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RE: Petition for a Health Claim for Eicosapentaenoic Acid and Docosahexaenoic Acid and Reduction of Blood Pressure in the General Population (Docket No. FDA-2014-Q-1146)

Dear Dr. Rice:

This letter responds to the health claim petition submitted by the Global Organization for EPA and DHA Omega-3s (GOED or you) pursuant to sections 403(r)(4) and 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4) and 343(r)(5)(D)). The Food and Drug Administration (FDA or the agency) received your petition on April 24, 2014.<sup>1</sup> The petition requested that FDA authorize a health claim for the relationship between the consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and reduction of blood pressure (BP). Based on discussions with you after we received the petition,<sup>2</sup> we reviewed it as a petition for a qualified health claim in accordance with the July 10, 2003 Task Force Final Report on the Consumer Health Information for Better Nutrition Initiative.<sup>3</sup>

The petition proposed the following model claims to be used on the labels or in the labeling of conventional foods and dietary supplements containing EPA and DHA:

EPA and DHA help lower blood pressure in the general population.

EPA and DHA reduce BP, a risk factor for CHD (coronary heart disease).

EPA and DHA reduce the risk of CHD.

Research shows that EPA and DHA may be beneficial for moderating BP, a risk factor for CHD.

Convincing scientific evidence indicates that EPA and DHA help lower blood pressure in the general population, with comparable reductions to those achieved with other diet and lifestyle interventions.

FDA filed the petition for comprehensive review on August 8, 2014 and posted the petition on the FDA website for a 60-day comment period, consistent with FDA's guidance on the procedures for the submission of qualified health claim petitions ("qualified health claim

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<sup>1</sup> This petition is a revision of an earlier petition on the same subject received by FDA on December 5, 2013. GOED submitted the revised petition after being notified by FDA that the original petition was incomplete and did not meet the health claim petition requirements in 21 CFR 101.70.

<sup>2</sup> See FDA Filing Letter for GOED Health Claim Petition, Docket No. FDA-2014-Q-1146-0002, <https://www.regulations.gov/document?D=FDA-2014-Q-1146-0002>.

<sup>3</sup> See FDA, "Consumer Health Information for Better Nutrition Initiative: Task Force Final Report," July 10, 2003 [<https://www.fda.gov/food/food-labeling-nutrition/consumer-health-information-better-nutrition-initiative-task-force-final-report>] (accessed May 17, 2019).

procedures guidance”).<sup>4</sup> The agency received a total of 22 comments in response to the petition. Comments were from industry, academia, food and health organizations, and individual consumers. FDA considered all 22 comments in its evaluation of the petition.

Of the 22 comments, six requested an extension of the 60-day comment period. In response, FDA extended the comment period for 45 days. The remaining comments included nine statements of support for the petition without additional information or substantiation. These comments stated that EPA and DHA (EPA/DHA) are important nutrients that lower blood pressure and that many people have low intakes of EPA/DHA. These comments also noted that consumers should have information about the health effects of EPA/DHA and that EPA/DHA supplements are safe and inexpensive. Two comments opposed to the petition were submitted, also without additional information or supporting evidence. These comments stated that dietary supplements should not bear health claims due to concerns of efficacy and safety.

Five comments provided additional information and evidence for use in FDA’s consideration of the petition. One of these comments did not express support for or opposition to the petition but did submit information on EPA/DHA intake levels to assist evaluation of the petition. Four comments stated that the petitioner had satisfactorily demonstrated a relationship between the consumption of EPA and DHA and reduction of blood pressure. These comments provided additional scientific studies and data, which were used in our evaluation of the relationship between EPA and DHA omega-3 fatty acids, blood pressure, and hypertension risk (see Section II of this letter).

This letter sets forth the results of FDA’s scientific review of the evidence for the qualified health claims requested in the petition. As explained in this letter, FDA has determined that the current scientific evidence supports the use of certain qualified health claims in the labeling of conventional foods and dietary supplements that contain EPA and DHA omega-3 fatty acids, concerning the relationship between these substances and reducing the risk of hypertension and coronary heart disease (CHD) by lowering blood pressure. Accordingly, this letter discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for the use of qualified health claims, for both conventional foods and dietary supplements, about consumption of EPA and DHA omega-3 fatty acids and reduced risk of hypertension and CHD through the intermediate link of lowering blood pressure. For brevity, these claims will be referred to as “the EPA/DHA qualified health claims” (or “an EPA/DHA qualified health claim” when referring to an individual claim) in this letter.<sup>5</sup> The “Conclusions” section of this letter contains the qualified health claim language for which FDA intends to exercise enforcement discretion.

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<sup>4</sup> See FDA, “Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements,” July 10, 2003

[<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-interim-procedures-qualified-health-claims-labeling-conventional-human-food-and>] (accessed May 17, 2019).

<sup>5</sup> As used in this letter, “EPA/DHA qualified health claim” is not intended to refer to any qualified health claim for EPA and DHA other than the ones that are the subject of this letter.

## I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and reduced risk of contracting a particular disease or health-related condition.<sup>6</sup> In a review of a qualified health claim, the agency first identifies the substance and the disease or health-related condition that are the subject of the proposed claim, as well as the population to which the claim is targeted.<sup>7</sup>

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether credible scientific evidence supports a relationship between the substance and the disease or health-related condition.<sup>8</sup> At this stage, the agency separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.<sup>9</sup>

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,<sup>10</sup> review articles,<sup>11</sup> and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-

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<sup>6</sup> See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA’s interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

<sup>7</sup> See FDA, “Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final,” January 2009 (“guidance on scientific evaluation of health claims”) [<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims>] (accessed May 17, 2019).

<sup>8</sup> For brevity, “disease” will be used as shorthand for “disease or health-related condition” in the rest of this letter except when distinguishing between the two or quoting or paraphrasing a regulation that uses the longer term.

<sup>9</sup> In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (e.g., disease). Intervention studies provide the strongest evidence for an effect. See *supra*, note 7.

<sup>10</sup> A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

<sup>11</sup> Review articles summarize the findings of individual studies.

analyses, review articles, and similar publications<sup>12</sup> to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.<sup>13</sup> If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine (IOM), 2005a). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker, 1991; National Research Council (NRC), 2011). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have that disease, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would

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<sup>12</sup> Other examples include book chapters, abstracts, letters to the editor, and committee reports.

<sup>13</sup> Although FDA does not generally use meta-analyses in its health claim evaluations for the reasons discussed in the text, the agency will include a meta-analysis in its scientific evaluation if the meta-analysis was conducted with pooled data from all the publicly available studies from which scientific conclusions can be drawn (based on the criteria in FDA's guidance on scientific evaluation of health claims) and the statistical analyses were properly conducted. See *supra*, note 7 [Section III.B, "Research Synthesis Studies"].

receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.<sup>14</sup> The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,<sup>15</sup> and the overall consistency<sup>16</sup> of the total body of evidence.<sup>17</sup> Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance-disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

## **A. Substance**

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food (defined to include both conventional foods and dietary supplements) or component of food (21 CFR 101.14(a)(2)). The petition identified EPA and DHA in combination as the substances that are the subject of the proposed claim. EPA and DHA are omega-3 fatty acids that are components of some fatty fish (primarily cold water fish), fish oils, other foods (e.g., seaweed), dietary supplements, and food ingredients (e.g., algal oils). Accordingly, the agency concludes that EPA and DHA omega-3 fatty acids are components of food and therefore meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

## **B. Disease or Health-Related Condition**

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition proposes model health claims about lowering blood pressure to reduce the risk of hypertension and coronary heart disease. Hypertension is a disease in which blood flows through blood vessels or arteries at higher than normal pressures.

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<sup>14</sup> See *supra*, note 7 [Section III.F].

<sup>15</sup> Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).

<sup>16</sup> Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B., The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300); See also Agency for Healthcare Research and Quality, “Systems to rate the scientific evidence” (March 2002) [<http://archive.ahrq.gov/clinic/epcs/sums/strengthsum.pdf>], defining “consistency” as “the extent to which similar findings are reported using similar and different study designs.”

<sup>17</sup> See *supra*, note 7 [Section III.F].

Hypertension is diagnosed when systolic blood pressure is  $\geq 140$  mmHg or diastolic blood pressure is  $\geq 90$  mmHg when measured on more than one occasion. Pre-hypertension occurs when systolic blood pressure is between 120-139 mmHg or diastolic blood pressure is between 80-89 mmHg.<sup>18</sup>

Blood pressure is the force of blood pushing against the walls of the arteries and blood vessels as the heart pumps blood. Hypertension, also called high blood pressure, is when this force against the artery walls is too high.<sup>19</sup> Pre-hypertension, where blood pressure is elevated (higher than normal) but not yet in the hypertensive range, increases the risk of developing hypertension in the future.<sup>20</sup> Pre-hypertension is a risk factor for hypertension, meaning that it is also a state of health leading to hypertension. Therefore, pre-hypertension is considered to be a health-related condition. In addition, pre-hypertension and hypertension are risk factors for other diseases, such as chronic kidney disease and cardiovascular disease (diseases of the heart and circulatory system, including coronary heart disease and stroke).<sup>21</sup> Thus, hypertension is a state of health leading to cardiovascular disease (CVD) and other diseases, as well as a disease in its own right. Because hypertension and pre-hypertension are both states of health leading to CVD and other diseases, they are also “health-related conditions” as defined in 21 CFR 101.14(a)(5).

Coronary heart disease (CHD) is one of the most common and serious forms of CVD and refers to diseases of the heart muscle and supporting blood vessels. A number of risk factors, including high blood total cholesterol, high low density lipoprotein (LDL) cholesterol levels, and high blood pressure, are associated with increased risk of developing CHD.<sup>22</sup> CHD is a disease as defined in 21 CFR 101.14(a)(5) because it involves damage to the heart and coronary arteries such that they do not function properly.<sup>23</sup>

### C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance that is the subject of a health claim is to be consumed at other than decreased dietary levels, the substance must be a food, a food ingredient, or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

For conventional foods, evaluating whether a substance is “safe and lawful” involves considering whether the substance (or, for substances that are inherent components of an ingredient, the ingredient containing the substance) is generally recognized as safe (GRAS), approved as a food

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<sup>18</sup> See NHLBI, “Your Guide to Lowering Blood Pressure” [[https://www.nhlbi.nih.gov/files/docs/public/heart/hbp\\_low.pdf](https://www.nhlbi.nih.gov/files/docs/public/heart/hbp_low.pdf)], pp. 2-3 (accessed August 3, 2018).

<sup>19</sup> See NHLBI, “High Blood Pressure” [<https://www.nhlbi.nih.gov/health-topics/high-blood-pressure>] (accessed August 3, 2018).

<sup>20</sup> See *supra*, note 18.

<sup>21</sup> See *supra*, notes 18-19.

<sup>22</sup> See NHLBI, “Ischemic Heart Disease” [<https://www.nhlbi.nih.gov/health-topics/ischemic-heart-disease>] (accessed May 17, 2019).

<sup>23</sup> See *supra*, note 22.

additive, or authorized by a prior sanction issued by FDA (21 CFR 101.70(f)). Dietary ingredients<sup>24</sup> in dietary supplements, however, are not subject to the food additive provisions of the Act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342). The applicable adulteration provisions of the Act require, for example, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))). Dietary ingredients that were not marketed in the United States before October 15, 1994, are also subject to the new dietary ingredient requirements in section 413 of the Act (21 U.S.C. 350b) and the corresponding adulteration provision in section 402(f)(1)(B) of the Act (21 U.S.C. 342(f)(1)(B)).

#### *EPA and DHA in Conventional Foods*

FDA has affirmed menhaden oil as GRAS with specific limitations on use to ensure that the total daily intake of EPA and DHA from conventional foods does not exceed 3 grams per person per day (g/p/d) (62 FR 30751; June 5, 1997) (codified at 21 CFR 184.1472). EPA and DHA are the major omega-3 fatty acids in fish oil and together comprise about 20 percent by weight of menhaden oil. FDA established maximum use levels of menhaden oil in certain food categories because of concerns over possible adverse effects of fish oil consumption on bleeding time, glycemic control, and LDL cholesterol (62 FR 30751 at 30757; June 5, 1997). In 2005, FDA published a final rule amending the GRAS affirmation regulation to reallocate the uses of menhaden oil in conventional food, while maintaining the total daily intake of EPA and DHA from menhaden oil at a level not exceeding 3 g/p/d (70 FR 14531; March 23, 2005) (codified at 21 CFR 184.1472). FDA placed specific limitations on the use of menhaden oil in food, including level of use, food categories, and the functional use of the ingredient, to ensure that the consumption of EPA and DHA from conventional food sources would not exceed 3 g/p/d. To further ensure that total intake of EPA and DHA from conventional food sources does not exceed 3 g/p/d, FDA also added a requirement that menhaden oil not be used as a food ingredient in combination with any other added oil that is a significant source of EPA and DHA.

FDA has received several GRAS notifications for food uses of other oils (e.g., algal oils and fish oils from species other than menhaden) that are also sources of EPA and/or DHA (GRAS Notice Nos. GRN000097, GRN000102, GRN000105, GRN000109, GRN000137, GRN000138, GRN000146, GRN000193, GRN000200, GRN000279, GRN000319, GRN000355, and GRN000553).<sup>25</sup> The GRAS notices for these oils proposed maximum use levels designed to keep total intake levels of EPA and DHA within the 3 g/p/d limit established in the regulation

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<sup>24</sup> The term “dietary ingredient” is defined in section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)) and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

<sup>25</sup> See FDA’s inventory of GRAS notices, available through links at <https://www.fda.gov/food/generally-recognized-safe-gras/gras-notice-inventory>.

specifying conditions under which menhaden oil is GRAS for use as a direct human food ingredient (21 CFR 184.1472). FDA responded without objection to these notifications.

Based on the data and information that FDA considered, which includes data and information that FDA relied upon in reaching its conclusions about the safety of EPA and DHA omega-3 fatty acids in the menhaden oil rulemakings, current usual intakes of the American general population, and the agency's recent review of adverse event reports and other scientific information for possible safety concerns, FDA concludes that the use of EPA and DHA, and sources of these substances -- such as menhaden oil, other fish oils, and algal oils -- as ingredients in conventional food is safe and lawful under 21 CFR 101.14(b)(3)(ii), provided that such use is consistent with FDA's GRAS regulation for menhaden oil (21 CFR 184.1472) and the conditions of use specified in other relevant GRAS notifications to which FDA did not object, including use limitations designed to ensure that daily intakes of EPA and DHA omega-3 fatty acids from conventional food sources do not exceed 3.0 g/day.

#### *Current Dietary Intake Levels*

Although some currently marketed dietary supplements provide a combined EPA and DHA intake of over 8 g/ day when taken as recommended in their labeling, current intake data indicate that for most of the population, total daily EPA and DHA intake is much lower. Data from NHANES 2009-2014 indicate that the mean total usual intake of EPA and DHA from conventional foods and dietary supplements for people age 4 years and older is 77 mg/day.<sup>26</sup>

#### *EPA and DHA in Dietary Supplements*

Under the Dietary Supplement Health and Education Act of 1994, dietary supplements that are not adulterated, misbranded, or otherwise in violation of applicable laws and regulations are lawful for sale in the United States. There is no current regulatory limit on the amount of EPA and DHA in dietary supplements.

In 2004, FDA considered the safety of EPA and DHA in dietary supplements as part of the agency's review of two petitions seeking qualified health claims about omega-3 fatty acids and reduced risk of coronary heart disease. Based in large part on the scientific evaluation in the 1997 GRAS affirmation final rule for the use of menhaden oil as a conventional food ingredient, the agency concluded that the use of EPA and DHA in dietary supplements is safe and lawful under 21 CFR 101.14(b)(3)(ii), provided that total daily intake of EPA and DHA from conventional food and dietary supplement sources does not exceed 3 g/day. As discussed earlier in this section, the 1997 GRAS affirmation final rule for menhaden oil concluded, based on an evaluation of the scientific literature available at that time, that intake of EPA and DHA over 3 g/day was not generally recognized as safe because of evidence that intake at such levels might lengthen bleeding time, increase LDL cholesterol, and adversely affect glycemic control in people with type 2 diabetes.

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<sup>26</sup> See "Memorandum to the File (Docket No. FDA-2014-Q-1146): Consumption estimates of EPA and DHA for individuals aged 4 years and older in the United States." (August 28, 2018).

Currently, dietary supplements are marketed with combined EPA and DHA content ranging from less than a milligram to 8 g/day. To evaluate whether dietary supplements at higher levels of EPA and DHA intake are safe and lawful, FDA has updated its safety review to examine more recent evidence regarding the effects of consuming EPA and DHA at levels above 3 g/day on glycemic control, blood cholesterol, and risk of excessive bleeding. After searching FDA's adverse event report database and evaluating relevant studies on EPA and DHA, we concluded that EPA and DHA intake up to 10 g/day appears to have no adverse effect on glycemic control, as measured by fasting blood glucose and HbA1c.<sup>27</sup> We further concluded that EPA and DHA intake does not appear to raise total cholesterol.<sup>28</sup> There is some evidence that EPA and DHA intake may raise LDL-cholesterol by approximately 2-4 mg/dL, but the studies are inconsistent, and there is also supportive, but not conclusive, evidence that EPA and DHA may reduce the risk of CHD by other mechanisms.<sup>29</sup> With regard to bleeding risk, we concluded that consumption of less than or equal to 5 grams/day of EPA and DHA does not increase the risk of excessive bleeding based on clinical trials that measured clinical outcomes such as bleeding episodes and blood loss.<sup>30</sup> Therefore, we conclude that dietary supplements that provide no more than 5 g/day EPA and DHA when used as recommended or suggested in their labeling are safe and lawful under 21 CFR 101.14(b)(3)(ii).

