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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371).

2. Section 101.71 is amended by adding new paragraph (e) to read as follows:

§ 101.71 Health claims: claims not authorized.

* * * * *

(e) Zinc and immune function in the elderly (insert cite and date of publication in the **Federal Register** of the final rule).

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 91-27163 Filed 11-26-91; 8:45 am]

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21 CFR Part 101

[Docket No. 91N-0103]

RIN 0905-AB67

Food Labeling: Health Claims and Label Statements: Omega-3 Fatty Acids and Coronary Heart Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing not to authorize the use on foods, including dietary supplements, of health claims relating to the association between omega-3 fatty acids and coronary heart disease (CHD). FDA has reviewed the scientific data on this topic and has tentatively concluded this evidence does not provide a basis upon which to authorize such a health claim. Examination of the epidemiological research on this topic revealed that the available studies applied only to the consumption of fish, which contain omega-3 fatty acids, and that it was not possible to ascribe any effects specifically to the omega-3 fatty acids. Examination of data from clinical studies revealed that the effects on blood lipids of fish oils containing omega-3 fatty acids were primarily a reduction of blood triglycerides, a blood lipid variable not considered to be an independent risk factor for CHD, but they had no effect on serum cholesterol, low-density lipoprotein (LDL) cholesterol, or high-density lipoprotein (HDL) cholesterol, the blood lipid variables most closely associated with risk of CHD. The scientific data are ambiguous on the effects of omega-3 fatty acids on blood pressure and other risk factors for CHD. Finally, the scientific data reveal unresolved safety issues: the potential for omega-3 fatty acids to increase LDL cholesterol of hyperlipidemics and to worsen control of blood glucose in diabetics.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John C. Wallingford, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-245-0835.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (Pub. L. 101-535) (the 1990 amendments), which amends the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary), and by delegation, FDA, to issue regulations authorizing nutrient content and health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under section 403(r) (1) (B) of the act (21 U.S.C. 343(r) (1) (B)).

Published elsewhere in this issue of the **Federal Register** is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs, and other nutritional substances (referred to generally as "substances") to a disease or health-related condition on food labels and in labeling. In this companion document, FDA has tentatively concluded that such claims would only be justified for substances in dietary supplements as well as in conventional foods if it determines, based on its review of the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(A)(ii), (b)(1)(A)(iv), and (b)(1)(a)(x)) that within 12 months of enactment, the Secretary shall issue

proposed regulations to implement section 403(r) of the act (21 U.S.C. 343(r)), and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including omega-3 fatty acids and heart disease, meet the requirements of the act. The 1990 amendments defined the subject topic area as the relationship between omega-3 fatty acids and heart disease, without defining heart disease. For the purpose of this document, heart disease is considered to be CHD, defined in the International Classification of Diseases as ischemic heart disease and related diseases, most notably heart attacks (Ref. 33). In this document, the agency will consider whether a claim on food or food products, including conventional foods and dietary supplements, about the relationship between omega-3 fatty acids and CHD, would be justified under the standard and criteria proposed in the companion document entitled "Food Labeling: General Requirements for Health Claims for Food."

B. Public Health Aspects

1. Coronary Heart Disease

Cardiovascular disease (disease of the heart or blood vessels) is a major public health problem in the United States. Cardiovascular diseases, primarily CHD and stroke, kill nearly as many Americans as all other diseases combined. Cardiovascular disease is also among the leading causes of disability. These facts hold despite the fact that over the past 15 years, the death rate for cardiovascular disease has declined dramatically: 35 percent for all cardiovascular diseases, 40 percent for CHD, and more than 50 percent for stroke (Ref. 36). Changes in lifestyles, risk factor reduction, and medical intervention were major contributors to this decline (Ref. 36).

CHD (disease of the arteries supplying blood to the heart muscle) is generally considered to be the most common, the most serious, and the earliest form of cardiovascular disease, frequently producing symptoms and health problems in middle-aged adults (Ref. 115). Despite a declining death rate from CHD since the mid 1960's, CHD still accounts for more deaths than any other disease or group of diseases (Ref. 34). More than 1.25 million heart attacks occur each year (two-thirds occur in men), and more than 500,000 people die as a result (Ref. 34). Significant degrees of CHD without easily detectable symptoms are also very common in the United States (Refs. 36 and 37). Thus the total affected population is considerably higher than the statistics on death and illness would indicate. In addition to its impact on the nation's health, CHD costs the U.S. economy over $50 billion annually (Ref. 37).

Because of the importance of cardiovascular disease, including CHD, as a public health problem, identification of modifiable risk factors has received considerable research and public health policy attention since the early part of this century. Fatty streaks and cholesterol were identified many years ago as prominent components of the blood vessel (arterial) lesions whose buildup caused a narrowing or blockage of the blood flow to the heart (Ref. 36). Following those early observations, a large base of scientific evidence has accumulated on the relationship of different types of dietary fats to the risk of CHD. Based on the weight of the scientific evidence now available, virtually all recent dietary guidelines for Americans, whether from the Federal government or from the health profession community, have noted the high dietary fat intake by the U.S. population and also the strong association of diets high in fat, particularly saturated fat, and cholesterol with increased risk of CHD (Refs. 34, 36, and 115).

An elevated blood cholesterol level has been implicated as a factor in the development of atherosclerosis (inadequate circulation of blood to the heart due to narrowing of the arteries), a major contributor to CHD. In atherosclerosis, a buildup of solid material in and on the walls of blood vessels occurs that restricts the flow of blood. This material, referred to as "plaque," usually contains an appreciable amount of cholesterol.

For many individuals, there appears to be a correlation between the severity of the plaque deposits and the levels of cholesterol in the blood. Furthermore, it is now established that a particular fraction of blood cholesterol, that associated with LDL, conveys an increased risk of atherosclerosis, while cholesterol associated with a different lipoprotein, HDL, conveys reduced risk of atherosclerosis and CHD (see companion document on health claims for cardiovascular disease and lipids, published elsewhere in this issue of the **Federal Register**). The relationship between atherosclerosis and very low-density lipoproteins (VLDL), independent of LDL, is not clear (Refs. 35, 36, and 115).

There does not appear to be a strong relationship between atherosclerosis and blood triglycerides (another type of blood lipid, although not a fraction of blood cholesterol). Any relationship between blood triglycerides and CHD found in studies disappears once the blood cholesterol components known to be related to CHD are taken into account (Refs. 4, 35, 36, and 115). A National Heart, Blood, and Lung Institute consensus conference is planned for the beginning of 1992 to reexamine the relationship between blood triglycerides, HDL, and CHD. Many questions about the buildup of plaque remain unanswered, however, including why plaque deposits are formed and to what extent the consumption of individual dietary components influence blood cholesterol levels.

2. Omega-3 Fatty Acids

Omega-3 fatty acids are lipids (fats) consisting of polyunsaturated fatty acids with three or more double bonds. The differences between saturated fatty acids and unsaturated fatty acids are discussed in the document on nutrient content claims on fat, saturated fat, and cholesterol published elsewhere in this issue of the **Federal Register**. Their unique characteristic is the location of the first double bond, which occurs at the third carbon from the methyl (or omega) end of the fatty acid. The family of omega-3 fatty acids includes linolenic acid (18 carbons, 3 double bonds), which is found predominantly in plant oils, and eicosapentaenoic acid (EPA, 20 carbons, 5 double bonds) and docosahexaenoic acid (DHA, 22 carbons, 6 double bonds), which are found in fish and other marine animals. Linolenic acid is a precursor of the two longer chain omega-3 fatty acids. However, not all linolenic acid is converted to EPA or DHA. Omega-3 fatty acids cannot be synthesized in humans from other classes of fatty acids. Thus, they must be supplied by dietary sources.

The most common food source of longer chain omega-3 fatty acids is fatty fish, such as salmon and mackerel (Ref. 83). Another important dietary source of omega-3 fatty acids in the United States is chicken that have been fed fish meal. Bulk and encapsulated preparations enriched with omega-3 fatty acids are now available in the United States.

3. Relationship of Omega-3 Fatty Acids and CHD

Although polyunsaturated fatty acids other than omega-3 fatty acids may affect the risk of CHD, the 1990 amendments direct FDA to consider the relationship of omega-3 fatty acids to CHD (section 3 (b) (1) (A) (x) of the 1990 amendments). Most of the relevant research testing the hypothesis that omega-3 fatty acids reduce the risk of

CHD has been conducted using fish or fish oils rich in EPA and DHA because these particular fatty acids are known to have physiological effects. For this reason omega-3 fatty acids are defined as EPA and DHA in this document. Other omega-3 fatty acids related to EPA and DHA are not generally found in amounts as high as EPA and DHA, and their activity is thought to be via metabolism to EPA or DHA.

Two major mechanisms have been hypothesized for beneficial effects of omega-3 fatty acids, reduction in atherosclerosis and decreased formation of blood clots (thrombosis) either because of increased coagulation times or with concomitant increased dissolution of clots that may be formed.

Much of the data on omega-3 fatty acids has been collected in populations with risk factors for CHD, including high dietary saturated fat, hyperlipidemia (high blood cholesterol or triglycerides), high blood pressure, tobacco smoking, stress, and sedentary lifestyle.

A reduction in risk of CHD following consumption of foods that contain omega-3 fatty acids is not sufficient to support a relationship between omega-3 fatty acids and CHD, because foods that contain omega-3 fatty acids contain many other substances that may affect the risk of CHD. Furthermore, consumption of foods rich in omega-3 fatty acids may displace other foods from the diet that contain dietary components related to CHD. To establish a relationship between omega-3 fatty acids and CHD, any observed effect must be shown to be specifically from the specific omega-3 fatty acid component of the food.

C. Omega-3 Fatty Acids: Regulatory History

In the **Federal Register** of July 31, 1986 (51 FR 27461), FDA published a notice of the filing of a petition seeking affirmation that the use of menhaden oil and partially hydrogenated menhaden oil as direct human food ingredients is generally recognized as safe (GRAS). In the **Federal Register** of September 15, 1989 (54 FR 38219), FDA affirmed that hydrogenated and partially hydrogenated menhaden oil are GRAS (21 CFR 184.1472) for use as an edible fat or oil, as defined in 21 CFR 170.3(n) (12). The agency has not yet acted on the GRAS status of the use of nonhydrogenated menhaden oil.

In recent years, fish oil products bearing claims for beneficial cardiovascular effects appeared in the marketplace. In 1988, FDA issued regulatory letters concluding that claims for cholesterol-lowering properties of fish oil supplements were drug claims, and that the evidence did not support the claims (Ref. 45). In response, the industry contended that the claims on fish oil supplements were not intended to be drug claims but were intended to comply with FDA's proposed rule on health messages (52 FR 28843, August 4, 1987), subsequently withdrawn and reproposed (55 FR 5176, February 13, 1990). Although additional information was submitted in support of these health messages (hereinafter referred to as health claims), FDA informed the industry in 1990 that the additional data were not adequate to support the claims, because of the preliminary nature of the evidence and because of unresolved safety concerns (Ref. 46). In an advance notice of proposed rulemaking published in the **Federal Register** of August 8, 1989 (54 FR 32610), FDA requested comments on, among other things, how to reasonably permit the use of claims on food labels linking food components to the risk of chronic diseases. The agency did not, however, specifically mention the topic of omega-3 fatty acids and CHD.

D. Evidence Considered in This Review

The agency has reviewed all relevant scientific evidence relating to omega-3 fatty acids and CHD. The scientific evidence reviewed by the agency included recent comprehensive reviews and recommendations of the Federal government: "The Surgeon General's Report on Nutrition and Health" (Ref. 34); the National Institutes of Health's National Cholesterol Education Program (NCEP) Report on "Detection, Evaluation and Treatment of High Blood Cholesterol in Adults" (Ref. 35); and the NCEP Report "Population Strategies for Blood Cholesterol Reduction" (Ref. 36). Other comprehensive reports were also reviewed: the National Academy of Sciences 1989 Report "Diet and Health: Implications for Reducing Chronic Disease Risks" (Ref. 115); the 1986 FASEB report on "Review of the Epidemiological and Clinical Evidence on the Role of Omega-3 Fatty Acids in Health and Disease" (Ref. 83); the 1989 Mitre Report on "Health Effects of Refined Menhaden Oil" (Ref. 72); and the 1991 FASEB report on "Cardiovascular Effects from Omega-3 Fatty Acids" (Ref. 100). The agency updated the conclusions reached by these documents by reviewing all human studies published subsequent to these documents and all new review articles (Refs. 10, 21, 82, 84, 89, 91, 111, 112, 127, 161, and 162). However, surveys and cross-sectional or prospective studies, other than intervention studies, that had been published before 1988, which were used to generate the hypothesis of a relationship between omega-3 fatty acids and CHD, were also reexamined. Animal studies were considered to the extent that they clarified human studies or suggested possible mechanisms of action.

E. Comments Received in Response to FDA Request for Scientific Data and Information

To ensure that its review was complete, in the **Federal Register** of March 28, 1991 (56 FR 12932), FDA requested scientific data and information on the 10 topics, including omega-3 fatty acids and CHD, identified by section 3 (b) (1) (A) of the 1990 amendments. The agency received a total of 15 comments in response to this request. All relevant scientific information submitted was considered in the FDA scientific summary.

One comment was from a private citizen, who submitted a computer search of medical literature.

Three comments were from professional organizations, informing FDA of their position on health claims. A comment from the Association of Food and Drug Officials expressed concern that there be significant scientific agreement for any claim and enumerated steps to protect against unfounded claims. A comment from the Association of State and Territorial Public Health Nutrition Directors urged that the amount of nutrients in the total daily diet be an important consideration and expressed concern that labels might contain too much information to be helpful to the consumer. One comment from the American Health Foundation dealt with the relationship between omega-3 fatty acids and cancer. This comment is outside the scope of the rulemaking.

The Government of Canada stated that under Canadian law, proposed health claims regarding heart disease would be considered drug claims.

Ten comments (including one book) were submitted by professional or trade organizations for food/food supplement manufacturers or individual food or supplement manufacturers. One comment from a chemical manufacturer provided information regarding the requirement for vitamin E when supplemental omega-3 fatty acids are consumed. Three comments from manufacturers or distributors of dietary supplement products and one trade organization for dietary supplement products commented on approaches for regulating health claims. Five comments from trade organizations, food manufacturers, or manufacturers/

distributors of dietary supplement products described properties of omega-3 fatty acids and provided bibliographic information for scientific information of the topic. One supplement manufacturer provided a listing of proposals for research on omega-3 fatty acids and an unpublished paper on the utility of fish oils in providing dietary omega-3 fatty acids. One comment from a trade organization included a copy of proceedings of an international conference on the effects of omega-3 fatty acids on bleeding. No original data about the effects of omega-3 fatty acids on CHD were presented in any comment. The information submitted will be considered in the agency's discussion of the relevant scientific evidence.

