

OLSSON, FRANK AND WEEDA, P. C.

ATTORNEYS AT LAW

SUITE 400

1400 SIXTEENTH STREET, N.W.

WASHINGTON, D. C. 20036-2220

(202) 789-1212

FACSIMILE (202) 234-3550

TISH E. PAHL  
ROBERT A. HAHN  
NAOMI J. L. HALPERN  
STEPHEN L. LACEY  
SHARON D. BROOKS  
RYAN W. STROSCHEIN  
EVAN P. PHELPS  
VALERIE B. SOLOMON\*

OF COUNSEL  
JUR. T. STROBOS  
JACQUELINE H. EAGLE  
KENNETH D. ACKERMAN  
MARK L. ITZKOFF

PHILIP C. OLSSON  
RICHARD L. FRANK  
DAVID F. WEEDA (1948-2001)  
DENNIS R. JOHNSON  
ARTHUR Y. TSIEN  
JOHN W. BODE\*  
STEPHEN D. TERMAN  
MARSHALL L. MATZ  
MICHAEL J. O'FLAHERTY  
DAVID L. DURKIN  
NEIL F. O'FLAHERTY  
PAMELA J. FIRMAN  
BRETT T. SCHWEMER

Sender's Direct Phone (202) 518-6320  
Sender's Direct Facsimile (202) 234-2686

\*PRACTICE WITHIN THE DISTRICT OF COLUMBIA  
IS LIMITED TO MATTERS AND PROCEEDINGS  
BEFORE FEDERAL COURTS AND AGENCIES

January 16, 2004

**BY FEDERAL EXPRESS**

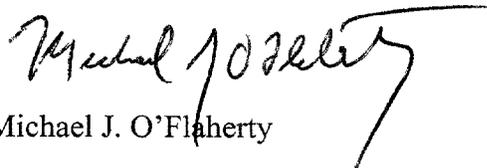
Felicia B. Satchell  
Division of Standards and Labeling Regulations (HFS-820)  
Office of Nutritional Products, Labeling,  
and Dietary Supplements  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
Harvey W. Wiley Federal Building  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

Re: Notification for a Nutrient Content Claim Based on an Authoritative Statement

Dear Ms. Satchell:

Enclosed for filing are duplicate copies of a notification for a nutrient content claim based on an authoritative statement, submitted pursuant to 21 U.S.C. §343(r)(2)(G). Your Office's attention to this matter is greatly appreciated.

Yours truly,

  
Michael J. O'Flaherty

MJO:jdm  
Enclosures

2004 N-0217

CPI

# OLSSON, FRANK AND WEEDA, P. C.

ATTORNEYS AT LAW

SUITE 400

1400 SIXTEENTH STREET, N.W.

WASHINGTON, D. C. 20036-2220

(202) 789-1212

FACSIMILE (202) 234-3550

TISH E. PAHL

ROBERT A. HAHN

NAOMI J. L. HALPERN

STEPHEN L. LACEY

SHARON D. BROOKS

RYAN W. STROSCHEIN

EVAN P. PHELPS

VALERIE B. SOLOMON\*

OF COUNSEL

JUR. T. STROBOS

JACQUELINE H. EAGLE

KENNETH D. ACKERMAN

MARK L. ITZKOFF

PHILIP C. OLSSON  
RICHARD L. FRANK  
DAVID F. WEEDA (1948-2000)  
DENNIS R. JOHNSON  
ARTHUR Y. TSIEN  
JOHN W. BODE\*  
STEPHEN D. TERMAN  
MARSHALL L. MATZ  
MICHAEL J. O'FLAHERTY  
DAVID L. DURKIN  
NEIL F. O'FLAHERTY  
PAMELA J. FURMAN  
BRETT T. SCHWEMER

\*PRACTICE WITHIN THE DISTRICT OF COLUMBIA  
IS LIMITED TO MATTERS AND PROCEEDINGS  
BEFORE FEDERAL COURTS AND AGENCIES

January 16, 2004

## NOTIFICATION FOR A NUTRIENT CONTENT CLAIM BASED ON AN AUTHORITATIVE STATEMENT

**Notifiers:** Alaska General Seafoods  
Kenmore, WA

Ocean Beauty Seafoods, Inc.  
Seattle, WA

Trans-Ocean Products, Inc.  
Bellingham, WA

**Subject:** Nutrient Content Claims for DHA, EPA, and ALA (Specific 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 Olsson, Frank and Weeda, P.C. (OFW), on behalf of the notifiers identified above, 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), eicosapentaenoic acid (EPA), and/or alpha-linolenic acid (ALA). The proposed nutrient content claims are based upon authoritative statements made by the Institute of Medicine (IOM), a subdivision of the National Academy of Sciences (NAS), in its September 5, 2002 report, *Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol,*

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 2

*Protein and Amino Acids* (IOM Macronutrients Report) (available in prepublication copy). These authoritative statements, in turn, are read and applied in light of recommendations expressed by the IOM in its December 11, 2003 report, *Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification* (IOM Guiding Principles Report) (available in prepublication copy).

This notification contains, as specified below, all requisite elements identified 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 Guidance Document). Attached hereto and constituting a part of this notification are the following:

#### IDENTITY OF SUBJECT NUTRIENTS

This notification concerns nutrient content claims specific to the omega-3 (*n-3*) fatty acids, DHA (22:6*n-3*), EPA (20:5*n-3*), and ALA (18:3*n-3*). DHA and EPA are considered long-chain (LC) polyunsaturated fatty acids (PUFAs), while ALA is termed a short-chain (SC) PUFA.

This notification does not propose nutrient content claims for "omega-3 fatty acids" or "omega-3s" generically or collectively.

Given significant biochemical and functional differences between the LCPUFAs, DHA and EPA, and the SCPUFA, ALA, claims specific to DHA and EPA and to ALA are warranted and, therefore, are being proposed. In this regard, of particular note, the sole dietary function of ALA is to serve as a precursor for synthesis of DHA and EPA in the body. IOM Macronutrients Report at 8-11. The IOM was unable to estimate a single Acceptable Macronutrient Distribution Range (AMDR) for all *n-3* fatty acids "[b]ecause the physiological potency of EPA and DHA is much greater than that for [ALA]." IOM Macronutrients Report at 11-2. Moreover, the strong, scientific evidence linking DHA/EPA consumption to reduced risk of coronary heart disease (CHD) is only evolving for ALA. The preamble to FDA's final rule originally considering a health claim for omega-3 fatty acids and CHD under the Nutrition Labeling and Education Act of 1990 (NLEA) provided: "FDA believes it has represented the potential nutrient-disease relationship appropriately by limiting its attention to EPA and DHA." 58 *Fed. Reg.* 2682, 2683 (Jan. 6, 1993). More recently, the agency reaffirmed its position that the nutrient-disease relationship properly is limited to DHA and EPA and reduced risk of CHD: "FDA's conclusion has not changed." Letter dated Oct. 31, 2000, from Christine J. Lewis, Ph.D., Director, Office of Nutritional Products, Labeling and Dietary Supplements (ONPLDS), Center for Food Safety and Applied Nutrition (CFSAN), FDA, to Jonathan W. Emord, Esq., regarding dietary supplement health claims for omega-3 fatty acids and CHD. Still more recently, the qualified health claim petition submitted by Martek Biosciences Corporation (Martek) concerns the benefit of

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 3

DHA/EPA, but not ALA, consumption on risk of CHD. Qualified Health Claim for Conventional Foods and Dietary Supplements Containing Omega-3 Fatty Acids, submitted to FDA on November 3, 2003 by petitioner, Martek (Docket No. 2003Q-0401).

DHA and EPA are nutrients present in foods derived from animals, but not from plants. IOM Macronutrients Report at 8-5. In contrast, ALA is provided by foods derived from plants.

Nutrient content claims specific to DHA and EPA and to ALA will serve the substantial interest of helping to educate consumers about the distinctive nutritional value and health benefits of DHA/EPA versus ALA (*i.e.*, all *n-3* PUFAs are not created equal), and about their respective food sources.