Above the 5 g/day level, however, there is not enough scientific evidence to draw a conclusion. Specifically, we could not draw any conclusions about bleeding risk associated with EPA and DHA intake at levels greater than 5 g/day because the published studies of the effects of EPA and DHA on risk of excessive bleeding did not evaluate doses at such higher intake levels.

Because the current scientific evidence does not show that dietary supplements that provide more than 5 g/day EPA and DHA are adulterated under the food safety provisions of the Federal Food, Drug, and Cosmetic Act, such products are lawful. Due to the lack of scientific evidence about risk of excessive bleeding at intakes of more than 5 g/day, however, we are unable to determine whether these products are safe within the meaning of the "safe and lawful" requirement for conventional foods and dietary supplement to bear a health claim (21 CFR 101.14(b)(3)(ii)). Because of the uncertainty about possible adverse effects on bleeding risk from consuming more than 5 grams EPA and DHA per day, FDA intends to consider, as a factor in the exercise of its enforcement discretion for any EPA/DHA qualified health claim, that dietary supplements bearing the qualified health claim provide no more than 5 g/day of EPA and DHA when used as labeled. In section IV, FDA describes this and other factors it plans to consider in the exercise of enforcement discretion for EPA/DHA qualified health claims.

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<sup>27</sup> See Memorandum to Docket No. FDA-2014-Q-1146: Survey of Comprehensive Reviews of the Effects of EPA and DHA Intake on Glycemic Control and Blood Cholesterol (June 17, 2019).

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

<sup>30</sup> See Memorandum to Docket No. FDA-2014-Q-1146: Review of Scientific Literature on EPA and DHA Intake and Risk of Excessive Bleeding (June 17, 2019).

## II. The Agency's Consideration of a Qualified Health Claim

The evidence included in the petition was for lowering blood pressure and reduced risk of hypertension. Lowering blood pressure is one of many mechanisms for lowering the risk of CHD. FDA and NIH have identified diastolic blood pressure (DBP) and systolic blood pressure (SBP) as surrogate endpoints for predicting risk of hypertension.<sup>31</sup> SBP and DBP are also surrogate endpoints for risk of CHD.<sup>32</sup> Since either elevated SBP ( $\geq 140$ mmHg) or DBP ( $\geq 90$  mmHg) can be used to diagnose hypertension, the reduction of either is beneficial in reducing the risk of hypertension (James et al., 2014; NHLBI, 2003). For the purposes of this review, the agency evaluated only studies that measured SBP, DBP, or incidence of hypertension. FDA did not evaluate the totality of the evidence for effects of EPA and DHA intake on other surrogate endpoints for CHD such as blood (serum or plasma) total cholesterol, blood (serum or plasma) LDL cholesterol, or other mechanisms of CHD risk. Rather, FDA evaluated the totality of the evidence for combined intake of EPA and DHA, which the petition describes as the substances that are the subject of the claim, and reducing the risk of hypertension and CHD through lowering SBP or DBP.

The petition cited 717 publications as evidence to substantiate the relationship for the proposed claims. These publications consisted of: 21 government documents; 7 reports, 29 review articles, 15 meta-analyses, 8 letters, 47 abstracts, 1 book chapter; 46 articles written in a foreign language without an English translation; 286 publications that evaluated the effect of intake of EPA, DHA, or both on blood pressure or risk of hypertension; and 260 publications describing studies that evaluated other substance-disease relationships or did not evaluate any substance-disease relationship.<sup>33</sup> The 286 publications evaluating the effect of EPA and DHA intake on blood pressure or risk of hypertension described a total of 277 studies, 245 intervention studies (discussed in Section II.B) and 32 observational studies (discussed in Section II.C). Comments on the petition cited 30 additional publications that were not already included in the petition. Of these 30 publications, there were 3 meta-analyses, 14 review articles, 5 books or book chapters, 1 letter, 2 government documents, and 3 other publications that did not evaluate the substance-disease relationship.<sup>34</sup> The remaining 2 publications (O'Sullivan et al., 2012; Skilton et al., 2013) were reports of observational studies that evaluated the relationship between EPA and DHA intake and blood pressure or risk of hypertension (discussed in Section II.C). In addition to the studies cited in the petition or in comments, FDA identified thirty publications<sup>35</sup> describing

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<sup>31</sup> FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Validated Surrogate Endpoint. 2017 Sep. [<https://www.ncbi.nlm.nih.gov/books/NBK453484/>] (accessed August 3, 2018). see *supra*, note 7 [Section III.C].

<sup>32</sup> *Id.*

<sup>33</sup> See "Memorandum to File (Docket No. FDA-2014-Q-1146): List of Publications Excluded from Review" (June 17, 2019).

<sup>34</sup> *Id.*

<sup>35</sup> Albert et al., 2015; Alfaddagh et al., 2017; Ansari et al., 2017; Augustine et al., 2014; Barbosa et al., 2017; Bosch et al., 2012; Carvalho et al., 2014; Chan et al., 2016a; Chan et al., 2016b; Clark et al., 2016; Clark et al., 2018; Elajami et al., 2017; Grieger et al., 2014; Harslof et al., 2014; Hlais et al., 2013; Kristensen et al., 2016; Kromhout et al., 2010; Lind et al., 2015; Logan and Spriet et al., 2015; Minihane et al., 2016; Moriyama et al., 2018; Nodari et

twenty-eight relevant intervention studies through a literature search for studies evaluating the relationship between EPA and DHA intake and blood pressure or risk of hypertension.

#### **A. Assessment of Review Articles, Meta-Analysis, Book Chapters, Letters, and Government Reports and Other Reports**

Although useful for background information, review articles, meta-analyses, book chapters, letters, and government reports do not contain sufficient information on the individual studies reviewed and, therefore, FDA could not draw any scientific conclusions from these sources. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., conventional food, dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, book chapters, letters, and government reports prevents the agency from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analyses, book chapter, letters, and government reports supplied by the comments and in the petition did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

#### **B. Assessment of Intervention Studies**

FDA evaluated 284 publications reporting on 273 intervention studies that represented three bodies of evidence related to the proposed health claims. These publications included studies investigating the relationship between (1) EPA intake and blood pressure or risk of hypertension; (2) DHA intake and blood pressure or risk of hypertension; and (3) intake of EPA and DHA combined and blood pressure or risk of hypertension.

Of these 273 intervention studies, conclusions could not be drawn from 169 for the reasons discussed below.<sup>36</sup>

In 24 studies, subjects consumed either only EPA<sup>37</sup> (15 studies) or only DHA<sup>38</sup> (9 studies). There were also three studies that contained both an EPA-only group and a DHA-only group, but

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al., 2011; Pase et al., 2015; Roncaglioni et al., 2013; Root et al., 2013; Soares et al., 2014; Su et al., 2015; Tavazzi et al., 2008; Witte et al., 2014; Wu et al., 2014.

<sup>36</sup> This section contains a general discussion of major flaws in the reports of intervention studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

<sup>37</sup> Croset et al., 1990; Dokholyan et al., 2012; Hagiwara et al., 2011; Haiden et al., 2012; Hall et al., 2008; Hamazaki et al., 1990; Harris et al., 2008; Iketani et al., 2013; Miyajima et al., 2001; Moriyama et al., 2013; Satoh et al., 2009; Shimizu et al., 1995; Takaki et al., 2011; Yamakawa et al., 2012; Yoshimura et al., 1987.

<sup>38</sup> Geppert et al., 2006; Harrison et al., 2004; Kelley et al., 2007; Neff et al., 2011; Sagara et al., 2011; Sanders et al., 2006; Stark et al., 2004; Surai et al., 2000; Theobald et al., 2007.

no group that consumed EPA and DHA combined.<sup>39</sup> Scientific conclusions about whether consuming EPA and DHA combined reduces the risk of hypertension cannot be drawn from these 27 studies because they were designed to test the independent effects of EPA or DHA on blood pressure, and not to test the effects of these two nutrients in combination. The physiological effects of a substance when consumed as a single nutrient may be different than its effects when consumed with other nutrients (IOM, 2005c; Sempos et al., 1999). Scientific conclusions about the substance-disease relationship cannot be drawn from studies that did not analyze whether intake of EPA and DHA combined is associated with risk of hypertension. Therefore, the 27 studies that evaluated intake of EPA or DHA as a single nutrient were eliminated from further review.<sup>40</sup>

Fifty-nine studies did not include a control group or other appropriate control to distinguish the effects of EPA and DHA on blood pressure from other factors that could affect blood pressure.<sup>41</sup> Without an appropriate control group, it cannot be determined if the changes in SBP or DBP were due to EPA and DHA intake or uncontrolled extraneous factors. Thus, scientific conclusions could not be drawn from these studies.

Twenty-nine studies<sup>42</sup> did not conduct statistical analysis to ensure an accurate comparison of results between the control and treatment groups. Statistical analysis is a critical factor in evaluating evidence for the substance-disease relationship because it provides the comparison between subjects consuming EPA and DHA and those not consuming EPA and DHA (i.e.,

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<sup>39</sup> Three studies (Mori et al., 1999, Grimsgaard et al., 1998, and Rontoyanni et al., 2012) had both EPA-only and DHA-only arms. The results of Mori et al., 1999, were also discussed in Woodman et al., 2002, Mori et al., 2003, and Mas et al., 2010.

<sup>40</sup> Thirteen of the 27 intervention studies that measured EPA only or DHA only contained other major flaws. For example, 10 studies did not include a control group or other appropriate control (Dokholyan et al., 2012; Hagiwara et al., 2011; Haiden et al., 2012; Hall et al., 2008; Iketani et al., 2013; Neff et al., 2011; Rontoyanni et al., 2012; Surai et al., 2000; Yamakawa et al., 2012; Yoshimura et al., 1987). One study (Moriyama et al., 2013) did not report a validated surrogate endpoint. Two studies (Croset et al., 1990; Hamazaki et al., 1990) did not conduct statistical analysis to ensure an accurate comparison of results between the control and treatment groups.

<sup>41</sup> Agouridis et al., 2012; Benito et al., 2006; Bhise et al., 2005; Bitzur et al., 2010; Caron-Dorval et al., 2008; Celik et al., 2008; Chin and Dart, 1994; Cicero et al., 2010; Clark et al., 2016; Clark et al., 2018; Damsgaard et al., 2008; Dangardt et al., 2010; De Caterina et al., 1993; de Jong et al., 2011; Deferne and Leeds, 1992; Delgado-Pando et al., 2014; Dixit et al., 2004; Doenyas-Barak et al., 2012; Ernst et al., 1988; Ernst et al., 1991; Farrell et al., 1998; Fiedler et al., 2005; Geppert et al., 2008; Grossman et al., 1993; Hackman et al., 2006; Hamazaki et al., 1984; Kappus et al., 2011; Kasim et al., 1988; Kho et al., 1989; Laidlaw and Holub, 2003; Leng et al., 1998; Lok et al., 2012; Madden et al., 2007; Manor et al., 2013; Olivieri et al., 1988; Parinyasiri et al., 2004; Rolf et al., 1990; Rose and Holub, 2006; Russo et al., 1995; Sanders and Hinds, 1992; Sanders et al., 1981; Santos et al., 2000; Schmidt et al., 1990; Schmidt et al., 1992; Simpson et al., 1991; Singer et al., 1983; Singer et al., 1984a; Singer et al., 1985a; Singer et al., 1985b; Singer et al., 1985c; Singer et al., 1990a; Singer et al., 1991; Singer et al., 1993; Surai et al., 2000; Svensson et al., 2004; Vakhapova et al., 2011; Valdivielso et al., 2009; Weisser et al., 1990; Yam et al., 2002; Yosefy et al., 1999.

<sup>42</sup> Bach et al., 1989; Bennett et al., 1995; Chan et al., 2002; Davidson et al., 1989; Dusing et al., 1990; Ebrahimi et al., 2009; Freund-Levi et al., 2006; Gans et al., 1990; Grundt et al., 1995; Haglund et al., 1990; Haines et al., 1986; Hellsten et al., 1993; Kristensen et al., 1987; Mackness et al., 1994; Nodari et al., 2011; Oldendzki et al., 2011; Passfall et al., 1993; Prisco et al., 1998; Sakamoto et al., 2000; Schaefer et al., 1996; Simao et al., 2010; Simao et al., 2012; Singer et al., 1984b; Singer et al., 1986a; Singer et al., 1986b; Szabo de Edelenyi et al., 2012; Vericel et al., 1999; Witte et al., 2014; Yosefy et al., 1996.

control group) to determine whether the study showed a reduction in blood pressure or risk of hypertension. Hence, scientific conclusions could not be drawn from these studies.

Twenty-two studies<sup>43</sup> did not measure incidence of hypertension or a validated surrogate endpoint of hypertension (SBP or DBP).<sup>44</sup> Because these studies did not measure incidence of hypertension or a validated surrogate endpoint of hypertension, no scientific conclusions about the relationship between EPA and DHA consumption and blood pressure or risk of hypertension could be drawn from them.

For two studies, the baseline blood pressure values were very different between the fish oil and control groups (Andreassen et al., 1997; Mills et al., 1989). When baseline values are significantly different between groups in a parallel study, this difference must be accounted for in the statistical analysis; otherwise, it is not possible to determine if differences between groups at the end of the study were due to the intervention or to the differences that already existed at the beginning of the study. Because this study did not properly adjust for the difference in baseline values, an accurate comparison of the results between the two groups is not possible. Thus, no scientific conclusions about a relationship between EPA and DHA and blood pressure or risk of hypertension could be drawn from these studies.

Two studies exposed subjects to experimental conditions that do not normally occur in everyday life and therefore are not relevant to the U.S. population (lower body negative pressure, cold pressor test) (Mills et al., 1990; Hughes et al., 1991). Because these studies do not represent real-world conditions, scientific conclusions about the relationship between EPA and DHA consumption and blood pressure or risk of hypertension could not be drawn from them.

To determine the independent effects of EPA and DHA in combination on blood pressure, intervention studies must control for the amount of sodium and potassium in the diet because both of these nutrients influence blood pressure. Adding EPA and DHA to the usual diet in the form of dietary supplements should not result in significant changes in the amount of sodium and potassium that subjects consume; thus, we did not eliminate such intervention studies if they did not report the levels of sodium and potassium consumed by the subjects. However, twenty-eight intervention studies<sup>45</sup> had designs that could lead to significant changes in the amount of sodium

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<sup>43</sup> Alexopoulos et al., 2004; Augustine et al., 2014; Badalamenti et al., 1997; Badalamenti et al., 1995; Bilo et al., 1988; Branten et al., 2002; Carvalho et al., 2014; de Fijter et al., 1995; Delarue et al., 2003; Lahoz et al., 1999; Larnkjaer et al., 2006; Matsumura et al., 2012; McVeigh et al., 1993; Nishizawa et al., 2006; Shah et al., 2007; Su et al., 2015; van der Heide et al., 1990; van der Heide et al., 1992; van der Heide et al., 1993; Ventura et al. 1993; Walser et al., 2006; Walser et al., 2008.

<sup>44</sup> See FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Validated Surrogate Endpoint. 2017 Sep. [<https://www.ncbi.nlm.nih.gov/books/NBK453484/>] (accessed August 3, 2018). See also Rasnake CM, Trumbo PR, Heinonen TM. Surrogate endpoints and emerging surrogate endpoints for risk reduction of cardiovascular disease. *Nutr Rev* 2008;66(2):76-81. See also Desai M, Stockbridge N, Temple R. Blood pressure as an example of a biomarker that functions as a surrogate. *AAPS J* 2006;8(1):E146-152.

<sup>45</sup> Derosa et al., 2009; Derosa et al., 2012; Donadio et al., 1994; Donadio et al., 1999; Dyerberg et al., 2004; Dyerberg et al., 2006; Erkkila et al., 2008; Fahs et al., 2010; Grieger et al., 2014; Gulseth et al., 2010; Gustafsson et al., 1996; Hallund et al., 2010; Harslof et al., 2014; Jain et al., 2002; Lind et al., 2015; Lindqvist et al., 2009;

and potassium consumed<sup>46</sup> but did not properly control for these nutrients and/or did not report the levels of these nutrients in the subjects' diets. Therefore, these studies were eliminated from further review because scientific conclusions about the relationship between EPA and DHA consumption and blood pressure or risk of hypertension could not be drawn from them.

After the elimination of the studies discussed above, 104 intervention studies (112 publications) remained from which scientific conclusions could be drawn about the relationship between EPA and DHA intake and blood pressure or risk of hypertension. Those studies are discussed below by category.

