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NOTIFICATION FOR A NUTRIENT CONTENT CLAIM BASED ON AN AUTHORITATIVE STATEMENT

Submitted by: Martek Biosciences Corporation
Columbia, MD

Subject: Nutrient Content Claims for DHA and ALA
(Omega-3 Fatty Acids)

Office of Nutritional Products, Labeling and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

To Whom It May Concern:

This notification is submitted by Hogan & Hartson L.L.P. on behalf of Martek Biosciences Corporation to the Food and Drug Administration (FDA), pursuant to section 403(r)(2)(G) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 343(r)(2)(G)), as amended by the Food and Drug Administration Modernization Act of 1997 (FDAMA), to propose nutrient content claims for foods and dietary supplements containing docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA). The nutrient content claims covered by this notification are based on authoritative statements made by the Institute of Medicine (IOM), a division of the National Academy of Sciences (NAS), in its 2002 report, *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids* (IOM Report) (prepublication). This notification contains all required elements as specified in FDA's *Guidance for Industry: Notification of a*

Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body (June 11, 1998)(FDA's Industry Guidance). 1/

Martek is limiting this notification to nutrient content claims for DHA and ALA and is not including nutrient content claims for eicosapentaenoic acid (EPA). DHA and EPA serve very different functions in the body and, therefore, Martek believes that it is important to establish separate daily values for these substances. DHA is an integral component of membrane structural lipids contained in nervous tissue, the retina, and the brain.

The nutrient content claims in this notification are based on a 1.6 g daily value for ALA and a calculated daily value of 160 mg for DHA. As will be discussed in more detail below, extensive review of DHA synthesis and turnover in the body demonstrate the importance of consuming DHA at this level. The data also support establishment of 1.6 g as the daily value for ALA.

I. INTRODUCTION

FDA did not object to, and allowed to go into effect by operation of law, a FDAMA notification filed on behalf of three seafood producers by Olsson, Frank and Weeda, P.C. (OF&W Notification) proposing nutrient content claims for foods and dietary supplements containing DHA, EPA, and ALA. 2/ Because the OF&W Notification was allowed to become effective even though it contains inconsistencies with FDA regulations and policies, confusion has resulted within the food industry which needs to be addressed. With this notification, Martek is taking the

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1/ *Guidance for Industry, Notification of a Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body*, FDA, Center for Food Safety and Applied Nutrition, Office of Food Labeling (June 11, 1998) accessed at www.cfsan.fda.gov/~dms/hclmguid.html on Jan. 10, 2005.

2/ The FDAMA Notification filed on behalf of Alaska General Seafoods, Ocean Beauty Seafoods, Inc., and Trans-Ocean Products, Inc. (Jan. 16, 2004) received no objection or response from FDA and became effective under operation of law on May 15, 2004.

opportunity to address the confusion by submitting a FDAMA notification that is consistent with the well-established FDA positions for nutrient content claims.

Confusion abounds as a result of the OF&W Notification for a number of reasons. First, a population-adjusted AI was used to set the Daily Value (DV) of the nutrients, instead of choosing the historically-used AI for the population group with the highest need level. The OF&W Notification used a population-weighted formula to suggest that the Adequate Intake (AI) should be 1.3 g/day for ALA and 130 mg/day for DHA. 3/ Second, the OF&W Notification deviated significantly from the FDA established definition for "excellent source" claims by only allowing those claims for DHA and EPA where a product contains 100% of the calculated daily value per reference amount customarily consumed (RACC) of those nutrients, instead of the long-established 20% threshold. 4/ In contrast, the OF&W Notification allows "excellent source" claims for ALA where products contain 20% or more of ALA per RACC, reflecting the current FDA definition. Finally, FDA has acknowledged that it disagrees with the OF&W Notification, but the Agency failed to provide clarification on the issues in question. 5/

3/ The IOM Report set the AI of ALA for adult males at 1.6 g. As explained in the OF&W Notification, OF&W used the population-weighted formula consistent with the recommendations issued by IOM in a another report that provided guidance on setting daily values. (*Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification* (Dec. 11, 2003) (prepublication).)

4/ "Excellent source" or "high" claims may be used on the label of foods provided that the food contains 20 percent or more of the RDI or the DRV per RACC. 21 C.F.R. § 101.54.

5/ Letter to Nancy Chapman, President, Advocates for Better Children's Diets, from Shellee Anderson, ONPLDS/CFSAN (June 25, 2004); letter to Barbara J. Moore, President and CEO, Shape Up America!, from Shellee Anderson, ONPLDS/CFSAN (June 25, 2004); letter to Jeffrey R. Prince, Vice President, American Institute for Cancer Research, from Shellee Anderson, ONPLDS/CFSAN (June 25, 2004). The three FDA letters noted that, because the 120-day period passed on May 15, 2004, manufacturers may lawfully label qualifying foods with the nutrient content claims detailed in the OF&W Notification. However, FDA

Martek is submitting this FDAMA notification in an effort to address the confusion surrounding these issues and resolve outstanding questions in an appropriate manner consistent with FDA regulations. This FDAMA notification covers nutrient content claims for ALA and DHA consistent with the statements made in the IOM Report and consistent with long-standing FDA regulatory definitions of specific claims. This notification bases the DV for ALA on the AI of 1.6 g established for adult males in the IOM Report, making no adjustments for intakes based on population-weighted averages. The DV for DHA can be calculated because the IOM Report specifically recognized that DHA can contribute up to 10% of the AI for ALA. 6/ The DV for DHA, therefore, can be calculated as 160 mg/day.

This notification also seeks to clarify that "excellent source" claims for DHA and ALA may be made on products containing 20% or more of the daily value of those nutrients. The OF&W Notification employed unprecedented reasoning when it claimed that excellent source claims should be limited to only those products that contained 100% of OF&W's calculated daily value for DHA. As discussed in more detail below, any source of these beneficial nutrients is an important and useful alternative for consumers that should be recognized, and all sources that contain 20% or more of the calculated daily value for DHA, the long-established qualifying level for this claim under 21 C.F.R. § 101.54(b), should be afforded the use of an "excellent source" claim.

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emphasized that "because the agency disagrees with [sic] basis for the notified nutrient content claims for EPA and DHA, FDA intends to initiate rulemaking" to define those claims. In a more recently issued letter, FDA merely states "[w]e are considering what to do in response to the notification." (Letter to Carol Tucker Foreman, Consumer Federation of America, from Lester M. Crawford, Acting Commissioner, FDA (Nov. 23, 2004).)

6/ We recognize that the IOM Report did not establish a separate AI for DHA. The IOM Report did, however, expressly determine that up to 10% of the total n-3 fatty acids can be contributed by DHA and EPA. Therefore, although the IOM Report does not contain a specific recommendation of a dietary reference intake for DHA or refer to a specific milligram level for DHA, the reference to a permissive level of 10% of total n-3 fatty acids allows calculation of a daily value for DHA.