#### IMPORTANCE OF NUTRIENT CONTENT CLAIMS FOR DHA, EPA, AND ALA

ALA cannot be synthesized by the human body. DHA and EPA can be synthesized in the body from ALA, but the conversion is affected by several factors, including the concentration of ALA as well as that of *n-6* fatty acids (*e.g.*, linoleic acid (18:2*n-6*)) (IOM Macronutrients Report at 8-25) and may not be sufficient for optimal health.<sup>1</sup> This limited nature of the conversion of ALA to LC *n-3* PUFAs recently has been reviewed by Muskiet *et al.*,<sup>2</sup> Emken,<sup>3</sup> and Salem *et al.*<sup>4</sup> Deficiency symptoms have been observed in human adults<sup>5,6</sup> and children<sup>7,8</sup> fed very low amounts of LC (DHA/EPA) and/or SC (ALA) *n-3* fatty acids for prolonged periods.

<sup>1</sup> De Deckere, Korver, O., Verschuren, P.M. and Katan, M.B. 1998. Health aspects of fish and *n-3* polyunsaturated fatty acids from plant and marine origin. *Europ. J. Clin. Nutr.* 52:749. Note: All papers and articles referenced in the footnotes to this notification are attached as Appendix 1.

<sup>2</sup> Muskiet, F.A.J., Fokkema, M.R., Schaafsma, A., Boersma, E.R. and Crawford, M.A. 2004. Is docosahexaenoic acid (DHA) essential? Lessons from DHA status regulation, our ancient diet, epidemiology and randomized controlled trials. *J.Nutr.* 134:183.

<sup>3</sup> Emken, E. 2003. Alpha-linolenic acid conversion to *n-3* LC-PUFAs. PUFA Newsletter, September 2003. <http://www.fatsoflife.com/article.asp?i=c&id=130>

<sup>4</sup> Salem, N., Lin, Y., Brenna, J.T. and Pawlosky, R.J. 2003. Alpha-linolenic acid conversion revisited. PUFA Newsletter, December 2003. <http://www.fatsoflife.com/article.asp?i=c&id=162>

<sup>5</sup> Bjerve, K.S., Fischer, S., Wammer, F. and Egeland, T. 1989.  $\alpha$ -Linolenic acid and long-chain  $\omega$ -3 fatty acid supplementation in three patients with  $\omega$ -3 fatty acid deficiency: effect on lymphocyte function, plasma and red cell lipids, and prostanoid formation. *Am. J. Clin. Nutr.* 49:290.

<sup>6</sup> Bjerve, K.S., Mostad, I.L. and Thoresen, L. 1987. Alpha-linolenic acid deficiency in patients on long-term gastric-tube feeding: estimation of linolenic acid and long-chain unsaturated *n-3* fatty acids requirement in man. *Am. J. Clin. Nutr.* 45:66.

<sup>7</sup> Holman, R.T., Johnson, S.B. and Hatch, T.F. 1982. A case of human linolenic acid deficiency involving neurological abnormalities. *Am. J. Clin. Nutr.* 35:617.

<sup>8</sup> Bjerve, K.S., Thoresen, L. and Børsting, S. 1988. Linseed and cod liver oil induce rapid growth in a 7-year-old girl with *n-3* fatty acid deficiency. *J. Parenter. Enteral Nutr.* 12:521.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 4

These symptoms can be resolved by providing dietary sources of LC (DHA/EPA) and/or SC (ALA) *n*-3 fatty acids, including fish oil, cod liver oil, ethyl  $\alpha$ -linolenate, soy oil, or linseed oil.

As discussed in more detail below, the IOM has established Adequate Intake (AI) values for ALA based on the prevention of essential fatty acid deficiency symptoms for children and adolescents (IOM Macronutrients Report at 8-37) and adults (p. 8-38).<sup>9</sup> The AI values for ALA for adolescents and adults 14 years or older are 1.1 grams per day (g/d) for females and 1.6 g/d for males. In addition, the IOM expressly concluded that up to 10% of the total *n*-3 fatty acids intake can be contributed by DHA and EPA.<sup>10</sup> IOM Macronutrients Report at 8-38. Furthermore, the IOM recently recommended that Daily Values (DV) for nutrition labeling purposes be calculated from the appropriate Daily Reference Intake (DRI) using a population-weighted formula based on census data. IOM Guiding Principles Report at 5-3. Application of this calculation to the AI for ALA results in a DV (population-weighted) for ALA of 1.3 g/d. Ten percent of the total *n*-3 fatty acids intake represented by this DV that can be contributed by DHA and EPA is 130 milligrams (mg).

Although the AI for *n*-3 fatty acids is based on the prevention of deficiency symptoms, there are other, more compelling public health policy reasons supporting authorization of the proposed nutrient content claims – especially for DHA and EPA. These reasons include:

1. DHA and EPA are the more biopotent forms of *n*-3 fatty acids.

The IOM Macronutrients Report states that "...the physiological potency of EPA and DHA is much greater than that for [ALA]..." (p. 11-2). The Report also concludes: "The essential role of [ALA] appears to be its role as precursor for synthesis of [EPA] and DHA." (p. 8-18) and, "[ALA] is not known to have any specific functions other than to serve as a precursor for synthesis of EPA and DHA." (p. 8-11) These conclusions support the premise that nutrient content claims specific to DHA and EPA, and apart from ALA, are appropriate.

---

<sup>9</sup> The IOM has also established an AMDR for ALA of 0.6 to 1.2 percent of dietary energy. The lower end of this range is based on the AI and reflects the amount of *n*-3 fatty acids necessary to prevent deficiency symptoms while the upper end of the range corresponds to the highest ALA intakes from foods consumed by individuals in the U.S. and Canada. IOM Macronutrients Report at 11-1.

<sup>10</sup> The IOM similarly concluded that up to 10 percent of the AMDR for ALA can be consumed as DHA and/or EPA. IOM Macronutrients Report at 11-2.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 5

2. DHA and EPA serve a variety of important physiological functions:
  - DHA is a vital component of membrane structural lipids and is present in very high concentrations in certain phospholipids of the nervous system and retina. IOM Macronutrients Report at 8-11.
  - EPA is the precursor of *n*-3 eicosanoids, which have been shown to have beneficial effects in preventing CHD, arrhythmias and thrombosis. IOM Macronutrients Report at 8-5. These EPA-derived eicosanoids also affect platelet aggregation, vessel wall constriction, and immune cell function. IOM Macronutrients Report at 8-14.
  - EPA and DHA may modulate the expression of autoimmune diseases through effects on eicosanoid metabolism and eicosanoid-independent mechanisms such as intracellular signaling pathways, transcription factor activity and gene expression.<sup>11</sup>
  - DHA is an integral component of brain function and may be important for the maintenance of cognitive activity during aging<sup>12</sup> and normal mental function, such as the avoidance of depression.<sup>13</sup>
  - EPA (and DHA) appears to inhibit triacylglycerol (TG) synthesis and very low density lipoprotein (LDL) secretion in the liver. IOM Macronutrients Report at 8-14. These effects may result in lower serum TG concentrations and a decrease in highly atherogenic small, dense LDL particles.<sup>14</sup>

The importance of DHA and EPA to human physiology and health maintenance provides further rationale for the authorization of nutrient content claims for these *n*-3 fatty acids.

---

<sup>11</sup> Simopoulos, A.P. 2002. Omega-3 fatty acids in inflammation and autoimmune diseases. *J. Am. Col. Nutr.* 21:495.

<sup>12</sup> Youdim, K.A., Martin, A., and Joseph, J.A. 2000. Essential fatty acids and the brain: possible health implications. *Int. J. Devl. Neuroscience* 18:383..

<sup>13</sup> Adams, P.D., Lawson, S., Sanigorski, A and Sinclair, A.J. 1996. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 31:S157.

