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December 17, 2003

Food and Drug Administration
Dockets Management Branch
5630 Fishers Lane,
Room 1061, HFA-305,
Rockville, MD 20852

Re: Docket No. 2003Q-0401
Health Claim Petition, Omega-3 Fatty Acids and Coronary heart Disease

These comments are submitted on behalf of The Omega-3 Working Group of the Council for Responsible Nutrition (CRN),[1] hereinafter called THE CRN OMEGA-3 WORKING GROUP. We provide these comments relating to health claims for omega-3 fatty acids (EPA and DHA) in response to a petition filed by J. Emord and Associates. The CRN OMEGA-3 WORKING GROUP includes representatives of most of the global suppliers of EPA and DHA and was formed to develop quality standards for these fatty acids and to disseminate information about their health benefits.

Actions Requested

THE CRN OMEGA-3 WORKING GROUP requests that Food and Drug Administration (FDA) issue a rule to authorize a health claim for the relationship between omega-3 fatty acids (EPA and DHA) and heart disease. We believe the evidence supports a claim for primary prevention in the general population and a separate claim for secondary prevention in people with a history of heart disease.

2003Q-0401 C5

[1] CRN is one of the leading trade associations in the dietary supplement industry.

THE CRN OMEGA-3 WORKING GROUP asks FDA to authorize the health claim for omega-3 fatty acids (EPA and DHA) for all types of foods, including both conventional foods and dietary supplement products. If the agency determines that there is not significant scientific agreement in support of an unqualified health claim, then we request consideration of a qualified claim with more positive language than the currently permitted qualified health claim for omega-3 fatty acids.

Summary

1. Statements regarding the relationship of omega-3 fatty acids (EPA and DHA) and heart disease should be authorized by FDA as health claims for inclusion in product labeling for both conventional foods and dietary supplements. The following health claim is supported by the totality of the currently available scientific evidence, and there is significant scientific agreement regarding its validity:

   Diets low in saturated fat and cholesterol that include long chain omega-3 fatty acids (EPA and DHA) may reduce the risk of heart disease.

2. As FDA evaluates this claim, the agency should also consider authorizing an unqualified secondary prevention claim for populations with pre-existing heart disease. The following health claim is supported by the totality of the currently available scientific evidence, and there is significant scientific agreement regarding its validity:

   Diets that contain generous amounts of long chain omega-3 fatty acids (EPA and DHA) may reduce the risk of additional events in people with a history of heart disease.

3. The *Pearson* ruling requires that FDA consider whether health claims should be permitted that include a disclaimer, if an unqualified claim of benefit is not supported by significant scientific agreement. THE CRN OMEGA-3 WORKING GROUP agrees that if FDA does not permit an unqualified claim about a health benefit or substance/disease relationship, FDA should authorize the use of an appropriately qualified claim that is truthful and non-misleading, with a less negative qualifier than the existing qualified health claim on this subject.

Scientific Evidence on Omega-3 Fatty Acids and Coronary Heart Disease

Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the risk of coronary heart disease (CHD). The potential cardioprotective effects of omega-3 fatty acids have been attributed to their to their anti-arrhythmic, anti-thrombotic, hypotriglyceridemic, anti-inflammatory, and hypotensive actions (Connor, 2000; Harris et al, 2003; Leaf et al, 2003).

Summary of Randomized Clinical Studies

Prospective, secondary prevention studies of CHD have demonstrated that omega-3 fatty acids can significantly reduce the incidence of cardiovascular events, CHD mortality, and sudden cardiac death. The majority of the studies reported favorable effects with fish consumption and with supplements containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

1) The Diet And Reinfarction Trial (DART) showed a 29% reduction in all-cause mortality over 2 years in male survivors of previous MI advised to increase their consumption of fatty fish, i.e., 200-400 grams per week providing 0.5 to 0.8 grams omega-3 fatty acids (Burr et al, 1989). The most significant reduction in mortality was observed in fatal MIs. A subsequent analysis of a subset of men receiving daily supplements of 1.5 grams of fish oil (900 mg EPA + DHA) suggested that the protective effect was likely due to long chain omega-3 fatty acids (Burr et al, 1994).

2) The Indian Experiment of Infarct Survival (Singh et al, 1997) investigated the effects of omega-3 fatty acids in survivors of MI supplemented with daily doses of fish oil (1.08 grams EPA, 0.72 grams DHA) or mustard oil (2.9 grams/day, ALA) or placebo. After 1 year both the fish oil and mustard oil groups had significant reductions in total cardiac events, nonfatal infarctions, arrhythmias, left ventricle enlargements, and angina pectoris compared to placebo group. However, the fish oil group, and not the mustard oil group, also had a significant reduction in cardiac deaths.

3) The GISSI-Prevention Study randomized over 11,000 patients with preexisting CHD to receive omega-3 fatty acids (0.85 grams as EPA + DHA), vitamin E, (0.3 grams), both, or neither (GISSI-Prevenzione Trial, 1999). After 3.5 years, the group given the omega-3 fatty

acids alone had a 15% reduction in the primary endpoint of death, nonfatal MI, and nonfatal stroke. There was also a 20% reduction in all-cause mortality and a 45% reduction in sudden death. In a subsequent time-course assessment of omega-3 fatty acids on mortality in these patients, total mortality and sudden death were reduced after only 3 months and 4 months of treatment, respectively (Marchioli et al, 2002).

4) The results of one study failed to show an effect of a supplement (3.5 grams of EPA + DHA) on cardiac events in Norwegian survivors of MI after 3 years when compared with corn oil (Nilsen et al, 2001). The explanation for this finding was that the habitual fish intake in Norway might have provided maximal protection beyond which no additional effects would be expected from omega-3 fatty acid supplementation.

5) A meta-analysis of studies by Bucher (2002) concluded that dietary and nondietary intake of omega-3 fatty acids from fish or EPA +DHA supplements reduced overall mortality, mortality due to MI and sudden death in patients with CHD. The risk ratios were 0.8 for nonfatal MI, 0.7 for fatal MI, and 0.7 for sudden death.

6) A recent review by Leaf and coworkers (2003) summarized the clinical and mechanistic studies that support the anti-arrhythmic effect of omega-3 fatty acids from fish oil in the prevention of sudden cardiac death. Based on the current evidence they support daily supplementation of 0.6 grams of EPA + DHA from fish oils for individuals with a personal or family history of CAD and 1 to 2 grams of EPA + DHA for those with a family history of sudden cardiac death. In an editorial, Siscovick and coworkers (2003) endorsed the evidence proposed by Leaf and coworkers supporting the efficacy of omega-3 fatty acids in the prevention of sudden cardiac death.