The scientific studies reviewed in this notification support 1.6 g and 160 mg for ALA and DHA, respectively, as the values that should be used for calculating nutrient content claims. The 2005 Dietary Guidelines Report also recognized the importance of DHA when it recommended consumption of two servings of fish per week, "particularly fish rich in EPA and DHA," for the cardioprotective effects of EPA and DHA. 7/ Although the Advisory Committee did not establish a dietary intake level for DHA and EPA, the Report stated that 8 ounces of fish high in omega-3 fatty acids would provide an average of nearly 500 mg per day. 8/ While the Advisory Committee's recommendations focused on CHD risk reduction levels, the IOM focused on the maintenance levels required by the body at which a deficiency is not existent. Regardless of the different approaches, both of these reports demonstrate the importance of maintaining a daily intake of DHA at higher levels than currently consumed by the average American.

II. REQUIRED ELEMENTS OF FDAMA NOTIFICATION

FDAMA (Section 403(r)(2)(G),(H) of the Food, Drug, and Cosmetic Act ("the Act") (21 U.S.C. § 343(r)(2)(G),(H)) permits manufacturers to use nutrient content claims if those claims are based on current, published, authoritative statements from certain federal scientific bodies, as well as from the National Academy of Sciences. FDA's Industry Guidance on FDAMA notifications provides the required contents of notifications:

> [A]s indicated by FDAMA, the notification is to include: (1) "the exact words used in the claim," (2) "a concise description of the basis upon which such person relied for determining that the requirements" for an authoritative statement "have been satisfied," (3) "a copy of the statement referred to...upon which such person relied in making the claim," and (4) for a nutrient content claim, "a balanced representation of the scientific literature relating to the nutrient level to which the claim refers."

7/ HHS and USDA, 2005 Dietary Guidelines Advisory Committee Report, Executive Summary at 5 and Section 4: Fats.

8/ *Id.* at Section 4: Fats, 27.

These required FDAMA notification elements are contained below.

A. Authoritative statement(s) relied upon

Under FDAMA, nutrient content claims may be based upon a published, authoritative statement by the National Academy of Sciences (NAS) or any of its subdivisions, which is currently in effect, and which identifies the nutrient level to which the claim refers. (21 U.S.C. § 343(r)(2)(G).) FDA's Industry Guidance sets forth the factors for what constitutes an authoritative statement as:

> FDAMA requires that the statement (1) identifies "the nutrient level to which the claim refers" for a nutrient content claim; (2) is "published by the scientific body," (3) is "currently in effect," and (4) shall not include a statement of an employee of the scientific body made in the individual capacity of the employee;" and additionally, FDA requires that the statement (5) should reflect a consensus within the identified scientific body if published by a subdivision of one of the Federal scientific bodies, and (6) should be based on a deliberative review by the scientific body of the scientific evidence.

In this case, the IOM Report contains findings, conclusions, and recommendations that constitute authoritative statements identifying nutrient levels for the adequate intake of ALA and recognizing the level that can be calculated for DHA. Attachment 1 contains the relevant chapters from the IOM Report that serve as the basis for this FDAMA Notification. Specifically, the IOM Report sets an AI for ALA of 1.6 g per day for adult men and 1.1 g per day for adult women. 9/ The IOM Report states that, "While intake levels much lower than the AI 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." 10/ These statements are found in the Summary Chapter of the IOM Report

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9/ IOM Report at S-4, Summary of the IOM Report; 8-2, Summary of Chap. 8, Dietary Fats: Total Fat and Fatty Acids; and 8-38.

10/ *Id.* at 8-2, Summary of Chap. 8, Dietary Fats: Total Fat and Fatty Acids.

and in the summary section of the Chapter on "Dietary Fats," sections of the Report that have been identified by IOM as sources of authoritative statements. 11/

The IOM Report, in the chapter on dietary fats, further elaborates on the AI for ALA and concludes that, "EPA and DHA can contribute up to 10 percent of the total n-3 fatty acid intake and therefore up to this percent can contribute towards the AI for alpha-linolenic acid." 12/ In further recognition of the importance of DHA, the IOM Report concludes that the acceptable macronutrient distribution range (AMDR) for ALA "is set at 0.6 to 1.2 percent of energy" and "up to 10 percent of this range can be consumed as eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA)." 13/ In addition, the IOM panel found that:

> "A growing body of literature suggests that higher intakes of alpha-linolenic, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may afford some degree of protection against CHD. Because the physiological potency of EPA and DHA is much greater than that for alpha-linolenic acid, it is not possible to estimate one AMDR for all n-3 fatty acids. Up to 10 percent of the AMDR can be consumed as EPA and/or DHA." 14/

The statements regarding the DHA and EPA contribution toward the AMDR for ALA are found in the "Summary" Chapter and in the summary section to the Chapter, "Macronutrients and Healthful Diets," sections of the IOM Report that are sources for authoritative statements.

11/ Letter to Laura Tarantino, Acting Director, ONPLDS/CFSAN, FDA, from Susanne A. Stoiber, Executive Director, IOM (May 5, 2004).

12/ IOM Report at 8-38.

13/ *Id.* at S-6, Summary of IOM Report.

14/ *Id.* at 11-2, Summary of Chap. 11, Macronutrients and Healthful Diets.

B. Description of the basis upon which a determination was made that the requirements for an authoritative statement have been satisfied

The Institute of Medicine, a subdivision of NAS, made authoritative statements in the IOM Report, which fulfill the preceding six requirements. Specifically:

1. The authoritative statements identify "the nutrient level to which the claim refers" as 1.6 g per day as the Adequate Intake for ALA and state that up to 10% (or 160 mg per day) of that can come from DHA and EPA.

2. The authoritative statements are published in the 2002 IOM Report and appear exclusively as findings, conclusions, or recommendations.

3. The authoritative statements continue to be in effect because the 2002 IOM Report is the latest version of that publication.

4. The authoritative statements are not those of an employee made in his/her individual capacity because they are contained in the published IOM Report developed by a panel of 21 experts in the field.

5. The authoritative statements reflect a consensus of a duly-appointed Panel chosen for their "special competences and with regard for appropriate balance." 15/

6. The authoritative statements are based upon a deliberative review of the relevant scientific evidence on DHA and ALA by the IOM's Panel on Dietary Reference Intakes for Macronutrients and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. In addition, the IOM Report completed the institutional review process.

15/ IOM Report at inside cover page.

Prior to the OF&W Notification, the only nutrient content claims established to date under FDAMA were based on authoritative statements, published in a 1998 IOM Micronutrients Report, identifying a level for choline. 16/ Similar in form to the IOM Report, that report recommended Daily Reference Intakes for certain micronutrients and an AI for choline, setting a precedent for using the IOM Report as the source of authoritative statements for a notification about nutrient content claims for ALA and DHA.

FDAMA states that "authoritative statements" from the National Academy of Sciences or its subdivisions are "limited to those that represent the consensus of a duly-appointed committee" and appear "explicitly as findings, conclusions or recommendations in a report that has completed the institutional report review process." Martek acknowledges that the Institute of Medicine has also offered its interpretation of the FDAMA authoritative statement requirements. The IOM has said that for FDAMA claims to be based on IOM reports, authoritative statements upon which those claims are based must be found in the Executive Summary of the reports or in "boxed" pages at the beginning of individual chapters. 17/

Based on the IOM's interpretation, the established AI for ALA is found in authoritative statements located in the Summary of the IOM Report and in the Summary section to Chapter 8. While Martek recognizes that a calculated AI for EPA and DHA is not referenced in a summary section, the IOM Report makes it clear, and repeats the recommendation, that EPA and DHA can contribute up to 10 percent of the AI for ALA. In addition, the IOM Report Summary and the Chapter 11 summary both identify an AMDR for ALA and expressly state that up to 10 percent of the AMDR can be consumed as EPA and/or DHA.

