nelson, G.J.; Schmidt, P.C. Ferreti, A.; Erickson, K.L.; Yu, R.; Chandra, R.K.; Mackey, B.E. 1999. Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. Lipids 34(4):317-324.

127. Almallah,Y.Z., Ewen, S.W., El-Tahir, A., Mowat, N.A., Brunt, P.W., Sinclair, T.S., Heys, S.D., Eremin, O. 2000. Distal proctocolitis and n-3 polyunsaturated fatty acids (n-3 PUFAs): the mucosal effect in situ. J Clin Immunol 20(1):68-76.

128. Gogos, C.A.; Ginopoulos, P.; Salsa, B.; Apostolidou, E.; Zoumbos, N.C.; Kalfarentzos, F. 1998. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severly ill patients with generalized malignancy: A randomized control trial. Cancer 82(2):395-402.

129. Krokan, H.E.; Bjerve, K.S.; Mørk, E. 1993. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. Biochim Biophys Acta 1168(1):59-67.

130. Nordøy, A., Bønaa, K.H., Nilsen, H., Berge, R.K., Hansen, J.B.; Ingebretsen, O.C. 1998. Effects of Simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 243(1):163-170.

131. Burns, C.P.; Halabi, S.; Clamon, G.H.; Hars, V.; Wagner, B.A.; Hohl, R.J.; Lester, E.; Kirshner, J.J.; Vinciguerra, V.; Paskett, E. 1999. Phase I clinical study of fish oil fatty acid capsules for patients with cancer cachexia: cancer and leukemia group B study 9473. Clin Cancer Res 5(12):3942-3947.

132. Hansen, J.B.; Grimsgaard, S.; Nilsen, H.; Nordøy, A.; Bønaa, K.H. 1998. Effects of highly purified eicosapentaenoic acid and docosahexaenoic acid on fatty acid absorption, incorporation into serum phospholipids and postprandial triglyceridemia. Lipids 33(2):131-138.

133. Wigmore, S.J.; Ross, J.A.; Falconer, J.S.; Plester, C.E.; Tisdale, M.J.; Carter, D.C.; Fearon, K.C. 1996. The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. Nutrition 12(1):S27-S30.

134. Palozza, P.; Sgarlata, E.; Luberto, C.; Piccioni, E.; Anti, M.; Marra, G.; Armelao, F.; Franceschelli, P.; Bartoli, G.M. 1996. n-3 Fatty acids induce oxidative modifications in human erythrocytes depending on dose and duration of dietary supplementation. Am J Clin Nutr 64(3):297-304.

135. Woodman, R.J.; Mori, T.A.; Burke, V.; Puddey, I.B.; Barden, A.; Watts, G.F.; Beilin, L.J. 2003. Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients. Atherosclerosis 166:85-93.

136. Parkinson, A.J.; Cruz, A.L.; Heyward, W.L.; Bulkow, L.R.; Hall, D.; Barstaed, L.; Connor, W.E. 1994. Elevated concentrations of plasma-3 polyunsaturated fatty acids among Alaskan eskimos. Am J Clin Nutr 59(2):384-388.

137. Foegh, M.L.; Hecker, M.; Ramwell, P.W. 1998. The eicosanoids: Prostaglandins, thromboxanes, leukotrienes, and related compounds. In: Katzung, B.G. (Ed.). Basic and Clinical Pharmacology (7th Ed.). Appleton & Lange; Stamford, Connecticut. pp. 304-318.

138. Kelley, D.S.; Rudolph, I.L. 2000. Effect of individual fatty acids of ω-6 and ω-3 type on human immune status and role of eicosanoids. Nutrition 16(2):143-145.

139. Danse, L.H.; Verschuren, P.M. 1978. Fish oil-induced yellow fat disease in rats. I. Histological changes. Vet Pathol 15(1):114-124.

140. Ruiter, A.; Jongbloed, A.W.; van Gent, C.M.; Danse, L.H.; Metz, S.H. 1978. The influence of dietary mackerel oil on the condition of organs and on blood lipid composition in the young growing pig. Am J Clin Nutr 31(12):2159-2166.

141. Boswell, K.; Koskelo, E.K.; Carl, L.; Glaza, S.; Hensen, D.J.; Williams, K.D.; Kyle, D.J. 1996. Preclinical evaluation of single-cell oils that are highly enriched with arachidonic acid and docosahexaenoic acid. Food Chem Toxicol 34(7):585-593.

142. Hempenius, R.A.; Van Delft, J.M.H.; Prinsen, M.; Lina, B.A.R. 1997. Preliminary safety assessment of an arachidonic acid-enriched oil derived from Mortierella alpina: Summary of toxicological data. Food Chem Toxicol 35(6):573-581.

143. Wibert, G.J.; Burns, R.A.; Diersen-Schade, D.A.; Kelly, C.M. 1997. Evaluation of single cell sources of docosahexaenoic acid and arachidonic acid: A 4-week oral safety study in rats. Food Chem Toxicol 35(10&11):967-974.

144. Rabbani, P.I.; Sheikh, N.M.; Chirtel, S.J.; Jackson, R.; Ruffin, G. 1999. Effects of long-term consumption of high doses of fish oil concentrates on clinical parameters in male and female rats. J Nutr Sci Vitaminol 45(5):553-565.

145. Arterburn, L.M.; Boswell, K.D.; Koskelo, E.; Kassner, S.L.; Kelly, C.; Kyle, D.J. 2000. A combined subchronic (90-day) toxicity and neurotoxicity study of a single- cell source of docosahexaenoic acid triglyceride (DHASCO® oil). Food Chem Toxicol 38(1):35-49.

146. Arterburn, L.M.; Boswell, K.D.; Henwood, S.M.; Kyle, D.J. 2000. A development safety study in rats using DHA-and ARA-rich single-cell oils. Food Chem Toxicol 38(9):763-771.

147. Hempenius, R.A.; Lina, B.A.R.; Haggitt, R.C. 2000. Evaluation of a subchronic (13-week) oral toxicity study, preceded by an in utero exposure phase, with arachidonic acid oil derived from Mortierella alpina in rats. Food Chem Toxicol 38(2&3):127-139.

148. Oarada, M.; Furukawa, H.; Majima, T.; Miyazawa, T. 2000. Fish oil diet affects on oxidative senescence of red blood cells linked to degeneration of spleen cells in mice. Biochim Biophys Acta 1487(1):1-14.

149. Hammond, B.G.; Mayhew, D.A.; Naylor, M.W.; Ruecker, F.A.; Mast, R.W.; Sander, W.J. 2001. Safety assessment of DHA-rich microalgae from Schizochytrium sp. I. Subchronic rat feeding study. Regul Toxicol Pharmacol 33(2):192-204.

150. Hammond, B.G.; Mayhew, D.A.; Robinson, K.; Mast, R.W.; Sander, W.J. 2001. Safety assessment of DHA-rich microalgae from Schizochytrium sp. III. Single-generation rat reproduction study. Regul Toxicol Pharmacol 33(3):356-362.

151. Danse, L.H.; Steenbergen-Botterweg, W.A. 1976. Early changes of yellow fat disease in mink fed a vitamin-E deficient diet supplemented with fresh or oxidised fish oil. Zentralbl Veterinarmed 23(8):645-660.

152. Danse, L.H.; Stolwijk, J.; Verschuren, P.M. 1979. Fish oil-induced yellow fat disease in rats. IV. Functional studies of the reticuloendothelial system. Vet Pathol 16(5):593-603.

153. Jones, D.; Howard, A.N.; Gresham, G.A. 1969. Aetiology of 'yellow fat' disease (pansteatitis) in the wild rabbit. J Comp Pathol 79(3):329-334.

154. Helgebostad, A.; Ender, F. 1973. Vitamin E and its function in the health and disease of fur bearing animals. Acta Agric Scand Suppl (19):79-83.

155. Danse, L.H.; Steenbergen-Botterweg, W.A. 1978. Fish oil-induced yellow fat disease in rats. II. Enzyme histochemistry of adipose tissue. Vet Pathol 15(1):125-132.

156. Danse, L.H.; Verschuren, P.M. 1978. Fish oil-induced yellow fat disease in rats. III. Lipolysis in affected adipose tissue. Vet Pathol 15(4):544-548.

157. Charnock, J.S.; Turner, J.; McIntosh, G.H. 1987. The occurrence of cardiac lipidosis and necrotic lesions in the hearts of rats following long-term feeding of different lipid supplemented diets. J Nutr Sci Vitaminol 33(1):75-87.

158. Verschuren, P.M.; Houtsmuller, U.M.; Zevenbergen, J.L. 1990. Evaluation of vitamin E requirement and food palatability in rabbits fed a purified diet with a high fish oil content. Lab Anim 24(2):164-171.

159. Farwer, S.R.; Der Boer, B.C.; Haddeman, E.; Kivits, G.A.; Wiersma, A.; Danse, B.H. 1994. The vitamin E nutritional status of rats fed on diets high in fish oil, linseed oil or sunflower seed oil. Br J Nutr 72(1):127-145.

160. Muggli, R. 1994. Physiological requirements of vitamin E as a function of the amount and type of polyunsaturated fatty acid. In: Galli, C.; Simopoulos, A.P.; Tremoli, E. (Eds.). Fatty Acids and Lipids: Biological Aspects. Proceedings of the 1st International Congress of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). Karger; Basel, Switz./New York. World Review of Nutrition and Dietetics, Vol. 75, pp. 166-168.

161. Ando, K.; Nagata, K.; Yoshida, R.; Kigugawa, K.; Suzuki, M. 2000. Effect of n-3 polyunsaturated fatty acid supplementation on lipid peroxidation of rat organs. Lipids 35(4):401-407.

000057

162. McGuire, S.O.; Alexander, D.W.; Fristche, K.L. 1997. Fish oil source differentially affects rat immune cell a-tocopherol concentration. J Nutr 127(7):1388-1394.

163. Burns, R.A.; Wibert, G.J.; Diersen-Schade, D.A.; Kelly, C.M. 1999. Evaluation of single-cell sources of docosahexaenoic acid and arachidonic acid: 3-month rat oral safety study with an in utero phase. Food Chem Toxicol 37(1):23-36.

164. Fujii, W.; Suwa, Y. 1998. [Unpublished] Final Report. 2) Mutagenicity Data. Prepared by Institute for Fundamental Research Suntory Ltd.

165. Bruijntjes-Rozier, T.; van Ommen, B. 2001. Bacterial Reverse Mutation Test with DHA-Oil 45. Prepared by TNO Nutrition and Food Research; Zeist, The Netherlands at the request of Axiva GmbH Ventures; Frankfurt am Main, Germany. TNO-Report V2505/08.

166. Kashima, M.; Sarwar, G. 2000. [Unpublished] Final Report. Chromosomal Aberration Test of DHA-Oil in Cultured Chinese Hamster Cells. Prepared by Nippon Experimental Medical Research Institute Co., Ltd.; Gunma-ken, Japan. Project No. H-99144.

167. Fujii, W.; Suwa, Y. 1998. [Unpublished] Final Report. 1) Acute Toxicology Data. Prepared by Institute for Fundamental Research Suntory Ltd.

168. Neda, K. 2000. [Unpublished Study]. An Acute Oral Toxicity of DHA-Containing Lipid in Rats. Celanese Ventures GmbH; Frankfurt am Main, Germany.

169. Neda, K. 2000. [Unpublished] Final Report: A 90-Day Repeated Oral Dose Toxicity Study of DHA-Containing Lipid in Rats. Prepared by Nippon Experimental Medical Research Institute Co., Ltd.; Gunma-ken, Japan. Project No. H-99142.

170. Kuilman, M.E.M.; Waalkens-Berendsen, D.H. 2001. Oral One-Generation Reproduction Study with DHA Oil 45 in Rats. Prepared by TNO Nutrition and Food Research; The Netherlands for Celanese Ventures GmbH, Germany. Project No. 41089, TNO Study No. 2633.

171. Squire and Williams. 2001. [Unpublished] Expert Pathology Panel Report Concerning the Gross and Histopathological Findings of a One-Generation Rat Reproduction Study of DHA45-Oil. August 9, 2001.

172. Jonnalagadda, S.S.; Egan, S.K.; Heimbach, J.T.; Harris, S.S.; Kris- Ethertonp.M. 1995. Fatty acid consumption pattern of americans: 1987-1988 USDA nationwide food consumption survey. Nutr Res 15(12):1767-1781.

173. Chanmugam, P.; Wheeler, C.; Hwang, D.H. 1984. Fatty acid composition of the testes of zinc-deficient rats: the effect of docosapentaenoic acid supplementation. J Nutr 114(11):2073-2079.

174. Milks, M.M.; Sprecher, H. 1985. Metabolism of 4,7,10,13,16- docosapentaenoic acid by human platelet cyclooxygenase and lipoxygenase. Biochim Biophys Acta 835(1):29-35.

175. Kanayasu-Toyoda, T.; Morita, I.; Murota, S. 1996. Docosapentaenoic acid (22:5, n-3), an elongation metabolite of eicosapentaenoic acid (20:5, n-3), is a potent stimulator of endothelial cell migration on pretreatment in vitro. Prostaglandins Leukot Essent Fatty Acids 54(5):319-325.

176. Akiba, S.; Murata, T.; Kitatani, K.; Sato, T. 2000. Involvement of lipoxygenase pathway in docosapentaenoic acid-induced inhibition of platelet aggregation. Biol Pharm Bull 23(11):1293-1297.

177. Tam, P.S.; Umeda-Sawada, R.; Yaguchi, T.; Akimoto, K.; Kiso, Y.; Igarashi, O. 2000. The metabolism and distribution of docosapentaenoic acid (n-6) in rats and rat hepatocytes. Lipids 35(1):71-75.

178. Hammond, B.G.; Mayhew, D.A.; Holson, J.F.; Nemec, M.D.; Mast, R.W.; Sander, W.J. 2001. Safety assessment of DHA-rich microalgae from Schizochytrium sp. II. Developmental toxicity evaluation in rats and rabbits. Regul Toxicol Pharmacol 33(2):205-217.

179. Merck. 2001. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. (13th Ed.). Merck & Co., Inc.; Whitehouse Station, New Jersey.

180. Piretti, M.V.; Viviani, R. 1989. Presence of 4α-methyl sterols in bivalve mollusc Scraparca inaequivalvis (Bruguiere): Their significance and metabolism. Comp Biochem Physiol B 93B(4):753-756.

181. Narumi, Y.; Takatsuto, S. 2000. Sterols in rice bran. J Jpn Oil Chem Soc 49(7):719-722.

182. Pelletier, X.; Belbraouet, S.; Mirable, D.; Mordret, F.; Perrin, J.L.; Pages, X.; Debry, G. 1995. A diet moderately enriched in phytosterols lowers plasma cholesterol concentrations in normocholesterolemic humans. Ann Nutr Metab 39(5):291-295.

183. Grundy, S.M.; Mok, H.Y.I. 1975. Effects of low dose phytosterols on cholesterol absorption in man. In: Greten, H. (Ed.). Lipoprotein Metabolism. Springer-Verlag; Berlin. pp. 112-118.

184. Nair, P.P.; Turjman, N.; Kessie, G.; Calkins, B.; Goodman, G.T.; Davidovitz, H.; Nimmagadda, G. 1984. Diet, nutrition intake, and metabolism in populations at high and low risk for colon cancer: Dietary cholesterol, ß-sitosterol, and stigmasterol. Am J Clin Nutr 40(Suppl. 4):927-930.

185. Ling, W.H.; Jones, P.J.H. 1995. Dietary phytosterols: A review of metabolism, benefits and side effects. Life Sci 57(3):195-206.

186. Jones, P.J.H.; MacDougall, D.E.; Ntanios, F.; Vanstone, C.A. 1997. Dietary phytosterols as cholesterol-lowering agents in humans. Can J Physiol Pharmacol 75(3):217-227.

187. Kritchevsky, D. 1997. Phytosterols. In: Kritchevsky, D.; Bonfield, C. (Eds.). Dietary Fiber in Health and Disease. Proceedings of the Fifth Washington Symposium on Dietary Fiber: The Vahouny Fiber Symposium, Washington, DC, Mar. 26-29, 1996. Plenum Press; New York. Advances in Experimental Medicine and Biology, Vol. 427, pp. 235-243.

188. Bahnweg, G. 1979. Studies on the physiology of thraustochytriales. I. Growth requirements and nitrogen nutrition of Thraustochytrium spp., Schizochytrium sp., Japonochytrium sp., Ulkenia spp., and Labyrinthuloides spp. Veroff Inst Meersforsch Bremerh 17:245-268.

189. Cavalier-Smith, T.; Allsopp, M.T.E.P.; Chao, E.E. 1994. Thraustochytrids are chromists, not fungi: 18s rRNA signatures of heterokanta. Philos Trans R Soc Lond B Biol Sci 346:387-397.

190. European Register of Marine Species. 2001. [Labyrinthulids and Thaustrochytrids, etc.]. In: The European Register of Marine Species. European Union, MAST (Marine Science and Technology) Programme; Dublin, Ireland. [http://erms.biol.soton.ac.uk/].

191. Honda, D.; Yokochi, T.; Nakahara, T.; Raghukumar, S.; Nakagiri, A.; Schaumann, K.; Higashihara, T. 1999. Molecular phylogeny of labyrinthulids and thraustochytrids based on the sequencing of 18S ribosomal RNA gene. J Eukaryot Microbiol 46(6):637-647.

192. Ulken, A.; Víquez, R.; Valient, C.; Campos, M. 1990. Marine fungi (Chytridiomycetes and Thraustochytriales) from a mangrove area at Punta Morales, Golfo de Nicoya, Costa Rica. Rev Biol Trop 38(2A):243-250.

193. Sathe-Pathak, V.; Raghukumar, S.; Raghukumar, C.; Sharma, S. 1993. Thraustochytrid and fungal component of marine detritus. I -- Field studies on decomposition of the brown alga Sargassum cinereum J. Ag. Indian J Mar Sci 22:159-167.

194. Azevedo, C.; Corral, L. 1997. Some ultrastructural observations of a thraustochytrid (Protoctista, Labyrinthulomycota) from the clam Ruditapes decussatus (Mollusca, Bivalvia). Dis Aquat Organ 31(1):73-78.

195. Naganuma, T.; Takasugi, H.; Kimura, H. 1998. Abundance of thraustochytrids in coastal plankton. Mar Ecol Progr Ser 162:105-110.

196. OmegaTech GmbH. 1997. Application for the Approval of DHA-rich Oil. Regulation (EC) No 258/97 of the European Parliament and of the Concil of 27th January 1997 concerning novel foods and novel food ingredients. [http://www.foodstandards.gov.uk/pdf_files/dha-rich_oil_novel_food_dossier.pdf]

197. Van Dolah, F.M. 2001. Diversity of marine and freshwater algal toxins. In: Botana, M. (Ed.). Seafood and Freshwater Toxins: Pharmacology, Physiology, and Detection. Marcel Dekker; New York. [as published at http://www.chbr.noaa.gov/CoastalResearch/DiversityEssay.htm and including http://www.chbr.noaa.gov/CoastalResearch/MapAlgae.htm]

198. Schaumann, K. 2003. Extended Expert's Report on the "Safety" of *Ulkenia* Sp.

000060

199. Fujii, W.; Suwa, Y. 1999. [Unpublished] Final Report: Mutagenicity Study of DHA-Producing Microorganism. Prepared by Institute for Fundamental Research Suntory Ltd. Report No. HMS-96-14.

200. Celanese Ventures. 1999. [Unpublished] Final Report: Acute Toxicity Study of DHA-Producing Microorganism in Mice. Celanese Ventures GmbH; Frankfurt am Main, Germany

201. Kroes, R.; Schaefer, E.J.; Squire, R.A.; Williams, G.M. 2003. A review of the safety of DHA45-oil. Food Chem Toxicol 41:1433-1446.

202. U.S. FDA. 2004. Substances affirmed as generally recognized as safe: Menhaden oil; Tentative final rule (21 CFR, Part 184, Docket No. 1999P-5332). Fed Reg (U.S.) 69 (10):2313-2317.