For the purposes of FDA's review, studies that measured blood pressure were sorted into two categories: 1) subjects with normal blood pressure or pre-hypertension (SBP $\leq$ 139 mm Hg or DBP  $\leq$  89 mm Hg) and 2) subjects with hypertension (SBP  $\geq$  140 mm Hg or DBP  $\geq$  90 mm Hg). Because the mechanisms by which EPA and DHA may reduce blood pressure in normotensive and hypertensive subjects are considered to be the same (Borghetti and Cicero, 2006; Mozaffarian et al., 2011), studies in hypertensive subjects were included in this review. Studies were further sorted into three categories based on the type of intervention: 1) studies in which subjects consumed EPA and DHA from fish oil supplements, prescription drugs, or foods enriched with EPA and DHA, but otherwise followed their usual diets; 2) studies in which subjects consumed EPA and DHA in fish oil supplements or foods enriched with EPA and DHA and made other changes in their diets (e.g. sodium restriction, substitution of fish oil for other food items); and 3) studies in which subjects consumed fatty fish as the source of EPA and DHA.

1. Studies that added prescription drugs containing highly purified fish oil to the diets of normal or pre-hypertensive subjects (SBP  $\leq$ 139 mmHg or DBP  $\leq$ 89 mmHg)

Lungershausen et al. (1994)<sup>47</sup> was a moderate quality randomized, double-blind, placebo controlled cross-over<sup>48</sup> study in which 42 Australian subjects consumed their usual diets plus either 4 g/day corn oil (control) or 4 g/day of Omacor (1.9 g/day EPA and 1.5 g/day DHA; 3.4 g/day total) for six weeks each period. SBP and DBP were significantly lower (P=0.012 and P=0.006, respectively)<sup>49</sup> with consumption of Omacor compared to the control.

Holman et al. (2009) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 732 British subjects with type II diabetes consumed 1) 2 g/day olive oil

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Margolin et al., 1991; Moriyama et al., 2018; Murphy et al., 2007; Ness et al., 1999; Oh et al., 1991; Paniagua et al., 2011; Rasmussen et al., 2006; Rossing et al., 1996; Sirtori et al., 1997; Soares et al., 2014; Von Houwelingen et al., 1987; Wong et al., 2013.

<sup>46</sup> The types of studies with designs that could lead to changes in levels of sodium and potassium consumed included: 1) studies in which the subjects consumed EPA and DHA in fish oil supplements or EPA and DHA-enriched foods and made other changes in their diets (e.g., sodium restriction, substitution of fish oil for other food items); 2) studies in which the subjects consumed fatty fish as the source of EPA and DHA.

<sup>47</sup> The results of this study were also discussed in Lungershausen and Howe, 1994.

<sup>48</sup> A cross-over design study involves all subjects crossing over from the intervention group to the control group, and vice versa, after a defined time period.

<sup>49</sup> For the outcome of a study to demonstrate a statistically significant difference between groups, P (probability value) must be  $< 0.05$ . See supra, note 7 [Section III.F].

(control) (n=178), 2) 2 g/day Omacor (920 mg/day EPA and 760 mg/day DHA; 1.7 g/day total) (n=183), 3) 2 g/day olive oil plus atorvastatin (Lipitor) (control) (n=183), or 4) atorvastatin (Lipitor) plus 2g/day Omacor (920 mg/day EPA and 760 mg/day DHA; 1.7 g/day total) (n=188) in addition to their usual diets for four months. There was no significant difference in SBP or DBP between the olive oil control group and the Omacor group. Additionally, there was no significant difference in SBP or DBP between the Lipitor plus olive oil control group and the Omacor group.

Mori et al. (2009) was a high quality randomized, double-blind, placebo controlled parallel trial in which 74 Australian subjects with chronic kidney disease consumed 1) 4 g/day olive oil (control) (n=15), 2) 4 g/day Omacor (1.8 g/day EPA and 1.5 g/day DHA; 3.4 g/day total) (n=20), 3) 4 g/day Omacor (1.8 g/day EPA and 1.5 g/day DHA; 3.4 g/day total) plus coenzyme Q (200 mg/day) (n=18), or 4) coenzyme Q (200 mg/day) (control) (n=21) in addition to their usual diets for eight weeks. There was no significant difference in SBP or DBP between the olive oil control group and Omacor group. However, SBP and DBP were significantly lower ( $P<0.001$ ) in the Omacor plus coenzyme Q group compared to the coenzyme Q control group.

Skulas-Ray et al. (2012) was a moderate quality randomized, double-blind, placebo controlled crossover trial in which 26 Australian subjects consumed 1) a corn oil control, 2) 1 g/day Lovaza (465 mg/day EPA and 375 mg/day DHA, 850 mg/day total) or 3) 4 g/day Lovaza (1.8 g/day EPA, 1.5 g/day DHA, 3.4 g/day total) for 8 weeks each period, in addition to their usual diets. Blood pressure was measured at rest and during a task that required subjects to prepare for two minutes and then deliver a 3-minute speech about a hypothetical situation. Subjects also completed a foot cold pressor task in which they immersed one foot in 39 ° F water for 2.5 minutes. There was no significant difference in SBP or DBP between the 850 mg/day EPA and DHA period and the placebo period at rest and during the speech task. There was also no significant difference in SBP or DBP between the 3.4 g/day total EPA and DHA period and the placebo period during rest or during the speech task. FDA did not evaluate the data from the foot cold pressor task because it does not reflect normal conditions that are relevant to the U.S. population. For the same reason, we did not evaluate data with regard to overall treatment effect because those data included blood pressure measurements from the foot cold pressor task.

Nordoy et al. (2001) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 42 Norwegian subjects consumed 2 g/day corn oil plus 10 mg/day atorvastatin (n=20) (control) in addition to a low-fat diet or 2 g/day Omacor (900 mg/day EPA and 780 mg/day DHA; 1.7 g/day total) plus 10 mg/day atorvastatin (n=22) in addition to a low-fat diet (30 percent total fat) for 5 weeks. SBP was significantly lower ( $P=0.03$ ) in the Omacor group as compared to the control group. There was no significant difference in DBP between the two groups.

Kim et al. (2011) was a moderate quality randomized, open label controlled parallel trial in which 61 Korean subjects consumed 20 mg/day simvastatin (Zocor) (n=31) (control) or 4 g/day Omacor (1.9 g/day EPA and 1.5 g/day DHA; 3.4 g/day total) plus 20 mg/day simvastatin (Zocor) (n=30) for 6 weeks. All subjects also followed a low cholesterol diet. There was no significant

difference in SBP or DBP between the control group and the Omacor plus simvastatin (Zocor) group.

### *Studies in subjects with CVD*

Elajami et al. (2017)<sup>50</sup> was a moderate quality randomized, open-label controlled parallel trial in which 262 American subjects with coronary artery disease (CAD) consumed their usual diet (control group) (n=128) or 4 g/day Lovaza (1.8 g EPA and 1.5 g DHA, 3.3 g/day total) (n=134) in addition to their usual diets for 1 year. There was no significant difference in SBP or DBP between the control group and the Lovaza group.

Chan et al. (2016a)<sup>51</sup> was a moderate quality randomized, single-blind, open-label controlled cross-over study in which 20 Australian subjects (4 subjects had CAD) on statins (with or without ezetimibe) consumed a standardized diet (44 percent carbohydrates, 33 percent fat, 20 percent protein and 278 mg cholesterol) (control) or 4 g/day Omacor (1.8 g EPA and 1.52 g DHA, 3.32 g/day total) in addition to the standardized diet for 8 weeks each period. SBP and DBP were significantly lower (P=0.01) with consumption of Omacor compared to the control period.

2. Studies that added prescription drugs containing highly purified fish oil to the diets of subjects with hypertension (SBP  $\geq$ 140 mmHg or DBP  $\geq$ 90 mmHg)

Pettersson et al. (1994) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 32 Swedish subjects with immunoglobulin A (IgA) nephropathy and proteinuria consumed 6 g/day corn oil (control) (n=17) or 6 g/day Omacor (3.3 g/day EPA and 1.8 g/day DHA; 5.1 g/day total) (n=17) for 6 months. There was no significant difference in SBP or DBP between the corn oil control group and the Omacor group.

Toft et al. (1995) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 78 Norwegian subjects consumed 4 g/day corn oil (control) (n=40) or 4 g/day Omacor (2.0 g/day EPA and 1.4 g/day DHA, 3.4 g/day total) (n=38) in addition to their usual diets for sixteen weeks. SBP was significantly lower (P=0.04) in the Omacor group compared to the corn oil control group. There was no significant difference in DBP between groups.

Lungershausen et al. (1997) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 32 Australian subjects with insulin-dependent diabetes mellitus (IDDM) or noninsulin-dependent diabetes mellitus (NIDDM) consumed 4 g/day corn oil (control) (n=16) or 4 g/day Omacor (2 g/day EPA and 1.4 g/day DHA; 3.4 g/day total) (n=16) in addition to their usual diets for 12 weeks. SBP was significantly lower (P=0.039) in the Omacor

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<sup>50</sup> The results of this study were also discussed in Alfaddagh et al., 2017.

<sup>51</sup> The results of this study were also discussed in Chan et al., 2016b.

group compared to the corn oil placebo control group. There was no significant difference in DBP between the control and Omacor groups.

Bonaa et al. (1990) was a moderate quality randomized, double-blind, controlled parallel trial in which 156 Norwegian subjects consumed 6 g/day corn oil control (n=78) or 6 g/day Omacor (3.3 g/day EPA and 1.8 g/day DHA; 5.1 g/day total) (n=78) in addition to their usual diets for 10 weeks. Sitting SBP was significantly lower (P=0.002) in the Omacor group compared to the corn oil control group. Sitting DBP was also significantly lower (P=0.011) in the Omacor group compared to the corn oil control group. Standing SBP and DBP were also significantly lower (P=0.002 and P=0.0001) in the Omacor group compared to the control group.

### *Studies in subjects with CVD*

Bosch et al. (2012) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 12,536 Canadian subjects who had or were at high risk for diabetes and at high risk for CVD events (history of myocardial infarction (MI), stroke, or revascularization) consumed 1 g/day olive oil (n=6,281) or 1 g/day Omacor (465 mg EPA and 375 mg DHA, 840 mg/day total) (n=6,255) in addition to their usual diets for 6.2 years. There was no significant difference in SBP or DBP between the control group and the Omacor group.

Holm et al. (2001) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 41 Norwegian subjects with a heart transplant consumed 4 g/day corn oil (control) (n=20) or 4 g/day Omacor (1.86 g/day EPA and 1.5 g/day DHA; 3.4 g/day total) (n=21) in addition to their usual diets for one year. The mean change in 24 hour SBP was significantly different (P=0.02) in the fish oil group compared to the corn oil control group, resulting in lower SBP in the EPA and DHA group compared to the control. However, there was no significant difference in the mean change in 24 hour DBP between the fish oil group and the control group.

### 3. Studies that added fish oil supplements to the diets of normal or pre-hypertensive subjects (SBP $\leq$ 139 mmHg or DBP $\leq$ 89 mmHg)

Ansari et al. (2017) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 43 Iranian subjects with type 2 diabetes consumed 3 capsules of paraffin (control) (n=22) or 3.8 g/day fish oil (1,800 mg EPA and 900 mg DHA, 2.7 g/day total) (n=21) in addition to their usual diets for 10 weeks. There was no significant difference in SBP with consumption of fish oil as compared to the control. However, DBP was significantly lower (P=0.040) in the fish oil group compared to the control.

Barbosa et al. (2017) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 80 Brazilian subjects consumed 3 g/day sunflower oil (control) (n=40) or 3 g/day fish oil (1.1 g/day EPA, 690 mg/day DHA, 1.8 g/day) (n=40) in addition to their usual diet for 2 months. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Kristensen et al. (2016) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 114 Danish subjects with psoriatic arthritis consumed 3 g/day olive oil (control) (n=56) or 3 g/day n-3 fatty acids from fish oil (~1.5 g EPA and ~1.5 g DHA, ~3 g/day) (n=58) in addition to their usual diets for 24 weeks. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Albert et al. (2015) was a moderate quality randomized, double-blind, controlled cross-over study in which 47 New Zealander subjects consumed 5 g/day canola oil (control) or 5 g/day mixture of krill (88%) and salmon oil (12%) (230 mg EPA, 154 mg DHA, 384 mg/day total) in addition to their usual diets for 8 weeks each period. There was no significant difference in SBP or DBP between the control group and the krill and salmon oil group.

Logan and Spriet (2015) was a moderate quality randomized, single-blind, placebo controlled parallel trial in which 24 Canadian women consumed either a standard diet (50 percent carbohydrates, 30 percent fat, 20 percent protein) and 3 g/day olive oil (control) (n=12) or a standard diet and 5 g/day fish oil (2 g EPA, 1 g DHA, 3 g/day total) (n=12) for 12 weeks. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Pase et al. (2015) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 72 Australian subjects consumed 6 g/day sunola oil (control) (n=32) or 6 g/day fish oil (480 mg EPA, 480 DHA, 960 mg/day total) (n=38) in addition to their usual diet. There was no significant difference in SBP or DBP between the control group and any of the fish oil group.

Wu et al. (2014) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 84 British subjects at moderate risk of CVD consumed 3 capsules of corn oil (control) or 3 capsules of fish oil (900 mg EPA, 600 mg DHA, 1.5 g/day) in addition to their usual diet for 8 weeks each period. Subjects were genotyped for the Asp298 endothelial nitric oxide synthase (eNOS) polymorphism that has been associated with increased risk of CVD. Subjects were stratified by gene variants GG (carriers of Glu/Glu) (n=40) and GT/TT (carriers of Glu/Asp or Asp/Asp) (n=44). There was no significant difference in SBP or DBP between the control group and the fish oil groups in carriers of the GG or the GT/TT genotype. There was also no significant difference in SBP or DBP between the control group and the fish oil group in all subjects.

Hlais et al. (2013) was a moderate quality randomized, single-blind, controlled parallel trial in which 98 Lebanese subjects consumed 1) 8 g/day sunflower oil (control) (n=20), 2) 2 g/day fish oil (990 mg EPA, 392 mg DHA, 1.382 g/day total) (n=22), 3) 1 g/day fish oil (495 mg EPA, 196 mg DHA, 691 mg/day) and 8 g/day sunflower oil (n=17), 4) 2 g/day fish oil (990 mg EPA, 392 mg DHA, 1.382 g/day total) 8 g/day sunflower oil (n=18), or 5) 4 g/day fish oil (1.98 g/ EPA, 784 mg DHA, 2.76 g/day total) and 8 g/day sunflower oil (n=21) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the control group and any of the fish oil groups.

Minihane et al. (2016) was a randomized, double-blind, placebo-controlled, crossover study in which 312 British subjects consumed 1) 3.2 g/day of a control oil (80/20 mixture palm oil and soybean oil), 2) 3.2 g/day fish oil (1.8 g/day EPA and DHA), or 3) 50/50 corn oil/fish oil with 700 mg/day EPA and DHA for 8 weeks each period. In the analysis of data for all subjects combined, there was no significant difference in SBP and DBP compared to control when subjects consumed either 3.2 g/day EPA and DHA or 700 mg/day EPA and DHA. The study also analyzed the data based on baseline hypertension status, dividing the subjects into two groups: 17 subjects who were described as having “dual hypertension” (SBP  $\geq$ 140 mmHg) and DBP  $\geq$ 90 mmHg) and 31 subjects who had isolated systolic hypertension (SBP  $\geq$ 140 mmHg but DBP  $\leq$ 90 mmHg). In the 31 subjects with isolated systolic hypertension, SBP was significantly lower (P=0.046) compared to control when the subjects consumed 1.8 g/day EPA and DHA or 700 mg/day EPA and DHA. In the 17 subjects with dual hypertension, however, there was no significant difference in SBP among the three diets. There was also no significant difference in DBP among the three diets in subjects with isolated systolic hypertension or dual hypertension.

Armstrong et al. (2012) was a moderate quality randomized, double-blind, placebo controlled, parallel study in which 98 American subjects of African American, Black or African ancestry consumed 5 g/day of corn oil/ soybean oil placebo (control) (n=46) or 5 g/day fish oil (2 g/day EPA and 1 g/day DHA; 3 g/day total) (n=49) in addition to their usual diets for six weeks. Subjects were stratified in both control and EPA and DHA groups based on ALOX5 (Arachidonate 5-lipoxygenase) gene variants that are common in people of African ancestry and are associated with a differential CVD risk. There was no significant difference in SBP or DBP between the two groups for all subjects or within genotypes.

Atar et al. (2012) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 73 Iranian women with type II diabetes consumed 2 g/day cornstarch (control) (n=34) or 2 g/day fish oil (720 mg/day EPA and 480 mg/day DHA; 1.2 g/day total) (n=39) in addition to their usual diets for 8 weeks. There was no significant difference in SBP or DBP between the EPA and DHA group and the cornstarch control group.

Carter et al. (2012) was a moderate quality randomized, double blind, placebo controlled parallel trial in which 67 normotensive or pre-hypertensive American subjects consumed 9 g/day olive oil (control) (n=33) or 9 g/day fish oil (1.6 g/day EPA and 1.1 g/day DHA; 2.7 g/day total) (n=34) for 8 weeks. There was no significant difference in SBP and DBP between the fish oil group (n=19) and the control group (n=19) in normotensive subjects. Additionally, there was no significant difference in SBP or DBP between the fish oil group (n=15) and the olive oil control group (n=14) in the pre-hypertensive subjects.