II. Review of the Scientific Evidence

A. Federal Government Documents

"The Surgeon General's Report on Nutrition and Health" (Ref. 34) described studies that correlated increased fish intakes with reductions in risk of CHD, while noting that not all studies found a relationship. Regarding plasma lipids, the report stated that diets rich in omega-3 fatty acids:

> * * * generally showed variable reductions in total cholesterol and LDL cholesterol. In some cases, LDL increased; HDL levels were either unchanged or increased * * * The most consistent effect has been a reduction in triglyceride and VLDL.

The report acknowledged the significance of research into the relationship between omega-3 fatty acids and CHD but did not make any specific recommendations regarding the consumption of omega-3 fatty acids. Additionally, the report cautioned that the benefits in the cited studies had not been shown to be attributable to omega-3 fatty acid intake and could be from some other factor associated with fish consumption.

A similar position was taken by the NCEP of the National Institutes of Health (Ref. 35):

> * * * There is little evidence that omega-3 fatty acids are useful for reducing LDL-cholesterol levels. Although it has been postulated by some that they will reduce the risk for CHD, this has not been established. Furthermore, it is not known whether long-term ingestion of these fatty acids will lead to undesirable side effects. The use of fish-oil capsules as a supplement in a therapeutic diet for high-risk cholesterol levels is not recommended here * * *
> (Ref. 35, p. 33).

Furthermore, this NCEP document distinguished reported protective effects of fish consumption from alleged protective effects of omega-3 fatty acids from fish:

> * * * Consumption of omega-3 fatty acids should be differentiated from that of fish. Some fish are rich in omega-3 fatty acids while others are not. Epidemiological data suggest that frequent consumption of fish of any type, seemingly independent of omega-3 fatty acids, is associated with reduced CHD risk. Whether this is true or not, fish can serve as a useful substitute for meats that are richer in saturated fats. * * *
> (Ref. 35, p. 33).

The NCEP's Expert Panel on Population Strategies for Blood Cholesterol Reduction (Ref. 35) did not comment on the relationship between omega-3 fatty acids and CHD but like the two other reports above, noted that:

> * * * Supplementation of the diet with omega-3 polyunsaturates, without altering the intake of saturated fatty acids, does not cause a lowering of LDL-cholesterol. * * *
> (Ref. 35, p. 38).

"The Surgeon General's Report on Nutrition and Health" (Ref. 34) and the NCEP reports encouraged consumption of fish, but none found adequate evidence that omega-3 fatty acids could reduce the risk of CHD. Further, the NCEP Reports (Refs. 35 and 36) specifically did not recommend fish oil supplements and cited the lack of evidence of beneficial effects and long-term safety and undesirable side effects.

B. Other Reports

The National Academy of Sciences (NAS) Committee on Diet and Health noted that reports of low rates of CHD among Greenland Eskimos, which provided the basis for interest in a possible relationship between omega-3 fatty acids and CHD, were poorly documented. The NAS cited eight major reviews and numerous individual papers on the effects of omega-3 fatty acids on plasma lipids and lipoproteins and cited the indepth review of Herold and Kinsella (Ref. 67) on eicosanoid effects of EPA and DHA on hemostasis and on metabolism of omega-3 fatty acids. NAS concluded that:

> * * * Their [omega-3 fatty acids] effects on LDL cholesterol vary, and data on the long-term health effects of large doses on omega-3 polyunsaturated fatty acids are limited. Limited epidemiologic data suggest that consumption of one or two servings of fish per week is associated with a lower CHD risk, but the evidence is not sufficient to ascertain whether the association is causal or related to the omega-3 polyunsaturated fatty acid content of fish.

The NAS Committee went on to recommend that omega-3 supplements should not be used, stating:

> * * * Although consumption of fish one or more times a week has been associated with a reduced risk of coronary heart disease, the committee does not recommend the use of concentrated fish oil supplements, because there is insufficient evidence that they are beneficial and the absence of long-term adverse effects has not been established.

In 1986, FDA contracted with the Life Sciences Research Organization (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) to review the evidence for the role of omega-3 fatty acids in health and disease (Ref. 83). The report concluded that fish consumption provided:

> * * * some degree of protection against the development of cardiovascular disease. Most studies have found an inverse relationship between fish consumption and coronary heart disease mortality. The omega-3 fatty acids in fish have been presumed to be responsible for these effects, but whether other compounds in fish may be involved remains to be determined.

The LSRO report also concluded that:

> * * * Clinical trials of the use of omega-3 fatty acids to reduce serum lipid levels in patients with various genetic and induced hyperlipidemias have generally been positive,

apparently meaning triglycerides and VLDL, given the full text of the report.

The LSRO report also cautioned that:

> * * * Animal studies indicate the potential for several deleterious effects. Toxicological evaluation of products containing these fatty acids, especially fish oil concentrate and derivatives, is needed.

FDA contracted for another report by the Mitre Corporation to define health effects of refined menhaden oil, a rich source of omega-3 fatty acids. This report (Ref. 72) identified major effects of omega-3 fatty acids as alterations in production of various bioactive compounds, increased bleeding (with particular concern for various bleeding conditions such as childbirth, ulcers, hemophilia, and menstruation), reduced platelet aggregation, and attenuation of inflammatory response. It also noted that effects on blood lipids other than triglycerides were not clearly established.

A second LSRO report contracted by FDA as part of FDA's information gathering effort divided the topic into six areas: Hypertension; thrombosis; the growth of the atherosclerotic plaque; hyperlipidemia and lipoprotein disorders; diabetes mellitus; and clinical trials in coronary patients. Brief synopses of selected scientific reports were presented in each section, followed by a summary of the full report and conclusions. LSRO concluded that there may be a decrease in total cholesterol and LDL concentrations without HDL being decreased but did

not explain how these conclusions were reached (Ref. 100). It concluded that there was an effect of omega-3 fatty acids on the development of the atherosclerotic plaque but cited only animal studies as evidence. It concluded that omega-3 fatty acids affect platelet function but did not provide evidence that the altered platelet function would or would not reduce the risk of CHD in humans. It described an effect of omega-3 fatty acids on blood pressure but did not distinguish between healthy and hypertensive subjects. Finally, it concluded that there was a basis in international epidemiological findings for a relationship between fish consumption and CHD but did not demonstrate that the omega-3 fatty acids in fish were the components responsible for the association.

In summary, omega-3 fatty acids were considered separately from total fat and polyunsaturated fat by the Federal government and other comprehensive reports, because these fatty acids may produce protective effects on CHD. None of these documents except the LSRO report found the evidence for a relationship between omega-3 fatty acids and CHD to be persuasive.

C. Review of the Scientific Literature

1. Evidence Reviewed

A number of human studies have been reported since publication of the Federal government and other comprehensive reports described above. FDA conducted a thorough review of the literature published between January 1988 and August 1991 and found numerous research papers directly and indirectly related to the topic.

The criteria that the agency used to select pertinent papers for its review were: (1) Presentation of primary data and adequate descriptions of study design and methodologies sufficient to allow an evaluation of the quality and relevance of the study, (2) availability in English, (3) a quantitative estimate of the amount of omega-3 fatty acids used, and (4) quantitative data on CHD or a marker associated with CHD. In general, FDA considered randomized, double-blind, placebocontrolled trials to be more valuable than other types of human studies because they were less susceptible to bias, and because they allowed inference about specific effects of omega-3 fatty acids.

Epidemiologic evidence for an association between omega-3 fatty acids and heart disease is of two types, descriptive and analytical. Descriptive epidemiology studies include correlational studies in which grouped population data are examined. Analytical epidemiology studies examine exposure and outcome in the same individual. These include cross-sectional studies in which dietary exposure (e.g., fish consumption) is measured at a single point in time and compared to a health outcome such as CHD, prospective studies in which dietary exposure is measured at the beginning of the study and the subjects are followed over time to compare exposure and health outcome, and intervention studies.

The criteria used in evaluating epidemiological studies included the following: (1) The reliability and accuracy of the methods used in food intake analysis and measurement of disease endpoints, (2) the choice of control subjects (e.g., hospital-based versus population-based), (3) the representativeness of subjects, (4) the control of confounding factors in data analysis, (5) the potential for misclassification of individuals with regard to dietary exposure or disease endpoints, (6) the presence of recall bias and interviewer bias, and (7) the degree of compliance and how compliance was assessed.

FDA evaluated the weaknesses and strengths of individual studies (see "Assessment" column of Tables 1 and 2). It then assessed the strength of the overall combined evidence (e.g., epidemiologic studies including clinical trials and animal studies), taking into account the strength of the association, the consistency of findings, specificity of the association, evidence for a biological mechanism, and presence or absence of a dose-response relationship. FDA's conclusions reflect the strength of the data and consistency of the results.

FDA considered encapsulated fish oils concentrated in omega-3 fatty acids to be a valid test material because such use provided some basis to find that the component responsible for observed effects was the omega-3 fatty acids. The agency also gave greater weight to studies in which compliance was documented with a biological marker of treatment, e.g., plasma or tissue phospholipid content of EPA and DHA, when measurements demonstrated internal validity of the study, and when the amount of omega-3 fatty acids in the total diet was assessed than to studies that were not as carefully done. FDA considered the level of dietary intake of omega-3 fatty acids used in a study, because the agency considered it important that if this substance is to be considered to be a food, intake levels should be consistent with an amount that could be consumed in a normal diet.

While FDA considered studies using healthy populations to be the most relevant to the issue, it also considered studies in subpopulations with CHD or risk factors for CHD. FDA extrapolated positive results from at-risk populations cautiously, however. While FDA assumes that the same mechanism of CHD risk is affected by omega-3 fatty acids in both high risk and generally healthy populations, the agency believes that the high risk population may be more sensitive to showing an effect. When it did make extrapolations, FDA considered it essential that data showing the same effect in the general population were also available.

FDA evaluated the weaknesses and strengths of individual studies reviewed (Tables 1 and 2). FDA then assessed the strength of the overall combined evidence (e.g., epidemiologic studies and animal studies) in light of five factors, strength of association, consistency of findings, specificity of the association, presence or absence of a dose-response relationship, and biologic plausibility of an association.

2. Epidemiologic Evidence

a. *Correlational and cross-sectional studies.* A protective effect EPA and DHA on the development of CHD was hypothesized based on data comparing rates of heart disease among Greenland Eskimos and Danes (Ref. 39). Greenlanders residing in Greenland had approximately tenfold lower death rates from ischemic heart disease than Greenlanders who had migrated to Denmark. Dietary factors were hypothesized to explain this difference. Compared to immigrant Greenlanders living in Denmark, those living in Greenland consumed comparable amounts of total fat but ate less than half the saturated fat; over 50 percent more monounsaturated and polyunsaturated fat; and nearly five times the amount of omega-3 fatty acids. However, since whale blubber and seal (also sources of omega-3 fatty acids) were consumed by the Greenlanders much more frequently than fish, components of the Eskimo diet other than omega-3 fatty acids may be important determinants of CHD risk.

Three studies found an inverse relationship between fish consumption and CHD, from rural Japanese, urban Japanese, Japanese Americans, and Caucasian Americans (Ref. 76) and among various Japanese communities (Refs. 68 and 75).

However, other similar studies have not found a relationship between fish consumption and CHD. An international correlational study found only a modest association between fish consumption and CHD mortality across widely

different populations (Ref. 23), and when other dietary variables were controlled, the relationship was no longer apparent. CHD mortality in two provinces in Canada was not correlated to per capita fish intake in those provinces (Ref. 74), nor was a correlation found in two Norwegian communities (Ref. 141) with different fish consumption.

b. *Prospective studies.* A prospective study of 852 men found that an average consumption of 30 grams (g) of fish per day over a 20-year period reduced the risk of CHD by more than 50 percent (Ref. 87). Two reports from the United States also found a beneficial effect attributable to fish consumption (Refs. 38 and 137).

Other studies in Honolulu (Ref. 25) and Norway (Ref. 158) did not find any relationship between fish consumption and risk of CHD. Also, a study from Sweden (Ref. 113) reported an effect, but it was not statistically significant. These nonintervention epidemiologic studies are summarized in Table 1.

One type of evidence that would support a causal relationship between two factors is a dose-response relationship, where the degree of effect of an active component is related to the amount of the component. In those studies that reported a protective effect of fish consumption on CHD, each found the effect was related to the amount of fish consumed (Refs. 87 and 137). One study related the risk to the calculated amount of omega-3 fatty acids in the diet (Ref. 38). The effect of fish consumption on CHD is seen with small amounts of fish (i.e., about 30 g per day (g/day)), and therefore, small amounts of omega-3 fatty acids (Ref. 88). The results from these studies are viewed by FDA as ambiguous. Not all the studies found a relationship between consumption of fish containing omega-3 fatty acids and CHD. Only one study related the protective effect to the calculated amount of dietary omega-3 fatty acids rather than to consumption of fish (Ref. 38). Other dietary variables known to be related to CHD were also correlated with fish consumption in these studies. For example, in the prospective study of 852 men (Ref. 87), a number of other dietary variables that may indepen dently be related to the risk of CHD were also related to fish consumption. In this study, men who consumed the largest amounts of fish also consumed significantly more alcohol and monounsaturated and polyunsaturated fatty acids than men who did not eat fish. Thus, dietary factors associated with fish intake other than omega-3 fatty acids may account for the observed positive correlations.

Furthermore, the estimated content of omega-3 fatty acids in the amount of fish reported to be protective against CHD is very low, so low that their level calls into question whether the omega-3 fatty acids in fish are the component responsible for the reported protective effect. Also, the dose-response relationships reported differ somewhat. In Kromhout et al. most of the reduction in risk occurred when only 1 to 14 g/day of fish were consumed (about 0.3 g EPA plus DHA) (Ref. 87). In contrast, the study that related CHD risk to estimates of omega-3 fatty acids consumed (rather than fish) found the effect was pronounced only among those who consumed the greatest amount of omega-3 fatty acids, 0.66 g/day on average (Ref. 38).

Finally, in the studies in which 20- or 25-year mortality from CHD was related to fish consumption (Refs. 87 and 137), dietary data were collected only during the first year of the study. Thus, these studies do not distinguish between a protective effect of fish consumption at an early point in life and an effect from chronic fish consumption. The shorter duration followup Multiple Risk Factor Intervention Trial (MRFIT) study estimated dietary consumption from 24-hour recall data collected approximately yearly over the 6-year followup and supports that continued consumption of omega-3 fatty acids, rather than simply early life consumption of fish, has a protective effect (Ref. 38).