Two of four clinical studies reported favorable effects of ALA, the precursor of EPA and DHA, in CHD disease.

1) The Indian Experiment of Infarct Survival described above (Singh et al, 1997) reported a significant reduction in cardiac events in the group consuming mustard seed oil (2.9 grams/day, ALA) for 1 year.

2) The Lyon Heart Study compared the reoccurrence rates of cardiac events in individuals consuming a Mediterranean diet (with increased amounts of ALA) or a typical Western diet (de Lorgeril et al, 1994, 1999). The difference in intakes of ALA between the two diet groups was 0.5 versus 1.5 grams per day. Marked reductions were observed in cardiac death, nonfatal MI, and other major secondary endpoints and minor events in the group consuming the Mediterranean diet. However, the benefits could not unambiguously be attributed to ALA because intakes of other dietary components were also different between the groups including saturated fat, cholesterol, monounsaturated fat, and fruits and vegetables.

3) In the Norwegian Vegetable Oil Experiment, men with no history of MI were randomized to receive daily doses of linseed oil (5.5 g per day of ALA) or sunflower seed oil for 1 year (Natvig et al, 1968). There were no differences in the number of new cases of CHD or sudden death in each treatment group and no differences in the number of deaths from any cause in the control versus the linseed oil group.

4) In the Mediterranean Alpha-Linolenic Enriched Groningen Dietary Intervention (MARGARIN) Study, free-living men and women with multiple CVD risk factors consumed margarines high in either ALA or linoleic acid (LA) and followed for 2 years (Bemelmans et al, 2002). The 10-year estimated ischemic heart disease risk decreased similarly in both groups. A trend toward fewer CVD events was observed in the group consuming ALA margarine.

A consistent finding in many studies reviewed by Gerster (1998) was that only a moderate increase in plasma or platelet ALA could be achieved following consumption of vegetable oils rich in ALA. A high proportion of the omega-6 fatty acid, linoleic acid (LA), found in typical Western diets, also appears to inhibit the uptake of ALA thereby limiting its availability as a precursor of EPA and DHA (Chan et al, 1993). In addition, there is evidence to suggest that dietary LA may negatively affect the efficiency of conversion of ALA to EPA and especially DHA. Using stable isotope tracers, Emken and coworkers (1994) determined a conversion rate of ALA to EPA of 6.0% and to DHA of 3.8% in humans. Moreover when dietary intake of LA was increased from 15 to 30 g/day, the conversion of both ALA and LA was reduced by 40-54%. Thus, in humans, body conversion of ALA to DHA is estimated to be below 5% (Brenna, 2002).

Summary of Epidemiological Studies

Several epidemiological studies within different populations of men and women related fish consumption with CHD. The majority of the studies reported favorable effects.

1) A reduction in CHD deaths, a 68% reduction in nonsudden death from myocardial infarction (MI) with daily fish consumption (≥ 35 grams) was observed in a 30-year follow-up of the Western Electric Study (Daviglus et al, 1997).

2) In an ecological study across 36 countries, fish consumption was associated with a reduced risk of mortality from all-cause, ischemic heart disease and stroke (Zhang et al, 1999).

3) A strong negative relationship between intake of omega-3 fatty acids from seafood and risk for sudden death was reported in a Seattle population-based, nested case-control study suggesting a cause and effect relationship (Siscovick et al, 1995, 2000). A modest intake of 5.5 grams of omega-3 fatty acids per month (equivalent to two fatty fish meals per week) was associated with a 50% reduction in the risk of primary cardiac arrest.

4) Oomen and coworkers (2000) reported a lower CHD mortality in populations from the Seven Countries Study that consumed fatty fish, but not lean fish suggesting that the protective effect may be due to EPA and DHA present in fatty fish.

5) In a prospective, 11-year follow-up of 20,551 men from the Physicians' Health Study (PHS), dietary fish consumption was associated with a reduced risk for total mortality and for sudden cardiac death in men consuming one fish meal per week compared to those consuming less fish (Albert et al, 1998). However, fish consumption was not associated with a reduced risk of total MI, non-sudden cardiac death or total CV mortality. These findings might have been due to the small fraction of the study population reporting little or no fish consumption.

6) A prospective, nested case-control analysis of men from the PHS provided supporting evidence for a cause and effect relationship between circulating levels of EPA + DHA and the risk of sudden cardiac death (Albert et al, 2002). Using men in the lowest quartile of

blood omega-3 fatty acid levels as a reference, the risk of sudden cardiac death was highly significantly reduced by 48%, 81%, and 90 % in the upper three quartiles of blood levels. The results of this study suggest that omega-3 fatty acids present in fish are strongly associated with a reduced risk of sudden death among men without prior cardiovascular disease

7) Similar findings were observed in the Kuopio Ischaemic Heart Disease Risk Factor Study, a prospective population study in Eastern Finland (Rissanen et al, 2000). Men in the highest quintile of serum DHA+DPA in all fatty acids had a 44% reduced risk of acute coronary events compared with men in the lowest quintile.

8) In a prospective, 12-year follow-up of the Health Professional Follow-up Study, a 40% lower risk of ischemic stroke was observed in men who consumed fish once per month compared with those who ate fish less often (He et al, 2002). These results suggest a that a low fish consumption was associated with a significantly lower risk of ischemic stroke.

9) In a prospective, 16-year follow-up of women in the Nurse's Health Study, the reduction in risk of CHD deaths from frequent fish consumption seemed to be stronger for CHD death than for nonfatal MI (Hu et al, 2002). In the same population of women, a higher consumption of fish among diabetic women was also associated with a lower CHD incidence and total mortality (Hu et al, 2003).

Some population studies did not report an association between fish intake and CHD mortality.

1) An inverse association between fish consumption and 25-year mortality from CHD was observed in the Seven Countries Study, but the association was not significant when confounding factors such as smoking were considered (Kromhout et al, 1996).

2) There was no benefit of fish intake on incidence and mortality from CHD in men during six years of follow-up of the Health Professional Follow-up Study (HPFS) (Ascherio et al, 1995).

3) In the EURAMIC Study (European Multicenter Case-Control Study on Antioxidants, Myocardial Infarction and Breast Cancer), adipose tissue DHA, a measure of long-term fish consumption, was not related to risk of MI (Guallar et al, 1999).