16/ *See* Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Nutrition, FDA, *Nutrient Content Claims Notification for Choline Containing Foods* (Aug. 30, 2001) (FDA Choline Document); Institute of Medicine, *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*, 1998) (IOM Micronutrients Report).

17/ Letter to Laura Tarantino, *supra* fn.11.

While Martek acknowledges that the FDA has not reached a decision on whether it is appropriate to base daily values on AMDRs, the IOM has recognized using AMDRs to set DVs in limited instances. Even though the status of AMDRs is under consideration, the IOM Report defines an AMDR as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients." 18/ The AMDR for ALA, and that 10 percent of the AMDR for ALA can be contributed by EPA and/or DHA, has been placed in summaries in the IOM Report, sections recognized by IOM as sources for authoritative statements.

The numerous recommendations, findings and conclusions found throughout the IOM Report, both in summary sections and in the report's body, in total, support the establishment of a calculated DV for DHA.

C. Exact words used in the claim

"Good source of ALA." ("Contains ALA," "Provides ALA") Contains __ mg of ALA per serving, which is ___% of the 1.6 g Daily Value for ALA. [Products would need to contain at least 160 mg of ALA per RACC to qualify for the claim.]

"Excellent source of ALA." ("High in ALA," "Rich in ALA") Contains __ mg of ALA per serving, which is __ % of the 1.6 g Daily Value for ALA. [Products would need to contain at least 320 mg of ALA per RACC to qualify for the claim.]

"More ALA." ("Fortified with ALA," "Enriched with ALA," "Added ALA," "Extra ALA," "Plus ALA") Contains __ % more of the Daily Value for ALA per serving than [reference food]. This product contains ___ mg of ALA which is ___% of the Daily Value for ALA (1.6 g). [Products would need to contain at least 160 mg or more ALA per RACC than an appropriate

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18/ IOM Report at S-5.

reference food and would comply with the requirements for relative claims found at 21 C.F.R. 101.13(j)).] 19/

"Excellent source of DHA." ("High in DHA," "Rich in DHA") Contains __ mg of DHA per serving, which is __ % of the 160 mg Daily Value for DHA. [Products would need to contain at least 32 mg of DHA per RACC to qualify for the claim.] 20/

The establishment of an AI for ALA and the allowance of 10% of total omega-3 fatty acid intake to be DHA provides a standard upon which nutrient content claims can be defined. In addition, FDA regulations already define "excellent" source claims, which should not be redefined as suggested by the OF&W Notification, but rather should remain consistent. Significantly, the only other nutrient content claims established under FDAMA, for choline containing foods, use existing, authorized definitions for all claims, including "excellent source" claims. Departure from this long-established, consistent approach to claim definitions has already caused, and would increasingly cause, much confusion in the marketplace and to consumers.

The OF&W Notification argues that while an "excellent source" claim for ALA can be made for foods that contain 20% of their proposed AI per RACC of 1.3 g, the same claim should only be made for DHA and EPA if the product contains 100% of their proposed AI per RACC of 130 mg. The precarious justification for this is based on the argument that DHA and EPA are "distributed narrowly in the food supply" and, thus, "must come from a small number of 'high' sources of these nutrients (*e.g.* fish), rather than a wide variety of less concentrated sources." OF&W claims that "only products that make a substantial contribution" (100% of their proposed DV) to recommended intake levels for cardioprotective effects should be allowed to make an "excellent source" claim.

19/ We are not proposing the use of either "more" or "good source" claims for DHA because the OF&W Notification did not propose the use of such claims.

20/ As previously discussed, we are not submitting a model claim for "excellent source of EPA" claims.

The OF&W Notification seems to make this argument for reasons that would disproportionately benefit certain seafood companies, to the detriment of consumers searching for a variety of DHA sources and to the exclusion of the rest of the food industry. Nevertheless, oils that are sources of DHA have been authorized for use in a wide variety of foods and fortification of those foods can be carried out successfully and appropriately. 21/ We do agree with OF&W's statement that permitting an "excellent source" claim for DHA only on those foods with 100% of the calculated DV per RACC would severely limit the foods (*e.g.*, to "fatty" fish) that could make an excellent source claim. Allowing such a claim that would have this result, however, would be contrary to the guiding principles used by FDA in the development of nutrient content claims.

Over the past 14 years as labeling and nutrient content claim regulations have developed, the agency has stressed the importance of encouraging the consumption of a wide variety of foods. In the Nutritional Labeling Education Act (NLEA) rulemakings, the agency expressly emphasized as a matter of policy the need for nutrient content claims to promote a diet containing a wide variety of foods. In defining "excellent source" and "good source" nutrient content claims, the agency emphasized that "the criteria for descriptive terms should be consistent with the levels of nutrients occurring naturally in foods, and that definitions for terms should allow for a reasonable number of foods to make the claim." 22/ For those reasons, FDA said that descriptive terms cannot be "considered useful to consumers if they can identify only very few foods or only specially formulated foods" and that "such criteria could discourage the consumption of a wide variety of foods." 23/ Through the rulemaking, FDA pointed to the IOM Committee report on

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21/ For example, menhaden oil and other sources of DHA and EPA are authorized for use in a wide variety of foods such as breads, cereals, yogurt, cheese, soup mixes, snack foods and others. *See* 21 C.F.R. § 184.1472.

22/ 56 Fed. Reg. 60421, 60443 (Nov. 21, 1991).

23/ *Id.* FDA pointed to the Institute of Medicine Committee report on nutrition labeling.

nutrition labeling as the source of information and recommendations the agency relied upon. 24/

For these reasons, FDA decided to half the required nutrient level in its proposed definition of "high," "excellent source," and "very good source," from 40 percent to 20 percent of U.S. RDA. 25/ The agency determined that this criterion would permit a "sufficient number of food items to allow consumers to use the claim in selecting a varied diet." 26/

Although DHA is found naturally in a wide variety of foods, it is found in very high levels in only a few. 27/ However, because DHA has also been

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24/ "The agency believes that there is merit in the IOM Committee's recommendations concerning the use of certain descriptive terms, especially when used for nutrient content claims intended to emphasize the presence of a nutrient." 56 Fed. Reg. at 60442.

25/ "The IOM Committee's review of the vitamin and mineral content of a variety of foods indicated that very few foods would be eligible to use the term "excellent source" as currently defined by FDA, even though many of the foods are recognized as important sources of specific nutrients. The IOM Committee further pointed out that most vitamins and minerals do not occur naturally at high levels in any one food. The IOM Committee's report stated that an adequate diet must be assembled from a variety of different foods, and it emphasized that such a varied diet was the type of dietary pattern that food labeling should encourage." 56 Fed. Reg. at 60442.

26/ 56 Fed. Reg. at 60442. In the 1993 nutrient content claim rulemakings, FDA retained its definition for "high" with the 20 percent eligibility level concluding "that the 20 percent eligibility level will permit *a sufficient number of food items* to bear a high claim *to allow consumers to use the claim in selecting a varied diet*, and that this level provides an appropriate basis for upper-level nutrient content claims and can readily be used by consumers to implement current dietary guidelines." 58 Fed. Reg. 2302, 2344 (Jan. 6, 1993) (*emphasis added*).