Overall, these studies are considered to be ambiguous because they are not capable of distinguishing the effects that are specific to omega-3 fatty acids from those that are related to fish consumption.

c. *Intervention studies.* Although experimental trials are considered to be the most useful to infer causal relationships, only one study of this type has been completed on omega-3 fatty acids and CHD (Ref. 16). The study was conducted among 2,033 male survivors of previous heart attacks who were advised to increase their consumption of fish and of fiber and to decrease fat intake. All combinations of these three types of advice were given. Another group, serving as a control, received no advice at all. Mortality was assessed over the following 2 years. Those subjects who were advised to increase fish consumption had a 29 percent lower death rate, attributable entirely to deaths from CHD, than subjects advised to increase fiber or decrease fat consumption but not advised to increase fish consumption. However, the rate of occurrence of a second heart attack was not different between the fish-advice and nonfish-advice groups. Fish consumption was measured by a dietary questionnaire in a subset of subjects in the fish-advice group. The amount of fish reported by Burr et al. to be protective was modest, approximately 200 to 400 g fish per week (Ref. 16).

Some (14 percent) of the men at 6 months into the trial, and more (22 percent) at the end of the 2-year trial, consumed encapsulated fish oil rather than the prescribed amount of fish (300 g per week, or about 2.5 g EPA per week). However, separate data for the fish consumers and fish oil consumers were not presented, so the effects of fish oils cannot be compared to the effects of fish consumption. No dose-response analysis was performed, and no biochemical data were reported documenting the ingestion and incorporation of omega-3 fatty acids. Data were not reported on the effects of advice about fish consumption on markers of CHD, i.e., serum cholesterol (although it was noted that the fish-advice group had increased total serum cholesterol at 6 months and unchanged total cholesterol after 2 years), making it difficult to put the results of this study into context of other studies reporting similar data.

3. Evidence Relating Omega-3 Fatty Acids to Intermediate or Surrogate Markers of CHD

Most information about the effects of omega-3 fatty acids on CHD has been derived from clinical trials using concentrated fish oils enriched in EPA and DHA and, in some cases, in purified methyl or ethyl esters of EPA and DHA. These studies have not measured occurrence of heart attack or CHD death as an endpoint but instead used surrogate markers for CHD, e.g., serum lipids, blood pressure, measures of clotting, and clot dissolution. While these markers are limited in their ability to predict CHD, they are easily measured and provide important information about intermediates in the disease processes. The amount of omega-3 fatty acid intake in studies using fish oils is usually greater than the amount of omega-3 fatty acids in fish diets associated with reduced risk of CHD.

The clinical effects of omega-3 fatty acids from fish oils are generally evaluated relative to two categories: Effects on atherosclerosis and on blood lipids closely correlated with atherosclerosis, and effects on thrombosis (aggregation of blood platelets and fibrin leading to blood clot formation) and hemostasis (the arrest of bleeding). However, there are other potential effects of omega-3 fatty acids

that could affect risk of CHD that also require evaluation, e.g., whether omega-3 fatty acids reduce blood pressure. Table 2 is a summary of data from clinical trials published since 1987.

a. *Atherosclerosis*—i. *Blood lipids.* The effects of fish oils and high fish diets on blood lipids have been studied because such effects, if demonstrated, would represent a mechanism by which omega-3 fatty acids could reduce risk of CHD. Although some studies of high fish diets reported reductions of serum cholesterol and LDL and VLDL cholesterol, these studies also involved substantial changes in other components of the diet, primarily the replacement of saturated fat with unsaturated fat (Refs. 17, 62, and 117). Thus, the effects could not be definitively attributed to omega-3 fatty acids. Most recent studies have used fish oil supplements containing omega-3 fatty acids rather than fish and have used a placebo containing alternate polyunsaturated fatty acids in an attempt to avoid confounding effects of other diet components.

The predominant blood lipid effects of fish oils in normal subjects, in subpopulations with diseases or medical conditions associated with increased risk of CHD, and in subjects with diagnosed CHD are decreased plasma triglycerides and VLDL which is rich in triglyceride and cholesterol. However, these blood lipids are not generally considered independent risk factors for CHD (Refs. 35, 36, and 115). The effects on total cholesterol, LDL cholesterol, and HDL cholesterol have been variable.

Most studies of normal, healthy adults show no significant effect that can be specifically attributed to fish oil on serum total cholesterol, LDL, or HDL cholesterol (Refs. 9, 14, 15, 17, 20, 24, 31, 43, 48, 49, 53, 54, 59, 73, 98, 99, 104, 109, 146, 150, 156, and 166). Only four of these studies were carried out in a randomized, double-blinded, placebo-controlled design (Refs. 6, 24, 54, 73, and 166), although other studies either randomized the subjects (Refs. 9, 14, 49, and 54) or matched test subjects and controls (Refs. 15, 20, 31, and 156). Some used a crossover design (Refs. 14 and 17). Some studies reported no effects of fish oils or used relatively small numbers of subjects, and may not have had sufficient statistical power to detect a difference (Refs. 15, 24, 31, 48, 59, 99, 104, and 146). Two studies used fish as the source of omega-3 fatty acids (Refs. 17 and 156) which does not provide a basis on which to separate the effects of omega-3 fatty acids from the effects of other components of fish or on which to separate the effects of polyunsaturated fatty acids from the effects of omega-3 fatty acids. The studies ranged in duration from only 3 weeks of treatment to 12 weeks.

The studies with the most rigorous design and largest number of subjects found that supplementation with fish oils, or increasing dietary fish consumption, resulted in decreased blood triglycerides among normal, healthy subjects (Refs. 9, 49, 54, and 156). The only studies among normal subjects where no decrease in triglycerides was found either used very small doses in a small numbers of subjects (Croset et al. 1990 used 100 mg EPA/d in 8 subjects; Lex 1990b used 900 mg EPA plus DHA/d in 9 subjects), or the decrease was marked but not statistically significant (Refs. 99 and 73).

The studies with the most rigorous design and largest number of subjects also found that there was no effect of fish oils on total serum cholesterol (Refs. 6, 9, 14, 49, 54, 73, and 166). The only study reporting decreased total cholesterol fed 30 to 40 percent of calories from fish oil, confounding effects of omega-3 fatty acids and polyunsaturated fatty acids (Ref. 59).

These same studies found no change in LDL cholesterol, except that Fumeron et al. (1991) reported increased LDL cholesterol. Similarly, most studies did not find a significant effect on total HDL cholesterol (Refs. 6, 9, 14, 31, 54, 73, and 166). Flaten et al. (1990) and Takimoto et al. (1989) reported a decrease in total HDL cholesterol at 6 weeks of supplementation, but these studies used relatively high doses (7.7 g EPA plus DHA/d and 8.2 g EPA plus DHA/d, respectively). Neither study controlled for polyunsaturated fatty acids. Compared to saturated fat diets, fish diets may reduce HDL cholesterol (Ref. 17), although an increase in HDL cholesterol was reported after fish paste, compared to meat paste supplements, were added to the diet (Ref. 17). Some investigators (Refs. 9 and 54) have reported that supplementation with fish oils increased HDL_2 cholesterol, the particular subfraction of HDL that is most closely related to decreased CHD risk (Ref. 3), whereas others found no change (Refs. 14 and 49).

Data have also been reported on the apoproteins associated with LDL (apoB) and with HDL (apoA), in contrast to the cholesterol associated with these lipoproteins. No effect of fish oils has been found (Refs. 6, 54, and 73). Although there are fewer data reported, it appears that apoprotein components of lipoproteins respond in the same manner as the cholesterol component, i.e., lower after feeding polyunsaturates, including fish oils, than after a saturated fat diet (Refs. 43 and 53).

Thus, except for a study in which very large amounts of fish oils were fed, recent studies have not found fish oils to modify total serum cholesterol, LDL cholesterol, HDL cholesterol, or the apoproteins associated with these lipoproteins in normal subjects. The possibility of a selective increase by fish oils containing omega-3 fatty acids of HDL_2 (a fraction of HDL) cholesterol, which is inversely related to CHD, is the most promising change in blood lipids yet reported, but the data reported to date are equivocal.

There have been many studies recently on the effects of fish oils on serum lipoproteins among hyperlipidemic subjects (people with elevated blood cholesterol with or without elevated triglycerides), hypertriglyceridemic subjects (people with high blood triglycerides), and subjects who already have CHD. Most of these studies had strict designs, including randomization with or without crossover, blinding, and placebo treatments (Refs. 26, 29, 43, 61, 63, 80, 105, 114, 119, 121, 129, 140, 150, 164, and 166), but similar results were found in less rigorously controlled studies (Refs. 28, 60, 107, 130, 146, and 148). As in normal, healthy persons, the most reproducible effect of fish oils containing omega-3 fatty acids in these subpopulations is a decrease in serum triglycerides with the most marked reductions for those subjects with highest starting values. In addition, in common with the results in normal subjects, most studies in hyperlipidemics found no change in total serum cholesterol. In contrast to normal subjects, however, most studies on hyperlipidemic subjects reported an increase in LDL cholesterol following fish oil supplementation (Refs. 26 (for males), 60, 61, 63, 80, 94, 114, 119, 121, 130, 140, 146, 164, and 166), although a few found no change compared to olive oil (Refs. 29, 105, and 107) or may not have had sufficient statistical power to detect a difference (Ref. 43). One reported a decrease (Ref. 148). The level of apoB has also usually been found higher after fish oil consumption (Refs. 29, 43, 60, 61, 133, and 140). HDL cholesterol is usually reported as not changed (Ref. 114), but some increases and decreases have been reported (Refs. 26 (males), 29, 63, and 130). Takimoto et al. (1989) and Radack et al. (1990) reported lower HDL_2 cholesterol.

ii. *Vessel wall effects.* Another way that omega-3 fatty acids could affect the process of atherosclerosis is through

changing the way cells of blood vessels respond to factors that promote atherosclerosis. The cells of blood vessels produce compounds from omega-3 fatty acids that have many functions related to the health of the blood vessel (Refs. 41, 48, 160, also see animal studies in Refs. 50, and 138). Some of these functions are keeping the muscle cells of the blood vessel wall relaxed, keeping the vessel elastic and pliant, and dissolving small blood clots attached to blood vessels. An increase in consumption of omega-3 fatty acids results in increased production of the compounds that relax or dilate the vessel wall at the same time that they decrease the formation of compounds that constrict the vessel wall (Ref. 28).

Through the compounds they form in the blood vessel wall, omega-3 fatty acids may prevent the infiltration of certain white blood cells, called monocytes, into the vessel wall, and monocytes themselves produce compounds that increase the inflammatory process (Refs. 82 and 162). Recent studies reported that white blood cells taken from normal men and hyperlipidemic men who consumed fish oil containing EPA plus DHA at levels as low as 1.3 g/day for 6 weeks have a reduced chemotactic response, i.e., they are not as strongly attracted to stimulants (Refs. 135 and 136).

An area studied recently is the effect of fish oils on restenosis, that is, the reclosing of a vessel after mechanical opening. Although the use of omega-3 fatty acids in this context is clearly a drug usage, these studies have been cited as evidence of the role of omega-3 fatty acids in the maintenance and normalization of vessel function. One study found reduced rates of restenosis when fish oil was given in addition to two other anticoagulant drugs beginning about the time the subjects underwent angioplasty (the term for the procedure used to open the vessel) (Ref. 30). However, this study was not blinded, and the results are limited to fish oil used in combination with other drugs. Other studies where double-blind conditions were maintained, where placebo controls were used, and where restenosis was confirmed by angiography, show no effect of fish oils (Refs. 56, 106, and 120).

In summary, the recent data on blood lipid responses of persons and among groups at high risk of CHD do not support the use of omega-3 fatty acids to reduce the risk of CHD. There is no effect of omega-3 fatty acids on blood cholesterol, LDL cholesterol, or apoB or apoA, and the effect on HDL cholesterol is ambiguous. There is very little data on the effects of omega-3 fatty acids on blood vessel integrity in humans, and it has not been established whether the type and magnitude of effects of compounds produced from omega-3 fatty acids results in a reduced risk for CHD.

b. *Thrombosis and hemostasis.* The other primary area in which omega-3 fatty acids may affect the risk of CHD is through their hypothesized effect on the formation and dissolution of blood clots (thrombosis and hemostasis). A decrease in clot formation, or an increase in the breakdown of clots, is generally believed to help prevent CHD deaths.

i. *Bleeding times.* One effect of omega-3 fatty acids is an increase in the time it takes for a small cut to stop bleeding. Bleeding times are often used as an indicator of the balance between necessary clotting (to prevent excessive bleeding) and excessive clotting (which may occlude blood flow). Increased bleeding times were observed among Greenland Eskimos by Dyerberg and Bang (Ref. 39) and were interpreted to be one of the reasons these people had reduced CHD risk. Many studies since have reported that fish oil supplementation increases bleeding times in normal subjects (Refs. 98 and 166) and in subjects either with risk factors for CHD or with diagnosed CHD (Refs. 28, 59, 95, 144, 145, and 166). However, some of these studies used quite high doses. Harris et al. used 28 g EPA plus DHA/d (Ref. 59). Levinson et al. used 50 milliliter (mL) maximum EPA or 18 g EPA plus DHA/d or used anticoagulants concurrently (Ref. 144). Others reported no effect (Ref. 57).

The bleeding time increase with fish oils is additive with increased bleeding following aspirin (Ref. 64). However, most reports suggest that serious bleeding is not an issue in patients supplemented with omega-3 fatty acids from fish oils even when fish oils were used in conjunction with aspirin (Refs. 22, 28, 56, 106, and 144). One recent review concluded that bleeding times are not correlated with serious bleeding (Ref. 125).

ii. *Platelet aggregation.* Another measure of clotting affected by omega-3 fatty acids is the aggregation of platelets, blood components that initiate clotting. This is an important area of study because spontaneous platelet aggregation has been reported to be inversely related to occurrence of heart attacks and CHD deaths in a population of survivors of a heart attack (Ref. 152). Platelet aggregation is generally considered to be decreased by fish oil consumption (Refs. 67, 70, 86, 159, and 162 for reviews; also in normal subjects see Refs. 2, 6, 24, 54, 96, 143, and 166). There were two studies among normal healthy subjects that found no effect (Refs. 73 and 150), but that result may be attributable to the small sample size. Reduced platelet aggregation has been reported for diseased populations (Ref. 28), except that there are other studies in which no effect was found (Ref. 93 through 95, and 134), possibly because of small numbers of subjects.

Other measures of platelet function, e.g., platelet activation, adhesiveness, and survival, are also affected by fish oils. Fish oil reduces platelet activation and adhesiveness and increases platelet survival (Refs. 94, 96, and 144).