Faghihi et al. (2012) was a moderate quality randomized, double-blind placebo controlled parallel trial in which 41 Iranian subjects (with schizophrenia, bipolar, or schizoaffective disorder on olanzapine plus either sodium valproate or lithium) consumed a placebo control (n=21) or fish oil (n=20) in addition to their usual diets for 6 weeks. The dose of fish oil was 1 g/day (300 mg/day total EPA and DHA) for week one, 2 g/day (600 mg/day EPA and DHA) for week 2, 3 g/day (900 mg/day EPA and DHA) for week three and through the end of the study.

There was no significant difference in SBP between the EPA and DHA group and the control group. DBP was not reported.

Ginty et al. (2012) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 34 British subjects consumed corn oil (control) (n=14) or 1 g/day EPA and 400 mg/day DHA (1.4 g/day total) (n=20) in addition to their usual diets for three weeks. All subjects also completed a psychological stress task (mental arithmetic) at baseline and at 21 days. The stress task included a two-minute pre-resting period, six-minute resting period, six-minute mental arithmetic period, and a six-minute recovery period. Blood pressure was measured every two minutes during the psychological stress task. There was no significant difference in SBP or DBP between the fish oil group and the corn oil control group at rest or during the psychological stress task.

Nilsson et al. (2012) was a moderate quality randomized, placebo controlled cross-over study in which 44 British subjects consumed a placebo control (366 mg/day dicalcium phosphate, 150 mg/day microcrystalline cellulose, and 4 mg/day magnesium salts of fatty acids) or 5 g/day fish oil (1.5 g/day EPA and 1.1 g/day DHA; 2.6 g/day total) for 5 weeks each period, in addition to their usual diets. The reduction in SBP was significantly greater ( $P<0.05$ ) with fish oil consumption compared to the control. There was no significant difference in the change in DBP with consumption of fish oil compared to the control.

Noreen and Brandauer (2012) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 40 American subjects consumed 4 g/day safflower oil (control) (n=20) or 4 g/day fish oil (1.6 g/day EPA and 800 mg/day DHA; 2.4 g/day total) (n=20) in addition to their usual diets for 6 weeks. SBP was significantly lower ( $P=0.004$ ) in the EPA and DHA group compared to the control group. There was no significant difference in DBP between the fish oil and control groups.

Dewell et al. (2011) was a moderate quality randomized, double-blind, placebo controlled parallel trial, in which 60 American subjects consumed 1) 4 or 6 g/day soybean oil (control) (n=20), 2) 4 g/day fish oil (700 mg/day EPA and 500 mg/day DHA; 1.2 g/day total) (n=20), or 3) 6 g/day fish oil (2.1 g/day EPA and 1.5 g/day DHA; 3.6 g/day total) (n=20) in addition to their usual diets for 8 weeks. There was no significant difference in SBP and DBP between the 4 g/day fish oil (1.2 g/day EPA and DHA) and control groups. SBP and DBP, however, were significantly lower ( $P<0.05$ ) in the 6 g/day fish oil group (3.6 g/day EPA and DHA) compared to the control group.

Sanders et al. (2011) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 310 British subjects consumed 1) 3 g/day olive oil (control) (n=71), 2) 3 g/day fish oil (0.45 g/day EPA and DHA) (n=80), 3) 3 g/day fish oil (0.9 g/day EPA and DHA) (n=79), or 4) 3 g/day fish oil (1.8 g/day EPA and DHA) (n=80) in addition to their usual diets for 12 months. There was no significant difference in SBP or DBP between the control group and either of the fish oil groups.

Sjoberg et al. (2010) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 67 Australian subjects consumed 1) 6 g/day sunola oil (control) (n=17), 2) 2 g/day fish oil (112 mg/day EPA and 524 mg/day DHA; 636 mg/day total) (n=16), 3) 4 g/day fish oil (224 mg/day EPA and 1.04 g/day DHA; 1.3 g/day total) (n=17), or 4) 6 g/day fish oil (336 mg/day EPA and 1.6 g/day DHA; 2 g/day total) (n=17) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the control group and any of the fish oil groups.

Wong et al. (2010) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 97 Chinese subjects with NIDDM consumed 4 g/day olive oil (control) (n=48) or 4 g/day fish oil (1.68 g/day EPA and 1 g/day DHA; 2.7 g/day total) (n=49) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the fish oil group and olive oil control group.

Buckley et al. (2009) was a moderate quality randomized, double blind, placebo controlled parallel trial in which 25 Australian subjects consumed 6 g/day sunflower oil (control) (n=13) or 6 g/day fish oil (1.5 g/day DHA and 0.36 g/day EPA; 1.9 g/day total) (n=12) in addition to their usual diets during five weeks of exercise training. DBP was significantly lower ( $P=0.04$ ) in the EPA and DHA group compared to the control group. There was no significant difference in SBP between the fish oil group and the control group.

Ferraro et al. (2009) was a moderate quality randomized, controlled parallel trial in which 30 Italian subjects with proteinuric IgA nephropathy consumed Renin-Angiotensin System Blockers (RASB) therapy only (ramipril 10 mg/day and irbesartan 300 mg/day) (n=15) (control) or RASB therapy plus 3 g/day fish oil (2.5 g/day total EPA and DHA) (n=15) in addition to their usual diets for 6 months. There was no significant difference in SBP or DBP between the two groups.

Maki et al. (2009) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 76 American subjects consumed 1) 2 g/day olive oil (control) (n=25), 2) 2 g/day krill oil (216 mg/day EPA and 90 mg/day DHA; 306 mg/day total) (n=25), or 3) 2 g/day menhaden oil (212 mg/day EPA and 178 mg/day DHA; 390 mg/day total) (n=25) in addition to their usual diets for 4 weeks. There was no significant difference in SBP or DBP between the krill oil group and the control group. SBP was significantly lower ( $P=0.032$ ) in the menhaden oil group compared to the control group. There was no significant difference in DBP between the menhaden oil group and the control group.

Meyer et al. (2009) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 48 Australian subjects consumed 1) 5 g/day sunola oil (control) (n=17), 2) 5 g/day fish oil (210 mg/day EPA and 810 mg/day DHA; 1 g/day total) (n=15), or 3) 5 g/day seal oil (340 mg/day EPA and 450 mg/day DHA; 790 mg/day total) (n=16) in addition to their usual diets for 6 weeks. SBP was significantly lower ( $P<0.05$ ) in the fish oil group compared to the sunola control group. SBP was also significantly lower ( $P<0.01$ ) in the seal oil group compared to the sunola control group. There was no significant difference in DBP between the control group and the fish oil group or seal oil group.

Micallef and Garg (2009) was a moderate quality randomized, double-blind placebo controlled parallel trial in which 60 Australian subjects consumed 1) 4 g/day sunola oil (control) (n=15), 2) 4 g/day sunola oil and 2 g/day plant sterol (control) (n=15), 3) 4 g/day fish oil (320 mg/day EPA and 1.12 g/day DHA; 1.4 g/day total) (n=15), or 4) 4 g/day fish oil (320 mg/day EPA and 1.12 g/day DHA; 1.4 g/day total) plus 2 g/day plant sterol (n=15) in addition to their usual diets for three weeks. There was no significant difference in SBP or DBP between the fish oil only group and the sunola control group. There was also no significant difference in SBP or DBP between the fish oil plus plant sterol group and the plant sterol control group.

Rizza et al. (2009) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 50 Italian subjects consumed 2 g/day olive oil (control) (n=24) or 2 g/day fish oil (1.7 g/day EPA and DHA) (n=26) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the fish oil group and the olive oil control group.

Barcelo-Coblijn et al. (2008) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 30 Canadian subjects consumed 1) 1 g/day sunflower oil (control) (n=9), 2) 600 mg/day fish oil (252 mg/day EPA and 3 mg/day DHA; 255 mg/day total) (n=11), or 3) 1.2 g/day fish oil (504 mg/day EPA and 6 mg/day DHA; 510 mg/day total) (n=10) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the sunflower oil control group and either of the fish oil groups.

Vernaglionone et al. (2008) was a moderate quality single-blind, placebo controlled sequential intervention<sup>52</sup> in which 24 Italian subjects on hemodialysis for end stage renal disease consumed 1) 2 g/day olive oil (control), 2) 2 g/day fish oil (900 mg/day EPA and 150 mg/day DHA; 1.05 g/day total), and 3) 2 g/day olive oil control again for 4 months each period. SBP and DBP were significantly lower ( $P \leq 0.05$ ) with fish oil consumption compared to the olive oil control.

Browning et al. (2007) was a moderate quality randomized placebo controlled cross-over study in which 30 British women consumed 5 g/day of an oleic and linoleic oil mixture (control) or 5 g/day fish oil (2.9 g/day DHA and 1.3 g/day EPA; 4.2 g/day total) for 12 week periods each, in addition to their usual diets. Subjects who were in the highest tertile for baseline serum sialic acid, a marker of inflammation, were assigned to the raised inflammatory status group (n=12) and subjects in the lowest tertile for baseline sialic acid were assigned to the reference group (n=18). In subjects with raised inflammatory status, there was no significant difference in SBP or DBP with consumption of fish oil as compared to the oleic and linoleic oil control. There was also no significant difference in SBP or DBP in the reference group with fish oil consumption as compared to the control.

Cazzola et al. (2007) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 155 Italian men were assigned to 1) 9 g/day corn oil (control) (n=40), 2) 6 g/day corn oil and 3 g/day fish oil (1.4 g/day EPA and 270 mg/day DHA; 1.6 g/day total) (n=39), 3) 3 g/day corn oil and 6 g/day fish oil (2.7 g/day EPA and 510 mg/day DHA, 3.2g/day total) (n=38) or 4) 9 g/day fish oil (4.1 g/day EPA and 810 mg/day DHA; 4.9 g/day total) (n=38)

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<sup>52</sup> In a sequential intervention, subjects receive a control and a treatment in a fixed sequence.

in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between any of the fish oil groups and the control group.

Hill et al. (2007) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 65 Australian subjects 1) consumed 6 g/day sunflower oil (control) (n=18), 2) consumed 7 g/day sunflower oil and followed a prescribed exercise regimen (control) (n=14), 3) consumed 6 g/day fish oil (360 mg/day EPA and 1.6 g/day DHA; 1.9 g/day total) (n=17), or 4) consumed 6 g/day fish oil (360 mg/day EPA and 1.6 g/day DHA; 1.9 g/day total) and followed the prescribed exercise regimen (n=16) in addition to their usual diets for twelve months. There was no significant difference in SBP or DBP between the fish oil groups and the sunflower oil control groups.

Barden et al. (2006) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 83 pregnant Australian women with allergic disease consumed 4 g/day olive oil (n=43) or 4 g/day fish oil (1.1 g/day EPA and 2.2 g/day DHA; 3.3 g/day total) (n=40) in addition to their usual diets from the 20<sup>th</sup> week of pregnancy until delivery at 36 weeks. There was no significant difference in SBP or DBP between the control and fish oil groups during pregnancy at 20, 30 or 36 weeks. There was also no significant difference in SBP or DBP between groups at 6 weeks post-delivery.

Damsgaard et al. (2006) was a moderate quality randomized, controlled parallel trial in which 83 Danish infants consumed standard infant formula or cow's milk (control) (n=43) or standard infant formula or cow's milk plus 5 ml of fish oil (~554 mg/day EPA and ~369 mg/day DHA; ~924 mg/day) (n=40) for 3 months. SBP was significantly lower (P=0.02) in the fish oil group compared to the control group. There was no significant difference in DBP between the two groups.

Monahan et al. (2004) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 18 American subjects consumed 10 g/day olive oil (control) (n=9) or 10 g/day fish oil (3 g/day EPA and 2 g/day DHA; 5 g/day total) (n=9) in addition to their usual diets for one month. There was no significant difference in SBP or DBP between the fish oil group and the olive oil control group.

Finnegan et al. (2003) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 91 British subjects consumed a diet that incorporated 1) 25 g/day margarine made from sunflower and safflower oils (control) (n=30), 2) 25 g/day margarine made from fish oil (500 mg/day EPA and DHA) plus an estimated 200 mg/day EPA and DHA from the subjects' usual diets for a target intake of 700 mg/day EPA and DHA (n=30), or 3) 25 g/day margarine made from fish oil (500 mg/day EPA and DHA) plus 3 g/day fish oil capsules (800 mg/day EPA and DHA) plus an estimated 200 mg/day EPA and DHA from the subjects' usual diets for a target intake of 1.5 g/day EPA and DHA (n=31) for 6 months. Actual intakes of EPA and DHA were 800 mg/day and 1.7 g/day in the two treatment groups. Subjects used the margarine provided by the study in place of the margarine they usually ate and otherwise maintained their usual diets. There was no significant difference in SBP or DBP between the control group and either of the fish oil groups.

Geelen et al. (2003) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 74 subjects from the Netherlands consumed 3.5 g/day high oleic sunflower oil (control) (n=35) or 3.5 g/day fish oil (700 mg/day EPA and 560 mg/day DHA; 1.3 g/day total) (n=39) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the fish oil and control groups.

Nestel et al. (2002) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 38 Australian subjects consumed 1) 4 g/day olive oil (control) (n=14), 2) 4 g/day fish oil (3.04 g/day EPA and 68 mg/day DHA; 3.1 g/day total) (n=12), or 3) 4 g/day fish oil (2.84 g/day DHA and 164 mg/day EPA; 3.0 g/day total) (n=12) in addition to their usual diets for 7 weeks. There was no significant difference in SBP or DBP between the control group and either of the fish oil groups.

Conquer et al. (1999) was a moderate quality randomized double-blind, controlled parallel trial in which 19 Canadian men consumed 20 g/day vegetable oil (control) (n=9) or 20 g/day seal oil (1.3 g/day EPA, 1.7 g/day DHA; 3.0 g/day total) (n=10) in addition to their usual diets for 42 days. There was no significant difference in SBP or DBP between the fish oil group and the vegetable oil control group.

McVeigh et al. (1994) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 20 Irish subjects with NIDDM consumed 10 g/day of olive oil (control) or 10 g/day of fish oil (1.8 g/day EPA and 1.2 g/day DHA; 3.0 g/day total) for 6 weeks each period, in addition to their usual diets. There was no significant difference in SBP and DBP between the fish oil group and the olive oil control group.

Chin et al. (1993) was a moderate quality randomized, single-blind, placebo controlled parallel study in which 29 Australian men consumed 1) 20 g/day mixed oil (palm, safflower, olive oil) (control) (n=9), 2) 5 g/day fish oil (890 mg/day EPA and 580 mg/day DHA; 1.5 g/day total) (n=8), 3) 10 g/day fish oil (1.8 g/day EPA and 1.2 g/day DHA; 2.9 g/day total) (n=6), or 4) 20 g/day fish oil (3.6 g/day EPA, 2.3 g/day DHA; 5.9 g/day total) (n=6) in addition to their usual diets for 28 days. There was no significant difference in SBP and DBP between the mixed oil control group and any of the fish oil groups.

Demke et al (1988) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 31 American subjects consumed 5 g/day safflower oil (control) (n=18) or 5 g/day fish oil (930 mg/day EPA and 790 mg/day DHA; 1.7 g/day total) (n=13) in addition to their usual diets for 28 days. There was no significant difference in SBP or DBP between the fish oil group and the safflower oil control group.

Deslypere et al. (1992) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 58 Belgian subjects consumed 1) 9 g/day olive oil and palm oil (control) (n=14), 2) 3 g/day fish oil (809 mg/day EPA and 165 mg/day DHA; 974 mg/day total) plus 6 g/day olive oil (n=15), 3) 6 g/day fish oil (1.6 g/day EPA and 329 mg/day DHA; 1.9 g/day total) plus 3 g/day olive oil (n=15), or 4) 9 g/day fish oil (2.4 g/day EPA and 495 mg/day DHA; 2.9

g/day total) (n=14) in addition to their usual diets for 1 year. There was no significant difference in SBP or DBP between the olive oil control group and any of the fish oil groups.

Flaten et al. (1990) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 56 Norwegian men consumed 14 g/day olive oil (control) (n=29) or 14 g/day fish oil (3.6 g/day EPA and 2.9 g/day DHA; 6.5 g/day total) (n=27) in addition to their usual diets for six weeks. There was no significant difference in SBP or DBP between the fish oil group and olive oil control group.

Mortensen et al. (1983) was a high quality double-blind, placebo controlled cross-over study in which 20 Danish men consumed 10 g/day vegetable oil (control) or 10 g/day fish oil (1.98 g/day EPA and 1.25 g/day DHA; 3.23 g/day total) for 4 weeks each period, in addition to their usual diets. SBP was significantly lower ( $P<0.05$ ) with fish oil consumption as compared to the vegetable oil control. However, there was no significant difference in DBP with fish oil consumption as compared to the control.

Ryu et al. (1990) was a moderate quality randomized, placebo controlled parallel trial in which 20 American men consumed 6 g/day wheat germ oil (control) (n=10) or 6 g/day marine oil (2.1 g/day EPA and 900 mg/day DHA; 3 g/day total) (n= 10) in addition to their usual diets for 4 weeks. There was no significant difference in SBP or DBP between the two groups.