27/ Under the OF&W Notification, few, if any, foods other than seafood would qualify for an "excellent source" of DHA claim.

authorized for use in numerous foods by fortification, FDA's policy can best be reflected by consistently allowing "excellent source" claims for DHA in products with 20% of the calculated DV per RACC, which would, in turn, encourage increased consumption of beneficial DHA. In this case, DHA would be treated no differently than other nutrients that are found in a wide variety of foods at varying levels and also used to fortify numerous food products.

FDA reviewed favorably a generally recognized as safe (GRAS) notification for Martek's algal oil for use in the fortification of numerous foods. 28/ Attachment 2 contains a table that identifies the maximum use level of Martek's algal oil in the various food categories covered by the GRAS notification and the maximum quantity of DHA that could be found in each RACC consistent with these use levels. A review of this table reveals that many products would qualify for the excellent source of DHA claim that is the subject of this FDAMA Notification. Attachment 3 is adapted from the table submitted in the OF&W Notification and identifies the levels of DHA and ALA that are found in each RACC of various types of seafood, oils and other foods. The information in Attachment 3 also establishes that there are many foods that would qualify for the DHA and ALA nutrient content claims that are the subject of this FDAMA Notification.

D. Balanced representation of the scientific literature relating to the nutrient level to which the claim refers

1. Nutrients at Issue: DHA and ALA

Omega-3 polyunsaturated fatty acids, particularly DHA, play an important role as structural membrane lipids, particularly in nerve tissue and the retina. DHA is a structural component of many body tissues, including the brain, eye, and heart. It is also believed to be important for the maintenance of cognitive activity during aging and normal mental function. ALA is the precursor for synthesis of DHA and EPA, which are formed in varying amounts in animal tissues,

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28/ Letter from George H. Pauli, Ph.D., Acting Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition to Samuel Zeller Ph.D. (Feb. 12, 2004) (accessed on Jan. 11, 2004 at http://www.cfsan.fda.gov/~rdb/opa-g137.html).

particularly fatty fish, but not in plant cells. While the body can synthesize DHA from ALA, the synthesis is slow and inefficient and the conversion is determined by several factors, including the background diet, age, gender, and the ratio between ALA and omega-6 fatty acids. In addition, as recognized by the IOM, ALA is not known to have any specific dietary functions other than to serve as a precursor for synthesis of DHA and EPA in the body. 29/

Studies now suggest that ALA synthesis alone does not produce the necessary DHA levels required by the human body. Therefore, it is important to get preformed DHA from the diet.

2. Overview of the Scientific Literature

FDA's Industry Guidance states that for FDAMA nutrient content claims the agency expects the submittal of a "balanced representation of the scientific literature" to include an account of how the literature either supports or fails to support the authoritative statement and a bibliography of scientific literature on the topic of the claim. A summary of the scientific literature is provided below and a bibliography can be found at Attachment 4.

i. Scientific reviews support establishment of 1.6 g as the DV for ALA.

The IOM Report contains the most up-to-date scientific support for the establishment of 1.6 g as the DV for ALA. We are attaching a copy of the relevant chapters from the Report to this notification instead of repeating the voluminous supporting material contained within the publication. Given the importance of the LA to ALA ratio, discussed in more detail below, increasing ALA consumption will result in more favorable LA to ALA ratios. Currently, the typical American diet has higher ratios than are suggested by scientific studies to be healthful. Increasing recommendations for daily ALA consumption will further encourage more Americans to adopt consumption of foods that will move them toward a more favorable LA to ALA ratio.

29/ IOM Report at 8-11.

ii. DHA is an essential structural component of the body. ALA only partially supplies the DHA necessary for healthy body tissues and function.

DHA is an integral component of all membranes in the body. Compared to other omega-3 fatty acids, DHA is significantly enriched in tissues such as the brain and retina where certain levels have been scientifically proven to be essential for optimal function of those tissues. DHA represents up to 20% of total fatty acids or approximately 1% of the total dry weight of the brain and up to 50% of the fatty acids in the retina (Uauy, Hoffman et al., 2001). The total DHA content within tissues is likely greater than that reported in most studies because conventional gas and thin-layer chromatography methods cannot detect DHA conversion products such as resolvins, plasmologens, and docosatriene products (Beaumelle, Vial, 1986; Gronert et al., 1999; Hong et al., 2003).

In contrast, concentrations of ALA and EPA in the brain and retina are minimal (Lauritzen et al., 2001). In fact, ALA typically represents less than 0.5% of the total fatty acids in cell membranes of any tissue in healthy human adults (Lauritzen et al., 2001). While ALA has also been called an "essential" fatty acid, its only known biological role in the body is to supply energy to the body and to serve as a substrate for formation of long-chain n-3 fatty acids. As explained in detail below, conversion of ALA to DHA is not only highly variable amongst individuals, it is clear that conversion of ALA to DHA is particularly inefficient in the U.S. population that consumes high levels of n-6 fatty acid, predominantly LA. More significantly, at any conversion rate, it is difficult for the body to meets its DHA requirements merely from ALA synthesis.

iii. Preformed DHA must be obtained from the diet to meet the body's basic needs. Significant losses of DHA from tissues occur over time if ALA alone, and no DHA, is provided.

Numerous clinical studies indicate that the human body cannot keep up with daily losses of DHA merely through the synthesis of DHA from ALA. DHA must be obtained from the diet to meet the basic needs of a healthy body. Although the IOM Report sets an AI for ALA at 1.1 –1.6 g per day depending on the lifestage/gender group, a more recent comprehensive review of the literature concerning the metabolism of ALA in men and women concluded that consumption

of 1-1.5 g of ALA per day is likely not sufficient to meet even modest demands for DHA to support membrane synthesis and turnover (Burdge 2004). While the IOM recommendation was based upon the premise that the primary biological role of ALA is to serve as a precursor of the longer-chain fatty acids, DHA and EPA, the IOM recognized that n-6 to n-3 ratios greater than 10:1 could significantly reduce the conversion of ALA to EPA and DHA. The production of DHA and EPA *in vivo* depends on the further metabolism of ALA via elongation of the carbon chain and desaturation to produce additional double bonds within the molecule. These metabolic conversions differ widely among subpopulations and are easily perturbed by other dietary factors such as n-6 fatty acids, trans fatty acids (Koletzko, 1992; Decsi et al., 2001), and chronic nutrient insufficiencies (SACN 2004). The use of population-weighted averages to further reduce the IOM established ALA adequate intake from 1.6 g to 1.3 g would compromise the body's supply of DHA and EPA.

Studies in humans have shown that conversion of ALA labeled with stable isotopes in human subjects typically favors production of the shorter-chain LCPUFA, EPA, and the metabolic complexity of *in vivo* synthesis of DHA appears to significantly limit the continued processing of ALA to DHA. For example, estimates of the extent of conversion of ALA to EPA in men are about 8% (Burdge et al., 2002; Emken et al., 1994), while the conversion efficiency based on kinetic measurements is about 0.2% (Pawlosky et al., 2001). The extent of conversion of ALA to DHA is less clear. The highest estimated fractional conversion is 4% (Emken et al., 1994), while others have either failed to detect significant DHA synthesis (Burdge et al., 2002) or estimated that less than 0.05% of ALA was converted to DHA (Burdge et al., 2003). The estimated conversion of labeled ALA in women of reproductive age was EPA 21% and DHA 9% (Burdge and Wootton, 2002), which suggests greater EPA and DHA synthesis compared with men using the same study design (Burdge et al., 2002). When the diet is rich in n-6 PUFA, conversion of ALA to DHA, but not necessarily EPA, is reduced by 40 to 50% (Gerster 1998; Burdge, Finnegan et al., 2003). Preformed DHA is, therefore, the best mechanism to provide adequate DHA to support growth and maintenance of DHA content in tissues.