Also, other blood-related properties besides platelets are affected by fish oils. Red blood cell deformability is increased and blood viscosity is decreased after consumption of fish oils (Refs. 18, 42, 145, and 160), which may affect the consequence of formation of small clots.

The relationship between platelet aggregation and the risk of heart attacks or CHD death in the general population is an important line of evidence that would support drug claims and perhaps health claims for omega-3 fatty acids. Although there is some evidence that changes in platelet aggregation may help prevent second heart attacks (Refs. 66 and 112), it has not been shown that changes in platelet aggregation in the general population will reduce the risk of CHD. The importance of other platelet or blood effects of omega-3 fatty acids on risk of CHD also has not been established.

iii. *Regulators of bleeding.* Markers for CHD other than cholesterol and blood lipids have also been found. One is the level of a plasma protein called fibrinogen, which is involved in blood clotting (Ref. 102). The effects of fish oils containing omega-3 fatty acids on fibrinogen were evaluated in 10 studies. One study had no control (Ref. 134), and one was confounded by concurrent anticoagulant therapy (Ref. 144). One compared fish paste to meat paste, so the effect of omega-3 fatty acids cannot be distinguished from other components in fish (Ref. 40). Among the remaining seven studies, six were randomized studies and one was a matched, controlled study. Four found a significant reduction in fibrinogen levels compared to olive oil (Refs. 49, 71, and 117) or soybean oil (at a high dose of omega-3 fatty acids only, not at a low dose, Ref. 57). One study found reduced fibrinogen in the group fed fish but not in the group fed fish oil (Ref. 20), raising the possibility that components of fish

other than the omega-3 fatty acids were responsible for the effect. In the remaining two studies, no effect was found compared to a corn oil placebo (Refs. 11 and 118), and one study showed that both corn oil and fish oil reduced fibrinogen comparably (Ref. 118), suggesting that the effect was produced by polyunsaturated fatty acids, not specifically omega-3 fatty acids.

Similarly, no clear relationship between omega-3 fatty acids and factors involved in dissolving blood clots has emerged (Refs. 29, 104, 150, and 131). Finally, a particular component of one of the lipoproteins, lipoprotein (a) is also considered a marker for atherosclerotic disease by its regulation of fibrinolysis, but the effects of omega-3 fatty acids on lipoprotein (a) have only been reported in abstracts.

iv. *Blood pressure.* One of the most consistently reported effects of omega-3 fatty acids from fish oils is a decrease in blood pressure. Among normal healthy subjects, reductions have been reported for systolic blood pressure (Refs. 6, 24, 49, and 80); reductions in diastolic blood pressure have not been significant (except Haglund et al. 1990, but the data for Haglund et al. 1990 are confounded because separate data were not reported for healthy subjects and subjects with CHD (Ref. 57)). One study among normal, healthy men showed that a mixed dietary supplement containing fish oil reduced systolic blood pressure, whereas no effect was seen when the supplement contained linseed oil or safflower oil (Ref. 80). Other studies in normal, healthy adults found that the reduction in blood pressure following consumption of fish oils was comparable to the reduction after consumption of other polyunsaturated oils (Refs. 20 and 49) or found no significant change after consumption of fish oils (Refs. 9 and 73).

In one report of a study of hypertensives (Ref. 11), a moderate dose (5.1 g/day) of purified ethyl esters of EPA and DHA for 10 weeks reduced blood pressure proportionally to the increase in plasma omega-3 fatty acids. Interestingly, no effect of fish oil was found among those subjects who habitually consumed three or more meals of fish per week. Controlled studies among hypertensives and among diabetics found reductions in both systolic and diastolic blood pressure (Refs. 11, 77, 85, 101, and 147). Very high amounts of fish oil (50 mL/day) were used in two of these studies (Refs. 85 and 95), and the placebo in one study was olive oil, not a high polyunsaturated oil (Ref. 77), so it is not clear if the effect of fish oil was because of polyunsaturated fatty acids or omega-3 fatty acids.

Whether the magnitude and duration of any decrease in blood pressure persist after longer term consumption of omega-3 fatty acids is not known. The longest duration of supplementation in the above studies was 12 weeks.

These results for effects of omega-3 fatty acids on blood pressure of normal subjects are ambiguous. Some studies found a reduction in systolic blood pressure after consumption of fish oils containing omega-3 fatty acids, whereas others did not. None of the studies found a significant reduction in diastolic blood pressure. Therefore, it also remains to be established that the normal, healthy population will reduce their risk of CHD via a reduction in blood pressure following consumption of omega-3 fatty acids.

In summary, there are a few established effects of omega-3 fatty acids from fish oils on thrombosis and hemostasis. Standardized bleeding times are increased, and platelet aggregation and function are reduced. However, direct relationships between the changes in bleeding times or platelet function and risk of CHD have not been established. While there is an established relationship between blood pressure and CHD, it has not been shown that omega-3 fatty acids specifically affect blood pressure in normal subjects in a way that would provide a protective benefit toward the risk of CHD. Effects of omega-3 fatty acids on other markers linked with CHD, e.g., fibrinogen or lipoprotein (a), have not been established.

4. Other Relevant Information

a. *Animal studies.* Animal studies, where the atherosclerosis may be measured directly, provide some evidence of an anti-atherogenic effect for omega-3 fatty acids. Studies in rabbits (Refs. 65 and 165), pigs (Ref. 81), rhesus or African green monkeys (Refs. 27 and 116), and dogs (Ref. 90) reported that incorporation of omega-3 fatty acids in a diet designed to promote atherosclerosis actually reduced development of atherosclerotic disease. However, other animal studies showed no reduction, or an increase, in atherosclerotic disease after dietary supplementation with omega-3 fatty acids (Refs. 19, 47, 51, 69, 97, 122, 123, 126, and 151). Thus, there are some data from studies in animals which suggest the possibility of a beneficial effect of omega-3 fatty acids on CHD, however, the data are equivocal.

b. *Safety considerations.* Trials of the effects of fish oils containing omega-3 fatty acids among diabetics show that total cholesterol, LDL cholesterol, or apoB may increase (Refs. 7, 77, 79, 108, 110, and 128). While some studies among insulin-dependent diabetics found no significant effect of fish oils on the ability to maintain desired levels of blood glucose (Refs. 77 and 124), others reported impaired glucose control (Ref. 55). Other studies on noninsulin-dependent diabetics reported that fish oil resulted in increased-blood glucose (Refs. 44, 52, 128, and 130). Adverse effects on blood glucose control have been reported for subjects who were both hypertriglyceridemic and diabetic, either insulin-dependent (Ref. 94) or noninsulin dependent (Ref. 146). In one study there was an increase in the blood triglyceride level over and above the initial level after fish-oil supplementation was discontinued (Ref. 124). Thus, use of fish oils containing omega-3 fatty acids may pose particular additional risks among diabetics, regarding both serum lipids and glycemic control.

III. Tentative Decision not to Authorize a Health Claim Relating Ingestion of Omega-3 Fatty Acids to Reduced Risk of Coronary Heart Disease

In evaluating the scientific evidence, FDA considered the strength of association of omega-3 fatty acids with CHD or surrogate markers for CHD, the consistency of findings among the many studies, the specificity of the outcome to omega-3 fatty acids, the presence or absence of a dose-response relationship, and biologic plausibility of an association.

FDA has determined that there is inadequate evidence to show that increased consumption of omega-3 fatty acids will reduce the risk of CHD. Furthermore, the review of scientific information reveals potential serious safety concerns about the use of fish oils containing omega-3 fatty acids by subpopulations who are at increased risk for CHD.

FDA attempted to determine whether there was significant scientific agreement among experts that the totality of publicly available scientific evidence supported the claim that omega-3 fatty acids reduce the risk of heart disease. FDA reviewed the position taken in numerous Federal government and other authoritative scientific reports and evaluated the totality of publicly available scientific evidence that has become available since those reports were written. The tentative decision to deny a health claim is based on the conclusions reached

following review of these various sources of information and conclusions.

"The Surgeon General's Report on Nutrition and Health," the National Academy of Science's Report on "Diet and Health: Implications for Reducing Chronic Disease Risk," and the National Cholesterol Education Program's "Detection, Evaluation and Treatment of High Blood Cholesterol in Adults" each concluded that there was inadequate evidence of a relationship between consumption of omega-3 fatty acids and CHD. FDA has rereviewed all the relevant cross-sectional data from which a relationship between omega-3 fatty acids and CHD was hypothesized, and all clinical intervention data published since these Federal government and other authoritative reports documents to determine whether the additional evidence is adequate to support a health claim for omega-3 fatty acids.

The LSRO report reached a different conclusion than the other authoritative reports by finding a relationship between omega-3 fatty acids and CHD. The report used only selected evidence, much of it from animal experiments with no clinical counterpart. Furthermore, it did not distinguish between the normal population and diseased subpopulations. Finally, it relied on international epidemiologic findings of a relationship between fish consumption and CHD that was not shown to be specific to omega-3 fatty acids.

The surveys, cross-sectional studies, and non-intervention prospective studies do not support a relationship between consumption of omega-3 fatty acids and CHD. Only a few studies found an association between fish intake and CHD, while others have found no association. Thus, there was not consistency of findings. None of the studies that reported a relationship distinguished fish consumption from other factors associated with fish consumption, and therefore they did not demonstrate specificity. Even in those studies reporting a relationship between fish consumption and CHD, it was not clear that the effects were because of the omega-3 fatty acids in fish. Also, the omega-3 fatty acid content of the fish diet associated with reduced CHD was so low that the importance of omega-3 fatty acids is questionable, i.e., calling into question the biologic plausibility of the relationship.

The data from intervention studies also do not establish a relationship between omega-3 fatty acids and risk of CHD. The most compelling type of evidence to support a diet-disease relationship is a prospective, double-blinded, placebo-controlled intervention study, using CHD morbidity and mortality as endpoints. To date, there is only one such trial (Ref. 16). The results of that study showed that increased consumption of fish does not reduce the risk of a second heart attack but may reduce the risk that the attack will be fatal. However, as with the nonintervention study data, this study did not provide evidence to attribute the benefit to omega-3 fatty acid intake rather than some other factor associated with fish consumption (specificity). Furthermore, no data were reported for biochemical surrogate markers of CHD (blood lipids, measures of thrombosis or hemostasis), so this report cannot easily be integrated with results of studies where such data were reported (consistency).

Less persuasive than prospective studies in which CHD is measured, but still very useful, are prospective clinical trials in which surrogate markers for CHD are measured. These studies have usually used encapsulated fish oils providing omega-3 fatty acids in amounts comparable to or higher than the amount that would be consumed on a high fish diet (approximately one g EPA plus DHA per day), for periods of weeks to 6 months. These studies have not been designed to show an effect on the development of atherosclerosis, so evidence is lacking on that topic. Recent studies have not found beneficial effects on blood lipids from intake of omega-3 fatty acids in normal, healthy persons or in persons at risk for CHD, the same conclusion reached in the Federal government and other authoritative reports (Refs. 34 through 36, 63, and 115) regarding the effects of fish oils on serum lipids. This conclusion was also reached in numerous studies (consistency), some of which were large or multicenter (strength of association).

An increase in bleeding times and a decrease in platelet aggregation have been observed consistently in normal healthy individuals as well as in diseased persons who consumed fish oils. The effects of decreased platelet aggregation are plausibly related to the intake of omega-3 fatty acids, and there is a dose-response relationship. What has not been established, however, is that platelet aggregation is a bona fide surrogate risk factor for CHD in the general population.

Omega-3 fatty acids have been shown to reduce blood pressure in hypertensive people to a small degree, which may bear on a relationship between omega-3 fatty acids and CHD. The effect was not of large magnitude, but it is specific to omega-3 fatty acids, has been reported by a number of investigators, a dose response was found, and the effect is plausible. However, it has not been established that omega-3 fatty acids reduce blood pressure in normal subjects (lack of consistency, weak effect, absence of dose-response relationship). Additionally, it has not been demonstrated that the magnitude and duration of changes in platelet function or blood pressure observed in short-term studies will persist during long-term consumption of omega-3 fatty acids. Finally, the potential that omega-3 fatty acids may further increase the risk of CHD, through increases in LDL cholesterol or apoB among diabetics and hyperlipidemics, and the potential that omega-3 fatty acids may worsen control of blood glucose in diabetics, are significant safety concerns.

In conclusion, the totality of scientific evidence does not support the claim that omega-3 fatty acids reduce the risk of CHD.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(1) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Economic Impact

The food labeling reform initiative, taken as a whole, will have associated costs in excess of the $100 million threshold that defines a major rule. Therefore, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354), FDA has developed one comprehensive regulatory impact analysis (RIA) that presents the costs and benefits of all of the food labeling provisions taken together. The RIA is published elsewhere in this issue of the **Federal Register**. The agency requests comments on the RIA.

VI. Comments

Interested persons may, on or before January 27, 1992, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Receiv comments may be seen in the offic above between 9 a.m. and 4 p.m., Monday through Friday.

VII. Effective Date

FDA is proposing to make these regulations effective 6 months after the publication of a final rule based on this proposal.

VIII. References

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

1. Abbey, M., P. Clifton, M. Kestin, B. Belling, P. Nestel, "Effect of Fish Oil on Lipoproteins, Lecithin: Cholesterol, Acyltransferase, and Lipid Transfer Protein Activity in Humans," *Arteriosclerosis*, 10:85–94, 1990.

2. Agren, J. J., O. Hanninen, A. Hanninen, K. Seppanen, "Dose Responses in Platelet Fatty Acid Composition, Aggregation, and Prostanoid Metabolism During Moderate Freshwater Fish Diet," *Thrombosis Research*, 57:231–28, 1990.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR Part 101 be amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 is revised to read as follows:

Authority: Secs. 4, 5, 6 of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 501, 502, 505, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 355, 371)

2. Section 101.71(f) is amended by adding new paragraph (f) to read as follows:

§ 101.71 Health claims: claims not authorized.

* * * * *

(f) Omega-3 fatty acids and coronary heart disease (insert cite and date of publication in the **Federal Register** of the final rule).

Dated: November 4, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

Note: The following tables will not appear in the annual Code of Federal Regulations.

