SuperOmega-3 Fish Oils

Goal

To supply the omega-3 (n- 3 or ω-3) fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as necessary to complement an individual's diet to achieve current recommendations from The World Health Organization (WHO), The International Society for the Study of Fatty Acids and Lipids (ISSFAL) and other expert recommendations including those suggesting people achieve an omega-3 index score greater than 8%. For those not regularly consuming (or cannot) appropriate fatty fish or certain uncommon plant foods, such as the majority of the U.S. population and other western developed nations, the SuperOmega-3 supplement would provide a corrective amount and ratio of marine sourced omega-3 fatty acids, in a mercury-free easy-to-ingest form, to meet these recommendations that are associated with healthier outcomes at all life-stages. Individuals receiving proper daily amounts of EPA and DHA allow these critical molecules respective maximum contribution to the structure and function of the cardiovascular, brain and vision systems, conveying a potential prophylactic effect. Additionally, the SuperOmega-3 ingredients are obtained from a certified sustainable source.

Note: *While approved prescription (or not) EPA and DHA products are often used for clinical purposes, that application is not relevant to this paper and discussion. It is not within the scope of this document to discuss the omega-3 (n- 3 or ω-3) fatty acids as a therapy (other than using studies to highlight their mechanisms of action within the human body). This document is solely dedicated to their intake contributions to creating and maintaining health, thus prophylactic effect or prevention, not treatment. This document forms the basis for establishing and incorporating the recommended intake of EPA and DHA that may maximize their indispensable contribution to structure and function in their many areas of action to help support health at each life-stage. In other words, quantifying intakes for protection/prevention, not treatments.*

Rationale

The omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found throughout the human body as they are necessary structural and functional body components during all life-phases. [1,2] Mammals cannot directly synthesize meaningful quantities of EPA and DHA[3] to meet current authoritative health recommendations of ~500 mg/day combined.[4] Therefore, as with vitamins and essential minerals, these indispensable fatty acids (FA) need to be supplied by the diet and/or supplements to achieve the recommended level for individuals seeking associated life-stage health benefits related to their lifelong contribution in structure and functioning of the cardiovascular, brain, vision and other body systems where EPA and DHA are indispensably operative.[5,6] In those not supplementing, intakes of EPA and DHA from all sources including alpha-linolenic acid (ALA) conversion, are well below recommendations in the majority of the U.S. population and other nations following similar dietary patterns.[7,8,9,10] If the food diet does not supply this average daily amount, supplementation is considered a viable solution in correcting dietary intake to meet current expert recommendations.[6]

Basic Structure and Functions

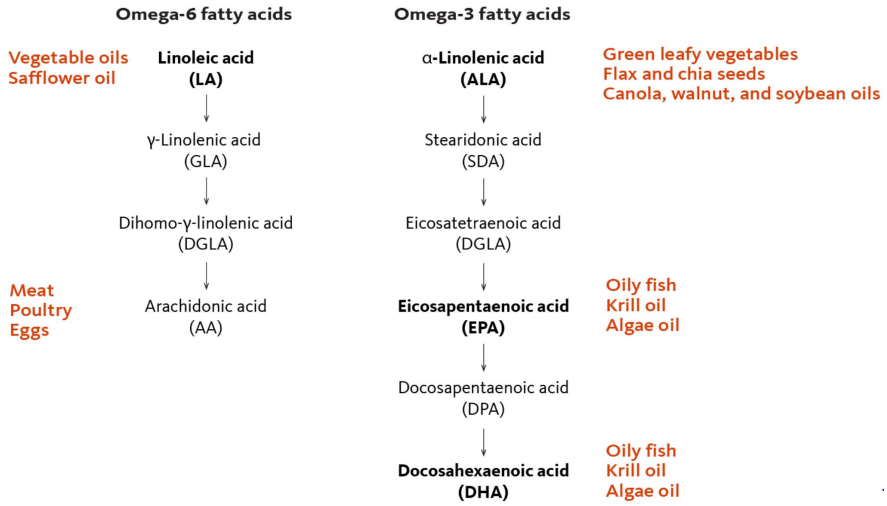
Polyunsaturated fatty acids (PUFA) are classified as such because they contain two or more double bonds and are further distinguished by the position of their first double bond in relation to the PUFAs methyl – (ω) end.[1]
An omega−3 fatty acid has multiple double bonds. As designated, the first double bond is between the third and fourth carbon atoms from the end of the carbon atom chain, hence ω-3. Further designation of omega-3s are long (>20 carbon atoms) and short chain (≤18 carbon atoms) with EPA and DHA being classified as long chain PUFA ω-3.[1,2]
Linoleic acid (LA), an omega-6 fatty acid, and alpha-linolenic acid (ALA), an omega-3 fatty acid, are the two essential fatty acids (EFA) and therefore must be supplied in the diet (see Figure 1).[1,2] Without EFA, humans cannot synthesize omega-3 fatty acids, (nor omega-6) because they lack the enzymes to produce double bonds at the ω-3 position.[3]
Humans can convert some ALA into EPA and then to DHA, but in generally insignificant amounts. [11,12] The parent fatty acid of the long-chain omega-3 fatty acids EPA and DHA is alpha-linolenic acid acquired from plant sources. Again, although humans can convert ALA supplied by the diet to the long-chain omega-3 fatty acids EPA and DHA, this

conversion is inefficient and limited.[13,14] In fact, Greupner et al., in their healthy test subjects, not only confirmed that the intake of ALA is not a sufficient source for the increase of EPA and DHA in people consuming Western diets, but also found that a high-ALA intake, while it does increase EPA, also leads to declining DHA concentrations.[15] Therefore, expert recommendations states that EPA and DHA be obtained from additional sources. In other words, practically speaking, reaching current recommended levels of EPA and DHA would require acquiring from food and dietary supplements as needed.[6,16,17,18,19] Additionally, long-term consumption of alpha-linolenic acid does not have the same desired effect as fish oil (marine source of EPA and DHA) on triglyceride concentrations, tissue DHA concentrations, or on susceptibility to oxidation of low-density lipoprotein (LDL) cholesterol and inflammation,[20,21] making marine omega- 3 sources the experts' recommendation.[4,6,22,23,24,25,26]

Fish such as herring, kipper, mackerel, menhaden, pilchard, salmon, sardines, and trout contain high amounts of the omega-3 fish oils.[6,13,27] Shellfish, such as oyster, shrimp, and scallop contain lesser amounts.[28] These fish oils are especially high in EPA and DHA, the two most studied omega-3 fatty acids purported to be responsible for the positive health outcomes seen in populations that consume higher amounts of fish.[29,30,31] As mentioned, EPA and DHA from fish function differently than their precursor alpha-linolenic acid, a plant-derived omega-3 fatty acid.[20,21] Although fish is a dietary source of omega-3 oils, fish (like humans) do not synthesize them; they obtain them from the prey fish, algae (microalgae in particular) or plankton in their diets.[32,33] The most widely available dietary source of EPA and DHA are the cold-water oily fish listed above. These fish have a profile of approximately seven times as much omega-3 oils as omega-6 oils.[28] Other oily fish, such as tuna, also contain omega-3 in somewhat lower amounts.[6,27,28,32,34]

The long chain omega-3s fatty acids, EPA and DHA, are crucial to cell membrane structure and function as they affect cell membrane properties such as fluidity, flexibility, permeability, and the activity of membrane-bound enzymes;[35,36] synthesis of eicosanoids, the chemical messengers that play important roles in immune and inflammatory responses;[31,37,38] vision due to the high concentration of DHA in the retina of the eyes;[39,40,41] central nervous system functioning (low DHA brain levels are associated with learning deficits);[42,43,44,45] and regulation of gene expression including those involved in fatty acid metabolism and inflammation.[46,47,48] These myriad indispensable functions of EPA and DHA become the rationale for achieving lifelong daily intake at recommended levels including supplementing when the diet falls short, because regular insufficient intake is associated with compromised structure and functional development and long-term health.

Figure 1 - Classes of Essential Fatty Acids - from the Linus Pauling Institute[49]



Dietary Intake versus Recommendations

Below are intakes versus recommendations, assuming recommendations of ~250-500 mg/day designated by our elected experts is the desired EPA/DHA daily intake necessary to achieve associated health benefits.