Sacks et al. (1994a)<sup>53</sup> (Trials of Hypertension Prevention) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 350 American subjects consumed 1) 6 capsules/day olive oil (control) (n=86), 2) 3 tablets of cellulose (control) (n=89), or 3) 6 g/day fish oil (1.44 g/day EPA and 960 mg/day DHA; 2.4 g/day total) (n=175) in addition to their usual diets for 6 months. There was no significant difference in SBP or DBP between the fish oil group and either control group.

Bonnema et al. (1995) was a moderate quality randomized, double-blind, controlled parallel trial in which 28 Danish subjects with diabetes (IDDM or NIDDM) and incipient nephropathy consumed 6 g/day olive oil (control) (n=14) or 6 g/day fish oil (2 g/day EPA and 1.3 g/day DHA; 3.3 g/day total) (n=14) in addition to a conventional diabetes diet for six months. There was no significant difference in SBP or DBP between the fish oil group and olive oil control group.

Donnelly et al. (1992) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 13 Canadian subjects with end stage renal disease consumed 12 g/day olive oil (control) or 12 g/day fish oil (2.16 g/day EPA and 1.4 g/day DHA; 3.6 g/day total) for 4 weeks each period, in addition to their usual diets. There was no significant difference in SBP or DBP with consumption of fish oil as compared to the olive oil control.

Bruckner et al. (1987) was a moderate quality randomized, single-blinded, placebo controlled trial in which 21 American men consumed 1.5 g/10 kg body weight/day of olive oil (control) (n=10) or 1.5 g/10 kg body weight/day fish oil (18 percent EPA and 12.64 percent DHA) (n=11)

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<sup>53</sup> The results of this study were also discussed in Sacks et al., 1994b and Cutler et al., 1992.

in addition to their usual diets for 3 weeks. There was no significant difference in SBP or DBP between the fish oil group and the olive oil control group.

Blonk et al. (1990) was a moderate quality randomized, controlled parallel trial in which 45 Dutch subjects consumed 1) no capsules (control) (n=10), 2) 3 g/day fish oil (900 mg/day EPA and 600 mg/day DHA; 1.5 g/day total) (n=11), 3) 6 g/day fish oil (1.8 g/day EPA and 1.2 g/day DHA; 3 g/day) (n= 10), or 4) 12 g/day fish oil (3.6 g/day EPA and 2.4 g/day DHA, 6 g/day) (n=14) in addition to their usual diets for 12 weeks. There was no significant difference in SBP or DBP between the control group and any of the fish oil groups.

Dart et al. (1989) was a moderate quality double-blind, placebo controlled cross-over trial in which 21 British subjects consumed 20 g/day olive oil (control) or 20 g/day fish oil (3.52 g/day EPA and 2.5 g/day DHA; 6 g/day total) for 2 months each period, in addition to a low-fat diet (30 percent total fat). SBP was significantly lower ( $P<0.05$ ) with consumption of fish oil compared to the olive oil control. There was no significant difference, however, in DBP with fish oil as compared to the control.

DiGiacomo et al. (1989) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 32 subjects with Raynaud's phenomenon consumed 12 capsules/day of olive oil (control) (n=16) or 12 capsules/day fish oil (3.96 g/day EPA and 2.64 g/day DHA; 6.6 g/day total) (n=16) in addition to their usual diets for 12 weeks. Blood pressure (SBP only) was measured by using a digital blood pressure cuff on left index finger. Readings were taken at room temperature and after the subjects' hands were immersed in water (hand immersion test) at 104°F, 77°F, 59°F, and 50°F until there was an absence of blood flow or pulse into the finger or until measurements were obtained at all water temperatures. There was no significant difference in digital SBP between the two groups at room temperature. FDA did not consider the data on digital SBP in subjects exposed to different water temperatures during the hand immersion test portion of the trial because these experimental conditions were designed to evaluate whether fish oil improves tolerance to cold temperatures and delays the onset of vasospasms associated with Raynaud's phenomenon by increasing blood flow and blood pressure. This portion of the trial was not designed to evaluate whether fish oil intake lowers blood pressure.

#### *Studies in subjects with CVD*

Tavazzi et al. (2008) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 6,975 Italian subjects with heart failure consumed 1 g/day placebo (control) (n=3,481) or 1 g/day fish oil (~ 386 mg to 401 mg EPA, ~464 to 481 mg DHA, ~850-882 mg/day total) (n=3,494) in addition to their usual diets for 3.9 years. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Axelrod et al. (1994) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 18 American subjects with NIDDM (4 subjects also had CAD) consumed 5 g/day safflower oil (control) (n=9) or 5 g/day fish oil (1.5 g/day EPA and 1.0 g/day DHA; 2.5 g/day total) (n=9) in addition to their usual diets for 6 weeks. SBP was significantly lower ( $P=0.043$ ) in the fish oil group compared to the safflower control group at 4 weeks. However, at

6 weeks SBP was not significantly lower between the two groups. Additionally, there was no significant difference in DBP between the two groups at 4 or 6 weeks.

Bairati et al. (1991) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 125 Canadian subjects with CAD consumed 15 g/day olive oil (control) (n=59) or 15 g/day fish oil (2.7 g/day EPA and 1.8 g/day DHA; 4.5 g day total) (n=66) in addition to their usual diets for six months. SBP was significantly lower ( $P<0.05$ ) in the fish oil group compared to the olive oil control group. There was, however, no significant difference in DBP between the two groups.

Rogers et al. (1987) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 60 British subjects with CVD consumed olive oil (control) (n=30) or fish oil (n=30). The length of the study varied from 17 to 42 days with a mean length of 32 days. Subjects consumed 16 mL/day of olive oil or fish oil supplements (2.9 g/day EPA and 1.9 g/day DHA; 4.8 g/day total) for one week. For the rest of the trial, subjects consumed 10 mL/day of olive oil or fish oil supplements (1.6 g/day EPA and 1.2 g/day DHA; 2.8 g/day total). There was no significant difference in mean SBP or DBP between the two groups. The percent attributable reduction in DBP, however, was significantly greater in the fish oil group ( $P<0.05$ ) compared to the olive oil control group.

Mehta et al. (1988) was a moderate quality randomized, double-blind, placebo controlled cross-over trial in which 8 American men with CAD consumed a placebo control or 18 capsules/day fish oil (3.2 g/day EPA and 2.2 g/day DHA; 5.4 g/day total) for 4 weeks each period, in addition to their usual diets. SBP was significantly lower ( $P<0.05$ ) with fish oil consumption compared to the control when blood pressure was taken in a supine (lying down) or erect (standing) position. SBP was also significantly lower ( $P<0.05$ ) after a 3-minute exercise test and a 6-minute exercise test. There was no significant difference in DBP between the fish oil period and the control period when blood pressure was taken in a supine or erect position or after a 3 or 6-minute exercise test.

O'Keefe et al. (2006) was a moderate quality randomized, double-blind, placebo controlled cross-over trial in which 18 American men with a history of MI consumed a 50:50 mixture of corn and olive oil (control) or 1.5 g/day fish oil (225 mg/day EPA and 585 mg/day DHA; 810 mg/day total) for 4 months each period. At the end of each test period, subjects completed an exercise stress test. Blood pressure was measured at baseline (before the test) and during the exercise stress test at peak heart rate. There was no significant difference in SBP with consumption of fish oil as compared to the control. However, DBP was significantly higher ( $P<0.05$ ) with fish oil consumption compared to the control.

Radaelli et al. (2006) was a moderate quality randomized, placebo controlled parallel trial in which 25 Italian subjects with post-MI systolic heart failure consumed a placebo control (n=10) or 2 g/day fish oil (630 mg/day EPA and 1.1 g/day DHA, 1.7 g/day total) (n=15) in addition to their usual diets for four months. There was no significant difference in SBP or DBP between the two groups.

4. Studies that combined EPA and DHA supplementation with other dietary interventions in normal or pre-hypertensive subjects (SBP  $\leq$ 139 mmHg or DBP  $\leq$ 89 mmHg)

Cobiac et al. (1991a) was a high quality randomized, double-blind, placebo controlled cross-over trial in which 50 Australian subjects consumed diets that provided 1) 8 g/day sunflower oil/low sodium (1,610 mg/day) (low sodium control diet), 2) 8 g/day sunflower oil/normal sodium (3,450 mg/day) (normal sodium control diet), 3) 8 g/day fish oil (2.5 g/day EPA and 1.7 g/day DHA; 4.2 g/day total)/low sodium (fish oil/low sodium diet), or 4) 8 g/day fish oil (2.5 g/day EPA and 1.7 g/day DHA; 4.2 g/day total)/normal sodium (fish oil/normal sodium diet) for 4 weeks each period. SBP and DBP were significantly lower ( $P < 0.05$ ) with consumption of the fish oil/low sodium diet as compared to the low sodium control diet. There was no significant difference in SBP or DBP with consumption of the fish oil/normal sodium diet as compared to the normal sodium control diet.

Cobiac et al. (1992) was a high quality randomized, double-blind, placebo controlled cross-over trial in which 106 Australian subjects consumed diets that provided 1) 8 g/day sunflower oil/low sodium (1,610 mg/day) (low sodium control diet), 2) 8 g/day sunflower oil/normal sodium (3,450 mg/day) (normal sodium control diet), 3) 8 g/day fish oil (2.5 g/day EPA and 1.7 g/day DHA; 4.2 g/day total)/low sodium (fish oil/low sodium diet), or 4) 8 g/day fish oil (2.5 g/day EPA and 1.7 g/day DHA; 4.2 g/day total)/normal sodium (fish oil/normal sodium diet) for 4 weeks each period. DBP was significantly lower ( $P < 0.02$ ) with consumption of the fish oil/low sodium diet as compared to the sunflower oil/low sodium control diet. There was no significant difference in SBP with consumption of the fish oil/low sodium diet as compared to the low sodium control diet. Also, there was no significant difference in SBP or DBP with the consumption of the fish oil/normal sodium diet as compared to the normal sodium control diet.

Kestin et al. (1990) was a high quality randomized, double-blind, placebo controlled parallel trial in which 22 Australian men consumed 188 g/day linoleic acid supplements (14.3 g/day linoleic acid) (control) ( $n=11$ ) or 188 g/day fish oil supplements (2.1 g/day EPA and 1.3 g/day DHA; 3.4 g/day total) ( $n=11$ ) for 6 weeks. The fish oil supplements were an emulsion of low-fat milk and fish oil. The control supplements were an emulsion of low fat milk and safflower oil (linoleic acid). A mixture of vegetable oils (olive and palm oil) and pure cholesterol were also added to both supplements to balance the amount of saturated, monounsaturated, and polyunsaturated fats and cholesterol in the test and control supplements. Subjects were instructed to consume a diet with 40 percent of energy from total fat, with 10 percent of energy from total fat coming from the fish oil or linoleic acid supplements. SBP was significantly lower ( $P=0.01$ ) in the fish oil group compared to the linoleic acid control group. There was no significant difference in DBP between the two groups.

Kenny et al. (1992) was a high quality randomized, double-blind, placebo controlled cross-over study in which 8 American men were fed a typical American diet providing 9 g/day safflower oil (control) or 9 g/day fish oil (2.5 g/day EPA and 1.08 g/day DHA; 3.6 g/day total) for 7 days each period. There was no significant difference in SBP or DBP with the fish oil diet as compared to the control diet.

5. Studies of EPA and DHA from fatty fish in normal or pre-hypertensive subjects (SBP  $\leq$ 139 mmHg or DBP  $\leq$ 89 mmHg)

Cobiac et al. (1991b) was a high quality randomized, controlled parallel trial in which 31 Australian men were divided into three groups: 1) control diet (n=6), 2) fish diet that included salmon (1 kg raw weight/wk) and sardines in salad oil (150 g/week) (4.5 g/day EPA and DHA) (n=12), or 3) 15 g/day fish oil (4.5 g/day EPA and DHA) (n=13) for 5 weeks. Subjects were instructed to limit fat intake to 30 percent of energy. The control group was provided lean steak, chicken breast and ham. They were also provided a milk based supplement that was a mixture of palm oil, safflower oil, olive oil, skim milk powder, cholesterol, sodium and potassium. The fish diet group was provided Atlantic salmon, Norwegian sardines, and a liquid supplement that contained less oil, some added cholesterol, no skim milk powder, and added sugar. The fish oil group consumed the same diet as the control but also consumed fish oil supplements. The fish oil supplement contained no added cholesterol, a small amount of palm and olive oil and no added cholesterol. The foods and supplements consumed by all three groups provided 10 percent of energy as fat and were matched for total polyunsaturated fat, monounsaturated fat, saturated fat, cholesterol, protein, fat, carbohydrate, sodium and potassium. There was no significant difference in SBP or DBP between the control group and either the fish diet group or the fish oil supplement group.

Ramel et al (2010) was a high quality randomized, single-blind, controlled parallel trial in which 278 subjects in Spain, Ireland, and Iceland consumed 1) no seafood and 6 capsules/day sunflower oil (control), 2) 150 g/day cod 3 times/week (~300 mg/day EPA and DHA), 3) 150 g salmon 3 times/week (~2.1 g/day EPA and DHA), or 4) 6 capsules/day fish oil (~1.3g/day EPA and DHA) for eight weeks. In addition, all subjects were instructed to decrease caloric intake by ~30 percent of estimated energy expenditure. To minimize the differences among diets, subjects were also instructed to consume ~30 percent of calories as total fat, ~50 percent of calories as carbohydrate (including ~20-25 g/day dietary fiber), and ~20 percent of calories as protein. There was no significant difference in SBP and DBP between the control group and either the fish (cod or salmon) group or the fish oil group.

Lara et al. (2007) was a moderate quality controlled cross-over study in which 41 British subjects consumed a standard diet (50 percent carbohydrates, 35 percent fat, 15 percent protein) containing 125 g/day salmon (800 mg/day EPA and 1.6 g/day DHA; 2.4 g/day total) or a standard diet containing no fish or fish oil supplements (control) for 4 weeks each. SBP and DBP were significantly lower (P=0.001 and P=0.009, respectively) with consumption of salmon as compared to the control.

Vandongen et al. (1993)<sup>54</sup> was a high quality randomized, controlled parallel trial in 120 Australian men. Five groups received 40 percent of calories from fat plus 1) olive/palm/safflower oil placebo (1:4.5:4.5 mixture) (control) (n=18), 2) fish diet that provided 1.3 g/day of EPA (DHA content not specified) plus olive/palm/safflower oil placebo (n=17), 3) 6 g/day fish

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<sup>54</sup> The results of this study were also discussed in Beilin et al., 1993.

oil (1.3 g/day EPA and 900 mg/day DHA; 2.2 g/day total) (n=17), 4) fish diet (1.3 g/day EPA; DHA content not specified) plus 6 g/day fish oil (1.3 g/day EPA and 860 mg DHA; 2.2 g/day total) (n=17), or 5) 12 g/day fish oil (2.6 g/day EPA and 1.7 g/day DHA; 4.3 g/day total) (n=16) for 12 weeks. Two groups received 30 percent calories from fat plus olive/palm/safflower oil placebo (n=17) (control) or fish diet (1.3 g/day EPA; DHA content not specified) plus olive/palm/safflower oil placebo (n=18) for 12 weeks. Subjects were provided fish to consume during one meal per day. There was no significant difference in SBP or DBP between any of the fish or fish oil groups and the control groups.

6. Studies that added fish oil supplements to the diets of subjects with hypertension (SBP  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg)

Kromhout et al. (2010) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 2,428 Dutch subjects with history of MI consumed a diet that incorporated ~18 g/day margarine (control) (n=1,236) or ~18 g/day margarine made with fish oil (~ 226 mg EPA, ~150 mg DHA, ~400 mg/day total) (n=1,192) for 40 months. Subjects used the margarine provided by the study in place of the margarine they usually ate and otherwise maintained their usual diets. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Root et al. (2013) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 51 American subjects consumed 3 g/day safflower oil (control) (n=27) or 3 g/day fish oil (1.05 g EPA, 690 mg DHA, 1.74 g/day total) (n=30) in addition to their usual diets for 4 weeks. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Landmark et al. (1993)<sup>55</sup> was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 18 Norwegian men consumed their usual diets plus 1) 10 capsules of olive oil (control), 2) 10 capsules of olive oil plus 40 mg/day nifedipine (blood pressure medication) (control), 3) 10 capsules of fish oil (1.8 g/day EPA and 2.8 g/day DHA; 4.6 g/day total), or 4) 10 capsules of fish oil (1.8 g/day EPA and 2.8 g/day DHA; 4.55 g/day total) plus 40 mg day nifedipine for 4 weeks each period. There was no significant difference in supine (lying down) or standing SBP or DBP with fish oil as compared to the olive oil control. There was also no significant difference in supine or standing SBP or DBP with fish oil plus 40 mg nifedipine as compared to olive oil plus 40 mg day nifedipine.

Levinson et al. (1990) was a high quality randomized, double-blind, placebo controlled parallel trial in which 16 American subjects consumed 50 g/day corn oil/palm oil (control) (n=8) or 50 g/day fish oil (9 g/day EPA and 6 g/day DHA; 15 g/day total) (n=8) in addition to their usual diet for 6 weeks. There was no significant difference in SBP between the two groups. However, DBP was significantly lower ( $p \leq 0.05$ ) in the fish oil group compared to the corn oil/palm oil control group.

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<sup>55</sup> The results of this study were also discussed in Mundal et al., 1993.