TABLE 1.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: SURVEYS, CROSS-SECTIONAL, AND CORRELATIONAL STUDIES

Reference	Design	Subjects	Duration	Base diet	Method	Comments	Findings
Bang et al. 1980 Advances in Nutrition Research 3:1.	Three expeditions: Dietary and blood lipids surveys. Comparison of CHD mortality rates and blood lipids between Greenlanders and Danes.	Cross-sectional studies including dietary survey. Blood lipids for 130 people, CHD rates based on hospital records.	3 short expeditions.	Greenlanders consumed 13.7 g omega-3 fatty acids/d and 5.4 g omega-6 fatty acids/d. Danes consumed 2.8 g omega-3 fatty acids/d and 10.0 omega-6 fatty acids/d.	Correlational	Other major risk factors for CHD including smoking, exercise, were not controlled. Sample size was small. Good hypothesis generating studies.	CHD rates and blood cholesterol were lower among Greenlanders in Greenland, who had high consumption of omega-3 fatty acid in marine foods, than among Greenlanders who migrated to Denmark, and who had lower omega-3 fatty acid consumption.
Crombie et al. 1987 European Heart Journal 8:560.	Cross-sectional	WHO mortality data and organization for economic cooperation and development statistics (Commodity).	Short-term	Per capita food consumption statistics.	Correlation between food consumption statistics and mortality rates from CHD in 16 nations.	Major CHD risk factors, spoilage, export of foods, genetic differences	Some nations with high fish consumption had high rates of CHD mortality and some nations with low fish consumption had low CHD mortality rates.
Curb and Reed 1985 New England Journal of Medicine 313:821.	Prospective study	7,615 healthy Japanese men.	12 years	Reported fish consumption (24 hour recall)	Adjusted for major risk factors associated with CHD.	Letter to the editor	No significant trend for CHD and fish consumption.
Dolecek and Grandits 1991 World Reviews of Nutrition and Dietetics 66:205.	Prospective study with periodic dietary surveys.	6,258 men	9 years	24 hour recall of dietary intake	Adjusted for major risk factors associated with CHD.	One of few studies to evaluate omega-3 fatty acid intake. Individuals with a history of CHD excluded from this study.	Mortality due to CHD inversely proportional to 20:5, 22:5 and 22:6 omega-3 fatty acids. Dose response effect reported.
Hirai et al. 1980 Lancet ii:1132.	Cross-sectional data used to correlate diet with CHD mortality rates in two villages with different fish consumption patterns.	42 healthy subjects from both fishing and farming communities in Chiba, Japan.	Short-term	Normal diet	Estimated fish, omega-3 fatty acid intake related to platelet aggregation, blood viscosity.	Hypothesis generating study; need cohort studies.	Inverse relationship between fish intake and rate of CHD mortality in the community.
Hunter et al. 1988 American Journal Preventive Medicine 4:5.	Nutritional survey data for fish consumption and CHD mortality data Canadian Atlantic provinces and Prairies.	Per capita average intakes of fish.	Short-term	Norma diet	Correlation of diet with CHD mortality rates.	Data do not relate to individuals, not adjusted for major risk factors for CHD. Need cohort data on food intake/CHD mortality.	Comparison did not indicate a measurable difference in CHD mortality rates despite greater fish consumption in Atlantic Provinces.
Iso et al. 1989 Internal Journal of Epidemiology 18:374.	Diet, clinical survey data correlated with CHD mortality rates. Cross-sectional design. Habitual fish intake questionnaire	136 men total 34–55 years old: rural Japanese, urban Japanese, Japanese Americans, Caucasian Americans.	Short-term	Normal diet	8–12 hour fasting blood samples for blood lipids. Systolic and diastolic blood pressure	Good survey techniques. Need cohort data on CHD mortality. This is primarily a hypothesis generating study.	Progressive decline in fish consumption from rural Japan to urban Japan, Japanese Americans and Caucasian Americans. There was an inverse correlation between CHD rates and fish consumption in these populations. Serum omega-3 fatty acids correlated most strongly with dark meat fish intake.
Kagawa et al. 1982 Journal Nutritional Sciences and Vitaminology 28:441.	Cross-sectional study	77 elderly persons on Kohame Island.	Short-term	Normal diet	Correlation	This is primarily a hypothesis generating study.	Higher serum levels of eicosapentaenoic acid and high density lipoprotein, lower salt intake and blood pressure in Islanders than mainland Japanese. Mortality due to hypertension and chronic heart disease lower than mainland Japan.

TABLE 1.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: SURVEYS, CROSS-SECTIONAL, AND CORRELATIONAL STUDIES—Continued

Reference	Design	Subjects	Duration	Base diet	Method	Comments	Findings
Kromhout et al. 1985 New England Journal of Medicine 312:1205.	Prospective study dietary questionnaire.	852 healthy men in Zutphen, Holland.	20 years	None	Adjusted or major CHD risk factors.	Inverse relationship between fish consumption and CHD mortality.	First study to report dose response. Noted lean fish, low in omega-3 fatty acids, had some protective effect against CHD.
Kromhout 1989 Journal Internal Medicine (suppl) 225:	Prospective study (number of subjects not given in paper). Review article presenting brief summary of previously unpublished information.	16 cohorts in 7 country study. Categorization of fish intake as group rather than as individuals.	15 years	Questionnaire at entry to survey level of fish consumption quintiles from <10 g/day to 200 g/day.	Correlation	Author suggested that CHD mortality not primarily dependent on level of fish consumption. Other behaviors including level of saturated fat in the diet are important. Need cohort data, unable to determine fish consumption in individuals with CHD mortality from this analysis.	Low mortality <20 deaths due to CHD per 1000 reported in all quintiles of fish intake. One cohort reporter 60 g/day average intake and had <120 deaths per 1000 due to CHD. Controlling these factors, fish consumption at a low level may be of importance in the prevention of CHD.
Norell et al. 1985 British Medical Journal 293:426.	Prospective	10,966 Swedes born between 1886–1925.	14 year followup.	Mail questionnaire	Adjusted for age, smoking, weight, sex, marital status, geography. Excluded people with history of hypertension, heart disease.	The author suggested the study supported a protective effect of fish consumption for CHD mortality. The data for this conclusion were weak.	The trend for CHD mortality versus fish consumption was barely significant at the 90% confidence level. The Chi square trend was not significant.
Shekelle et al. 1985 New England Journal of Medicine 313:820.	Prospective dietary questionnaire.	1931 middle aged men	25 years	Normal diet	Adjusted for major risk factors associated with CHD.	Letter to the editor	Inverse trend for risk of death and fish consumption.
Simonsen et al. 1987 Acta Medica Scandinavica 222:237.	Correlation of diet and serum lipids with CHD mortality rates in these communities.	14 males each from farming and fishing community.	Short-term	Normal diet	Correlation	Smoking, sample size, medical records.	No differences in CHD rates in the two communities despite 2.5 fold greater fish consumption in the coastal group.
Vollset et al. 1985 New England Journal Medicine 313:820.	Prospective study	11,000 healthy, middle aged men.	14 years	Questionnaire on diet, fish consumption.	Adjusted for major risk factors associated with CHD.	Letter to the editor	No relationship between fish consumption and CHD except in men under 45 years old.