U.S. Intake: due to current dietary habits, the median intake of omega-3 fatty acids EPA and DHA for Americans is approximately 128 mg/day,[9,50] well below the proposed level[7,8,9,10,23,24,26,25,26,51,52,53,54]

IOM recommendation: While the Food and Nutrition Board of the U.S. Institute of Medicine (IOM) has established adequate intake (AI) levels for the parent fatty acids of omega 6 and 3 (ALA 1.1 g/d for females and 1.6 g/d for males and linoleic acid (LA) 12 g/d for females and 17 g/d for males) there is no call out for adequate EPA and DHA intakes.[18,23,55] Since the conversion from these EFA creates an impractical solution in achieving the expert recommendations of their "downstream" indispensable omega-3 fatty acids, EPA and DHA,[13,14,15,16] progressive experts are calling for EPA and DHA to become labeled as essential, meaning ingesting direct marine sources of these long-chain PUFA in the recommended daily amounts (~250-500 mg/d), analogous to the way in which the Dietary Reference Intakes classify recommended amounts of vitamins and essential minerals to achieve better health.[5,6,54,56,57]

The European Food Safety Authority (EFSA) dietary recommendations for EPA and DHA based on cardiovascular risk considerations for European adults are between 250 and 500 mg/day.[58,59]

The World Health Organization (WHO) recommends an acceptable macronutrient distribution range (AMDR) for EPA plus DHA at 250-2,000 mg/day (the upper limit applying specifically to heart health).[4]

GOED/The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommends that healthy adults receive a minimum of 500 mg/day of EPA plus DHA for cardiovascular health.[60,61]

The American Heart Association recommends that people eat a variety of fish (preferably oily) at least twice weekly.[62,63] Two servings (3.5 ounces each) of oily fish are purported to provide approximately 500 mg of EPA plus DHA.[6,27] Pregnant women and children should avoid fish that typically have higher levels of methyl mercury.[63] People with specific heart health problems are advised to consume approximately 1 g/day of EPA plus DHA preferably from oily fish or to consider EPA and DHA supplements in consultation with a physician.[64] Patients who need to lower serum triglycerides may take 2-4 g/day of EPA plus DHA supplements under a physician's care.[64] And finally, the results of epidemiological studies provide consistent evidence that increasing dietary omega-3 fatty acid intake is associated with heart health through mechanisms other than lowering LDL cholesterol. In particular, increasing fish consumption to at least two servings of oily fish per week has been associated with significant structure and function improvements.[63,65] This amount would provide about 400-500 mg/day of EPA plus DHA or approximately 3-4 times more than normal dietary intake.[57]

Summary: Intake and Recommendation of EPA & DHA

- Current U.S. intake without supplementation: 128 mg/d*
    - Average adult consumes less than one serving of fish weekly
- Adequate Intake (not necessarily recommended) is set at 250 mg/d
- Current expert (noted above) recommendations are 400-500 mg/d to help support long-term health in generally healthy individuals
- Clinical recommendations range from 500-4,000 mg/d based on physician diagnosis and treatment
    - Generally prescribed FDA approved Omega-3 formula

* Produces a score of <4% on the Omega-3 Index (see below)

Current omega-3 EPA/DHA from food intake as shown in the map below (Figure 2) gives rationale for supplementation to correct dietary intakes to the recommended levels associated with better health outcomes at all life-stages.[4,6,7,8,23,24,25,26,58,59,60,61,62,63,64] For those unable (allergies, mercury fears, etc.) or unwilling (food preferences, veganism, concern for fish sustainability, etc.) to meet this health recommendation, supplementation would be the responsible health professional course of action.[6] Although existing dogma represents eight ounces of fatty fish weekly

can supply the current AHA and DGA "recommended" amounts of marine EPA/DHA,[66] emerging science has tested this boundary by incorporating an Omega-3 Index test invented by Dr. William Harris of the Sanford School of Medicine at the University of South Dakota.[54,67,68]

Figure 2 – Global Omega-3 Status Map

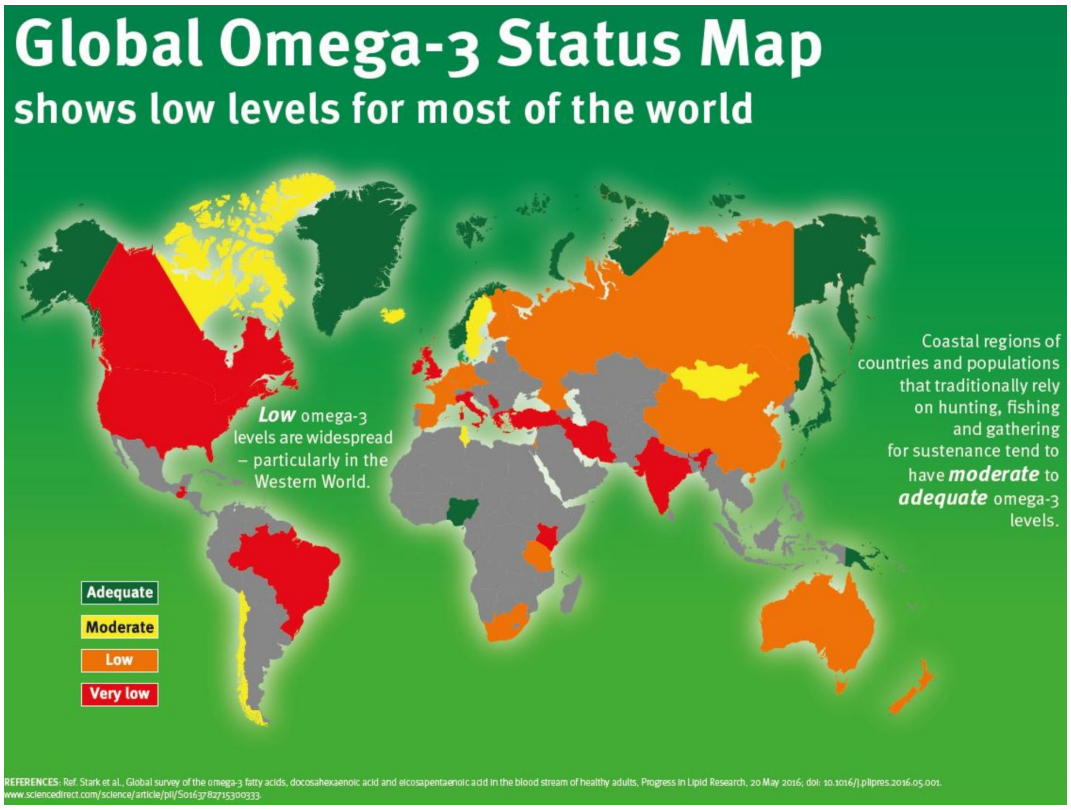


Figure 2: A review of 298 studies produced this map showing regions with worrisome low EPA/DHA blood levels include all the Americas. Central and southern Europe, the Middle East, south east Asia and Africa.[69]

The Omega-3 Index and Supplementation

The omega -3 index is the percentage of the two omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in total erythrocyte fatty acids.[54,67,68] When determined with a highly standardized and specific analytical methodology (HS-Omega- 3 Index), it describes an individual's status of EPA+DHA.[54,67,68] A HS-Omega-3 Index (O3I) below the target range of 8% to 11% has been found to be associated with early health problems.[54,67,68,70] Along with increasing cardiovascular risk factors,[71] a low HS-Omega-3 Index is associated with suboptimal brain structure and function,[72] measured as reaction time or executive function,[73,74,75] where supplementation to raise levels has shown improvements in various aspects of brain structure and function.[76,77,78,79,80,81,82,83,84] Therefore, proposed health zones are: high risk <4%; intermediate risk 4-8%; and low risk >8%.[54,56,67,68,75,85] With greater than 8% being the omega-3 index goal for healthy aging, the AHA recommendation of one to two seafood meals a week was tested and found to be significantly insufficient in reaching the desired level. In fact, according to McDonnell et al., among non–supplement users, only 3% of subjects consuming one fish serving per week and 17% eating ≥2 servings per week reached an O3I ≥8.0%. Among those consuming ≥2 fish servings per week, only those also taking an average of 1,100 mg/day of supplemental EPA + DHA had a median O3I ≥8.0%. Additionally, for non-fish eaters, it took supplemental EPA + DHA intake with an average of 1,300 mg/day to achieve an O3I of 8.0%.[86] The authors conclusion: This study suggests that following the AHA guidelines does not produce an O3I ≥8%,

and although fish oil supplements clearly raise EPA and DHA blood levels,[87,88] taking one serving per day of most omega-3 supplements will not reach the desired O3I range.[86] Jackson et al. confirmed these results and conclusions.[89] Further, Walker et al. reported that for 95% of people to raise their O3I from 4% (current level of 95% of Americans and other nations is <4% as shown in Figure 2[7,10,69]) to 8% it would require a dose of 2,000 mg of EPA+DHA, far above the AHA and DGA recommendation (500 mg/day to reduce risks) for prevention.[90] Additionally, they showed that the AHA/DGA/WHO recommendation of one to two servings per week of fatty fish (assumed to supply 500 mg/day of EPA+DHA) only raised the O3I from 4% to 6%, still well below the O3I range of 8-12%, which is an indicator of better overall health including supporting heart, brain, eye and joint health when part of a healthy lifestyle.[90] Mindful this daily dose to raise the O3I from 4-8% in 13 weeks, probably means once this level is achieved, the daily dose over a lifetime, could be lower. That said, the daily EPA+DHA recommendation by the AHA/WHO/DGA never reached the 8%.

Basic Recommendation

Based on current data supporting the associated health benefits of the marine sourced omega-3 fatty acids EPA and DHA at intake levels that can achieve an O3I of ≥8%, which is approximately three to four servings per week of fatty fish, 500-1,000 mg/day from a fish oil supplement or a combination of the two makes these numbers the responsible recommendation to be included as a healthy lifestyle action to support health at each life stage. Given that 95% of the U.S. populations and others eating similar diets have an O3I ≤4%, supplementation becomes warranted for the majority.

Proposed Mechanisms of Action in Supporting Health & Aging

The following section contains brief overviews from scientific literature describing EPA and DHA's potential mechanisms of action in supporting health including the structure and/or functional aspects in areas these molecules are present such as heart, brain, eyes, etc., which also gives rise to recommended intake amounts to be incorporated as a healthy lifestyle measure to yield a potential prophylactic effect in tissues where in EPA and DHA are indispensably in a state of dynamic action.