<sup>14</sup> Wong, S. and Nestle, P.J. 1987. Eicosapentaenoic acid inhibits the secretion of triacylglycerol and of apoprotein B and the binding of LDL in Hep G2 cells. *Atherosclerosis* 64:139

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 6

3. DHA and EPA (and possibly ALA) reduce the risk of CHD and stroke.

The IOM Macronutrients Report (p. 11-40) states, "Growing evidence suggests that dietary *n*-3 [PUFAs] [EPA] and [DHA] reduce the risk of [CHD] and stroke."<sup>15</sup> ALA may also be important in this regard, but the scientific evidence supporting its cardioprotective properties is less extensive than for DHA and EPA. Recent studies not cited in or published since the IOM Macronutrients Report in this area are briefly discussed immediately below.

A controlled intervention trial<sup>16</sup> (the GISSI study) that provided a total of 850-882 mg EPA and DHA as ethyl esters per day (with or without vitamin E) to myocardial infarction (MI) patients significantly reduced mortality after only three months and sudden death after just four months in a population of 11,323 adult subjects.

Dwyer and co-workers<sup>17</sup> identified subjects (n=470) from the Los Angeles Atherosclerosis Study with a polymorphism in the 5-lipoxygenase gene promoter that increases risk for atherosclerosis. It is estimated that up to 6% of the US population, particularly blacks and Asian-Americans, may have this genotype. The researchers found that intima-media thickness, as a measure of atherosclerosis, was significantly (P<.001) enhanced by dietary n-6 fatty acids (as reported by food recalls) and decreased by dietary n-3 fatty acids (EPA+DHA). These findings remained significant after multivariate analysis that included biologic, behavioral, and preventative treatment variables. The authors concluded that dietary n-6 fatty acids may significantly enhance the atherogenic effect of this genotype while dietary n-3 fatty acids attenuate this effect.

Yli-Jama *et al.*<sup>18</sup> reported that serum concentrations of DHA and EPA were lower among MI patients than healthy individuals in a case-control study of 207 men and women aged 45-75. In addition, the percentage content of total LC *n*-3 PUFAs was associated with decreased risk of MI in this population.

<sup>15</sup> The Report (p. 11-1 to 11-2) also states: "A growing body of literature suggests that higher intakes of [ALA], [EPA] and [DHA] may afford some degree of protection against CHD.

<sup>16</sup> Marchioli, R. *et al.* 2002. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction. Time-course analysis of the results for the Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 105:1897.

<sup>17</sup> Dwyer, J.H. *et al.* 2004. Arachidonate 5-lipoxygenase promoter genotype, dietary arachidonic acid, and atherosclerosis. *N. Engl. J. Med.* 350:29.

<sup>18</sup> Yli-Jama, P., Meyer, H.E., Ringstad, J. and Pedersen, J.I. 2002. Serum free fatty acid pattern and risk of myocardial infarction: a case-control study. *J. Int. Med.* 251:19.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 7

Similar results were obtained in a nested case-control study of 94 victims of sudden death due to CHD and 184 matched controls from the Physicians' Health Study.<sup>19</sup> The intake of *n*-3 fatty acids found in fish (DHA/EPA) was strongly associated with reduced risk of sudden death, as evidenced by serum fatty acid concentrations. The concentration of ALA was not associated with sudden death, but serum levels of this fatty acid are not a reliable indicator of long-term dietary intake because much of it is rapidly oxidized as an energy source.

Another observational study<sup>20</sup> from the Harvard School of Public Health among 84,688 members of the Nurses' Health Study cohort reported that fish and *n*-3 fatty acids (*i.e.*, DHA, EPA and ALA) consumption was associated with a lower risk of CHD (especially CHD mortality) during a 16-year follow-up period. The data were adjusted for age, smoking and other CHD risk factors.

Nilsen *et al.*<sup>21</sup> did not find a reduction in the incidence of cardiac events among 300 acute CHD patients given either 4 g/d of DHA/EPA or corn oil during a 12-24 month follow-up period. The authors speculated that the dose may have been inadequate to produce an effect in this population, or that an equal benefit was produced by both dietary treatments. A negative control group was not included in this study.

A nested case-control study<sup>22</sup> of 54 fatal CHD victims and 125 matched controls found an inverse association between the concentrations of DHA and EPA in blood and risk of death. The blood samples were drawn two years before the cardiac event. There was a tendency for a similar protective effect for ALA, but the association was not statistically significant after controlling for CHD risk factors.

---

<sup>19</sup> Albert, C.M., Campos, H., Stampfer, M.J., Ridker, P.M., Manson, J.E., Willett, W.C. and Ma, J. 2002. Blood levels of long-chain *n*-3 fatty acids and the risk of sudden death. *N. Engl. J. Med.* 346:1113.

<sup>20</sup> Hu, F.B., Bronner, L., Willett, W.C., Stampfer, M.J., Rexrode, K.M., Albert, C.M., Hunter, D. and Manson, J.E. 2002. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *J. Am. Med. Assn.* 287:1815.

<sup>21</sup> Nilsen, D.W.T., Albrechtsen, G., Landmark, K., Moen, S., Aarsland, T. and Woie, L. 1999. Effects of a high-dose concentrate of *n*-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am. J. Clin. Nutr.* 74:50.

<sup>22</sup> Lemaitre, R.N., King, I.B., Mozaffarian, D., Kuller, L.H. Tracy, R.P. and Siscovick, D.S. 2003. *n*-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am. J. Clin. Nutr.* 77:319.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 8

ALA intake was not associated with CHD incidence in a 10-year prospective observational study of 667 men aged 64-84 who were free of CHD at baseline.<sup>23</sup> The data were adjusted for coronary risk factors and dietary components including *trans* fatty acids. This study did not investigate a possible association between EPA and/or DHA and CHD incidence.

Hu *et al.*<sup>24</sup> reported that higher consumption of fish and LC *n*-3 fatty acids (DHA/EPA) was associated with reduced risk of CHD incidence and total mortality among 5,103 female nurses diagnosed with type 2 diabetes, but free of CHD. The study had a follow-up period of 16 years and results were adjusted for age, smoking and other CHD risk factors.

A cross-sectional observational study<sup>25</sup> of 4440 white subjects aged 25-93 found that dietary linolenic acid was inversely associated with mean serum triacylglycerol concentration after adjusting for age, body mass index, waist-to-hip ratio, intakes of energy, total fat, carbohydrates, LC *n*-3 PUFAS and fruits and vegetables, as well as HDL-cholesterol concentrations, alcohol use, smoking, physical activity and history of diabetes mellitus and coronary artery disease.

In addition to these studies, several review papers<sup>26,27,28</sup> and a meta-analysis<sup>29</sup> have concluded that intake of *n*-3 PUFAs (*i.e.*, EPA/DHA and/or ALA) reduces the risk of CHD and/or total mortality.

Once again, the scientific evidence summarized above supports the authorization of nutrient content claims for DHA and EPA.

---

<sup>23</sup> Oomen, C.M., Ocké, M.C., Feskens, E.J.M., Kok, F.J. and Dromhout, D. 2001.  $\alpha$ -linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. *Am. J. Clin. Nutr.* 74:457.

<sup>24</sup> Hu, F.B., Cho, E., Rexrode, K.M., Albert, C.M. and Manson, J.E. 2003. Fish and long-chain  $\omega$ -3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation* 107:1852.

<sup>25</sup> Djoussé, L., Hunt, S.C., Arnett, D.L., Province, M.A., Eckfeldt, J.H. and Ellison, R.C. 2003. Dietary linolenic acid is inversely associated with plasma triacylglycerol: the National Heart, Lung, and Blood Institute Family Heart Study. *Am. J. Clin. Nutr.* 78:1089.

<sup>26</sup> Mori, T.A. and Beilin, L.J. 2001. Long-chain omega 3 fatty acids, blood lipids and cardiovascular risk reduction. *Curr. Opin. Lipidol.* 12:11.

<sup>27</sup> Harris, W.S., Park, Y. and Isley, W.L. 2003. Cardiovascular disease and long-chain omega-3 fatty acids. *Curr Opin. Lipidol.* 14:9.