Abbreviations used: CHD, coronary heart disease; d, days

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Abbey et al. 1990 *Arteriosclerosis* 10:85.	Randomized, double-blind, 3 oils.	6 weeks	3.4 g EPA plus DHA (MaxEPA) v safflower, linseed oils.	11 normotensive mildly hypercholesterolemic males.	NS Chol, HDL, IDL; ↑ LDL; ↓ TGs, VLDL TG and chol, apoB, apoA–I, apoA–II; ↑ ratio of apoA–1/apoA–II.	Concurrent linoleic acid (omega-6) and linolenic acid (omega-3) control groups allow conclusions about omega-3 fatty acid specific effects. Dietary intake was controlled, compliance was monitored by plasma fatty acids. Comparisons v baseline values, following 3-week safflower oil run-in ↓ HDL on linseed oil only. See Kestin et al. 1990
Agren et al. 1990 *Thrombosis Research* 57:565.	Randomized, dose response.	12 weeks	0.25, 0.5, 0.6 and 1.1 g EPA + DHA from freshwater fish.	100 healthy male students.	↓ platelet aggregation to collagen, ADP in two highest fish consumption groups; ↓ TXB, in high amount, longest time group; NS bleeding.	Effects on 1.5 fish meals/weeks (0.5 g EPA plus DHA) with 12-week duration of exposure. Moderate amount of freshwater fish intake can modified platelet function. Concurrent 0.4 fish meal/week control group was present. Dropouts not explained; N=13, 14, or 15 in Table 2. Design doesn't allow conclusions about omega-3 fatty acid specific effects.
Azar et al. 1989 *Kidney International* 36 (suppl 27):S239.	Non-blinded, uncontrolled.	1 month	6 g MaxEPA/d	7 male and 6 female hemodialysis patients.	NS Chol, apoA; ↓ TGs, apoB, and apoB/apoA ratio.	Hyperlipidemia of hemodialysis patients received 6 g/d of MaxEPA for 1 mo had beneficial effect. The investigator suggested that long-term multicenter studies are needed to confirm the efficacy and tolerance of FO. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Bach et al. 1989 *Annals of Nutrition Metabolism* 33:359.	Randomized double-blind placebo-controlled trial.	5 weeks	1.3 or 2.5 g EPA plus DHA from salmon oil/d v Miglyol 812.	30 healthy adults	NS Chol, LDL, HDL, TGs; ↓ BP, plasma viscosity, RBC rigidity, platelet aggregation.	The control oil (Miglyol 812) consists of TG of primarily octanoic acid and decanoic acid. No fatty acid composition of the control and the test diet was given. The compliance of the diet was not monitored.
Bagdade et al. 1990 *Diabetes* 39:426.	Non-blinded uncontrolled.	3 months	6 g EPA plus DHA, SuperEPA.	8 normolipidemic insulin-dependent diabetic women.	↓ TGs; ↑ Chol, HDL_2, apoA; NS LDL, apoB, HDL_3.	IDDM and NIDDM may respond to omega-3 fatty acids differently. No deterioration of diabetes control. Long-term benefits/toxicity not established. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Blonk et al. 1990 *American Journal Clinical Nutrition* 52:120.	Randomized, dose-response.	12 weeks	1.5, 3, 6 g EPA plus DHA ethyl esters/d.	45 normotriglyceridemic males.	↓ TGs, HDL_3; ↑ HDL_2, HDL_3; HDL_3; NS Chol, VLDL, LDL, total HDL; NS BP, bleeding time, RBC deformability, leukocyte killing.	Normal diets, with < 1 fish meal/week. Includes a 12-week washout, showing return to baseline for most variables. Compliance indicated by plasma phospholipids. Most of the observed changes occurred on the lowest dose.
Bonaa et al. 1990 *New England Journal Medicine* 322:795.	Randomized non-blinded, placebo controlled.	10 weeks	5.1 g EPA plus DHA as ethyl ester/d v corn oil.	157 hypertensive healthy, age 34 to 60.	NS Chol, HDL; ↓ BP linear with change in plasma EPA plus DHA; NS bleeding, fibrinogen.	FO decreased BP varies in different demographic and biochemical subgroups. In this study, 32% of the subjects did not decrease BP, despite an increased intake of EPA.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Borkman et al. 1989 *Diabetes* 38:1969.	Randomized, double-blind, placebo controlled.	3 weeks each.	10 g MaxEPA/d or 10 g safflower oil, with 3-week washout between.	10 non-insulin dependent diabetics.	NS Chol, LDL, HDL; ↓ TGs for hypertriglyceridemics only; NS c-peptide, fasting insulin, insulin sensitivity.	Controlled (diabetic) diet; ↑ fasting glucose comparable on both oils.
Bowles et al. 1991 *Angiology* ZZ:187.	Non-blinded uncontrolled.	6 months	2.8 g EPA in FO/d	120 vessels in 105 patients undergoing angioplasty.	NS v historic rates of restenosis.	Numerous shortcomings, including inclusion, exclusion criteria, unblinded uncontrolled, poor compliance.
Brown et al. 1990 *American Journal Clinical Nutrition* 52:825.	Randomized crossover.	6 weeks	5 g MaxEPA/d or lean fish (0.2 g EPA) plus 5 g MaxEPA.	12 healthy males	↓ TGs, VLDL; NS Chol, LDL, HDL_2, HDL_3.	Uncontrolled weekend evening meals, otherwise diet was controlled. Compliance was measured by the level of EPA in RBC The calorie intake of the control group (2968 Kcal) was 10% more that the FO (2633 Kcal) group.
Brown and Roberts 1991 *Arteriosclercsis and Thrombosis.*	Matched, single-blind, placebo controlled.	6 weeks	5 g FO v olive oil	11 healthy subjects on FO, 14 controls.	NS Chol; ↓ TGs on FO, HDL on olive oil.	Eructation revealed group to all FO subjects, but none of controls. ↓ post prandial lipemia in FO subjects. FO not characterized. Compliance by RBC fatty acids. Drop-outs accounted.
Burr et al. 1989 *The Lancet* ii:757.	Randomized, parallel, multi-center.	2 years	Fish advice (or MaxEPA at 0.9 g EPA plus DHA/d) v fat advice v fiber advice.	2033 men post heart attack.	↓ total deaths in fish advice v other groups, attributed to CHD death; NS second MI.	This is the only study to date which assessed effect of omega-3 fatty acids on CHD per se. Design doesn't allow conclusions about omega-3 fatty acid-specific effects, because effects of fish are not distinguished from effects of omega-3 fatty acids.
Childs et al. 1990 *American Journal of Clinical Nutrition* 52:632.	Non-blinded multiple crossover.	3 weeks	4 diets w 36% fat with EPA plus DHA as: 0.2%, butter; 6.7%, poliack; 9.4%, tuna; 6.2%, salmon blend.	8 normolipidemic males.	↓ TGs, VLDL, Chol, apoA-I and apoA-II on all fish diets, LDL on all but the pollack diet; HDL_2 ↓ on pollack, ↑ on salmon; HDL_3 on pollack, tuna.	Daily energy intake varied (2550–3618 kcal/d) among individuals. Saturated fat diet was used as positive control, no concurrent polyunsaturated fat control. The differential effects of pollack v other fish may be due to its higher ratio of EPA:DHA.
Clark et al. 1989 *Kidney International* 36:653.	Non-blinded uncontrolled.	5 weeks	6 g or 18 g MaxEPA/d.	12 subjects with systemic lupus erythematosus.	↓ TGs, VLDL; ↑ HDL, ↑ PGI_3; NS Chol PGI_2; ↓ platelet aggregation, blood viscosity, RBC flexibility; NS platelet serotonin, serotonin release.	All patients were receiving prednisone at doses ranging from 10 mg on alternate days to 20 mg daily. The results did not indicate an improvement in clinical outcome for patients with lupus nephritis.
Cobiac et al. 1991 *American Journal of Clinical Nutrition* 53:1210.	Matched, parallel design.	5 weeks	4.5 g EPA plus DHA from salmon plus sardines in siid oil v MaxEPA v palm, safflower olive oil mix.	25 mildly hypertensive men.	NS Chol, LDL, apoB, apoA-I, apoA-II, BP; ↓ TGs, VLDL; ↑ HDL on both fish and FO ↓ fibrinogen, TXB, ↑ bleeding on fish only.	3 week run-in on controlled diet including liquid supplement. Stratified by BP, TGs, Chol to matched groups; fish, FO or control (basal) diets. Fish diet EPA:DHA was 1:2, MaxEPA is 2:1. The BP effects were comparable in the 3 treatments. Bleeding, fibrinogen and thrromboxane changes occurred only on the fish diet, suggest they are EPA-specific effects.
Croset et al. 1990 *Thrombosis Research* 57:1.	Randomized, double-blind, placebo controlled trial.	2 months	100 mg EPA/d as purified TG plus tocopherol v vitamin E.	8 healthy elderly subjects, 8 controls.	NS Chol, TGs; ↓ platelet aggregation; NS arachidonic acid metabolites; ↑ tocopherol in platelets; NS fibrinolytic activity; ↓ systolic BP.	Decrease in platelet aggregation occurred on this very low dose (100 mg/d), despite no change in platelet or plasma EPA concentration Purified EPA containing TG as unique EPA source.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Dart et al. 1989 *Atherosclerosis* 80:119.	Double-blind, placebo controlled crossover.	2 months	20 mL MaxEPA v olive oil.	14 male and 7 female hypercholesterolemic subjects.	NS Chol; ↓ TGs, VLDL; for males ↑ LDL and HDL, for females NS LDL, HDL.	Sex differences in HDL response appears real. Body weight gain on placebo in both men and women.
DeCaterina et al. 1990 *Circulation* 82:428.	Non-blinded uncontrolled.	28 days	3 g EPA plus 1 g DHA/d (PGE technology, MA).	13 males 2 females with coronary artery disease.	↓ TGs; NS Chol; ↑ PGI_2; ↓ TXB_2; platelet aggregation ↑ bleeding.	No placebo-treated concurrent control group. Assays of tissues from supplemented subjects indicate direct and indirect effects of omega-3 fatty acids on production of platelet function regulators.
Deck and Radack 1989 *Archives of Internal Medicine* 149:1857.	Randomized double-blind placebo controlled crossover.	8 weeks	4.6 g EPA plus DHA/d source not specified v olive oil.	8 hypertriglyceridemics.	↓ TGs; ↑ apoB, HDL; NS LDL.	Small sample size may limit the ability to detect statistically significant changes in LDL cholesterol.
Dehmer et al. 1988 *New England Journal of Medicine* 319:733.	Randomized non-blinded.	1 week prior to angioplasty for 6 months.	5.4 g EPA plus DHA/d (MaxEPA—).	82 male candidates for angioplasty.	↓ restenosis rates	Concurrent use aspirin (325 mg/p/d) and dipyridamole (225 mg/p/d) in the control and test groups.
DeLany et al. 1990 *American Journal of Clinical Nutrition* 52:477–85.	Non-blinded, matched by serum cholesterol.	5 weeks	3 diets; basal; 5; or 20 g FO substituted for margarine (Sanomega).	15 healthy male college students.	20 g FO ↓ TGs; NS Chol, HDL, apoA-I, apoB on both FO diets.	The trial was conducted in healthy males consuming a constant controlled diet. Implementation of controlled diet alone decreased serum TG. A further reduction of serum TG was observed in 20 g FO.
Demke et al. 1988 *Atherosclerosis* 70:73.	Randomized, double-blind placebo controlled.	28 days	5 g MaxEPA v safflower oil placebo.	31 hypercholesterolemic subjects.	↑ Chol, LDL, HDL, HDL_2; NS TG, bleeding, TXB_2; no changes in placebo.	The results of the experiment question the benefit of FO supplement to the hypercholesterolemic patient. It is one of the few studies reporting ingestion of oil supplement has adverse effects; indigestion, diarrhea, headache abdominal cramps, etc. Dietary intake was not controlled.
Emeis et al. 1989 *Blood* 74:233.	Stratified, randomized.	6 weeks	Fish paste (1.7 g EPA plus 3 g DHA) v meat paste.	37 normal healthy males in fish group, 39 in meat group.	NS TPA, fibrinogen, c-reactive protein, insulin, plasminogen activity; ↑ PAI-1 activity.	Design doesn't allow conclusions about omega-3 fatty acid-specific effects. 2-week run-in on the meat diet. Compliance monitored by urinary lithium. ↑ PAI is a risk factor for reinfarction.
Endres et al. 1989 *New England Journal of Medicine* 320:265.	Non-blinded uncontrolled.	6 weeks	18 g MaxEPA	9 healthy adults	↓ interleukin 1, tumor necrosis factor.	Initial study group consisted of 6 subjects, three more persons entered the study six months later. Since the results were similar the data was pooled. No concurrent control. No dietary control and the mean calorie varied from 2000 to 3000 kcal/d. The FO effect on the synthesis of IL-1b continued 10-week after omega-3 fatty acids supplementation.
Ernst 1989 *Journal of Internal Medicine Supplement* 225:129.	Randomized, double blind, placebo controlled.	6 weeks, 2 weeks each of 0.6 g EPA, 1.2 g EPA and 1.8 g EPA sequentially.	Neither the FO or the placebo were characterized.	20 healthy men	Reduced blood viscosity at 4 and 6 weeks.	Initial data demonstrating comparability of the treatment and control groups not shown. Other dietary controls not used, and values for the placebo group were lower at 4 and 6 weeks, but NS.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Failor et al. 1988 *Metabolism* 37:1021.	Non-blinded crossover, parallel control group.	3 weeks each w 3-week washout.	Saturated fat v safflower v salmon (and salmon oil).	4 familial combined hyperlipidemics, 4 normal controls.	↓ TG, apoA-1 in normals Familial combined hyperproteinemia ↓ TGs.	Good experimental design. Dietary intake 3was recorded and compliance was monitored by RBC omega-3 fatty acids measurement. Small n may be the reason some differences were not found.
Fasching et al. 1991 *Diabetes* 40:583.	Non-blinded randomized, crossover to no supplement.	2 weeks each with 3-week washout.	30 mL FO/d EPAX 5000, Fabrikker, Oslo,6.3 g EPA + DHA.	8 subjects with impaired glucose tolerance.	↓ TGs, Chol, LDL, apoB; NS HDL, apoA-I; NS insulin, blood glucose.	1 kg gain (NS) in 2 weeks! Suboptimal control; Doesn't separate effects of omega-3 fatty acids from other oil components/cals.
Fisher et al. 1990 *American Journal of Clinical Nutrition* 51:804.	Non-blinded uncontrolled.	6 weeks	6 g EPA plus DHA/d, (30 mL cod liver oil).	9 normal subjects	↓ monocyte free radical production.	Dietary intake was not controlled. Design doesn't allow conclusions about omega-3 fatty acid-specific effects. The potential mechanisms of foam cell formation and its relationship with omega-3 fatty acids were discussed.
Flaten et al. 1990 *American Journal of Clinical Nutrition* 52:300.	Non-blinded randomized.	6 weeks	14 g FO (7.7 g EPA plus DHA)/d (Fabrikkar, Norway) v olive oil.	64 healthy males	↓ TGs, NS Chol; ↓ HDL, HDL_2; NS glucose; NS BP; 12% ↓ fibrinogen; NS gamma glutamyl transferase, monocyte LDL receptor activity.	Olive oil was the concurrent oil control group. Compliance was checked by RBC total omega-3 fatty acids composition. Calorie and major nutrient intake were comparable for the control and test group.
Friday et al. 1989 *Diabetes Care* 12:276.	Non-blinded uncontrolled.	8 weeks	8 g EPA plus DHA methyl esters/d (RES-Q1000).	8 non-insulin-independent diabetics.	↓ Chol, TGs, VLDL; NS LDL, HDL insulin; ↑ glucose.	No fatty acid composition was given on the Marine-lipid concentrate (RES-Q 1000, a methyl ester of EPA and DHA). Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Friday et al. 1991 *Arteriosclerosis and Thrombosis* 11:47.	Randomized, non-blinded, placebo-controlled multiple treatment trial.	3 weeks each with 3-week washouts.	12 g EPA plus DHA/d (salmon oil) v safflower oil.	5 familial hypercholesterolemics, 5 normal controls.	Comparable results for FH and normals, ↓ TGs, Chol, LDL, HDL v butter diet.	Precisely matched diets, small numbers but large changes in lipids. The n-3 content is quite high.
Fumeron et al. 1991 *American Journal of Clinical Nutrition* 54:118.	Randomized, butter-controlled.	3 weeks each.	6 g MaxEPA/d	36 normal, young, healthy males.	↓ TGs, VLDL-TG; NS Chol, apoB, apoA-I, total HDL, but ↑ HDL_2, apoE, LDL; ↓ platelet aggregation, ↓ PAI; PAI correlated to LDL.	Among the few studies showing ↑ HDL in normals (v butter). The ↑ PAI activity and LDL may offset ↓ platelet aggregation and ↑ HDL_2 regarding net CHD risk.
Glauber et al. 1988 *Annals of Internal Medicine* 108:663.	Non-blinded uncontrolled.	4 weeks	18 g MaxEPA/d	6 males insulin-dependent diabetics.	↑ fasting glucose; ↓ glucose tolerance, fasting insulin, insulin response.	Deterioration of NIDDM patients' diabetic state by FO supplement but no evidence of adverse effect by fish. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Grigg et al. 1989 *Journal of American College Cardiology* 13:665.	Randomized, double-blind placebo-controlled.	4 months	3.0 g EPA plus DHA/d from MaxEPA v 50% olive oil, 50% corn oil.	108 subjects undergoing angioplasties.	↓ TGs, NS chol; NS in restenosis rate.	Restenosis evaluated by angiography.
Haglund et al. 1990 *Journal of Internal Medicine* 227:347.	Non-blinded uncontrolled, partial crossover.	3 to 4 weeks or 6 months.	15 or 30 mL ESKIMO-3 (Cardinova, Sweden) soybean oil placebo.	33 subjects either healthy or with coronary artery disease.	↓ TGs, Chol; ↑ HDL; ↓ BP, fibrinogen in high dose group; NS bleeding.	Data for normal and CHD patients are pooled. Similarly, tables compare results for each treatment to pooled initial values for all subjects.
Hardarson et al. 1989 *Journal of Internal Medicine* 226:33.	Non-blinded crossover intervention.	6 weeks	20 mL cod liver oil/d.	18 males 33-70 yrs	NS arrythmia	Subjects were an average of 8 days after onset of symptoms. Various drugs were taken by the patients. Dietary intake was not controlled.
Harris et al. 1988a *Journal of Lipid Research* 29:1451.	Multiple, sequential, non-blinded intervention.	4 weeks and 3 weeks.	24 g or 28 g EPA plus DHA/d from salmon oil Max EPA respectively.	7 and 8 normal subjects.	↓ TGs, VLDL; ↓ LDL v saturated fat diet, but NS v vegetable oil diet; NS HDL.	No wash out period between each test periods. High amount of omega-3 fatty acids.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Harris et al. 1988b *Annals of Internal Medicine* 109:465	Single-blind, placebo controlled	6 weeks	12 mL SuperEPA/d v safflower oil	11 hypertriglyceridemics, 7 with hypercholesterolemia.	↓ TGs, ↑ LDL, apoB; NS HDL.	Plasma lipoprotein changes should be monitored and long-term effects should be evaluated.
Harris et al. 1988c *American Journal of Clinical Nutrition* 48:992	Non-blinded uncontrolled, crossover	6 weeks each.	18 g MaxEPA or same amount of EPA and DHA from SuperEPA.	8 male type IV hyperlipidemics.	↑ TGs; NS Chol, ↑ LDL, apoB.	Methyl ester of EPA and DHA causes the same effects as TG-EPA and TG-DHA. This is a test for more concentrate omega-3 fatty acids supplement.
Harris et al. 1990 *American Journal of Clinical Nutrition* 51:399	Non-blinded uncontrolled, dose response	6 weeks	15, 25 or 40 mL MaxEPA/d.	10 hypertriglyceridemic subjects.	↓ TGs on each, little additional effect at high doses, ↓ VLDL; ↓ Chol but no effect of high doses; ↑ LDL, HDL on higher 2 doses.	High doses confound effects of increased calories. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Hostmark et al. 1988 *British Medical Journal* 297:180	Randomized double-blind placebo-controlled supplement	6 weeks plus 6 weeks.	14 g FO/d; 6.5 g EPA+DHA (Apothekernes Labs AS, Norway) v olive oil	64 males ages 35-40.	↓ fibrinogen 13% at 3, 6 weeks.	The reduction in fibrinogen was less at 6 weeks than at 3 weeks. Longer-term studies are needed for assessment of effects of chronic consumption of omega-3 fatty acids.
Hughes et al. 1990 *Atherosclerosis* 84:229	Randomized, double-blind, placebo-controlled two way crossover.	30 days each, with 30-day washouts.	5 g EPA plus DHA/d (Promega), wheat germ oil control.	13 normal and 15 hypertensive males.	↑ Chol, LDL, apoB in hypertensives only; NS TG, BP, serum androgens, plasma glucose, insulin, platelet aggregation.	The hypertensives had ↑ apoB and ↓ HDL and ↓ androgens v normals at baseline. Reductions in TGs and VLDL were nearly 50% in normals and 40% in hypertensives, but did not reach statistical significance due to large variations.
Inagaki and Harris 1990 *Atherosclerosis* 82:237.	Non-randomized uncontrolled.	4 weeks	6 g EPA plus DHA/d (SuperEPA).	6 hypertriglyceridemics.	↓ TGs, VLDL, apoC; NS, LDL, apoA, apoE; ↑ HDL, apoB.	Useful regarding mechanism of changes in lipoprotein levels, separated TG from Chol and apoproteins.
Jensen et al. 1989 *New England Journal of Medicine* 321:1572.	Randomized, double-blind placebo-controlled crossover.	8 weeks	4.6 g EPA plus DHA/d from a water soluble cod liver oil preparation v olive oil.	14 males, 4 females insulin-dependent diabetics.	NS Chol, HDL; ↑ LDL; ↓ VLDL, TGs; ↓ BP;.	Concurrent olive oil control group was present Dietary intake was not controlled. Eight weeks washout period was long enough to restore the parameters tested to the pre supplementary level. No change in insulin or blood glucose.
Kasim et al. 1988 *Journal of Clinical Endocrinology Metabolism* 67:1	Non-blinded longitudinal.	8 weeks	1.6 g EPA plus 1.1 g DHA/d (MaxEPA).	22 insulin-independent diabetics w/o hyperlipidemia.	NS Chol, LDL, HDL; ↑ apoB; ↓ BP.	All patients received hypoglycemic agents. Compliance was monitored by questionnaires and counting the FO capsules. No plasma fatty acids composition was analyzed.
Kestin et al. 1990 *American Journal of Clinical Nutrition* 51:1028	Randomized, double-blind, 3 oils.	6 weeks	3.4 g EPA plus DHA (maxEPA), v safflower, linseed oils.	11 normotensive mildly hypercholesterolemic males.	NS Chol, HDL; ↑ LDL, ↓ TGs, VLDL.	Concurrent linoleic acid (omega-6) and linolenic acid (omega-3) control groups were present. Dietary intake was controlled, compliance was monitored by plasma fatty acids. Comparisons v baseline values, following 3 week safflower oil run-in ↓ HDL on linseed oil only. See Abbey et al. 1990
Knapp and FitzGerald 1989 *New England Journal of Medicine* 320:1037.	Randomized, non-blinded.	4 weeks	10 or 50 mL MaxEPA v safflower oil of a mixed vegetable oil.	8 hypertensive males in each of 4 groups.	↓ BP on high dose only	No total calorie/d was given but one of the dose level used in the study was quite large (50 mL/d).