Heart Health

Typical Western diets have a notoriously lopsided ratio of omega-6 to omega-3 fatty acids, [91,92,93] reported to contain an omega-6 (O6) to omega-3 (O3) fatty acid (FA) intake ratio in a range of 10-20:1, primarily because of low omega-3 intake and ubiquity of omega-6 food sources leading some scientists to call out this ratio (specifically omega-6 intakes) as a major contributor to inflammation leading to poor heart health including early organ failure.[91,92,93,94,95] I has often been proposed that the O6 to O3 ratio should be <4:1 like our early ancestors to support health.[91,92,93,94,95,96,97,98] However, this may be an oversimplification, and because omega-6 fatty acids, such as linoleic acid, are also necessary diet components, the goal should be to consume proper amounts of O6 and O3 for supporting health irrespective of a ratio – i.e. cutting down sources of O6 FA, won't matter much if you're not getting recommended amounts of O3FA (a ratio of <4:1 would not be helpful if the O3I is <4%).[99,100] At this moment in science, for long-term health, some fats are considered better than others: good ones include mono- and polyunsaturated fats (both O6 and O3), bad are the industrial-made trans fats, with saturated fats generally falling somewhere in the middle depending on lifestyle factors.[101,102] Confusion and controversy over fatty acid recommendations often come from studying groups of fatty acids (e.g. PUFA, saturated fatty acids [SFA], trans fats, etc.) rather than individual FA, including substituting a group for another group (e.g. PUFA for SFA or PUFA for carbohydrates) to decide a clinical endpoint.[26,103,104,105] In this vein, omega-3 FA, specifically EPA and DHA, are considered anti-inflammatory molecules, while omega-6, specifically linoleic acid and arachidonic acid (AA) are discussed as pro-inflammatory, and although inflammation is necessary response to protect injury, mitigate infections, etc., too much for too long can be harmful in many areas of the body such as in the cardiovascular system, and thus O6 FAs are often vilified.[106,107] Unfortunately, FA recommendations are not that "black or white," meaning, the answer to the O6/03 "ratio" is not as simple as defining the fatty acids' (FA) inflammation properties since each FA has important unique structure and function roles including both pro and anti-

inflammation actions in tissues throughout the body. Moreover, related to diet differences, Zhuang et al. findings from two independent nationwide cohorts on the associations between specific PUFA intake and mortality in China and America concluded the following: *"Different sub-types of PUFAs divergently are associated with mortality, and the investigated associations also vary between Chinese and U.S. populations. Marine omega-3 PUFA and AA may be more protective for the Chinese population compared with the U.S. population; high consumption of ALA and LA may lower risk of death for the U.S. population, but elevate mortality for Chinese population."*[108]

Summarizing what we do know, unless someone is consuming a diet extremely high in processed vegetable and seed oils (e.g. sunflower, corn, soybean, etc.) along with other poor lifestyle choices, the ratio of O-6 to O3 would be a non-factor by consuming at least the recommended amounts of O-3 described above to achieve the desired O3I: approximately two to four servings per week of oily fish, 500-1,000 mg/day of supplements or a combination of the two (range based on diet and individual/genetic efficiency in conversion from plant intake of omega-3 ALA). In other words, it may not be that our omega-6 intake is too high, it's that our omega-3 intake is too low along with other controllable lifestyle factors.[100] To further emphasize this point, Marklund et al. in the largest to date harmonized, individual-level pooled analysis across 30 prospective studies from 13 countries, found higher in vivo levels (using biomarkers rather than recall) of the omega-6 PUFA LA were associated with *lower* risk of CVD events, specifically, CVD mortality and stroke. Further the, omega-6 PUFA AA levels were not associated with higher risk, and actually associated with lower CVD risk in some analyses.[100] Combine this result with the well documented low intake of marine Omega-3s and associated benefits of achieving an O3I of ≥8%, the best solution calls for raising O3 intake, which regular consumption of certain fish and/or supplementation can accomplish, rather than shooting for a specific ratio and is likely the rationale for the AHA and other authoritative bodies adopting this policy for heart health.[26,58,63,109,110,111]

EPA and DHA Primary Mechanisms of Action in Support of Heart Health

Collectively, thousands of studies have shown EPA and DHA to demonstrate heterogenous properties in support of cardiovascular (CV) health including, but not limited to: regulating gene expression[46,47,48,112] including through interaction with transcription factors to favorably effect lipid metabolism[46,113,114] and inflammation properties such as inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B thus reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor γ and binding to the G protein coupled receptor GPR120;[31] possibly mitigating oxidative-induced DNA injury in vascular cells;[48] enhancing vasodilation;[115] positive contribution as components of membrane glycerophospholipids to membrane properties;[36] blood pressure[116,117,118] and heart rate lowering effects,[119,120] with all these properties likely synergistically related to the health of the CV system and life-stage outcomes. However, as it relates to CV health, investigations have primarily focused on the O3 FA high level/basic contributions in controlling triglycerides (including transcription regulators acting as ligands for specific nuclear receptors/transcriptional factors – i.e. binding to proliferator-activated receptor alpha (PPARα) to reduce TG,[121]) and vascular inflammation (e.g. lipid mediator precursor).

Subclinical (defined as denoting a health issue not yet severe enough to be readily detectable or display overt symptoms) inflammation and high triglyceride (TG) levels (poor lipid profiles) are recognized as primary factors in the development of poor cardiovascular health and related events.[26,122] While prescription EPA and DHA are an AHA approved therapy for elevated triglycerides, that use is not relevant to this paper, but does highlight actions of the two O3 FA.[64] To the crux of this discussion is EPA and DHAs protective roles in both supporting healthy lipid profiles and management of inflammation, which has prompted EPA/DHA fish oil intake to become a DGA and AHA (and other authoritative bodies noted throughout) recommendation for prevention in the development of poor CV health.[25,26,63,123,124,125,126]

Cardiovascular Inflammation

While lipid mediators derived from O6 PUFA, such as arachidonic acid (AA) have primarily pro-inflammatory functions (also inhibit inflammatory cytokines and stimulate anti-inflammatory lipoxin[31,127]) and chronic overexpression is associated with unwanted amounts of inflammation,[106,128] lipid mediators derived from omega-3 PUFA metabolism (eicosanoids and other oxylipins [chemical messengers]) have inflammation-resolving properties, and partly explain the protective effects that are often seen with omega-3 PUFA ingestion.[31,38,57,129] Along these lines, EPA/DHA compete with AA for conversion in these metabolic pathways and helps explain one of their inflammation lowering mechanisms – i.e. a reduction in formation of AA-derived proinflammatory eicosanoids (e.g. prostaglandin E2 and leukotriene B4).[31,128] Simultaneously, enzymatic conversion of EPA and DHA yields their potent lipid mediators including specialized pro-resolving lipid mediators such as protectins and resolvins, which actively work to turn off the inflammatory response and yield a greater degree of prostaglandin I_2 production, which offers vasodilatory and antiplatelet effects.[130,131,132] Further, in a study by Ostermann et al. which involved supplementing people for 12 months consuming a western diet (low in EPA/DHA) found a linear dose response and uniformed increase in DHA/EPA derived oxylipins demonstrating that these oxylipins are dependent on substrate (O3 PUFA) availability. They concluded that: "the more n–3 PUFAs (i.e., EPA + DHA) consumed with the diet, the higher the plasma concentrations of EPA- and DHA-derived oxylipins."[38]

To further highlight EPA/DHA's vascular protective actions, Alfaddagh et al. found that supplementing EPA/DHA (3 grams for 30 months) to reach an O3I of ≥4%, prevented the progression of coronary artery plaque in non-diabetic subjects with poor CV health. Non-diabetic subjects in the lowest quartile (O3I <3.43%) receiving no supplementation had significant progression of fibrous, calcified and total plaque.[133]

Triglycerides/Lipid Profiles

Lipid profiles highlighting triglyceride (TG) levels are common indicators of CV health, including TG-rich lipoprotein levels in the circulation, in which the O3 FAs, EPA and DHA make important lifetime contributions that effect the structure and functional outcomes of the CV system.[6,25,26,123,124,125,126,134,135] Omega-3 fatty acids in prescription and non-prescription forms have been shown in numerous studies using clinical doses up to 6 g/d to lower elevated triglyceride levels.[136,137,138,139,140,141,142,143,144,145,146,147,148,149]

EPA and DHA's favorable effects on circulating TG levels are primarily through their interactions with apolipoprotein B (apo B)-containing lipoproteins. Apo B is a protein involved in the metabolism of lipids and the predominant protein constituent of lipoproteins such as very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL, the "bad cholesterol"), the leading causes of poor CV health.[150]

Triglycerides are carried in the circulation as TG-rich lipoprotein particles, primarily in VLDL fraction in a fasted condition and as VLDL and chylomicrons in the fed state.[134,135] On the other hand, high-density lipid protein (HDL) significantly decreases the connection between TG levels and poor CV health.[134,135] The triglyceride-lowering effect of EPA and DHA appears to result from the combined effects[31,64,65,151] of inhibition of lipogenesis and stimulation of lipoprotein lipase activity,[140,152] faster clearance of chylomicrons,[140,153] stimulation of fatty acid oxidation in liver,[152,154,155] and a decrease in liver fat.[156,157,158,159] These proposed 03 actions in lowering TGs are bolstered by the Oscarsson et al. review on EPA and DHA mechanisms of actions on apo B containing lipoproteins (readers are reminded that doses used in many reviewed studies are EPA/DHA treatment and prescription doses but because of this, O3s potential mechanisms are easier to elucidate/highlight).[160] Assessing 65 articles on studies in humans evaluating the mechanisms of action of EPA and DHA on apolipoprotein B-containing lipoproteins, including TG-rich lipoproteins LDL/VLDL the authors summarized their findings which have been directly outlined below:

Summary of Key Findings from Oscarsson et al. [160]

- There is no clear difference between DHA and EPA with respect to reducing fasting or postprandial TG levels.