<sup>28</sup> Lichtenstein, A.H. 2003. Dietary fat and cardiovascular disease risk: quantity or quality? *J. Women's Health* 12:109.

<sup>29</sup> Bucher, H.C., Hengstler, P., Schindler, C. and Meier, G. 2002. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am. J. Med.* 112:298.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 9

4. Feeding ALA to non-fatty acid deficient individuals can increase tissue concentrations of DHA and/or EPA, but it is not known whether optimum status of these fatty acids can be achieved without feeding the preformed compounds.

The IOM Macronutrients Report (p. 8-25) states, "Unfortunately, very few studies are available on the rates of formation of arachidonic acid and DHA from their precursors in humans fed diets differing in linoleic acid and [ALA] content, and with or without controlled amounts of arachidonic acid, EPA and DHA." In addition, a workshop conducted under the auspices of the European Academy of Nutritional Sciences (*see* footnote 1 above) concluded that the beneficial effects of EPA/DHA cannot be fully reproduced by ALA, and that the efficiency of ALA in raising plasma EPA is low. The workshop concluded that more data from randomized controlled clinical trials is required to determine optimal recommendations for marine and non-marine sources of *n*-3 fatty acids. In addition, Muskiet *et al.* (*see* footnote 2 above) has concluded that DHA is likely to be essential in humans because its biochemical status is influenced by dietary intake due to a variety of factors including limited conversion of ALA. The factors that limit conversion of ALA to DHA/EPA have also been recently discussed by Emken and Salem *et al.* (*see* footnotes 3 and 4 above).

These observations further highlight the importance of authorizing nutrient content claims to promote consumption of dietary sources of DHA and EPA.

5. Dietary sources of DHA, EPA, and ALA are recommended by the American Heart Association.

The American Heart Association (AHA) recently revised its dietary guidelines to recommend consuming fish, sources of DHA and EPA, twice weekly to reduce risk of CHD. *See generally* <<http://www.americanheart.org/presenter.jhtml?identifier=810>>. In addition, a recent scientific statement from the AHA<sup>30</sup> concluded that in addition to regular consumption of fish (or a fish oil supplement) the public would benefit from total intakes of approximately 1.5 to 3 g/d of ALA.

6. Content claims for DHA and EPA would be a meaningful adjunct to health claims about these nutrients, as contemplated by the NLEA and FDAMA.

As the agency is aware, a qualified health claim relating *n*-3 fatty acids (DHA/EPA) to reduced CHD risk is, consistent with present public health policy, the first receiving consideration by FDA under new procedures implementing its Consumer Health Information for

---

<sup>30</sup> Kris-Etherton, P.M., Harris, W.S., Appel, L.J; for the Nutrition Committee. 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106:2747.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 10

Better Nutrition Initiative. *See generally* Petition for Amended Health Claim for Foods and Dietary Supplements: "Consumption of Omega-3 Fatty Acids May Reduce the Risk of Coronary Heart Disease"; submitted to FDA on June 23, 2003 by petitioners, Wellness Lifestyles, Inc. (d/b/a American Longevity) and Life Extension Foundation Buyers Club, Inc. (Wellness Lifestyles petition) (Docket No. 2003Q-0401).<sup>31</sup> The Final Report of the Consumer Health Information for Better Nutrition Task Force had recommended that a health claim relating consumption of foods high in *n-3* fatty acids to reduced risk of heart disease be one of the first allowed by the agency under new procedures for qualified health claims. Consumer Health Information for Better Nutrition Initiative: Task Force Final Report (July 10, 2003).

More recently, the agency again was petitioned for a qualified health claim relating DHA and EPA *n-3* fatty acids to reduced CHD risk: "A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease." *See generally* Qualified Health Claim for Conventional Foods and Dietary Supplements Containing Omega-3 Fatty Acids, submitted to FDA on November 3, 2003 by petitioner, Martek (Docket No. 2003Q-0401). Appropriately, ALA was not included in this petition because the level of science about its role in CHD risk reduction is not as advanced.<sup>32</sup>

A qualified health claim already is permitted in labeling dietary supplements.<sup>33</sup> Letters dated Feb. 8, 2002 and Feb. 16, 2001, from Christine J. Lewis, Ph.D., Director, ONPLDS, CFSAN, FDA, to Jonathan W. Emord, Esq., addressing conditions for a dietary supplement health claim for omega-3 fatty acids (DHA and EPA) and CHD.

---

<sup>31</sup> On October 15, 2003 Ocean Nutrition Corporation (ONC) submitted a "Request for Expansion of Enforcement Discretion for Omega-3 Fatty Acids". ONC generally refers to "Omega-3s" or "Omega-3 Fatty Acids" in the submission. However, the summary of the submission refers to EPA/DHA products. "There is no legal, scientific or public health justification for FDA to decline to permit the use of the qualified health claim to conventional foods fortified with ONC's EPA/DHA products." *See* Docket No. 2003Q-0401.

<sup>32</sup> Nevertheless, the nutrient content claims proposed for ALA by this notification are appropriate because they are based on the prevention of fatty acid deficiency symptoms for which the evidence is compelling. The other benefits of ALA provide additional rationale for the authorization of the proposed nutrient content claims, but are not essential from a regulatory perspective.

<sup>33</sup> Nevertheless, like ONC, the Council for Responsible Nutrition (CRN), a prominent dietary supplement trade association, in December 17, 2003 comments submitted to FDA on the Wellness Lifestyles petition, supported extending the qualified health claim to conventional foods. *See* Docket No. 2003Q-0401.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 11

7. Government policymakers urge the dissemination of information about *n-3* fatty acids, particularly DHA and EPA.
  - a. OIRA/OMB Administrator John D. Graham

The Office of Management and Budget (OMB) last May urged the Departments of Health and Human Services (DHHS) and Agriculture (USDA) to revise our nation's dietary guidelines to disseminate information about *n-3* fatty acids as widely as possible to American consumers. Letter dated May 22, 2003, from John D. Graham, Office of Information and Regulatory Affairs (OIRA), OMB, to Claude A. Allen, Deputy Secretary, DHHS, and James R. Moseley, Deputy Secretary, USDA. Dr. Graham stated: "Health researchers have found that Americans can significantly reduce the risk of heart disease with a modest change in their diets. The government should make this life-saving information [about *n-3* fatty acids] as widely available as possible." Press Release (2003-13) dated May 22, 2003, from OMB, Executive Office of the President.

Nutrient content claims highlighting food sources of DHA and EPA will help immeasurably in this consumer education initiative.

- b. FDA Commissioner Mark B. McClellan

The proposed nutrient content claims will advance agency goals recently expressed by Commissioner McClellan, including: facilitating consumers' selection of products that are a part of a healthy diet; encouraging industry to compete in product development and promotion on the basis of nutrition and health; and generally shifting the market to a greater focus on science-based information and the health consequences of positive dietary choices. *See generally* Speech before the Harvard School of Public Health, Remarks by Mark B. McClellan, M.D., Ph.D., Commissioner, FDA (July 1, 2003). The Commissioner used replacing saturated and *trans* fats with monounsaturated fatty acids and PUFAs, such as *n-3* fatty acids, as his first example of the kind of health information he would like to see available and influencing the dietary choices of mainstream consumers. *Id.*

Similarly, at the October 23, 2003 FDA Public Meeting on Obesity, Commissioner McClellan remarked:

[T]he task force on consumer health information for better nutrition, which issued its final report in July, 2003, ... was charged with developing an FDA-regulated and overseen process to help

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 12

consumers get more accurate information about the health consequences of their food choices.

The FDA believes that the process for making science-based health claims when combined with our strong enforcement work will help people choose healthier products while protecting them from companies that make false or misleading claims and will create an environment that encourages companies for helping develop foods that help consumers follow a healthy diet and reduce problems of obesity and chronic illness.

[W]e need to take steps to encourage food producers to make truthful science-based claims about the healthy benefits of their products....

