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January 30, 2004

VIA HAND DELIVERY
Tomoko Shimakawa, Sc.D.
Food and Drug Administration
Office of Nutritional Products,
Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
Room 4A036
College Park, MD 20740

Re: Docket Number 2003Q-0401

Dear Dr. Shimakawa:

Enclosed please find the supplemental submission of American Longevity, Inc. and Life Extension Foundation Buyers Club, Inc. to Docket Number 2003Q-0401.

Please do not hesitate to contact us with any questions.

Sincerely,

Claudia A. Lewis-Eng

Claudia A. Lewis-Eng
Kathryn E. Balmford

Enclosure

2003Q-0401

C6

Before the
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

In re: Qualified Health Claim (QHC)	)	
Omega-3 Fatty Acids and Coronary	)	**Docket No. 2003Q-0401**
Heart Disease Health Claim	)	

SUPPLEMENTAL SUBMISSION OF AMERICAN LONGEVITY, INC. AND LIFE EXTENSION FOUNDATION BUYERS CLUB, INC.

American Longevity, Inc.,[1] and Life Extension Foundation Buyers Club ("Petitioners") hereby seek leave to supplement the record in the above-referenced proceeding with the attached scientific report by Michael John Glade, Ph.D., CNS, FACN (Exhibit A). Dr. Glade's report is directly responsive to the Comments of Martek Biosciences Corporation (hereinafter "Martek") that call into question whether foods and dietary supplements containing omega-3 fatty acids may also contain unsafe levels of mercury. Petitioners respectfully request that FDA consider the attached report of Dr. Glade when evaluating the Martek Comments.

Martek's Comments were filed with FDA two days after the comment period closed; hence, the Petitioners did not have an opportunity to respond to the health and safety issues presented in those Comments while the comment period was open. In the attached report, Dr. Glade rebuts Martek's argument that the presence of mercury interferes with the beneficial effects of omega-3 fatty acids.

After examining the scientific evidence concerning mercury levels in fish and dietary supplements (including, but not limited to, data from FDA and the American Heart Association), Dr. Glade, concludes that disclaimers are appropriate to alert the

[1] Wellness Lifestyles, Inc. has changed its name to American Longevity, Inc.

public to the need for avoiding excess consumption of mercury that may be found in certain fish.

For foods containing 1 ppm total mercury or less, Dr. Glade recommends the following disclaimer: "[Name of seafood], like all seafood, may contain trace amounts of mercury, an environmental contaminant that may cause harm to developing fetuses and young children. FDA recommends that pregnant women, women who may become pregnant, nursing mothers and young children eat no more than 12 ounces of a variety of fish weekly."

For dietary supplements containing 1 ppm total mercury or less, Dr. Glade recommends the following disclaimer: "Limited preliminary evidence suggests that total daily consumption of the omega-3 fatty acids from dietary supplements should not exceed 3000 mg."

Dr. Glade recommends that FDA prohibit the use of the qualified health claim for shark, king mackerel, swordfish and tilefish because of the amounts of mercury found in those fish. Moreover, Dr. Glade recommends that the use of the qualified health claim for dietary supplements be limited to those supplements containing no more than 1 ppm total mercury.

Although the comment period for this docket has expired, consideration of the

information contained in Dr. Glade's report may aid the CFSAN staff in avoiding error in the assessment of mercury.

Respectfully submitted,

AMERICAN LONGEVITY INC., AND
LIFE EXTENSION FOUNDATION
BUYERS CLUB, INC.

By: _____
Jonathan W. Emord
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Date submitted: January 30, 2004

EXHIBIT A

An Evaluation of a Qualified Health Claim for Conventional Foods and Dietary Supplements Containing Omega-3 Fatty Acids

I have examined the document ("Doc") submitted on November 3, 2003, by Martek Biosciences Corporation ("Martek") to the US Food and Drug Administration (FDA) ("Qualified Health Claim for Conventional Foods and Dietary Supplements Containing Omega-3 Fatty Acids"). My findings follow.

The FDA "action level" for regulatory action of 1 ppm methylmercury content emphasized in this document intentionally recognizes the "dilution effect" of the remainder of the diet and relies on that effect in determining that 1 ppm of methylmercury is an upper limit of safety that remains safe for most of the population. [Doc references 36, 37, and 38] As an additional safety buffer in setting this limit, FDA intended to attempt to limit consumers' exposure to methylmercury to no more than 10% of the lowest intakes of total mercury (9 ppm) that were reported to be associated with adverse symptoms. [Doc reference 37] However, affected individuals had been consuming this amount of mercury daily for years before initial neurological symptoms appeared; the appearance of symptoms was reported to require blood total mercury concentrations of at least 200 ppb (reported to be about 2500% the blood total mercury concentrations found in adults with limited consumption of methylmercury-containing seafood). [Doc reference 37]

