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Center for Foods and Applied Nutrition
Office of Nutritional Products
Labeling and Dietary Supplements
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Dear Sirs / Madams:

I am responding to comments raised by the FDA concerning the omega-3 fatty acid health claims.

1. The position of NHLBI on omega-3 fatty acids is well stated in the National Cholesterol Education Program report, which was published by the NHLBI in September 2002 (1). A committee wrote the report, and their work was carried out in the year 2000-2001. This clearly means that the report is now considerably out of date. The recent evidence about the role of omega-3 fatty acids in preventing cardiac arrhythmias and sudden death is not covered at all by the NHLBI report. This work was not available to the committee of the NHLBI at the time the members drew up their report. In fact, the entire report on pages V-14ff does not mention any anti-arrhythmic effects or alludes to any such references. Even so, the recommendation then was that "the strength of the evidence is only moderate at present."

   It is important to recognize that 15 peer-reviewed studies have been published since the NHLBI report was completed (2-16). None of these appeared in the report. While it would be presumptions to indicate how the committee might strengthen its recommendations from "moderate" to strong, if it looked now at the recent studies, no one could disagree that the strength of evidence that omega-3 fatty acids might prevent cardiac arrhythmias and sudden death has now been greatly augmented as presented in the previous review submitted to the FDA by William Connor (17).

   The NHLBI report supports the American Heart Association's recommendation that fish be included as a part of a CHD–risk reduction diet. Another section of the report, page VI-16, suggested that doses of fish oil, from 3-12 grams per day, have been used in the treatment of hypertriglyceridemia. This section also states that "n-3 fatty acids can be a therapeutic option in secondary prevention" of coronary heart disease. "More definitive clinical trials

are required before relatively high intakes of n-3 fatty acids can be strongly recommended for either primary or secondary prevention." As indicated by references cited (2-16), many new definitive clinical trials have now been reported.

The report does not mention any safety concerns in these regards, especially as regards the possibility of bleeding from omega-3 fatty acids intake.

In summary, the NHLBI report is excellent but simply could not address the more recent evidence on the value of omega-3 fatty acids in preventing arrhythmias and sudden death because these studies had not yet been published when the expert committee reviewed the available literature. The recent work strongly supports a health benefit from omega-3 fatty acids in coronary heart disease.

2. The safety of the omega-3 supplementation/fish oil consumption (in particular concerning its anti-coagulation effects): "Is there "a bleeding tendency of fish oils?" The answer to this question is that reports on hundreds of humans have not indicated bleeding problems from fish/fish oil use. There is, however, a mild anti-thrombic action of omega-3 fatty acids from fish oil to inhibit the aggregation of platelets, which has been noted in all of the reviews on the subject (18). The EPA of fish oil inhibits the formation of thromboxane A_2, an enzyme formed naturally in the body in response to injury, and which causes the aggregation and clumping of platelets to stop bleeding from a wound. Blocking thromboxane A_2 might theoretically cause bleeding. The action of aspirin is somewhat similar in inhibiting this same enzyme system. One would anticipate a mild bruising effect in a very few individuals, similar to what the same individuals might experience from the use of aspirin. To be noted is the fact that all adults over the age of 50, if they follow current medical recommendations to prevent coronary disease and stroke, would be taking one baby aspirin (81 mg) per day to inhibit platelet function much in the same way that fish oil inhibits platelet function. Aspirin, of course, does not have any anti-arrhythmic action.

From the past literature on the use of fish and fish oil, there is a very little evidence that bleeding is a problem. In fact, in some of the studies, angioplasty has been performed in individuals receiving fish oil; bleeding was not a problem. In other studies, there have been extensive surgical procedures, such as vascular surgery, in individuals pretreated with fish oil. The surgeons did not encounter bleeding as a problem during the operations (19).

In earlier studies in the 1970's, very large amounts of fish and fish oil were fed to reduplicate the Eskimo experience. For a few individuals, the platelet count was reduced, but no bleeding episodes were reported (20). The bleeding time in those studies was increased because the platelet aggregation was reduced. It was a physiological, not a pathological, reaction. This action was the reason that the fish oil was administered to begin with, to retard the formation of platelet blood clots, or to retard thrombosis, which would be beneficial in our population so inclined to coronary thrombosis and stroke.

The FDA report from the Federal Register Volume 62, #108, lists menhaden oil as generally safe. Reference is made to the bleeding time, "when consumption of fish oil is limited to 3 grams or less of EPA and DHA, there is no significant risk for increased

bleeding time beyond the normal range." Some fish oils providing more than 3 grams per day of EPA and DHA have generally been found "to produce increases in the bleeding time that are significant." The FDA concluded that the safety of menhaden oil is generally recognized only at levels that limit the intake of EPA and DHA to 3 grams or less per day. One gram of menhaden oil in a capsule contains 300 mg of EPA and DHA. The total amount of menhaden oil which the FDA would allow, in terms of it containing no more than 3 grams of EPA and DHA per day, would actually amount to 10 grams of menhaden oil. This is an amount that clinicians in practice of medicine would not use very often. Nor is this an amount recommended to prevent cardiac arrhythmias and sudden death.