4) Osler and coworkers (2003) also did not report a protective effect of fish consumption on all-cause mortality or incident CHD in a Denmark population as a whole. However, among subjects with a high risk of CHD, there was a nonsignificant inverse relation between fish intake and CHD morbidity. Since there were relatively few cases in this subset of the study population, it could not be ruled out that frequent consumption of fish benefits those at high risk for CHD.

Explanations for the conflicting data in epidemiological studies may include differences in the type of fish meal consumed (Oomen et al, 2000; Mozaffarian et al, 2003) and how fish intake was estimated in different populations (Sheard, 1998). Kromhout and coworkers (1996) suggested that the conflicting data may reflect differences in definitions of sudden death, and the residual confounding of reference groups that had a less healthy lifestyle. The lack of effect observed in the HPFS may also be due to the study population of health professionals who may have reached the limit of benefit from lifestyle modifications. In the EURAMIC Study, only survivors of MI were evaluated, thus it is possible that individuals who did not survive consumed less fish (Guallar et al, 1999). The protective effect of fish consumption in reducing risk of CHD also relates to the CHD risk of the study population. In a rigorous analysis of 11 prospective studies, the protective effect of fish consumption reduced CHD mortality 40% to 60% in high risk populations, but not low risk populations (Marckmann and Gronbaek, 1999).

It is also speculated that the potential adverse effects of methylmercury, a contaminant found in certain fish may diminish the health benefits of EPA + DHA derived from fish (Rissanen et al, 2000). However, this issue requires further study because recent studies have reported conflicting results with regard to the effects of methymercury on CHD risk (Ahlquist et al, 1999; Salonen et al, 2000).

Three of five epidemiological studies reported an association between α-linolenic acid (ALA) intake and a lower risk of MI and CHD disease.

1) A dose-response relationship between ALA intake and reduction in risk of fatal ischemic heart disease was observed in women in the Nurses' Health Study (NHS) (Hu et al, 1999).

2) Similar finding were reported for men in the Health Professionals' Study (HPS), in which ALA intake was associated with a 0.41 relative risk for acute MI (Ascherio et al, 1996). In this study and the NHS, the lowest quintile intakes were ranged from 0.7 to 0.8 grams ALA per day and the highest quintile intakes ranged from1.4 to1.5 grams ALA per day.

3) In a cross sectional analysis of the National Heart, Lung, and Blood Institute Family Heart Study, ALA intake was associated with a reduced odds prevalence of coronary artery disease of ~ 40% in men and 50% to 70% in women (Djousse et al, 2001). In a more recent cross-sectional analysis of this population, linolenic acid intake was associated with a lower risk of carotid atherosclerosis specifically prevalence of carotid plaques and lower carotid intima-media thickness (Djousse et al, 2003).

4) In the EURAMIC study, Guallar and coworkers (1999) reported an inverse relationship between adipose ALA levels and risk for MI, but this became insignificant after controlling for classic risk factors, primarily smoking.

5) In the Zutphen Elderly Study, there was no beneficial effect of ALA intake on risk of CAD incidence in men (Oomen et al, 2001). Potential explanations for these findings were that ALA was associated with trans fatty acid intake and the collection of the dietary intake data had several limitations.

In summary, data from epidemiological and clinical studies suggest that omega-3 fatty acids, especially those from marine sources:

- may reduce the risk of cardiovascular-related death by 29-52% and reduce the risk of sudden cardiac death by 45-81% (Carroll and Roth, 2002).
- the greater number of studies reporting the protective effects of marine-derived omega-3 fatty acids compared to those reporting benefits from plant-derived omega-3 fatty acids suggests that the current scientific evidence is stronger for EPA + DHA than for their precursor, ALA.

Based on the evidence from the prospective secondary prevention studies, intakes of EPA + DHA ranging from 0.5 to 1.8 grams per day from fatty fish or EPA + DHA supplements significantly reduced cardiac and all-cause mortality.

Reports from Scientific Organizations

American Heart Association

The American Heart Association endorsed the emerging clinical benefits of omega-3 fatty acids and CVD observed in epidemiological and clinical trials in recommendations published in 2000, 2002, and 2003 (Krauss et al, 2000, 2002, and 2003). In the 2003 recommendations, the AHA supported the view that the scientific evidence is stronger for EPA + DHA than for their precursor, ALA (Kris-Etherton et al, 2003). The report states,

"Randomized trials have convincingly documented that omega-3 fatty acids can significantly reduce the occurrence of CVD events in patients with coronary artery disease. The strongest evidence to date is from studies in which marine-derived omega-3 fatty acids have been consumed as supplements or fish. Additional clinical studies are needed to confirm the cardioprotective benefits of ALA.", and "ALA appears to be less potent than EPA and DHA."

The AHA advocates a dietary approach to increasing EPA + DHA intake by healthy adults, i.e. fish consumption two times per week and plant-derived omega-3 fatty acids, but also recognized that protective levels for CAD may be difficult to achieve by diet alone. Thus, the AHA recommended supplemental intakes of EPA and DHA by individuals with CAD of ~1.0 gram per day and for those needing triglyceride-lowering, intakes of 2 to 4 grams per day under the direction of a physician .

To summarize, the AHA recommendations include:

- **For the general healthy population:** Eat a variety of fish (preferably oily fish) at least twice a week. Also include foods rich in alpha-linolenic acid in the diet.
- **For patients with documented CHD:** Consume 1 g of EPA/DHA per day, preferably from oil fish. EPA/DHA supplements could be considered in consultation with the physician.
- **For patients with elevated triglycerides:** Consume 2 to 4 grams of EPA/DHA per day, as dietary supplements, under a physician's care.

Workshop on the Essentiality of and the Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids - 1999

In1999, an international group of experts from academia, government, international organizations and industry convened to discuss the importance of omega-3 fatty acids in infant nutrition, in cardiovascular disease and in mental health. The sponsors of the workshop included the National Institute on Alcohol Abuse and Alcoholism (NIH); the Office of Dietary Supplements (NIH); The Center for Genetics, Nutrition and Health; the International Society for the Study of Fatty Acids and Lipids (ISSFAL); and the National Institute of Child Health and Human Development (NIH).

Based on intake levels of healthy people, the working group from this workshop recommended an adequate intake level for adults of 0.65 grams of EPA + DHA per day (0.3% of energy) based on a 2000 kcal diet (Simopoulos et al, 1999).

Institute of Medicine

A review of the epidemiological and clinical studies on the health benefits of omega-3 fatty acids was published in 2002 by the Institute of Medicine (IOM) in *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids* (Institute of Medicine, 2002). Studies published as of 2001 were reviewed by an expert panel. In the final IOM report, it was concluded that ALA was an essential fatty acid based on the evidence that humans do not synthesize ALA and that the lack of ALA results in adverse symptoms in clinical studies.