203. U.S. FDA. 2004. Agency Response Letter GRAS Notice No. GRN 000137. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

204. U.S. FDA. 2004. Agency Response Letter GRAS Notice No. GRN 000138. U.S. Food and Drug Administration (U.S. FDA), Center for Food Safety and Applied Nutrition (CFSAN), Office of Food Additive Safety.

205. Melkonian, M. 2003. Expert's Report on the Safety of *Ulkenia* (Thraustochytriales) in a Human-biological Context.

ATTACHMENT 1

CURRICULA VITAE OF EXPERT PANEL MEMBERS

CURRICULUM VITAE

Surname	KROES
Christian name	Robert
Date and place of birth	
Civil status	
Present position	Director of the IRAS, Institute for Risk Assessment Sciences - formerly RITOX, Research Institute for Toxicology (RITOX), Utrecht University Professor in Biological Toxicology, Utrecht University (Medical, Veterinary and Biology Faculties). Director HECTIC BV : consultancy firm in Toxicology and Risk Assessment
Languages	Dutch, English, French, German
Education	Veterinary surgeon, Utrecht University (1957-1964)
Degrees attained	B.Sc. (1960) M.Sc. in veterinary sciences (1963) D.V.M. (1964) Ph.D. in pathology (1970) Certified toxicologist * (1988) Certified laboratory animal pathologist * (1989) (Registers for certification in The Netherlands were opened in the years specified)
Postdoctoral research training	Veterinary pathology (1964 - 1965) Human pathology (1966 - 1967) Experimental animal pathology (1968 - 1969)
Specialisation	Laboratory animal pathology, toxicology, oncology and risk assessment (1970 - present)

Career (detailed career on request)

1964-1971 Pathologist at the National Institute of Public Health and Environmental Protection (RIVM, Bilthoven, The Netherlands)

1971-1972 Research Fellowship of International Agency for Research on Cancer, spent at the National Cancer Institute, Experimental Pathology Branch,Bethesda, USA.

1972-1977 Head Department of Oncology, RIVM, Bilthoven, The Netherlands

1977-1979 Deputy Director CIVO-TNO, Institute for Nutrition and Food Research, Zeist, The Netherlands

1979-1983 Director Institute CIVO Toxicology and Nutrition, TNO, Zeist, The Netherlands

1983-1989 Director RIVM, Bilthoven, The Netherlands

1989-1996 Deputy Director-General RIVM, Bilthoven, The Netherlands

1995-1999 Programme Co-ordinator European Science Foundation Programme on Environment and Health (part-time)

1988-present Professor in Biological Technology (Risk Assessment), Utrecht University (part-time)

1995-present Director of IRAS, Institute for Risk Assessment Sciences - formerly RITOX, Research Institute for Toxicology (RITOX), Utrecht University (part-time)

1996- present Private Consultant in Toxicology and Risk Assessment (HECTIC BV). Advisor to a.o.: Hoechst, Roche, Coca Cola, Nestle, Red Bull, Martin Bauer, Cantox, Celanese Ventures, B

International activities **(past and present)**

WHO

- Member of numerous experts committees on toxicology, oncology and environment and health
- Co-editor of : Principles and Methods for Evaluating the Toxicity of Chemicals, Part I - Environmental Health Criteria 6, WHO Geneva 1978.
- Member of the Advisory Board of the WHO European Centre on Environment and Health
- Chairman of the fact finding mission East Europe (Poland, Tsjechoslowak Republik, Hungary and Rumania)

	-	Member of the steering group First European Conference on Environment and Health to draw the European Charter on Environment and Health
	-	Member of the European Environment and Health Committee
	-	Member of Expert Panel on Integrated Risk Assessment
	-	IPCS: member of several advisory committees o.a the working Group on Integrated Risk Assessment
	-	
IARC	-	Member or chairman of expert committees of more than 10 IARC monographs
	-	Member Scientific Council (1981-1984)
	-	Member Governing Council (1984-1994)
	-	Member of several expert meetings
	-	Member of Fellowship Selection Committee
	-	Member of the working group on the appraisal of long/short term toxicity tests (1979 and 1986)
WHO/FAO	-	Member of expert committee on environmental quality and safety (anabolic agents in animal production.
	-	Temporary advisor to JECFA 1999 ,2000,2001, 2003 and 2004
OECD	-	Member of the expert group on short-term toxicity testing
	-	Member of the expert group on long-term toxicity testing
	-	Member of the expert group on mutagenicity toxicity testing
	-	Chairman of the working group on acute toxicity
	-	Consultant OECD in matters on toxicology and environment
EU	-	Member of the High Level Committee of Experts "Europe against Cancer"
	-	Chairman of the Subcommittee Prevention of Europe against Cancer
	-	Chairman of Scientific Committee on Toxicology and Ecotoxicology
	-	Member of the Scientific Committee of Cancer Experts
	-	Member of the expert group on anabolic agents in animal production
	-	Member of the Scientific & Technical Committee Tobacco Research
	-	Member of the Scientific Steering Committee DG SANCO(Public Health)
	-	Member of the Scientific Committee of the European Environment Agency, Copenhagen

	-	Member subgroup Harmonisation Risk Asessment DG SANCO
EUROTOX	-	President of EUROTOX 2002 - 2004-08-25 Past President of EUROTOX 2004-2006
IUTOX	-	President Elect IUTOX 2004-2007
Benelux	-	Member of the expert group on anabolic agents in animal production
ILSI	-	Member of the expert group on Pathology and Toxicology (International Life Sciences Institute)
	-	Member of the Board of Trustees ILSI GLOBAL
	-	Member of the Board of Trustees ILSI HESI
	-	Member of the Board of Directors ILSI Risk Sciences Institute
	-	Member of the Board of Directors ILSI Europe
	-	Chairman Working Group on Toxicology ILSI Europe
	-	Member of the ILSI Novel Food Committee
	-	Member of the ILSI Committee Short-term tests
	-	Chair of several ILSI Expert Groups
	-	President ILSI Europe (as from 1999)
USA	-	Councillor of the Special Section Carcinogenesis SOT
	-	Member of the International Expert Panel on Carcinogen Risk Assessment
Editor-in-Chief	-	Human and Experimental Toxicology (as from 1998 until 2003)

Member of the Editorial Board of

- Cancer Letters
- Cell Biology and Toxicology
- Journal of Experimental Pathology
- Cancer (Dutch)
- Principles and Methods for evaluating the toxicity of chemicals (WHO)
- Nutrition and Health (Dutch)
- Monographs on Pathology and Laboratory Animals
- Nutrition in practice (Dutch)
- Dutch Journal on Veterinary Medicine
- Veterinary Quarterly
- Journal of Optimal Nutrition
- ILSI Monographs
- Toxicology Letters

National activities (**past and present**)

Governmental

- Member advisory group concerning the coordination of cancer research in The Netherlands
- Member and chairman of the National Health Council Committee for evaluating the carcinogenicity of chemicals
- Member of the National Health Council Committee for evaluating the mutagenicity of chemicals
- Member of the Dutch Nutrition Council
- Member of the National Co-ordination Committee on Cancer Research
- Member of the National Co-ordination Committee of Toxicological Research
- Member of the Advisory Committee on Good Laboratory Practice
- Member of the Advisory Group on Toxicology under the Dutch Food Law
- Member of the National Nutrition Council
- Chairman Advisory Committee on Nutrition and Cancer
- Member of the Advisory Council of the National Health Council
- Member of the National Health Council Advisory Group Toxicology and Ecotoxicology
- Member of the National Health Council Advisory Group on Human Milk
- Member of the National Health Council Coordination Group
- Member of the National Health Council Advisory Group on Biotechnology
- Member of the National Health Council Advisory Group on Organic Solvents
- Member of the Coordination Committee of Radioactive Compounds and Xenobiotics
- Chairman Interdepartmental Committee on Good Laboratory Practice
- Chairman Preliminary Committee on the Safety of Novel Foods
- Member of the National Platform Critical Material
- Chairman of the Scientific Programme Committee VWS-NOW-EU congress "Innovative research and appropriate health care for the European Citizens"

Non-Governmental **(past and present)**

- Chairman and member of the Dutch Scientific Council on Cancer Research of the National Academy of Sciences
- Chairman of the Dutch Society of Laboratory Animal Science
- Member of the Governing Board of the Dutch Federation for Laboratory Animal Science
- Chairman of the Coordination Group on Toxicological Research / TNO
- Chairman of the Dutch Committee on Laboratory Animal Science
- Member and Chairman of the Governing Board of the Dutch Nutrition Foundation
- Member of the Governing Board of TNO-Nutrition
- Chairman of the Governing Board of Utrecht Toxicology Center

- Member of the Financial Committee of the Promotion Action on Toxicology at the Department of Education and Sciences
- Member of the Expert Council of Standards
- Member and Vice President of the Governing Board of the Board of Accreditation
- Member of Programme Advisory Board of TNO Nutrition

Memberships

- American Association for Cancer Research
- Society of Toxicology
- European Association for Cancer Research
- National Academy of Sciences (USA)
- European Society of Toxicology (Eurotox President 2002-2004)
- Society for Risk Analysis
- Dutch Society of Toxicology
- Dutch Society of Oncology
- Dutch Society for Laboratory Animal Science
- Dutch Society of Nutrition
- Dutch Society of Pathology
- Dutch Veterinary Association
- Dutch Nutrition Association

Updated August 2004

PUBLICATIONS R. KROES FROM 1990 ONWARDS **

1990

148 Kroes, R. and V.J.Feron (1990)
Toxicity testing, strategies and conduct
In : Progress in Predictive Toxicology, D.B. Clayson, I.C. Munro, P. Shubik, J.A. Swenberg eds.
Elseviers Science Publishers B.V., Amsterdam

149 Feron, V.J., Fl. De Vrijer, R. Kroes en R.J.J. Hermus (1990)
Relatieve gezondheidsrisico's van additieven, contaminanten en nutriënten
Voeding 6; 142-146

150 Kroes, R. (1990)
Hoe veilig is ons voedsel, wat betreft chemische toevoegingen en verontreinigingen ?
In : Voedingsbericht 305-358
SDU, The Hague

151 Kroes, R. (1990)
Strategies in toxicity testing and risk assessment
In : Proceedings International Seminar on Advanced Toxicology
Sevilla, October 28-30; 69-83

152 Kroes, R. (1990)
Risk assessment of carcinogenic substances : a pragmatic approach
In : Report of the Seminar on "The setting of a common selection scheme of dangerous substances"
Como (Italy), July 12-13, 1990

153 Kroes, R. (1990)
Current guidelines for toxicity testing : their strengths and weaknesses
In : Re-evaluation of current methodology of toxicity testing including gross nutrients
R. Kroes and R.M. Hicks (proceeding editors) Fd. Chem. Toxic. Vol. 28 no. 11; 789-790

154 Kroes, R. and R.M. Hicks (1990)
Introduction
In : Re-evaluation of current methodology of toxicity testing including gross nutrients
R. Kroes and R.M. Hicks (proceeding editors) Fd. Chem. Toxic. Vol. 28 no. 11; 733

1991

155 Kroes, R. en P.G.N. Kramers (1991)
Chemische stoffen en Volksgezondheid
In : Tijdschrift voor Diergeneeskunde 116; 180-186

156 Kroes, R. (1991)
Europe against Cancer (Abstract)
In : Symposium overview. American Health Foundation's 20th Anniversary International Symposium on Causes and Prevention of Cancer
Preventive Medicine 20; 546

157 Kroes, R. (1991)
Preface
In : Monitoring dietary intakes, ILSI Monographs, Springer Verlag; pp VI-VII

158 Kroes, R. (1991)
Dietary intakes : Summary and perspectives
In : Monitoring dietary intakes, ILSI Monographs, Springer Verlag; pp 251-252

1992

159 Kroes, R. (1992)
Safety assessment in relation to carcinogens
In : Food Policy Trends in Europe, H. Deelstra, M. Fondu, W. Ooghe and R. van Havere (eds.), ILSI Europe, Brussels; pp186-197

160 Kroes, R. and E.M. den Tonkelaar (1992)
The assessment of chronic effects of pesticides on humans
In : Methods to Assess Adverse Effects of Pesticides on non-target Organisations, C.R.G. Tardiff (ed.) SCOPE
Published by John Wiley and Sons Ltd., NYU Medical Center, New York; pp 155-170

161 Kroes, R., W. Slooff and H.A.M. de Kruijf (1992)
Linking human toxicology and ecotoxicology in environmental hazard assessment : twinning for the better
In : Proceedings in international conference on environmental and industrial toxicology : research and applications, Bangkok (Thailand), January 20-24, 1992

162 Bosland, M.C., M.K. Prinsen, A. Rivenson, J. Silverman, E. Fiala, G.M. Williams, R. Kroes, J.H. Weisburger (1992)
Induction of proliferative lesions of ventral prostate, seminal vesicle and other accessory sex glands in rats by N-Methyl-N-Nitrosourea : Effect of castration, pre-treatment with cyproterone acetate and testosterone propronate and rat strain
In : The Prostate 20; 339-353

163 Kroes, R. (1992)
Risk Assessment
Eurotox Newsletter 1 February (1992); 5

164 Kroes, R. (1992)
Kwantitatieve risico-aspecten van chemische stoffen in het voedsel
De Ware(n) Chemicus 22; 125-128

165 Kroes, R. (1992)
Risk assessment : past, present and future (abstract)
In : Proceedings The Second Princess Chulabhorn Science Congress Environment, Science and Technology : The Challenges of the 21st Century
Bangkok, Thailand, November 2-6, 1992

166 Kroes, R. (1992)
Milieu - dier - mens. Inleiding door de voorzitter
Tijdschrift voor Diergeneeskunde 117; 587-588

1993

167 Gelderen, C.E.M. van, T.J.F. Savelkoul, J.L. Blom, W. van Dokkum, R. Kroes (1993)
The no-effect level of Sodium Bromide in Healthy Volunteers
Human & Exp. Toxicology 12; 9-14

168 Kroes, R. (1993)
Minder risico's bij veel kankers door meer groenten en fruit
Kanker 17 no. 1; 4-6

169 Kroes, R., I. Munro and E. Poulsen (1993)
Workshop on the scientific evaluation of the safety factor for the acceptable daily intake (ADI) : Editorial summary
Food Additives and contaminants, vol. 10, no. 3; 269-273

1994

170 Kroes, R. and J.H. Weisburger (1994)
Mechanisms in nutrition and cancer - San Servolo, Venice, 12-14 October 1992
Meetings reports, Eur. J. Cancer : 3; 293-298

171 Lucas Luijckx, N.B., G.N. Rao, E. McConnell, G. Wurtzen and R. Kroes (1994)
The intake of chemicals related to age in long-term toxicity studies - considerations for risk assessment
Regulatory Toxicology and Pharmacology 20; 96-104

172 Kroes, R. and J.H. Weisburger (1994)
Diet and cancer
In : Nutrition, Cambridge Publishers (in press)

1995

173 Kroes, R. (1995)
Toxicity testing and human health
In : Risk Assessment of Chemicalss : An Introduction
C.J. van Leeuwen and J.L.M. Hermans editors (1995) Kluwer Academic Publishers

174 Boyle, P., U. Veronesi, M. Tubiana, F.E. Alexander, F. Calis da Silva, L.J. Denis, J.M. Freira, M. Hakama, A. Hirssch, R. Kroes, C. la Vacchia, P. Maisonneuwwe, J.M. Martin-Moreno, J. Newton-Bishop, J.J. Pindborg, R. Saracci, C. Scully, B. Standaaert, H. Storm, S. Blanco, R. Malbois, N .Bleehan, M. Dicato and S. Plesnicar (1995)
Special article European School of Oncology Advisory Report to the European Commission for the "Europe against Cancer Programme", Europe Code against Cancer
Eur. J. Cancer 9; 1395-1405

1996

175 Kroes, R. (1996)
The use of mechanistic data in the risk assessment of ten chemicals : an introduction to the chemical-specific reviews
Phar. Ther. 71; 1-5

176 Kroes, R. (1996)
Risk Management in relation to food and its components
In : J. de Vries (eds.). Food Safety and Toxicology. CRC Press, Boca Raton, New York, London, Tokyo; pp. 215-335

177 Kroes, R. (1996)
In-vivo studies, their strength and weaknesses
In : C. Maltoni, M. Sofritti, W. Davis (eds.). The scientific basis of cancer chemoprevention. Elsevier, Amsterdam, Lausanne, New York, Oxford, Shannon, Tokyo; pp. 119-128

178 Occurrence and Significance of Ochratoxin A in Food
Battaglia R., T. Hatzold and R. Kroes (eds.)
Food Additives and Contaminants (1996), S 1-57

179 Battaglia R., T. Hatzold and R. Kroes (1996)
Guest editorial : Conclusions from the workshop on Ochratoxin in food, organised by ILSI Europe in Aix-en-Provence
In : Occurrence and significance of Ochratoxin A in Food
Food Additives and Contaminants (1996), S 1-3

180 Kroes, R. (1996)
Levensstijl, milieu en kanker
In : Vragen over Kanker : Het antwoord van de huisarts
C.J. Stolk (ed.) Boerhave Commissie voor Postacademisch Onderwijs in de Geneeskunde, RU Leiden, pp. 57-71

1997

181 Innovative research and appropriate health care for the citizens in Europe. Proceedings of the international conference on the occasion of The Netherlands EU Presidency
Evered D., R. Kroes and E.C. Klasen (eds.)
European Commission 1997, EUR 17786EN

1998

182 Applicability of the ADI to infants and children
Clayton B, R. Kroes, J.C. Larsen and G. Pascal (eds.)
Food Additives and Contaminants (1998), Volume 15, S 9 1-89

183 Kroes, R
Rejoinder, reply to a letter to the editor
Food Additives and Contaminants (1998), Volume 15 (1) 124

183 Munro, I.C. and R. Kroes (1998)
Application of a threshold of toxicological concern in the safety evaluation of certain flavouring substances
In : WHO Food Additives Series 40, Safety evaluation of certain food additives and contaminants, Annex 5 : 499-532, WHO Geneva 1998.

1999

184 Munro, I.C., E. Kennepohl and R. Kroes (1999)
A procedure for the safety evaluation of flavouring substances
Food Chemical Toxicology, 37 : 207-232.

185 Kroes, R. (1999)
Research needs for the next millenium.
Environment and Health 7/8 : 10.

186 Kroes, R. (1999)
Current Research Priorities
Naturopa 90 : 26.

187 Kroes, R. (1999)
Furfural Monograph
In : WHO Food Additives Series 42, Safety evaluation of certain food additives, 51st Meeting of the Joint FAO/WHO Expert Committee on Food Additives - JECFA, pag. 33-56, WHO Geneva 1999.

188 Kroes, R. (Ed.) (1999)
An Environment for Better Health. Integrated report on the ESF Environment and Health Research Programme.
European Science Foundation, Strasbourg, France (June 1999)

2000

189 Kroes, R. (2000)
Pan-European research challenges in toxicology and epidemiology : twinning for the better.
Toxicology Letters Vol. 125: 573-575

190 Kroes, R., C. Galli, I. Munro, B. Schilter, L.-A. Tran, R. Walker and G. Würtzen (2000)
Threshold of toxicological concern for chemical substances present in the diet : A practical tool for assessing the need for toxicity testing
Food Chemical Toxicology Vol. 38: 255-312.

193 Assessing Health Risks from Environmental Exposure to Chemicals: the Example of Drinking Water (2000).
Proceedings of an ILSI Europe workshop held in May 1998 in Munich, Germany. Eisenbrandt, G., Hofer, M., Kroes, R., and Shuker, L. eds. Food and Chemical Toxicology, Volume 38, Supplement 1, pp S1-S110.