Meland et al. (1989) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 40 Norwegian men consumed 20 g/day olive oil and corn oil (control) (n=20) or 20 g/day fish oil (3.6 g/day EPA and 2.4 g/day DHA; 6.0 g/day total) (n=20) in addition to their usual diet for six weeks. There was no significant difference in SBP or DBP between the fish oil group and the olive oil and corn oil control group.

Radack et al. (1991) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 33 American subjects consumed 6 g/day safflower oil (control) or 6 g/day fish oil (1.2 g/day EPA and 840 mg/day DHA; 2.0 g/day total) for 12 weeks each period, in addition to their usual diets. DBP was significantly lower ( $p<0.05$ ) in the fish oil group compared to the control group. There was no significant difference in SBP with consumption of fish oil compared to control.

Steiner et al. (1989) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 28 Swiss subjects consumed 1) 4 capsules/day of salad oil (control), 2) 4 capsules of fish oil (560 mg/day EPA and 240 mg/day DHA; 800 mg/day total), or 3) 8 capsules of fish oil (1.1 g/day EPA and 480 mg/day DHA; 1.6 g/day total) for 4 weeks each period, in addition to their usual diets. SBP and DBP were significantly lower ( $P<0.05$ ) compared to control when consuming 800 mg/day EPA and DHA or 1.6 g/day EPA and DHA.

Urakaze et al. (1989a)<sup>56</sup> was a moderate quality randomized, controlled parallel study in which 30 Japanese renal allograft recipients followed their usual diets (control) (n=16) or consumed 5.4 g/day fish oil (1.5 g/day EPA and 700 mg/day DHA; 2.2 g/day total) in addition to their usual diets (n=14) for 6 months. There was no significant difference in SBP or DBP between the two groups.

Wang et al. (2008) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 52 Chinese subjects consumed 3 placebo capsules (control) (n=26) or 3 g/day fish oil (540 mg/day EPA and 360 mg/day DHA; 900 mg/day total) (n=26) for 8 weeks. There was no significant difference in SBP or DBP between the control and fish oil groups.

Schmitz et al. (2002) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 24 American subjects with chronic kidney disease who had a newly constructed vascular graft consumed 4 g/day corn oil (control) (n=12) or 4 g/day fish oil (1.8 g/day EPA and 960 mg/day DHA; 2.7 g/day total) (n=12) in addition to their usual diets for 12 months. SBP and DBP were significantly lower ( $P<0.05$ ) in the fish oil group compared to the control group.

Wing et al. (1990) was a moderate quality randomized, double-blind, placebo controlled cross-over trial in which 20 Australian subjects consumed 15 g/day olive oil (control) or 15 g/day fish oil (2.7 g/day EPA and 1.8 mg/day DHA; 4.5 g/day total) for 8 weeks each period, in addition to

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<sup>56</sup> The results of this study were also discussed in Urakaze et al., 1989b.

their usual diets. There was no significant difference in SBP and DBP between the fish oil period and the control period.

Gray et al. (1996) was a moderate quality randomized, double-blind, placebo controlled parallel trial in which 19 American subjects consumed 18 g/day corn oil (n=10) (control) or 18 g/day fish oil (2.16 g/day EPA and 1.28 g/day DHA; 3.44 g/day total) (n=9) in addition to their usual diets for 8 weeks. There was no significant difference in SBP or DBP between the fish oil group and the corn oil control group.

Cussons et al. (2009) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 25 Australian women with polycystic ovary syndrome consumed 4 g/day olive oil (control) or 4 g/day fish oil (1.08 g/day EPA and 2.24 g/day DHA; 3.3 g/day total) for 8 weeks each period, in addition to their usual diets. SBP was significantly lower (P=0.018) with fish oil as compared to the control. Similarly, DBP was significantly lower (P=0.005) with fish oil as compared to the control.

Morris et al. (1993) was a moderate quality randomized, double-blind, placebo controlled cross-over trial in which 18 American subjects consumed 1) an olive oil placebo (control), 2) 6 g/day fish oil (2.08 g/day EPA and 684 mg/day DHA; 2.8 g/day total), or 3) 12 g/day fish oil (4.1 g/day EPA and 1.4 g/day DHA; 5.5 g/day total) for 12 weeks each period. During the placebo period, half of the subjects were given 6 g/day of olive oil and half were given 12 g/day of olive oil to ensure blinding. There was no significant difference in SBP or DBP with 6 g/day fish oil as compared to the control. Similarly, there was no significant difference in SBP or DBP with 12 g/day fish oil as compared to the control.

duPlooy et al. (1992) was a moderate quality randomized, single-blind, placebo controlled parallel trial in which 26 South African subjects consumed 0.5 mL olive oil (control) (n=12) for 24 weeks or cumulative doses of fish oil (n=14). Subjects in the fish oil group consumed 1) 0.05 mL fish oil (10 mg/day EPA and 3 mg/day DHA; 13 mg/day total), 2) 0.5 mL fish oil (100 mg/day EPA and 33 mg/day DHA; 133 mg/day total), 3) 5 mL fish oil (1.0 g/day EPA and 333 mg/day DHA; 1.3 g/day total), and 4) 50 mL fish oil (10 g/day EPA and 3.3 g/day DHA; 13.3 g/day total) for six weeks each (n=14) for a total of 24 weeks, in addition to their usual diets. There was no significant difference in SBP or DBP between any of the EPA and DHA doses and the control group.

Norris et al. (1986) was a moderate quality randomized, double-blind, placebo controlled cross-over trial in which 16 British subjects consumed 16.5 g/day of a placebo or 16.5 g/day fish oil (3.2 g/day EPA and 2.1 g/day DHA; 5.2 g/day total) for six weeks each, in addition to their usual diets. When blood pressure was taken with subjects lying down, SBP was significantly lower (P<0.02) with fish oil as compared to the control, but DBP was not significantly different. When blood pressure was taken with subjects standing, DBP was significantly lower (P<0.05) with fish oil as compared to the control, but SBP was not.

Lofgren et al. (1993) was a moderate quality randomized, double-blind, placebo controlled cross-over study in which 38 American men consumed 20 g/day safflower oil (control) and 20 g/day

fish oil (3.6 g/day EPA and 2.4 g/day DHA; 6.0 g/day total) for 12 weeks each, in addition to an American Heart Association step 1 diet. There was no significant difference in SBP or DBP between the control and fish oil diets.

### *Study in subjects with CVD*

Roncaglioni et al. (2013) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 12,505 Italian subjects with multiple CVD risk factors or atherosclerotic vascular disease consumed 1 g/day olive oil (control) (n=6,266) or 1 g/day fish oil (850 mg/day EPA and DHA total) (n=6,239) in addition to their usual diets for 5 years. There was no significant difference in SBP or DBP between the control group and the fish oil group.

Hendra et al. (1990) was a moderate quality randomized, double-blind, placebo controlled parallel study in which 80 British subjects with NIDDM (17 subjects also had CAD and 7 had nephropathy) consumed 10 g/day olive oil (control) (n=40) or 10 g/day fish oil (1.8 g/day EPA and 1.2 g/day DHA; 3 g/day total) (n=40) for six weeks each, in addition to their usual diets. There was no significant difference in SBP or DBP with consumption of fish oil as compared to control.

#### 7. Studies that combined EPA and DHA with other dietary interventions in subjects with hypertension (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg)

Howe et al. (1994) was a high quality randomized, double-blind, placebo controlled parallel trial in which 56 Australian subjects were assigned to one of four groups: 1) normal sodium and 8 g/day olive oil (n=14), 2) normal sodium and 8 g/day fish oil (5 g n-3<sup>57</sup> fatty acids) (n=14), 3) low sodium and 8 g/day olive oil (n=14), 4) low sodium and 8 g/day fish oil (5 g/day n-3 fatty acids) (n=14) for six weeks. In the two normal sodium groups, subjects were given delayed-release sodium tablets that provided an additional 1,840 mg/day (80 mmol/day) sodium to restore sodium intake to between 3,450 and 3,634 mg/day (150 to 158 mmol/day). In the two low sodium groups, the subjects were given placebo tablets in lieu of sodium supplements to maintain blinding. The sodium intake in the low sodium groups was around 1,610 mg/day to 1,840 mg/day (70 to 80 mmol/day). There was no significant difference in SBP or DBP between the normal sodium/fish oil group and the normal sodium/olive oil control group. Additionally, there was no significant difference in SBP or DBP between the low sodium/fish oil group and the low sodium/olive oil control group.

Singer et al. (1990b)<sup>58</sup> was a high quality, single-blind cross-over study in which 16 German men consumed 80 mg/day propranolol and 9 g/day fish oil (1.8 g/day EPA and 1.1 g/day DHA;

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<sup>57</sup> “N-3” is a common scientific abbreviation for “omega-3.”

<sup>58</sup> This study also included a subgroup (n=15) that consumed 9 g/day fish oil (1.8 g/day EPA and 1.1 g/day DHA; 2.9 g/day total) for 36 weeks followed by 9 g/day olive oil (control) for 4 weeks. The statistics comparing these two groups were not reported. Additionally, the olive oil period was an inappropriate control since the duration was only four weeks compared to the 36 week duration of the fish oil period. Since the duration of the study for the control and treatment periods did not match and the statistics between the groups were not reported, scientific conclusions could not be drawn by comparing SBP and DBP readings with consumption of fish oil to SBP and DBP readings

2.9 g/day total) for 12 weeks, followed by 80 mg/day propranolol and 9 g/day olive oil placebo for 12 weeks, and finally 80 mg/day propranolol for 12 weeks. Subjects were instructed to consume an isocaloric diet that substituted the polyunsaturated fat in the fish oil supplement for an equal amount of saturated fat in other foods from their usual diet (e.g. cold cuts, meat, sausage or cheese). With propranolol and fish oil consumption, SBP and DBP were significantly lower ( $P<0.01$ ) compared to propranolol alone. SBP and DBP were also significantly lower ( $P<0.01$ ) with propranolol and fish oil compared to propranolol and olive oil.

Hughes et al. (1990) was a high quality randomized, double-blind, placebo controlled cross-over study in which 13 normotensive American men and 13 hypertensive American men consumed 10 capsules/day of wheat germ oil (77 mg of oil per capsule) (control) or 10 g/day fish oil (3.5 g/day EPA and 1.5 g/day DHA; 5.0 g/day total) for thirty days each period. Subjects were also instructed to consume an isocaloric diet with 35-50 percent of calories from fat. There was no significant difference in SBP and DBP in normotensive subjects between the control group and the EPA and DHA group. Similarly, there was no significant difference in SBP and DBP in hypertensive subjects between the control group and the EPA and DHA group.

Knapp et al. (1989) was a moderate quality randomized, placebo controlled parallel trial in which 30 American men consumed 1) 50 mL/day safflower oil (control) (n=8), 2) 50 ml/day of mixed oils (n=8) (control), 3) 50 mL/day of fish oil (9.0 g/day EPA and 6 g/day DHA; 15 g/day total) (n=8), or 4) 10 mL/day fish oil (1.8 g/day EPA and 1.2 g/day DHA; 3 g/day total) (n=8) for four weeks. Subjects reduced the intake of fat in their usual diets to account for fat intake from the fish oil supplements. There was no significant difference in SBP or DBP between the safflower oil control group and the 10 mL or 50 mL fish oil groups. There was no significant difference in SBP or DBP between the mixed oil control group and the 10mL fish oil group. SBP and DBP, however, were significantly lower ( $P<0.015$  and  $P<0.038$ , respectively) in the 50-mL fish oil group compared to the mixed oil control group.

### **C. Assessment of the Relevant Observational Studies**

FDA reviewed 34 observational studies that evaluated the effect of EPA and DHA intake on risk of hypertension or blood pressure. For the reasons discussed below, no scientific conclusions about the relationship between EPA and DHA intake and blood pressure or risk of hypertension could be drawn from any of the observational studies.<sup>59</sup>

Eighteen observational studies estimated EPA and DHA intake from foods in the diet.<sup>60</sup> In observational studies that calculate nutrient intake from conventional foods, these calculations

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with consumption of olive oil. The high quality rating applies only to the part of the study described in the main text, not the part described in this footnote.

<sup>59</sup> This section contains a general discussion of major flaws in the reports of observational studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

<sup>60</sup> Asserhoj et al., 2009; Beegom et al., 1997; Ebbesson et al., 2007; Jarvinen et al., 2006; Jolly et al., 2011; Leary et al., 2005; Mirmiran et al., 2012; Monge-Rojas et al., 2005; Morris et al., 1995; Oken et al., 2007; O'Sullivan et al., 2012; Rytter et al., 2012; Skilton et al., 2013; Titova et al., 2013; Ueshima et al., 2007; Ulbak et al., 2004; van

are based on recorded dietary intake methods such as food frequency questionnaires, diet recall interviews, or diet records, in which the types and amounts of foods consumed are estimated. A common weakness of observational studies is the limited ability to ascertain the actual food or nutrient intake for the population studied as a result of poor memory, over- or underestimation of portion sizes, and recall bias (Flegal et al., 1999). Furthermore, the nutrient content of foods can vary (e.g., due to type of fish, soil composition, food processing and cooking procedures, or storage conditions such as duration and temperature). Thus, FDA cannot ascertain an accurate amount of EPA and DHA consumed based on reported dietary intake of foods.

Intakes of EPA and DHA have been shown to correlate well with the percent EPA and DHA in erythrocytes ( $r=0.95$ ), plasma phospholipids ( $r=0.60$ ), and whole blood ( $r=0.97$ ) (Patterson et al., 2015). Therefore, FDA considers these biomarkers to be valid and reliable measures of EPA and DHA intake. Biomarkers that are reliable estimates of nutrient intake are not affected by the limitations of estimating food intake in observational studies as discussed above.

Sixteen observational studies<sup>61</sup> measured a valid biomarker of intake for EPA and DHA. However, none of these observational studies controlled for sodium and potassium intake or smoking, all of which are known to affect blood pressure (IOM, 2005b; FDA, 2009). Therefore, no scientific conclusions about the association between EPA and DHA intake and blood pressure or hypertension risk could be drawn from these studies.

### **III. Strength of the Scientific Evidence**

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the U.S. population or a target subgroup, whether study results supporting the proposed claim have been replicated,<sup>62</sup> and the overall consistency<sup>63</sup> of the total body of evidence.<sup>64</sup> Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

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Woudenbergh et al., 2009; Xun et al., 2011. Three of the 18 studies (Ulbak et al.2004; Asserhoj et al., 2009; and Rytter et al., 2012) were observational follow-up studies to an intervention study that did not evaluate the relationship between EPA and DHA and blood pressure or hypertension risk.

<sup>61</sup> Arnarson et al., 2012; Ayer et al., 2009; Dewailly et al., 2001; Godin et al., 2003; Huang et al., 2010; Huang et al., 2012; Kagawa et al., 1982; Leng et al., 1994; Liu et al., 2011; Mayneris-Perxachs et al., 2010; Novgorodtseva et al., 2011; Oda et al., 2005; Park et al., 2010; Van Rossem et al., 2012; Wennberg et al., 2007; Zhang et al.,2012.

<sup>62</sup> See *supra*, note 15.

<sup>63</sup> See *supra*, note 16.

<sup>64</sup> See *supra*, note 7 [Section III. F].

As discussed in Section II, the totality of scientific evidence about a possible relationship between EPA and DHA and risk of high blood pressure includes 112 publications<sup>65</sup> reporting on 104 intervention studies from which scientific conclusions can be drawn. Seventy-five of these studies were conducted in subjects with normal blood pressure or pre-hypertension (SBP ≤ 139 mmHg or DBP ≤ 89 mm Hg), and 29 studies were conducted in subjects with hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg). Of those 104 studies that looked at the relationship between blood pressure and combined intake of EPA and DHA from conventional foods, dietary supplements or prescription drugs, only 36<sup>66</sup> showed a statistically significant benefit. The duration of these moderate to high quality studies showing a benefit ranged from four weeks to one year, and the combined dose of EPA and DHA ranged from 390 mg/day to 15 g/day. The remaining 68 intervention studies that showed no benefit were also moderate to high quality randomized controlled trials. The duration of these studies ranged from 7 days to one year, with EPA and DHA intake ranging from 13 mg/day to 13 g/day. One study (O'Keefe et al., 2006) showed a statistically significant increase in DBP with EPA and DHA consumption. None of the other 67 studies reported a statistically significant effect of EPA and DHA intake from conventional foods, dietary supplements, or prescription drugs.

Based on the findings of these 104 intervention studies, FDA concludes there is some credible evidence suggesting a relationship between the combined intake of EPA and DHA from conventional foods, dietary supplements, or prescription drugs and blood pressure reduction.