The panel's review of studies on omega-3 fatty acids and CHD focused on the overwhelming majority of studies that specifically examined the impact of EPA and DHA, rather than ALA. The report recognized that EPA and DHA were associated in many studies with preventing CHD, arrhythmias, and thrombosis. However, the expert panel did not establish a Recommended Dietary Allowance (RDA) or adequate intake (AI) for EPA and DHA, on the basis of this evidence. Instead, they established a dietary recommendation based on the amount of omega-3 fatty acids needed to avoid a deficiency of essential fatty acids. They recommended an adequate intake (AI) for ALA, based on the highest median intake of ALA by free-living adults in the United States, in which a deficiency is nonexistent.

The AI for adults was established at 1.6 and 1.1 grams of ALA per day for men and women, respectively. The report further noted that "Small quantities of EPA and DHA may contribute to a reversal of a deficiency" and noted that, currently, "EPA and DHA comprise up to 10% of total omega-3 fatty acid intake." These observations are related to current patterns of intake and to avoidance of essential fatty acid deficiency, and not to potential protection against risk of heart disease.

Other National Bodies:

A number of other countries (Canada, Sweden, United Kingdom, Australia, Japan), as well as the World Health Organization and the North Atlantic Treaty Organization, have made formal dietary recommendations for the general population for intakes of omega-3 fatty acids. Typical recommendations are in the range of 0.3 to 0.5 grams per day of EPA/DHA and 0.8 to 1.1 grams per day of alpha-linolenic acid. (Kris-Etherton et al, 2002)

Recommendations of THE CRN OMEGA-3 WORKING GROUP
Regarding the Level of Omega-3 Fatty Acids
In Foods Bearing a Health Claim

Based on the results of clinical studies and recommendations from the AHA and the consensus of an international community of experts organized by ISSFAL, THE CRN OMEGA-3 WORKING GROUP believes that a health claim should be permitted for conventional foods, fortified foods, and dietary supplements providing meaningful levels of EPA and DHA. We believe the evidence supports a health claim for primary prevention in the general population and a separate health claim for secondary prevention in people with a history of heart disease.

1. The prospective secondary prevention studies observed significant reductions in cardiac and all-cause mortality with EPA + DHA intake ranges between 0.5 to 1.8 grams per day.

2. The AHA has recommended increased consumption of fish (2 servings per week) and plant-based sources of ALA for the general population and ~ 1.0 grams of EPA + DHA per day from fish or supplements for individuals with CHD.

3. Consensus of an international community organized by ISSFAL has recommended 0.65 grams of EPA + DHA per day.

4. THE CRN OMEGA-3 WORKING GROUP proposes **0.5 grams EPA + DHA per day,** the lower end of the range of intakes shown to be beneficial in clinical studies, as a target daily intake for the primary prevention health claim, whether the source be from conventional foods, food fortification, or dietary supplements. In other health claim rules, FDA has adopted various rationales for calculating the threshold amount of the target nutrient that must be provided by foods. In cases where the substance eligible for the health claim did not have an established DV, the agency has generally established 25% of the target daily intake as the amount required per serving of the food. This was done in the case of the oat, psyllium, soy protein, and stanol/sterol ester claims. In cases where the substance has an established DV, the general requirements for health claims provide that the food should contain 20% of the DV in order to be eligible for the claim. This rule was applied for purposes of the calcium claim. However, FDA has permitted several health claims for foods that have only 10% of the DV and thus qualify as a "good source" of a nutrient, in order to make a larger number of foods eligible for the claim. This was the option selected in the case of the claims for dietary fiber, antioxidants, and folate. Since there is no DV established for long chain omega-3 fatty acids (EPA and DHA), the appropriate model in this case would be the first one mentioned above, requiring that the food provide **25% of the target intake per serving, or 125 mg.** Fatty fish that naturally contain EPA and DHA will generally provide levels considerably above this amount. Several varieties of salmon, for example, provide 680 mg to 1.8 grams of EPA and DHA per 3-ounce serving, and other fish (sardines, mackerel, trout, tuna) also provide amounts in excess of 240 mg per 3-ounce serving, ranging upward to 1.7 g. However, numerous foods are currently being fortified with EPA and DHA, and the amounts added may in some cases not reach the threshold of 125 mg per serving. If the agency determines that it would be desirable for such products to be eligible for the claim, it may be appropriate to consider a lower threshold of **100 mg per serving.**

5. THE CRN OMEGA-3 WORKING GROUP proposes **1.0 gram EPA + DHA per day** as a target daily intake for the secondary prevention health claim, whether the source be from conventional foods, food fortification, or dietary supplements. For the secondary prevention claim, the qualifying level for conventional or fortified foods should be 25%

of this amount, or **250 mg EPA + DHA per day.** The recognized rich conventional food sources of long chain omega-3 fatty acids will be able to meet this qualifying level.

6. EPA and DHA are fatty acids not effectively synthesized in the body. EPA and DHA are precursors of cellular membrane lipids, eicosanoids, which are important mediators in normal physiological and inflammatory processes. As precursors for these processes, EPA and DHA compete with another class of lipids that are more prevalent in the Western Diet -- the omega-6 fatty acids. The conversion of the shorter chain omega-3 polyunsaturated fatty acid, alpha linoleic acid ALA to eicosapentanoic and docosahexanoic is poor in humans as demonstrated by Emken et al. (Presentation by Emken at 2003 Annual Meeting, American Oil Chemists Society, DRI Symposium Workshop, Appendix 1)

7. During the previous rulemaking on health claims for omega-3 fatty acids (EPA and DHA) and heart disease, FDA concluded that "fish oils reduce plasma triglycerides." Studies published since that time using both dietary supplement and conventional food sources of omega-3 fatty acids (EPA and DHA) in both normal and sub populations (hyperlipidemic, heart disease and diabetic) continue to support the effectiveness and safety of EPA and DHA for lowering triglycerides. In addition, there are significant other beneficial effects linked to EPA and DHA that could contribute to prevention of heart disease (Connor 2000, Harris et al 2003, Leaf et al 2003). These include:

   - Prevention of arrhythmia (ventricular tachycardia and fibrillation);
   - Antithrombotic activity;
   - Hypolipidemic properties on triglycerols and VLDLs;
   - Precursors of prostaglandins and leukotrienes;
   - Inhibition of cytokine and mitogen synthesis;
   - Stimulation of endothelial-derived nitric oxide;
   - Anti-inflammatory properties; and
   - Inhibition of atherosclerosis.