2002

194 Kroes, R and Kozianowski, G (2002)
Threshold of toxicological concern (TTC) in food safety assessment
Toxicology Letters Vol. 127: 43-46

195 Haighton LA, Hlywka JJ, Doull J, Kroes R, Lynch BS, Munro IC. An evaluation of the possible carcinogenicity of bisphenol A to humans.
Regul Toxicol Pharmacol. 2002; 35 (2 Pt 1):238-54.

196 Food Safety in Europe (FOSIE): Risk Assessment of Chemicals in Food and Diet (2002)

Barlow, S., Dybing, E., Edler, L., Eisenbrand, G., Kroes, R. and van den Brandt, P. (Guest Editors)
Food and Chemical Toxicology Vol. 40: (2-3)

197 Kroes, R., D.Muller, J.Lambe, M.R.H.Lowick, J.van Klaveren, J.Kleiner, R.Massey, S.Mayer, I.Urieta, P.Verger and A.Visconti (2002)
Assessment of Intake from the Diet
Food and Chemical Toxicology Vol. 40:327-385

198 Munro IC, Haighton LA, Hlywka JJ, Lynch BS, Doull J, Kroes R. (2002)
Carcinogenicity bioassay of bisphenol A. Toxicol Sci.;66(2):356.

199 Munro, I.C., Haighton, L.A., Hlywka, J.J., Lynch, B.S., Doull, J., and Kroes, R. (2002). Response to Carcinogenicity of Bisphenol A: Revisited. Toxicol. Sci.; 70(4), 283-284

2003

200 Munro, I.C., Haighton, L.A., Hlywka, J.J., Lynch, B.S., Doull, J., and Kroes, R. (2003). Response to does exposure to bisphenol A represent a human health risk? Regul. Toxicol. Pharmacol. 37: 409-410

201 Renwick, A.G., Barlow, S.M., Hertz-Picciotto, I. Boobis, A.R., Dybing, E., Edler, L., Eisenbrand, G., Greig, J.B., Kleiner, J., Lambe, J., Muller, D.J.G., Smith, M.R., Tritscher, A., Tuijtelaars, S., van den Brandt, P.A., Walker, R., Kroes, R. (2003)
Risk characterisation of chemicals in food and diet.
Food and chemical Toxicology 41: 1211-1271

202 Kroes, R., Schaefer, E.J., Squire, R.A., Williams, G.M. (2003)
A review of the safety of DHA45-oil.
Food and Chemical Toxicology 41: 1433–1446

203 Munns, R.W., Kroes, R., Veith, G., Suter II, G.W., Damstra, T. and Waters, M.D.(2003) Approaches for Integrated Risk Assessment, Human and Ecological Risk Assessment 9: 267-272

204 Munns, R.W., Suter II, G.W., Damstra, T., Kroes, R., Reiter, L.W. and Marafante, E. (2003) Integrated Risk Assessment – Results from an International Workshop, Human and Ecological Risk Assessment 9: 379-386

205 Kroes, R. (2003) Safety issues of botanicals and botanical preparations in functional foods, Toxicology 191: 9 (abstract)

2004

206 Kroes, R, A.G. Renwick, M. Cheeseman, J. Kleiner, I. Mangelsdorf, Piersma, B. Schilter, J. Schlatter, F. van Schothorst, J.G. Vos, G Wurtzen
A Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet (2004)
Food and Chemical Toxicology 42: 65-83

206 Kroes, R (2004) Risk Assessment of Chemicals in Food; Future Challenges

Proceedings Fifth Princess Chulabhorn International Science Congress " Evolving Genetics and its Global Impact" August 16-29 2004, Bangkok, Thailand. P 251-254.

207 Kroes, R. and Walker, R (2004) Safety issues of botanicals and botanical preparations in functional foods, Toxicology 198: 213-220

208 Kroes, R. (2004) Structure-Based Thresholds of Toxicological Concern(TTC): Guidance for Application to Substances Present at Low Levels in the Diet Toxicologic Pathology 32(Suppl.2): 93

* A list of all publications by prof.dr. R. Kroes, including the ones before 1990 (147 papers), is available on request.

CURRICULUM VITAE

Name: Ernst John Schaefer, M.D. 07/20/04
Date of Birth:
Citizenship: United States
Marital Status:
Current Positions: Professor of Medicine
Tufts University School of Medicine
Distinguished Professor of Nutrition
Friedman School of Nutrition Science and Policy at Tufts University
Chief, Lipid Metabolism Laboratory, and Senior Scientist,
Jean Mayer USDA Human Nutrition Research Center
on Aging at Tufts University
Director, Lipid and Heart Disease Prevention Program
Division of Endocrinology, Metabolism, Diabetes, and Molecular Medicine
Tufts-New England Medical Center
Director, Cardiovascular Research Laboratory
Friedman School of Nutrition Science and Policy at Tufts University
Boston, MA
Present Address: Lipid Metabolism Laboratory

Education: 1968 - B.A., Harvard University, Cambridge, MA, (biology)
1970 - B.M.S., Dartmouth Medical School, Hanover, NH.
1972 - M.D., Mount Sinai School of Medicine, New York, NY.
Board Certification: American Board of Medicine
American Board of Internal Medicine

Brief Summary: Dr. Schaefer received his B.A. cum laude from Harvard University, his B.M.S. from Dartmouth Medical School, and his M.D. with honors from Mt. Sinai School of Medicine; he did his medical residency at Mt. Sinai Hospital, New York, and an endocrinology fellowship at the National Institutes of Health, where he also was a senior investigator. Since 1982 he has been at Tufts University where he is currently a Professor of Medicine at Tufts University School of Medicine, Director of the Lipid and Heart Disease Prevention Program, and Senior Scientist and Chief of the Lipid Metabolism Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. He was the recipient of the J.D. Lane Award of the U.S. Public Health Service (1981), the Irvine H. Page Arteriosclerosis Research Award from the American Heart Association (1981), the Saul Horowitz Jr. Research Award, Mt. Sinai School of Medicine (1989), the Oliver Smith Award of New England Medical Center for Patient Care (1999,2001), the E.V. McCollum Research Award of the American Society for Clinical Nutrition (2000), and a Distinguished Faculty Award from Tufts University (2001). Since 1997 he has been a member of Who's Who in America. He is an author or co-author of over 400 publications and served on the first and second adult treatment panels of the National Cholesterol Education Program of the National Institutes of Health, on the Nutrition and Metabolism Study Section of the NIH, and the Nutrition Committee of the American Heart Association. Dr. Schaefer is the U.S. editor of the journal Atherosclerosis. His research focuses on the nutritional and genetic regulation of plasma lipoproteins, and their relationship to coronary heart disease risk, and on the dietary and drug treatment of lipid disorders, as well as on optimal diets for the prevention of heart disease in the elderly.

Employment: 1971 Research Rotation on Lipoproteins, Albert Einstein College of Medicine,
(Drs. Paul Roheim, Howard Eder).
1972-1975 The Mount Sinai Hospital, New York, New York, Medical Internship,
First and Second Year Medical Residency (Dr. Solomon Berson, Dr. Fenton Schaffner, Dr. Richard Gorlin)
11/74-4/75 Guest Investigator, Rockefeller University, New York, New York;

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	(on elective time from Mt. Sinai); (Dr. Paul Schreibman).
1975-1978	Staff Associate, Molecular Disease Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; (Dr. Robert Levy, Dr. Bryan Brewer).
1978-1980	Endocrinology Fellow, National Institutes of Health, Bethesda, MD. (Dr. Bruce Weintraub).
1980-1982	Senior Investigator, Molecular Disease Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD. (Dr. Bryan Brewer).
1982-	Chief, Lipid Metabolism Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA. (Drs. Hamish Munro, Harold Sandstead, Irwin Rosenberg, Robert Russell).
1982-2004	Director, Lipid Clinic and Lipid Division, New England Medical Center, Boston, MA
1982-1989	Associate Professor of Medicine, Tufts University School of Medicine, Boston, MA
1982-1989	Associate Professor of Nutrition, School of Nutrition, Tufts University, Medford, MA
1989-	Professor of Nutrition, School of Nutrition Science and Policy, Tufts University Medford, MA
1989-	Professor of Medicine, Tufts University School of Medicine, Boston, MA
2004-	Director, Lipid and Heart Disease Prevention Clinic and Research Program, Cardiovascular Research Associates, Inc.

Military Service:1975-82: Surgeon, Commissioned Corps, U.S. Public Health Service.

Societies:
Fellow, American Heart Association, Council on Arteriosclerosis
Fellow, American Federation of Clinical Research
Fellow, American Society of Clinical Investigation
Fellow, American Institute of Nutrition
Fellow, American College of Physicians
Member, American Association for the Advancement of Science

Honors:
B.A., cum laude, Harvard University, 1968.
Mosby Book Award for Excellence in Clinical Medicine, Mount Sinai School of Medicine, Class of 1972.
J. D. Lane Investigator Award, U.S. Public Health Service Professional Association (shared with D.W. Anderson, Ph.D. and H. Bryan Brewer, Jr., M.D.), 1981.
Irvine H. Page Arteriosclerosis Research Award for Young Investigators, American Heart Association Council on Arteriosclerosis, 1981.
Saul Horowitz Jr. Memorial Research Award, Mt. Sinai School of Medicine, NY, 1989.
Outstanding Publication of the Year, 1992, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University (shared with J.S. Cohn).
Oliver Smith Award for excellence, compassion, and service to patients at New England Medical Center, 1999, 2001.
E.V. McCollum Award, American Society for Clinical Nutrition, 2000.
Distinguished Faculty Award, Tufts University, 2001.

Special Scientific Recognition, Professional Activities:
USA-USSR First Lipoprotein Symposium and Scientific Exchange, Leningrad, 1981.
David Rubinstein Lecture, Canadian Lipoprotein Club, Quebec, 1982.
Seminar in Medicine, Beth Israel Hospital, Boston, 1983.
Reviewer, NHLBI Program Projects, 1982-present.
Member, American Heart Association, Council on Arteriosclerosis, Credentials Committee, 1984-1986.
Member, American Heart Association, Lipoprotein Metabolism Grant Review Committee, 1983-1987.
Member, American Heart Association, Council on Arteriosclerosis, Program Committee, 1985-1987.
Member, Parent Committee for Evaluation of Specialized Centers of Research on Arteriosclerosis, National Heart, Lung, and Blood Institute, 1985-1986.
Member, Parent Committee for Evaluation of National Demonstration and Education Programs in Arteriosclerosis, NHLBI, 1986.
Member, Editorial Board, Circulation, 1983-1986.
Member, Editorial Board, Metabolism, 1985-1992.
Member, Editorial Board, Journal of Nutrition, 1987-1992.
Member, National Cholesterol Education Program, Expert Panel on Adult Detection and Treatment (ATP I), National Heart, Lung and Blood Institute, National Institutes of Health, 1986-1987.
Member, Nutrition Study Section, National Institutes of Health, 1986-1990.

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USA-USSR Second Lipoprotein Symposium and Scientific Exchange, Bethesda, MD, 1986.
Member, Policy Board, Atherosclerosis Risk in Communities, National Heart, Lung and Blood Institute, 1986-present.
Member, Cholesterol Education Program, American Heart Association, Massachusetts Affiliate, 1988-1996; Chairman 1990-1991.
Member, American Heart Association Nutrition Committee, 1989-1992;
Chairman, Program Committee 1989-1991.
Member, National Cholesterol Education Program, Second Expert Panel on Adult Detection and Treatment (ATP II), National Heart Lung and Blood Institute, National Institutes of Health, 1991-1992.
Member, Metabolism Study Section, National Institutes of Health, 1995-2000; Chairman 1998-2000.
U.S. Editor and Reviews Editor, *Atherosclerosis*, 1997 - present.
Member, US-Italy Scientific Exchange, 2002.

Major Current Research Support:

1. Tufts University Contract with the U.S. Department of Agriculture at the Human Nutrition Research Center on Aging at Tufts University, Lipoproteins, Nutrition, and Aging Contract 53-3K06-5-10 (10/82-present; E.J. Schaefer, M.D., Principal Investigator).
2. National Institutes of Health, Caloric Density, Obesity, and Cardiovascular Risk, Grant R01HL-57981; (8/1/99 - 7/30/04, E.J. Schaefer, M.D., Principal Investigator).
3. National Institutes of Health, Human Metabolic and Genetic Core Laboratory, Tufts-New England Medical Center, Boston Obesity Nutrition Research Center, Center Grant with Boston University, Harvard School of Public Health, and Beth Israel Deaconess Medical Center, Harvard Medical School, (7/1/03 – 6/30/08; E.J. Schaefer, M.D., Core Laboratory Director, B. Corkey, Principal Investigator).
4. National Institutes of Health, Pharmacogenetics of Statins, Grant R01 HL 074753 (3/1/04 – 2/29/08. E.J. Schaefer, MD, Principal Investigator).
5. Veterans Affairs Contract Central Laboratory for Diabetes Intervention Study, (9/1/01 – 8/30/07, E.J. Schaefer, Principal Investigator).
6. National Institutes of Health, HDL Subspecies and Coronary Heart Disease, (4/1/00 – 4/30/05, B.F. Asztalos, Ph.D., Principal Investigator).
7. National Institutes of Health, Hormone Replacement, Inflammation, and Coronary Artery Disease, (11/1/03 – 10/30/06, S. Lamon-Fava, M.D., Ph.D., Principal Investigator).
8. National Institutes of Health R01HL-54727, Dietary Fat, Plasma Lipids and other CHD Risk Factors (5/96- present, A.H. Lichtenstein, D.Sc., Principal Investigator).
9. National Institutes of Health, Markers of Cholesterol Metabolism and Heart Disease, (11/1/03 – 10/30/06, A.H. Lichtenstein, D.Sc., Principal Investigator).

Research Interests:

The nutritional and genetic regulation of plasma lipoproteins, the relationship of lipoproteins to atherosclerosis, and the dietary and drug treatment of lipid disorders, and the development of optimal diets for the prevention of heart disease in the elderly.

Significant Original Research Accomplishments

1. Documentation of transfer of chylomicron apoA-I and apoA-II to plasma HDL and its recirculation in vivo and in vitro (references 4, 38, 322).
2. Documentation of metabolic and genetic defect studies in Tangier disease, a form of genetic HDL deficiency (references 6,15 19, 24, 36, 54, 66, 221, 348, 364, 381, 369).
3. Description of first kindred in which plasma apoA-I was lacking, associated with marked HDL deficiency and premature atherosclerosis and delineation of molecular defect (references 30, 66, 79, 137).
4. Description of first kindred in which plasma apoE was lacking, associated with marked accumulation of chylomicron remnants and atherosclerosis, delineation of molecular defect (references 28, 82, 90).
5. Documentation that apoA-I fractional catabolism is a major determinant of HDL cholesterol and apoA-I plasma levels, and that apoA-I catabolism is enhanced in the setting of hypertriglyceridemia (references 6, 33, 42, 86, 332).
6. Documentation that females produce more apoA-I than do males, and that estrogen administration increases apoA-I production (references 33, 52, 293).
7. Documentation that restriction fragment length polymorphisms within or adjacent to the apoA-I, C-III, A-IV, apoB and apoA-II genes are not useful markers for coronary heart disease risk (references 83, 119, 120, 152, 161, 179).
8. Documentation that an intestinal cell line ($CaCo_2$) synthesizes apolipoproteins and lipoproteins and can be utilized for studies on nutritional effects of lipoprotein production in vitro (references 94, 109, 197).
9. Development of methodology to carry out population studies (with the Framingham Heart Study) to assess normal ranges and the utility of apolipoproteins, lipoproteins and their isoforms and genotypes, fatty acids, and lipoprotein subspecies as biochemical markers of premature coronary artery disease (references 95, 96, 101, 102, 195, 212, 213, 214, 216, 219, 220, 224, 227, 229, 233, 238, 240, 252, 259-265, 267, 268, 270, 272, 273, 274, 275, 281, 286, 287, 290, 297).
10. Precise studies documenting postprandial alterations in plasma lipoproteins and fat soluble vitamins in the young and the elderly (references 112, 115, 123, 131, 135, 144, 146, 149, 202, 394).
11. Documentation that cells can make HDL following apoA-I gene transfection (reference 97).
12. Research on the diagnosis and management of lipid disorders (references 10, 13, 15, 17-19, 24, 26, 27, 53, 58, 64, 65, 67, 69, 74, 77, 84, 85, 89, 91-93, 99, 106, 108, 124, 126, 140-143, 154, 156, 168, 169, 175, 189, 190, 194, 199, 204, 244, 250, 251, 252, 253, 255, 270, 271, 280, 304, 307).
13. Development of stable istope methods to study the effects of diet and aging on cholesterol and apolipoprotein kinetics in the constantly fed state (references 144, 155, 180, 186, 217, 218, 249, 278, 279, 283, 284, 293, 295, 299, 302).
14. Delineation of lipoprotein abnormalities and familial lipoprotein disorders and other disorders associated with premature coronary artery disease (references 62, 63, 65, 66, 71, 75, 83, 91, 92, 113, 114, 117, 118, 154, 162, 163, 171, 173, 178, 184, 190, 198, 209, 213, 214, 219, 220, 224, 235, 237, 238, 244, 264, 307).
15. Effects of estrogen replacement on plasma lipoproteins in elderly women (references 116, 127, 139, 153, 175, 188).
16. Definitive studies on factors (mainly triglyceride levels) affecting LDL particle size and documentation that LDL size is not an independent risk factor for coronary heart disease (references 103, 110, 127, 138, 165, 178 191, 192, 265).
17. Documentation of the effects of dietary fat saturation and dietary cholesterol as well as antioxidants and lovastatin on plasma lipoprotein metabolism and hepatic and intestinal apolipoprotein and LDL receptor mRNA levels and diet-induced aortic foam cell formation in monkeys and hamsters (references 147, 174, 182, 218, 222, 231, 241, 242, 243, 247, 256, 291, 298).
18. Documentation of the effects of dietary fats and cholesterol on plasma lipoprotein composition, metabolism, and immune status in humans (references 17, 26, 112, 115, 128, 144, 165, 181, 193, 196, 210, 211, 217, 218, 223, 228-230, 234, 256, 258, 259, 276, 282, 285, 288, 294, 301, 305, 306, 402).
19. Documentation that specific common mutations within the apoE gene and the apoA-IV gene affect the LDL cholesterol lowering response to dietary saturated fat and cholesterol restriction and HMG CoA reductase inhibitors. (references 223, 229, 244, 255, 276, 294, 389).
20. Documentation of the efficacy of various National Cholesterol Education Program Step 2 diets and variability in response in LDL cholesterol lowering (references 201, 247, 250, 251, 256, 257, 258, 276).
21. Documentation that ad libitum diets restricted in fat (15% of calories) promote weight loss and LDL cholesterol lowering (230, 252).
22. Development and evaluation of methods to directly measure serum Lp(a), LDL, and remnant lipoprotein cholesterol levels (216, 241, 297, 405).
23. Documentation of the effect of fat feeding on human intestinal apoB mRNA levels and editing (234).

BIBLIOGRAPHY * invited reviews

1. Levy RI, Blum CB, Schaefer EJ: The composition, structure and metabolism of high density lipoproteins. In Greten, H. (ed.),

Lipoprotein Metabolism, Berlin, Springer-Verlag, p. 56-64, 1976.*

2. Schaefer EJ, Hughes JR: Socioeconomic factors and maternal and child health care. *Medical Care,* 14:535-543, 1976.

3. Gordon M, Schaefer EJ, Finkel M: Treatment of protein losing gastropathy with atropine. *Am J Gastroenterol.* 66:535-539, 1976.

4. Schaefer EJ, Jenkins LL, Brewer HB Jr: Human chylomicron apolipoprotein metabolism. *Biochem. Biophys. Res. Commun.* 80:405-412, 1978.

5. Schaefer EJ, Eisenberg S, Levy RI: Lipoprotein apolipoprotein metabolism. *J. Lipid Res.* 19:667-687, 1978.*

6. Schaefer EJ, Blum CB, Levy RI, Jenkins LL, Alaupovic P, Foster DM, Brewer HB Jr: Metabolism of high density lipoprotein apolipoproteins in Tangier disease. *N. Eng. J. Med.* 299:905-910, 1978.

