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November 3, 2003

VIA REGULAR MAIL

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

Re: Docket Number 2003Q-0401

To Whom it May Concern:

We are submitting to this docket a copy of the qualified health claim petition (without attachments) for conventional foods and dietary supplements containing omega-3 fatty acids that Martek Biosciences Corporation (Martek) submitted today. As explained in the petition, Martek decided to submit a separate petition because the aforementioned petition does not address the significant scientific issues that are presented by the presence of mercury, including methylmercury, in fish oils and fish and the minimum levels of DHA and/or EPA needed to qualify for the health claim.

If you have any questions or comments regarding this comment, please feel free to contact us.

Sincerely,

Martin J. Hahn

Attachmentge

2003Q-0401

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November 3, 2003

VIA OVERNIGHT DELIVERY

Food and Drug Administration
Office of Nutritional Products, Labeling
and Dietary Supplements (HFS-800)
5100 Paint Branch Pkwy.
College Park, MD 20740

To Whom it May Concern:

We are enclosing an original and one copy of a qualified health claim petition that is being submitted by our client, Martek Biosciences Corporation (Martek). We also are enclosing a CD that contains an electronic copy of the petition and attachments. Given the size of the petition and attachments, the original and copy are being sent in different express delivery boxes.

We thank you in advance for your consideration of this petition.

Sincerely,

Martin J. Hahn

Attachments

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Qualified Health Claim for Conventional Foods and Dietary Supplements Containing Omega-3 Fatty Acids	)	Docket No. _____

Submitted by

Martek Biosciences Corporation

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Petition for a Qualified Health Claim

November 3, 2003

PETITIONER:	Martek Biosciences Corporation
POST OFFICE ADDRESS:	6480 Dobbin Road Columbia, MD 21045
SUBJECT:	Beneficial Relationship between the Omega-3 Fatty Acids, DHA and EPA, and a Reduced Risk of Coronary Heart Disease

Food and Drug Administration
Office of Nutritional Products, Labeling
and Dietary Supplements (HFS-800)
5100 Paint Branch Pkwy.
College Park, MD 20740

The undersigned submits this Petition on behalf of Martek Biosciences Corporation (Martek) pursuant to sections 403(r)(4) and 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Food and Drug Administration (FDA) procedures for review of "qualified health claims" described in Agency Guidance for Industry and FDA published on July 11, 2003. 1/ This Petition requests that FDA exercise enforcement discretion with respect to a health claim regarding the relationship between diets containing omega-3 fatty acids (ω-3 fatty acids) and a reduced risk of coronary heart disease (CHD). Enforcement discretion is sought for the following claim, among similar claims described more fully below:

> A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease.

1/ 68 Fed. Reg. 41387 (July 11, 2003).

Foods eligible to bear the proposed claim are dietary supplements and conventional foods that contain at least 32 milligrams of ω-3 fatty acids per reference amount customarily consumed (RACC). For purposes of this Petition, "omega-3 fatty acids" include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Alpha linolenic acid (α-linolenic acid), for which the science relative to CHD risk reduction is not as advanced, is not included.

Martek believes that the proposed claim will assist consumers in maintaining healthful dietary practices by succinctly conveying the state of the current science regarding ω-3 fatty acids. In 2000, FDA reviewed the science then in existence and agreed to exercise enforcement discretion with respect to a similar health claim for dietary supplements. 2/ This Petition seeks to extend this exercise of enforcement discretion to conventional foods such as foods that are formulated to contain a meaningful level of ω-3 fatty acids and fish. We recognize that FDA currently is reviewing a separate qualified health claim petition regarding the relationship between omega-3 fatty acids and a reduced risk of coronary heart disease. 3/ While we concur with that petition's conclusion that there are sufficient data to support the placement of this qualified health claim in Category B, we do not believe that the petition currently before the agency adequately addresses the significant scientific issues that are presented by the presence of mercury, including methylmercury, in fish oils and fish and the minimum levels of DHA and/or EPA needed to qualify for the health claim. This petition addresses these and other important issues.

The presence in fish and fish derivatives of mercury, a contaminant that can harm the developing nervous systems of unborn children, infants and young children, is an issue that must be addressed in the health claim. Both FDA

2/ Letter from Christine J. Lewis, Ph.D., Director, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition to Jonathan W. Emord, Esq., Emord & Associates, P.C., Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease (Oct. 31, 2000) [hereinafter, "FDA October 2000 Omega-3 Letter"] (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~dms/ds-ltr28.html).

3/ Qualified Health Claim for OMEGA-3 Fatty Acids and Coronary Heart Disease Health (2003Q-0401) Submitted by Wellness Lifestyles, Inc. D/B/A American Longevity and Life Extension Foundation Buyers Club, Inc. (Sept. 3, 2003) (Accessed on Oct. 30, 2003 at http://www.fda.gov/ohrms/dockets/dockets/03q0401/03q-0401-qhc0001-01-vol1.pdf).

and the Environmental Protection Agency have issued advisories cautioning against the consumption of certain fish due to mercury contamination. A March 2001 FDA advisory cautions against the consumption of shark, swordfish, king mackerel and tilefish by pregnant woman, women of childbearing age, nursing mothers and young children. The FDA advisory allows these groups to eat other fish, provided the weekly intake does not exceed 12 ounces. In addition to the adverse effects of mercury on the developing child's nervous system, data also indicate that mercury may offset the cardio-protective effects of ω-3 fatty acids.

Given the high levels of mercury reported in shark, swordfish, king mackerel and tilefish, Martek proposes that these fish, or any other fish that similarly becomes included in a future FDA advisory, should be ineligible for the proposed health claim. When the health claim appears on other fish, Martek believes that the health claim should be accompanied by an informational statement advising pregnant women, women of childbearing age, nursing mothers and young children that they should not eat more than 12 ounces of fish per week. In addition, Martek believes that sources of ω-3 fatty acids derived from fish (such as fish oils) should be ineligible for the health claim unless the oil has been tested and found to contain less than 0.025 parts per million (ppm) of mercury. These additional criteria are necessary to ensure that the proposed health claim is truthful and not misleading on all foods on which it appears.

As required by 21 C.F.R. § 101.70, the following major sections comprise the Petition:

I. Statement of Compliance with Preliminary Requirements

II. Summary of Scientific Support for the Claim

III. Analytical Data

IV. Model Health Claims

V. Description of Attachments

VI. Environmental Impact

VII. Conclusion and Certification

I. STATEMENT OF COMPLIANCE WITH PRELIMINARY REQUIREMENTS

The proposed claim meets all preliminary requirements for health claims, as specified in 21 C.F.R. §§ 101.14 and 101.70 as described below.

A. Omega-3 fatty acids are a "substance" as defined by FDA

As required, the subject of the proposed claim, ω-3 fatty acids, are a "substance" as defined in 21 C.F.R. § 101.14(a)(2), in that ω-3 fatty acids are "a component of food." Omega-3 fatty acids have long been consumed in the food supply as components of fish and fish oils and are also directly derived from algal sources.

B. Omega-3 fatty acids confer "nutritive value"

Omega-3 fatty acids support normal growth, maintenance, and development, the hallmarks of "nutritive value." Alpha-linolenic acid, a precursor to DHA and EPA, is classified nutritionally as an "essential" nutrient, meaning that it cannot be synthesized by the body and must be present in the diet for health maintenance. The essential role of α-linolenic acid is believed to be its role as precursor for synthesis of EPA and DHA, ω-3 fatty acids that are critical to the proper functioning of cell membranes, blood vessels, the brain, and the nervous system.

C. Omega-3 fatty acids are safe when consumed at levels necessary to qualify for the proposed claim

Omega-3 fatty acids are safe when consumed as nutrients in conventional food and dietary supplements. Omega-3 fatty acids occur in conventional foods with a long history of safe use, such as fish, and are generally recognized as safe (GRAS) when used as direct food ingredients intended to increase ω-3 intake. With regard to dietary supplement uses, FDA has determined that ω-3 fatty acids pose no significant or unreasonable risk of illness or injury, so long as total daily intakes of DHA and EPA from conventional food and dietary supplements do not exceed three grams per person per day (3 g/p/d).

1. Conventional Food

Fish, and particularly fatty fish, provide a meaningful level of ω-3 fatty acids. Fish have long been a staple of the human diet and there is no doubt that fish can be a safe source of ω-3 fatty acids. Certain fatty fish, such as tilefish, king mackerel, swordfish and shark, may contain significant levels of contaminants such

as mercury. These fish species would be ineligible for the proposed health claim due to the health concerns associated with mercury, including methylmercury, and the potential for this contaminant to offset the cardio-protective effects of ω-3 fatty acids.