In the majority of studies examining the effects of feeding a high ALA diet, plasma levels of EPA and docosapentaenoic acid (DPA) increased, but levels of DHA remained stable or slightly decreased, further demonstrating that ALA is not the most efficient way to supply DHA to tissues. Recently, Pawlosky et al. (2003) examined the impact of a high saturated fat diet vs a high polyunsaturated fat diet on the utilization of ALA for LCPUFA synthesis. Regardless of background diet, a

bolus 1 g dose of ALA ethyl ester resulted in less than 1% of plasma ALA utilized for LCPUFA synthesis. Even in studies where extremely high levels of ALA were used (4.5 to 9.5 g per day), EPA concentration in peripheral blood mononuclear cells increased, and DHA levels in the same cells decreased. Burge attributes the decrease in DHA as an indicator of DHA insufficiency and suggests that the level of ALA is not sufficient to supply adequate amounts of DHA to meet tissue demands (Dyerburg 1980; Sanders TA 1983; Singer 1986; Kestin, Clifton et al., 1990; Chan, McDonald et al., 1993; Kelly DS 1993; Freese R 1994; Allman, Pena et al., 1995).

In human adults, Pawlosky et al. (Pawlosky, Hibbeln et al., 2003) calculated the half-life (18±8 hr) and the mean flow rate (7.2 mg/hr) for the removal of deuterated-DHA from plasma. In 24 hours, the mean flow rate parameter yielded a net loss of about 173 mg. This value represents the total DHA catabolized or taken up into other organ systems and provides an estimate of the amount required on a daily basis to maintain the plasma DHA concentration. However, the whole body requirement may be much higher. The most recent National Health and Nutrition Examination Survey (NHANES) effort over-sampled seniors in an effort to better understand the nutrient status of this population. DHA intake according to this survey averaged 65 mg/day among men and women 71+ years. If one assumes an optimized conversion of 117 mg of DHA daily from ALA in women (9% of 1.3 g ALA (based on CFSII reported mean intake for ages 70+) is converted into DHA), and that the average intake may be as low as 50 mg DHA for seniors, the net DHA status for older women may be about 167 mg. Current literature clearly supports the need for at least 173 mg/day to maintain tissue status. This would suggest a dietary deficit among this subpopulation with no margin of adequacy to ensure maintenance of tissue DHA levels. Clinical studies conducted on primates also demonstrate that if no source of DHA is provided, levels of DHA are not maintained in the brain. Pawlosky et al. (2001) studied how a diet containing linolenic acid (0.08% of energy) as the sole source of n-3 fatty acid affected the brain DHA content of rhesus monkeys over a period of five years. During that time, brain DHA levels decreased by 33%, or approximately a 6% loss per year.

It has also been demonstrated in recent studies that ALA alone is not sufficient to support maternal DHA levels during pregnancy and lactation and that increasing ALA intake does not translate into DHA production. De Groot et al. (2004) failed to find any effect of 2.8 g ALA supplemented daily during pregnancy on maternal or neonatal DHA status even when supplementation occurred against a background dietary ratio of 5:1 LA:ALA, thought to be optimal to support the

conversion of ALA to DHA (FAO/WHO). Interestingly, the level of supplementation used by De Groot et al. (2004) is more than double that currently recommended by the IOM and the LA:ALA in the study population is roughly half that consumed by women in the U.S. (CSFII Tables, IOM Report). Importantly, Francois et al (2003) have reported that dietary ALA supplementation (10.7 g/day) of women living in North America has no effect on breast milk or maternal plasma phospholipid DHA indicating that support of maternal DHA status post-partum relies directly on DHA from the diet. In contrast, several studies have found that increasing the level of DHA in the diet of lactating women an additional 200 mg (total intake about 300 mg/day) maintains higher breast milk DHA levels (Jensen et al, 2000; Fidler et al., 2001).

An ALA AI higher than the OF&W Notification should be established because dietary factors, in addition to ALA intake and ratios to LA, can limit LCPUFA synthesis especially in vulnerable subpopulations. Recent studies have also identified other factors that may interfere with DHA production *in vivo* or increase DHA requirements to a level that could not be supplied exclusively from ALA conversion. For example, trans fatty acids in maternal plasma among North American women have been reported at levels sufficient to reduce the availability of DHA to the fetus (Elias and Innis, 2001; Decsi et al., 2001). Dietary insufficiencies of micronutrients that serve as co-factors in the further metabolism of ALA to DHA may also serve as limiting factors to adequate DHA status (SACN 2004). It has also been reported that diets low in protein (Joshi et al., 2003), high in sucrose (El Hafidi et al., 2001), or that include modest consumption of alcohol (Hirosue and Hosogai, 1993) also impair LCPUFA status.

iv. Current American diets are not providing adequate levels of DHA for maintenance, let alone enough DHA to support brain and tissue growth and cardioprotective effects.

Dietary research and scientific studies show that most Americans today are not getting enough DHA in their daily diets. This has not always been the case: traditional diets once included greater consumption of, among other things, organ meats, eggs, and fatty fish, all of which provide DHA. In fact, considering current consumption rates in the American diet, dietary intake of preformed DHA in many American children is likely not even supplying the brain with sufficient DHA to replace DHA losses due to turnover, let alone providing

sufficient DHA to support brain growth. Moreover, current food consumption patterns suggest that preformed DHA in the U.S. diet is progressively decreasing. High DHA sources, such as canned sardines, have decreased by half since 1970 (USDA 1999c) and while fish consumption has increased from 6.9 to 9.8 per capita from 1970, 48% of that increase is from fresh/frozen shellfish, a low fat/low DHA source (USDA 1999c).

Between birth and 5 years of age, the human brain increases approximately 3.5-fold in mass and DHA content increases from 1 g to approximately 4.5 g (calculated from Martinez, 1992). While the rate of DHA accretion slows after 3 years, significant accretion continues between 3 and 5 years of age (Martinez, 1992). Based on DHA accretion curves from autopsy brains and estimates of DHA uptake in primates, average daily dietary DHA intake required for the brain to accrete 3.5 g of DHA between birth and 5 years of age would be greater than 120 mg/ day (calculated from Martinez, 1992 and adjusted for DHA uptake as referenced in Su et al., 1999). In addition, some amount of DHA is lost from tissues daily and must be replaced to maintain optimal DHA tissue levels. Turnover can be estimated from isotopic studies that measure the amount of fatty acid extracted from plasma and retained by a tissue. Rates of DHA turnover in brain and other tissues of the body have not been studied in primates, but data from rodents suggests that between 2 and 8% of esterified DHA present in brain is replaced daily (Rapoport et al., 2001).