According to FDA, very limited human data has suggested the mutually exclusive possibilities that human fetuses are more resistant to maternal exposure to methylmercury than are pregnant women, although "the fetus may be more susceptible than the mother to the adverse effects of methylmercury." [Doc references 37 and 38] Nonetheless, in 2001, FDA recommended that "at-risk consumers" (defined by FDA as women who are pregnant or who may become pregnant, women who are breastfeeding and young children) completely avoid the consumption of shark, king mackerel, swordfish and tilefish. [Doc reference 38] This "at-risk" group was encouraged to consume up to 12 ounces of other fish species weekly. In addition, FDA stated "There is no harm in eating more than 12 ounces of fish in one week as long as you don't do it on a regular basis." [Doc reference 38] The consumption of other fish species was judged to be safe for all other individuals, in amounts up to 7 ounces weekly of species containing 0.5 to 1 ppm of methylmercury and in amounts up to 14 ounces weekly of species containing less than 0.5 ppm (typically, small tuna – skipjack, albacore, shrimp, pollack, salmon, cod, catfish, clams, flatfish, crabs and scallops). [Doc reference 38]

The FDA recommendation of limiting the consumption of fish to 7 ounces weekly of species containing up to 1 ppm of methylmercury, or 14 ounces weekly of species containing up to 0.5 ppm of methylmercury, allow for maximum chronic methylmercury intakes of up to 196 micrograms weekly, or 28 micrograms daily, even by "at-risk consumers" (7 ounces weekly = 1 ounce daily; 1 ounce = 28 grams; 28 grams = 28,000,000 micrograms; 1 ppm of 28,000,000 micrograms is 28 micrograms). [Doc reference 38] A more restrictive FDA recommendation for "at-risk consumers" to limit fish consumption to about 3 ounces monthly allows for maximum chronic methylmercury intakes of up to 3 micrograms daily (3 ounces monthly = 0.1 ounce daily; 0.1 ounce = 2.8

g; 2.8 g = 2,800,000 micrograms; 1 ppm of 2,800,000 mirograms = 2.8 micrograms). [Doc reference 38] It is interesting to note that this more restrictive limit is between 20% and 30% of the intake limits (10 to 15 micrograms daily) recommended most recently by the Joint Expert Committee on Food Additives and Contaminants of the World Health Organization and Food and Agriculture Organization. [Doc reference 40] The American Heart Association (AHA) has concluded that "For middle-aged and older men and postmenopausal women, the benefits of fish consumption far outweigh the risks within the guidelines established by the FDA and Environmental Protection Agency." [Doc reference 2] For others, the risks can be managed by adherence to the guidelines established by the FDA and EPA. [Doc reference 2]

Martek, [Doc p. 5] the FDA [Doc references 4 and 5] and the AHA [Doc references 2 and 3] advocate consumption of (DHA + EPA) in amounts up to 3 g daily "from all added sources." The FDA recommended maximum daily methylmercury intake will not be exceeded by individuals with daily consumption of 3 g of (EPA + DHA) as dietary supplements or as food additives even if the methylmercury content of such supplements or additives is as high as 1 ppm (3 g = 3,000,000 micrograms; 1 ppm of 3,000,000 micrograms = 3 micrograms). In addition, the AHA has stated that refined and concentrated omega-3 fatty acid products contain virtually no methylmercury. [Doc references 2 and 3] Clearly, according to the recommendations of the FDA, there is no scientific justification for imposing a maximum mercury limitation on dietary supplements or foods fortified with omega-3 fatty acids that is different from that imposed on foods *per se*.

Martek cited 2 studies in an erroneous attempt to support a claim that mercury interferes with the actions of omega-3 fatty acids. In the first study, Guallar et al. [Doc reference 41] performed a case-control study of men who had experienced a nonfatal myocardial infarction and compared them to similar men drawn from the local population. Their data demonstrated that the multivariate-adjusted odds ratio (OR) for myocardial infarction was significantly increased by the greatest exposure to environmental mercury from all sources (determined from measurements of the mercury content of toenail clippings). In addition, there was weak but statistically significant support for the conclusion that men with the greatest adipose tissue content of DHA (presumably reflecting DHA consumption) were at lower risk for nonfatal myocardial infarction. However, these investigators found "no interaction between mercury and DHA with respect to their associations with the risk of myocardial infarction (P for the interaction = 0.61)." In other words, the effects of mercury were not found to oppose or prevent the beneficial effects of DHA on the risk of suffering a nonfatal myocardial infarction.

In the other case-control study cited by Martek, Yoshizawa et al. [Doc reference 42] found that the multivariate-adjusted risk for coronary heart disease (defined as either coronary artery surgery or nonfatal or fatal myocardial infarction) was not significantly affected by toenail mercury content. These investigators also reported that they found no evidence of any interaction between mercury and omega-3 fatty acids on the risk for coronary heart disease (including myocardial infarction). In addition, the results of

neither study rule out the possibility that omega-3 fatty acids may effectively oppose the toxic effects of environmental methylmercury.