Conventional foods also may be fortified with marine oils or other sources of DHA and EPA, such as DHA-rich single cell oil (DHASCO) derived from microalgal species. FDA has affirmed menhaden oil, a source of marine ω-3 fatty acids, as GRAS for use in a variety of foods, provided that the combined intake of EPA and DHA from all added sources does not exceed 3 g/p/d. 4/ The basis for the 3 g/p/d limitation was FDA's conclusion that fish oils providing this amount of EPA and DHA would not be expected to present concerns regarding increased bleeding time, diminished glycemic control, or increased LDL cholesterol. 5/

Since affirming menhaden oil as GRAS, FDA has responded without objection to several GRAS notifications for marine and algal oils that contain DHA and EPA for use in a variety of foods at specific levels. The agency has stated that it has no questions regarding GRAS notifications for tuna oil (GRN 000109), 6/ fish oil concentrate (GRN 000105), 7/ and small planktivorous pelagic fish body oil (GRN 000102). 8/ FDA also completed a favorable review of Martek's DHASCO (GRN

4/ 21 C.F.R. § 184.1472.

5/ 62 Fed. Reg. 30751 (June 5, 1997).

6/ Letter from Alan M. Rulis, Ph.D., Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition to Anthony Young, Piper Rudnick, LLP (Dec. 4, 2002) (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~rdb/opa-g109.html).

7/ Letter from Alan M. Rulis, Ph.D., Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition to Nancy L. Schnell, Unilever United States, Inc. (Oct. 15, 2002) (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~rdb/opa-g105.html).

8/ Letter from Alan M. Rulis, Ph.D., Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition to Dr. Edward Iorio, Jedwards International (Sept. 3, 2002) (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~rdb/opa-g102.html).

000041) 9/ as a source of DHA for use in infant formulas (when combined with arachidonic acid at the levels and ratios specified in the GRAS notification). Other ingredients also provide DHA and/or EPA and foods could be formulated with these ingredients to the extent that such ingredients are either GRAS or the subject of an approved food additive regulation.

As will be discussed in more detail below, we believe that conventional foods that are fortified with DHA and/or EPA should be eligible for the claim when providing at least 32 milligrams of DHA and/or EPA per RACC, which is used to determine the serving size for products. Martek selected the 32 milligram level because it reflects 20% of the value of DHA and/or EPA discussed in the IOM Macronutrient Report. Moreover, this level would help ensure that consumers would not exceed three grams of DHA and/or EPA per day even when consuming multiple foods that have been fortified with DHA and/or EPA.

2. Dietary Supplements

In October 2000, FDA determined that ω-3 fatty acids pose no significant or unreasonable risk of illness when used in dietary supplements, provided that total daily intakes of DHA and EPA from conventional food and dietary supplements combined do not exceed 3 g/p/d. To provide for an adequate margin of safety, FDA further stated its intent to exercise enforcement discretion with respect to a qualified health claim for ω-3 fatty acids and CHD only for dietary supplements that suggest or recommend a daily intake of no more than 2 grams of DHA and EPA. 10/ FDA encouraged manufacturers, however, to limit their dietary supplement products bearing the qualified health claim to products recommending or suggesting daily intakes of 1 gram or less of DHA and EPA ω-3 fatty acids. FDA based this recommendation on epidemiologic data on fish consumption suggesting that intakes below 1 g/p/d may provide a beneficial effect on reducing CHD risk.

9/ Letter jointly signed by Alan M. Rulis, Ph.D., Director, Office of Food Additive Safety and Christine J. Lewis, Ph.D., R.D., Director, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition to Henry Linsert, Jr., Martek Biosciences Corporation (May 17, 2001) (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~rdb/opa-g041.html).

10/ *See,* FDA October 2000 Omega-3 Letter, *supra* note 2.

D. Omega-3 fatty acids reduce the risk of CHD, a disease for which the general U.S. population is at risk

FDA has repeatedly characterized coronary heart disease (CHD) as one of the most common and serious forms of cardiovascular disease and a major public health concern in the United States. 11/ CHD, which refers to diseases of the heart muscle and supporting blood vessels, accounts for more deaths in the United States than any other disease or group of diseases. According to FDA, early management of risk factors for CHD is a major public health goal that can assist in reducing risk of CHD. Therefore, CHD is a disease for which the general U.S. population is at risk and continues to be an appropriate subject of a health claim under the FFDCA. As will be discussed in more detail below, there are extensive data showing that the ω-3 fatty acids, DHA and EPA, reduce the risk of CHD, a disease for which the general U.S. population is at risk.

11/ *See, e.g.*, 21 C.F.R. §§ 101.75, 101.77, 101.81, 101.82, 101.83.

II. SUMMARY OF SCIENTIFIC SUPPORT FOR THE CLAIM

Scientific information and evidence in support of the proposed health claim and eligibility criteria, including criteria addressing mercury content of fish, include the following:

- The clinical, epidemiological and other data previously reviewed by FDA that established the scientific foundation for the qualified health claim for dietary supplements containing DHA and/or EPA;
- The clinical, epidemiological, and other data reviewed by the Institute of Medicine in its 2002 review of dietary reference intakes (DRIs) for macronutrients;
- New scientific evidence and information published subsequent to the IOM report on macronutrients, including public health recommendations, review papers, and new references on secondary and primary prevention of CHD;
- Available information regarding the levels of ω-3 fatty acids that are likely to be meaningful in terms of CHD risk; and
- Available information regarding concerns posed by mercury, including methylmercury, in seafood, which has been linked to neurological concerns and may offset the cardio-protective properties of ω-3 fatty acids.

As described more fully below, the available evidence supports, at a minimum, a "Category B" health claim to inform consumers of the credible evidence regarding ω-3 fatty acids and CHD risk.

A. Scientific Background and Regulatory Precedent

1. Background

Essential fatty acids (EFA), including ω-6 and ω-3 fatty acids, play an important role in normal human growth and development and provide important cardio-protective qualities. Omega-6 and ω-3 fatty acids are derived from the precursors linoleic acid and α-linolenic acid, respectively. In the U.S., intake of ω-3 fatty acids is ≈ 1.6 g/d with ≈ 1.4 g/d from α-linolenic acid and merely 0.1 – 0.2 g/d

(100 to 200 mg) from EPA and DHA. 12/ The conversion from α-linolenic acid to DHA is less than that to EPA.

2. The qualified health claim for dietary supplements

In October 2000, FDA announced that it would exercise enforcement discretion and allow a qualified health claim for dietary supplements to describe the relationship between ω-3 fatty acids and CHD risk. 13/ In doing so, FDA summarized its findings regarding the state of the science at that time. The agency concluded that, although the available evidence did not, in the agency's opinion, reflect significant scientific agreement, the weight of the scientific evidence in support of a qualified claim outweighed the evidence against a claim. The agency reasoned that evidence from intervention trials with CHD as an endpoint was strongly favorable in diseased populations, and suggestive evidence indicated that the benefit to diseased populations would carry over to the general population because ω-3 fatty acids have similar physiological effects in diseased and general populations. The agency also relied upon observational trials with CHD as an endpoint in the general population, which the agency described as similarly suggestive of a beneficial relationship between ω-3 fatty acids and reduction of CHD risk.

Based on its review of the scientific literature, FDA concluded that the available data and information supported a qualified claim describing the available evidence as "suggestive" but not "conclusive." 14/ The language currently accepted by FDA is "Consumption of omega-3 fatty acids may reduce the risk of heart disease. FDA evaluated the data and determined that, although there is scientific evidence supporting the claim, the evidence is not conclusive." 15/ The claim that is

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12/ Institute of Medicine, Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids, at 8-38 (National Academy Press 2002) [hereinafter "Macronutrient Report"].

13/ *See*, FDA October 2000 Omega-3 letter, *supra*, n.2.

14/ *Id.*

15/ Letter from Christine J. Taylor, Ph.D., Director, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition to Jonathan W. Emord, Esq., Emord & Associates, P.C. Responding to a Request to Reconsider the Qualified Claim for a Dietary Supplement Health Claim

proposed in this Petition conveys the same essential meaning as the currently authorized language, but would be authorized for use on both conventional foods and dietary supplements.

3. The IOM report

In 2002, the Institute of Medicine (IOM) published *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (1) (the so-called "Macronutrient Report"), 16/ which contains an extensive review of the epidemiological and clinical evidence on the health benefits associated with ω-3 fatty acids. The IOM established an adequate intake (AI) and an acceptable macronutrient distribution range (AMDR) for α-linolenic acid, the ω-3 fatty acid precursor of DHA and EPA. The evidence considered by the IOM included major epidemiological and clinical studies published as of 2001.

The Macronutrient Report establishes an adequate intake (AI) for α-linolenic acid of 1.6 and 1.1 g/day for men and women, respectively. The IOM characterizes α-linolenic acid as essential because humans cannot synthesize it and because a lack of the nutrient results in adverse clinical symptoms. The IOM notes, however, that "the essential role of α-linolenic acid appears to be its role as precursor for synthesis of eicosapentaenoic acid and DHA." 17/ The IOM recognized the important, seemingly essential, role of DHA and EPA in the diet, by basing the essentiality of α-linolenic acid on its role as a precursor for DHA and EPA.

The expert panel based the AI on the highest median intake of α-linolenic acid by adults in the United States, where a deficiency is basically nonexistent in free-living populations. 18/ The expert panel recognized that small amounts of EPA and DHA can contribute toward the reversal of a ω-3 fatty acid deficiency and as such allowed DHA and EPA to contribute up to 10 percent of the AI for α-linolenic acid.