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<sup>65</sup> Albert et al., 2015; Alfaddagh et al., 2017; Ansari et al., 2017; Armstrong et al., 2012; Atar et al., 2012; Axelrod et al., 1994; Bairati et al., 1991; Barbosa et al., 2017; Barcelo-Coblijn et al., 2008; Beilin et al., 1993; Bosch et al., 2012; Barden et al., 2006; Blonk et al., 1990; Bonna et al., 1990; Bonnema et al., 1995; Browning et al., 2007; Bruckner et al., 1987; Buckley et al., 2009; Carter et al., 2012; Cazzola et al., 2007; Chan et al., 2016a; Chan et al., 2016b; Chin et al., 1993; Cobiac et al., 1991a; Cobiac et al., 1991b; Cobiac et al., 1992; Conquer et al., 1999; Cussons et al., 2009; Cutler et al., 1992; Damsgaard et al., 2006; Dart et al., 1989; Demke et al., 1988; Deslypere et al., 1992; Dewell et al., 2011; DiGiacomo et al., 1989; Donnelly et al., 1992; duPlooy et al., 1992; Elajami et al., 2017; Faghihi et al., 2012; Ferraro et al., 2009; Finnegan et al., 2003; Flaten et al., 1990; Geelen et al., 2003; Ginty et al., 2012; Gray et al., 1996; Hendra et al., 1990; Hill et al., 2007; Hlais et al., 2013; Holm et al., 2001; Holman et al., 2009; Howe et al., 1994; Hughes et al., 1990; Kenny et al., 1992; Kestin et al., 1990; Kim et al., 2011; Knapp et al., 1989; Kristensen et al., 2016; Kromhout et al., 2010; Landmark et al., 1993; Lara et al., 2007; Levinson et al., 1990; Lofgren et al., 1993; Logan and Spriet, 2015; Lungershausen and Howe, 1994; Lungershausen et al., 1994; Lungershausen et al., 1997; Maki et al., 2009; McVeigh et al., 1994; Mehta et al., 1988; Meland et al., 1989; Meyer et al., 2009; Micallef and Garg, 2009; Minihane et al., 2016; Monahan et al., 2004; Mori et al., 2009; Morris et al., 1993; Mortensen et al., 1983; Mundal et al., 1993; Nestel et al., 2002; Nilsson et al., 2012; Nordoy et al., 2001; Noreen and Brandauer, 2012; Norris et al., 1986; O'Keefe et al., 2006; Pase et al., 2015; Pettersson et al., 1994; Radack et al., 1991; Radaelli et al., 2006; Ramel et al., 2010; Rizza et al., 2009; Rogers et al., 1987; Roncaglioni et al., 2013; Root et al., 2013; Ryu et al., 1990; Sacks et al., 1994a; Sacks et al., 1994b; Sanders et al., 2011; Schmitz et al., 2002; Singer et al., 1990b; Sjoberg et al., 2010; Skulas-Ray et al., 2012; Steiner et al., 1989; Tavazzi et al., 2008; Toft et al., 1995; Urakaze et al., 1989a; Urakaze et al., 1989b; Wu et al., 2014; Vandongen et al., 1993; Vernaglione et al., 2008; Wang et al., 2008; Wing et al., 1990; Wong et al., 2010.

<sup>66</sup> Ansari et al., 2017; Axelrod et al., 1994; Bairati et al., 1991; Bonna et al., 1990; Buckley et al., 2009; Chan et al., 2016a; Cobiac et al., 1991a; Cobiac et al., 1992; Cussons et al., 2009; Damsgaard et al., 2006; Dart et al., 1989; Dewell et al., 2011; Holm et al., 2001; Kestin et al., 1990; Knapp et al., 1989; Lara et al., 2007; Levinson et al., 1990; Lungershausen et al., 1994; Lungershausen et al., 1997; Maki et al., 2009; Mehta et al., 1988; Meyer et al., 2009; Minihane et al., 2016; Mori et al., 2009; Mortensen et al., 1983; Nilsson et al., 2012; Nordoy et al., 2001; Noreen and Brandauer, 2012; Norris et al., 1986; Radack et al., 1991; Rogers et al., 1987; Schmitz et al., 2002; Singer et al., 1990; Steiner et al., 1989; Toft et al., 1995; Vernaglione et al., 2008.

However, this evidence is highly inconsistent. The findings of the minority of intervention studies that found a statistically significant lowering of blood pressure from combined intake of EPA and DHA are undermined by the larger body of evidence that found no effect on blood pressure (or, in one study, a statistically significant rise in DBP). Study results were inconsistent regardless of baseline SBP or DBP or the study duration (7 days to five years). Results were also inconsistent in studies conducted in subjects with preexisting CVD (including CAD and other forms of CHD). In addition, results were inconsistent across the whole range of EPA and DHA intakes studied (13 mg/day to 15 g/day). Consistency of the findings among similar and different study designs is important for evaluating causation and the strength of the evidence. Lack of consistency among studies evaluating the same substance-disease relationship weakens the strength of the evidence. Therefore, FDA concludes that while there is some credible evidence suggesting that combined intake of EPA and DHA from conventional foods and dietary supplements may reduce the risk of hypertension by lowering blood pressure, this evidence is inconclusive and highly inconsistent.

#### **IV. General Requirements for Health Claims and Enforcement Discretion Factors**

A qualified health claim about reducing the risk of hypertension or CHD on the label or in the labeling of conventional foods and dietary supplements containing EPA and DHA in combination is required to meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception of the requirement that the health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. Other exceptions to the general requirements for health claims that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims are discussed below, as well as enforcement discretion factors specific to qualified health claims describing how consuming EPA and DHA in combination may reduce the risk of hypertension or CHD by lowering blood pressure.

##### **A. Daily Dietary Intake Needed to Achieve the Claimed Effect**

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for “high” has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)). However, the agency finds that this provision cannot be applied to qualified health claims for combined EPA and DHA and reduced risk of hypertension because, as discussed in Section III, the scientific evidence for this relationship, which is inconclusive and highly inconsistent, does not support the establishment of a recommended daily dietary intake level for the general U.S. population.

##### **B. Level of EPA and DHA Intake From Dietary Supplements When Used as Labeled**

For a substance to be eligible for a health claim, its use at the levels necessary to justify a claim must be demonstrated to be safe and lawful (21 CFR 101.14(b)(3)(ii)). In Section I.C of this letter (“Safety Review”), we discussed the limited conditions of use under which EPA- and

DHA-containing ingredients (e.g., menhaden oil, other fish oils, algal oils) are GRAS for use in conventional foods. The limitations on conditions of use are designed to ensure that total daily intake of EPA and DHA from conventional foods does not exceed 3 g/day. There is, however, no current limit on the amounts of EPA and DHA that may be used in dietary supplements.<sup>67</sup>

In the absence of a limit on the amounts of EPA and DHA that may be used in dietary supplements, we evaluated evidence on risks related to the use of EPA and DHA to determine whether we should consider the level of EPA and DHA in a dietary supplement as a factor in the exercise of our enforcement discretion for use of the qualified health claim. Because the FD&C Act directs us to evaluate the safety of a dietary supplement in the context of the conditions of use recommended or suggested in its labeling (see 21 U.S.C. 342(f)(1)), we focused on the total daily intake of EPA and DHA that a dietary supplement provides when used as labeled, rather than on the EPA and DHA content of a single capsule or dose of the product.

Health claims in the labeling of conventional foods and dietary supplements are used as a marketing tool to encourage consumers to buy and consume the products that bear them. Health claims have been shown to increase sales of the products on which they appear (Roe et al., 1999). Thus, FDA's exercise of enforcement discretion for EPA/DHA qualified health claims may result in increased intake of EPA and DHA. Because of this potential for greater consumption of EPA and DHA, we evaluated information on possible adverse effects on glycemic control, blood cholesterol, and risk of excessive bleeding at levels of EPA and DHA intake currently available in dietary supplements on the U.S. market (i.e., up to 8 g/day of EPA and DHA combined).<sup>68</sup> Recent comprehensive reviews suggest that intake of EPA and DHA has no adverse effects on glycemic control in subjects with normal glucose levels or in subjects with type II diabetes. These reviews also suggest that intake of EPA and DHA does not raise total cholesterol. Based on our evaluation of several comprehensive reviews, the evidence as to whether EPA and DHA intake increases low density lipoprotein cholesterol (LDL-C) is inconsistent. While some reviews suggest that there is a small but statistically significant increase in LDL-C of approximately 2 to 4 mg/dL, another review suggests that long-term consumption of EPA and DHA does not lead to an adverse effect on LDL-C. Additionally, there is some evidence that despite any potential increase in LDL-C, EPA and DHA intake may reduce the risk of CHD through other mechanisms.<sup>69</sup>

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<sup>67</sup> Dietary ingredients in dietary supplements are not required to be GRAS for their intended use, although FDA can set a regulatory limit on the level of a dietary ingredient to prevent adulteration. See 21 U.S.C. §§ 321(s)(6), 342(f), 371(a). FDA has not set any regulatory limit on the level of EPA, DHA, or other omega-3 fatty acids in dietary supplements.

<sup>68</sup> See Memoranda to Docket No. FDA-2014-Q-1146: Review of Scientific Literature on EPA and DHA Intake and Risk of Excessive Bleeding (June 17, 2019) and Survey of Comprehensive Reviews of the Effects of EPA and DHA Intake on Glycemic Control and Blood Cholesterol (June 17, 2019).

<sup>69</sup> See, e.g., "Letter Responding to Health Claim Petition dated November 3, 2003 (Martek Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease" (September 2004). [<http://wayback.archive-it.org/7993/20171114183727/https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072932.htm>].

Our review of the evidence on bleeding risk found that adverse events were rarely experienced in the studies we evaluated, which looked at intakes of EPA and DHA up to 5.4 g/day. The average dose seen in the studies was around 5 g/day. Based on the data from these studies, we conclude that ingestion of less than or equal to 5 g/day of EPA and DHA from dietary supplements is unlikely to cause excessive bleeding. With little or no data on intakes over 5 g/day, the potential effects on bleeding risk at those levels of intake are less clear. Therefore, to ensure that consumption of high-potency EPA and DHA supplements based on the presence of EPA/DHA qualified health claims in product labeling does not increase the potential for adverse effects, we intend to consider, as a factor in the exercise of our enforcement discretion, that dietary supplements bearing the claim not provide more than 5 gr/day of EPA and DHA combined when used according to their labeling.<sup>70</sup>

### **C. Minimum Content of EPA and DHA to Prevent Consumer Deception**

As a factor in the exercise of our enforcement discretion, we are specifying a minimum amount of combined EPA and DHA that a conventional food or dietary supplement bearing an EPA/DHA qualified health claim should contain. The purpose of this minimum content enforcement discretion factor is to prevent consumer deception from health claims on the labels of products that contain only trivial or insignificant amounts of EPA and DHA. To identify an appropriate minimum content amount, FDA considered the two lowest levels of combined EPA and DHA evaluated in the studies that demonstrated a benefit in lowering blood pressure. As discussed in sections III and IV.A, the scientific evidence for such a benefit does not support the establishment of a recommended daily dietary intake level because it is inconclusive and highly inconsistent; however, limiting our consideration of enforcement discretion to products that contain EPA and DHA in amounts that have been observed to lower blood pressure in at least some well-conducted scientific studies will help ensure that consumers do not see the claim on products that contain so little EPA and DHA that they are very unlikely to provide any such benefit.

The lowest level of intake among the studies that showed a benefit in lowering blood pressure was 0.39 g/day EPA and DHA (Maki et al., 2009). The next lowest level of intake among studies that showed a benefit in lowering blood pressure was 0.8 g/day EPA and DHA (Meyer et al., 2009; Steiner et al., 1989). Although the lowest intake (0.39 g/day) was in the study by Maki et al. (2009), the studies by Steiner et al. (1989) and Meyer et al. (2009) with the next lowest level of EPA and DHA (0.8 g/day) provide a more scientifically appropriate basis for a minimum content amount. The Maki et al. (2009) study was conducted in U.S. subjects and looked at intake of EPA and DHA from two different sources, krill oil and menhaden oil, compared to a control. There was no significant difference in SBP or DBP when the krill oil was used as a

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<sup>70</sup> We considered whether the level of 5 g/day from dietary supplements should be adjusted downward to allow for intake of EPA and DHA from conventional foods and decided no adjustment was necessary. The studies we evaluated provided EPA and DHA supplements as an addition to subjects' usual diets, which (with the possible exception of a few subjects with eating patterns outside the norm) would already contain some EPA and DHA. Therefore, the results of the studies on bleeding risk with intakes of up to 5 g/day EPA and DHA from the test product reflect the subjects' intake of EPA and DHA from all sources, including the EPA and DHA that was in the subjects' usual diet.

source of EPA and DHA (0.3 g/day). However, there was a benefit in lowering SBP, but not DBP, when menhaden oil was provided as the source of EPA and DHA (0.39 g/day). The authors of Maki et al. (2009) noted that because blood pressure was not lowered when krill oil was the source of EPA and DHA, and only SBP but not DBP was significantly lowered when menhaden oil was the source of EPA and DHA, the benefit in lowering SBP from menhaden oil could be a chance finding. For this reason, we believe the 0.39 g/day amount from the study by Maki et al. should not be the basis for the minimum amount of EPA and DHA content in a conventional food or dietary supplement that bears an EPA/DHA qualified health claim.

The Steiner et al. (1989) study was conducted in Swiss subjects with hypertension and evaluated two levels of EPA and DHA, 0.8 g/day and 1.6 g/day. In this study, both levels of intake significantly lowered SBP and DBP. The third study, Meyer et al. (2009), provided 0.8 g/day of EPA and DHA from seal oil and was conducted in Australian subjects with normal blood pressure or pre-hypertension. In this study, SBP, but not DBP, was significantly lowered after consumption of EPA and DHA from seal oil. Since these two studies showed a benefit in lowering blood pressure among subjects with a wide range of blood pressure levels (normal, pre-hypertensive, and hypertensive), we conclude that they provide the most scientifically appropriate basis for a minimum amount of EPA and DHA in conventional foods and dietary supplements that bear an EPA/DHA qualified health claim.

As discussed in the Safety Review section, usual intake of EPA and DHA in the United States is very low (mean total intake of 77 mg/day from all sources for people age 4 years and older). Because of the low level of intake and the number of foods containing EPA and DHA being very limited (primarily fish and seafood products), we do not find it necessary to divide the 0.8 g/day minimum amount among multiple eating occasions throughout the day. Unlike some nutrients that can be found in many types of foods that may be consumed throughout the day, we do not expect the typical U.S. diet to include EPA- and DHA-containing foods on multiple eating occasions during the day. Therefore, we are specifying 0.8 g EPA and DHA (combined total) as the minimum amount per serving for a conventional food or dietary supplement to bear an EPA/DHA qualified health claim.

We are uncertain how much consumers will increase their intake of EPA and DHA from conventional foods and dietary supplements due to the use of qualified health claims about the relationship between intake of EPA and DHA in combination and reduced risk of hypertension and CHD through the mechanism of blood pressure reduction. To help consumers gauge their total intake of EPA and DHA, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that conventional foods and dietary supplements that bear an EPA/DHA qualified health claim state the amount of EPA and DHA per serving in the claim. Alternatively, dietary supplements may declare the amount of EPA and DHA per serving in “Supplement Facts,” instead of in the claim (see 21 CFR 101.36(b)(3)). Information on the content of EPA and DHA allows consumers to understand how their food and dietary supplement choices fit into the context of their total daily diet, as required by 21 CFR 101.14(d)(2)(v).

#### **D. Total Fat, Saturated Fat, and Cholesterol Enforcement Discretion Factors for CHD-related Health Claims**

In regulations authorizing health claims about reducing the risk of CHD through a cholesterol-lowering mechanism, FDA has generally required, with a few exceptions, that foods bearing such claims meet the "low fat" criterion defined by 21 CFR 101.62(b)(2), the "low saturated fat" criterion defined by 21 CFR 101.62(c)(2), and the "low cholesterol" criterion defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR 101.75, 101.77, 101.81, 101.82, and 101.83). We discuss below how the agency intends to consider these criteria as factors in deciding whether to exercise enforcement discretion for EPA/DHA qualified health claims about reducing the risk of hypertension and CHD by lowering blood pressure.

##### **“Low fat” criterion**

Several of the authorized health claims about reduced risk of CHD require foods bearing the claim to meet the definition of "low fat" in 21 CFR 101.62(b)(2) (see authorized claims in 21 CFR 101.75, 101.77, 101.82, and 101.83). The "low fat" requirement was first introduced in the regulation authorizing a health claim about reducing the risk of CHD by lowering intake of saturated fat and cholesterol (21 CFR 101.75). In the proposed rule for that claim (56 FR 60727 at 60739; November 27, 1991), FDA stated that, although total fat is not directly related to increased risk for CHD, it may have significant indirect effects on CHD risk. The agency explained that low fat diets facilitate reducing the intake of saturated fat and cholesterol to recommended levels. Furthermore, the agency noted that obesity is a major risk factor for CHD, and that dietary fats, which have more than twice as many calories per gram as proteins and carbohydrates, are major contributors to total calorie intakes.

FDA has made several exceptions to the “low fat” requirement in CHD health claims, and its views on dietary fat and health have evolved with changes in nutrition science. For example, instead of the "low fat" criterion, fish and game meat are required to meet the "extra lean" criterion in the authorizing regulation for the health claim about saturated fat and cholesterol and reduced risk of CHD (21 CFR 101.75(c)(2)(ii)), as these foods are appropriately included in a diet low in harmful fats and cholesterol. Additionally, a food that bears the plant sterol/stanol esters and CHD health claim is not required to be “low fat,” but the food’s total fat content may not exceed the total fat disqualifying level in 21 CFR 101.14(a)(4) (see 21 CFR 101.83(c)(2)(iii)(C)). In explaining the exception from the "low fat" criterion for foods that bear the plant sterol/stanol esters claim, FDA noted that the 2000 Dietary Guidelines for Americans changed the earlier recommendation for a diet low in total fat to a recommendation for a diet moderate in total fat, replacing the previous focus on limiting total fat with a focus on keeping intake of saturated fat and cholesterol low (65 FR 54686 at 54708; Sept. 8, 2000). The current Dietary Guidelines for Americans (2015-2020 Dietary Guidelines) no longer recommend limiting total fat intake (USDA, 2015). Instead, the 2015-2020 Dietary Guidelines prioritize increasing intakes of polyunsaturated and monounsaturated fats and decreasing intakes of saturated fat and *trans* fat.