7. Schaefer EJ, Levy RI, Anderson DW, Danner RN, Brewer HB Jr, Blackwelder WC: Plasma-triglycerides in regulation of HDL-cholesterol levels. *Lancet* 2:391-393, 1978.

8. Schaefer EJ, Foster DM, Jenkins LL, Lindgren FT, Berman M, Levy RI, Brewer HB Jr: The composition and metabolism of high density lipoprotein subfractions. *Lipids* 14:511-521, 1979.

9. Schaefer EJ, Levy RI: Composition and metabolism of high density lipoproteins. In *Lipoprotein Metabolism*, Eisenberg, S. (ed.), Prog. Biochem. Pharmacology. S. Karger, Basel. Vol. 15, pp. 186-201, 1979.*

10. Chu FC, Kuwabara T, Cogan PG, Schaefer EJ, Brewer HB Jr: Ocular manifestations of familial high density lipoprotein deficiency (Tangier disease). *Arch. Opthalmol.* 97:1926-1928, 1979.

11. Brewer HB Jr, Schaefer EJ, Osborne JC Jr, Zech, LA: High density lipoproteins: an overview. In *Report on the High Density Lipoprotein Workshop*, Lippel, K. (ed.), U.S. DHEW NIH Publ. 79-1661, pp. 29-41, 1979.*

12. Brewer HB Jr, Schaefer EJ, Zech LA, Osborne JC JR: Human plasma lipoproteins: structure, function, and metabolism. In *Lipoproteins and Coronary Heart Disease.* (ed.) H. Greten, P.O. Lang, G. Schettler, Verlag G. Witzstrock, pp. 7-16, 1979.*

13. Reinertson JE, Schaefer EJ, Brewer HB Jr, Moutsopoulos H: Sicca syndrome in type V hyperlipoproteinemia. *Arthritis and Rheumatism* 23:114-118, 1980.

14. Brewer HB Jr, Schaefer EJ, Zech LA, Bronzert TJ: Tangier disease. In *Atherosclerosis V, Proceedings of the 4th International Symposium.* B. Schettler, A. Gotto, Jr. (eds.), Springer Verlag, pp. 680-683, 1980.*

15. Schaefer EJ, Zech LA, Schwartz DS, Brewer HB Jr: Coronary heart disease prevalence and other clinical features in familial high density lipoprotein deficiency (Tangier disease). *Ann. Int. Med.* 93:261-266, 1980.

16. Nakaya Y, Schaefer EJ, Brewer HB Jr: Activation of human post heparin lipoprotein lipase by apolipoprotein H (B-2 glycoprotein 1). *Biochem. Biophys. Res. Comm.*, 95:1165-1172, 1980.

17. Ernst ND, Fisher M, Bowden P, Schaefer EJ, Levy RI: Changes in lipids and lipoproteins resulting from a modified fat diet. *Lancet* 2:111-113, 1980.

18. Lipson LC, Bonow RO, Schaefer EJ, Brewer HB Jr, Lindgren FT: Effect of exercise conditioning on plasma high density lipoproteins (HDL) and other lipoproteins. *Atherosclerosis* 37:529-538, 1980.

19. Schaefer EJ, Anderson DW, Zech LA, Lindgren FT, Bronzert TJ, Rubalcaba EA, Brewer HB Jr: Metabolism of high density lipoprotein subfractions and constituents in Tangier disease following the infusion of high density lipoproteins. *J. Lipid Res.* 22:217-226, 1981.

20. Gregg RE, Zech LA, Schaefer EJ, Brewer HB Jr: Type III hyperlipoproteinemia: defective metabolism of an abnormal apolipoprotein E. *Science* 211:584-586, 1981.

21. Anderson DW, Schaefer EJ, Bronzert TJ, Lindgren FT, Forte T, Starzl TB, Niblack GD, Zech LA, Brewer HB Jr: Transport of apolipoprotein A-I and A-II by human thoracic duct lymph. *J. Clin. Invest.* 67:857-866, 1981.

22. Papadopoulos NM, Schaefer EJ, Anderson DW: High density lipoprotein heterogeneity demonstrated by electrophoresis. *Clin. Chem.* 27:197-198, 1981 (letter).

23. Berman MD, Ishak KG, Schaefer EJ, Barnes S, Jones EA: Syndromatic hepatic ductular hypoplasia (arteriohepatic dysplasia): a clinopathologic study of three patients. *Dig. Dis. Sci.* 26:485-497, 1981.

24. Alaupovic P, Schaefer EJ, McConathy WJ, Fesmire JD, Brewer HB Jr: Plasma apolipoprotein concentrations in familial apolipoprotein A-I and A-II deficiency (Tangier disease). *Metabolism* 30:805-809, 1981.

25. Jahn C, Osborne JC Jr, Schaefer EJ, Brewer HB Jr: In vitro activation of the enzymic activity of hepatic lipase by A-II *FEBS Lett.* 131:366-368, 1981.

26. Schaefer EJ, Levy RI, Ernst ND, Van Sant FD, Brewer HB Jr: The effect of low cholesterol, high polyunsaturated fat, and low fat diets on plasma lipid and lipoprotein cholesterol levels in normal and hypercholesterolemic subjects. *Am. J. Clin. Nutr.* 34:1758-1763, 1981.

27. Corash L, Anderson J, Poindexter B, Schaefer EJ: Platelet function and survival in patients with severe hypercholesterolemia. *Arteriosclerosis* 1:443-448, 1981.

28. Ghiselli G, Schaefer EJ, Gascon P, Brewer HB Jr: Type III hyperlipoproteinemia associated with apolipoprotein E deficiency. *Science* 214:1239-1241, 1981.

29. Papadapoulos NM, Schaefer EJ, Anderson DW. Demonstration of heterogeneity in high density lipoprotein subfraction (letter). *Clin. Chem.* 27:197-198, 1981.

30. Schaefer EJ, Heaton WH, Wetzel MG, Brewer HB Jr: Plasma apolipoprotein A-I absence associated with marked reduction of high density lipoproteins and premature coronary artery disease. *Arteriosclerosis* 2:16-26, 1982.

31. Kay LL, Ronan R, Schaefer EJ, Brewer HB Jr: Tangier disease: a structural defect in apolipoprotein A-I. *Proc. Natl. Acad. Sci.* U.S.A. 79:2485-2488, 1982.

32. Spiegel RJ, Schaefer EJ, Magrath IT, Edwards BK: Plasma lipids in leukemia and lymphoma. *Am. J. Med.* 72:775-782, 1982.

33. Schaefer EJ, Zech LA, Jenkins LL, Aamodt RA, Bronzert TJ, Rubalcaba EA, Lindgren FT, Brewer HB Jr: Human apolipoprotein A-I and A-II metabolism. *J. Lipid Res.* 23:850-862, 1982.

34. Morrow J, Schaefer EJ, Huston DP, Rosen SW: The POEMS syndrome: studies in a patient with IgG kappa monoclonal gammapathy but no polyneuropathy. *Arch. Int. Med.* 142:1231-1234, 1982.

35. Ghiselli G, Schaefer EJ, Zech LA, Gregg RE, Brewer HB Jr: Increased prevalence of apolipoprotein E4 in type V hyperlipoproteinemia. *J. Clin. Invest.* 70:474-477, 1982.

36. Schaefer EJ, Kay L, Zech LA, Lindgren FT, Brewer HB Jr: Tangier disease: high density lipoprotein deficiency due to defective metabolism of an abnormal apolipoprotein A-I (apoA-I Tangier). *J. Clin. Invest.* 70:934-945, 1982.

37. Ghiselli G, Gregg RE, Zech LA, Schaefer EJ, Brewer HB Jr: Phenotype study of apolipoprotein E isoforms in hyperlipoproteinemic patients. *Lancet* 2:455-457, 1982.

38. Schaefer EJ, Wetzel MG, Bengtsson G, Scow RO, Brewer HB Jr, Olivercrona T: Transfer of human lymph chylomicron constituents to other lipoprotein density fractions during in vitro lipolysis. *J. Lipid Res.* 23:1259-1273, 1982.

39. Brewer HB Jr, Schaefer EJ, Osborne JC, Zech LA: Recent advances in the structure, function, and metabolism of plasma

lipoproteins. In *Lipoproteins and Aging*, H. Kaffarnik (ed.), Springer Verlag p1-21, 1982.*

40. Schaefer EJ, Zech LA, Gregg RE, Brewer HB Jr: The metabolism of high density lipoproteins. USA-USSR First Lipoprotein Symposium. *NIH Publication* 83-1966:105-122, 1983.*

41. Jahn CE, Osborne JC, Schaefer EJ, Brewer HB Jr: Apo A-II specific activation of hepatic lipase enzymic activity: identification of a major HDL apoprotein as the activating plasma component in vitro. *European J. Biochem.* 131:25-29, 1983.

42. Zech LA, Schaefer EJ, Jenkins LL, Rubalcaba EA, Bronzert TJ, Aamodt RL, Brewer HB Jr: Metabolism of human apolipoproteins A-I and A-II: compartmental models. *J. Lipid Res.* 24:60-71, 1983.

43. Schaefer EJ: Dietary and drug treatment. pp. 633-637. In Brewer, H.B. Jr., moderator, Type III hyperlipoproteinemia: diagnosis, molecular defects, pathology and treatment. *Ann. Int. Med.* 98(1):623-640, 1983.*

44. Ghiselli G, Schaefer EJ, Light JA, Brewer HB Jr: Apolipoprotein A-I isoforms in human lymph: effect of fat absorption. *J. Lipid Res.* 24:731-736, 1983.

45. Schaefer EJ: High density lipoproteins in health and disease. In Glueck, C.J. *Perspectives in Lipid Disorders.* McGraw-Hill, 1:4-9, 1983.*

46. Schaefer EJ: Disorders of lipoprotein metabolism associated with apolipoprotein deficiencies. Proceedings of the Workshop on Apolipoprotein Quantitation. *NIH Publication* 83-1266:54-70, 1983.*

47. Osborne JC, Brewer HB Jr, Bronzert TJ, Schaefer EJ, Tate RL: Molecular properties of plasma apolipoproteins. Proceedings of the Workshop on Apolipoprotein Quantitation. *NIH Publication* 83-1266:179-199, 1983.*

48. Schaefer EJ, Levy RI: The role of the liver in hyperlipoproteinemia. In *Liver in Metabolic Diseases.* L. Bianchi, W. Gerok, L. Landmann, K. Sickinger, G.A. Stalder, (eds.) MTP Press Limited. pp. 41-47, 1983.*

49. White RW, Schaefer EJ, Papadopoulos NM: The effect of growth hormone administration on lipids and lipoproteins in growth hormone-deficient patients. *Proc. Soc. Exp. Biol. Med.* 173:63-67, 1983.

50. Sweet JB, Callihan MD, Schaefer EJ, Tarpley TM: Tangier disease with oral abnormalities. *Internat. J. of Oral Surgery* 12:110-114, 1983.

51. Schaefer EJ, Woo R, Kibata M, Bjornsen L, Schreibman T: The mobilization of triglyceride but not cholesterol or tocopherol from human adipocytes during weight reduction. *Am. J. Clin. Nutr.* 37:749-754, 1983.

52. Schaefer EJ, Foster DA, Zech LA, Brewer HB Jr, Levy RI: The effect of estrogen administration on plasma lipoprotein metabolism in premenopausal females. *J. Clin. Endocr. Metab.* 57:262-270, 1983.

53. Meng MS, Gregg RE, Schaefer EJ, Hoeg JM, Brewer HB Jr: Presence of two forms of apolipoprotein B in patients with dyslipoproteinemia. *J. Lipid Res.* 24:803-809, 1983.

54. Schaefer EJ, Triche TJ, Zech LA, Stein E, Kemeny MM, Brennan MF, Brewer HB Jr: Massive omental reticuloendothelial cell lipid uptake in Tangier disease following splenectomy. *Am. J. Med.* 75:521-526, 1983.

55. Starzl TE, Chase HP, Ahrens EH, MacNamara DJ, Bilheimer DW, Schaefer EJ, Rey J, Porter KA Porter, Stein E, Francaville A, Benson LN: Portacaval shunt in patients with familial hypercholesterolemia. *Ann. Surgery* 198:273-283, 1983.

56. Zech LA, Schaefer EJ, Osborne JO, Aamodt RL, Brewer HB Jr: High density lipoprotein metabolism. In *Pathophysiology of Plasma Proteins*, (Mariani G., ed.) pp. 333-356, MacMillan, New York, 1983.*

57. Malinow MR, Brown BG, Wissler RW, Stein O, Stein Y, Schwartz SM, Schonfeld G, Schaefer EJ, Thompson GR. Atherosclerosis, regression, arterial wall cell interactions, and atherogenic lipoproteins. *Arteriosclerosis* 3:627-630, 1983.*

000082

58. Spiegel RJ, Schaefer EJ, Magrath IT, Edwards BK. Fluorescence polarization as a parameter of plasma lipids in patients with hematologic malignancies. *Leuk. Res.* 7:647-654, 1983.

59. Fleischmajer R, Schaefer EJ, Gal AE, Pentchev PG, Tint GS: Normolipemic subcutaneous xanthomatosis. *Am. J. Med.* 75:1065-1070, 1983.

60. Osborne JO, Schaefer EJ, Lee N, Zech L: Molecular properties of radioiodinated apolipoprotein A-I. *J. Biol. Chem.* 259:347-353, 1984.

61. Bieri JG, Hoeg JM, Schaefer EJ, Zech LA, Brewer HB Jr: Vitamin A and vitamin E replacement in abetalipoproteinemia. *Ann. Intern. Med.* 100:235-239, 1984.

62. Schaefer EJ: Premature coronary artery disease: familial lipoprotein disorders entities, mechanism, and recognition. *Primary Cardiology* 10(4):151-180, 1984.*

63. Schaefer EJ: Premature coronary artery disease: familial lipoprotein disorders. Therapy: medical and surgical. *Primary Cardiology* 10(5):71-78, 1984.*

64. Hoeg JM, Demosky SJ, Schaefer EJ, Starzl TE, Brewer HB Jr: Characterization of hepatic low density lipoprotein binding and cholesterol metabolism in normal and homozygous familial hypercholesterolemic subjects. *J. Clin. Invest.* 73:429-436, 1984.

65. Sprecher DS, Schaefer EJ, Kent K, Gregg RE, Zech LA, Hoeg JM, McManus B, Roberts D, Brewer HB Jr: Cardiovascular features of homozygous familial hypercholesterolemia: analysis of 16 patients. *Am. J. Cardiol.* 54:20-30, 1984.

66. Schaefer EJ: The clinical, biochemical, and genetic features in familial disorders of high density lipoprotein deficiency. *Arteriosclerosis* 4:303-322, 1984.*

67. Newman RP, Schaefer EJ, Thomas CB, Oldfield E: Abetalipoproteinemia and metastatic spinal cord glioblastoma. *Arch. Neurol.* 41:554-556, 1984.

68. Gregg RE, Zech LA, Schaefer EJ, Brewer HB Jr: Apolipoprotein E metabolism in normolipoproteinemic human subjects. *J. Lipid Res.* 25:1167-1176, 1984.

69. Cogan DG, Rodrigues M, Chu FC, Schaefer EJ: Ocular clinico-pathology in abetalipoproteinemia. *Arch. Opthal.* 91:991-998, 1984.

70. Ginns EI, Barranger JA, McClean SW, Sliva C, Young R, Schaefer EJ, Goodman SI, McCabe RB. A juvenile form of glycerol kinase deficiency with episodic vomiting, acidemia, and stupor. *J. Pediatrics* 5:736-739, 1984.

71. Schaefer EJ, Levy RI: *Disorders of lipid transport. Current Diagnosis,* R. Conn (ed.) W.B. Saunders Co., 7th Edition, p. 762-770, 1985.*

72. Hoeg JM, Demosky SJ, Gregg RE, Schaefer EJ, Brewer HB Jr: Distinct hepatic receptors for low density lipoprotein and apolipoprotein E in humans. *Science* 227:759-761, 1985.

73. Bojanovski D, Gregg RE, Ghiselli G, Schaefer EJ, Zech LA, Light JA, Brewer HB Jr: Human apolipoprotein A-I isoprotein metabolism: proapoA-I conversion to mature apoA-I. *J. Lipid Res.* 26:185-193, 1985.

74. Hoeg JM, Schaefer EJ, Romano CA, Bou E, Pikus AM, Zech LA, Bailey KR, Gregg RE, Wilson PWF, Sprecher DL, Grimes AM, Sebring NG, Ayres EJ, Jahn CE, Brewer HB Jr: Neomycin and plasma lipoproteins in type II hyperlipoproteinemia. *Clin. Pharm. and Therapeutics* 36:555-565, 1985.

75. Sprecher DL, Hoeg JM, Schaefer EJ, Zech LA, Gregg RE, Lakatos E, Brewer HB Jr: The association of LDL receptor activity, LDL cholesterol level, and clinical course in homozygous familial hypercholesterolemia. *Metabolism* 34:294-299, 1985.

76. Hoeg JM, Demosky SJ Jr, Schaefer EJ, Starzl TE, Porter KA, Brewer HB Jr: The effect of portacaval shunt on hepatic lipoprotein

metabolism in familial hypercholesterolemia. *J. Surg. Res.* 39:369-377, 1985.

77. Schaefer EJ, Levy RI: The pathogenesis and management of lipoprotein disorders. *N. Eng. J. Med.* 312:1300-1310, 1985.*

78. Libby P, Miao P, Ordovas J, Schaefer EJ: Lipoproteins increase growth of mitogen stimulated arterial smooth muscle cells. *J. Cell Physiol.* 24:1-8, 1985.

79. Schaefer EJ, Ordovas JM, Law S, Ghiselli G, Kashyap ML, Srivastava LS, Heaton WH, Albers JJ, Connor WE, Lemeshev Y, Segrest J, Brewer HB Jr: Familial apolipoprotein A-I and C-III deficiency, variant II. *J. Lipid Res.* 26:1089-1101, 1985.

80. Jahn CE, Schaefer EJ, Taam L, Hoofnagel J, Jones EA, Brewer HB Jr: Lipoprotein abnormalities in primary biliary cirrhosis: association with hepatic lipase inhibition as well as altered cholesterol esterification. *Gastroenterology* 89:1266-1278, 1985.

81. Wilson PWF, Zech LA, Gregg RE, Schaefer EJ, Hoeg JM, Sprecher DL, Brewer HB Jr: Estimation of VLDL cholesterol in hyperlipidemia. *Clin. Chem. Acta.* 151:285-291, 1985.

82. Zannis V, Ordovas JM, Claradas C, Cole FS, Forbes G, Schaefer EJ: mRNA and apolipoprotein synthesis abnormalities in peripheral blood monocyte-macrophages in familial apolipoprotein E deficiency. *J. Biol. Chem.* 260:12891-12894, 1985.

83. Ordovas JM, Schaefer EJ, Salem D, Ward RH, Glueck CJ, Vergani C, Wilson PW, Karathanasis SK: Apolipoprotein A-I gene polymorphism associated with premature coronary artery disease and familial hypoalphalipoproteinemia. *N. Engl. J. Med.* 314:671-677, 1986.

84. Schaefer EJ, Rees, DM, Siguel EN: Nutrition, lipoproteins and atherosclerosis. *Clinical Nutrition* 5:99-ll, 1986.*

85. Schaefer EJ: Lipoprotein metabolism and lipid disorders. *Masters in Cardiology.* 3:14-24, 1986.*

86. Schaefer EJ, Ordovas JM: Metabolism of the apolipoproteins A-I, A-II, and A-IV. In *Methods in Enzymology,* Plasma Lipoproteins, Part B: Characterization, Cell Biology and Metabolism (J. Segrest, J. Albers, eds.). Academic Press. 129:420-442, 1986.*

87. Triau JE, Arbetter J, Schaefer EJ: Impaired hepatocyte binding, uptake and degradation of glucosylated low density lipoproteins. *Biochim. Biophys. Acta* 877:359-365, 1986.