The expert panel also reviewed the extensive data submitted on the health benefits associated with consumption of macronutrients within desirable

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for Omega-3 Fatty Acids and Coronary Heart Disease (Feb. 8, 2002) (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~dms/ds-ltr28.html).

16/ Macronutrient Report, *supra,* note 12.

17/ *Id.* at 8-18.

18/ *Id.* at 8-38.

ranges. The IOM expert committee established AMDRs for macronutrients, including α-linolenic acid. By definition, an AMDR is the "range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients." 19/ The IOM panel established an AMDR for α-linolenic acid of 0.6 to 1.2% of energy and recognized that up to 10% of the AMDR can be consumed as EPA and/or DHA. 20/ The panel explained that, "[b]ecause the physiological potency of EPA and DHA is much greater than that for α-linolenic acid, it is not possible to estimate one AMDR for all n-3 fatty acids." 21/ The lower boundary range of the AMDR is based on the AI while the upper boundary is based on the highest α-linolenic acid intakes from diets consumed by individuals in the United States. 22/

By establishing an AMDR for α-linolenic acid, the expert panel concluded that there is a range of intake that may reasonably be associated with a reduced risk of a disease. A closer review of the Macronutrient Report reveals that the EPA and/or DHA components of α-linolenic acid are primarily responsible for the reduced risk of disease. Indeed, with regard to the studies on cardiovascular disease and stroke, the overwhelming majority of studies examined by the expert panel focused on the studies that had been conducted on DHA and EPA specifically rather than on α-linolenic acid.

There are numerous comments in the Macronutrient Report recognizing important health benefits associated with ω-3 fatty acids, including, but not limited to the statements below.

- In the summary section of the chapter on "Dietary Fats: Total Fat and Fatty Acids," the expert panel states "While intake levels much lower than the AI [for α-linolenic acid] occur in the United States without the presence of a deficiency, the AI can provide the beneficial health effects associated with the consumption of *n*-3 fatty acids (see Chapter 11)." 23/

19/ *Id.* at S-5.

20/ *Id.* at 11-2.

21/ *Id.* at 11-1 to 11-2.

22/ *Id.* at 11-1.

23/ *Id.* at 8-2.

- In the summary section of Chapter 11, which addresses "Macronutrient and Healthful Diets," the expert panel states, "A growing body of literature suggest that higher intakes of α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may afford some degree of protection against CHD [Coronary Heart Disease]." 24/

- The Macronutrient Report summarizes the data on health benefits associated with diets containing ω-3 fatty acids. The opening paragraph of this section states "Growing evidence suggests that dietary *n*-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid (DHA)) reduce the risk of coronary heart disease (CHD) and stroke." 25/

- The Macronutrient Report identifies the mechanisms that may affect the ability of ω-3 fatty acids to reduce the risk of cardiovascular disease by preventing arrhythmias, reducing atherosclerosis, decreasing platelet aggregation by inhibiting the production of thromboxane, decreasing plasma triacylglycerol concentrations, producing a small increase in high-density lipoprotein (HDL) cholesterol with an accompanying decrease in triacylglycerol concentrations, decreasing proinflammatory eicosanoids and moderately decreasing blood pressure. 26/

- The Macronutrient Report then summarizes the extensive epidemiological evidence, non-clinical intervention evidence, and randomized controlled clinical trial evidence that have been conducted on the relationship between ω-3 fatty acids and CHD and stroke. The vast majority of these studies examined the impact of dietary sources of DHA and EPA, rather than α-linolenic acid, on CHD and stroke. 27/

24/ *Id.* at 11-1 to 11-2.

25/ *Id.* at 11-40.

26/ *Id.* at 11-40 to 11-43.

27/ *Id.*

- In the section summarizing the expert panel's basis for establishing an AMDR for α-linolenic acid, the panel states "the above studies suggest that α-linolenic acid, EPA and DHA may provide beneficial health effects when consumed at moderate levels." 28/ The panel further notes that ALA "is not known to have any specific functions other than to serve as a precursor for synthesis of EPA and DHA." 29/

There remain certain open questions regarding the relationship between ω-3 fatty acids and CHD and stroke. Some of this uncertainty is reflected in the Macronutrient Report, which does characterize several studies as not showing a significant association between fish or fish oils and a reduced risk of CHD. Nonetheless, the number and quality of studies cited by the IOM, as well as the IOM's establishment of an AMDR that expressly incorporates DHA and/or EPA, provide a reasonable basis for concluding that the evidence in support of a health claim for ω-3 fatty acids is unlikely to be reversed. Of note, the IOM finds that "[t]here are now 4 randomized controlled clinical trials which all show a benefit of fish and/or fish oils or alpha-linolenic acid on CHD prevention." 30/ FDA regards the randomized controlled clinical trial to be the "gold standard" of interventional studies.

B. Summary of New Scientific Evidence and Information

In preparation for this Petition, Martek performed an extensive search of the available scientific literature to identify references published subsequent to those included in the IOM report that contribute to the further understanding of the effects of fatty acids on risk of CHD. 31/ The following discussion describes the new

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28/ *Id.* at 8-11.

29/ *Id.* at 11-45

30/ *Id.* at 11-41.

31/ Medical (Biosis, SciSearch, EMBASE, MEDLINE) and Nutritional (AGRICOLA, CAB Abstracts, Food Sci.&Tech.Abs, FOODLINE, Foods Adlibra, AGRIS) databases were searched. Search terms included: polyunsaturated fatty acid, docosahexaenoic acid, eicosapentaenoic acid, linolenic acid, fish oil, cod liver oil, menhaden oil, arrhythmia, cardiovascular, coronary, cvd, cad, myocardial, blood pressure, hypertension, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertriglyceride. The original output of nearly 2,400 items (published since 1999 and limited to human studies) was then restricted to articles, review papers, and

evidence identified, and focuses broadly on the following areas: extension of scientific support in favor of the position that consumption of ω-3 fatty acids reduces the risk of CHD, new references on secondary and primary prevention of CHD, and papers highlighting opposing viewpoints. A copy of each article referenced (*i.e.*, **(1)** through **(42)**) is attached.

1. Public health recommendations and reviews following the IOM report continue to reflect scientific acknowledgement of the benefit of ω-3 fatty acids

Since the Macronutrient Report was released, a growing body of literature has been published, with the emerging evidence largely supportive of the benefit of ω-3 fatty acids for both primary and secondary prevention of CHD. The new evidence includes updated recommendations of the American Heart Association (AHA) **(2)**, a respected public health organization, as well as numerous review articles. Viewed collectively, these documents reflect impressive endorsement within the scientific community of the beneficial relationship between ω-3 fatty acids and reduced CHD risk.

One of the most important documents, an updated AHA Scientific Statement **(2)** on cardiovascular disease and fish, fish oil, and ω-3 fatty acids, was issued in November 2002. The new AHA recommendations include the following:

- Patients without documented CHD should consume (preferably) oily fish twice per week as well as oils and foods rich in α-linolenic acid.
- Patients with documented CHD should consume ≈ 1g of EPA plus DHA per day, preferably with oily fish; supplements of EPA plus DHA could be considered in consultation with a physician.
- Patients in need of triglyceride lowering should consume 2-4 g/d of EPA plus DHA provided as capsules under a physician's care.

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clinical trials/controlled studies (eliminating notes, editorials, corrections, and letters to the editor), yielding about 1000 citations. The search was further limited by using key words in the title, resulting in 524 citations. These were manually perused and the most current post-IOM report citations were chosen; 49 citations made the final cut for inclusion in this petition.

The AHA Scientific Statement indicates scientific endorsement for the role of ω-3 fatty acids in the prevention of cardiovascular outcomes, noting that "omega-3 fatty acid supplements can reduce cardiac events (e.g., death, nonfatal MI [myocardial infarction], nonfatal stroke) and decrease progression of atherosclerosis in coronary patients."**(2)** The AHA also states its opinion, however, that "additional studies are needed to confirm and further define the health benefits of ω-3 fatty acid supplements for both primary and secondary prevention." Notably, the statement specifically addresses the distinction between α-linolenic acid, and DHA and EPA, reinforcing the importance of limiting this petition to DHA and/or EPA rather than opening it up to the broader class of ω-3 fatty acids, which also includes ALA. The AHA's statement also discusses the need for consumers to be aware of both the benefits and risks of fish consumption in view of the known safety concerns regarding environmental contaminants.

In an editorial earlier this year, Kris-Etherton et al. **(3)** further communicate the AHA Scientific Statement recommendations. The authors assert that "Randomized trials have convincingly documented that omega-3 fatty acids can significantly reduce the occurrence of CVD events in patients with coronary artery disease."

Hu and Willett **(4)** extensively examined literature through May 2002 for epidemiological and clinical investigations of dietary factors, identified 147 pertinent citations that were analyzed for quality and relevance, and concluded that "...compelling evidence from metabolic studies, prospective cohort studies, and clinical trials in the past several decades indicates that ... to increase consumption of ω-3 fatty acids from fish, fish oil supplements, or plant sources... is one of at least three dietary strategies that are effective in preventing CHD."