This analysis of the data provided by the two studies cited by Martek [Doc references 41 and 42] is in concordance with that of the AHA [Doc reference 3] and leads to the conclusion that statements such as "data also indicate that mercury may affect the cardio-protective effects of ω-3 fatty acids," [Doc p. 3] "This study demonstrated that high mercury content can offset the cardio-protective effects of the DHA (and/or EPA) derived from fish consumption," [Doc p. 28] "The presence of mercury may offset the cardio-protective effects of ω-3 fatty acids," [Doc p. 30] "greater intake of mercury may also offset the cardio-protective effect of ω-3 fatty acids such as DHA, as shown by Guallar (41)," [Doc p. 31] "and may diminish the protective effects of omega-3 fatty acids on heart health," [Doc p. 31] "the potential for mercury to offset the cardio-protective benefits of DHA" [Doc p. 32] and "and that may diminish the cardiovascular benefits of ω-3 fatty acids" [Doc p. 33] are redundant misrepresentations of the findings and statements of the investigators whose work is being cited, are inherently misleading and are scientifically unfounded.

The AHA has concluded that "intakes of EPA+ DHA ranging from 0.5 to 1.8 grams per day (either as fatty fish or supplements) significantly reduce the number of deaths from heart disease and all causes." [Doc reference 3] (It should be noted that the lowest of these recommendations is about 500%, and the highest of these recommendations is about 1800%, of the highest median intake of EPA + DHA reported in the US.) [Doc reference 1, Appendix Tables E-12 and E-14] In addition, the AHA has concluded that "In randomized clinical trials (RCTs) that enrolled patients with coronary heart disease, omega-3 fatty acid supplements significantly reduced CV [cardiovascular] events (death, nonfatal heart attacks, nonfatal strokes). Omega-3 supplements can also slow the progression of atherosclerosis in these patients." [Doc reference 3] The suggestion that the methylmercury content of omega-3 fatty acid supplements may have interfered with the beneficial effects of these supplements contradicts these conclusions and is scientifically incredible.

The Institute of Medicine has concluded that "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 [coronary heart disease]," [Doc reference 1, pp. 11-1 and 11-2] that "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" [Doc reference 1, p. 11-40] and that "*n*-3 Polyunsaturated fatty acids have also been reported to reduce blood pressure in hypertensives." [Doc reference 1, p. 11-40] Because the clinical trial evidence upon which these conclusions are based was produced almost exclusively with the use of dietary supplements containing omega-3 fatty acids, [Doc reference 1, p. 11-41-43] it is unlikely that the beneficial effects associated with the consumption of dietary supplements containing omega-3 fatty acids were opposed or prevented by the consumption of dietary supplements containing omega-3 fatty acids.

In 2001, the US Environmental Protection Agency (EPA) anticipated the Institute of Medicine, the FDA and the federal Office of Management and Budget and stated that "Fish is an excellent source of nutrition and most people have no reason to limit their fish consumption." [Doc reference 39] In the summer of 2003, Dr. Mark McClellan, Commissioner, FDA, stated that "significant studies indicate a heart benefit from consuming a diet high in omega-3 fatty acids." [Doc reference 47] Dr. John D. Graham, Administrator, Executive Office of the President, Office of Management and Budget, also declared that "epidemiological and clinical studies find that an increase in consumption of omega-3 fatty acids results in reduced deaths due to CHD (coronary heart disease)." [Doc reference 49] Because the primary dietary sources of the omega-3 fatty acids have been the salt-water fishes, [Doc p. 4 at paragraphs A, C, C.1.; Doc reference 2; this document, reference 1] the obvious and oft-touted "heart health benefits" of the consumption of the usual dietary sources of the so-clearly beneficial nutrients cannot be effectively opposed or prevented by the consumption of the usual dietary sources of those nutrients.

In conclusion, the scientific evidence supports the following:

For foods and fortified foods containing 1 ppm total mercury or less:

> The omega-3 fatty acids DHA and EPA (fish oils) reduce the risk of coronary heart disease. [Name of seafood], like all seafood, may contain trace amounts of mercury, an environmental contaminant that may cause harm to developing fetuses and young children. FDA recommends that pregnant women, women who may become pregnant, nursing mothers and young children eat no more than 12 ounces of a variety of fish weekly.

For dietary supplements containing 1 ppm total mercury or less:

> The omega-3 fatty acids (DHA and EPA) reduce the risk of coronary heart disease. Limited preliminary evidence suggests that total daily consumption of the omega-3 fatty acids from dietary supplements should not exceed 3000 mg.
>
> The omega-3 fatty acid, DHA, reduces the risk of coronary heart disease. Limited preliminary evidence suggests that total daily consumption of the omega-3 fatty acids from dietary supplements should not exceed 3000 mg.
>
> The omega-3 fatty acid, EPA, reduces the risk of coronary heart disease. Limited preliminary evidence suggests that total daily consumption of the omega-3 fatty acids from dietary supplements should not exceed 3000 mg.

It appears reasonable to prohibit shark, king mackerel, swordfish and tilefish from carrying any health claim regarding the omega-3 fatty acids. It is reasonable to limit the health claims appropriate for dietary supplements to dietary supplements containing no more than 1 ppm total mercury.

[signature on file]
Michael J. Glade, Ph.D., F.A.C.N., C.N.S.

[date]

[1] U.S. Department of Agriculture, Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 16, 2003. File 15: Finfish and Shellfish Products. Nutrient Data Laboratory Home Page, http://www.nal.usda.gov/fnic/foodcomp, accessed January 22, 2004.