   The effects listed above have been demonstrated through *in vitro* and *in vivo* animal studies and in clinical studies that continue to examine the role of omega-3 fatty acids

(EPA and DHA) in modulating all of these effects. The data are very strong in supporting the link between omega-3 fatty acids (EPA and DHA) and triglycerol lowering, antithrombotic activity, and anti-arrhythmic activity.

8. Certain issues regarding the safety of omega-3 fatty acids (EPA and DHA) – prolonged bleeding time, alteration of glycemic control and elevation of LDL cholesterol -- have been raised in the past. FDA considered these issues in the affirmation of the general recognition of safety of menhaden oil and determined that consumption of up to 3g/day of EPA and DHA is safe.

9. **Safety and Contaminants in Fish Derived Products.** Fish oil products marketed by the vast majority of producers today are made by using specific refining techniques ensuring the removal of contaminants such as mercury, other heavy metals, pesticides and dioxins, often to levels below detection. THE CRN OMEGA-3 WORKING GROUP recently developed a monograph specifically addressing these and other issues affecting high quality oils and powders. The U.S. Pharmacopeia is currently reviewing a monograph for EPA and DHA that will also specifically establish tolerances or limits for contaminants associated with such natural products. Highly refined fish oils are safe to ingest at the levels recommended, when added to foods or when consumed as supplements, and indeed have been demonstrated to have much lower levels of environmental contaminants than many of the fresh fish recommended by several scientific bodies.

10. Clinical and epidemiological evidence support the positive health benefits of increasing the intake of omega-3 fatty acids (EPA and DHA) in the American diet. The totality of the evidence examining cardiovascular disease endpoints as well as clinical effects supports an association of long chain omega-3 fatty acids (EPA and DHA) with a reduced risk of heart disease. FDA approval of a health claim will aid consumers by providing meaningful information on the health benefits of products containing omega-3 fatty acids (EPA and DHA). Permitting unqualified health claims for these well recognized beneficial nutrients would also be consistent with the FDA's stated intention to develop dietary guidance regarding the importance of omega-3 fatty acids, in the context of a

major initiative to make more and better information about conventional foods and dietary supplements available to the public.

11. In addition to providing health messages which are truthful and not misleading to consumers, the proposed health claim may provide reductions in health costs to consumers, insurers and the Federal government through the reduction of the incidence of cardiovascular disease. The American Heart Association and other institutions have estimated the annual costs of CVD to the nation to be approximately three hundred billion dollars. There is a very real potential for omega-3 polyunsaturated fats (EPA and DHA) to ameliorate CVD and accordingly to reduce medical costs relating to CVD. THE CRN OMEGA-3 WORKING GROUP is currently supporting a study seeking to more accurately quantify this benefit. Even if the reduction were as low as ten percent, this would represent a saving of thirty billion dollars in the nation's annual health care costs.

Omega-3 Fatty Acids Eligible for the Health Claim

Omega-3 Fatty Acids (EPA and DHA) are defined in this submission as in FDA's previous ruling on this issue[2]. In the previous rulemaking, FDA limited the term omega-3 fatty acids (EPA and DHA) to eicosapentaenoic acid (EPA, 20 carbons, 5 double bonds) and docosahexaenoic acid (DHA, 22 carbons, 6 double bonds). The source of EPA and/or DHA can be naturally occurring in conventional food, added to conventional food, or provided in the form of a dietary supplement.

Language of the Health Claim for Primary Prevention:

1. **Diets low in saturated fat and cholesterol that include long chain omega-3 fatty acids (EPA and DHA) may reduce the risk of heart disease.**

2. **Development of heart disease depends on many factors. Eating a diet low in saturated fat and cholesterol and high in long chain omega-3 fatty acids (EPA and DHA) may reduce the risk of heart disease.**

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[2] Food Labeling: Health Claims and Label Statements: Omega-3 Fatty Acids and Heart disease. January 6, 1993 *Federal Register* 58 (b) at p 2683.

Foods Eligible for the Health Claim for Primary Prevention

In order to bear the health claim for primary prevention, foods must contain a minimum of 125 mg of long chain omega-3 fatty acids (EPA/DHA) per RACC and be a low fat, low saturated fat, low trans fat, low cholesterol food.

Dietary Supplements Eligible for the Claim for Primary Prevention

In order to bear the health claim for primary prevention, dietary supplements must provide at least 500 mg EPA/DHA per day and must meet quality standards equivalent to those specified in the monograph for long chain omega-3 fatty acids (EPA and DHA) established by the CRN Omega-3 Working Group.

Language of the Health Claim for Secondary Prevention:

Diets that contain generous amounts of long chain omega-3 fatty acids (EPA and DHA) may reduce the risk of additional events in people with a history of heart disease.

Foods Eligible for the Health Claim for Secondary Prevention

In order to bear the health claim for secondary prevention, foods must contain a minimum of 250 mg of long chain omega-3 fatty acids (EPA/DHA) per RACC and be a low fat, low saturated fat, low trans fat, low cholesterol food.

Dietary Supplements Eligible for the Claim for Secondary Prevention

In order to bear the health claim for secondary prevention, dietary supplements must provide at least 1000 mg EPA/DHA per day and must meet quality standards equivalent to those specified in the monograph for long chain omega-3 fatty acids (EPA and DHA) established by the CRN Omega-3 Working Group.

Conclusion

THE CRN OMEGA-3 WORKING GROUP appreciates FDA's consideration of these comments, as the agency considers once again whether to authorize an unqualified primary prevention health claim relating to long chain omega-3 fatty acids (EPA and DHA) and reduced risk of heart disease. We also urge consideration of a health claim for secondary prevention relating to a reduced risk of additional events in people who already have a history of heart disease. Both of these claims are supported by the available scientific evidence, and there is significant scientific agreement regarding their validity, as shown by current recommendations of the American Heart Association and other organizations, nations, and international bodies.

Respectfully,

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Appendix 3.