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Lehtonen et al. 1989 *Gerontology* 35:311.	Non-blinded, comparison to isocaloric diet.	3 weeks	70 to 80 mL MaxEPA/d.	17 healthy geriatric patients.	↓ Chol, VLDL, LDL, TG, apoA, HDL; NS apoB.	The fat content of the isocaloric control period is not given. This is a very large amount of FO. The majority of the patients discontinued the study due to unpleasant taste of the supplement oil.
Lempert et al. 1988 *American Journal of Kidney Diseases* 11:170.	Non-blinded, uncontrolled.	4 weeks and 20 weeks post-supplementation.	25 mL MaxEPA/d	11 stable dialysis patients, hypercholesterolemic, hypertriglyceridemic.	↓ TG, NDL; ↑ LDL; NS bleeding, platelet aggregation.	↓ HDL found 20 weeks after discontinuation, but little other data regarding treatment/condition during the washout. The nature of the disease and concurrent dialysis in this population make it impossible to extrapolate to the general population.
Levine et al. 1989 *Archives of Internal Medicine* 149:1113.	Non-blinded uncontrolled.	6 weeks	20 mL cod liver oil	10 hyperlipidemics	↑ Chol, LDL; NS HDL, TGs; ↑ platelet survival; NS platelet aggregation.	All the patients had long-standing history of hyperlipidemia. No concurrent oil control group. This study is one of the few studies that found plasma TG did not change after omega-3 fatty acids ingestion (20 mL/d).
Levinson et al. 1990 *American Journal of Hypertension* 3:754.	Randomized double-blind placebo-controlled parallel.	6 weeks	50 mL MaxEPA v palm oil, corn oil mix.	8 hypertensives	↓ TGs, NS Chol, HDL, LDL apoA and apoB; ↑ bleeding; NS platelet aggregation; ↓ Bp.	One patient receiving FO withdrew because of GI discomfort. Because of adverse effects, the daily dose of oil was reduced by 20% and 25% in two patients in the FO group, and by 20% in one patient in the vegetable oil group.
Li and Steiner 1990 *Blood* 76:938.	Non-blinded parallel	25 days	6 g EPA from MaxEPA.	8 normal adults	↓ platelet aggregation, adhesiveness.	Elegant study showing an effect on platelet adhesiveness. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Lox 1990a *General Pharmacology* 21:241.	Non-blinded uncontrolled.	30 days	0.9 g EPA plus DHA/d (MaxEPA).	9 healthy males	↓ Chol, LDL; NS TGs; ↑ HDL; ↑ bleeding; NS platelet aggregation.	Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Lox 1990b *General Pharmacology* 21:295.	Non-blinded uncontrolled.	30 days	0.9 g EPA plus DHA/d (MaxEPA).	43 healthy females, with or without oral contraceptive use, 13 menopausal females.	↓ Chol, ↑ LDL in non-oral contraceptive users; ↓ TGs in oral contraceptive users.	The difference between oral contraceptive users and non-oral contraceptive users may be important
Margolin et al. 1991 *American Journal of Clinical Nutrition* 53:562.	Randomized, double-blind crossover.	8 weeks	9 g FO (RES-Q1000) v corn oil.	46 elderly hypertensive subjects.	↓ TGs; ↑ LDL; NS Chol, HDL; ↓ BP.	Inclusion BP was systolic >160 or diastolic >90. Excellent design with 3 week wash out between the 8 week treatments.
Mehta et al. 1988a *American Journal of Medicine* 84:45.	Randomized, double-blind placebo-controlled crossover.	4 weeks	3.2 g EPA 2.2 g DHA/d (MaxEPA) v lecithin.	8 males w CHD 52-73 yrs.	↓ TGs; NS Chol, HDL, LDL; ↓ BP, ↓ neutrophil aggregation, chemotaxis.	Placebo not characterized in this paper, identified from companion paper (see Mehta 1988, American Heart Journal). There was large variation of TG level in the placebo group.
Mehta et al. 1988b *American Heart Journal* 116:1201.	Randomized, double-blind placebo-controlled crossover.	4 weeks	3.2 g EPA 2.2 g DHA/d (MaxEPA) v lecithin.	8 males w CHD 52-73 yrs.	↓ PAI; NS TPA	Various parameters were compared between CAD patient and normal subjects. Lecithin was the concurrent control. Dietary intake was not controlled.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Miller et al. 1988 *Clinica Chimica Acta* 178:251.	Multicenter, randomized double-blind placebo-controlled.	3 months	10 g MaxEPA/d v olive oil.	48 hypertriglyceridemics.	↓ TGs; NS Chol, LDL, HDL	This is a multicenter 3 study. In the summ section the investig reported minor GI dist ance in both groups in the discussion sec the author stated that g MaxEPA/d was well erated. Compliance not monitored.
Milner et al. 1989 *American Journal of Cardiology* 64:294.	Randomized	6 months	4.5 g EPA plus DHA/d (MaxEPA) v no supplement.	84 post-angioplasty patients.	↓ restenosis by symptoms, NS by angiography.	All patients received asp and calcium block American Heart Asso tion phase III diet. Des doesn't allow conclusi about omega-3 fatty a specific effects. Concc tant use of other medi tions, reduction in sm ing. Reocclusions not sessed by angiography
Mölgaard et al. 1990 *Atherosclerosis* 81:1.	Non-blinded, placebo control.	16 weeks	15 g MaxEPA/d v olive oil.	9 type III hyperlipoproteinemics.	↓ Chol, TG, VLDL, apoB; NS LDL, HDL, apoA-I.	The European Atheroscle sis Society diet was r ommended to the tients. No compliar was monitored. Conc rent olive oil con group.
Mori et al. 1988 *Clinical Experimental Pharmacology Physiology* 15:333.	Non-blinded uncontrolled.	3 weeks	15 g MaxEPA/d	10 insulin-dependent male diabetics.	↑ Chol, LDL, HDL; ↓ TGs	Design doesn't allow c clusions about omeg fatty acid-specific effe
Mori et al. 1989 *Metabolism* 38:404.	Non-blinded, parallel control.	3 weeks	15 g MaxEPA/d v same in non-diabetics.	10 insulin-dependent male diabetics, 10 normal controls.	↑ Chol, LDL, HDL, HDL_2 ↓ TGs among diabetics; NS Chol, LDL, HDL, HDL_2 TGs among normals; Chol, LDL and TG still different 6 weeks after discontinuation.	Compliance by plate phospholipids fatty ac and pill count. Usual d activity were to be ma tained.
Nozaki et al. 1991 *American Journal of Clinical Nutrition* 53:638.	Non-blinded uncontrolled.	24 days	20 g Promega/d	12 male hypertriglyceridemics.	↓ TGs, VLDL; ↑ LDL; NS HDL.	No alcohol and isocalc controlled diet was us in the protocol. Des doesn't allow conclusic about omega-3 fatty ac specific effects.
Radack et al. 1989 *Annals of Internal Medicine* 111:757.	Randomized double-blind placebo-controlled supplement.	20 weeks	1.1 or 2.2 g EPA plus DHA/d (source not specified) v olive oil.	25 hyperlipidemic, disease free.	↓ fibrinogen	Excellent design. Com ance was assessed plasma fatty acid analy
Radack et al. 1990a *Journal of American College Nutrition.*	Randomized, double-blind crossover.	8 weeks each 4-week washout, 6-week run-in.	4.6 g EPA plus DHA, olive oil during washout, corn oil control.	6 hyperlipoproteinemics types IIb or IV.	↓ fibrinogen comparably on FO and corn oil; NS TPA, PAI, bleeding.	Excellent design; althou the n was small, mean values do not s gest differences miss due to small sample, is any difference betwe corn oil and FO sugge ed.
Radack et al. 1990b *American Journal of Clinical Nutrition* 51:599.	Randomized, double-blind placebo-controlled.	20 weeks	2.2 or 1.1 g FO/d from McNeil, 41% as n-3 fatty acids v olive oil.	10, 7 and 8 hypertriglyceridemics, respectively.	↑ LDL, ↓ HDL_2 on 2.2 g/d group, ↑ apoB on both doses of FO.	Excellent design includes week run in, AMA di 92% compliance, app priate subjects for clain
Reis et al. 1989 *The Lancet* ii:177.	Randomized, double-blind placebo-controlled.	6 months	6 g EPA plus DHA/d (SuperEPA or Promega).	204 patients for coronary angioplasty.	NS effect on restenosis	In a randomly select subset of 42 patients (4 186), plasma PL was ar lyzed. Higher GI sic effect was significan higher in FO group (48 than placebo group. P cebo not characterized.
Reis et al. 1990 *American Journal of Cardiology* 66:1171.	Randomized, double-blind placebo-controlled.	6 months	6 g EPA plus DHA/d (SuperEPA or Promega) v olive oil.	89 patients for coronary angioplasty.	↓ TGs; ↑ LDL in Promega group and hypertriglyceridemic subjects of Super-EPA group.	Only subset of patients h LDL separated by ultr centrifugation. Most LDL chol levels were c culated rather than mea ured.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Rillaerts et al. 1989 *Diabetes* 38:1412.	Non-blinded, uncontrolled.	10 weeks	2.7 g EPA plus DHA/d (MaxEPA).	12 stable insulin-dependent diabetics.	↓ TGs, VLDL; ↑ HDL; NS LDL during washout ↑ TGs, VLDL.	Dietary intake was controlled, exchanging sunflower, corn or safflower oil with omega-3 fatty acids. Calorie intake varied from 1800 to 2200 kcal, depend on individual needs. Approximately 5.6 g omega-6 fatty acids/d was exchanged with 2.7 g omega-3 fatty acids/d.
Schectman et al. 1988 *Diabetes* 37:1567.	Single-blind crossover.	1 month	4.0 or 7.5 g EPA plus DHA (MaxEPA).	13 non-insulin dependent diabetics v safflower oil.	↓ TGs, VLDL, NS Chol, LDL, HDL; ↑ apoB; ↑ fasting glucose, ↓ glucose tolerance.	Subjects were on their usual diet (uncontrolled). Compliance was obtained by capsule counting. Increase LDL chol and apoB were not dependent on amount of omega-3 fatty acids.
Schectman et al. 1989a *Arteriosclerosis* 9 345.	Single-blind crossover.	1 month	4.0 g/d EPA plus DHA (MaxEPA) for 1 month, 1-month washout, followed by 7.5 g/d for 1 month v safflower oil.	18 hypertriglyceridemic subjects.	↓ TGs; NS Chol, HDL, apoA-I on both treatments; NS on control.	Significant body weight gain on each treatment. Saturated fat was held constant.
Schectman et al. 1989b *Annals of Internal Medicine* 110:346.	Non-blinded uncontrolled.	6 months	10 g EPA plus DHA/d months 1 to 3; 4 g/d months 4 to 6 (Omega-500).	16 hypertriglyceridemics (5 also hypercholesterolemic); 6 noninsulin-dependent diabetics.	Initially ↓ TGs, but less each month, by 6 months only ↓ 11%; worse glucose tolerance, ↑ glycosolated hemoglobin in diabetics; ↑ HDL on high dose.	Dietary intake was not controlled. GI side effects were considered and reported. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Schmidt et al. 1988a *Artery* 15:316.	Non-blinded randomized after placebo.	12 weeks	4.5 g EPA plus DHA/d v vegetable oil.	14 patients with angina.	NS plasminogen, PAI; ↑ fibrinolysis.	Concurrent vegetable oil control was used. No fatty acid composition of control and test oil was given. Uncontrolled use of omega-3 fatty acids supplementation in patients with stable angina pectoris was cautioned by the investigator.
Schmidt et al. 1988b *Scandinavian Journal of Clinical and Laboratory Investigations,* Suppl.	Randomized, double-blind, placebo controlled.	12 weeks	4.8 g EPA plus DHA/d (MaxEPA) v vegetable oil.	36 patients with angina.	NS antithrombin III, protein C.	4-week run-in on vegetable oil control.
Schmidt et al. 1989a *Thrombosis and Haemostasis* 62:797.	Non-blinded uncontrolled.	6 weeks	6 g n-3 (3.3 EPA, 1.8 DHA) (Jahre, Norway).	17 hyperlipidemics (9 type IIa, 8 type IV.	↓ TGs; NS Chol, LDL, HDL; ↑ apoB, ↓ apoA-I; ↑ protein C in type IIa, ↓ type IV;.	No concurrent oil control group, uncontrolled dietary intake and large amount of test oil. Dietary compliance was not monitored and GI side effect was not reported. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Schmidt et al. 1989b *Journal of Internal Medicine* 225 (Suppl 1):201.	Non-blinded uncontrolled.	6 weeks	4 g EPA plus DHA/d (Jahre, Norway).	10 insulin-dependent diabetics.	NS fibrinogen, TPA, PAI, platelet aggregation; ↑ neutrophil, NS monocyte chemotaxis.	Very few changes in this population; the chemotaxis results are different than for normals. The meaning of changed neutrophil chemotaxis is unclear. Design doesn't allow conclusions about omega-3 fatty acid-specific effects.
Schmidt et al. 1989c *Atherosclerosis.*	Non-blinded uncontrolled.	6 weeks	5.3 g cod liver oil/d	12 normal, healthy males.	↓ neutrophil, monocyte migration toward autologous serum or chemical attractant.	Usual diets throughout. The lack of a control oil prevents firm conclusion about the specificity of the effect as due to omega-3 fatty acids.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Schmidt et al. 1991 *Arteriosclerosis and Thrombosis* 11:429.	Randomized, non-blinded dose-response.	6 weeks	6 g or 1.3, 4 or 9 g n-3 fatty acids (Fabrikker, Oslo).	17 hyperlipidemics and 10 healthy ...en.	↓ monocyte chemotaxis in all, ↓ neutrophil in type IIa and in normals, not type IV on 1.3 g/d.	Virtually all the effect is w the lowest dose. The a thors interpret this mean the effect w probably not due to pol unsaturated fatty acic but a polyunsaturate fatty acid control wou have allowed a strong conclusion.
Skeaff and Holub 1988 *Thrombosis Research* 51:105.	Non-blinded v washout.	6 weeks	20 mL MaxEPA/d	8 normal males	↓ platelet aggregation	A methodology and protoc for biochemical mech nism of action of omega fatty acids on platel function. Design doesr allow conclusions abo omega-3 fatty acid-speci ic effects.
Silverman et al. 1991 *American Journal of Clinical Nutrition* 53:1165.	Non-blinded, crossover.	2 individual meals.	6.16 and 5.15 g EPA plus DHA from FO (Promega) or tuna, respectively.	10 normal, healthy males.	↓ platelet aggregation to one of four agonists; NS bleeding, membrane omega-3 fatty acids.	The study was undertake primarily to measure al sorption of omega-3 fat acids from FO v fish EP absorption from fish wa about 3 fold greater tha from FO, but there wa no difference in DHA at sorption rate.
Simons et al. 1990 *Australia New Zealand Journal of Medicine* 20:689.	Randomized double-blind placebo-controlled crossover.	12 weeks	2 or 4 g EPA plus DHA/d HIMEGA (ethyl esters) v olive oil.	13 hypertriglyceride-mics and 9 hypercholesterole-mics.	↓ TGs; HDL, and ($p < 0.06$) Chol; NS LDL, apoA-1, apoB.	Himega is ethyl ester prepa ration of FO fatty acid The study shows compa rable results for the ne and traditional FO.
Simonsen et al. 1988 *Acta Medica Scandinavica* 223:491.	Non-blinded, uncontrolled.	3 weeks	20 mL cod liver oil, about 5 g EPA plus DHA.	2 groups of 15 normal healthy males.	NS Chol, bleeding, TXA_2 ↑ HDL in the population with low fish consumption.	There was an alternate c control.
Smith et al. 1989 *Thrombosis Research* 53:467.	Non-blinded, uncontrolled.	4 weeks	3.4 g EPA plus DHA as ethyl esters (K85, Norsk Hydro).	35 male and 5 female survivors of myocardial infarction.	↓ TGs; NS HDL, blood glu-cose, PAI; ↑ Chol, LDL, bleeding, fibrinogen.	Points out interaction c omega-3 fatty acids witi anticoagulants.
Solomon et al. 1990 *Current Medical Research Opinion* 12:1.	Randomized double-blind placebo-controlled parallel longitudinal.	3 months	2.8 g EPA, 2 g DHA (MaxEPA) v olive oil.	10 stable angina patients.	NS angina	Concurrent olive oil contrc was used. The subjec number (5/group) was toc small. Subjects kept thei usual diet and life-style Compliance was as sessed by RBC-PL fatt acid analysis. No side ef fects were reported.
Stacpoole et al. 1989 *Metabolism* 38:946.	Non-blinded uncontrolled, two doses.	6 months, 3 months on 2 diets.	1.1, 2.3, or 4.5 g EPA plus DHA/ 1000 Kcal (MaxEPA).	21 hyperlipoproteine-mics 6 diabetics, 6 normals.	In diabetics ↓ TGs; ↑ LDL; NS Chol, HDL; TG and LDL changes show dose-response; Glycemic con-trol worse in 4 insulin-de-pendent diabetics; In con-trols ↓ TG, VLDL; NS Chol.	Two kinds (MaxEPA or Su perEPA) of omega-3 fatt acids test materials were used. Compliance was monitored by monthly vis-iting the clinic and evalu-ated by a physician and dietitian rather than plasma fatty acids com-position American Heart Association phase III diet was used as basal diet.
Steiner et al. 1989 *Journal of Hypertension* 7 (suppl 3):S73.	Randomized, placebo-controlled crossover, followed by non-blinded, uncontrolled phase.	8 weeks blind, 4 weeks open.	1.6 g EPA plus DHA blind v salad oil, 3.2 g EPA plus DHA non-blind.	28 hypertensives, including 10 with hypertriglyceride-mia or hypercholesterole-mia.	↓ BP for self-recorded and casual clinic-recorded; NS prostacyclin, thromboxane.	Considerable systematic dif-ference between self-re-ported and clinic-reported BP data suggests signifi-cant patient bias, detecta-ble by fish-smell belching. Quantitative data not pre-sented, making compari-son with other BP studies difficult.
Subbaiah et al. 1989 *Atherosclerosis* 79:157.	Non-blinded uncontrolled.	30 days	7.5 g EPA plus DHA/d as SuperEPA.	14 hypercholesterole-mics w/o hypertriglyceride-mics.	↓ TGs, VLDL, LDL; ↑ HDL.	Patients on American Heart Association phase I diet for at least 3 mo before entering the study and continue the same diet during the test period.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Sweny et al. 1989 *Nephrology Dialysis Transplantation* 4:1070.	Non-blinded uncontrolled.	6 months	60 mg EPA plus DHA/kg (MaxEPA).	14 adult transplant recipients.	↓ TGs. NS Chol	No concurrent oil control group, uncontrolled dietary intake except dietary protein intake was kept constant. Compliance was not monitored and GI side effect was not reported. Antihypertensive and immunosuppressive drugs were administered.
Takimoto et al. 1989 *Thrombosis Research* 54:573.	Non-blinded uncontrolled, partial crossover.	30 days	20 mL MaxVita 5.6 g EPA 2.6 g DHA.	14 normal healthy subjects, 4 were hypercholesterolemic and hyperlipidemic.	↓ Tgs, HDL; NS Chol	There was no side effect or GI disturbance was reported when 20 mL control or test oil vas taken in a single dose. Wheat germ oil containing alpha linolenic acid was used as control oil.
Urakaze et al. 1989 *Nephron* 53:102.	Non-blinded uncontrolled, controlled for ciclosporin.	6 months	1.5 g EPA 0.7 g DHA/d (source not specified).	14 renal allograft patients.	↑ RBC filterability, prevented ↑ in platelet aggregation in controls.	Non specified sardine oil concentrate was used. Food intake was not monitored during the study but EPA content in RBC was measured for compliance. Antihypertensive and immunosuppressive drugs were administered.
Vacek et al. 1989 *Biomedicine and Pharmacotherapeutics* 43:375.	Double-blind placebo-controlled crossover.	6 weeks	9 g EPA plus DHA from (MaxEPA) v 1:1 palm: cottonseed oil.	8 CHD patients	↓ TGs; NS Chol, LDL, HDL; NS angine.	The control was a mixture of palm and cottonseek oils. No fatty acid composition was given of this control oil. Dietary intake was not controlled.
Valdini et al. 1990 *Journal of Family Practice* 30:55.	Randomized, double-blind, placebo-controlled crossover.	12 weeks each.	1.8 g EPA plus DHA/d (MaxEPA) v olive oil.	25 hypercholesterolemics.	↓ TGs; NS Chol, LDL, HDL	Usual diets, small but practical dose; some patients were on lipid altering medication concurrently.
van Houwelingen et al. 1990 *American Journal of Clinical Nutrition* 51:393.	Multicenter, matched controls by TGs and blocd pressure.	6 weeks	mackerel (4.7 g EPA+DHA) or meat paste.	84 healthy males	NS Chol, LDL; ↓ TGs at 3 and 6 weeks; at 6 weeks ↑ apoB v meat paste; NS v initial on meat paste.	Excellent design, includes 2 week run in; doesn't distinguish fish from n-3 fatty acids, large amt of n-3s.
Vessby and Boberg 1990 *Journal of Internal Medicine* 228:165.	Randomized double-blind placebo controlled crossover.	8 weeks	10 g MaxEPA v olive oil.	14 non-insulin dependent diabetics.	both oils ↓ VLDL, Chol, apoA-II; MaxEPA also ↓ TGs, BP, but NS between treatments; HbA_{1c}, glucose disappearance ↑ on MaxEPA, ↓ on olive oil.	Indicates potential adverse effect on glucose by omega-3 fatty acids.
Wahlqvist et al. 1989 *The Lancet* ii:944.	Non-blinded uncontrolled.	7 day diet records.	100 g fish/week	31 healthy 22 non-insulin-dependent diabetics.	↑ arterial compliance in fish group; ↓ posterior tibial artery resistance in healthy subjects.	Very small amount of fish (rather than FO supplement) was used in this study. Fish eaters were defined as those who ate one serving (100 g) or more of fish in a week. No total and/or a range of omega-3 fatty acids was given in the study.
Weintraub et al. 1988 *Journal of Clinical Investigation* 82:1884	Non-blinded uncontrolled.	25 days	3 diets; saturated fat; safflower oil; FO at 30% of fat.	8 healthy normolipidemic males.	↓ TGs, Chol more by FO than safflower; ↓ VLDL, LDL, HDL comparable v saturated fat diet except apoA ↓ on FO v saturated fat.	The fat content (42%) of the diet was too high but the study design using two controls, saturated fat and omega-6 fatty acids was good.
Wilt et al. 989 *Annals of Internal Medicine* 111:900.	Randomized, double-blind placebo-controlled crossover.	12 weeks each with 4-week washout.	20 g MaxEPA v safflower oil.	38 males w hypercholesterolemia.	↓ TGs; ↑ LDL; NS Chol HDL, apoA, apoB.	Patients were on American Heart Association step one low cholesterol, low sat fat diet and large amount of FO (20 g/p/d) was used. No GI side effect was reported. Compliance was monitored by blinded pill count and questionnaire rather than plasma lipid analysis.