88. Gregg RE, Zech LA, Schaefer EJ, Stark D, Wilson D, Brewer HB Jr: Abnormal in vivo metabolism of apolipoprotein E4 in humans. *J. Clin. Invest* 78:815-821, 1986.

89. Schaefer EJ: Lipid lowering agents other than anion exchange resins acting in the gastrointestinal tract. In J. Shepherd, R.I. Levy (eds.) *Pharmacologic Control of Hyperlipidemia.* J.R. Prous Science Publishers, Barcelona, pp. 119-132, 1986.*

90. Schaefer EJ, Gregg RE, Ghiselli G, Forte TM, Ordovas JM, Zech LA, Lindgren FT, Brewer HB Jr: Familial apolipoprotein E deficiency. *J. Clin Invest.* 78:1206-1219, 1986.

91. Schaefer EJ, McNamara JR, Mitri C, Ordovas JM: Genetic high density lipoprotein deficiency states. *Atherosclerosis VII, Proceedings of the Seventh International Symposium on Atherosclerosis,* Excerpta Medica, Amsterdam, pp. 183-186, 1986.*

92. Schaefer EJ, McNamara JR, Mitri C, Ordovas JM: Genetic high density lipoprotein deficiency and atherosclerosis. Angel A., Frohlich J., (eds.) Lipoprotein Deficiency Syndromes. *Adv. Exp. Biol. Med.* 201:1-15, 1986.*

93. Ellis JK, Russell RM, Makrauer FL, Schaefer EJ: Increased risk of vitamin A toxicity in severe hypertriglyceridemia. *Ann Intern Med.* 105:877-879, 1986.

94. Hughes T, Sasak V, Ordovas JM, Forte T, Lamon-Fava S, Schaefer EJ: A novel cell line (Caco-2) for the study of intestinal lipoprotein synthesis. *J. Biol. Chem.* 262:3762-3767, 1987.

95. McNamara JR, Schaefer EJ: Automated enzymatic standardized lipid analyses for plasma and lipoprotein fractions. *Clin. Chim.*

Acta 166:1-8, 1987.

96. Ordovas JM, Litwack-Klein LE, Schaefer MM, Wilson PWF, Schaefer EJ: Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. *J. Lipid Res.* 28:371-380, 1987.

97. Lamon-Fava S, Ordovas JM, Mandel G, Forte TM, Goodman RH, Schaefer EJ: Secretion of apolipoprotein A-I in lipoprotein particles following transfection of the human apolipoprotein A-I gene into 3T3 cells. *J. Biol. Chem.* 262:8944-8947, 1987.

98. Farber HN, Arbetter J, Schaefer EJ, Hill SP, Dallal G, Grimaldi R, Hill NS: Acute metabolic effects of an endurance triathlon. *Ann Sports Med.* 32:131-138, 1987.

99. Schaefer EJ: Diagnosis and management of ocular abnormalities in abetalipoproteinemia in Research in Retinitis Pigmentosa, E. Zrenner, H. Krastel, H. H. Goebel, (eds.) *Adv. in Biosciences.* 62:579-581, 1987.*

100. Woods M, Schaefer EJ, Morrill A, Goldin BR, Longcope C, Dwyer JD, Gorbach SL: Effects of menstrual cycle phase on plasma lipids. *J. Clin. Endocr. Metab.* 65:321-323, 1987.

101. Ordovas JM, Peterson JP, Santaniello P, Cohn J, Wilson PWF, Schaefer EJ: Enzyme linked immunosorbent assay for human plasma apolipoprotein B. *J. Lipid Res.* 28:1216-1224, 1987.

102. Siguel EN, Chee KW, Gong J, Schaefer EJ: Criteria for plasma essential fatty acid deficiency as assessed by capillary column gas liquid chromatography. *Clin. Chem.* 33:1869-1873, 1987.

103. McNamara JR, Campos H, Ordovas JM, Peterson J, Wilson PWF, Schaefer EJ: Effect of gender, age, and lipid status on low density lipoprotein subfraction distribution: results from the Framingham Offspring Study. *Arteriosclerosis* 7:483-490, 1987.

104. Prioli RP, Ordovas JM, Rosenberg I, Schaefer EJ, Pereira MEA. Similarity of cruzin, an inhibitor of Trypanosoma cruzi neuraminidase, to high-density lipoprotein. *Science* 238:1417-1419, 1987.

105. Cohn JS, Schaefer EJ. Sample lipolysis for quantification of apolipoprotein B. *Clin. Chem.* 33:338-339, 1987 (letter).

106. Samuel P, Chin B, Schoenfeld BH, Schaefer EJ, Gonasun LM: Comparison of the effect of pindolol versus propranolol on the lipid profile in patients treated for hypertension. *Br. J. Clin. Pharm.* 24:(Suppl.1)63S-64S, 1987.

107. Schaefer EJ, Rifkin RD, Genest J: Diagnosis and management of lipid disorders. *Cardiovascular Reviews and Reports* 8(11):19-22, 1987.*

108. Schaefer EJ: When and how to treat the dyslipidemias. *Hospital Practice* 23 (1):69-80, 83-84, 1988.*

109. Hughes T, Ordovas JM, Schaefer EJ. Regulation of apolipoprotein B synthesis and secretion by Caco-2 cells: lack of fatty acid effects and control by intracellular calcium ion. *J Biol. Chem.* 263:3425-3431, 1988.

110. McNamara JR, Campos H, Ordovas JM, Wilson PWF. Gradient gel electrophoretic analysis of low density lipoproteins. *Am. Biotech. Lab.* 6(1):1-4, 1988.*

111. Rosenberg IH, Schaefer EJ: Dietary saturated fat and cholesterol. *N. Eng. J. Med.* 318:1270-1271, 1988 (editorial).*

112. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ: Postprandial plasma lipoprotein changes in human subjects of different ages. *J. Lipid. Res.* 29:469-478, 1988.

113. Genest J, Corbett H, McNamara JR, Schaefer MM, Salem DN, Schaefer EJ: Effect of hospitalization on high density lipoprotein cholesterol in patients undergoing elective angiography. *Am. J. Cardiol.* 61:998-1000, 1988.

114. Schaefer EJ, McNamara JR, Ordovas JM: Lipoprotein Abnormalities in Premature Coronary Artery Disease. In *Atherosclerosis Reviews,* R.I. Levy, (ed.) 17:21-27, 1988.*

115. Cohn JS, McNamara JR, Cohn SD, Ordovas JM, Schaefer EJ: Plasma apolipoprotein changes in the triglyceride-rich lipoprotein fraction of human subjects fed a fat-rich meal. *J. Lipid Res.* 29:925-936, 1988.

116. Campos H, McNamara JR, Wilson PWF, Ordovas JM, Schaefer EJ: Differences in low density lipoprotein subfractions and apolipoproteins in premenopausal and postmenopausal women. *J. Clin. Endocr. Metab.* 67:30-35, 1988.

117. Schaefer EJ, McNamara JR, Genest J, Ordovas JM: Clinical significance of hypertriglyceridemia. *Sem. Thrombosis and Hemostasis* 14:143-148, 1988.*

118. Schaefer EJ, McNamara JR, Genest J, Ordovas JM: Genetics and abnormalities of plasma lipoproteins. *Clin. Chem.* 34(8):B9-B12.*

119. Genest J, Ordovas J, Robbins A, King DC, Frossard PM, Schaefer EJ: Two new apoB gene polymorphisms:RsI and Rs2 *Nucleic Acids Research* 16:8746, 1988.

120. Genest J, Ordovas JM; Robbins AH, King DC, Frossard PM, Schaefer EJ: Two new apoB gene polymorphisms: Rs3 and Rs4. *Nucleic Acids Research* 16:8747, 1988.

121. Schaefer EJ: Sleep abnormalities in patients on lovastatin. *N. Engl. J. Med.* 319:1222, 1988 (letter).

122. Triau JE, Meydani SN, Schaefer EJ: Oxidized low density lipoproteins stimulate prostacyclin production by human vascular endothelial cells. *Arteriosclerosis* 8:810-818, 1988.

123. Cohn JS, McNamara JR, Schaefer EJ: Lipoprotein concentrations in the plasma of human subjects as measured in the fed and fasted states. *Clin. Chem.* 34:2456-2459, 1988.

124. Samuel P, Kirkendall W, Schaefer EJ, Chin B, Schoenfeld BH, Gonasun LM, Lieberman S: Effects of isradipine, a new calcium channel antagonist, versus hydrochlorthiazide on serum lipids and apolipoproteins in patients with systemic hypertension. *Am. J. Cardiol.* 62:1068-1071, 1988.

125. Ordovas J, Schaefer EJ: Coronary artery disease, lipid disorders, and genetic polymorphisms. *Ann. Biol. Clin.* 46:24-29,1988.*

126. The Expert Panel. Report of the National Cholesterol Education Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults. *Arch. Intern. Med.* 148: 36-69, 1988.*

127. Lamon-Fava S, Fisher EC, Nelson ME, Evans WE, Miller JS, Ordovas JM, Schaefer EJ: Effect of exercise and menstrual cycle status on plasma lipids, low density lipoprotein particle size, and apolipoproteins. *J. Clin. Endocr. Metab.* 68:17-21, 1989.

128. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonneman G, Van Der Meer JWM, Cannon JG, Klempner M, Schaefer EJ, Wolff SM, Dinarello CA: Dietary n-3 polyunsaturated fatty acids suppress synthesis of interleukin-1 and tumor necrosis factor. *N. Eng. J. Med.* 320:265-271, 1989.

129. Schaefer EJ, Moussa PB, Wilson PWF, McGee D, Dallal G, Castelli WP: Plasma lipoproteins in healthy octogenarians: lack of reduced high density lipoprotein cholesterol levels: Results from the Framingham Heart Study. *Metabolism* 38:293-296, 1989.

130. Dallal GE, Choi E, Jacques P, Schaefer EJ and Jacob RA: Ascorbic acid, HDL cholesterol, and apolipoprotein A-I in an Elderly Chinese population in Boston. *J. Amer. Coll. Nutr.* 8:69-74, 1989.

131. Cohn JS, McNamara JR, Krasinski SD, Russell RM, Schaefer EJ: Role of triglyceride rich lipoproteins from the liver and intestine in the etiology of postprandial peaks in plasma triglyceride concentration. *Metabolism* 38:484-490, 1989.

132. McNamara JR, Adolfsen J, Campos H, Ordovas JM, Albers JJ, Usher D, Schaefer EJ: Screening for lipoprotein (a) elevations in plasma and assessment of size heterogeneity using gradient gel electrophoresis. *J. Lipid Res.* 30:747-755, 1989.

133. Siguel E, Schaefer EJ: Aging and nutritional requirements of essential fatty acids in J. Beare Rogers in *Dietary Fat Requirements in Health and Disease* p. 1653-1689, Amer. Oil Chemists Society, Champaign, Il, 1989.*

000086

134. Schaefer EJ, McNamara JR, Genest JJ, Ordovas JM: Genetic high density lipoprotein deficiency. in N.E. Miller, (ed.) High Density Lipoproteins and Atherosclerosis II. *Excerpta Medica,* Amsterdam, 1989; pp.29-36.*

135. Meydani M, Cohn JS, Macauley JB, McNamara JR, Blumberg JB, Schaefer EJ: Postprandial changes in the plasma concentration of alpha and beta-tocopherol in human subjects fed a fat rich meal supplemented with fat soluble vitamins. *J. Nutr.* 119:1252-1258, 1989.

136. Breslow JL, Deeb S, Lalouel JM, Le Boeuf R, Schaefer EJ, Tyroler HA, Wilson PWF, Young S: Workshop II. Genetic susceptibility to atherosclerosis. In: AHA Conference Report on Cholesterol, A.M. Gotto Jr., (ed.) *Circulation* 80:724-728, 1989.*

137. Ordovas JM, Cassidy DK, Civeira F, Bisgaier CL, Schaefer EJ: Familial apolipoprotein A-I, C-III, and A-IV deficiency with marked high density lipoprotein deficiency and premature atherosclerosis due to a deletion of the apolipoprotein A-I, C-III, and A-IV gene complex. *J. Biol. Chem.* 264:16339-16342, 1989.

138. Lamon-Fava S, McNamara JR, Farber HW, Hill NS, Schaefer EJ: Acute changes in lipid, lipoprotein, apolipoprotein and low density lipoprotein particle size after an endurance triathlon. *Metabolism* 38:921-925, 1989.

139. Gorbach SL, Schaefer EJ, Woods M, Longcope C, Dwyer JT, Goldin BR, Morrill-Labrode A, Dallal G: Plasma lipids and endogenous sex hormones in healthy young women. J. Clin. Endocr. *Metabolism* 38:1077-1081, 1989.

140. Schaefer EJ: Hyperlipoproteinemia In: Conn's Current Therapy, Rakel R. E., (ed.) W.B. Saunders Co., Philadelphia, PA, pp. 516-525, 1990.*

141. McNamara JR, Cohn JS, Wilson PWF, Schaefer EJ: Calculated values for low density lipoprotein cholesterol in the assessment of lipid abnormalities and coronary disease risk. *Clin. Chem.* 36:36-42, 1990.

142. Kaufman HW, McNamara JR, Anderson KM, Wilson PWF, Schaefer EJ: How reliably can compact chemistry analyzers measure lipids? *JAMA* 263:1245-1249, 1990.

143. Schaefer EJ: The Hyperlipoproteinemias and other lipoprotein disorders in *Principles and Practice of Endocrinology and Metabolism,* K. L. Becker, (ed.) J.B. Lippincott, Philadelphia, pp. 1229-1241, 1990.*

144. Cohn JS, Wagner DA, Cohn SD, Millar JS, Schaefer EJ: The measurement of very low density lipoprotein and low density lipoprotein apoB-100 and high density lipoprotein A-I synthesis in human subjects using deuterated leucine: effect of fasting and feeding. *J. Clin. Invest.* 85:804-811, 1990.

145. Choi SK, McGrandy RB, Dallal GE, Russell RM, Jacob RA, Schaefer EJ, Sadowski JA: The prevalence of cardiovascular risk factors among elderly Chinese Americans. *Arch. Intern. Med.* 150:413,-418, 1990.

146. Krasinski SD, Cohn JS, Schaefer EJ, Russell RM: Post-prandial plasma retinyl ester response is greater in older subjects compared with younger subjects. *J. Clin. Invest.* 85:883-892, 1990.

147. Nicolosi RJ, Stucchi AF, Kowala MC, Hennessy LK, Hegsted DM, Schaefer EJ: Effect of dietary fat saturation and cholesterol on low density lipoprotein composition and metabolism. I. In vivo studies of receptor and non-receptor mediated catabolism of LDL in Cebus monkeys. *Arteriosclerosis* 10:119-128, 1990.

148. Genest JJ, McNamara JR, Ordovas JM, Martin-Munley S, Jenner JL, Millar JS, Salem DN, Schaefer EJ: Effect of elective hospitalization on plasma lipoprotein cholesterol and apolipoproteins A-I, B, and Lp(a). *Am. J. Cardiol.* 65:677-679, 1990.

149. Krasinski SD, Cohn JS, Russell RM, Schaefer EJ: Postprandial plasma vitamin A metabolism in humans: a reassessment of the use of plasma retinyl esters as markers for intestinally-derived chylomicrons and their remnants. *Metabolism* 39:357-365, 1990.

150. Ordovas JM, Civeira F, Genest J, Schaefer EJ: Genetic high density lipoprotein deficiency states. In: Biotechnology of Dyslipidemias: Applications in Diagnosis and Control. (C. Lenfant, et al., eds), Raven Press, New York, pp. 261-273, 1990.*

000087

151. Schaefer EJ: High Density Lipoproteins and Coronary Heart Disease. Gower Medical Publishing, New York, pp. 1-38, 1990.*

152. Genest JM, Ordovas JM, McNamara JR, Robbins AM, Meade T, Cohn SD, Salem DN, Wilson PWF, Masharani U, Frossard PM, Schaefer EJ: DNA polymorphisms of the apolipoprotein B gene in patients with premature coronary artery disease. *Atherosclerosis* 82:7-17, 1990.

153. Campos H, Wilson PWF, Jimenez D, McNamara JR, Ordovas JM, Schaefer EJ: Differences in apolipoproteins and low density lipoprotein subfractions in postmenopausal women on and off estrogen therapy: Results from the Framingham Study. *Metabolism* 39:1033-1038, 1990.

154. Genest JJ, McNamara JR, Salem DN, Wilson PWF, Schaefer EJ, Malinow MR: Plasma homocyst(e)ine levels in men with premature coronary artery disease. *J. Am. Coll. Cardiol.* 16:1114-1119, 1990.

155. Lichtenstein AH, Cohn JS, Hachey DLK, Millar JS, Ordovas JM, Schaefer EJ: Comparison of deuterated leucine, valine, and lysine in the measurement of human apolipoprotein A-I and B kinetics. *J. Lipid Res.* 31:1693-1701, 1990.

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

157. Hunninghake DB, Knopp RH, Schonfeld G, Goldberg AC, Brown WV, Schaefer EJ, Margolis S, Dobs AS, Mellies MJ, Insull W Jr, Stein EA: Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. *Atherosclerosis* 85:81-89, 1990.

158. Dupont J, White PJ, Carpenter MP, Schaefer EJ, Meydani SN, Elson CE, Woods M, Gorbach SL: Food Uses and Health Effects of Corn Oil. *Journal of the American College of Nutrition* 9(5):438-470, 1990.*

159. Schaefer EJ: Hyperlipoproteinemia in: Conn's Current Therapy 1991. Rakel R.E., (ed.), W.B. Saunders Co., Philadelphia pp. 515-522, 1991.*

160. Wardell MR, Rall Jr SC, Schaefer EJ, Kane JP, Weisgraber KH: Two apolipoprotein E5 variants illustrate the importance of the position of additional positive charge on receptor-binding activity. *J. Lipid Res.* 32:521-528, 1991.

161. Ordovas JM, Civeira F, Genest J, Robbins AH, Meade T, Pocovi M, Frossard PM, Masharani U, Wilson PWF, Salem DN, Ward RH, Schaefer EJ: Restriction fragment length polymorphisms of the apolipoprotein A-I, C-III, A-IV gene locus: Relationships with lipids, apolipoproteins, and coronary artery disease. *Atherosclerosis* 87:75-86, 1991.

162. Genest JJ, McNamara JR, Salem DN, Schaefer EJ: Prevalence of risk factors in men with premature coronary artery disease. *Am. J. Cardiol.* 67:1185-1189, 1991.

163. Genest J, Jenner JL, McNamara JR, Ordovas JM, Silberman SR, Wilson PWF, Schaefer EJ: Prevalence of lipoprotein (a) [Lp(a)] excess in coronary artery disease. *Am J Cardiol* 67:1039-1045, 1991.

164. Campos H, Bailey SM, Gussak LS, Siles X, Ordovas JM, Schaefer EJ: Relationships of body habitus, fitness levels and cardiovascular risk factors including lipoproteins and apolipoproteins in a rural and urban Costa Rican population. *Arteriosclerosis* 11:1077-1088, 1991.

165. Campos H, Willet WC, Peterson RM, Siles X, Bailey SM, Wilson PWF, Posner BM, Ordovas JM, Schaefer EJ: Nutrient intake comparisons between Framingham and rural and urban Puriscal, Costa Rica: associations with lipoproteins, apolipoproteins, and LDL particle size. *Arteriosclerosis* 11:1089-1099, 1991.

166. Shapiro AC, SN Meydani, M Meydani, F Morrow, JR McNamara, EJ Schaefer, S Endres, CA Dinarello: The effect of fish oil supplementation on plasma alpha tocopherol, retinol, lipid, and lipoprotein levels in normolipidemic subjects. *Nutr. Res.* 11:539-548, 1991.