Although estimates of DHA turnover in the human brain have not been experimentally derived, turnover of arachidonic acid (ARA) in the human brain has been measured and is known to be approximately 10-fold lower than turnover of arachidonic acid in rodents. Therefore, a conservative estimate of DHA turnover in humans would likely mirror the relative magnitude that is observed for arachidonic acid turnover in humans. If it were assumed that the same 10-fold difference in amount of fatty acid turnover observed between human and rat brain ARA also applied to turnover of DHA, then 0.2-0.8% of brain DHA would be replaced daily in the human. Thus, the amount of DHA lost from the brain due to turnover on a daily basis would range between 10 and 50 mg per day. Given that average daily DHA intakes of American children range between 22 to 30 mg daily, current dietary intake of preformed DHA alone would likely not be able to provide sufficient DHA to support optimal brain growth, and more astonishingly, would not even be able to supply the brain with sufficient DHA to replace DHA losses due to turnover.

The current Continuing Survey of Food Intake by Individuals (CSFII) data indicate that the DHA intake in the U.S. averages about 57 mg for all individuals, about one-half to one-third of that suggested by the IOM, depending on population group. The data also indicate among subpopulations, where the scientific literature supports higher DHA consumption, the intake of preformed DHA is quite low. For example, pregnant and lactating women are reported to have the lowest DHA intake among women of childbearing age with a mean of 52 ± 12 mg/day versus 62-71 mg/day among women of child-bearing age (14-50 yrs). 30/ It is problematic that the CSFII data for pregnant and lactating women is self-acknowledged as poor due to a small sample size. The pregnant and lactating data may therefore be an over or underestimate. Considering the FDA advisory that pregnant and lactating women should limit intake of certain fish due to concerns with methylmercury, the number may in fact be an overestimate. 31/ Children ages 1-5 years also are reported to have low intakes of DHA ranging from 30-50 mg/day.

The recent NHANES specifically over-sampled children 5 years or younger to produce more precise nutrition information in this population group. NHANES data indicates that children in this age group consume only 20-30 mg/day of preformed DHA. The NHANES data also provide preformed DHA intakes not available from the current CSFII data. It appears that youth in America (< 18 years) may be at risk for compromised DHA status because the estimated intake of preformed DHA for this population group is 30 mg/day with a ratio of LA:ALA of 10.5:1.

30/ IOM Report at E-15.

31/ FDA 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 Jan. 10, 2005, at http://www.cfsan.fda.gov/~dms/admehg.html, superseded by What You Need to Know about Mercury in Fish and Shellfish: 2004 EPA and FDA Advice for Women Who Might Become Pregnant, Women Who Are Pregnant, Nursing Mothers, Young Children (March 19, 2004), accessed on Jan. 10, 2005, at http://www.cfsan.fda.gov/~dms/admehg3.html.

v. Current ratios of LA:ALA in the U.S. may compromise optimal conversion of ALA to DHA, particularly among vulnerable subpopulations with high DHA requirements. Consequently, even the IOM's current ALA AI may be insufficient to meet the DHA needs of these subpopulations.

The IOM Report recognized that the omega-6:omega-3 PUFA ratio, and more specifically the LA:ALA ratio, is an important factor affecting an individual's ability to meet omega-3 PUFA requirements. 32/ The IOM Report cites the FAO/WHO recommendation for LA to ALA intake in adults of 5:1-10:1 as reasonable. It also noted research in rats suggesting that a ratio of 8:1 maintains normal tissue fatty acid concentrations (Bourre et al., 1996). Moreover, the IOM recognized that increased LA:ALA ratios significantly reduce production of both LA and ALA metabolites (Emken 1994). Due to concern about certain subpopulations known to have higher requirements for DHA, such as pregnant and lactating women, the IOM stated that the LA to ALA ratio should be a special consideration (8-39) because a high ratio can inhibit conversion of ALA to DHA.

Current estimates from the CSFII 33/ indicate that the majority of the U.S. population is at or above the upper limit of the 10:1 LA:ALA ratio recommended by FAO/WHO and well above the IOM's suggested 5:1 ratio. 34/ U.S. ratio means based on CSFII data for the entire population range from 9.8:1-10.9:1. Among pregnant and lactating women, the range from the 50th percentile through the 99th is 9.8:1 to 9.2:1. In women of childbearing age (14-50 yrs), the range is 9.8:1-10.3:1. This problem is exacerbated among low income women (ratio=10.6:1, USDA 1999a) and, in particular, women of childbearing age participating in the U.S. Food Stamp Program (ratio=10.7:1, USDA 1999b). The LA:ALA ratio for children from 1-5 years of age ranges from 9.4-10.4:1. 35/ Interestingly, even

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32/ IOM Report at 8-25 and 26.

33/ *Id.* at E10 and E11.

34/ *Id.* at 8-40.

35/ IOM Report at E10 and E11.

children who consume diets within the FAO/WHO recommended LA to ALA ratio, and who consume 1.6 g of ALA, may receive enough DHA and n-3 LCPUFA precursors to support brain growth, but likely would not ingest sufficient n-3 fatty acids to support growth and turnover DHA requirements of the whole body.

While the CSFII data is often considered the "gold standard" for nutrition monitoring, unique and reliable data is also available from NHANES. Based upon the most recent NHANES data, minority populations may have even greater risk of inadequate DHA nutriture, given the much greater consumption of LA compared to ALA. The most recent NHANES data represent an over-sampling of Mexican Americans and non-Hispanic African Americans, children $\leq$ 5 years old, and adults $\geq$ 60 years old to produce more precise estimates for these population groups (Wang et al., 2004). These data indicate that Mexican Americans, particularly women, normally consume a diet that results in a 12.1:1 LA:ALA ratio and that the LA:ALA ratio of non-Hispanic Blacks is 11.2. The NHANES data also indicates that children 5 or younger have a typical LA:ALA ratio of 10:1. Importantly, all of these values are at the upper limit or in excess of the suggested 10:1 ratio of LA:ALA that would support optimal conversion of ALA to DHA *in vivo* (FAO/WHO). Therefore, these subpopulations may be at even greater risk for diseases associated with insufficiency of DHA.

Furthermore, current food consumption patterns suggest that LA:ALA ratios are progressively increasing over time. Fats and oils are defined as those used directly by consumers, like butter on bread, as well as that used in commercially prepared cookies, pastries, and fried foods. The 1999 survey reports that consumption of salad and cooking oils had doubled since 1970 (USDA 1999c). USDA 1989-91 data indicate that women from 19-50 years old ate more fat from salad dressing than any other food (USDA 1999c). Disappearance data indicates that in 1997, each American consumed 65 more pounds of grain products and 13 more pounds of fats and oils compared to 1970 (USDA 1999c), two food categories that contain LA and are consumed in sufficient quantities to significantly contribute to total dietary LA intake. Although disappearance data typically overestimates fat and oil consumption because only a portion of oil used in commercial deep-fat frying is directly consumed, exposure to LA-rich products has increased in proportion to the use of fat and oil directly. Data also indicate a shift away from animal fat toward vegetable fat. In 1970, fats and oils contributed 63% of PUFA to the food supply and meat, poultry, and fish contributed 20%. By 1994, the amount of PUFA

contributed by vegetable fats increased to 69% and that contributed by meat, poultry, and fish decreased to 15% (USDA 1999c).