- The major mechanism explaining reduced fasting serum TG associated with omega-3 FA treatment is reduced VLDL production, including a reduced number and size of VLDL particles. The reduced VLDL production results in a faster conversion of VLDL particles to IDL and LDL.
- OM3FA supplementation partly corrects the underlying disorder responsible for the atherogenic dyslipidemia in patients with type 2 diabetes by reducing hepatic production of VLDL1.
- Potential mechanisms for the inhibitory effect of OM3FAs on VLDL production include improved hepatic insulin sensitivity, reduced liver fat and increased whole-body fatty acid oxidation.
- There is a relationship between DHA and the apoE4 isoform of apoE, which results in an increased production of LDL from VLDL as well as in a reduced hepatic uptake of LDL via competition with apoE4-enriched VLDL2. Therefore, patients with the apoE4 variant could contribute to an overall increase in LDL-C in trials using OM3FA formulations containing DHA.
- OM3FAs increase LPL activity, likely by increased expression of the gene and reflected as increased pre-heparin LPL activity. Increased LPL activity can explain the higher clearance rate of TG-rich lipoproteins postprandially, but normally not in the fasted state because LPL capacity is not rate-limiting when TG levels are not high.
- Treatment with OM3FAs reduces plasma levels of PCSK9 but does not reduce LDL-C levels. Therefore, PCSK9 is unlikely to be of major importance for LDL-C levels following treatment with OM3FA.

Apo apolipoprotein, DHA docosahexaenoic acid, EPA eicosapentaenoic acid, IDL intermediate-density lipoprotein, LDL low-density lipoprotein, LDL-C low density lipoprotein cholesterol, LPL lipoprotein lipase, OM3FA omega-3 fatty acid, PCSK9 proprotein convertase subtilisin/kexin type 9, TG triglyceride, VLDL very-low-density lipoprotein

Supporting Heart Health – Case for Protection Not Treatment

The above data in this section was to inform the reader of what science currently knows about how EPA/DHA function in the cardiovascular system (CVS). Although many of the above content/studies were related to treatments using dietary supplement or prescription EPA/DHA at doses greater than recommended daily intakes, they highlight the EPA/DHA mechanisms of action in the CVS. Therefore, this data reinforces the basis for the established daily intake amounts, noted in the rationale section above, to offer the necessary support/protection for the CVS (prophylactic effect) that is associated with better health outcomes at each life-stage with the goal of avoiding treatment when the root cause is chronic inadequate EPA/DHA intake.

Eye Health

DHA is a key essential fatty acid found in the retina[161,162,163,164,165] and is involved in visual/retina development and protective actions also described as oxidative preconditioning (authors define as an "acquired protection or resilience by a cell, tissue, or organ to a lethal stimulus enabled by a previous sublethal stressor or stimulus"[166]).[41,165,167,168] Simply put, oxidative preconditioning requires DHA – i.e. preventative levels. Photoreceptor outer segments in the eyes are constantly being renewed which may require a steady supply of DHA to maintain proper functioning.[164,169] The systematic review and meta-analysis of 38 trials including 53 intervention arms across critical stages of brain development (pregnancy through infancy) by Shulkin et al.,[40] found a significant benefit of omega–3 PUFA supplementation (EPA, DHA or in combination) on infant cognitive development and visual acuity, which as the authors stated, is consistent with the timing of retinal and visual cortex neurodevelopment, much of which occurs postnatally."[40,170] Blockage of the blood vessels that supply the retina contributes to poor aging eye health, thus the beneficial effects of omega-3 fatty acids on the retina may be due to DHA and EPA's antithrombotic and hypolipidemic effects.[164,171,172] Epidemiological studies have suggested that the omega-3 fatty acids, DHA and EPA, are protective of ocular health.[164,171,173,174,] In fact, many studies including a 12 year study demonstrated that participants reporting the highest omega-3 fatty acid intake had significantly fewer age-related eye problems than their peers.[175,176] van Leeuwen et al. completed a comprehensive review and evolving perspective on lipid profiles, intake and metabolism's role in eye health, and makes the point of our paper: EPA and DHA have a clear protective role in establishing and supporting

the eye structure and function throughout life, where supplement trials for treatment of age related ocular weaknesses (i.e. after the fact) show mixed results.[176,177] To this point, bio-actives like EPA, DHA and nutrients like vitamins and essential minerals do not work in a vacuum, they are synergistic in construction and maintenance of mammals from the beginning of life.[1,5,7] Like all the nutrition molecules that construct the human body from the beginning of life, EPA and DHA are symbiotic with the other nutritional components that make up common areas of the human entity. They are synergistic with myriad other nutrient's actions in their respective EPA/DHA-dependent systems, as each one has many unique roles in multiple processes, any of which will be compromised if chronic intake is below what we know to be acceptable of any of symbiotic molecules (i.e. recommendations).[1] Meaning, repletion or correction is often too late or too short to allow the necessary nutrient synergy effect or lacked other required synergistic nutrients at adequate levels to fix a latent/insidious condition. However, and because of this noted synergy, better attempts at treatments are now using combined nutritional components in formulas. Recognizing EPA/DHA and other synergistic nutritional components' role in eye structure and function, nutrition is now part of the routine management of eye health for many ophthalmologists.[178] Ophthalmologists choosing to use nutritional supplements (e.g. lutein, zeaxanthin, zinc, omega-3, and vitamins) are well-informed regarding current scientific studies.[178,179]

Supporting Eye Health – Case for Creation and Protection, Not Treatment

The above data in this section was to summarize, to the reader, what science currently knows about how EPA/DHA participates in ocular structure/function and connected systems. Therefore, this data reinforces the basis for the established daily intake amounts, noted in the rationale section above, to offer the necessary support/protection for the creation and maintenance of optical health (prophylactic effect) that may help avoid treatment when the root cause is chronic inadequate EPA/DHA intake.

Brain/Cognitive Structure and Function

The human brain, like other organs, has a unique structural and functional fatty acid composition that includes both omega-6 and omega-3 FA with DHA being quantitively the most important omega-3 FA (200-300 times higher brain levels than EPA).[1,180] Therefore, along with other brain nutrients essential to its structure and function, adequate levels of structural/functional fatty acids are critical to short and long term brain health including being protective against early cognitive aging, and to be sure, higher levels (O3I >8%) of DHA/EPA are associated with better brain health across a lifespan.[181,182,183] Further, in part due to their anti-inflammatory properties, O3 FA are also important to neurogenesis[184] (process of new neurons being formed in the brain), an action scientists recently discovered continues throughout the human lifespan.[185]

DHA and EPA, for many of the reasons described in the sections above related to their mechanisms of actions within the CV and ocular systems (e.g. membrane structure/function, inflammation mediation properties, vasodilation etc.), are likewise indispensable for brain structure and function throughout the human lifespan.[7,181,182,184,186,187] The acquisition of these FA during gestation and infancy is critical to the development of a healthy brain (most of the brain's structural development takes place from conception to age 3 years) and has given rise to recommending proper maternal and offspring intake.[187,188,189,190] In the brain, as with everything discussed so far related to proper EPA/DHA intake and natural development, health creation/protection and risk prevention, the recommended intake can be met with regular consumption of fatty fish, but if not, which is common because of warnings of fish pollution/mercury, especially during pregnancy, supplementing to correct the gap between recommendations and diet intake is warranted for all ages and genders in order to maintain the various lipid pools that supply EPA/DHA.[187,191] Additionally, the genotype of genes (individual variations) involved in metabolism and the endogenous production of DHA/EPA are a "wildcard" in not just estimating conversion of precursor molecules (e.g. plant sources) and other FA metabolism competition, but also for predicting proper intakes to achieve desired levels and associated outcomes.[192] An individual's FA metabolism adds to the recommendation of getting direct marine sources of EPA/DHA. For example, persons with the ApoE-ϵ4 polymorphism exhibit a disturbed DHA metabolism and lower response to EPA

and DHA supplementation.[193] In other words, the effect of fish or PUFA intake on cognition may, at least in part, be dependent on apolipoprotein E (APOE) genotype[192,193,194]

EPA/DHA have clear neuroprotective properties and unique and indispensable roles in neuronal membranes, essential for proper brain structure and function,[195] including, but not limited to, modulating the membrane biophysical properties such as membrane fluidity, permeability, phase behavior, fusion and cell signaling.[35,196,197] Additionally, DHA derived anti-inflammatory mediators (e.g. neuroprotection [NPD-1]) in neuroprotection are crucial in brain cell survival and repair throughout the aging process.[195,198,199]

These indispensable roles of EPA and DHA in brain development, structure and function have led scientists to not solely rely on the creation of the dietary recommendations necessary to realize the brain's health potential throughout life, but also to explore the use of omega-3 intakes as an adjunct method in cognitive therapy and protection.[77,80,82,84,200,201,202,203] In fact, with all the mounting scientific and empirical evidence of practitioner use of omega–3 PUFAs in treating/supporting aspects of mental health, the International Society for Nutritional Psychiatry Research (ISNPR) organized an expert panel to perform a literature review and a Delphi process to develop evidence-based practice guidelines for use of n–3 PUFAs in mental health.[204] From their expert analysis, the effective recommended dosage/formulation should be 1–2 g/day of net EPA, from either EPA or an EPA/DHA (> 2: 1). Their consensus on formulation and dosage is relatively the same as the daily recommendations published throughout this paper to establish O3's contribution to health creation and maintenance for all persons, and also the amount necessary to achieve an O3I of >8%. This begs the question of how the thousands of subjects who benefited from this modality would have fared with lifelong adequate levels – i.e. potentially reduced or avoided related symptoms. To be fair not all meta-analyses have come to the same conclusions. Some have found a null effect of O3 treatments for specific mental disorders.[205,206] But again, we are not advocating for anything other than meeting recommendations throughout a lifespan, whether from food, with or without supplementing, to reach the goal intake associated with better health outcomes when compared to chronic O3 deficits.[4,6,7,8,23,24,25,26,58,59,60,61,62,63,64,88,90] Further, the heterogony of mental health causes and symptoms, FA metabolism, baseline O3 levels, and other individual lifestyle and genome factors, suggests that the use of O3 supplementation as therapy would be a crapshoot.[207,208,209,210] But everyone achieving recommendations from the onset of life, like with other essential nutrition (e.g. vitamins and essential minerals) that are responsible for the creation of the human entity, would give clinicians a solid baseline to better recommend therapies for improving brain/cognitive performance and health when necessary and throughout aging.