Another recent review from Canada concurs with the prevailing viewpoint that ω-3 fatty acids provide a cardiovascular benefit. In this review, Holub **(5)** emphasizes dietary supplementation with fish oil concentrates, which have shown potential to reduce progression of CHD and related mortality, as well as sudden death.

Harris et al. **(6)** summarized recent epidemiological and clinical findings to further support the cardio-protective benefit of ω-3 fatty acids. They conclude that individuals with coronary artery disease may reduce their risk of sudden death by increasing intake of long-chain ω-3 fatty acids.

In another review published in June 2003, Leaf et al. **(7)** specifically examined the role of ω-3 polyunsaturated fatty acids (PUFA) in prevention of arrhythmic deaths, including sudden cardiac death. Citing the clinical evidence

from the DART trial, the Mediterranean ALA rich diet trial, the GISSI-Prevenzione trial and its re-analysis published just last year, Singh's trial, and the case-control analysis from the Physicians' Health Study, the authors conclude that the evidence that fish oil fatty acids can prevent sudden cardiac death in humans has been strengthened. The authors also make a number of "personal recommendations." These include the AHA advice that everyone should have at least two meals of oily fish per week, recommendations for the use of a fish oil supplement of 600 mg/d EPA plus DHA for those with either a family or personal history of heart disease, and recommendations for a supplemental intake of 1-2 g/d EPA plus DHA if there is a family history of sudden cardiac death.

In an accompanying editorial to the Leaf article, Siscovick et al. **(8)** affirms that evidence supports the role of both dietary ω-3 essential fatty acids (EFA) intake and PUFA supplements in clinical prevention of sudden cardiac death. As well, the editorial notes that the ratio of ω-6 EFA to ω-3 EFA is important; current AHA guidelines do not distinguish between dietary intake of the ω-3 PUFA α-linolenic acid and the ω-6 PUFA linoleic acid. The editorial concludes that policymakers should consider a new indication for treatment with ω-3 PUFA supplements in secondary prevention of CHD and sudden cardiac death, which is stated to be a low-cost, low-risk intervention.

Bhatnagar and Durrington **(9)** reviewed the role of ω-3 fatty acids in prevention and treatment of atherosclerosis. A thorough recounting of observational studies and clinical trials was completed, including the Lyon Diet Heart Study, GISSI-Prevention trial and re-analysis, and Scandinavian Simvastatin Survival Study (4S). Data on ω-3 fatty acids and lipid metabolism, blood pressure and endothelial function, platelets and hemostatic variables, and growth and inflammatory markers were assessed, and data on the combined use of HMG CoA reductase inhibitors and ω-3 fatty acids were highlighted. The authors conclude that ω-3 fatty acids are valuable in preventing sudden death following MI and that ω-3 fatty acids are just as effective as statins in secondary prevention.

Nordoy's review article **(10)** focuses on the role of ω-3 fatty acids either alone or in combination with statin therapy, discussing the documented effects of ω-3 fatty acids against CHD in both primary and secondary prevention trials. An appraisal of the role of ω-3 fatty acids in post-MI management in the United Kingdom by Izzat and Avery **(11)** concludes that an EPA plus DHA supplement may be a useful adjuvant treatment in secondary prevention because oily fish consumption in the United Kingdom is poor, has the disadvantages of possible toxic contaminants, large caloric content, and may be distasteful to some.

In a meta-regression analysis of randomized trials performed by Geleijnse et al. **(12)** blood pressure response to fish oil supplementation was examined. Results showed that high intake of fish oil (median dose 3.7 g/d) may lower blood pressure, especially in older and hypertensive subjects.

Sacks and Katan **(13)** reviewed randomized clinical trials to examine the effects of dietary fats on plasma lipoproteins and cardiovascular disease. The authors conclude that fish oil fatty acids lower triglycerides, but not LDL cholesterol.

Bucher's **(14)** meta-analysis of randomized trials (dietary vs. non-dietary intake of ω-3 fatty acids, or control diet or placebo in patients with CHD) suggested that dietary and non-dietary ω-3 fatty acid intake reduces overall mortality, mortality due to MI, and sudden death.

An examination of data on consumption of fish oils and the decreased risk of stroke was conducted by Skerrett and Hennekens **(15)**. Epidemiological data had previously shown an inverse relationship between consumption of fish oils and stroke, but results from five prospective studies were less consistent, with more convincing data indicating a decrease in risk of thrombotic but not hemorrhagic stroke.

Carroll and Roth **(16)** reviewed the evidence for the cardio-protective effects of ω-3 fatty acids and concluded that their use may show benefit and ought to be considered in patients with documented CHD. It is noted that the ω-3 fatty acids are reasonably well tolerated, with adverse effects including bloating, gastrointestinal symptoms, hyperglycemia, slight increase in LDL cholesterol, and "fishy taste" in the mouth.

Taken individually or as a whole, these publications indicate that among the nutritional options, the evidence for the efficacy of ω-3 fatty acids is strong. The ω-3 fatty acids have powerful antithrombotic actions and EPA and DHA inhibit development of atherosclerosis. Perhaps the most striking finding is that ω-3 fatty acids have been shown to decrease sudden death from ventricular fibrillation.

2. New studies of secondary prevention reinforce the beneficial effects of ω-3 fatty acids

Ten new studies on secondary prevention of CHD were identified. These studies used different interventions (diet, fish oils, ω-3 fatty acid supplements, α-linolenic acid) and measured various outcomes (fatal ischemic heart

disease, non-fatal MI, CHD progression, biochemical indices). Many of the new studies address α-linolenic acid, the precursor to DHA and EPA.

A single blind, randomized trial (N=1000) by Singh et al. **(17)** measured the effect of an Indo-Mediterranean diet on coronary artery disease progression in high-risk patients with angina pectoris, MI, or surrogate risk factors for coronary artery disease. The intervention group followed a diet with increased intake of whole grains and mustard or soybean oil (mean intake of α-linolenic acid was two-fold greater), while the control group followed a local diet similar to the National Cholesterol Education Program (NCEP) prudent diet. A significant reduction in serum cholesterol was noted in both groups. Significant reductions in total cardiac endpoints ($P<0.001$), non-fatal MI ($P<0.001$), and sudden cardiac deaths ($P=0.015$) were observed in the intervention group, leading the authors to conclude that an Indo-Mediterranean diet rich in α-linolenic acid may be more effective in both primary and secondary prevention than the NCEP step 1 diet.

In a second trial involving diet, middle-aged Indian subjects (40 men and 40 women), Ghafoorunissa et al. **(18)** followed their own home-prepared diets using blended oils (different proportions of α-linolenic acid and linoleic acids) for cooking or ω-3 fatty acids from fish oils. Results showed that neither blend of oil, in either sex, reduced plasma lipid or apolipoprotein levels, but linoleic acid and ω-3 long chain fatty acids had increases in plasma and platelet phospholipids. The investigators concluded that improvement in cereal-based diets through use of oils providing ω-3 fatty acids may contribute to prevention of CHD in Indians.

A case-control cohort study, conducted by Lemaitre et al. **(19)** nested in the Cardiovascular Health Study, investigated associations of plasma phospholipid concentrations (EPA, DHA, and α-linolenic acid) as biomarkers of intake with risk of fatal ischemic heart disease and non-fatal MI in older adults (≥ 65 years). Results showed a higher combined dietary intake of EPA plus DHA was associated with a lower risk of fatal ischemic heart disease, but not with non-fatal MI, which is consistent with possible anti-arrhythmic effects of fatty acids. The data on α-linolenic acid merely suggested a possible benefit.

A population-based, case-control study in Costa Rica conducted by Baylin et al. **(20)** examined the association between adipose tissue α-linolenic acid and nonfatal acute MI in patients with nonfatal MI (N=482) and an equal number of controls. An inverse association between α-linolenic acid and nonfatal MI was observed, leading the authors to suggest that consumption of vegetable oils rich in α-linolenic acid confers protection against CHD.

The MARGARIN study conducted by Bemelmans et al. **(21)** assessed the effect of increased α-linolenic acid on cardiovascular risk factors, estimated the risk of ischemic heart disease at two years, and the effect of dietary counseling on dietary habits in a population with multiple cardiovascular risk factors (elevated total serum cholesterol, high blood pressure, use of antihypertensive medications, etc.). Random, double-blind assignment was made for subjects to consume a margarine rich in either α-linolenic or linoleic acid. Subjects with cardiovascular risk factors received either dietary counseling or a posted leaflet outlining the Dutch dietary guidelines. Results showed both the α-linolenic and linoleic acid diets similarly decreased risk of CHD and group dietary counseling was effective.

A letter to the editor by Lanzmann-Petithory et al. **(22)** challenges the conclusions of the MARGARIN study, stating that it is misleading to regard the effects of α-linolenic and linoleic acid as similar. The letter points out that after two years of follow up, the number of cardiovascular events was nine in the linoleic acid group and just two in the α-linolenic acid group ($P < 0.20$), representing 78% fewer ischemic events; thus, it should not be concluded that the number of cardiovascular events could not be significantly decreased with use of α-linolenic acid.