TABLE 2.—OMEGA-3 FATTY ACIDS AND CORONARY HEART DISEASE: CLINICAL STUDIES—Continued

Reference	Design	Duration	Amount	Subjects	Findings	Comments
Zucker et al. 1988 *Artherosclerosis* 73:13.	Randomized, crossover.	6 weeks	3.2 g EPA 2.2 g DHA (MaxEPA) v safflower oil.	9 normal, 16 hyperlipoproteinemics.	↓ TGs, VLDL; ↑ LDL in type IV hyperlipoproteinemics; NS Chol, TG, LDL, HDL among normals.	Safflower oil was used a control oil. The stu design was double blir but many of the subjec reported identifying th FO by its characterist aftertaste. This is one the very few article r ported FO aftertaste in double blind study.

Abbreviations used: NS, not statistically significantly different; Chol, cholesterol; VLDL, very low-density lipoprtein cholesterol; LDL, low-density lipoprote cholesterol; HDL, high-density lipoprotein cholesterol, TGs, triglycerides; apoA, apoprotein A (a protein in high-density lipoprtoein); apoB; apoprotein B (a protein low-density lipoprotein); apoE, apoprotein E (a protein in many lipoproteins, most notably VLDL and HDL; CHD, coronary heart disease; FO, fish oil; TX thromboxane; TPA, tissue plasminogen activator; PAI, plasminogen activator inhibitor; v, versus; /d per day.

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21 CFR Part 101

[Docket No. 91N-0094]

RIN 0905-AB67

Food Labeling: Health Claims; Calcium and Osteoporosis

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to authorize the use on food labels and in labeling of health claims relating to the association between calcium and osteoporosis. FDA has reviewed the available scientific data under the provisions of the Nutrition Labeling and Education Act of 1990. Based on its review, FDA has tentatively concluded that there is significant scientific agreement among qualified experts that this data supports that calcium intake has a significant impact on bone health. The agency proposes that for a product to be eligible to bear such a claim, one serving of the product must contain a minimum of 20 percent of the Recommended Daily Intake (RDI) for calcium or 180 milligrams (mg) in an assimilable form.

DATES: Written comments by February 25, 1992. The agency is proposing that any final rule that may issue based upon this proposal become effective 6 months following its publication in accordance with requirements of the Nutrition Labeling and Education Act of 1990.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Mona S. Calvo, Center for Food Safety and Applied Nutrition (HFF-265), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-9564.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Nutrition Labeling and Education Act of 1990

On November 8, 1990, the President signed into law the Nutrition Labeling and Education Act of 1990 (Pub L. 101-535) (the 1990 amendments), which amend the Federal Food, Drug, and Cosmetic Act (the act). The 1990 amendments, in part, authorize the Secretary of Health and Human Services (the Secretary) to issue regulations authorizing nutrient content or health claims on the label or labeling of foods. With respect to health claims, the new provisions provide that a product is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition, unless the claim is made in accordance with the procedures and standards established under section 403(r)(1)(B) of the act (21 U.S.C. 343(r)(1)(B)).

Published elsewhere in this issue of the **Federal Register** is a proposed rule to establish general requirements for health claims that characterize the relationship of nutrients, including vitamins and minerals, herbs or other nutritional substances (referred to generally as "substances") to a disease or health-related condition on food labels and in labeling. In this companion document, FDA has tentatively determined that such claims would be justified only for substances in dietary supplements as well as in conventional foods if the agency determines based on the totality of the publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles) that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence.

The 1990 amendments also require (section 3(b)(1)(a)(ii), (b)(1)(A)(vi), and (b)(1)(A)(x)) that, within 12 months of their enactment, the Secretary shall issue proposed regulations to implemen section 403(r) of the act (21 U.S.C. 343(r)), and that such regulations shall determine, among other things, whether claims respecting 10 topic areas, including calcium and osteoporosis, meet the requirements of the act. In this document, the agency will consider whether a label or labeling claim on food or food products, including conventional foods and dietary supplements, on the relationship between calcium and osteoporosis would be justified under the standard proposed in the companion document entitled "Food Labeling: General Requirements for Health Claims for Food."

FDA has followed the general concepts and criteria proposed in the companion document in considering whether to propose to authorize the use on the labels and labeling of food of health claims for calcium and osteoporosis. In the companion document, FDA has proposed that, in evaluating whether support exists for a health claim, it will consider the levels and safety of a nutrient within the context of its use in the daily diet. Before a health claim for a particular nutrient will be authorized, it is necessary that the nutrient be safe and lawful for use in food at the level found to have an effect on a disease or health condition.

The topic of calcium and osteoporosis involves a substance which has recognized uses both as a component of food and of drugs. The agency has looked at all data relevant to this topic whether the data involved tests at dietary levels or at therapeutic levels. The agency thought this necessary to