Summary

This section on omega-3's actions/roles in human health, including their indispensable participation in structural formations and maintenance, applies to all age groups from the beginning of life since all humans at all life stages require the same essential nutrition to create, develop and maintain life. The differences, especially for vitamins and essential minerals, are the amounts necessary for proper health and development during different life phases. The needed amounts of O3 are fairly constant throughout life but are especially critical in early structural and functional development (see table below).[6,55] Additionally, slight overages have virtually no negative effects and may deliver added benefits. Therefore, regardless of age, gender or desired health and fitness goal, all humans are encouraged to consume at least the minimum required amounts of O3 fatty acids, preferably from marine sources, as plant sources including their uneven O3 conversion, are not easily measured. Unlike vitamins and essential minerals (VMs) that are impossible to correctly quantify*** because they are basically invisible in foods - not to mention too many to accurately identify and vitamin and mineral presence in any food is dependent on the food's region of origin - the O3 amount as shown throughout this document necessary to achieve an O3I of >8% can be obtained through diet, since marine sources on a person's plate are easily identifiable, thus quantifiable. If the food recommendation of two to four servings of fatty fish weekly are not met, proper correction amount of supplementation is encouraged for all age groups, which is also easily quantified. As opposed to chronic O3 deficits common in our societies, by meeting the O3 recommendations throughout life, the human body through maximizing the indispensable developmental, structure

and functional actions of O3 as described here, will at the very least have a higher potential in achieving long-term health in areas where O3s are active and deliver better life-phase and aging outcomes.

Table 1 - NIH Omega-3 Fatty Acid Fact Sheet for Health Professionals[6]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	0.5 g	0.5 g		
7–12 months*	0.5 g	0.5 g		
1–3 years**	0.7 g	0.7 g		
4–8 years**	0.9 g	0.9 g		
9–13 years**	1.2 g	1.0 g		
14–18 years**	1.6 g	1.1 g	1.4 g	1.3 g
19-50 years**	1.6 g	1.1 g	1.4 g	1.3 g
51+ years**	1.6 g	1.1 g		

*As total omega-3s

**As ALA

****Of all the human essential nutrition, vitamins and minerals are the most difficult to attain in proper amounts (RDAs) as they are for the most part "invisible in our foods", not to mention vast variations in food levels of nutrients before consumption based on origin, shipping, cooking, etc. These recommended (RDAs) amounts were not known or available during periods of significantly shorter lifespans but are now known and necessary to support our current lifespan's potential health. These facts along with all studies of human food intake that clearly establish that virtually no one reaches the vitamin and mineral RDA of all nutrients through food alone (including fortified foods), makes daily consumption of a complete low dose vitamin and mineral supplement that contains, at a minimum the known under-consumed vitamins and minerals, a responsible recommendation by all health professionals.*

Beginning of Life and Beyond

As detailed and scientifically referenced above, O3 recommendations are to be met for a lifetime including during pregnancy, infancy and adolescent years, as these years are especially important to structural and functional developmental during the growing child's "windows" of opportunity to maximize O3's role in their development.[40,41,42,211,212,213] Unfortunately, as reported by Zhang et al. and others,[9] the majority of U.S. pregnant women and women of childbearing-age consumed significantly lower amounts of seafood than what the DGA recommends, which leads to low intakes of EPA and DHA.[214] In fact, 100% of the population did not consume the 2015-2020 recommendations of eight ounces of fatty fish per week and over 95% did not meet the conservative daily recommendation of only 250 mg EPA and DHA, which is well below the amount needed to reach an O3I >8% that throughout life is associated (including achieving with supplementation) with better birth outcomes such as fat free structure, fetal health, neurodevelopment and cognition, and reduced risk of post birth allergies.[215,216,217,218,219,220,221,222,223] For both pregnant and women of childbearing age, mean daily food intakes of both EPA and DHA were about the same: 18-20 mg of EPA and 55-60 mg of DHA.[214] Since fish intake is often inappropriately or appropriately (potential toxins) discouraged during pregnancy,[6] these low intake amounts should remind all health professionals to insist on supplementation to achieve at least the recommended amounts because DHA and EPA's structural and functional contributions are especially crucial during fetal development,[187,188,189,190,211,212,213] including the Cochrane Database's of systematic review finding that supplementation of DHA/EPA during pregnancy slashes the risk of preterm birth.[217] Primary findings from the overall analysis found that the optimum daily dose was a supplement containing between 500 and 1,000 mg of long-chain omega-3 fats (containing at least 500 mg of DHA)

starting at 12 weeks of pregnancy: 1) lowers the risk of having a premature baby (less than 37 weeks) by 11% (from 134 per 1,000 to 119 per 1,000 births); 2) lowers the risk of having an early premature baby (less than 34 weeks) by 42% (from 46 per 1,000 to 27 per 1,000 births) and 3) reduces the risk of having a small baby (less than 2500 g) by 10%.[217] The structural, functional and related behavioral benefits of proper O3 intake including through supplementation continues throughout infancy, youth and adolescence.[124,207,211,224,225,226,227,228,229]

Athletes

Youth and adult athletes are like everyone else in the fact that O3 FAs are known under-consumed nutrients for this population leaving them vulnerable to the same health and recovery consequences described throughout this paper.[230,231] Simply stated, no one is immune to the benefits of a lifetime of meeting nutritional guidelines including consuming the DHA and EPA intake recommendation necessary to achieve an O3I >8%.[230,232,233] But athletes and others such as military/soldiers who take part in regular vigorous activities, restricted food intakes and/or operate under stressful conditions, regular under-consumption may significantly undercut daily needed physical and mental recovery.[232,234] To be sure, athletes and military personnel are often encouraged to supplement regardless of food intake to aid in injury prevention, musculoskeletal and cognitive recovery and to reduce structural damage from mild traumatic brain injury (concussion) to potentially attenuate the subsequent cognitive function decline.[232,233,235,236] In a study by Philpott et al. giving soccer players 1,100 mg/day of DHA/EPA added to their normal whey protein and carbohydrate recovery supplement lowered post exercise serum creatine kinase and showed a protective role in maintaining the structural integrity of the muscle cell membrane, which reduced the severity of the subjects muscle soreness following eccentric-type muscle damaging exercise, suggesting a long-term recovery benefit.[237] A similar study design using rugby players found the same results but also found supplementation to help maintain the subjects' explosive power.[238] Other studies using high dose EPA/DHA (high EPA to DHA ratios) have found similar results related to attenuation of muscle soreness, stiffness and exercise damage and immune support.[239,240,241,242,243] Increased intake of EPA and DHA lowered heart rate at sub maximal workload through enhanced stroke volume and cardiac output.[244,245] Heart and muscle used oxygen more effectively, and heart rate returned faster to baseline after exercise.[244,245] These results correlated strongly with the HS-Omega-3 Index discussed above,[54,56,67,68,75,246] as did Hingley et al., when they found 1 g/day of O3 FA supplementation to successfully raise the O3I and subsequently increased O3 FA skeletal muscle incorporation and modulated oxygen consumption during intense exercise.[247] Probably due to an increase incorporation of O3 FAs in muscle and nerve cells,[35,36,248] EPA and DHA supplementation demonstrate positive effects on muscle function,[249,250,251] especially for neuromuscular adaptation and can be surmised to have multiple positive roles for exercise damage and presumably subsequent muscle function and performance.[252,253] Therefore, for athletes, supplementation (and/or regular weekly oily fish consumption) benefits may be from improved daily recovery that compound over time allowing greater and prolonged muscular/cardiovascular training adaption[238,254,255,256] as opposed to the typical athlete's diet contributions that shows they test <4% on the O3I,[7,10,69,230,231,232] which is within the proposed high health risk level zones.[54,67,68] The magnitude of gains would be theoretically predicated on O3 baseline values before increasing consumption and length of time maintaining the proposed ideal O3I of >8%, which 1-2 g of EPA/DHA daily can generally achieve.[86,89,90] Further, older exercisers have been shown to increase the results of resistance training when adding fish oil supplements of ~3 g/day (2.1 g EPA/0.7 g DHA), specifically measured as enhanced grip strength and lowering blood pressure compared to resistance training alone.[257] This is not surprising since it has been shown that regular ingestion of O3 FA compared to placebo can enhance muscle mass purportedly via an up-regulation of protein kinase B (Akt)-mammalian target of rapamycin (mTOR)-p70 ribosomal protein s6 kinase 1 (p70s6K1) signaling in healthy people of all age groups. Thus proper amounts of omega-3 fatty acids including supplemental amounts above standard recommendations, may make skeletal muscle more sensitive to anabolism.[249,251,257,258,259,260]