FDA agrees that increasing consumption of heart-healthy fats and decreasing consumption of unhealthy fats is more important in reducing CHD risk than consuming diets low in total fat. Therefore, FDA has decided not to consider as an enforcement discretion factor whether a dietary supplement or conventional food that bears an EPA/DHA qualified health claim meets the "low fat" criterion.

#### “Low saturated fat” criterion

For individual foods other than fish (discussed below under “Extra lean criterion for fish”) and dietary supplements, FDA intends to consider, as a factor in the exercise of its enforcement discretion for the use of an EPA/DHA qualified health claim, that the food meets all "low saturated fat" criteria in 21 CFR 101.62(c)(2)). This food category includes primarily foods that do not normally contain EPA and DHA but have been enriched with EPA- and DHA-containing ingredients. For meal products as defined in 21 CFR 101.13(l) and main dishes as defined in 21 CFR 101.13(m), FDA intends to consider, as a factor in the exercise of its enforcement discretion, that such foods meet all "low saturated fat" criteria in 21 CFR 101.62(c)(3).

For dietary supplements, FDA intends to consider, as a factor in the exercise of its enforcement discretion for the use of an EPA/DHA qualified health claim, that the dietary supplement meets the first low saturated fat criterion in 21 CFR 101.62(c)(2)(i) by containing no more than 1 g saturated fat per reference amount customarily consumed (RACC).<sup>71</sup> However, FDA does not intend to consider as an enforcement discretion factor for dietary supplements the additional “low saturated fat” criterion in 21 CFR 101.62(c)(2) that the product contain no more than 15 percent of calories from saturated fat. Among dietary supplements, products that contain 100% fish oil as the source of EPA and DHA would contain the highest amounts of saturated fat. In a fish oil, 20 - 30 percent of calories come from saturated fat (USDA, 2018). Because 100 percent fish oil dietary supplements have no other source of calories than fish oil and reformulation to reduce the percent of calories from saturated fat is not possible, such supplements would never be able to meet the 15 percent criterion in 21 CFR 101.62(c)(2). Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements that bear an EPA/DHA qualified health claim meet the "equal to or less than 1 g of saturated fat per RACC" criterion in 21 CFR 101.62(c)(2), but does not intend to consider the “no more than 15 percent of calories from saturated fat” criterion as a factor in the exercise of its enforcement discretion.

#### “Low cholesterol” criterion

For individual foods other than fish (discussed below under “Extra lean criterion for fish”) and dietary supplements, FDA intends to consider, as a factor in the exercise of its enforcement discretion for an EPA/DHA qualified health claim, that the food meets the low cholesterol

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<sup>71</sup> The reference amount customarily consumed (RACC) for a food represents the amount of that food customarily consumed per “eating occasion” (meal or snack) in the United States. FDA sets the RACCs for various foods and food categories in its food labeling regulations (see 21 CFR 101.12). The serving sizes declared on food labels (“label serving sizes”) are based on, but not necessarily identical to, the RACC (see 21 CFR 101.9(b)).

criterion of no more than 20 mg per RACC or per 50 grams (21 CFR 101.62(d)(2)). As with saturated fat, supplements that contain 100% fish oil as the source of EPA and DHA would contain the highest amounts of cholesterol. Fish oil dietary supplements in liquid form usually have a serving size of one teaspoon (containing 4.5 g of total fat). One teaspoon of fish oil contains about 22 – 34 mg of cholesterol (USDA, 2018), which would exceed the “low cholesterol” criterion per RACC and per 50 g. Because fish oil dietary supplements in liquid form usually have no other components and reformulation to reduce the cholesterol is not possible, such liquid supplements would never be able to meet the “low cholesterol” criterion per RACC or per 50g. Therefore, FDA does not intend to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements in liquid form that bear an EPA/DHA qualified health claim meet the “low cholesterol” criterion per RACC or per 50 g.

With regard to combined EPA and DHA dietary supplements in other forms (e.g., softgel or gummy), FDA intends to consider, as a factor in its discretion for the use of an EPA/DHA qualified health claim, that the dietary supplement meet the low cholesterol criterion of no more than 20 mg per RACC. Supplements that contain 100% fish oil, such as single-ingredient fish oil softgels, would contain the highest amounts of cholesterol. Fish oil softgels usually have a serving size of 1 - 2 softgels. FDA estimates that 1 - 2 softgels weigh about 1 - 3 g and contain about 0.5 - 2 g of fish oil. This small amount of fish oil would not contain enough cholesterol to exceed the criterion of 20 mg per RACC, but the cholesterol content of 100% fish oil softgels per 50 g would far exceed the 20 mg criterion. FDA estimates that 50 g of fish oil would contain about 240 to 380 mg of cholesterol (USDA, 2018). However, since it is highly unlikely that individuals would consume 50 g per day of dietary supplements containing combined EPA and DHA, FDA has decided that it is not necessary to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements containing combined EPA and DHA contain no more than 20 mg of cholesterol on a 50g basis.

#### “Extra lean” criterion for fish

FDA has defined fish in 21 CFR 123.3(d) as “fresh or saltwater finfish, crustaceans, other forms of aquatic animal life (including, but not limited to, alligator, frog, aquatic turtle, jellyfish, sea cucumber, and sea urchin and the roe of such animals) other than birds or mammals, and all mollusks, where such animal life is intended for human consumption.” For the purpose of EPA/DHA qualified health claims in the labeling of products that are essentially all fish, FDA intends to consider certain factors in the exercise of its enforcement discretion. We consider “products that are essentially all fish” to mean fish without any added ingredients and fish with an “insignificant amount”<sup>72</sup> of added fat or carbohydrate, as defined in 21 CFR 101.9(f)(1). Raw fish, boiled fish, and broiled fish are examples of products that are essentially all fish.

The regulation authorizing a health claim about diets low in saturated fat and cholesterol and reduced risk of CHD excepts fish from the "low saturated fat" criterion and "the low cholesterol"

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<sup>72</sup> “An ‘insignificant amount’ shall be defined as that amount that allows a declaration of zero in nutrition labeling, except that for total carbohydrate, dietary fiber, and protein, it shall be an amount that allows a declaration of ‘less than 1 gram.’” 21 CFR 101.9(f)(1).

criterion (21 CFR 101.75(c)(2)(ii)). Instead, fish is required to be "extra lean" as defined in 21 CFR 101.62(e)(4) (contains less than 5 g total fat, less than 2 g saturated fat, and less than 95 mg cholesterol per reference amount customarily consumed and per 100 g).

Most oily fish that are rich in EPA and DHA omega-3 fatty acids exceed the "extra lean" criterion for saturated fat (2 g of saturated fat per RACC) but do not exceed the saturated fat disqualifying level (4 g of saturated fat per RACC). One of the ways that FDA determines whether to consider a nutrient content criterion as a factor in the exercise of its enforcement discretion is whether there are risk reduction data among healthy individuals that would suggest that there may be a benefit from consumption of the food, even though the food does not meet the nutrient content criterion. Such data, for purposes of this review, would include data showing an association with a lower risk of hypertension or CHD in observational studies conducted in apparently healthy individuals. Because we have concluded that the findings of some studies show that intake of EPA and DHA in combination may reduce the risk of hypertension and CHD by lowering blood pressure, FDA has decided that it is not necessary to consider, as a factor in the exercise of its enforcement discretion for products that are essentially all fish, that such products meet the "extra lean" criterion for saturated fat. However, FDA has decided to consider, as a factor in the exercise of its enforcement discretion for products that are essentially all fish, that such products meet the "extra lean" criterion for cholesterol (95 mg of cholesterol per RACC). Most fish that are rich sources of EPA and DHA do not exceed the "extra lean" criterion for cholesterol; thus, this approach should not disqualify many products that are essentially all fish. As discussed earlier, FDA now considers limiting intake of total fat unimportant; therefore, FDA does not intend to consider the "extra lean" criterion for total fat as a factor in deciding whether to exercise its enforcement discretion. This approach is consistent with the agency's decision not to consider the "low fat" criterion as a factor in the exercise of its enforcement discretion for use of the EPA/DHA qualified health claims in the labeling of products that are essentially all fish.

## **E. Disqualifying Nutrient Levels**

Under the general requirements that apply to all health claims, a food may not bear a health claim if the total fat, saturated fat, cholesterol, or sodium content of the food exceeds the disqualifying level for that nutrient (21 CFR 101.14(e)(3)). For individual foods, the disqualifying nutrient levels are 13 g of total fat, 4 g of saturated fat, 60 mg of cholesterol and 480 mg of sodium per RACC, per label serving size, and per 50 g if the RACC is 30 g or less or 2 tablespoons or less (21 CFR 101.14(a)(4)).

Dietary supplements containing EPA and DHA in combination generally meet the disqualifying nutrient levels per RACC and per labeled serving size, as they have small RACCs and serving sizes. However, given the fact that most of these products are composed almost entirely of oil, supplements containing EPA and DHA typically exceed the disqualifying nutrient levels per 50 g. Considering the small serving sizes of supplements containing EPA and DHA and the daily intake amounts typically recommended in the labeling of these products, however, it is unlikely that consumers would consume 50 g of dietary supplements containing combined EPA and DHA under normal circumstances. Thus, FDA intends to exercise enforcement discretion for such

supplements with respect to the requirement for foods with a small RACC (30 g or less or two tablespoons or less) to meet the disqualifying nutrient level for fat per 50 g as a condition of bearing an EPA/DHA qualified health claim.

## **F. 10 Percent Minimum Nutrient Content Requirement**

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the Daily Value for vitamin A, vitamin C, iron, calcium, protein, or dietary fiber per RACC (see 21 CFR 101.14(e)(6)). The purpose of this provision is to prevent the use of health claims on foods of minimal nutritional value.

*Conventional Foods.* The 10 percent minimum content requirement applies to conventional foods that bear an EPA/DHA qualified health claim. The 10% minimum nutrient content requirement per RACC for protein is 5 grams. Products that are essentially all fish almost always contain more than 5 grams of protein per RACC. Thus, such products would generally meet the minimum nutrient requirement because of their protein content. Other conventional foods may or may not meet the requirement, depending on their composition. FDA does not intend to exercise enforcement discretion for the use of EPA/DHA qualified health claims in the labeling of conventional foods that do not meet the 10 percent minimum content requirement.

*Dietary Supplements.* The 10 percent minimum nutrient content requirement does not apply to dietary supplements (21 CFR 101.14(e)(6)).

## **V. Conclusions**

Based on FDA's consideration of the scientific evidence submitted with the petition and other pertinent scientific evidence, FDA concludes that the current scientific evidence is appropriate for consideration of qualified health claims regarding intake of EPA and DHA in combination and lowering blood pressure to reduce the risk of hypertension and CHD, provided that the qualified health claims are appropriately worded to avoid misleading consumers.

The petition proposed the following model claims to be used on the labels or in the labeling of conventional foods and dietary supplements that contain EPA and DHA in combination:

EPA and DHA help lower blood pressure in the general population.

EPA and DHA reduce BP, a risk factor for CHD (coronary heart disease).

EPA and DHA reduce the risk of CHD.

Research shows that EPA and DHA may be beneficial for moderating BP, a risk factor for CHD.

Convincing scientific evidence indicates that EPA and DHA help lower blood pressure in the general population, with comparable reductions to those achieved with other diet and lifestyle interventions.

The first and last proposed claims discuss the possible blood pressure lowering effects of combined intake of EPA and DHA without specifying the disease or health-related condition that is the subject of the claim. Health claims are defined as claims that characterize the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). Blood pressure is neither a disease nor a health-related condition; rather, it is a biomarker that is a diagnostic criterion for certain diseases and health-related conditions, such as hypertension, CHD, and pre-hypertension. Blood pressure levels also affect the risk of certain diseases and health-related conditions, including hypertension and CHD (see Section I.B, “Disease or Health-Related Condition”). To meet the definition of a health claim, the proposed claims that mention only blood pressure-lowering must be modified to describe the relationship between combined intake of EPA and DHA and reducing the risk of hypertension or CHD.

The third proposed claim discusses EPA and DHA and reduced risk of CHD. As noted in section II, the evidence included in the petition was for lowering blood pressure and reduced risk of hypertension. Lowering blood pressure is one of many mechanisms for lowering the risk of CHD. FDA did not evaluate the totality of the evidence for effects of combined EPA and DHA intake on other surrogate endpoints for CHD such as blood (serum or plasma) total cholesterol, blood (serum or plasma) LDL cholesterol, or other mechanisms of CHD risk. Rather, FDA evaluated the totality of the evidence for effects of combined EPA and DHA intake and reducing the risk of hypertension and CHD by lowering SBP and/or DBP. Therefore, to make the third proposed claim complete and enable the public to comprehend the information provided, as required by 21 CFR 101.14(d), we are modifying it to clarify that the mechanism for the possible reduction in CHD risk is lowering blood pressure (see claim 3a, below). Alternatively, the same scientific concept could be conveyed by saying that consuming EPA and DHA in combination may reduce the risk of CHD by reducing the risk of hypertension (see claim 3b, below).

All of the proposed claims lack qualifying language disclosing the limited scientific evidence supporting the claim. This information is necessary to prevent the claims from misleading consumers. Adding it will inform consumers about the level of science supporting the claim and prevent them from being misled about the strength of the supporting evidence. FDA also believes that information on the amount of EPA and DHA in a product is necessary to enable consumers to understand the claim and its significance in the context of their daily diet, as required by 21 CFR 101.14(d)(2)(v). As discussed above in section IV.A, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that the amount of EPA and DHA in the product be stated, either as a combined total or separately for each nutrient, on the labels of conventional foods and dietary supplements that bear an EPA/DHA qualified health claim. Because the nutrition labeling regulations do not permit the amount of EPA and DHA in a food to be declared in the Nutrition Facts label, consumers will not be aware of how much EPA and DHA is in a conventional food bearing the claim unless that information is included in the claim itself. For dietary supplements, however, the amount of EPA and DHA per serving need not be stated in the claim as long as it is declared in “Supplement Facts” in accordance with 21

CFR 101.36. Information on EPA and DHA content allows consumers to understand how their food and dietary supplement choices and intake fit into the context of their total daily diet (see 21 CFR 101.14(d)(2)(v)).

The fifth and final proposed claim states, “*Convincing scientific evidence* indicates that EPA and DHA help lower blood pressure *with comparable reductions to those achieved with other diet and lifestyle interventions*” (emphasis added). Describing the level of evidence supporting the claim that EPA and DHA help lower blood pressure as “convincing” is not accurate. That term overstates and therefore mischaracterizes the strength of the evidence for a relationship between EPA and DHA intake and reduced risk of hypertension through blood pressure reduction. As discussed in section III of this letter, the evidence suggesting that intake of EPA and DHA in combination from conventional foods and dietary supplements may reduce the risk of hypertension by lowering blood pressure is inconclusive and highly inconsistent. Only a minority of the studies (36 out of 104) showed a beneficial effect on blood pressure, and results were inconsistent among studies across the entire range of study durations and levels of combined EPA and DHA intake. Further, the proposed claim’s assertion that EPA and DHA produce “comparable reductions [in blood pressure] to those achieved with other diet and lifestyle interventions” is not supported by any credible scientific evidence. The studies from which scientific conclusions could be drawn did not evaluate how the effects of consuming combined EPA and DHA compare with the effects of other diet and lifestyle interventions on blood pressure. Because the scientific evidence does not support portions of this proposed claim and modifying the claim to exclude the unsubstantiated portions results in a claim nearly identical to the first proposed claim, FDA is including only the remaining four proposed claims in its consideration of enforcement discretion.

In light of the above considerations, FDA intends to consider the exercise of its enforcement discretion for the following qualified health claims:

1. Consuming EPA and DHA combined may help lower blood pressure in the general population and reduce the risk of hypertension. However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
2. Consuming EPA and DHA combined may reduce blood pressure and reduce the risk of hypertension, a risk factor for CHD (coronary heart disease). However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
- 3a. Consuming EPA and DHA combined may reduce the risk of CHD (coronary heart disease) by lowering blood pressure. However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
- 3b. Consuming EPA and DHA combined may reduce the risk of CHD (coronary heart disease) by reducing the risk of hypertension. However, FDA has concluded that the evidence is

inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.

4. Research shows that consuming EPA and DHA combined may be beneficial for moderating blood pressure, a risk factor for CHD (coronary heart disease). However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.

Dietary supplements need not declare the amount of EPA and DHA per serving in the claim if it is declared in “Supplement Facts” in accordance with 21 CFR 101.36.

FDA intends to consider exercising its enforcement discretion for the above qualified health claims when all enforcement discretion factors identified in Section IV of this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will support a qualified health claim for claims that were denied, that will no longer support the use of the above qualified health claims, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

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