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

000088

168. Schaefer EJ: Diagnosis and Management of Lipid Disorders In: *Methods for Clinical Laboratory Measurements of Lipids and Lipoprotein Risk Factors*, Rifai N., Warnick W. R., (eds) AACC Press pp. 1-16, 1991.*

169. Schaefer EJ: Diagnosis and Management of Lipoprotein Disorders. In: *Drug Treatment of Hyperlipidemia* Rifkin B., Lenfant C., (eds.) M. Dekker pp. 17-52, 1991.*

170. Farber HW, Schaefer EJ, Franey R, Grimaldi R, Hill, NS: The endurance triathlon: metabolic changes after each event and during recovery. *Medicine and Science in Sports and Exercise* 23(8):959-965, 1991.

171. Genest JJ Jr, McNamara JR, Upson B, Salem DN, Ordovas JM, Schaefer EJ, Malinow MR: Prevalence of familial hyperhomocysteinemia in men with premature coronary artery disease. *Arteriosclerosis and Thrombosis* 11:1129-1136, 1991.

172. Meydani SN, Lichtenstein AH, White PS, Goodnight SH, Elson CE, Woods M, Gorbach SL, Schaefer EJ: Food use and health effects of soybean and sunflower oils. *J. Am. Coll. Nutr.* 10:406-428, 1991.*

173. Genest JJ, Bard JM, Fruchart JC, Ordovas JM, Wilson PWF, Schaefer EJ: Plasma apolipoproteins (a), A-I, A-II, B, E, and C-III containing particles in men with premature coronary artery disease. *Atherosclerosis* 90:149-157, 1991.

174. Stucchi AF, Hennessy LK, Vespa DB, Weiner EJ, Osada J, Ordovas JM, Schaefer EJ, Nicolosi RJ: Effect of corn and coconut oil-containing diets with and without cholesterol on high density lipoprotein apoprotein A-I metabolism and hepatic apoprotein A-I mRNA levels in Cebus monkeys. *Arteriosclerosis and Thrombosis* 11:1719-1729, 1991.

175. Schaefer EJ: Diagnosis and Treatment of Lipid Disorders. *Endocrinology and Metabolism American College of Physicians MKSAP IX* Herschman J., (ed.), Philadelphia Part A, book 4, pp. 160-166, 1991.*

176. Lamon-Fava S, Jimenez D, Christian JC, Fabsitz RR, Reed T, Carmelli D, Castelli, WP, Ordovas JM, Wilson PWF, Schaefer EJ: The NHLBI Twin Study: heritability of apolipoprotein A-I, B and low density lipoprotein subclasses and concordance for lipoprotein (a). *Atherosclerosis* 91:97-106, 1991.

177. Campos H, Siles X, Vives M, Ordovas JM, Mata L, Schaefer EJ: Prevalence of cardiovascular risk factors in rural and urban Puriscal, Costa Rica. *Circulation* 85:648-658, 1992.

178. Campos H, Genest JJ, Blijlevens E, McNamara JR, Jenner J, Ordovas JM, Wilson PWF, Schaefer EJ: Low density lipoprotein particle size and coronary artery disease. *Arteriosclerosis and Thrombosis* 12:187-195, 1992.

179. Civeira F, Genest J, Pocovi M, Salem DN, Herbert PN, Wilson PWF, Schaefer EJ, Ordovas, JM: The MspI restriction fragment length polymorphism 3' to the apolipoprotein A-II gene: relationships with lipids, apolipoproteins, and premature coronary artery disease. *Atherosclerosis* 92:165-176, 1992.

180. Genest JJ, McNamara JR, Ordovas JM, Jenner JL, Millar JS, Silberman SR, Anderson KM, Wilson PWF, Salem DN, Schaefer EJ: Prevalence of lipoprotein cholesterol and apolipoprotein A-I, B and Lp(a) abnormalities in men with premature coronary artery disease. *J. Am. Coll. Cardiol.* 19:792-802, 1992.

181. Posner BM, Martin-Munley SS, Smigelski C, Cupples LA, Cobb JL, Schaefer E, Miller DR, D'Agostino RB: Comparison of techniques for estimating nutrient intake: the Framingham Study. *Epidemiology* 3:171-177, 1992.

182. Hennessy LK, Osada J, Ordovas JM, Nicolosi RJ, Brousseau ME, Schaefer EJ: Effects of dietary fatty acids and cholesterol on liver lipid content and hepatic apolipoprotein A-I, B and E and LDL receptor mRNA levels in Cebus monkeys. *J Lipid Res* 33:351-360;1992.

183. Schaefer EJ: Lipids In: *Nutritional Status of the Elderly: The Boston Study* Hartz, S. C., Russell, R. M., Rosenberg, I. H., (eds.) Smith-Gordon Co., Ltd., London. pp. 65-74, 1992.*

184. Genest JJ, Martin-Munley S, McNamara JR, Ordovas JM, Jenner J, Meyers R, Wilson PWF, Schaefer EJ: Prevalence of familial lipoprotein disorders in patients with premature coronary artery disease. *Circulation* 85:2025-2033, 1992.

185. Nicolosi RJ, Schaefer EJ: Pathobiology of hypercholesterolemia and atherosclerosis: Genetic and environmental determinants of elevated lipoprotein levels. In: *Prevention of Coronary Heart Disease* Ockene IS, Ockene JK (eds). Little, Brown and Company, Boston, pp. 69-102, 1992.*

186. Lichtenstein AH, Hachey DL, Millar JS, Jenner JL, Booth L, Ordovas JM, Schaefer EJ: Measurement of human apolipoprotein B-48 and B-100 kinetics in triglyceride-rich lipoproteins using [5,5,5-$^2H_3$] leucine. *J. Lipid Res.* 33:907-914, 1992.

187. Gong J, Rosner B, Rees DG, Berson EL, Weigel-DeFranco, Schaefer EJ: Plasma docosahexaenoic acid levels in various genetic forms of Retinitis Pigmentosa. *Investigative Opthalmology and Visual Science* 33:2596-2602, 1992.

188. Granfone A, Campos H, McNamara JR, Schaefer MM, Ordovas JM, Schaefer EJ: Effects of estrogen replacement on plasma lipoproteins and apolipoproteins in dyslipidemic postmenopausal women. *Metabolism* 41:1193-1198, 1992.

189. Schaefer EJ: The hyperlipoproteinemias and other lipoprotein disorders. In: *Vascular Medicine*, Loscalzo, J., Creager, M. A., and Dzau, V. J., (eds). Little Brown, Boston pp. 575-594, 1992.*

190. Schaefer EJ, Ordovas JM. Diagnosis and management of high density lipoprotein deficiency states. *High Density Lipoproteins and Atherosclerosis III* (N.E. Miller and A.R. Tall, eds). Elsevier Science Publishers, Amsterdam, pp. 235-251, 1992.*

191. McNamara JR, Jenner JL, Li Z, Wilson PWF, Schaefer EJ: Change in low density lipoprotein particle size is associated with change in plasma triglyceride concentration. *Arteriosclerosis and Thrombosis* 12:1284-1290, 1992.

192. Campos H, Blijlevens E, McNamara JR, Ordvoas JM, Wilson PWF, Schaefer EJ: LDL particle size distribution: results from the Framingham Offspring Study. *Arteriosclerosis and Thrombosis* 12:1410-1419, 1992.

193. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ: Hydrogenation impairs the hypolipidemic effect of corn oil in humans. *Arteriosclerosis and Thrombosis* 13:154-161, 1993.

194. Expert Panel. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II) *JAMA* 269;3015-3023, 1993.*

195. Jenner JL, Ordovas JM, Lamon-Fava S, Schaefer MM, Wilson PWF, Castelli WP, Schaefer EJ: Effects of age, gender, and menopausal status on plasma lipoprotein (a) levels: The Framingham Offspring Study. *Circulation* 87:135-1141, 1993.

196. Meydani SN, Lichtenstein AH, Cornwall S, Meydani M, Goldin BR, Rasmussen H, Dinarello CA, Schaefer EJ: Immunologic effects of National Cholesterol Panel Step 2 diets with and without fish derived on three fatty acid enrichment *J. Clin. Invest.* 92:105-113, 1993.

197. Reisher SR, Hughes TE, Ordovas JM, Schaefer EJ, Feinstein SI: Increased expression of apolipoprotein genes accompanies differentiation in the intestinal cell line Caco-2. *Proc. Natl. Acad. Sci. USA* 90:5757-5761, 1993.

198. Schaefer EJ, Genest JJ, Ordovas JM, Salem DN, Wilson, PWF: Familial lipoprotein disorders and premature coronary artery disease. *Current Opinion in Lipidology* 4:288-298, 1993.*

199. Schaefer EJ, New recommendations for the diagnosis and treatment of plasma lipid abnormalities. *Nutrition Reviews*, 51:246-252, 1993.*

200. Lyu L-C, Schaefer EJ: Plasma lipoprotein and apolipoprotein levels in Taipei and Framingham. *Arteriosclerosis and Thrombosis* 13:1429-1440, 1993.

201. Lichtenstein AH, Carrasco W, Jenner JL, Ausman L, Ordovas JM, Schaefer EJ: Effects of canola, corn, olive, and rice bran oil on fasting and post-prandial lipoproteins in humans as part of a National Cholesterol Education Program Step 2 diet. *Arteriosclerosis and Thrombosis* 13:1533-1542, 1993.

202. Cohn JS, Johnson EJ, Millar JS, Cohn SD, Milne RW, Marcel YL, Russell RM, Schaefer EJ: The contribution of apoB-48 and apoB-100 triglyceride-rich lipoproteins to post-prandial increases in plasma triglycerides and retinyl esters. *J. Lipid Res.* 34:2033-

2040, 1993.

203. Genest JJ Jr, Bard JM, Fruchart JC, Ordovas JM, Schaefer EJ. Familial hypoalphalipoproteinemia in premature coronary artery disease. *Arteriosclerosis and Thrombosis* 13:1728-1737, 1993.

204. Chait A, Brunzell JD, Denke MA, Eisenberg D, Ernst ND, Franklin FA, Ginsberg H, Kotchen TA, Kuller L, Mullis RM, Nichaman MZ, Nicolosi RJ, Schaefer EJ, Stone NJ, Weidman WH. Rationale of the Diet Heart Statement of the American Heart Association. Report of the Nutrition Committee. *Circulation* 88:3008-3029;1993.*

205. Osada J, Pocovi M, Nicolosi RJ, Schaefer EJ, Ordovas JM. Nucleotide sequences of the *Macaca fascicularis* apolipoprotein C-III and A-IV genes. *Biochim Biophys Acta Gene Struct Expression* 1172:335-339, 1993.

206. Osada J, Garces C, Sastre J, Schaefer EJ, Ordovas JM. Molecular cloning and sequence of the cynomolgus monkey apolipoprotein A-II gene. *Biochim Biophys Acta Gene Struct Expression* 1172:340-342, 1993.

207. Lamon-Fava S, Jenner JL, Jacques PF, Schaefer EJ: Effects of dietary intakes on plasma lipids, lipoproteins, and apolipoproteins in free-living elderly men and women. *Am. J. Clin. Nutr.* 59:32-41, 1994.

208. Schaefer EJ, Lamon-Fava S, Jenner JL, Ordovas JM, Davis CE, Lippel K, Levy RI: Lipoprotein(a) levels predict coronary heart disease in the lipid research clinics coronary prevention trial. *JAMA* 271:999-1003, 1994.

209. Schaefer EJ: Familial lipoprotein disorders and premature coronary artery disease. In: Lipid Disorders D. Hunninghake (ed), Medical Clinics of North Amercia 78(1) pp. 21-39, 1994.*

210. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ: Hypercholesterolemic effect of dietary cholesterol in diets enriched in polyunsaturated and saturated fat. *Atherosclerosis and Thrombosis* 14:168-175, 1994.

211. Ferretti A, Meydani SN, Lichtenstein AH, Flanagan FP, Schaefer EJ. Prostaglandin E metabolite excretion in normolipidemic subjects is lowered by a moderate reduction of n-6/n-3 polyunsaturate ratio and total fat intake. *Nutrition Research*, Vol 14 No. 2 pp. 185-193, 1994.

212. Lichtenstein AH, Carrasco W, Jenner JL, Ausman L, Ordovas JM, Schaefer EJ. Rice bran oil consumption and plasma lipid levels in moderately hypercholesterolemic humans. *Arteriosclerosis and Thrombosis* 14:549-556, 1994.

213. Schaefer EJ, Lamon-Fava S, Jenner JL, McNamara JR, Ordovas JM, Davis CE, Abolafia JM, Lippel K, Levy RI. Lipoprotein(a) levels and risk of coronary heart disease in men. The Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA* 271:999-1003, 1994.

214. Rodriguez CR, Seman LJ, Ordovas JM, Jenner J, Genest JJ Jr, Wilson PWF, Schaefer EJ. Lipoprotein (a) and coronary heart disease. *Chemistry and Physics of Lipids* Vol. 67/68: 389-398, 1994.

215. McNamara JR, Huang C, Massov T, Teng-Leary E, Warnick GR, Rubins HB, Robins SJ, Schaefer EJ. Modification of the Dextran-Mg^{2+} HDL cholesterol precipitation method for use with previously frozen plasma. *Clin Chem.* 40/2:233-239, 1994.

216. Seman LJ, Jenner JL, McNamara JR, Schaefer EJ. Quantification of lipoprotein (a) in plasma by assaying cholesterol in lectin bound plasma fraction. *Clin Chem* 40:400-403, 1994.

217. Jones PJH, Lichtenstein AH, Schaefer EJ, Namchuk GL. Effect of dietary fat selection on plasma cholesterol synthesis in older moderately hypercholesterolemic subjects. *Arteriosclerosis and Thrombosis* 14:542-548, 1994.

218. Jones PJH, Lichtenstein AH, Schaefer EJ. Interaction of dietary fat type and cholesterol level on cholesterol synthesis measured using deuterium incorporation. *J Lipid Res.* 35:1093-1101; 1994.

219. Schaefer EJ, Lamon-Fava S, Ordovas JM, Cohn SD, Schaefer MM, Castelli WP, Wilson PWF, Factors associated with low and elevated plasma high density lipoprotein cholesterol and apolipoprotein A-1 levels in the Framingham Offspring Study. *J. Lipid Res.* 35:871-882, 1994.

220. Schaefer EJ, Lamon-Fava S, Cohn SD, Schaefer MM, Ordovas JM, Castelli WP, Wilson PWF: Effects of age, gender, and menopausal status on plasma low density lipoprotein cholesterol and apolipoprotein B levels in the Framingham Offspring Study. *J. Lipid Res.* 35:779-792, 1994.

221. Serfaty-Lacrosniere C, Lanzberg A, Civeira F, Isaia P, Berg J, Janus ED, Smith MP, Pritchard PH, Frohlich J, Lees RS, Ordovas JM, Schaefer EJ: Homozygous Tangier disease and cardiovascular disease *Atherosclerosis* 107:85-98, 1994.

222. Brousseau ME, Ordovas JM, Nicolosi RJ, Schaefer EJ: Effects of dietary fat saturation on plasma lipoproteins(a) and hepatic apolipoprotein(a) mRNA concentrations in cynomolgus monkeys. *Atherosclerosis* 106:109-118, 1994.

223. Mata P, Ordovas JM, Lopez-Miranda J, Lichtenstein AH, Clevidence B, Judd JT, Denke MA, Schaefer EJ. Apolipoprotein A-IV phenotype affects diet induced plasma low density lipoprotein cholesterol lowering. *Arteriosclerosis and Thrombosis* 14:884-891, 1994.

224. Schaefer EJ, Lamon-Fava S, Johnson S, Ordovas JM, Schaefer MM, Castelli WP, Wilson PWF. Apolipoprotein E phenotype affects plasma lipoprotein levels in a gender and menopausal status dependent manner. Results from the Framingham Offspring Study. *Arteriosclerosis and Thrombosis* 14:1105-1113, 1994.

225. Schaefer EJ, McNamara JR. Chemistry: routine diagnostic testing for ApoA-I, Apo-B, Lp(a), and LDL cholesterol in clinical laboratories *Clin Laboratory Science* 7:205-208; 1994.*

226. Schaefer EJ. Commentary. Apolipoproteins and coronary heart disease. *Eur. J. Clin. Invest.* 24:441-443; 1994.*

227. Li Z, McNamara JR, Ordovas JM, Schaefer EJ. Analysis of high density lipoproteins by a modified gradient gel electrophoresis method. *J. Lipid Res.* 35:1698-1711; 1994.

228. Lyu LC, Shieh MJ, Posner BM, Ordovas JM, Dwyer JT, Lichtenstein AH, Cupples LA, Dallal GE, Wilson PWF, Schaefer EJ: Relationship between dietary intake, lipoproteins, and apolipoproteins in Taipei and Framingham. *Am. J. Clin. Nutr.* 60:765-774; 1994.

229. Lopez-Miranda J, Ordovas JM, Mata P, Lichtenstein AH, Clevidence B, Judd JT, Schaefer EJ: Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. *J. Lipid Res.* 35:1965-75; 1994.

230. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ: Short term consumption of a low-fat diet beneficially affects plasma lipid concentrations only when accompanied by weight loss. *Arteriosclerosis and Thrombosis* 14:1751-1760; 1994.

231. Ahn, Y-S, Smith D, Schaefer EJ, Ordovas JM. Dietary fat saturation affects apolipoprotein gene expression and high density lipoprotein size distribution in Golden Syrian hamsters. *Journal of Nutrition* 124:2147-2155; 1994.

232. Cheung MC, Lichtenstein AH, Schaefer EJ. The effects of a diet restricted in saturated fat and cholesterol on the composition of apolipoprotein A-I containing particles in the fasting and fed state. *Am J Clin Nutr* 60:911-918; 1994.

233. Wilson PWF, Myers RH, Larson MG, Ordovas JM, Wolf PA, Schaefer EJ. Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. *JAMA* 272:1666-1671; 1994.

234. Lopez-Miranda J, Kam N, Osada J, Rodriguez C, Fernandez P, Contois J, Schaefer EJ, Ordovas JM. Effect of fat feeding on human intestinal apolipoprotein B mRNA levels and editing. In: *Biochemical and Biophysical Research Communications* 1214:143-147; 1994.

235. Bostom AG, Gagnon DR, Cupples LA, Wilson PWF, Jenner JL, Ordovas JM, Schaefer EJ, Castelli WP. A prospective investigation of elevated lipoprotein(a) detected by electrophoresis and cardiovascular disease in women. The Framingham Heart Study. *Circulation* 90:1688-1695; 1994.

236. Lyu LC, Posner BM, Shieh MJ, Lichtenstein AH, Cupples LA, Dwyer JT, Wilson PWF, Schaefer EJ. Cross-cultural comparisons

between Taipei Chinese and Framingham Americans: dietary intakes, blood lipids, and apolipoproteins. *Asia Pacific J Clin Nutr* 3:119-125;1994.

237. Lyu LC, Shieh M-J, Bailey SM, Dallal GE, Carrasco WI, Ordovas JM, Lichtenstein AH, Schaefer EJ. Relationship of body mass distribution with cardiovascular risk factors in healthy Chinese. *Ann Epidemiol* 4:434-444;1994.

238. Schaefer EJ, Genest JJ, Ordovas JM, Salem DN, Wilson PWF. Familial lipoprotein disorders and premature coronary artery disease. *Atherosclerosis* 108:S41-S54;1994.*

239. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PWF, Belanger AJ, O'Leary DH, Wolf PA, Schaefer EJ, Rosenberg IH. Association between plasma homocysteine concentrations and extracranial carotid artery stenosis. *N Engl J Med* 332:286-291; 1995.

240. Jacques PF, Sulsky SI, Perrone GE, Jenner J, Schaefer EJ. Effect of vitamin C supplementation on lipoprotein cholesterol, apolipoprotein, and triglyceride concentrations. *Ann Epidemiol* 5:52-59;1995.

241. McNamara JR, Cole TG, Contois JH, Ferguson CA, Ordovas JM, Schaefer EJ: Immunoseparation method for measuring low-density lipoprotein cholesterol directly from serum evaluated. *Clin. Chem.* 41:232-240; 1995.