Summary

Nothing excludes athletes from achieving the recommended EPA and DHA intakes for general health. Therefore, like everyone else at every age, at a minimum they would consume these indispensable fatty acids from foods and/or supplements to achieve the recommendation. However, from data discussed in this section and a recent critical review by Philpott et al.,[261] it appears that supplementing O3 FAs beyond the standard recommendation of ~500 mg/day of EPA and DHA may support the more favorable adaptations described above in response to intense exercise, especially compared to general food intakes of EPA and DHA.[253] In this vein, as thoroughly reviewed by Ochi et al., common dosages used by researchers in athletes/exercisers that demonstrated benefits range between one and six grams daily and used for a minimum of four to eight weeks.[253] Since O3FA supplementation is not an acute/direct ergogenic aid, it would presumably take weeks to months of regular ingestion to maintain desired tissue levels to acquire purported affected tissue adaptation benefits, unless the user had severely low baseline EPA/DHA levels (i.e. compounding better daily adaptation offering the potential to improve performance over time compared to training with the common lower EPA and DHA levels). Most experts recommend between one to two grams daily as a general athletic guideline with an approximate 2:1 EPA to DHA ratio. All data considered, this recommendation may be appropriate for this population since they require more than just daily living recovery, and one to two grams daily generally gets users to the desired O3I of >8%, especially if the source is supplements, thus additive to dietary EPA and DHA. Further, this amount appears to have no downside and possibly only upside, where chronic ingestion of greater than three grams daily generally requires qualified monitoring.[262]

Body Composition

Based on EPA and DHA's basic mechanisms of action in different tissues as described above, these O3 FAs have been studied for their potential contribution in body composition or weight control, and not just looking at BMI correlations to O3 food intake values,[263] but using supplementation above basic currently known health requirements in varying cohorts of trial subjects to determine if there is a therapeutic application for weight control.[264,265] The evidence is not compelling that O3 supplementation is a successful adjunct to a weight/fat loss program[263,264,265,266] other than: maintaining health if intake is below recommendations allowing EPA and DHA's contribution to proper tissue functioning especially if subjects achieve an O3I of >8%;[54,56,67,68,75,85,243,246] potentially helpful to unique cohorts based on genetic sensitivities to the presence of O3 in varying amounts;[31,192,263] and favorably affecting energy partitioning such as increases in fat oxidation potentially leading to the preservation of LBM during an energy deficit.[252,253,264,265,266] Further proposed mechanisms of action related to O3s effects on body composition or weight control are described by Albracht-Schulte et al. as: "modulating lipid metabolism; regulating adipokines such as adiponectin and leptin; alleviating adipose tissue inflammation; promoting adipogenesis, and altering epigenetic mechanisms."[265] Readers are referred to this article for more on EPA and DHA's potential relationship to body composition.

Early Studies and Summary

Notwithstanding the above including the Zhang et al. meta-analysis of randomized control trials (RCTs) and no strong data to support O3 supplementation as an adjunct aid for improving body composition or weight loss, below are results from a few earlier studies (some were in the meta-analysis) that directly investigated O3 supplementation's direct impact on body composition.

The results of a double-blind study by Noreen et al. showed that six weeks of supplemental fish oil significantly increased lean mass, and significantly reduced fat mass in healthy adults.[267] Likewise, Couet et al. observed a significant 0.88 kg reduction in fat mass, and a non-significant 0.20 kg increase in lean mass following three weeks of an increased consumption of fish oil.[268] In their study, they added fish oil to the diet, but kept total fat and energy constant between the treatments.[268] Similarly, Hill et al. found a significant reduction in fat mass following 12 weeks of supplementation with fish oil in overweight subjects. They also observed a non-significant increase in lean mass.[269] Thorsdottir et al.[270] found that supplementation with fish oil or inclusion of fish in an energy-restricted diet resulted in significantly greater weight loss in young men. They also found that young men taking the fish oil supplements had a

significantly greater reduction in waist circumference compared to the control group, and the group that increased their dietary intake of fish. Nevertheless, the conclusion from the meta-analysis of RCTs by Zhang et al. was "that n-3 PUFA might effectively reduce waist circumference and triglyceride levels in overweight and obese adults, but n-3 PUFA may not effectively reduce body weight. Given the small number and poor quality of RCTs included in the meta-analysis, these results are inconclusive."[264]

Finally, Huang et al. and others have found significant diet-gene interactions of habitual consumption of n–3 PUFAs or fish, with overall genetic susceptibility on long-term weight change. All concluded that high long-chain n–3 PUFA and fish intake may attenuate the genetic influence on long-term weight change suggesting a role in weight management in at least in persons genetically susceptible to weight gain.[263,271,272,273,274]

In summary, while there is little evidence that long chain O3 FA intake plays a direct role in assisting weight loss, meeting EPA and DHA recommendations for overall health, and especially during caloric restriction, so that these indispensable FAs can make their contribution to daily tissue recovery and proper signaling, can only improve outcomes during pursuit of fitness goals. And high O3 (>8% O3I) intake may offer the potential to help protect against weight gain.

Controversies, Confusion and Misinformation

There are no controversies related to persons of all ages achieving the daily recommendations of EPA and DHA shown above through food intake and/or supplementation. Further, intake that reaches >8% on the O3I are clearly associated with health benefits as opposed to lower levels with no known potential downside. Nevertheless, unclear or misinformation abounds including media translations of omega-3 clinical trials, failed trials, marketing spins, hyperbole, potential contraindications or adverse outcomes. Therefore, this section will help update readers with current known facts related to common long chain O3 FA confusion or misinformation.

Prostate Health

Omega-3 supplements or fish consumption is not a treatment for poor prostate health but nor does their recommended consumption put people at greater risk.[4,57,58,60,62,65,275] The preponderance of evidence actually supports the opposite[275,276,277,278,279] or no effect:[280,281] VT Le et al. reported for the American Heart Association that DHA and EPA levels were not found to be positively related to poor prostate health and in fact, the findings of studies (using supplements) suggested a protective potential. These results are in line with recent randomized trials of omega-3 supplementation (VITAL, REDUCE-IT), which also found higher EPA and DHA levels including from supplements, to have a potential protective effect on both prostate health and the cardiovascular system.[275,277] The controversial study in 2013 by Brasky et al., now infamous, was a classic example of a combination of misrepresented data leading to a conclusion that the lay media contorted into an eye-catching headline.[282]

The Controversial Study

The study that made headlines was published in the Journal of the National Cancer Institute on July 10, 2013. The researchers concluded that men with higher blood concentrations of animal-based omega-3s had a 44-71% increased risk of developing prostate cancer compared to those with the lowest levels.[282] Specifically, higher blood levels of the omega-3 fat DHA correlated to higher prostate cancer risk, while no correlation was found for EPA and ALA. The study measured omega-3 blood levels in the participating men and did not include information on the volunteers' eating habits, thus researchers could not differentiate between the effects of fatty acids from fish or supplements. Furthermore, no fish oil supplements were actually given as part of this study and the overwhelming majority of the participants *did not* take fish oil supplements. As noted by experts, a big problem with this observational study looking at correlations only, is that the factor you are looking at (DHA levels) may be completely irrelevant, compared to other factors.[283] For example, in this study:

- 53% of the subjects with prostate cancer were smokers
- 64% of the cancer subjects regularly consumed alcohol

In addition, 80% of the cancer subjects were overweight or obese. Obesity is clearly associated with prostate cancer and some studies have found obesity to increase risk up to 57%,[284,285,286] especially for aggressive prostate cancer (PCa) and PCa-specific mortality[287]—a percentage that falls in the middle of that 44-71% range attributed to high DHA serum levels in the study in question. Considering the extensive body of literature that supports the anti-inflammatory effects of omega-3 fatty acids, at present there is no credible biological mechanism (nor is one suggested in the article) that would explain why these essential fatty acids might increase risk of prostate cancer, and the fact that most studies suggest that intake of long-chain omega-3 fatty acids may support prostate health,[275,276,277,278,279,288] this study does not lend much to science. The American Heart Association, the World Health Organization (WHO), the U.S. Institute of Medicine's Food Nutrition Board (IOM FNB) and the 2015 Dietary Guidelines for Americans all have current policies advising Americans to eat more fatty fish to get the benefits of omega-3 fish oils and it is highly unlikely this one weak correlation would change that advice and in fact it did not.[64,65] Omega-3s can also be obtained by taking supplements as needed.[5,6,87,88]

Is Krill Oil Better Than Fish Oils?

That depends on who you ask. At present, the answer still leans towards using fish oil as the source to supply the recommended daily intakes of EPA and DHA, and simply because the discovery, existing and on-going evidence of their benefits comes from science studying fish oil. In other words, while krill oil has begun being studied as a source of EPA and DHA, virtually all the studies cited here, and most of all clinical trials studying EPA and DHA's health effects use fish oil sources. Further, the only prescription omega-3 fatty acids currently available are omega-3 fatty acid ethyl esters (contains both EPA and DHA ethyl esters) from fish because this form has the scientific backing necessary for a prescription medicine.[289,290] While Krill oil does supply EPA/DHA, can raise the O3I,[291] and has been shown to positively effect aspects of lipid profiles,[292] overall outcomes from ingestion may differ from the well-known results of fish derived EPA/DHA.[293,294] At this point in time it seems prudent for the general population to rely on omega-3 sources that have received greater scientific scrutiny as described throughout, including fatty fish and fish oil, and of course necessary for those being treated for cardiovascular purposes with fish oil medication. Moreover, Krill oil is extracted from Antarctic krill, tiny shrimp-like crustaceans, and thus chemically different than fish oil in that it contains a tiny amount of the carotenoid astaxanthin and choline, a B-vitamin like substance, which also lends to Krill oil having a unique mechanism of action, particularly in gene expression.[295,296] Additionally, the EPA and DHA found in krill oil is primarily incorporated in phospholipid as opposed to omega-3 fatty acids in fish being mostly present as triglycerides or ethyl esters,[297] all of which may give rise to the potential minor bioavailability differences.[298,299]

Krill oil per gram of EPA and DHA is significantly more expensive that fish oil counterparts partially because of processing difficulties (following the harvest, immediate processing is necessary to prevent decay) .[300] This increase in cost is often justified by health and bioavailability statements that claim krill oil is superior to fatty fish sources of omega-3 fatty acids.[298,300,301,302] The absorption/bioavailability arguments are difficult to defend because krill oil supplements generally contain less EPA and DHA. Backes et al. reported pure Krill oil products' doses ranged from ~45 to 200 mg per softgel compared to ~300 to 2,250 mg per softgel of fish oil.[294,300,303] It is not important which fatty acid gets into the body faster, since dosing is daily/regular in order to achieve the desired levels -i.e. once levels are achieved, intake is maintained for life to sustain desired levels.[299]

In summary, Krill oil may be an acceptable option for the general healthy public to raise the O3I to desired levels and meeting EPA and DHA recommended intakes, but potential shortcomings compared to fish oil sources include:

- Far less scientific evidence to directly link the krill oil source of DHA and EPA to the same safety and efficacy data established by from fish oil sources.
- Krill oil products are reported to deliver EPA and DHA at approximately 30 cents/100 mg while fish oil ranges from one to 10 cents for equal content.
- Krill populations are essential in the marine food chain and harvesting for supplements is a major ecological concern because of global warming and higher potential of spoilage during processing.
- Krill oil supplements can trigger an allergic reaction in people allergic to shrimp and other crustaceans.