In essence, establishing nutrient content claims to facilitate consumer identification and choice of foods and dietary supplements that are significant sources of DHA and EPA necessarily will advance the public health policy and agency goals noted above.

\* \* \* \* \*

In summary, the available evidence clearly warrants the authorization of nutrient content claims for DHA, EPA, and ALA. As discussed below, the establishment of an AI and calculation of a DV for ALA, and the allocation of 10% of total *n-3* fatty acids intake to DHA and EPA, based on the avoidance of fatty acid deficiency symptoms, provides a quantitative standard upon which such claims can be defined. The critical role of *n-3* fatty acids (especially DHA and EPA) in human physiology, the body of evidence that DHA and EPA (and to a lesser extent ALA) may reduce the risk of CHD and stroke, the uncertainty as to whether ALA itself can provide all the beneficial effects of LC *n-3* PUFAs, recommendations for consumption of *n-3* fatty acids by the AHA, the consumer information benefits of supporting health claims with nutrient content claims, and current government policymaker urgings are clear indications of the merit of authorizing nutrient content claims specific to DHA, EPA, and ALA. In addition, the availability of nutrient content claims will encourage industry to provide quantitative information on food labels and will foster public health by facilitating educational programs on the respective benefits and food sources of DHA, EPA, and ALA *n-3* fatty acids.

Factual statements about DHA/EPA/ALA content already may be made in conventional food and dietary supplement labeling pursuant to 21 C.F.R. §101.13(i). However, advancement of the public health policy and agency goals discussed above is not available through nutrient

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 13

content claims already defined by regulation. Making specific DHA/EPA/ALA content claims available in this circumstance is precisely what was contemplated by Congress in enacting the NLEA and FDAMA, and is consistent with the clearly articulated policy goals of OIRA/OMB Administrator Graham and Commissioner McClellan.

DETERMINATION THAT REQUIREMENTS FOR AN AUTHORITATIVE STATEMENT  
HAVE BEEN SATISFIED

Under FDAMA, nutrient content claims may be predicated upon a published, authoritative statement of the NAS or any of its subdivisions, which is currently in effect, and which identifies the nutrient level to which the claim(s) refers. 21 U.S.C. §343(r)(2)(G). The statement may not be simply that of an individual employee made in the individual capacity of the employee. *Id*

The legislative history of the authoritative statement mechanism elucidates Congress' intent that it "makes streamlined procedures available for the [FDA] to permit more scientifically sound nutrition information to be provided to consumers through ... nutrient content claims." H.R. Rep. No. 399, 105<sup>th</sup> Cong., 1<sup>st</sup> Sess. 95 (1997).

FDA's Guidance Document reflects the agency's belief that authoritative statements should be based upon a deliberative review of the relevant scientific evidence.

The National Research Council (NRC) Governing Board has published a Policy Statement describing which NAS publications are deemed to be authoritative statements. It provides:

In the conduct of studies with regard to relationships between diet and health, and in the course of research relating to questions under study, it is possible that reports of the NRC or IOM may describe associations between foods, nutrients, or food components and aspects of health. These statements would not necessarily represent authoritative statements of the NRC or IOM because they might not summarize the totality of the evidence that would be required by the [NAS] when formulating an authoritative statement. For example, a report may contain descriptions of the work of others or, on occasion, minority reports expressing the views of individuals. Descriptive materials and minority reports, as examples, are not considered authoritative statements of the [NAS] or any of its subdivisions.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 14

For purposes of [FDAMA], authoritative statements of the [NAS] or any of its subdivisions, including the ... [IOM], are limited to those that represent the consensus of a duly-appointed committee ... so that they appear explicitly as findings, conclusions, or recommendations in a report that has completed the institutional report review process.

In concert, the FDAMA, its legislative history, FDA's Guidance Document, and the NRC Governing Board's Policy Statement establish specific requirements for authoritative statements. Essentially, bearing in mind the legislative intent to provide consumers with more scientifically sound information through nutrient content claims, authoritative statements should be deemed proper basis for such claims if they:

- are published;
- currently in effect;
- identify the nutrient level to which the claims refer;
- are not that of an employee made in the individual capacity of the employee;
- are based upon a deliberative review of the relevant scientific evidence;
- represent the consensus of a duly-appointed IOM committee;
- appear explicitly as findings, conclusions, or recommendations; and
- appear in a report that has completed the institutional report review process.

The IOM, a subdivision of NAS, made authoritative statements, as detailed below, about DHA, EPA, and ALA in the IOM Macronutrients Report. These statements satisfy the foregoing requirements:

- The statements are published in the IOM Macronutrients Report.
- The statements remain currently in effect.
- The statements identify the DHA/EPA and ALA levels to which the claims refer.
- The statements are not those of an employee of the NAS/IOM made in her/his individual capacity, nor do they simply describe the work of others or express minority report views; rather, the IOM Macronutrients Report summarizes the totality of evidence about DHA, EPA, and ALA *n-3* fatty acids prerequisite to NAS formulating the authoritative statements.
- The statements are based upon a deliberative review of the relevant scientific evidence on DHA, EPA, and ALA *n-3* fatty acids by the IOM's Panel on Dietary Reference Intakes for Macronutrients.
- The statements represent the consensus of the duly-appointed Panel and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements  
January 16, 2004  
Page 15

- The statements appear explicitly as findings, conclusions, or recommendations in the IOM Macronutrients Report.
- The IOM Macronutrients Report has completed the institutional review process.

The only nutrient content claims established to date under FDAMA were predicated upon authoritative statements identifying a level for choline, published in a 1998 IOM report, entitled *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline* (IOM Micronutrients Report). That report recommended DRIs for certain micronutrients, including an AI for choline. Based on notification of the authoritative statements identifying the AI for choline, FDA authorized “high”-type, “good source”-type, and “more”-type claims to characterize the choline content of conventional foods and dietary supplements. ONPLDS, CFSAN, FDA, *Nutrient Content Claims Notification for Choline Containing Foods* (Aug. 30, 2001) (FDA’s Choline Document). The IOM Micronutrients Report is identical in nature to the IOM Macronutrients Report, setting a precedent for using the IOM Macronutrients Report as the source of authoritative statements for a notification about nutrient content claims for DHA, EPA and ALA.

AUTHORITATIVE STATEMENT

The IOM Macronutrients Report contains explicit findings, conclusions, and recommendations that constitute an authoritative statement identifying nutrient levels for DHA and EPA and for ALA, upon which the proposed nutrient content claims properly may be based.

The IOM Macronutrients Report sets an AI of ALA for the following age/gender categories:

AI for Men/Boys

4-8 years	0.9 g/day of [ALA]
9-13 years	1.2 g/day of [ALA]
14-18 years	1.6 g/day of [ALA]
19-30 years	1.6 g/day of [ALA]
31-50 years	1.6 g/day of [ALA]
51-70 years	1.6 g/day of [ALA]
> 70 years	1.6 g/day of [ALA]

AI for Women/Girls

4-8 years	0.9 g/day of [ALA]
9-13 years	1.0 g/day of [ALA]
14-18 years	1.1 g/day of [ALA]

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 16

19-30 years	1.1 g/day of [ALA]
31-50 years	1.1 g/day of [ALA]
51-70 years	1.1 g/day of [ALA]
> 70 years	1.1 g/day of [ALA]

Moreover, the Report expressly provides:

Because of a lack of evidence for determining the requirement for *n-3* fatty acids, an AI is set based on the highest median intake of [ALA] by adults in the United States where a deficiency is basically nonexistent in free-living populations ... and rounding. Small amounts of EPA and DHA can contribute towards reversing an *n-3* fatty acid deficiency .... 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 [ALA]....

IOM Macronutrients Report at 8-38. A copy of this authoritative statement is attached, as specified in FDA's Guidance Document, as Appendix 2 to this notification.