In effect, current ratios of LA:ALA in the U.S. may compromise optimal conversion of ALA to DHA, particularly among vulnerable subpopulations with high DHA requirements. The current ALA AI established by the IOM may be insufficient to meet the DHA needs of these subpopulations. Therefore, it should not be lowered further to a population-weighted average as notified by the OF&W Notification. As the IOM has indicated, the current intakes of preformed DHA are quite low in populations that require higher levels of this nutrient. Use of the higher rather than the lower ALA AI to support total DHA status is indicated.

Given that the maximum conversion of ALA to DHA may be about 9% in women (Brudge and Wootton, 2002) and 4% in men (Emken et al., 1994), a maximum of 99 mg of DHA in women (1.1 ALA AI x 0.09 x 100) and 64 mg of DHA in men (1.6 g ALA AI x 0.04 x 100) may be derived from ALA assuming an ideal LA:ALA intake, which is seldom the case. While a dose response study of varying LA:ALA ratios on DHA derivation has not been completed, it has been suggested that a range of 5:1-10:1 is ideal. Current LA:ALA ratios in the U.S. meet the upper limit of, or exceed, these recommendations in several subpopulations. Regardless, if one assumes that 99 mg (women) and 64 mg (men) of DHA are provided daily from ALA and that the average intake from dietary sources of DHA may be as low as 20-50 mg for certain vulnerable subpopulations, the net DHA status for many may be as low as 84-119 mg. Current literature supports the need for higher levels of DHA for maintaining tissue status during many life phases including growth and development in infancy and childhood and during a woman's pregnancy and lactation, as well as cardioprotective and other benefits.

vi. Pregnant and lactating women represent a large segment of the population vulnerable to inadequate intake of DHA. Intake of preformed DHA by pregnant women in amounts higher than currently consumed in the U.S. and higher than that suggested by the IOM for EPA and DHA combined are supported by the scientific literature published since the IOM completed its review.

The IOM established an n-3 PUFA AI for infants in addition to an ALA AI citing that n-3 PUFA provide DHA that is important for the developing brain

and retina (IOM Report at 8-36). The IOM further states that this n-3 PUFA AI is largely based upon the average n-3 PUFA content of maternal tissue, specifically human milk (IOM Report at 8-36). Interestingly, however, the IOM failed to establish an n-3 PUFA AI for pregnant women. The IOM did, however, establish an AI for ALA during pregnancy suggesting that that pregnant women achieve 1.3 g ALA per day, which is higher than the 1.1 g AI for women.

The IOM failed to establish an n-3 LCPUFA AI during pregnancy because evidence was not available to show that increasing intakes of DHA in pregnant and lactating women consuming diets that meet requirements for n-6 and n-3 fatty acids have any physiologically significant benefit to the infant (IOM Report at 8-39). Since the IOM review, a significant amount of data have been published that recognize the role of DHA during pregnancy on pregnancy outcomes of physiologic benefit to the infant, fetal nutrition as evident by DHA levels at birth, and maternal DHA status post-partum for the support of lactation and the possible prevention of post-partum depression.

During pregnancy the supply of nutrients to the fetus depends on both maternal diet and adipose tissue stores. The critical importance of maternal DHA stores for fetal supply of LCPUFA is demonstrated by studies of placental tissue. Recent work by Haggarty et al. (1999) suggests that the placenta preferentially accumulates DHA compared to all other LCPUFA and preferentially utilizes non-esterified free fatty acids (NEFA) compared to triglycerides. NEFA are mobilized during fasting and largely represent the fatty acid composition of adipose tissue stores; triglycerides predominate in the circulation when in a fed state.

Adipose tissue stores represent long-term patterns of dietary intake and do not readily fluctuate in response to short-term dietary modifications. Due to the static nature of adipose fatty acids the DHA intake of a woman before pregnancy and during early pregnancy may be as, or more, important than that consumed throughout her pregnancy. It has been reported that maternal plasma phospholipid DHA levels increase during early pregnancy, independent of dietary intake, perhaps due to increased mobilization from stores or due to changes in hepatic DHA synthesis and/or utilization (Otto et al., 2001). Indeed, first trimester DHA plasma phospholipid DHA predicts DHA levels throughout pregnancy and this early status appears to determine both fetal and maternal DHA status at delivery (Rump and Hornstra, 2002; Smuts et al., 2003).

Early epidemiologic studies have suggested that n-3 LCPUFA may play a role in extending gestation closer to term (Olsen et al., 1989) and subsequent high dose n-3 LCPUFA intervention trials have strengthened this hypothesis (Olsen et al., 1992, FOTIP). Since the IOM review, at least two prospective and two intervention trials have been published regarding the role of n-3 LCPUFA intake and specifically DHA on gestational outcomes.

Olsen and Secher (2002) conducted a prospective study of seafood intake during early pregnancy in a cohort of 8,729 pregnant women living in Denmark. Data were analyzed by quintiles of estimated long-chain n-3 PUFA intake and quartiles of seafood meal frequency. Women who took fish oil supplements were excluded. Quartiles of seafood intake were defined as: zero per week, more than zero but less than once a month, 1-3 times a month, and once or more often per week. Quintiles of n-3 intake were defined as 0 mg, up to 38 mg, > 38 –92 mg, >92 –146 mg, >146-215 mg/day. The results from both intake estimation methods were the same. All results were adjusted for previously identified covariants including: sex of the infant, maternal smoking, alcohol consumption, maternal age, parity, height, and pre-pregnant weight.

The occurrence of preterm delivery differed significantly across the quartiles of seafood intake, falling from 7.1% in the group that reported never consuming fish to 1.9% in the group reporting fish consumption at least once a week. Gestational age was significantly ($P<.001$) increased by an average of 3.3 days from the lowest quintile of n-3 PUFA intake to the highest. A similar pattern was seen for adjusted birth weight across intake quintiles with an 84 g increase in weight between the lowest and highest quintile. Adjusted odds for preterm delivery were increased by a factor of 3.6 when comparing the lowest quartile (zero consumption) to the highest of seafood consumption. Based on the quintiles of estimated n-3 PUFA intake the authors estimated the working range of dose response relation was mainly from zero intake up to 150 mg n-3 PUFA per day. The authors suggest that consumption of n-3 PUFA below 150 mg/ day is a strong risk factor for preterm delivery and low birth weight. The current estimated average n-3 PUFA (EPA+DHA) intake of pregnant and lactating women in the U.S is 72 mg/day (IOM Report at E13 and E15).

Grandjean and coworkers (2001) studied a cohort of 182 singleton term births in the Faroe Islands during a 12-month period determining the concentration of fatty acids and seafood contaminants in blood samples as predictors of gestational length and birth weight. Seafood intake among women in this study was estimated using previously validated food frequency questionnaires. The majority (90%) of the population was reported to consume at least 3 fish dinners per week. Gestational age was determined using ultrasound and date of last menstruation. All results were adjusted for previously identified covariants including: maternal height, maternal weight, smoking during pregnancy, diabetes, parity, gestational length, and sex of the infant. Gestational length showed a strong positive association with cord serum phospholipid DHA concentration. When all fatty acids were entered as independent variables in regression analyses, DHA was the best predictor ($P<.001$). An increase in the relative concentration of DHA in cord serum phospholipid by 1% was associated with an increase in gestation of 1.5 days. There was no relationship between EPA and gestational length ($P<.41$) and a negative relationship between EPA and birth weight ($P<.015$). An increase in relative EPA concentration of 1% was associated with a decrease in birth weight by 246 g. These results indicate a relationship between length of gestation and maternal DHA status even in a high seafood consuming population.