Plant Sources of EPA and DHA

Plant sources, such as nuts and seeds including flaxseed, are rich in the essential fatty acid, alpha linolenic acid (ALA), which can be converted to EPA and DHA though inefficiently and therefore not a suggested source for achieving recommended intakes.[11,12,13,14,15] Studies of ALA metabolism in healthy young men indicate that approximately 8% of dietary ALA is converted to EPA and 0-4% is converted to DHA.[304,17] In healthy young women, approximately 21% of dietary ALA is converted to EPA and 9% is converted to DHA.[16,304] Other potential shortcoming with seed oils/ALA such as flaxseed as a source in achieving the daily recommendation for EPA and DHA is that they contain relatively high amounts of omega-6 fatty acids which compete with the benefits of omega-3s (see Heart Health Section above for more on O6/O3 ratios) including hindering precursor molecule conversion to DHA.[11,12,13,14,15,20] To be fair as described in the Heart Health section, ALA and other components of specific plant oils can contribute other unique health benefits when consumed in proper amounts and especially in the presence of suggested daily intake of EPA and DHA that confirm a >8% O3I.[99,100,108]

Vegan/Vegetarian and Fish Allergies

From all data it appears vegans may have to supplement to achieve daily adequate intake of EPA and DHA with a heavier emphasis on DHA since there is very low to no plant source precursor molecule (e.g. ALA) conversion to DHA as noted above.[16,17,304,305] As in fish and krill, plants in aquaculture such as seaweed and microalgae can directly provide DHA and EPA and in fact is the primary source of transfer to omnivores (fish consume the algae/seaweed, animals consume the fish).[306,307] Additionally, microalgae sources of EPA and DHA may be a more sustainable long term solution for supplementation as awareness of the need to meet recommendations increases.[308] Therefore, supplements from microalgae are a common solution for vegans/vegetarians and persons with fish allergies to help reach recommendations[305,309,310] since, as noted, seed or nut oils may not be enough and possibly counterproductive if considered the sole source.

For a comprehensive review on veganism and acquiring adequate daily EPA and DHA including dietary supplement use, readers are referred to the review by Burns-Whitmore et al. titled: *Alpha-Linolenic and Linoleic Fatty Acids in the Vegan Diet: Do They Require Dietary Reference Intake/Adequate Intake Special Consideration?*[305] The review found that most studies show that vegans consume very low to no amounts of EPA and DHA unless they supplement. And because of inconsistent intake and conversion of ALA, along with the amount of dietary linoleic acid, vegans may need an ALA daily intake of two to four times the AI/DRI or 2.2–4.4 g/day (or 1.1 g/day per 1,000 Kcals) in the diet in order to achieve the healthier proposed omega-6 to omega-3 ratio of 4:1, and if dietary linoleic acid is higher than recommended as it usually is, it should be reduced.[305] Most of these conclusions add up to a greater need for supplementation than the omnivore, especially in athletes and active persons of all ages.[305,309,310] Individuals with fish allergies should check food (claiming fortified with omga-3s) and supplement labels to insure that the source of the omega-3s in the food is not from fish.

Excessive Bleeding

Not relevant to meeting omega-3 recommendations (~500 mg/day of EPA and DHA), which has no contraindications for normal healthy persons, fish oil ***supplementation*** has been contraindicated before surgery or in people using blood thinners. In other words, high doses of fish oils, while helpful for clinical treatments, may also decrease blood coagulation and increase the risk of bleeding.[311] Current evidence does not support these earlier warnings,[312,313] but erring on the side of caution seems appropriate, and therefore it is the attending health professionals decision to discontinue or limit supplementation under certain circumstances.

Current Evidence

A systematic review of RCTs by Begtrup et al. concluded: fish oil supplements appropriately reduced platelet aggregation (clumping platelets in blood that can lead to clots) in healthy subjects but the effect was not reflected in increased bleeding risk during or after surgery and therefore the "systematic review does not support the need for discontinuation of fish oil supplements prior to surgery or other invasive procedures."[312] Other studies have confirmed

these results and called for "reconsideration of current recommendations to stop fish oil or delay procedures prior to cardiac surgery..[314]

Further, Warfarin, the commonly prescribed anticoagulant used as necessary for the prevention of stroke in persons with atrial fibrillation (AF) and in treatment or prevention of deep vein thrombosis (DVT) was studied in combination with fish and krill oil supplements by Pryce et al.[313] The author's assessed the impact of fish and krill oil supplementation on warfarin control and bleeding incidence in AF and DVT users. Overall, it was found that fish and krill oils did not significantly alter warfarin "time in therapeutic range" or bleeding incidence, in both men and women. The conclusion was: "Omega-3 supplementation with fish and krill oil does not significantly affect long-term warfarin control and bleeding and thromboembolic events when consumed concurrently in patients managed at an anticoagulation clinic."[313]

Failed Studies

While we have all the scientific data required for supporting the recommended amount of EPA and DHA necessary to potentially optimize (albeit a range) these nutrients' contribution to the human structure, function and health from the beginning of life until the end,[4,6,7,8,23,24,25,26,58,59,60,61,62,63,64] readers are warned to scrutinize results of omega-3 trials tied to treatment endpoints.[315,316,317,318] We do not need more studies to validate that we need the minimum recommended amounts for health protection, but as EPA and DHA recommendations/prescriptions relate to "treatments," (e.g. cardiovascular events, cognitive decline, etc.) these topics should start and remain in the domain of clinicians and researchers. The popular press notoriously reports study findings out of context to create headlines and especially if it is shocking or against the norm.[316,319] Good news is expected and therefore often goes unreported.[26,64,126] Worse, unintentionally or not, the media can make a positive study sound bad or misleading.[320]

First, omega-3 trials that have failed to produce a positive outcome, certainly never delivered a negative outcome, but more importantly, conclusions of nutrient trials, whether it is EPA, DHA or vitamins and minerals, yielding null effects are for many reasons including, but not limited to:

- Inaccurate compliance monitoring based on recall instead of changing biomarkers to validate ingestion
- Baseline levels not tested
- Wrong dosages or not specified
- True placebo is not possible since all living humans have some exposure to omega-3 fatty acids – baseline levels should always be factored
- Trials are too short (essential nutrition works synergistically lifelong to create and maintain health)
- Lack of the long-term nutrient synergy component – i.e. EPA/DHA do not work in a vacuum like a drug. Studies using isolated nutrients such as EPA/DHA, cannot accurately test them according to a drug model (RCTs) because, other than correcting individual frank deficiencies, nutrients work in synergy over a lifetime. Meaning, you could consume EPA/DHA at recommended levels or more, but if you are regularly low on other essential nutrients (as most people are) such as vitamins, minerals and other bio-actives (e.g. lutein, lycopene, zeaxanthin, etc.) that allow EPA/DHA to execute their mechanisms of actions, supplementing as a treatment would be useless
- Started too late in life (disease is unknown at start of trial but may be taking hold) including no possible nutrient "catch-up"
- Drugs such as statins masking results (effective medications can mask positive effects of supplements
- Sick people (pre-existing conditions) often start taking fish oil supplements -reverse causality
- Wrong end points – prevention versus treatment – i.e. measuring something supplementation cannot fix including for the many reasons as mentioned here, especially lack of lifetime nutrient synergy
- Genetic factors: specific polymorphisms; the way certain chemistry reacts to "ideal amounts" or where they are in a disease state, etc.[93,108,183,192,193,194,229,321]

To clarify, we believe and applaud that studies/RCTs are needed when EPA and DHA are studied for treatments of disease/aging since, because if found effective, their negative side-effects may be none to minimal relative to drug treatments.[322,323,324,325] In this case RCTs would again, as in the study of pharmaceutical agents, be the gold standard protocol. This review does not represent EPA and DHA in treatments, but rather health creation and protection, by meeting recommendations for a lifetime through food and/or supplementation, as necessary. Further, since EPA and DHA are now considered "essential through diet," there is no downside to proper supplementation as described here, only a potential upside (i.e. regardless of confounders, no studies found supplementation harmful, but most found it helpful) to maintaining the EPA and DHA recommendation from the beginning of life to the end.