A prospective examination of the association between fish intake and ω-3 fatty acids and risk of CHD and total mortality was performed in 5103 female nurses with type 2 diabetes (but free of CHD or cancer at baseline) by Hu et al. **(23)**. Results showed significantly lower mortality with higher fish consumption, a trend toward lower incidence of CHD and lower total mortality with higher consumption of ω-3 fatty acids.

The effect of ω-3 and ω-6 polyunsaturated fatty acids (PUFA) on plaque stability in a population awaiting carotid endarterectomy was examined in a randomized, controlled trial by Thies et al. **(24)**. Patients received either sunflower oil (ω-6) or fish oil (ω-3) in capsule form until surgery. Concentrations of EPA, DHA, and linoleic acid were measured in carotid plaques. Results showed that ω-3 PUFAs from fish-oil supplementation were incorporated into atherosclerotic plaques and induced changes that enhanced plaque stability but the consumption of ω-6 PUFAs does not affect carotid plaque composition or stability.

In a placebo-controlled, parallel study with 150 moderately hyperlipidemic subjects, Finnegan et al. **(25)** compared the effects of increased dietary intakes of α-linolenic acid and EPA plus DHA on atherogenic risk factors. Changes in fasting or postprandial lipid, glucose, or insulin concentrations, or in blood pressure were not significantly different between the ω-3 interventions and the ω-6 controls. A significant difference was noted in fasting triacylglycerols ($P < 0.05$) between the 1.7 g/d EPA plus DHA group versus the 9.5g/d α-linolenic acid

group. The authors concluded that dietary α-linolenic acid and EPA plus DHA have different physiologic effects at biologically equivalent doses.

Finally, a small (N = 20) study by Engler et al. **(26)** in children ages 9 to 19 years with familial hypercholesterolemia (FH) or familial combined hyperlipdemia (FCH) demonstrated that "DHA supplementation decreases the atherogenic lipoprotein profile due to a shift to larger LDL and HDL particles. This effect may decrease the risk of early CHD in hyperlipidemic children." This same study also looked at the effect of DHA versus the NCEP II diet on endothelial dysfunction in hyperlipidemic children. The authors concluded that "DHA supplementation improves endothelial function in children with FH and FCH without affecting biomarkers for oxidative stress or inflammation."

3. New studies of primary prevention reinforce beneficial effects of ω-3 fatty acids

Eight new articles on primary prevention and risk of CHD were identified, including one review article and five clinical investigations. Similar to the studies on secondary prevention, different dietary interventions were used and various cardiovascular outcomes were measured.

Ascherio **(27)** briefly reviewed the current epidemiological evidence supportive of the hypothesis that coronary disease risk depends upon the 'quality' and not 'quantity' of dietary fat, and that increased consumption of polyunsaturated fats (linoleic acid and linolenic acid) appear to reduce CHD risk.

Mozaffarian et al. **(28)** examined the associations of fish consumption with ischemic heart disease risk in older adults (≥ 65 years) and how different types of fish meals relate to risk. This population-based, prospective cohort study of 3910 adults, free of cardiovascular disease, showed that modest consumption of tuna or other broiled or baked fish, and not fried fish, was associated with lower risk of ischemic heart disease.

Another study measured the presence of atherosclerotic plaques and carotid intima-media thickness and examined association with dietary linolenic acid in 1575 participants free of coronary artery disease, stroke, hypertension, and diabetes. In this study by Djousse et al. **(29)**, results showed that higher consumption of total linolenic acid was associated with lower prevalence odds of carotid plaques but was not significantly related to carotid artery disease.

Torres et al. **(30)** investigated the relationships between fish intake and concentrations of serum EPA and DHA, and the effects of EPA and DHA on serum lipids and lipoproteins. Two groups of men, in a fishing village and in a

farming village, participated in the study; daily fish intake was ten times greater in the fishing village and ischemic heart disease mortality was four times higher in the farming village. Results showed a significant decrease in serum triacylglycerol and total cholesterol, a significant increase in serum concentrations of EPA and DHA, and a non-significant decrease in serum LDL-cholesterol, in the fishing village. The authors conclude that their data reinforces that high intake of ω-3 fatty acids protect against CHD.

The longitudinal, cohort NHANES I Epidemiologic Follow-up Study reported by Gillum et al. **(31)**, included 8825 black and white women and men (age 25 to 74 years) who did not report a history of heart disease at the time. Fish consumption at baseline was obtained from a three-month food frequency questionnaire. White men with fish consumption of one time/week showed an adjusted rate risk of death about ¾ that of men who never consumed fish; similar, non-significant trends were seen in white and black women, but not black men. No consistent association of fish consumption and CHD incidence or mortality was observed.

A small study (N=31) by Laidlaw and Holub **(32)** examined the triacylglycerol-lowering effects and the fatty acid patterns of serum phospholipids of different levels of gamma-linolenic acid supplementation in combination with a constant intake of EPA plus DHA versus EPA plusDHA alone. Results showed a favorable alteration in the blood lipid and fatty acid lipid profiles of healthy women with both a mixture of 4g EPA plus DHA or 2g gamma-linolenic acid.

In a prospective, nested case-control analysis, Albert et al. **(33)** examined blood levels of long chain ω-3 fatty acids and the risk of sudden death in apparently healthy men (17-year follow-up from the Physicians' Health Study). Results showed baseline blood levels of long chain ω-3 fatty acids were inversely related to the risk of sudden death, both before and after adjustment for potential confounding, which led the authors to conclude that the ω-3 fatty acids found in fish are strongly associated with a reduced risk of sudden death in men without CHD.

Lastly, Forsyth et al. **(34)**, in a follow-up (mean 70.1 months [SD 3.5 months]) of a multicenter randomized controlled trial to determine whether supplementation of infant formula with long chain polyunsaturated fatty acid (LCPFUA) influenced blood pressure in later childhood, the authors concluded that "dietary supplementation with LCPFUAs during infancy was associated with lower blood pressure in later childhood."

4. Only five recent publications do not support a beneficial relationship between ω-3 fatty acids and CHD

Three clinical trials and two reviews that do not support a relationship between ω-3 fatty acids and CHD were identified in the current literature. The three trials addressed, respectively, the relationship between fish consumption and CHD incidence in a Danish population, the effects of purified EPA and DHA on glycemic control in type 2 diabetic patients with treated hypertension, and the progression of carotid atherosclerosis in patients with coronary artery disease who were given 1.65 g/d of ω-3 fatty acids in the form of fish oil supplements. The two reviews provided commentary on the new AHA recommendations and the distinction between nutrition and pharmacology.

Osler et al. **(35)** investigated the relationship between fish consumption, all-cause mortality, and incidence of CHD in a Danish population (N=4513 men and 3984 women) aged 30-70 years. No evidence for an inverse association between CHD or all cause mortality and fish consumption was noted. In a small subgroup of high-risk participants, a non-significant inverse relationship between fish consumption and CHD morbidity was observed. It should be noted that the estimates in the high-risk subgroup went in the right direction, and lack of statistical significance may have been due to lack of power associated with the small sample size [N=242]. The results of this study are in contrast to other studies in populations with higher rates of CHD than the Danish population.

A double-blind, parallel group, placebo-controlled trial by Woodman et al. **(36)** measured the effects of purified EPA and DHA on glycemic control in type 2 diabetic patients with treated hypertension. In this small sample of 39 men and 12 post-menopausal women, results showed that in those who received 4g/d EPA or DHA, similar benefits in lipids (decrease in serum triacylglycerols, increase in HDL), but an adverse effect on glycemic control (measured by fasting glucose), was seen. Neither EPA nor DHA had significant effects on fasting insulin, insulin sensitivity, or stimulated insulin release. The authors postulate that the findings related to effects on glycemic control in type 2 diabetics may be related to the dose of ω-3 fatty acids, other conditions (hypertension) that may affect insulin sensitivity, and lack of strict adherence to diet during the intervention. As well, the triacylglycerol lowering effect of ω-3 fatty acids may be related to an increase in hepatic glucose output. The results suggest that 4g/d purified EPA or DHA does not provide advantages over fish or fish oil supplements with respect to effects on glycemic control.

A trial by Angerer et. al. **(37)** examined the progression of carotid atherosclerosis in 223 patients with coronary artery disease who were given 1.65 g/d

of ω-3 fatty acids for two years. Of the 171 patients who completed the study, the percentage of patients showing progression was similar between groups (38% in the fish oil group vs. 35% in the placebo group), which led the authors to conclude that dietary supplementation with ω-3 fatty acids did not demonstrate an effect of slowing atherosclerotic progression in the carotid arteries.

In a recent editorial comment, Grundy **(38)** stated "[a]vailable data suggest that higher intakes of N-3 fatty acids will reduce various forms of CVD, especially sudden cardiovascular death." Grundy, nonetheless, questions the recommendations of the recent AHA guideline, specifically characterizing as "problematic" the recommendation for use of fish oil supplements in patients with established CHD. While citing the lack of confirmatory evidence with definitive controlled clinical trials, Grundy duly notes that the cost of such confirmatory trials would be prohibitive.