242. Brousseau ME, Ordovas J, Osada J, Fasulo J, Robins S, Nicolosi R, Schaefer EJ: Dietary monounsaturated and polyunsaturated fatty acids are comparable in their effects on hepatic apolipoprotein mRNA abundance and liver lipid concentrations when substituted for saturated fatty acids in cynomolgus monkeys. *J Nutrition* 125:425-436; 1995.

243. Otto J, Ordovas JM, Smith D, VanDongen D, Nicolosi RJ, Schaefer EJ. Lovastatin inhibits diet induced atherosclerosis in FIB Golden Syrian hamsters. *Atherosclerosis* 114:19-28; 1995.

244. Ordovas JM, Lopez-Miranda J, Perez-Jimenez F, Rodriguez C, Park JS, Cole T, Schaefer EJ. Effect of apolipoprotein E and A-IV phenotypes on the low density lipoprotein response to HMG CoA reductase inhibitor therapy. *Atherosclerosis* 113:157-166;1995.

245. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, McNamara JR, Ordovas JM. Lipoproteins, nutrition, aging, and atherosclerosis. *Am J Clin Nutr* 61:726S-740S;1995.*

246. Clevidence BA, Reichman ME, Judd JT, Muesing RA, Schatzkin A, Schaefer EJ, Li Z, Jenner J, Brown CC, Sunkin M, Campbell WS, Taylor PR. Effects of alcohol consumption on lipoproteins of premenopausal women. *Arterioscler Thromb Vasc Biol* 15:179-184;1995.

247. Brousseau ME, Schaefer EJ, Stucchi AF, Osada J, Vespa DB, Ordovas JM, Nicolosi RJ. Diets enriched in unsaturated fatty acids enhance apolipoprotein A-I catabolism but do not affect either its production or hepatic mRNA abundance in cynomolgus monkeys. *Atherosclerosis* 115:107-119;1995.

248. Schaefer EJ, Lamon-Fava S, Spiegelman D, Dwyer JT, Lichtenstein AH, McNamara JR, Goldin BR, Woods MN, Morrill-Labrode A, Hertzmark E, Longcope C, Gorbach SL. Changes in plasma lipoprotein concentrations and composition in response to a low fat, high fiber diet are associated with changes in serum estrogen concentrations in premenopausal women *Metabolism* 44:749-756; 1995.

249. Millar JS, Lichtenstein AH, Cuchel M, Dolnikowski GG, Hachey DL, Cohn JS, Schaefer EJ. Impact of age on the metabolism of VLDL, IDL, and LDL apolipoprotein B-100. *J Lipid Res* 36:1155-1167;1995.

250. Schaefer EJ, Robins SJ, Patton GM, Sandberg MA, Weigel-DiFranco CA, Rosner B, Berson EL. Red blood cell membrane phosphatidylethanolamine fatty acid content in various forms of retinitis pigmentosa. *J Lipid Res* 36:1427-1433;1995.

251. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, Contois JH, Li Z, Rasmussen H, McNamara JR, Ordovas JM. Efficacy of a National Cholesterol Education Program Step 2 Diet in normolipidemic and hyperlipidemic middle aged and elderly men and women. *Arterioscler Thromb & Vasc Biol* 15:1079-1085;1995.

252. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, McNamara JR, Schaefer MM, Rasmussen H, Ordovas JM. Body weight and low-

density lipoprotein cholesterol changes after consumption of a low fat ad libitum diet. *JAMA* 274:1450-1455;1995.

253. Welty FK, Ordovas JM, Schaefer EJ, Wilson PWF, Young SG. Identification and molecular analysis of two apoB gene mutations causing low plasma cholesterol levels. *Circulation* 92:2036-2040;1995.

254. Myers RH, Schaefer EJ, Wilson PWF, D'Agostino R, Bachman DL, Ordovas JM, Au R, Cobb JL, Wolf PA. Apolipoprotein E allele 4 is associated with dementia in the Framingham Study. In: *Research Advances in Alzheimer's Disease and Related Disorders*. J.W. Wiley and Sons, Iqbal K, Mortimer JA, Winblad B, Wishlewski HM, pp 63-70;1995.

255. Ordovas JM, Lopez-Miranda J, Mata P, Perez-Jimenez F, Lichtenstein AH, Schaefer EJ. Gene-diet interaction in determining plasma lipid response to dietary intervention. *Atherosclerosis* 118 Suppl. S11-S27;1995.*

256. Robins SJ, Fasulo J, Patton GM, Schaefer EJ, Smith DE, Ordovas JM. Gender differences in the development of hyperlipidemia and atherosclerosis in hybrid hamsters. *Metabolism* 44:1326-1331;1995.

257. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, Contois JH, Li Z, Goldin BR, Rasmussen H, McNamara JR, Ordovas JM. Effects of National Cholesterol Education Program Step 2 diets relatively high or relatively low in fish-derived fatty acids on plasma lipoproteins in middle-aged and elderly subjects. *Am J Clin Nutr* 63:234-241;1996.

258. Cuchel M, Schwab US, Jones PJH, Vogel S, Lammi-Keefe C, Li Z, Ordovas J, McNamara JR, Schaefer EJ, Lichtenstein AH. Impact of hydrogenated fat consumption on endogenous cholesterol synthesis and susceptibility of low-density lipoprotein to oxidation in moderately hypercholesterolemic individuals. *Metabolism* 45:241-247;1996.

259. Beard CM, Barnard RJ, Robbins DC, Ordovas JM, Schaefer EJ. Effects of diet and exercise on qualitative and quantitative measures of LDL and its susceptibility to oxidation. *Arterio Thromb & Vasc Biol* 16:201-207;1996.

260. Contois JH, McNamara JR, Lammi-Keefe CJ, Wilson PWF, Schaefer EJ. Reference intervals for plasma apolipoprotein A-I as determined with a commercially available immunoturbidometric assay: results from the Framingham Offspring Study. Clin Chem. *Clin Chem* 42:(4)507-514;1996.

261. Contois JH, McNamara JR, Lammi-Keefe CJ, Wilson PWF, Schaefer EJ. Reference intervals for plasma apolipoprotein B as determined with a commercially available immunoturbidometric assay: results from the Framingham Offspring Study. *Clin Chem.* 42:(4)515-523;1996.

262. Lindpaintner K, Lee M, Larson MG, Rao VS, Pfeffer MA, Ordovas JM, Schaefer EJ, Wilson AF, Wilson, PWF, Vasan RS, Myers RH, Levy D. Absence of association or genetic linkage between the angiotensin-converting-enzyme gene and left ventricular mass. *NEJM* 334:1023-1028;1996.

263. Myers RH, Schaefer EJ, Wilson PWF, D'Agostino RD, Ordovas JM, Espino A, Au R, White RF, Knoefel JE, Cobb JL, McNulty KA, Beiser A, Wolf PA. Apolipoprotein E4 association with dementia in a population based study *Neurology* 46:673-677;1996.

264. Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Seman LJ, Wilson PWF, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *JAMA* 276:544-548;1996.

265. McNamara JR, Small DM, Li Z, Schaefer EJ. Differences in LDL subspecies involve alterations in lipid composition and conformational changes in apolipoprotein B. *J Lipid Res* 37:1924-1935;1996.

266. Li Z, McNamara JR, Fruchart JC, Luc G, Bard JM, Ordovas JM, Wilson PWF, Schaefer EJ. Effects of gender and menopausal status on plasma lipoprotein subspecies and particle sizes. *J Lipid Res* 37:1886-1896;1996.

267. McNamara JR, Warnick GR, Leary ET, Wittles E, Nelson FE, Pearl MF, Schaefer EJ. Multi-center evaluation of a patient administered test for blood cholesterol measurement. *Preventive Med* 25:583-592;1996.

268. Contois JH, McNamara JR, Vogel S, Lammi-Keefe CJ, Wilson PWF, Schaefer EJ. Reference intervals for plasma apolipoprotein (a) as determined with a commercially available immunoturbidometric assay: results from the Framingham Offspring Study. *Clin Chim Acta* 253:21-35;1996.

000094

269. Craig SB, Bandini LG, Lichtenstein AH, Schaefer EJ, Dietz WH. The impact of physical activity on lipids, lipoproteins, and blood pressure in preadolescent girls. *Pediatrics* 98:389-395;1996.

270. Siegel RD, Cupples A, Schaefer EJ, Wilson PWF. Lipoproteins, apolipoproteins, and low density lipoprotein size among diabetics in the Framingham Offspring Study. *Metabolism* 45:1267-1272;1996.

271. Schaefer EJ, Lamon Fava S, Cole T, Sprecher DL, Cilla DD Jr, Balagtas CC, Rowan JP, Black DM. Effects of regular and extended-release gemfibrozil on plasma lipoproteins and apolipoproteins in hypercholesterolemic patients with decreased HDL cholesterol levels. *Atherosclerosis* 127:113-122;1996.

272. Lahoz C, Osgood D, Wilson PWF, Schaefer EJ, Ordovas JM. Frequency of phenotype discrepancies at the apolipoprotein E locus in a large population study. *Clin Chem* 42:1817-1823;1996.

273. Wilson PWF, Schaefer EJ, Larson MG, Ordovas JM. Apolipoprotein E alleles and risk of coronary disease: a meta-analysis. *Arterioscl Thromb & Vasc Biol* 16:1250-1255;1996.

274. Lamon-Fava S, Wilson PWF, Schaefer EJ. Impact of body mass index on coronary heart risk factors in men and women. The Framingham Offspring Study. *Arterioscl Thromb & Vasc Biol* 16:1509-1515;1996.

275. Selhub J, Jacques PF, Boston AG, D'Agostino RB, Wilson PWF, Belanger AJ, O'Leary DH, Wolf PA, Rush D, Schaefer EJ, Rosenberg IH. Relationship between plasma homocysteine, vitamin status and extracranial carotid-artery stenosis in the Framingham Study Population. *J Nutr* 126:1258S-1265S;1996.

276. Schaefer EJ, Lamon-Fava S, Ausman LM, Ordovas JM, Clevidence BA, Judd JT, Goldin BR, Woods M, Gorbach S, Lichtenstein AH. Individual variability in lipoprotein cholesterol response to National Cholesterol Education Program Step 2 diets. *Am J Clin Nutr* 65:823-830;1997.

277. Johnson RC, Chapman SM, Dong ZM, Ordovas JM, Mayadas TN, Herz J, Hynes RO, Schaefer EJ, Wagner DD. Absence of P-selectin delays fatty streak formation in mice. *J Clin Invest* 99:1037-1043;1997.

278. Welty FK, Lichtenstein AH, Barrett PHR, Dolnikowski GG, Ordovas JM, and Schaefer EJ. Decreased production and increased catabolism of apolipoprotein B-100 in apolipoprotein B-67/B-100 heterozygotes. *Arterioscler Thromb Vasc Biol* 17:881-888;1997.

279. Tilly-Kiesi M, Lichtenstein AH, Ordovas JM, Dolnikowski GG, Malmstrom R, Taskinen MR, and Schaefer EJ. Subjects with apoA-I (Lys_{107}□0) exhibit enhanced fractional catabolic rate of apoA-I in Lp(AI) and apoA-II in Lp(AI with AII). *Arterioscler Thromb Vasc Biol* 17:873-880;1997.

280. Schaefer EJ. Effects of dietary fatty acids on lipoproteins and cardiovascular disease risk: summary. *Am J Clin Nutr* 65 (Suppl) 1655S-1656S; 1997.*

281. Farrer LA, Cupples LA, Kukull WA, Volicer L, Wells JM, Kurz A, Green RC, Chui H, Duara R, Auerbach SA, Larsen E, Lautenschlager N, Wolf PA, D'Agostino RD, Ordovas JM, Schaefer EJ, Growden JH, Haines JL. Risk of Alzheimer's disease is associated with parental age among apolipoprotein E $\epsilon 4$ heterozygotes. *Alzheimer's Research* 3:83-91;1997.

282. Nelson GJ, Schmidt PC, Bartolini G, Kelley DS, Phinney SD, Kyle D, Silberman S, Schaefer EJ. The effects of dietary arachidonic acid on plasma lipoprotein distributions, apoproteins, blood lipid levels, and tissue fatty acid composition in humans. *Lipids* 32:427-433;1997.

283. Welty FK, Lichtenstein AH, Barrett PHR, Dolnikowski GG, Ordovas JM, and Schaefer EJ. Production of apolipoprotein B-67 in apolipoprotein B-67/B-100 heterozygotes: technical problems associated with leucine contamination in stable isotope studies. *J Lipid Res* 38:1535-1543;1997.

284. Cuchel M, Schaefer EJ, Millar JS, Jones PJH, Dolnikowski GG, Vergani C, and Lichtenstein AH. Lovastatin decreases de novo cholesterol synthesis and LDL apoB-100 production rates in combined-hyperlipidemic males. *Arterioscler Thromb Vasc Biol*

000095

1997;17:1910-1917.

285. Davidson MH, Maki KC, Kalkowski J, Schaefer EJ, Torri SA, and Drennan KB. Effects of docosahexaenoic acid on serum lipoproteins in patients with combined hyperlipidemia: a randomized, double-blind, placebo-controlled trial. *J Am Coll Nutr* 1997;16(3):236-243.

286. Campos H, Lopez-Miranda J, Rodriguez C, Albajar M, Schaefer EJ, and Ordovas JM. Urbanization elicits a more atherogenic lipoprotein profile in carriers of the apolipoprotein A-IV-2 allele than in A-IV-1 homozygotes. *Arterioscler Thromb Vasc Biol* 1997;17:1074-1081.

287. Vogel S, Contois JH, Tucker KL, Wilson PWF, Schaefer EJ, and Lammi-Keefe CJ. Plasma retinol and plasma and lipoprotein tocopherol and carotenoid concentrations in healthy elderly participants of the Framingham Heart Study. *Am J Clin Nutr* 1997;66:950-958.

288. Ellison RC, Moore LL, Proctor MH, Nguyen UDT, Schaefer EJ, and Stare FJ. Effect of response to a low-fat diet among adolescent males on their adult blood cholesterol levels. *Preventive Med* 1997;26:686-693.

289. Schaefer EJ and McNamara JR. Overview of the Diagnosis and Treatment of Lipid Disorders. Chap. 2. In: Handbook of Lipoprotein Testing. Rifai N, Warnick GR, and Dominiczak MH, Eds. *AACC Press* 1997;25-47.*

290. Kiel DP, Myers RH, Cupples LA, Kong XF, Zhu XH, Ordovas J, Schaefer EJ, Felson DT, Rush D, Wilson PWF, Eisman JA, and Holick MF. The *Bsm*I vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density. *J Bone Miner Res* 1997;12:1049-1057.

291. Smith D, Botet JP, Cantuti-Castelvetri I, Schaefer EJ, Ordovas JM. Influence of age, diet, and laboratory caging on lipid profile among FIB hamsters. *Nutr Res* Res 10:1569-1575;1997.

292. Ehrenborg E, Clee SM, Pimstone SN, Reymer PWA, Hoogendijk CF, Davis HJ, Bissada N, Miao L, Gagne SE, Greenberg LJ, Henry R, Henderson H, Ordovas JM, Schaefer EJ, Kastelein JTP, Kotze MJ, Hayden MR. Ethnic variation and in vivo effects of the -93□g promoter variant in the lipoprotein lipase gene. *Arterioscler Thromb Vasc Biol* 17:2672-2678;1997.

293. Tilly-Kiesi M, Lichtenstein AH, Joven J, Vilella E, Cheung MC, Carrasco WV, Ordovas JM, Dolnikowski G, Schaefer EJ. Impact of gender on the metabolism of apolipoprotein A-I in HDL subclasses LpAI and LpAI:AII in older subjects. *Arterioscler Thromb Vasc Biol* 17:3513-3518;1997.

294. Tall A, Welch C, Applebaum-Bowden D, Wassef M, and the Working Group. Interaction of diet and genes in atherogenesis report of an NHLBI Working Group. *Arterioscler Thromb Vasc Biol* 17:3326-3331;1997.*

295. Jones, PJH, Ausman LM, Croll DH, Feng JY, Schaefer EJ, and Lichtenstein AH. Validation of deuterium incorporation against sterol balance for measurement of human cholesterol biosynthesis. *J Lipid Res* 39:1111-1117;1998.

296. Lamon-Fava S, Sadowski JA, Davidson KW, O'Brien ME, McNamara JR, Schaefer EJ. Plasma lipoproteins as carriers of phylloquinone (vitamin K_1) in humans. *Am J Clin Nutr* 67:1226-1331;1998.

297. McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PWF, Ordovas JM, Schaefer EJ. Remnant lipoprotein cholesterol and triglyceride reference ranges from the Framingham Heart Study. *Clin Chem* 44(6):1224-1232;1998.

298. Pitman WA, Osgood DP, Smith D, Schaefer EJ, Ordovas JM. The effects of diet and lovastatin on regression of fatty streak lesions and on hepatic and intestinal mRNA levels for the LDL receptor and HMG CoA reductase in F1B hamsters. *Atherosclerosis* 138:43-52;1998.

299. Jones PJH, Ausman LM, Croll DH, Feng JY, Schaefer EJ, and Lichtenstein AH. Validation of deuterium incorporation against sterol balance for measurement of human cholesterol biosynthesis. *J Lipid Res*39:1111-1117;1998.

300. Meydani SN, Meydani M, Blumberg JB, Leka LS, Pedrosa M, Diamond R, Schaefer EJ. Assessment of the safety of supplementation with different amounts of vitamin E in healthy older adults. *Am J Clin Nutr* 63:311-318;1998.

000096

301. Schwab US, Sarkkinen ES, Lichtenstein AH, Li Z, Ordovas JM, Schaefer EJ, Uusitupa MIJ. The effect of quality and amount of dietary fat on the susceptibility of low density lipoprotein to oxidation in subjects with impaired glucose tolerance. *Eur J Clin Nutr* 52:452-458;1998.

302. Millar JS, Lichtenstein AH, Dolnikowski GG, Ordovas JM, Schaefer EJ. Proposal of a multicompartmental model for use in the study of apolipoprotein E metabolism. *Metabolism* 47:(8) 922-928;1998.

303. Schaefer EJ and Brousseau ME. Diet, lipoproteins, and coronary heart disease. *Lipid Disorders.* In: Endocrinology and Metabolism Clinics of North America 27:711-732;1998.*

304. Schaefer EJ, Brousseau ME, McNamara JR, Cohn JS, Lichtenstein AH, Genest JJr, Seman LJ, Lamon-Fava S, Ordovas JM. Diagnosis and management of lipoprotein disorders: a review and update. Part I: Lipoprotein metabolism, familial lipoprotein disorders, and the rationale for treatment of lipid disorders. *Nutr in Clin Care* 1:71-79;1998.

305. Judd JT, Baer DJ, Clevidence BA, Muesing RA, Chen SC, Weststrate JA, Meijer GW, Wittes J, Lichtenstein AH, Vilella-Bach M, Schaefer EJ. Effects of margarine compared with those of butter on blood lipid profiles related to cardiovascular disease risk factors in normolipemic adults fed controlled diets. *Am J Clin Nutr* 68:768-777;1998.

306. Schwab US, Vogel S, Lammi-Keefe CJ, Ordovas JM, Schaefer EJ, Li Z, Ausman LM, Gualtieri L, Goldin BR, Furr HC, Lichtenstein AH. Varying dietary fat type of reduced-fat diets has little effect on the susceptibility of LDL to oxidative modification in moderately hypercholesterolemic subjects. *J Nutr* 128:1703-1709;1998.

307. Schaefer EJ. Recognition and management of patients with lipoprotein disorders. In *Primary Cardiology* Goldman L, Braunwald E, ed., W.B. Saunders, p.445-467;1998.*

308. Ordovas JM, Cupples LA, Wilson PWF, Lahoz C, Levy D, Otvos JD, McNamara JR, Gagne E, Hayden M, Schaefer EJ. Advances in cardiovascular risk prediction: new biochemical and genetic markers. In *Atherosclerosis XI* Excerpta Medica International Congress Series 1155:425-431;1998.*

309. O'Donnell CJ, Lindpaintner K, Larson MG, Rao VS, Ordovas JM, Schaefer EJ, Myers RH, Levy D. Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. *Circulation* 97:1766-1772;1998.