Most recently, Smuts and coworkers (2003) reported the results of a randomized, double-blind, controlled clinical trial supplementing pregnant women in the U.S. with DHA from DHA-rich eggs on gestational outcomes. Women (n=291) were recruited prior to their third trimester and gestational age was determined via ultrasound. Women were predominately African American and lower socioeconomic status. High-risk pregnancies were excluded although women with prior preterm deliveries were accepted. The rate of prior preterm delivery at baseline did not differ between the control and supplemented groups and averaged 7%. The national average for preterm delivery in the U.S. is estimated at 12% (March of Dimes). All results were controlled for previously identified influential covariants. Based on egg consumption and analyzed DHA content of eggs, women in the DHA supplemented group consumed an additional 137 mg of DHA and women in the ordinary egg group consumed 30 mg DHA per day. Neither egg contained detectable EPA. After controlling for potential confounders, the length of gestation in the DHA supplemented group increased by 6 days ($P<.009$). Infants from the DHA group were an average of 83 g heavier than those born of mothers in the control group. Increased birth weight was not statistically significant but

consistent with the findings of Olsen and Secher (2002) who reported an 84 g increase in birth weight when women consumed at least 150 mg n-3 LCPUFA. Importantly, the study of Smuts et al. (2003) was only powered to determine a significant outcome for length of gestation. Olsen and Secher (2002) reported an average of a 3 day increase in gestation length with higher n-3 LCPUFA intake while the current study results indicated 6 additional days. Smuts et al. (2003) controlled for a greater number of previously determined confounders than Olsen and Secher (2002), prior to controlling for these variables Smuts et al. reported a 2.6 day increase in gestation length.

One U.S. observational study (Oken et al., 2004) of pregnant women (n=2109) has reported no relationship between EPA+DHA intake and length of gestation, and an inverse relationship between these fatty acids and fetal growth (birth weight adjusted for length of gestation). It is difficult, however, to determine the validity of these results or the specificity to combined EPA+DHA intake versus EPA intake alone. The results of the current study were based on intake measured via a semi-quantitative food frequency questionnaire (SFFQ) without accompanying serum fatty acid measurements. The only other report of LCPUFA and reduced birth weight was by Grandjean and co-workers (2001) who specifically reported an inverse relationship between serum EPA, but not DHA, and reduced birth weight. The accuracy of gestation length as measured in the Oken study is also questionable. Twenty percent of the women in the study did not have ultrasound data available and, in up to 10% of cases where both ultrasound and date of last menstrual period (LMP) were available, gestational age according to LMP varied by more than 10 days as compared to ultrasound, forcing the authors to rely solely on ultrasound data. Unfortunately, the SFFQ utilized in the Oken study may also have been of limited validity. The questions on the SFFQs differed between trimesters but were only calibrated with a pilot sample of serum fatty acids during the first trimester. However, this calibration resulted in a reported 1.7% increase in red blood cell LCPUFA for every 1 gram consumed among African American women but a 4.8% increase among Caucasians, suggesting that the instrument may have been invalid in the16% of the population that was African American. While dietary data was collected in all trimesters, the authors only used first and second trimester data because of insurmountable differences between the design of these questionnaires and the third trimester questionnaire.

Interestingly, at least one U.S. supplementation study showing benefits to gestation length and birth weight occurred during the third trimester and was among a predominately African American population (Smuts et al, 2003). In addition, because the third trimester questionnaires were excluded, the lowest intake category assessed by the remaining SFFQ was less than once per month, which admittedly hindered the authors' ability to discern the effects of infrequent fish consumption (Oken et al., 2004). In fact, the majority of women (quartiles 2-4) reported consuming between 90-360 mg of EPA+DHA per day compared to the current USDA reported mean intake of 72 mg among pregnant and lactating women. The higher EPA+DHA intake within this costal-based community (Boston, Mass.) of well-educated (87% with some college or a college degree), older (65% 35 years or older) women experiencing their 2nd or greater pregnancy (70%) questions the valid extrapolation of these results to more vulnerable subpopulations in the U.S.

Recent data indicate that ALA alone is not sufficient to support maternal DHA levels during pregnancy. De Groot et al. (2004) failed to find any effect 2.8 g ALA supplemented daily during pregnancy on maternal or neonatal DHA status even when supplementation occurred against a background dietary ratio of 5:1 LA:ALA, thought to be optimal to support the conversion of ALA to DHA (FAO/WHO). Interestingly, the level of supplementation used by De Groot et al. (2004) is more than double that currently recommended by the IOM and the LA:ALA in the study population roughly half that consumed by women in the U.S. (CSFII Tables, IOM Report).

Taken in total the above studies suggest DHA is strongly associated with gestational length. Preterm birth which is defined as birth prior to 37 weeks of gestation is the leading cause of neonatal death in the U.S. and accounts for up to 12% of all births (March of Dimes). The majority of the studies above suggest that women consuming a minimum of 137-150 mg of DHA per day may observe increases in gestational length and possibly birth weight compared to women consuming little or no DHA and that an optimal LA:ALA does not change the relationship between DHA and gestation length. The above results further suggest that EPA may be detrimental to pregnancy outcomes. In failing to establish an AI for n-3 fatty acids during pregnancy IOM suggested that there was no evidence that maternal DHA status impacted infant physiologic outcomes. The data are now available and establish the importance of receiving 137-150 mg of DHA per day

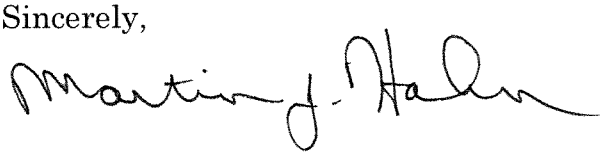
during pregnancy. Gestational age is an important predictor of infant morbidity and mortality as well as social development (Hediger et al., 2002). The important role of DHA during pregnancy, and the possibly detrimental role of EPA, provide further support to the establishment of separate daily values for EPA and DHA.

IV. CONCLUSION

This notification proposes nutrient content claims for omega-3 fatty acids, DHA and ALA, which are based on authoritative statements in the IOM Report and supported by extensive scientific literature contained herein. The IOM Report specifies that the adequate intake of ALA for adult males, the population group with the highest need, is 1.6 g/day. The IOM Report also specifies that 10% of the total omega-3 fatty acids can be supplied by DHA, which allows for a calculated DV for DHA of 160 mg/day. Consistent with FDA's long-established claim definitions, "excellent source" claims for ALA should be permitted on food products containing at least 20% of the daily value for ALA (*i.e.* 320 mg or more) and "excellent source" claims for DHA should be permitted on food products containing 20% or more of the calculated daily value for DHA (*i.e.*, 32 mg or more).

Based on the reasons and scientific data contained above, we respectfully request acceptance of this notification and authorization of the proposed nutrient content claims.

Sincerely,



Martin J. Hahn
Counsel to Martek Biosciences Corp.

Attachment 1: Relevant Chapters from IOM Report
Attachment 2: DHA Levels in Foods Fortified with Algal Oils
Attachment 3: Foods and Oils Containing DHA and/or ALA
Attachment 4: Bibliography of Scientific References