De Lorgeril and Salen **(39)** address points regarding differences between dietary α-linolenic acid and long-chain ω-3 fatty acids and note that the use of dietary supplements is very different from ingesting fatty fish, which contain many nutrients other than lipids. They further make the case that not all fish is safe because contaminants (i.e., methylmercury) reduce the cardio-protective effects of ω-3 fatty acids. Finally, they question the extrapolation of nutritional data to pharmacologic applications.

5. A growing body of scientific evidence increasingly supports the relationship between ω-3 fatty acids and a reduced risk of CHD

In summary, the relationship between ω-3 fatty acids and CHD risk continues to receive widespread attention in the scientific community. The extensive study and ongoing analysis have generated numerous scientific publications as well as publications in the lay press. Both governmental reports and distinguished scientific organizations, such as the AHA, have endorsed the epidemiological and clinical data to disseminate recommendations for the American public regarding appropriate intake of ω-3 fatty acids. Multiple review articles support a conclusion that the cardio-protective qualities of ω-3 fatty acids are increasingly recognized and accepted by qualified scientists.

Admittedly, it can be difficult to directly compare among and between studies because different dietary interventions or supplements may be used and a wide range of cardiovascular and other endpoints may be examined. As Grundy **(38)** pointed out, additional randomized trials are still needed to solidify scientific support and fully elucidate the underlying mechanisms and specific dosage

recommendations. The AHA **(2)** concurs, noting that "additional studies are needed to confirm and further define the health benefits of ω-3 fatty acid supplements for both primary and secondary prevention."

Although reasonable minds may differ as to whether the available evidence rises to the level of significant scientific agreement, a qualified claim for the cardio-protective properties of ω-3 fatty acids in conventional foods and dietary supplements is supported by a strong body of credible scientific evidence. This evidence includes numerous clinical trials and epidemiological data that have been favorably reviewed by FDA, the IOM, the AHA, and others in the scientific community, as well as new and emerging evidence. Evidence published subsequent to the IOM report, in particular, provides significant additional scientific support for a qualified health claim, and provides no evidence that calls into question the scientific rationale underlying FDA's October 2000 determination allowing the use of a qualified ω-3 claim on dietary supplements. Accordingly, although ω-3 fatty acids continue to be the subject of some debate, it is increasingly clear that the proposed claim is supported by impressive agreement throughout the scientific community.

The evidence available to date supports, at a minimum, a "Category B" health claim, because there is a growing body of evidence demonstrating that ω-3 fatty acids reduce the risk of CHD. Moreover, because the available information supports a benefit for both conventional foods and dietary supplements, the claim should be extended to conventional foods, including foods such as fish and foods to which DHA and/or EPA have been added for purposes of increasing ω-3 fatty acid intake. Omega-3 fatty acid dietary supplementation and fortification of food are particularly important because the dietary EPA plus DHA enrichment levels used in clinical trials are not realistically achievable by eating currently available foods, especially given typical North American eating patterns reported by Morris **(40)**.

C. Foods Bearing the Proposed Claim Should Contain Meaningful Amounts of ω-3 Fatty Acids

FDA has not yet established a daily value for ω-3 fatty acids. Food products eligible to bear the contemplated health claim, however, should contain a meaningful amount of ω-3 fatty acids, specifically DHA and/or EPA, per RACC. The IOM AMDR provides a reasonable basis for determining the meaningful level of DHA and/or EPA because the IOM has determined that this level of DHA and/or EPA has been shown to provide desired health effects in terms of CHD and stroke risk reduction.

Historically, where FDA has established a daily value (DV) for a nutrient that is the subject of a proposed health claim, the agency has looked to the established definitions for "good source" and "excellent source" to define the foods that qualify for the claim. 32/ In the absence of a DV, however, FDA has looked to other reference standards and factors that may bear on the qualifying level determination. For example, in authorizing a health claim for fruits, vegetables, and grain products that contain soluble fiber, for which there is no DV, FDA set the qualifying level at 10 percent of the soluble fiber intake recommended by an expert panel convened by the Life Sciences Research Office (LSRO). 33/

We believe that a similar approach is justified in this instance. The IOM expert panel established an AMDR for α-linolenic acid at 0.6 to 1.2 percent of energy and recognized that up to 10 percent of this range can be consumed as EPA and/or DHA. The lower boundary of the AMDR is based on the AI for α-linolenic acid, which is 1.1 and 1.6 grams per day for women and men, respectively. 34/ The recommended intake of DHA and/or EPA on the lower end of the AMDR, therefore, is 110 to 160 milligrams.

Applying FDA's "excellent source" rationale for nutrient content claims to DHA and/or EPA, a food may reasonably be regarded to provide a meaningful amount of these nutrients if it contains at least 20% of the recommended intake level. Using the AI for adult men of 1.6 grams of α-linolenic acid, of which DHA and/or EPA may contribute up to 160 milligrams, we believe a food should qualify for the contemplated claim if it contains at least 20% or 32 milligrams of DHA and/or EPA per RACC. 35/ Such a qualifying level would ensure that foods bearing the claim contain a meaningful and realistic level of DHA and/or EPA. In light of the extensive data regarding the benefits of DHA and EPA, fortification should be permitted to reach this qualifying level.

32/ 62 Fed. Reg. 3583, 3592 (Jan. 23, 1997).

33/ 58 Fed. Reg. 2552, 2574 (Jan. 6, 1993).

34/ "Adequate intake" is defined to mean "the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate." Macronutrient Report at S-2.

35/ We believe that the AI for adult men provides the most appropriate reference standard based on FDA's general practice of considering the needs of the most vulnerable population in establishing a DV.

Although Martek is unaware of any conclusive evidence concerning the level of ω-3 fatty acids beyond which no benefit would be expected, the safety determinations for ω-3 fatty acids require reasonable assurances that total daily intakes will not exceed 3 g/p/d from all sources. By allowing foods fortified with at least 32 milligrams of DHA and/or EPA to be eligible for the claim, there will be little concern that fortification would lead to consumption of over three grams of DHA and/or EPA.

D. Consumers Should Be Advised of Mercury Concerns

1. Foods that may be eligible to bear the proposed claim may contain mercury, including methylmercury

Dietary oily fish, fish oils, and fish oil concentrates are often used to provide increased intake of the ω-3 fatty acids EPA and DHA in accordance with current dietary recommendations. Such supplementation has enormous public health implications in both primary and secondary prevention of CHD. It is well known that the content of ω-3 fatty acids varies widely among fish species, being high in oily fish (e.g., salmon, mackerel, etc.) and low in lean fish (e.g., flounder, cod, etc.). Adhering to the guidance of ingesting oily fish at least twice a week, however, is not without risk. Fish and the oils derived from fish may contain contaminants such as the heavy metal, mercury.

Mercury is present throughout the environment, in plants, and in animals, as a result of both natural processes (e.g., degassing from the earth's crust) and industrial pollution (e.g., pollution caused by burning of industrial wastes). Trace amounts of mercury accumulate in water, where it is converted to the more toxic form of methylmercury by bacteria. Methylmercury in water is taken in by fish, with larger, predatory fish accumulating higher levels. The FDA action level for methylmercury in fish, shellfish, crustaceans, and other aquatic animals—the level at which legal action may be recommended—is 1 ppm. 36/ FDA's action level of 1 ppm for methylmercury in fish and other seafood was established to limit consumers' methylmercury exposure to levels 10 times lower than the lowest levels

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36/ U.S. Food and Drug Administration, Compliance Policy Guides Sec. 540.600, Fish, Shellfish, Crustaceans, and Other Aquatic Animals – Fresh, Frozen, or Processed – Methylmercury (CPG 7108.7) (11/6/84 rev. 3/95).

associated, at the time the action level published, with adverse effects (paresthesia) observed in mercury poisoning incidents. 37/

Because exposure to toxic levels of mercury may result in both neurologic and renal damage, FDA and the U.S. Environmental Protection Agency have issued advisories regarding fish consumption by individuals in the most vulnerable populations—women who are pregnant or may become pregnant, nursing mothers, and young children. The FDA Advisory recommends that at-risk consumers completely avoid species that may contain high levels of methylmercury: shark, king mackerel, swordfish, and tilefish. 38/ The Advisory recommends that intake of other species be limited, on average, to no more than 12 ounces per week, and that a variety of species be consumed. The Environmental Protection Agency's Advisory, which applies to non-commercial fish, recommends that high-risk individuals limit their consumption of fish caught by family and friends to one meal per week. 39/ According to the Environmental Protection Agency, this translates to six ounces of cooked fish or eight ounces of uncooked fish per adult and two ounces of cooked fish or three ounces of uncooked fish per young child.

For consumers other than pregnant women, women of childbearing age who may become pregnant, and children, FDA has recommended that regular consumption of fish species with methylmercury levels around 1 part per million (ppm)—such as shark and swordfish—be limited to about 7 ounces per week. For fish with levels averaging 0.5 ppm, FDA has recommended that regular

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37/ U.S. Food and Drug Administration, Mercury in Fish: Cause for Concern? FDA Cons Mag (Sept. 1994) (Accessed July 30, 2003 at http://www.fda.gov/fdac/reprints/mercury.html).