Omega-3 Health Economics Literature Abstraction (Exponent Project #WD00756.000)

Studies with Drug Intervention

Citation & Study Type	Population	Intervention(s)	Outcomes
Albert et al., 2002 Prospective cohort study with 17-year follow-up (*Physicians' Health Study*)	N=22,071 US men with no hx of MI aged 40-84 years	▪ aspirin ▪ beta-carotene ▪ aspirin and beta-carotene, or ▪ both placebos Fish intake obtained via FFQ	Age-, smoking-, and risk-adjusted RR of sudden death from cardiac causes was lower for highest quartiles of n-3 intake at baseline (6.87%) vs. lowest intake quartile (3.58%) (RR=0.10, 95% CI 0.02 to 0.48) and for second-highest quartile (5.63%) vs. lowest intake quartile (RR=0.19, 95% CI 0.05 to 0.69)
Durrington et al., 2001 Randomized, controlled, double-blind trial (24 weeks) with three year open extension	N=59 UK pts aged ≤75 years with CHD receiving Simvastatin	▪ Omacor* (2g bid) (n=30), or ▪ placebo (n=29)	Omacor pts had significant decreases in triglycerides and very low density lipoprotein cholesterol at all assessments (3, 6, 12 months) AEs reported by over half the participants (22 Omacor patients, 17 placebo patients)

Citation & Study Type	Population	Intervention(s)	Outcomes
Marchioli et al., 2002 Randomized, open-label, parallel, clinical trial, 3.5-year follow-up *(GISSI-Prevenzione)*	N=11,324 pts with recent (≤ 3 months) MI 14.7% women	▪ n-3 PUFAs 1g/d (n=2836) ▪ vitamin E 300mg/d (n=2830) ▪ both (n=2830), or ▪ control (n=2828) All groups instructed in lifestyle and dietary changes	Both 2-way and 4-way analyses found decreased RR of main endpoints (death/non-fatal MI/non-fatal stroke and cardiovascular death/non-fatal MI/non-fatal stroke) for n-3 recipients Secondary analyses of all fatal events, cardiovascular deaths, cardiac death, coronary death, sudden death (all significantly lower for n-3 recipients) and other deaths and non-fatal cardiovascular events (similar across groups) Note: Several GISSI publications exist, but each includes additional verification of previously-published outcomes.
Nenseter et al., 2000 Randomized, double-blind, parallel-treatment study with 12- week follow-up	70 Norwegians with hypercholesterolemia Aged 30-75 Nonsmokers	▪ fish powder (10 g/day) (n=36), or ▪ placebo (n=34) Pts provided blood samples	Non-significant increase in omega-3 levels between groups Researchers speculate dose may have been too low or population may have had high levels at baseline
Nilsen et al., 2001 Randomized controlled, double-blind trial with 18-months follow-up	N=300 pts with an acute MI 21% women Mean age 64 years	▪ 2 capsules of corn oil, or ▪ Omacor-R bid	Unadjusted HR was not significantly different across treatment groups for single or combined cardiac events (cardiac death, resuscitation, recurrent MI, or unstable angina)

Citation & Study Type	Population	Intervention(s)	Outcomes
Singh et al., 1997 Randomized, double-blind, placebo-controlled trial with 1-year of follow-up *(Indian Experiment of Infarct Survival)*	N=360 Indian men with suspected AMI Mean age 48.5, 48.0, and 49.2 for the fish oil, mustard oil, and placebo group, respectively	▪ fish oil (1.08 g/day EPA) (n=122) ▪ mustard oil (2.9 g/day α-linolenic acid) (n=120), or ▪ placebo (n=118)	Non-significant reduction in sudden cardiac deaths for treatment groups vs. placebo Significant reduction in total cardiac deaths and nonfatal reinfarction for both treatment groups vs. placebo Significant decrease in total cardiac events for fish oil pts vs. placebo (RR=0.70, 95% CI 0.29 to 0.90)
von Schacky et al., 1999 Randomized, controlled, double-blind trial with 2-year follow-up	N=223 pts with CAD 12% women Mean age 58-59 years	▪ fish oil concentrate, or ▪ placebo containing fatty acids matching usual European diet (6 g/day for 3 months and 3 g/day for next 21 months)	Progression or regression of CAD via angiogram No data on RR of death or coronary events presented

Studies with Non-Drug Interventions

Citation & Study Type	Population	Intervention(s)	Outcomes
Burr et al., 1989 Randomized, controlled trial with 2-year follow-up *(Diet And Reinfarction Trial – DART)*	N=2033 European men with first MI aged <70 years	▪ receive dietary advice on fat, fish, and fiber ▪ no dietary advice	At 2 years, physiological tests confirmed following dietary advice Participants who received fish advice (estimate 2.4 g EPA/week at 2 years) had significantly fewer deaths (all and IHD) than those who did not receive fish advice (estimate 0.6 g EPA/week at 2 years) Adjusted RR of death or IHD event by fish advice (RR=0.71, 95% CI 0.54 to 0.93 and RR=0.84, 95% CI 0.84 to 1.07, respectively)
de Lorgeril et al., 1999 Randomized, single blind trial with 27-month follow-up (*Lyon Diet Heart Study*)	N=425 French pts aged <70 years hospitalized for MI (204 control, 219 experimental)	Pts who agreed to participate (experimental group) were told to adhere to a Mediterranean-type diet (more bread, more root vegetables and green vegetables, more fish, fruit at least once daily, less red meat, and use of margarine, use of rapeseed and olive oil) Others (control group) were advised to watch their diets in general	Three different composite endpoints developed: ▪ CO 1 – cardiac death and nonfatal MI ▪ CO 2 – CO 1 plus unstable angina, stroke, heart failure, pulmonary or peripheral embolism ▪ CO 3 – CO 1 plus minor events requiring hospital admission Mediterranean diet was associated with a significantly lower RR for each composite endpoint (multivariate proportional-hazards analyses) Other risk factors examined included age, smoking, cholesterol, blood pressure, leukocyte count (all not significant), sex, and aspirin use

Studies with No Interventions (Fish Consumption Measured)

Citation & Study Type	Population	Intervention(s)	Outcomes
Ascherio et al., 1995 Prospective cohort with 6-year follow-up (*Health Professionals Follow-up Study*)	N=44,895 US men without CVD aged 40-75	Participants completed food-frequency diaries	Age-adjusted RR 1.19 (95% CI, 1.02 to 1.39) for coronary event for highest n-3 intake group (mean 5.8 servings per week) vs. lowest (mean 1.2 servings per week) Age-adjusted RR 1.10 (95% CI, 0.56 to 2.13) for sudden death not significantly different for the highest vs. lowest n-3 intake groups Age-adjusted RR 1.16 (95% CI, 0.89 to 1.53) for coronary event for highest fish consumption group vs. lowest group Data on dark-meat fish vs. other fish and adjustments for cardiovascular risk factors
Daviglus et al., 1997 Prospective cohort with 30-year follow-up (*Chicago Western Electric Study*)	N=1822 US men without CVD aged 40-55 years	Participants interviewed by nutritionist about consumption	Adjusted RR of death from MI, CHD, and nonsudden MI death at 30 years were lower for those consuming ≥35 g/day of fish compared with those consuming 0g/day (RR=0.56, RR=0.62, R=0.33 respectively) Data on RR of death of MI, CHD, CVD, and all causes for 2 other levels of fish consumption (1-17 g/day, and 18-34 g/day).
Dewailly et al., 2001 *(1990 Quebec Heart Health and Nutrition Survey)*	N=1460 51% women Mean age 40 (18-74)	Participants provided dietary information at home interviews and blood samples at clinic visits; fish intake data obtained by FFQ	Positive associations between EPA and DHA with a number of clinical measures, including LDL cholesterol, HDL cholesterol, plasma glucose, blood pressure, triacylglycerols, and insulin