These authoritative statements identify nutrient levels of 1.6 g (1,600 mg) for ALA, and of 160 mg for DHA and EPA, *i.e.*, 10% of the total *n-3* fatty acids intake marked by the 1.6 g AI for ALA.<sup>34</sup> These values are based on the highest age/gender AI for ALA. Use of these values is analogous to the approach previously used by FDA to authorize nutrient content claims for choline under the FDAMA, where the highest AI similarly was used. *See generally* FDA's Choline Document.

As noted earlier, the IOM Guiding Principles Report (at page 5-3) provides recommendations on how DRIs should be used to determine new DVs for nutrition labeling. The report concluded that the Estimated Average Requirement is the most appropriate DRI for this purpose, followed by the AI, and lastly the AMDR. The appropriate DRIs would be used to calculate new DVs on a population-weighted basis with respect to age and gender using census

<sup>34</sup> The 10% level for DHA and EPA has been understood to be an effective AI for these nutrients:

The adequate intake (AI) of the omega-3 fatty acid, [alpha]-linolenic acid, during pregnancy is 1.4 g/d and during lactation 1.3 g/d (Natl. Academy of Sciences 2002). EPA and DHA can contribute up to 10% of the AI for [alpha]-linolenic acid. Therefore, the effective AI for EPA plus DHA for pregnant and lactating women is 0.14 and 0.13 g/d, respectively (Natl. Academy of Sciences 2002).

Shim, S.M., Santerre, C.R., Burgess, J.R., and Deardorff, D.C. 2003. Omega-3 fatty acids and total polychlorinated biphenyls in 26 dietary supplements. *J. Food Science* 68(8): 2436.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 17

data. The values that result from this calculation (*see* Appendix 3) using 2005 projected U.S. census data (as used in the IOM Guiding Principles report) and the AIs for ALA are 1.3 g/d for ALA and 130 mg/d for DHA and EPA (*i.e.*, 10% of the total *n-3* fatty acids intake per the IOM Macronutrients Report) . These values are the basis of the nutrient content claims proposed in this notification.

Under the FDAMA, because these nutrient levels are identified for DHA, EPA, and ALA in an authoritative statement, nutrient content claims properly must be authorized for each pursuant to this notification. 21 U.S.C. §343(r)(2)(G)(i).

BALANCED REPRESENTATION OF SCIENTIFIC LITERATURE RELATING TO  
NUTRIENT LEVELS TO WHICH PROPOSED CLAIMS REFER

Total *n-3* fatty acids intake, based upon data from the Continuing Survey of Food Intakes by Individuals (1994-96, 1998), for men and women ranges from 1.3-1.8 g/d and 1.0-1.2 g/d, respectively. IOM Macronutrients Report at 8-45. The average intake of *n-3* PUFAs is approximately 0.7% of energy. *Id.*

The median intake of ALA ranges from approximately 1.2-1.6 g/d for men and 0.9-1.1 g/d for women. IOM Macronutrients Report at 8-45.

The IOM Macronutrients Report established AIs for ALA for persons four years and older based on the highest median intakes of ALA among age/gender segments of the U.S. population where a deficiency is basically nonexistent in free-living individuals. IOM Macronutrients Report at 8-37. This report further recommended that DHA and EPA can contribute up to 10% of the total *n-3* fatty acids intake. *Id.*

The AIs of ALA for each age/gender segment of the population provided in the IOM Macronutrients Report were used to calculate a DV according to the formula provided in the IOM Guiding Principles Report. As noted above, the resulting values are 1.3 g for ALA and 130 mg for DHA and EPA.

FDA's Guidance Document specifies the agency's expectation that, as part of the balanced representation of the scientific literature, a bibliography on the topic of the claims would be compiled and submitted. Chapter 8 of the IOM Macronutrients Report presents a balanced summary of the scientific literature supportive of the nutrient levels identified therein for DHA, EPA, and ALA. The chapter provides the basis for the authoritative statements from which this notification derives. The bibliography from Chapter 8 of the IOM Macronutrients Report is attached to this notification as Appendix 4. As noted previously, the AI of ALA and

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 18

the 10% contribution of DHA and EPA are based on avoidance of fatty acid deficiency symptoms (*e.g.*, dermatitis), and the specific references cited in Chapter 8 that pertain directly to this notification (*i.e.*, are directly applicable to the authoritative statements) are noted below:

- Bjerve, K.S., Mostad, I.L. and Thoresen, L. 1987. Alpha-linolenic acid deficiency in patients on long-term gastric-tube feeding: Estimation of linolenic acid and long-chain unsaturated n-3 fatty acid requirement in man. *Am. J. Clin. Nutr.* 45:66.
- Bjerve, K.S., Thoresen, L, Mostad, I.L. and Alme, K. 1987. Alpha-linolenic acid deficiency in man: Effect of essential fatty acids on fatty acid composition. *Adv. Prostaglandin Thromboxane Leukot Res.* 17:862.
- Bjerve, K.S., Thoresen, L. and Børsting, S. 1988. Linseed and cod liver oil induce rapid growth in a 7-year-old girl with n-3 fatty acid deficiency. *JPEN J. Parenter. Enteral Nutr.* 12:521.
- Bjerve, K.S. 1989. n-3 Fatty acid deficiency in man. *J. Intern. Med.* 225:171.
- Bjerve, K.S., Fischer, S., Wammer, F. and Egeland, T. 1989.  $\alpha$ -Linolenic acid and long-chain  $\omega$ -3 fatty acid deficiency: Effect on lymphocyte function, plasma and red cell lipids, and prostanoid formation. *Am. J. Clin. Nutr.* 49:290.
- Holman, R.T., Johnson, S.B. and Hatch, T.F. 1982. A case of human linolenic acid deficiency involving neurological abnormalities. *Am. J. Clin. Nutr.* 35:617.

A search of the existing literature revealed no additional reports describing patients with essential fatty acid deficiency symptoms that responded to exogenous sources of ALA. This search is attached as Appendix 5.

In addition, the limited capacity of humans to convert ALA to DHA/EPA was noted in the IOM Macronutrients Report (at 8-25) and several other experts have observed that this limited capacity suggests that preformed DHA is a provisionally essential nutrient (see footnotes 1-4). These observations reinforce the IOM's conclusion that 10% of the total n-3 fatty acids intake marked by the AI for ALA can be provided by DHA/EPA

WORDING AND QUALIFYING LEVELS FOR PROPOSED NUTRIENT CONTENT CLAIMS

The exact words of the proposed claims will state each in a manner that is an accurate representation of the authoritative statement, and that will enable the public to comprehend the

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 19

information provided and to understand the relative significance of such information in the context of a total daily diet.

The authoritative statements from the IOM Macronutrients Report, as quoted above, identify nutrient levels to which the proposed claims refer. The nutrient levels for ALA are identified as AIs for 13 distinct age/gender segments of the population ranging from 0.9 g/d for boys and girls age 4-8 years, to 1.6 g/d for males aged 14 years and above. The nutrient level for DHA and EPA is identified as 10% of the total *n-3* fatty acids intake and of these AIs. Moreover, as noted previously, the IOM Guiding Principles Report recommends weighting by population in arriving at a DV for a nutrient. Thus, the nutrient content claims proposed below would refer to the nutrient levels identified in the IOM Macronutrients Report, weighted by population.