38/ Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration. Consumer advisory: an important message for pregnant women and women of childbearing age who may become pregnant about the risks of mercury in fish (March 2001) (Accessed on Oct. 30, 2003 at http://www.cfsan.fda.gov/~dms/admehg.html).

39/ Office of Water, U.S. Environmental Protection Agency. Consumption Advice Fact Sheet. National advice on mercury in fish caught by family and friends: for women who are pregnant or may become pregnant, nursing mothers, and young children (January 2001). EPA-823-/f-01-004 (Accessed Oct. 30, 2003 at http://www.epa.gov/waterscience/fishadvice/factsheet.html).

consumption be limited to approximately 14 ounces per week. FDA has published data regarding the methylmercury content of a variety of fish and shellfish.

Most recently, in June of this year, the Joint Expert Committee on Food Additives and Contaminants (JECFA) of the World Health Organization 40/ (WHO) and Food and Agriculture Organization (FAO) reduced by half the recommended tolerable intake limits of methylmercury for expectant mothers. The provisional tolerable weekly intake (PTWI) of methylmercury was cut from 3.3 micrograms/kg body weight to 1.6 micrograms/kg body weight.

2. Mercury, including methylmercury, can counteract beneficial effects of ω-3 fatty acids

In addition to presenting neurological concerns, mercury is of particular concern with regard to the proposed claim because it may offset the cardio-protective properties of ω-3 fatty acids found in fish. In a multinational case-control study, Guallar **(41)** evaluated the joint association of mercury levels in toenail clippings with DHA levels in adipose tissue with the risk of a first MI in men. After adjustment for the mercury levels and for coronary risk factors, the DHA level was shown to be inversely associated with the risk of myocardial infarction (MI) (P=0.02 for trend). This study demonstrated that high mercury content can offset the cardio-protective effects of the DHA (and/or EPA) derived from fish consumption.

A study by Yoshizawa et al. **(42)** evaluated the effect of mercury intake and risk of cardiovascular disease. Unlike the Guallar (41) study, which examined whether mercury levels could offset the cardio-protective effects of ω-3 fatty acids, Yoshizawa looked merely at the relationship between mercury levels and risk of CHD regardless of ω-3 fatty acid intake. Using a nested case-control design, Yoshizawa investigated the association between mercury levels in toenails and risk of CHD among male health professionals aged 40-75 years, with no previous history of heart disease. Results showed the mean mercury level was significantly (P <0.001) correlated with fish consumption and was significantly higher in dentists than in non-dentists. After control for other risk factors, however, the mercury level was not significantly associated with risk of CHD. The authors concluded that

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40/ Food and Agriculture Organization of the United Nations/World Health Organization, Joint FAO/WHO Expert Committee on Food Additives, Sixty-first Meeting, JECFA/61/SC, (June 10-19, 2003) (Accessed on Oct. 30, 2003 at http://www.chem.unep.ch/mercury/Report/JECFA-PTWI.htm).

although their results did not support an association between mercury exposure and development of CHD, a weak association could not be ruled out.

Indeed, as both Izzat **(11)** in the United Kingdom and Kris-Etherton **(3)** in the United States have recently pointed out, the safety of fish with their potential adverse effects due to the environmental pollutants make it difficult to wholeheartedly recommend increased consumption of fish. Further, Kris-Etherton notes that "the availability of high-quality ω-3 fatty acid supplements, free of contaminants, is an important prerequisite to their extensive use."

3. Advisory language is needed to ensure the proposed claim is truthful and not misleading on all foods on which it appears

The health concerns posed by mercury are serious and warrant special consideration in development of a health claim for ω-3 fatty acids. A food is misbranded under the FFDCA if its label or labeling is false or misleading in any particular. 41/ A label may be deemed misleading based on information that is provided therein, pursuant to section 403(a) of the FFDCA, or based on a failure of the label to reveal material facts, pursuant to section 201(n) of the Act. Under section 201(n), an omitted fact may be deemed "material" either in light of representations made on a label or in labeling, or in light of consequences that may result from use of the article.

In addition to these general requirements, which apply to all foods, FDA has developed specific requirements to ensure the appropriate use of health claims to further public health objectives. Collectively, these requirements advance the congressional intent that health claims facilitate healthy dietary practices, and not merely provide information on isolated substance-disease relationships. 42/

Significantly, the agency has provided by regulation that health claims must be complete, truthful, and not misleading. In requiring that health claims be "complete," FDA advised as follows:

> It is imperative that consumers be informed of factors other than the consumption or nonconsumption of the substance that significantly

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41/ FFDCA § 403(a).

42/ 58 Fed. Reg. 2478, 2489 (Jan. 6, 1993).

> bear on the claimed effect on a disease or health-related condition. 43/

Health claims also must enable the public to understand the relative significance of the information in the claim in the context of a total daily diet. 44/ Among the concerns that led to enactment of the NLEA were deceptive claims that selectively highlighted beneficial dietary information related to one disease, but that remained silent about another, related characteristic that may affect the risk of the same (or another) disease. 45/ Concern was also expressed, in the NLEA legislative history and administrative record, that foods bearing health claims must not contain properties that may be harmful to health. This history and regulatory precedent establish that health claims must contemplate and address all pertinent factors that are reasonably and directly expected to bear on disease risk.

The agency has also acknowledged that, in some circumstances, a health claim may present unique safety concerns to a subpopulation of consumers. In such circumstances, the agency has advised that the at-risk consumers should be put on notice of the potential harm:

> If at some point in the future, the agency approves a health claim that has some safety concern to any subpopulation of consumers, the agency will, of course require that the claim include sufficient information to alert that subpopulation. 46/

The potentially serious nature of mercury contamination warrants special consideration in a health claim for ω-3 fatty acids. The presence of mercury may offset the cardio-protective effects of ω-3 fatty acids, affecting the disease that is the subject of the proposed claim, and causing the claim to be misleading if it appears on fish containing mercury at elevated levels. Moreover, families with concerns regarding heart disease may target fatty fish for increased consumption based on the health claim, without realizing that limitations in intake are prudent to prevent unintended adverse consequences in fetuses or young children.

43/ *Id.* at 2511.

44/ *Id.* at 2489; 21 C.F.R. § 101.14(d)(2)(v).

45/ 58 Fed. Reg. at 2489-90.

46/ *Id.* at 2511-12.

Accordingly, mercury-specific limitations and advisory language are needed to ensure that the proposed health claim is complete, reveals information relevant to the intake of fatty fish in the context of the total diet, and reveals facts material in light of the claim and in light of the consequences of over consumption of fish.

4. Health claim eligibility must be consistent with FDA and Environmental Protection Agency advisories on mercury

To ensure that labels or labeling of foods bearing the proposed health claim are not false or misleading by reason of mercury content, this Petition proposes that the health claim not be permitted to appear on the four species of fatty fish that contain the highest levels of mercury—tilefish, swordfish, king mackerel, and shark. According to FDA data, the mean mercury content of these species is, respectively, 1.45 ppm to 0.96 ppm. These mean levels are more than twice the levels of other fish and shellfish analyzed by FDA and approach or exceed the FDA action level of 1 ppm. Promotion of these foods for increased consumption would not assist consumers in maintaining healthful dietary practices consistent with public health recommendations; promotion of these foods for cardio-protective benefits would be false or misleading.

For fish other than tilefish, swordfish, king mackerel, and shark, an informative statement is needed to alert the vulnerable population of the need to restrict fish intake. The failure to include this informative statement could lead those in the vulnerable populations to increase fish consumption to over 12 ounces of cooked fish per week under the mistaken belief that increased fish consumption would result in a healthier diet. The proven cardiovascular benefits of increased fish consumption must be weighed against the proven adverse effects of mercury on those in the vulnerable population. In addition, greater intake of mercury may also offset the cardio-protective effect of ω-3 fatty acids such as DHA, as shown by Guallar **(41)**.

Martek believes that the issues presented by oceanic mercury contamination are best addressed by requiring an informative statement that would accompany the cardiovascular health claim when it appears on the label or in the labeling of those fish that are eligible for the claim (*i.e.*, all fish other than tilefish, king mackerel, shark, and swordfish). Martek believes that this would be accomplished by the following informative statement:

> [Name of seafood], like all seafood, may contain trace levels of mercury, an environmental contaminant. At high levels, mercury may cause harm to developing fetuses and young children, and may diminish the protective effects of omega-3 fatty acids on heart health. To minimize

the risk of mercury exposure, FDA recommends that pregnant women, women who may become pregnant, nursing mothers, and young children eat no more than 12 ounces of cooked fish per week and choose a variety of fish rather than a single type.

Martek also believes that the proposed health claim should be prohibited on ω-3 fatty acid-containing ingredients (such as fish oils) that contain mercury in any form, including methylmercury. While single cell oil sources of ω-3 fatty acids and many of the processed fish oil sources of ω-3 fatty acids may be essentially free of mercury or have very low levels of this contaminant, fish oils do have the potential to contain mercury. Martek asserts that the health claim should be prohibited on food products with ω-3 fatty acid-containing ingredients unless the ingredient has been shown to contain less than 0.025 ppm of mercury. Martek selected the maximum level of 0.025 ppm (rather than 0.01 ppm representing the lower range reported as being in fish by FDA) because that is the limit of detection for the most sensitive test accepted as standard by the Association of Official Analytical Chemists (AOAC).