Citation & Study Type	Population	Intervention(s)	Outcomes
He et al., 2002 Prospective cohort study with 12-year follow-up *(Health Professional Follow-up Study)*	N=43,671 US male health care professionals aged 40-75 years No previous stroke, MI, coronary artery surgery, angina pectoris, peripheral arterial disease, diabetes, transient ischemic attack or other CAD	Participants completed a questionnaire about diet, lifestyle, and medical history	RR adjusted for smoking, BMI, physical activity, other risk factors and based on cumulative average fish intake Consumption of fish 1-3 times per month was associated with a significant reduction in risk of ischemic stroke (RR, 0.57, 95% CI, 0.35-0.95); no further benefit was observed at higher levels of fish intake Multivariate RR for men who consumed fish ≥ once per month vs. < once per month was 0.56 (95% CI, 0.38-0.83) for ischemic stroke, 1.36 (95% CI, 0.48-3.82) for hemorrhagic stroke, and 0.72 (95% CI, 0.52-1.01) for total stroke
Iso et al., 2001 Prospective cohort study with 14-year follow-up *(Nurses' Health Study)*	N=79,839 female RNs in the US aged 30-55 years No hx of cancer, angina, MI, diabetes, coronary revascularization, stroke or other CAD	Participants completed questionnaire about lifestyle and medical history	Age-, and smoking-adjusted RR for total stroke was lower for those who ate fish once per week compared to those who ate it < once per month (RR 0.66, 95% CI, 0.47 to 0.93) Higher frequency of fish intake was associated with a decreased RR (adjusted for age and smoking status, p for trend=0.005) of total stroke Higher quintile of average n-3 polyunsaturated fatty acid level was associated with a decreased RR for total stroke (adjusted for age and smoking, p for trend=0.01); women in highest quintile of intake had reduced risk of total stroke (RR adjusted for age and smoking, 0.66, 95% CI, 0.51 to 0.86)

Citation & Study Type	Population	Intervention(s)	Outcomes
Orencia et al., 1996 Long-term, prospective population study with 30-year follow-up *(Chicago Western Electric Study)*	N=1847 US men aged 40-55 years	Participants completed interviews of dietary patterns	Categorized into groups by fish intake, ≥35g/day, 18 to 34 g/d, and 1 to 17 g/d, risk of fatal stroke for fish consumers compared with nonconsumers were 1.34 (0.53 to 3.41) 0.96 (0.41 to 2.21) and 1.00 (0.43 to 2.33) for intake groups, respectively Hazard ratios adjusted for age, SBP, cigarette smoking, serum cholesterol level, diabetes, ECG abnormalities, table salt use, alcohol intake, and macronutrients and micronutrients No significant differences in fatal or nonfatal stroke by fish consumption
Tavani et al., 2001 Case-control study	N=985 Italians aged 25-79 years Cases admitted to hospital with nonfatal AMI (507) Controls admitted to hospital for reason other than AMI (478)	Participants completed interviews on diet and lifestyle	OR (adjusted for age, sex, smoking, and other risk factors) for nonfatal AMI was 0.68 (95% CI, 0.47 to 0.98) for those with highest n-3 PUFA intake (≥2 portions of total fish/wk) compared with patients with lowest tertile of n-3 PUFA intake (<1 portion of fish/wk)

Studies with No Intervention (Fatty acids measured)

Citation & Study Type	Population	Intervention(s)	Outcomes
Albert et al., 1998 Prospective cohort study with 11 year follow-up (Physicians' Health Study)	20,551 US men, no Hx MI, stroke, TIA, cancer, aged 40-84 years at baseline	Participants completed semiquantitative food frequency on fish consumption	Adjusted (age, Hx CVD, BMI, smoking, Hx diabetes, Hx hypertension, Hx hypercholesterolemia, alcohol, exercise, vitamin supplements) RR for sudden death at 11 years was lower for those in the highest quintile of omega-e fatty acid intake (≥ 7.4 g/month) vs. lowest (<0.3 g/mo). (RR = 0.43, 95% CI 0.20-0.93)
Erkkilä et al., 2003 Prospective cohort study (secondary prevention) with 5-year follow-up	285 men and 130 women with CAD, aged 33-74 years	Dietary intakes estimated by food records. Fatty acid intake estimated by measuring composition of serum cholesteryl esters (CEs)	Adjusted for CVD risk factors, RRs for CVD mortality in the highest intake tertile compared to the lowest tertile were: 0.33 (95% CI: 0.11, 0.96; p(trend)=0.063) for ALA; 0.33 (0.12, 0.93, p(trend)=0.056) for EPA; and 0.31 (0.11, 0.87, p(trend)=0.026) for DHA. Adjusted for CVD risk factors, RRs for CAD mortality in the highest tertile of fatty acids in serum cholesteryl esters, compared to the lowest tertile was: 0.31 (0.08, 1.14, p(trend)=0.034) for EPA.
Guallar et al., 2002 Case-control study	N=1408 European and Israeli men aged ≤70 years Cases with first acute MI (n=684) ; Controls with no hx of MI (n=724)	Fatty acids in adipose tissue assayed and DHA levels calculated	Adjusted (BMI, smoking status, alcohol intake, mercury levels, other risk factors) OR for first MI significantly lower for highest quintile of DHA levels compared to the lowest quintile (OR=0.59, 95% CI 0.30 to 1.19) OR of first MI by quintile of mercury level was 2.16 (95% CI 1.09 to 4.29)