The American Heart Association report on fish consumption and cardiovascular disease was buttressed by many more recent references (21) than the previously cited NHLIB report. The AHA recommended that patients with documented coronary heart disease consume at least 1 gram of EPA plus DHA per day, preferably from oily fish. Supplements should also be considered in consultation with physicians. Since the average American consumes no more than 0.2 gram of EPA plus DHA from fish at the present time, it is very clear that most individuals with coronary heart disease would need to take 3 to 4 one-gram capsules of menhaden oil each day to meet this recommendation. This would provide approximately one gram of EPA and DHA. Please note that the one-gram recommendation is only one-third of the upper safe limit as promulgated by the FDA (this being no more than 3.0 grams of EPA and DHA).

The American Heart Association report also advocates a dose of 2 to 4 grams per day of EPA and DHA in the medical management of hypertriglyceridemia (21).

In regards to safety of omega-3 fatty acids, an abstract has been submitted to the American Heart Association by John McAnulty, M.D. reporting a clinical trial of 1.8 grams EPA and DHA to prevent ventricular arrhythmias in 200 patients. This amount of omega-3 fatty acids, well below the upper limit, indicated by the FDA, did not give rise to bleeding or other significant side effects.

In summary, there is widespread agreement that, in amounts of fish or fish oil used to prevent cardiac arrhythmias and sudden death, that bleeding would not be a problem.

3. Evidence about the effective doses of omega-3 fatty acids, the safe upper limit and optimum range (the point beyond which risk increases without benefits), is in abundance from epidemiological data and clinical trials. This is expressed in terms of servings of fish per week, especially fatty fish, and amounts of EPA plus DHA provided by fish oil. One of the surprising aspects of these numerous data is the relatively low amount of EPA plus DHA that produce an effect. Two servings of fish per week, in general, are associated with a 50 percent reduction in coronary risk (2-16). In the clinical trials of omega-3 fatty acids the amount of EPA and DHA has been approximately 1 gram a day up to 1.8 grams per day. There are no data to indicate any discrimination between those two doses. The American Heart Association report on "fish consumption and CVD" suggests 1 gram of EPA plus DHA, either from fish or fish oil (21). This can be supplied, for example, by as little as 3 to 4.5 oz of salmon or 3 oz of sardines, one to two servings per week. Following

the American Heart Association recommendation of two meals of fatty fish a week, one assumes that a serving size is 6 oz (a reasonable amount). Then one would be supplying an upper amount of 18 grams of EPA plus DHA a week from Chinook salmon to a lower amount of 2 grams per week from lower fat species of salmon. The amount of menhaden oil to supply 1 gram of EPA plus DHA would be three 1-gram capsules, or three grams per day. The most extensive clinical trial used a dose of about 1-gram of EPA plus DHA (3). This is the same amount that the American Heart Association report suggested for coronary prevention.

The evidence is very strong, as presented earlier, that all of these doses are thought to be safe. Benefit in increasing the amount above 1 gram of EPA plus DHA would be minimal as far as coronary disease and sudden death prevention are concerned. Note that all of these amounts are considerably less than the GRAS upper limit set by the FDA of 3 grams of EPA plus DHA per day. When one considers the treatment of hypertriglyceridemia, higher doses would be needed. This is beyond the scope of prevention of coronary disease and sudden death. One serving of the fattiest salmon (Chinook) supplies 9 grams of EPA plus DHA. Calculated on a daily basis would be 1+ grams per day of EPA plus DHA. These amounts of fish and fish oil would certainly double the red blood cell concentrations of EPA plus DHA, a concentration needed for optimal coronary prevention as indicated by the study of Siskovich et al, quoted earlier (15).

In summary, relatively low amounts of omega-3 fatty acids as EPA and DHA have had a therapeutic effect in coronary prevention and could be safely consumed without the danger of any bleeding or other side effects. These doses have generally been only one-third of the upper limit of safety already specified by the FDA as safe (below 3 grams of EPA and DHA). No additional benefit would be expected by exceeding the one gram of EPA plus DHA per day.

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CROSS-REFERENCED LIST OF SCIENTIFIC ARTICLES CITED BY DR. CONNOR IN HIS ORIGINAL OMEGA-3 FATTY ACIDS/CORONARY HEART DISEASE REPORT AND IN HIS SUPPLEMENTAL LETTER

Connor's Supplemental Letter	**Connor's Original Report**
Reference 1	N/A
Reference 2	Reference 4
Reference 3	Reference 8
Reference 4	Reference 10
Reference 5	Reference 11
Reference 6	Reference 13
Reference 7	Reference 14
Reference 8	Reference 15
Reference 9	Reference 17
Reference 10	Reference 18
Reference 11	Reference 19
Reference 12	Reference 20
Reference 13	Reference 21
Reference 14	Reference 16
Reference 15	Reference 22
Reference 16	Reference 23
Reference 17	N/A
Reference 18	N/A
Reference 19	N/A
Reference 20	N/A
Reference 21	Reference 12

Please note that Letter References 1 and 18-20 were not submitted in the original petition. Instead, those references are attached hereto. Letter Reference 17 refers to Dr. Connor's original report that was submitted with the original petition as Exhibit 2.