Although the menhaden oil GRAS affirmation regulation would allow up to 0.5 ppm of mercury, we believe that products bearing the health claim should have the lowest possible level of mercury. Given the health concerns with mercury contamination, the potential for mercury to offset the cardio-protective benefits of DHA and the availability of DHA and other omega-3 sources that have undetectable levels of mercury, we believe that the maximum level of mercury, including methylmercury, should be set at 0.025 ppm when an oil source is added to a food for purposes of qualifying for the health claim.

While we believe that fish oil sources of DHA and EPA should be analyzed for mercury before products are eligible to bear the health claim, we do not believe that it is appropriate to require an analysis of fish for mercury content. The mercury levels of fish have been well documented by data developed by the Environmental Protection Agency and FDA. In addition, analysis for mercury is unnecessary because the fish eligible to bear the claim would carry an informative statement cautioning against the consumption by the vulnerable population of more than 12 ounces of cooked fish per week.

E. Public Health Benefit

The public health stands to benefit from the proposed claim in two significant respects. First, authorization of the claim for conventional foods is expected to lead to increased intake of DHA and EPA. There is now credible scientific evidence indicating that increased intake of DHA and EPA will reduce the

risk of CHD, a serious disease that is estimated to result in the deaths of millions of Americans each year and impose billions of dollars in direct and indirect costs. 47/ Indeed, Dr. Mark McClellan, Commissioner of Food and Drugs, has repeatedly identified omega-3 fatty acids as an ideal candidate for a qualified health claim. In doing so, Dr. McClellan has expressed his view that "significant studies indicate a heart benefit from consuming a diet high in omega-3 fatty acids. 48/ The Office of Management and Budget (OMB) similarly has noted that "epidemiological and clinical studies find that an increase in consumption of omega-3 fatty acids results in reduced deaths due to CHD." 49/ OMB asked for revisions to the "*Dietary Guidelines*" and the "*Food Guide Pyramid*" noting the "significant potential improvement in public health suggested by current evidence" on the importance of reducing foods high in *trans* fatty acids and increasing consumption of foods rich in ω-3 fatty acids. Expert groups like the American Heart Association similarly recognize the relationship between ω-3 fatty acids and a reduced risk of CHD.

Second, by including, as appropriate, advisory language as proposed herein, the proposed health claim will ensure that increased intake of foods such as fatty fish does not inadvertently result in increased intake of mercury, a dangerous contaminant that poses risk to developing fetuses and young children, and that may diminish the cardiovascular benefits of ω-3 fatty acids.

47/ Ray Formanek, Jr., Mission: Promoting, Protecting the Public Health – FDA Commissioner Mark B. McClellan, *FDA Consumer* (Mar.-Apr. 2003).

48/ *Id.*

49/ Letter from John D. Graham, Ph.D., Administrator, Executive Office of the President Office of Management and Budget to Honorable Claude A. Allen, Deputy Secretary, Department of Health and Human Services (DHHS) and Honorable James R. Mosely, Deputy Secretary, Department of Agriculture (May 27, 2003).

III. ANALYTICAL DATA

Several reliable methods are available to confirm the amount of ω-3 fatty acids contained in conventional food or dietary supplements that may bear the qualified health claim. Available methods include the Association of Official Analytical Chemists (AOAC) Official Method #991.39, Fatty Acids in Encapsulated Fish Oils and Fish Oil Methyl and Ethyl Esters.

IV. MODEL HEALTH CLAIM

The following qualified model health claims are proposed for use on the labels or in labeling for conventional foods and dietary supplements that contain a minimum of 32 mg of ω-3 fatty acids per RACC. Consistent with FDA's health claim regulations, these model claims are justified by the summary of scientific data provided in section II of this Petition. In its guidelines establishing the interim procedures for qualified health claims, FDA provides an example of the qualifying language that could be used on an FDA Category B health claim. FDA indicates that an appropriate qualifier for a Category B claim would be "although there is scientific evidence supporting the claim, the evidence is not conclusive," while recognizing that the precise language "may vary depending on the specific circumstances of each case." 50/

Martek recommends the use of language that closely tracks the language used in the IOM Macronutrient Report regarding the relationship between DHA and/or EPA and CHD (with the exception of eliminating the reference to ALA). Martek believes that the currently available science would support the use of the following qualified claim:

> A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease. 51/

This statement is based on the language used by the IOM Expert Panel in the "Summary" section for "Chapter 11, Macronutrients and Healthful Diets." After

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50/ Guidance for Industry and FDA, Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Dietary Supplements, pg. 2 (July 2003).

51/ Martek does not believe that the phrase "higher intakes of omega-3 fatty acids" is a nutrient content claim when used in this context. The phrase does not imply that the omega-3 fatty acids are present at a specific level in the product but instead informs the consumer that the benefits of omega-3 fatty acids are observed when DHA and ARA are consumed at levels higher than that found in the average diet. To the extent that FDA is concerned that this proposed use of "higher" is subject to regulation as a nutrient content claim, Martek would recommend using the following alternative claim: "A growing body of scientific literature suggests that the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease."

reviewing the extensive data on DHA and EPA, this authoritative body issued a similar statement summarizing the important role of DHA and EPA in reducing the risk of coronary heart disease. 52/ In instances such as this when an expert body has reviewed the available data and issued a statement summarizing the data, we believe that FDA should give deference to the language used by the expert body when determining the language that should be used in the related qualified health claim.

The proposed qualified health claim captures the recommendations of the authoritative body convened by the IOM while providing language that is needed to distinguish this claim from an unqualified health claim. The language is qualified by characterizing the scientific data as a "growing body of scientific literature" and by using the term "some degree of protection" against CHD. These qualifying terms let the consumer know that while there is a growing body of evidence in support of the claim, the data are not yet sufficiently clear to state unequivocally that DHA and/or EPA can reduce the risk of coronary heart disease. Because the proposed model language closely tracks the language used in the IOM Macronutrient Report and is appropriately qualified, we believe that, under these specific circumstances, it would be appropriate for the agency, in this instance, to allow the use of a qualified statement that varies from the suggested language found in the agency interim guidance document.

Martek also believes that when the qualified health claim appears on fish, there must be an informational statement that advises the vulnerable subpopulation of the health concerns associated with eating more than 12 ounces of cooked fish per week. Martek provides examples of the qualified health claims that it believes would be appropriate on dietary supplements and conventional foods that are formulated with DHA and EPA rich ingredients and on the labeling of those fish that are eligible to bear the claim.

The following proposed model claims would be permitted to appear on dietary supplements and conventional foods eligible to bear the claim, with the exception of fish. Slightly different variations of the claim would be authorized to

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52/ The IOM report concludes, "A growing body of literature suggests that higher intakes of α-linolenic, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may afford some degree of protection against CHD." We omitted α-linolenic acid from the claim because the data in this submission establish that the relationship between α-linolenic acid and a reduced risk of CHD is not as advanced as the data for DHA and EPA.

highlight EPA and DHA collectively or independently. Fish-derived ingredient sources of ω-3 fatty acids would be ineligible for the claim unless the ingredient contains less than 0.025 ppm of mercury.

> A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease.
>
> A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acid DHA may afford some degree of protection against coronary heart disease.
>
> A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acid EPA may afford some degree of protection against coronary heart disease.

The following proposed model claim would be required for use on fish, other than those fatty fish containing significant levels of mercury, for which the proposed health claim would not be permitted:

> A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease. [Name of seafood], like all seafood, may contain trace levels of mercury, an environmental contaminant. At high levels, mercury may cause harm to developing fetuses and young children, and may diminish the protective effects of omega-3 fatty acids on heart health. To minimize the risk of mercury exposure, FDA recommends that pregnant women, women who may become pregnant, nursing mothers, and young children eat no more than 12 ounces of fish per week and choose a variety of fish rather than a single type.

Finally, tilefish, swordfish, king mackerel and shark would be ineligible for the health claim due to the high levels of mercury, including methylmercury, reported in these species.

V. DESCRIPTION OF ATTACHMENTS

This Petition includes the following attachments:

1. Copies of computer literature searches done by the petitioner; and

2. Copies of articles cited.

VI. ENVIRONMENTAL IMPACT

An environmental assessment is not required because the preparation of a submission seeking FDA review of a health claim is subject to a categorical exclusion under 21 C.F.R. 25.32.

VII. CONCLUSION AND CERTIFICATION

For the foregoing reasons, the Petitioner requests that FDA exercise enforcement discretion concerning a qualified health claim regarding the relationship between ω-3 fatty acids and CHD. Pursuant to 21 C.F.R. 101.70(h), I hereby certify that, to the best of my knowledge, this Petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known to the Petitioner to be pertinent to the evaluation of the proposed health claim.

Yours very truly,

MARTEK BIOSCIENCES CORPORATION

By _____

James P. Hoffman, M.D.
Medical Director