The wording (but not the qualifying level) of nutrient content claims authorized by 21 C.F.R. §101.54(b) are proposed to characterize the level of DHA and EPA, and the wording (and the qualifying levels) of nutrient content claims authorized by 21 C.F.R. §101.54(b), (c), and (e) are proposed to characterize the levels of ALA, in conventional foods and dietary supplements based upon population weighted values of 130 mg/d (DHA/EPA) and 1.3 g/d (ALA). These values are calculated from nutrient levels identified in the IOM Macronutrients Report, as adjusted according to the IOM Guiding Principles Report. Specifically, the following claims are proposed for use in labeling a conventional food or dietary supplement containing a qualifying nutrient level:

- “High”-Type Claims

high in DHA omega-3 / high in EPA omega-3 / high in ALA omega-3 / rich in DHA omega-3 / rich in EPA omega-3 / rich in ALA omega-3 / excellent source of DHA omega-3 / excellent source of EPA omega-3 / excellent source of ALA omega-3

- “Good Source”-Type Claims

good source of ALA omega-3 / contains ALA omega-3 / provides ALA omega-3

- “More”-Type Claims

more ALA omega-3 / fortified with ALA omega-3 / enriched with ALA omega-3 / added ALA omega-3 / extra ALA omega-3 / plus ALA omega-3

The parenthetical, “(an omega-3),” could be substituted for “omega-3” in each of the claims. Also, the terms “omega-3 DHA,” “omega-3 EPA,” and “omega-3 ALA” could be used

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 20

alternatively to name the nutrients.<sup>35</sup> For the consumer educational reasons discussed above and for consistency with evolving industry practice, it is imperative to include both the specific *n*-3 fatty acid (*i.e.*, “DHA”/“EPA”/“ALA”) and “omega-3” in naming the nutrient.

For DHA and EPA, “high”-type claims will characterize products containing 130 mg or more DHA/EPA per reference amount customarily consumed (RACC) (*i.e.*, 100% of 130 mg).<sup>36</sup> This is a departure from the qualifying level for such claims typical under 21 C.F.R. §101.54(b) but, as discussed below, is warranted. For ALA, “high”-type claims will characterize products containing 260 mg or more of ALA (*i.e.*, 20% of 1.3 g) per RACC). This is consistent with the qualifying level typical under 21 C.F.R. §101.54(b).

“Good source”-type claims are not proposed to characterize DHA/EPA content. For ALA, “good source”-type claims will characterize products containing 130 mg or more of ALA (*i.e.*, 10% of 1.3 g) per RACC. This is consistent with the qualifying level typical under 21 C.F.R. §101.54(c).

“More”-type claims are not proposed to characterize DHA/EPA content. For ALA, “more”-type claims will characterize products containing at least 130 mg (*i.e.*, 10% of 1.3 g) more ALA per RACC than an appropriate reference food. This is consistent with the qualifying level typical under 21 C.F.R. §101.54(e).

“High”-type and “good source”-type claims about DHA, EPA, and ALA content will be accompanied by one of the following statements:

- Contains \_\_\_ mg of [DHA/EPA/ALA] per serving, which is \_\_\_% of the Daily Value for [{DHA/EPA (130 mg)} or {ALA (1.3 g)}].
- Contains \_\_\_% of the Daily Value for [DHA/EPA/ALA] per serving. The Daily Value for [{DHA/EPA is 130 mg} or {ALA is 1.3 g}]

<sup>35</sup> “Omega-3 DHA” and “omega-3 EPA” are terms used in CRN’s Omega-3 Working Group voluntary monograph, available at <<http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf>>.

<sup>36</sup> Such use of “high”-type claims is consistent with the agency’s own informal characterization of the level of *n*-3 fatty acids in fish: “... fish and other seafood long have been considered to be good sources of protein with the added advantage of being low in saturated fat and high in healthy omega-3 fatty acids.” *Advice For Women Who Are Pregnant, Or Who Might Become Pregnant, and Nursing Mothers, About Avoiding Harm To Your Baby Or Young Child From Mercury in Fish and Shellfish* (available at <<http://www.fda.gov/oc/opacom/mehgadvisory1208.html>>) (advising pregnant women to avoid shark, swordfish, king mackerel and tilefish that contain potentially harmful levels of mercury, but to eat other types of fish in moderation for their health benefits).

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 21

“More”-type relative claims about ALA content will include and be accompanied by statements such as the following:

- “\_\_% [10% or greater] more of the Daily Value for ALA per serving than [reference food]. This product contains \_\_ mg ALA omega-3 per serving, which is \_\_% of the Daily Value for ALA omega-3 (1.3 g). [Reference food] contains \_\_ mg ALA omega-3 per serving.”<sup>37</sup>

As noted, the qualifying levels and accompanying statements for the proposed claims are based on population weighted nutrient levels, as recommended in the IOM Guiding Principles Report. However, to the extent that FDA deems this approach premature, the qualifying levels and accompanying statements alternatively could be based on the nutrient levels identified in the IOM Macronutrients Report without population weighting, *i.e.*, 160 mg for DHA and EPA, and 1.6 g (1,600 mg) for ALA.

The “high”-type claims proposed for DHA and EPA, as noted, are premised on setting the qualifying level for such claims at 100% of the population-weighted nutrient level identified in the IOM Macronutrients Report. Limiting such claims for DHA and EPA content to conventional food and dietary supplement sources containing at least 100% of this value (*i.e.*, 130 mg) is warranted for several, practical reasons:

1. The amount of DHA/EPA per serving of products eligible to bear a “high”-type claim would be consistent with the amount of these *n-3* fatty acids currently recommend for reducing the risk of CHD.

The AHA has concluded that intakes of DHA plus EPA from 0.5 to 1.8 g/d significantly reduce subsequent cardiac and all-cause mortality in CHD patients (*see* footnote 30 above), and recommends that all healthy adults consume 1-2 servings of fish (particularly fatty fish) per week to “confer cardioprotective effects.”<sup>38</sup> Typical recommendations for DHA/EPA for healthy individuals range from 300 – 500 mg/d. Limiting nutrient content claims for DHA/EPA to foods and dietary supplements that contain a minimum of or 130 mg per RACC ensures that only products that make a substantial contribution to such recommended intake levels are eligible to bear the claim. This approach also is consistent with the fact that DHA/EPA is distributed very narrowly in the food supply. This being the case, the recommended intake of LC *n-3* PUFAs must come from a small number of “high” sources of these nutrients (*e.g.*, fish), rather than a

<sup>37</sup> These accompanying statements for “high”-, “good source”-, and “more”-type claims are modeled on the accompanying statements authorized in FDA’s Choline Document.

<sup>38</sup> Krauss, R.M. *et al.* 2000. AHA Dietary Guidelines. Revision 2000. A statement for health care professionals from the Nutrition Committee of the American Heart Association. *Circulation* 102:2284.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 22

wide variety of less concentrated sources. Therefore, it seems inadvisable to allow the relatively few foods that otherwise would qualify for "high"-type, "good source"-type, or "more"-type claims to bear such designations because their cardioprotective contributions would be relatively modest.

2. Use of the nutrient content claim will differentiate the "fatty" varieties of fish from their leaner (less cardioprotective) counterparts.

As noted above, the AHA has emphasized fatty fish in their dietary guideline, recommending the consumption of 1-2 servings of this food per week. Limiting nutrient content claims for DHA/EPA to foods or dietary supplements that contain a minimum of 130 mg per RACC will allow industry to call attention to fish given highest priority by AHA. Specifically, varieties of fish that would qualify for "high"-type claims for both DHA and EPA include salmon, tuna, herring, sardines, trout and others. *See* Table 1 below.

3. Foods fortified with DHA and/or EPA will be assured of providing significant amounts of these nutrients, and practical constraints will limit the number of foods that can be fortified. This approach is consistent with the scientific criteria for fortification as recommended in Chapter 6 of the IOM Guiding Principles Report.

Limiting DHA/EPA content claims to "high"-type claims will provide a strong incentive for industry to use only meaningful amounts of DHA/EPA when choosing to fortify conventional foods and to formulate dietary supplements. This approach will prohibit foods and supplements supplying smaller, inconsequential amounts of DHA/EPA from calling attention to the nutrients in labeling claims.

Furthermore, the addition of LC *n*-3 PUFAS to foods is limited by practical considerations. DHA/EPA are highly susceptible to oxidation so that shelf life and packaging constraints are significant. Some sources of these essential fatty acids may also impart objectionable organoleptic properties to food vehicles, and economic constraints may also be limiting. These practical constraints will make fortification of most foods with DHA/EPA infeasible, and will provide inherent safeguards that the use of such fortification will be limited in scope and nutritionally appropriate.