310. Lichtenstein AH, Kennedy E, Barrier P, Danford D, Ernst ND, Grundy SM, Leveille GA, VanHorn L, Williams CL, Booth SL. Dietary fat consumption and health. *Nutrition Reviews* 56(5):S3-S28;1998.

311. Welty FK, Lahoz C, Tucker KL, Ordovas JM, Wilson PWF, Schaefer EJ. Frequency of apoB and apoE gene mutations as causes of hypobetalipoproteinemia in the Framingham Offspring Population. *Arterio Thromb Vasc Biol* 18:1745-1751;1998.

312. Seman LJ, McNamara JR, Schaefer EJ. Lipoprotein(a), homocysteine, and remnant-like particles: emerging risk factors. *Curr Opin Cardiol* 1999;14:186-191.

313. Tucker KL, Chen H, Vogel S, Wilson PWF, Schaefer EJ, Lammi-Keefe CJ. Carotenoid intakes, assessed by dietary questionnaire, are associated with plasma carotenoid concentrations in an elderly population. *J Nutr* 1999;129:438-445.

314. Velez-Carrasco W, Lichtenstein AH, Welty FK, Li Z, Lamon-Fava S, Dolnikowski GG, Schaefer EJ. Dietary restriction of saturated fat and cholesterol decreases HDL apoA-I secretion. *Arterioscler Thromb Vasc Biol* 1999;19:918-924.

315. Larson I, Hoffmann MM, Ordovas JM, Schaefer EJ, Marz W, Kreuzer J. The Lipoprotein lipase *Hin*dIII polymorphism: Association with total cholesterol and LDL cholesterol, but not with HDL and triglycerides in 342 females. *Clin Chem* 45:(7)963-968;1999.

316. Seman LJ, DeLuca C, Jenner JL, Cupples LA, McNamara JR, Wilson PWF, Castelli WP, Ordovas JM, Schaefer EJ. Lipoprotein(a)-cholesterol and coronary heart disease in the Framingham Heart Study. *Clin Chem* 45:(7)1039-1046;1999.

317. Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. Effects of different forms of dietary hydrogenated fats on serum

lipoprotein cholesterol levels. *NEJM* 340(25):1933-1940;1999.

318. Ordovas JM, Schaefer EJ. Genes, variation of cholesterol and fat intake, and serum lipids. *Current Opin Lipid* 10:15-22;1999.

319. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 341:410-418;1999.

320. Handelman GJ, Nightingale ZD, Lichtenstein AH, Schaefer EJ, Blumberg JB. Lutein and zeaxanthin concentrations in plasma after dietary supplementation with egg yolk. *Am J Clin Nutr* 70:247-251;1999.

321. Couture P, Otvos JD, Cupples LA, Wilson PWF, Schaefer EJ, Ordovas JM. Association of the A-204C polymorphism in the cholesterol 7α-hydroxylase gene with variations in plasma low density lipoprotein cholesterol levels in the Framingham Offspring Study. *J Lipid Res* 40:1883-1889;1999.

322. Velez-Carrasco W, Lichtenstein AH, Barrett PHR, Sun Z, Dolnikowski GG, Welty FK, Schaefer EJ. Human apolipoprotein A-I kinetics within triglyceride-rich lipoproteins and high density lipoproteins. *J Lipid Res* 40:1695-1700;1999.

323. Welty FK, Lichtenstein AH, Barrett PHR, Dolnikowski GG, Schaefer EJ. Human apolipoprotein (Apo) B-48 and Apo B-100 kinetics with stable isotopes. *Arterioscler Thromb Vasc Biol* 1999;19:2966;2974.

324. Mascioli EA, McLennan CE, Schaefer EJ, Lichtenstein AH, Hoy C-E, Christensen MS, Bistrian BR. Lipidemic effects of an interesterified mixture of butter, medium-chain triacylglycerol and safflower oils. *Lipids* 34,889-894;1999.

325. Lamon-Fava S, Ordovas JM, Schaefer EJ. Estrogen increases apolipoprotein (Apo) A-I secretion in Hep G2 cells by modulating transcription of the Apo A-I gene promoter. *Arterioscler Thromb Vasc Biol* 1999;19:2960-2965.

326. Aguilar CA, Talavera G, Ordovas JM, Barriguete JA, Guillen LE, Leco ME, Pedro-Botet J, Gonzalez-Barranco J, Gomez-Perez FJ, Rull JA. The apolipoprotein E4 allele is not associated with an abnormal lipid profile in a Native American population following its traditional lifestyle. Atherosclerosis 1999;142:409-414.

327. Ordovas JM, Schaefer EJ. Treatment of dyslipidemia: genetic interactions with diet and drug therapy. Curr Atheroscler Rep 1999;1:16-23.

328. Kastelein JJ, Ordovas JM, Wittekoek ME, Pimstone SN, Wilson WF, Gagne SE, Larson MG, Schaefer EJ, Boer JM, Gerdes C, Hayden MR. Two common mutations (D9N, N291S) in lipoprotein lipase: a cumulative analysis of their influence on plasma lipids and lipoproteins in men and women. Clin Genet 1999;56:297-305.

329. McNamara JR, Seman LJ, Schaefer EJ. The laboratory's role in identifying lipid and lipoprotein risk factors for CHD. MLO Med Lab Obs 1999;31:24-28,30-36,51.

330. Couture P, Otvos JD, Cupples LA, Wilson PWF, Schaefer EJ, Ordovas JM. Absence of association between genetic variation in the promoter of the microsomal triglyceride transfer protein gene and plasma lipoproteins in The Framingham Offspring Study. Atherosclerosis 148:337-344,2000.

331. Larson IA, Ordovas JM, DeLuca C, Barnard JR, Feussner G, Schaefer EJ. Association of apolipoprotein (Apo)E genotype with plasma apo E levels. *Atherosclerosis* 148:327-335;2000.

332. Velez-Carrasco W, Lichtenstein AH, Li Z, Dolnikowski GG, Lamon-Fava S, Welty FK, Schaefer EJ. Apolipoprotein A-I and A-II kinetic parameters as assessed by endogenous labeling with [$^2H_3$] leucine in middle-aged and elderly men and women. *Arterioscler Thromb Vasc Biol* 20:801-806;2000.

333. Couture P, Otvos JD, Cupples LA, Lahoz C, Wilson PWF, Schaefer EJ, Ordovas JM. Association of the C-514T polymorphism in the hepatic lipase gene with variations in lipoprotein subclass profiles: The Framingham Offspring Study. *Arterioscler Thromb Vasc Biol* 20:815-822;2000.

334. Schwab US, Ausman LM, Vogel S, Li Z, Lammi-Keefe CJ, Goldin BR, Ordovas JM, Schaefer EJ, Lichtenstein AH. Dietary cholesterol increases the susceptibility of low density lipoprotein to oxidative modification. *Atherosclerosis* 149:83-90;2000.

335. Brousseau ME, Schaefer EJ, Dupuis J, Eustace B, Van Eerdewegh P, Goldkamp AL, Thurston LM, FitzGerald MG, Yasek-McKenna D, O'Neill G, Eberhart GP, Weiffenbach B, Ordovas JM, Freeman MW, Brown RH Jr., Gu JZ. Novel mutations in the gene encoding ATP-binding cassette 1 in four Tangier disease kindreds. *J Lipid Res* 41:433-441;2000.

336. Schaefer EJ, Augustin JL, Schaefer MM, Rasmussen H, Ordovas JM, Dallal GE, Dwyer JT. Lack of efficacy of a food-frequency questionnaire in assessing dietary macronutrient intakes in subjects consuming diets of known composition. Am J Clin Nutr 2000;71:746-751.

337. El-Swefy S, Schaefer EJ, Seman LJ, vanDongen D, Sevanian A, Smith DE, Ordovas JM, El-Sweidy M, Meydani M. The effect of vitamin E, probucol, and lovastatin on oxidative status and aortic fatty lesions in hyperlipidemic-diabetic hamsters. *Atherosclerosis* 149:277-286;2000.

338. Schaefer EJ and Seman LJ. The diagnosis and management of lipoprotein disorders. In Medical Management of Diabetes Mellitus. Leahy JL, Clark NG, Cefalu WT (Eds). Marcel Dekker, Inc., NY. 499-526.*

339. Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, Martinez A, Lahoz C, Coltell O, Wilson PWF, Schaefer EJ. Association of cholesteryl ester transfer protein - *Taq*IB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk. The Framingham Study. *Arterioscler Thromb Vasc Biol* 2000;20:1323-1329.

340. Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PWF, Ordovas J, Schaefer EJ, Dawson-Hughes B, Kiel DP. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr* 71:1201-1208;2000.

341. Ordovas JM, Schaefer EJ. Genetic determinants of plasma lipid response to dietary intervention: the role of the *APOA1/C3/A4* gene cluster and the *APOE* gene. *British J Nutr* 83:S127-S136;2000.*

342. Marsh JB, Welty FK, Schaefer EJ. Stable isotope turnover of apolipoproteins of high-density lipoproteins in humans. Curr Opin Lipidol 11:261-266;2000.*

343. Wityk RJ, Kittner SJ, Jenner JL, Hebel JR, Epstein A, Wozniak MA, Stolley PD, Stern BJ, Sloan MA, Price TR, McCarter RJ, Macko RF, Johnson CT, Earley CJ, Buehholz DW, Schaefer EJ. Lipoprotein(a) and the risk of ischemic stroke in women. Atherosclerosis 150:381-388,2000.

344. Welty FK, Lichtenstein AH, Barrett PHR, Jenner JL, Dolnikowski GG, Schaefer EJ. Effects of apoE genotype on apoB-48 and apoB-100 kinetics with stable isotopes in humans. Arterio Thromb Vasc Biol 20:1807-1810;2000.

345. Brousseau ME, Eberhart GP, Dupuis J, Asztalos BF, Goldkamp AL, Schaefer EJ, Freeman MW. Cellular cholesterol efflux in heterozygotes for Tangier disease is markedly reduced and correlates with high density lipoprotein cholesterol concentration and particle size. J Lipid Res 41:1125-1135;2000.

346. Sun Z, Larson IA, Ordovas JM, Barnard JR, Schaefer EJ. Effects of age, gender, and lifestyle factors on plasma apolipoprotein A-IV concentrations. Atherosclerosis 151:381-388;2000.

347. Jenner JL, Jacques PF, Seman LJ, Schaefer EJ. Ascorbic acid supplementation does not lower plasma lipoprotein(a) concentrations. Atherosclerosis 151:541-544;2000.

348. Asztalos BF, Roheim PS, Milani RL, Lefevre M, McNamara JR, Horvath KV, Schaefer EJ. Distribution of apoA-I containing HDL subpopulations in patients with coronary heart disease. *Arterioscler Thromb Vasc Biol* 2000;20:2670-2676.

349. Schaefer EJ, Brousseau, ME. Benefits of reducing low-density lipoprotein cholesterol concentrations to <100 mg/dl. *Preventive Cardiol* 2000;2:136-139.

350. Brousseau ME, Schaefer EJ. Diet and coronary heart disease: clinical trials. Curr Athero Reports 2000;2:487-493.

351. Meigs JB, Ordovas JM, Cupples LA, Singer DE, Nathan DM, Schaefer EJ, Wilson PW. Apolipoprotein E isoform polymorphisms are not associated with insulin resistance: the Framingham Offspring Study. Diabetes Care 2000;23:669-674.

352. Shearman AM, Ordovas JM, Cupples LA, Schaefer EJ, Harmon MD, Shao Y, Keen JD, DeStefano AL, Joost O, Wilson PW, Housman DE, Myers RH. Evidence for a gene influencing the TG/HDL-C ratio on chromosome 7q32.3-qter: a genome-wide scan in the Framingham study. Hum Mol Genet 2000;9:1315-1320.

353. McNamara JR, Shah PK, Nakajima K, Cupples LA, Wilson PWF, Ordovas JM, Schaefer EJ. Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study. *Atherosclerosis* 2001;154:229-236.

354. Millar JS, Lichtenstein AH, Ordovas JM, Dolnikowski GG, Schaefer EJ. Human triglyeride-rich lipoprotein apoE kinetics and its relationship to LDL apo B-100 metabolism. Atherosclerosis 155:477-485;2001.

355. Lichtenstein AH, Jauhiainen M, McGladdery S, Ausman LM, Jalbert SM, Vilella-Bach M, Ehnholm C, Frohlich J, Schaefer EJ. Impact of hydrogenated fat on high density lipoprotein subfractions and metabolism. J Lipid Res 42:597-604;2001.

356. Schaefer EJ, Augustin JL, McNamara JR, Seman LJ, Bourdet KL, Meydani MM, Holay S. Lipid lowering and weight reduction by home-delivered dietary modification in coronary heart disease patients taking statins. Am J Cardiol 87:1000-1003;2001.

357. Lahoz C, Schaefer EJ, Cupples LA, Wilson PWF, Levy D, Osgood D, Parpos S, Pedro-Botet J, Daly JA, Ordovas JM. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. Atherosclerosis 154:529-537;2001.

358. Asztalos BF, Brousseau ME, McNamara JR, Horvath KV, Roheim PS, Schaefer EJ. Subpopulations of high-density lipoproteins in homozygous and heterozygous Tangier disease. Atherosclerosis 156:217-225,2001.

359. Sun Z, Lichtenstein AH, Dolnikowski GG, Welty FK, Schaefer EJ. Human apolipoprotein A-IV metabolism within triglyceride-rich lipoproteins and plasma. Atherosclerosis 156:363-372;2001.

360. Maki KC, Davidson MH, Umporowicz DM, Schaefer EJ, Dicklin MR, Ingram KA, Chen S, McNamara JR, Gebhart BW, Ribaya-Mercado JD, Perrone G, Robins SJ, Franke WC. Lipid responses to plant-sterol-enriched reduced-fat spreads incorporated into a National Cholesterol Education Program Step 1 diet. Am J Clin Nutr 74:33-43;2001.

361. Lyu LC, Yeh CY, Lichtenstein AH, Li Z, Ordovas JM, Schaefer EJ. Association of sex, adiposity, and diet with HDL subclasses in middle aged Chinese. Am J Clin Nutr 74:64-71;2001.

362. Saltzman E, Das SK, Lichtenstein AH, Dallal GE, Corrales A, Schaefer EJ, Greenberg EJ, Roberts SB. An oat-containing hypo caloric diet reduces blood pressure and improves lipid profile beyond effects of weight loss in men and women. J Nutr 131:1465-1470;2001.

363. McKenney JM, McCormick LS, Schaefer EJ, Black DM, Watkins ML. Effect of niacin and atorvastatin on lipoprotein subclasses in patients with atherogenic dyslipidemia. Am J Cardiol 88:270-274;2001.

364. Russo GT, Meigs JB, Cupples LA, Demissie S, Otvos JD, Wilson PWF, Lahoz C, Cucinotta D, Couture P, Mallory T, Schaefer EJ, Ordovas JM. Association of the Sst-1 polymorphism at the APOC3 gene locus with variations in lipid levels, lipoprotein subclass profiles and coronary heart disease risk: the Framingham Offspring Study. Atherosclerosis 158:173-82,2001.

365. Pedro-Botet J, Schaefer EJ, Bakker-Arkema RG, Black DM, Stein EM, Corella D, Ordovas JM. Apolipoprotein E genotype affects plasma lipid response to atorvastatin in a gender specific manner. Atherosclerosis 158:183-94,2001.

366. Sun Z, Welty FK, Dolnikowski GG, Lichtenstein AH, Schaefer EJ. Effects of a National Cholesterol Education Program Step II Diet on apolipoprotein A-IV metabolism within triacylglycerol-rich lipoproteins and plasma. Am J Clin Nutr 2001;74:308-14.

367. Davidson MH, Maki KC, Umporowicz DM, Ingram KA, Dicklin MR, Schaefer E, Lane RW, McNamara JR, Ribaya-Mercado JD, Perrone G, Robins SJ, Franke WC. Safety and tolerability of esterified phytosterols administered in reduced-fat spread and salad dressing to healthy adult men and women. J Am Coll Nutr 20:(4)307-319,2001.

368. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB, for the VA-HIT Study Group. Relation of gemfibrozil treatment and lipid levels with major coronary events. VA-HIT: A randomized controlled trial. JAMA 2001;285:1585-91.

369. Schaefer EJ, Brousseau ME, Diffenderfer MR, Cohn JS, Welty FK, O'Connor J, Dolnikowski GG, Wang J, Hegele RA, Jones PJ. Cholesterol and apolipoprotein B metabolism in Tangier disease. Atherosclerosis 2001;159:231-236.

370. Schaefer EJ, Audelin MC, McNamara JR, Shah PK, Tayler T, Daly JA, Augustin JL, Seman LJ, Rubenstein JL. Comparison of fasting and postprandial plasma lipoproteins in subjects with and without coronary heart disease. Am J Cardiol 2001;88:1129-1133.

371. Galluzzi JR, Cupples LA, Otvos JD, Wilson PWF, Schaefer EJ, Ordovas JM. Association of the A/T54 polymorphism in the intestinal fatty acid binding protein with variations in plasma lipids in the Framingham Offspring Study. Atherosclerosis 159:417-424,2001.

372. Corella D, Tucker K, Lahoz C, Coltell O, Cupples LA, Wilson PWF, Schaefer EJ, Ordovas JM. Alcohol drinking determines the effect of the apoE locus on LDL cholesterol in men: the Framingham Offspring Study. Am J Clin Nutr 2001;73:736-745.

373. Brousseau ME, Bodzioch M, Schaefer EJ, Goldkamp AL, Kielar D, Probst M, Ordovas JM, Aslanidas C, Lackner K, Rubins HB, Collins D, Robins SJ, Wilson PWF, Schmitz G. Common variants in the gene encoding ATP-binding cassette transporter 1 in men with low HDL cholesterol levels and coronary heart disease. Atherosclerosis 154:607-611,2001.

374. Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, Wilson PWF, Schaefer EJ, Tucker K. Polyunsaturated fatty acids modulate the effects of the apoA-I, 6-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner. The Framingham Study. Am J Clin Nutr 75:38-46,2002.

375. Schaefer EJ. E.V. McCollum Award Lecture: Lipoproteins, nutrition, and heart disease. Am J Clin Nutr 2002;75:191-212.

376. Lichtenstein AH, Ausman LM, Jalbert SM, Vilella-Bach M, Jauhiainen M, McGladdery S, Erkkila AT, Ehnholm C, Frohlich J, Schaefer EJ. Efficacy of a therapeutic lifestyle change/step 2 diet in moderately hypercholesterolemic middle-aged and elderly female and male subjects. J Lipid Res 2002;43:264-273.

377. Sung NH, Leka LS, Lichtenstein AH, Ausman LM, Schaefer EJ, Meydani SN. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. J Lipid Res 2002,43:445-452.

378. Lichtenstein AH, Ausman LM, Jalbert SM, Vilella-Bach M, Jauhiainen M, McGladdery S, Erkkila AT, Ehnholm C, Frohlich J, Schaefer EJ. Efficacy of a therapeutic lifestyle change/step 2 diet in moderately hypercholesterolemic middle-aged and elderly female and male subjects. J Lipid Res 2002;43:264-273.

379. Sung NH, Leka LS, Lichtenstein AH, Ausman LM, Schaefer EJ, Meydani SN. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. J Lipid Res 2002;43:445-452.

380. Batista MC, Schaefer EJ. Diagnosis and Management of Lipoprotein Abnormalities. Nutr Clin Care 2002;5:115-123.

381. Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM, Wilson PWF. Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the Framingham Offspring Study. Diabetes Care 2002;25:989-994.

382. Lamon-Fava S, Schaefer EJ, Garuti R, Salen G, Calandra S. Two novel mutations in the sterol 27-hydroxylase gene causing