Citation & Study Type	Population	Intervention(s)	Outcomes
Hu et al., 1999 Prospective cohort with 10-year follow-up *(Nurses' Health Study)*	N=76,283 US women aged 38-63 at baseline, without CAD or cancer	Participants completed a food frequency diary	Age-, smoking-, and risk-adjusted RR of fatal CHD at 10 years was lower for those with the highest α-linolenic acid intake (1.36 g/day) vs. lowest (0.71 g/day) (RR=0.55, 95% CI 0.32 to 0.94) Age-, smoking- and risk-adjusted RR of nonfatal MI at 10 years was similar across quintiles of α-linolenic acid intake
Hu et al., 2002 Prospective cohort with 16-year follow-up (*Nurses' Health Study*)	N=84,688 US women Aged 34-59 at baseline, Without CVD or cancer	Participants completed semiquantitative food frequency questionnaire	Age-, smoking-, *trans*-fats, P/S ratio, fiber, and other CVD risk factor-adjusted RR of CHD at 16 years was lower for those in the highest quintile of omega-3 fatty acid intake (0.24% of calories) vs. lowest (0.03% of calories) (RR=0.69, 95% CI 0.57 – 0.84) The corresponding association for fatal CHD was stronger (RR=0.62, 95% CI 0.44 – 0.88)
Jouven et al., 2001 Prospective study with average of 22-year follow-up *(Paris Prospective Study I)*	N=5250 French men employed by Paris Civil Service aged 42-53 years	Participants underwent physical examination including ECG, physical, blood samples, and questionnaires from 1967-1972; second examination deadline 1/94	RR (adjusted for age, BMI, heart rate, SBP or DBP, smoking, parental hx of MI and parental hx of sudden death, cholesterol, triglycerides, fasting plasma glucose and insulin concentration) for NEFA associated with sudden death was 1.70 (95% CI, 1.21 to 2.13), with fatal MI RR 0.94 (0.75 to 1.09) Note: NEFA (also called free fatty acids)

Citation & Study Type	Population	Intervention(s)	Outcomes
Lemaitre et al., 2002 Case-control study nested in the *Cardiovascular Health Study*	N=358 US men and women aged ≥65 years Cases (179; 54 with fatal MI and other IHD death, 125 with nonfatal MI); Controls (179) matched by sex, clinical site and entry cohort, no hx of IHD or stroke	For Cardiovascular Health Study, at baseline and 3rd year of follow-up, participants completed standard health questionnaires, clinical exam, and gave blood samples Nested-case control study measured plasma phospholipid concentrations of n-2 polyunsaturated fatty acids in blood samples	OR of fatal IHD associated with each SD increase in plasma phospholipid polyunsaturated fatty acid concentration (DHA and EPA) was 0.30, (95% CI, 0.12 to 0.76); for a 1-SD increase in α-linolenic acid, OR was 0.48 (95% CI, 0.24 to 0.96); linoleic acid was associated with an increased risk of incident fatal MI (OR 2.42, 95% CI, 1.07 to 5.43) None of the PUFAs were associated with risk of nonfatal MI Note: Cases had more IHD risk factors at baseline
Oomen et al., 2001 Prospective cohort study with 10-year follow-up (*Zutphen Elderly Study*)	N=667 Dutch men without CAD aged 64-84 years	Participants completed a food frequency interview	Age-, and energy-adjusted RR of CAD (fatal and non-fatal) at 10 years was 2.23 (95% CI, 1.32 to 3.76) for the highest consumption tertile (≥0.58% of energy) vs. lowest (<0.45% of energy) from α-linolenic acid; p for trend was 0.003
Pedersen et al., 2000 Case control study	N=219 Norwegians aged 45-75 years with no serious diseases Cases with first AMI (112); Controls (107)	Subcutaneous adipose tissue taken from the buttock by needle aspiration to determine content of fatty acids Diet assessed using validated FFQ; total energy and fatty acid composition calculated using official Norwegian food composition table	OR for risk of MI (adjusted for age, sex, waist-to-hip ratio, smoking, family hx of CHD, and content of trans fatty acids) in highest quintile of VLC n-3 fatty acids versus lowest quintile was 0.17 (95% CI, 0.04-0.76) and the p for trend 0.016 Trans fatty acids, linoleic and α-linolenic acid were intercorrelated and associated with an increased risk of MI

Citation & Study Type	Population	Intervention(s)	Outcomes
Rissanen et al . 2000 Prospective cohort study with average of 10-years follow-up (*Kuopio Ischaemic Heart Disease Risk Factor Study*)	N=1871 Finnish men with no CHD aged 42-60	Serum DHA+DPA assessed at baseline	Age-, smoking-, and risk-adjusted RR of acute coronary events 0.44 (95% CI, 0.11 to 0.65) for highest quintile of serum DHA+DPA (<3.58%) compared with lowest quintile (<2.38%) Fish or n-3 consumption not evaluated directly
Simon et al., 1995 Nested case-control study with average of 6.9 years of follow-up (*Usual Care group of the Multiple Risk Factor Intervention Trial*)	N=188 US men aged 35-57 Cases (94), Controls (94)	Annual physical examinations. Serum n-3 levels at baseline used as proxy for dietary n-3 intake.	n-3 fatty acids and linoleic acid inversely associated with CHD risk, although not all associations were statistically significant Two n-3 polyunsaturated fatty acids, DPA and DHA were significantly associated with CHD in multivariate models; OR (phospholipid) per one standard deviation increase in variable was 0.67 (95% CI, 0.47-0.95) for DPA and 0.66 (95% CI, 0.46-0.94) for DHA
Vli-Jama et al., 2002 Case-control study	N=207 Norwegians Aged 45-75 years Cases hospitalized with first MI (103); Controls (104)	Participants provided fasting blood sample to be analyzed for fatty acid content.	Multivariate OR for MI (adjusted for age, sex, wait-to-hip ratio, smoking, family hx of CHD, and education) was 0.20 (95% CI 0.06-0.63) for highest vs. lowest quartile of VLC n-3 fatty acids Odds ratios presented for linoleic acid, oleic acid, steric acid, and myristic acid

Abbreviations

ALA	alpha linolenic acid
AMI	acute myocardial infarction
CAD	coronary artery disease
CHD	coronary heart disease
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
FFA	serum free fatty acid
FFQ	food frequency questionnaire
HDL	high-density lipoprotein
HR	hazard ratio
IHD	ischemic heart disease
LDL	low-density lipoprotein
MI	myocardial infarction
NEFA	nonesterified fatty acids
PUFA	polyunsaturated fatty acids
SBP	systolic blood pressure
TIA	transient ischemic attack
VLC n-3	very long-chain omega-3 fatty acids

*Omacor is a concentrate of omega-3, long chain, polyunsaturated fatty acids from fish oil

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Appendix 1.
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