#### OTHER REQUIREMENTS

Foods and dietary supplements bearing the proposed nutrient content claims will have to comply with all relevant provisions of 21 C.F.R. §101.13.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 23

ANALYTICAL METHODOLOGY

The amount of DHA, EPA, and ALA contained in a food or dietary supplement that may be a candidate for bearing a proposed nutrient content claim can be ascertained by several gas chromatography methods, including the AOAC International (AOAC) Official Method 991.39, Fatty Acids in Encapsulated Fish Oils and Fish Oil Methyl and Ethyl Esters. AOAC Official Method 991.39 is attached as Appendix 6 to this notification.

EXEMPLARY FOOD AND DIETARY SUPPLEMENT SOURCES OF DHA/EPA/ALA ELIGIBLE FOR PROPOSED CLAIMS

DHA and EPA are present in significant amounts in most cold-water fish (e.g., salmon, tuna, flounder, and sardines). ALA is present in significant amounts in several common vegetable oils (e.g., canola, flaxseed, soybean) and food sources (e.g., walnuts, flaxseeds). The DHA, EPA, and ALA *n-3* fatty acid content of common foods that contain these nutrients and the nutrient content claims they will qualify for under this notification are provided in Table 1 below.

Table 1  
DHA/EPA/ALA Content\* and Claim Eligibility of Selected Fish, Foods, and Oils

Food	DHA		EPA		ALA**	
	mg per RACC	Claim	Mg per RACC	Claim	mg per RACC	Claim
<b>FISH (raw)</b>						
Striped bass	497	High	144	High	13	-
Bluefish	441	High	214	High	0	-
Carp	97	-	202	High	230	Good source
Catfish	176	High	57	-	82	-
Cod, Atlantic	102	-	54	-	1	-
Cod, Pacific	115	-	68	-	2	-
Dolphin fish	75	-	17	-	4	-
Fish, flatfish (flounder and sole)	90	-	79	-	7	-
Fish Fillet, fried (91g)	N/A	-	N/A	-	446	High
Fish sticks	108	-	73	-	146	Good source
Grouper	187	High	23	-	9	-
Haddock	107	-	50	-	2	-
Halibut	248	High	60	-	118	-

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 24

Herring	733	High	603	High	88	-
Mackerel	1,191	High	763	High	135	Good source
Ocean perch	179	High	68	-	48	-
Pike, Northern	63	-	28	-	18	-
Pike, Walleye	191	High	73	-	12	-
Pollock, Atlantic	297	High	60	-	0	-
Pompano, Florida	334	High	149	High	0	-
Rockfish, Pacific	173	High	120	-	14	-
Roughy, Orange	0	-	1	-	1	-
Salmon, Atlantic, wild	948	High	273	High	251	Good source
Salmon, Atlantic, farmed	1,099	High	525	High	80	-
Salmon, coho, wild	558	High	365	High	133	Good source
Salmon, pink	498	High	356	High	29	-
Sardines, canned in oil, drained	280	High	260	High	273	High
Sea bass	369	High	137	High	0	-
Shark	448	High	268	High	24	-
Snapper	221	High	43	-	3	-
Sturgeon	79	-	165	High	85	-
Sunfish	61	-	31	-	9	-
Surimi	205	High	133	High	6	-
Trout	449	High	172	High	132	Good source
Tuna, bluefin	757	High	241	High	0	-
Tuna, canned in water	294	High	128	-	39	-
Whitefish	800	High	269	High	156	Good source
<b>FOODS</b>						
Flaxseed	0	-	0	-	5,437	High
DHA-enriched egg***	154	High	3	-	87	-
Walnuts	0	-	0	-	2,574	High
<b>OILS</b>						
Canola oil	0	-	0	-	1,302	High
Cod liver oil	1,492	High	938	High	127	-
Corn oil	0	-	0	-	95	-
Cottonseed oil	0	-	0	-	27	-

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 25

Flaxseed oil	0	-	0	-	7,249	High
Menhaden oil	1,164	High	1,791	High	203	Good source
Olive oil	0	-	0	-	107	-
Peanut oil	0	-	0	-	0	-
Sardine oil	1,449	High	1,379	High	180	Good source
Sesame oil	0	-	0	-	41	-
Soybean oil	0	-	0	-	925	High
Sunflower oil	0	-	0	-	27	-
Walnut oil	0	-	0	-	1,414	High

\*Source: USDA National Nutrient Database for Standard Reference, Release 16 (July 2003).

\*\*Based on total (undifferentiated) 18:3 fatty acids.

\*\*\*Abril, J.R., Barclay, W.R., Abril, P.G. Safe use of microalgae (DHA GOLD) in laying hen feed for the production of DHA-enriched eggs. CAB International 2000. *Egg Nutrition and Biotechnology* (eds Sim, S., Nakai, S., Guenter, W.). Chapt. 15, pp 197-202.

Dietary supplement sources of DHA and EPA include salmon oil, tuna oil, menhaden oil,<sup>39</sup> cod liver oil, and herring oil. Capsule sizes typically range from 400 mg to 2000 mg.

#### SUPPORT FOR NOTIFICATION

Sectors of industry marketing foods that are candidates for the proposed nutrient content claims have expressed keen interest in this notification. For example, Alaskan and Atlantic salmon purveyors, in addition to the notifiers, are eager to use the claims in labeling their fresh and smoked products. An example of a Ducktrap™ Sliced Cold Smoked Atlantic Salmon product label that would bear a claim is attached as Appendix 7 to this notification.

#### CONCLUSION

This notification proposes nutrient content claims for DHA omega-3, EPA omega-3, and ALA omega-3. The claims, which will be used in labeling conventional foods and dietary supplements containing a qualifying level of a nutrient, are based on authoritative statements in the IOM Macronutrients Report that identify a level for each nutrient, which has been translated into a population-weighted value in accordance with a calculation recommended in the IOM Guiding Principles Report. For DHA and EPA omega-3, “high”-type claims will characterize

<sup>39</sup> FDA has published a tentative final rule that amends the conditions under which uses of menhaden oil in conventional foods (but not in dietary supplements) will be affirmed as generally recognized as safe (GRAS) under 21 C.F.R. §184.1472. 69 *Fed. Reg.* 2313 (Jan. 15, 2004). Under the rule, menhaden oil may not be used in combination with any other added oil that is a significant source of DHA or EPA. The regulation already sets limits on menhaden oil in specific food categories to ensure that total intake of DHA and EPA does not exceed 3 g per person per day. The tentative final rule does not affect the merits of this notification.

Letter to Office of Nutritional Products, Labeling  
and Dietary Supplements

January 16, 2004

Page 26

products containing at least 100% of this value (*i.e.*, 130 mg). For ALA omega-3, “high”-type, “good source”-type, and “more”-type claims will characterize products containing, respectively, at least 20% (*i.e.*, 260 mg), 10% (*i.e.*, 130 mg), and 10% more (relative to a reference product) of this value (*i.e.*, 1.3 g).<sup>40</sup> Each claim will be accompanied by a statement(s) that will enable the public to comprehend the information provided and to understand its relative significance in the context of a total daily diet.

Pursuant to the legal authority and reasons specified above, we urge favorable acceptance of this notification and authorization of the proposed nutrient content claims.

Respectfully submitted,



Michael J. O'Flaherty

---

<sup>40</sup> As noted, if FDA determines use of the population-weighted values to be inappropriate, the nutrient content claims simply will refer instead to the unweighted levels identified in the IOM Macronutrients Report (*i.e.*, 160 mg for DHA and EPA omega-3 and 1.6 g for ALA omega-3), using the same percentages (*i.e.*, 100% for DHA and EPA omega-3 and 20%/10%/10% more for ALA omega-3) to set qualifying levels for the claims. In this eventuality, in keeping with the streamlined procedures contemplated by Congress for FDAMA nutrient content claim notifications, rather than rejecting the notification, which seems unwarranted on this basis, FDA simply may convey its determination directly to the undersigned and memorialize it in the agency's letter (*e.g.*, FDA's Choline Document) informing the public about parameters for the claims.