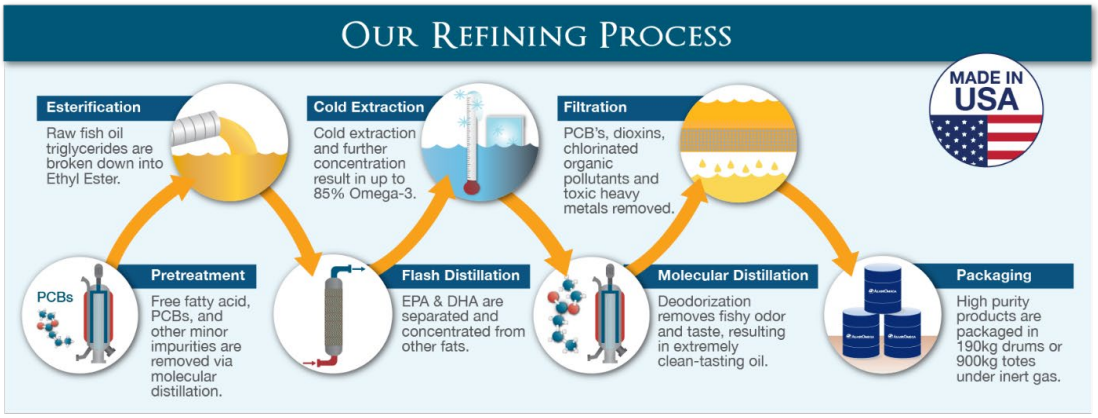
Supplement Forms, Dosage and EPA/DHA Ratio in Meeting Recommendations for General Health and Prevention

While there is some evidence that high dose DHA increases the O3I more than high dose EPA,[326] it is conceded that for the general health protection, both are required.[4,6,7,8,23,24,25,26,58,59,60,61,62,63,64,118] Further, dietary DHA can be reconverted to EPA but the reverse has not been observed.[160]

All data to date assessed, if someone does not consume two to four servings weekly of fatty fish (closer to four if attempting to reach >8% on the O3I), they need to add a correction amount of EPA and DHA through supplementation to achieve the minimum recommendations of 250-500 mg/day combined, or more (500-1,000 mg/day) as needed to reach an O3I >8%. If supplementation is needed, the general dosage recommendation that should universally achieve desired DHA and EPA levels, from at least the minimum requirement to the potentially more desirable measure of a >8% O3I, has been shown to be 500-1,000 mg/day of a combination of EPA and DHA with the EPA:DHA ratio of ~1.5:1.[4,6,7,8,23,24,25,26,58,59,60,61,62,63,64,118] The range is based on individual diet exposure (including plant source/ALA conversion) to EPA and DHA, so that virtually everyone would meet recommendation regardless of diet (lower exposure, higher in the range if >8% O3I is the goal), body weight[327] or genetics.[93,108,183,192,193,194,229,321] The EPA/DHA ratio of 1.5:1 ratio is also maintained in higher dose treatments (see Oscarsson et al. in Table 2).[160] Additionally, supplements containing EPA and DHA in different lipid structures such as unmodified fish oil triglycerides, re-esterified triglycerides, free fatty acids or ethyl esters, does not appear to effect EPA and DHA incorporation into tissues/blood in healthy adults.[299]

Best Practices in Harvesting, Manufacturing and Refining Processes

For readers interested in the journey of EPA and DHA extraction from oceans to supplement form, AlaskaOmega® adheres to strict and sustainable certified processes found here. The company's refining process depicted in the graphic below guarantees a sustainable, clean, safe and fresh final product.



Qualified Health Claims

This review is not meant to support specific health claims related to EPA and DHA. Rather, the crux of this paper is to persuade health professionals to inform clients to consume the recommended amounts of DHA and EPA in order to assure their indispensable structure and function contributions within the human body can proceed at their full potential in delivering better health outcomes when compared to under-consumption (prophylactic actions).[4,6,7,8,23,24,25,26,58,59,60,61,62,63,64,118] Achieving the recommendations described throughout this document can be accomplished through diet and/or diet and supplements. For those readers interested, the FDA's response to petitioned specific EPA and DHA health claims are found here FDA Letter of Enforcement Discretion. Again, these are not related to this paper but appear to be logical extended conclusions.

Data Summary

Just as vitamins and essential minerals daily intake recommendations (DRIs) are established for best overall health, the daily recommendation for each life-stage, including children, of EPA and DHA has been established to support the areas where these nutrients participate in creating and maintaining their respective target organ/tissue structure and functions such as the heart/cardiovascular system, brain, eye, etc. Chronic shortages of these critically important fatty acids, as with most people living in developed western societies, compromise all areas of the body that are EPA and DHA dependent.

Assessing all current data related to EPA and DHA's contribution to human structure, function and health protection, expert recommendations for the combined daily intake of EPA and DHA range between 250-1,000 mg/da. At least 500-1,000 mg/day may be necessary to achieve an O3I of >8%, which represents the amount of EPA and DHA in the blood associated with greater overall health creation and protection. Reaching the recommended levels has proved unrealistic without regularly ingesting proper marine sources (e.g. fatty fish) or utilizing the option to correct the deficit with a combined EPA and DHA supplement, hence diet and supplements as necessary, are the current unambiguous expert recommendation to achieve proper levels.

Practitioners should not confuse meeting daily lifelong EPA and DHA recommendations through diet and/or supplementation established for best health outcomes and prevention at all life-stages, with supplementation being explored as treatments yielding mixed study results. Essential nutrients, such as vitamins, minerals, amino acids and fatty acids, including EPA and DHA, work synergistically over a lifetime to form and maintain the human entity and therefore cannot be studied in a vacuum like drugs. There are too many confounders for studying essential nutrition beyond simply wrong study endpoints, such as baseline levels of DHA/EPA, disease taken hold but unnoticed (insidious progression) at start of supplementation, late in life correction of necessary EPA/DHA, lack of synergistic nutrients availability, use of pharmaceuticals that mask O3 contributions, genetic variability, other poor lifestyle choices, etc. Scientists have found all the data needed to support supplementing if you have low baseline EPA/DHA because of diet, which is easy to assess without a blood test – simply look at your diet and see at least two to four servings per week of fatty fish, and you should not need to supplement, unless for clinical reasons beyond the scope of this document. If not consuming this amount and unable/unwilling to alter the diet to accomplish the recommendation, supplement the difference, which can be any combination of the two (diet and/or supplement), such as one to two servings weekly of fatty fish and 500 mg/day of a supplement to make the correction.

General Population EPA/DHA Recommendation for all Ages

For health creation and protection, if not consuming at least two to four servings weekly of oily fish, take a supplement containing at least 500 mg of combined EPA and DHA with an approximate EPA:DHA ratio of 1.5:1 to correct the shortfall, (up to 1,000 mg/day if diet is without fatty fish and/or if an O3I of >8% is the goal). Different EPA and DHA ratios or amounts may be appropriate for clinical purposes including during pregnancy.

Typical Use

- Persons of all ages who are not consuming two to four servings (or 8-16 oz) of fatty fish weekly and does not have fish allergies or unless medical reasons prevail as diagnosed by a qualified health professional.
    - Take one to two soft gels with any meal as necessary to correct the food delivery gap.
        - Take one if consuming more than one serving weekly of fatty fish but less than three servings.
        - Take two if consuming less than one serving weekly of fatty fish.
    - Increase only if supervised by a licensed health professional.

Precautions

dotFIT SuperOmega-3 is mercury free and use at the recommended dosage is safe for most people. Pregnant women and nursing mothers can use as recommended and monitored by a physician. Because of the possible anti-thrombotic effect of fish oil supplements, earlier advice was for hemophiliacs and those taking warfarin (Coumadin) to exercise caution in their use.[328,329,330] More recent evidence suggest that standard use of EPA and DHA supplementation does not increase the risk of bleeding or significantly affect long-term warfarin control and bleeding and thromboembolic events when consumed concurrently in patients managed at an anticoagulation clinic."[313] Although recent evidence argues against earlier warnings about ceasing fish oil supplementation before any surgical procedure,[312,313] erring on the side of caution seems appropriate, and therefore it is the attending health professional's call to discontinue or limit supplementation under certain circumstances. Further, since doses greater than three grams daily might decrease platelet aggregation and increase the risk of bleeding, the FDA recommends that consumers limit intake of DHA and EPA to three grams daily, with no more than two grams daily from a dietary supplement.[262,311] Both doses are above the recommendations found here. Conflicting results have been reported regarding the effects of fish oil supplements on glycemic control in those with glucose intolerance including Type II diabetics.[331,332] While there is no evidence that fish oil supplements have detrimental effects on glucose tolerance, insulin secretion or insulin resistance in non-diabetic subjects, some early studies indicated that fish oil supplements might have detrimental effects in those groups.[331,332] Recently, better designed studies have not reported these adverse effects or advantages.[317,333] Diabetics should discuss the use of these supplements with their physician(s) and note if the supplements affect their glycemic control. Diabetics who take fish oil supplements should be monitored by their physicians.

Contraindications

- Anyone taking greater than three (3) grams per day through supplementation should do so only under the care of their physician due to risk of excessive bleeding at higher doses.[331]
- Should not be used if the individual is on anticoagulants or has uncontrolled hypertension unless approved by personal physician,[262,311,328,329] as fish oil supplementation might have additive effects in lowering blood pressure in patients treated with antihypertensives[6,116,117,118,335]
- Three (3) grams per day or greater may raise blood sugar and LDL cholesterol in susceptible people with diabetes using continuous large dosages[262,311,331,334]

Adverse Reactions

For fish oils containing EPA and DHA, adverse reaction are rare but may include can include fishy taste, belching, nosebleeds, nausea, and loose stools.[335] High doses of fish oils might also decrease blood coagulation and increase the risk of bleeding[262,311]

Upper Limit/Toxicity

The Institute of Medicine (IOM) has not established a Tolerable Upper Limit (UL) for any of the omega-3 fatty acids but noted that high doses of DHA and/or EPA (900mg/day of EPA plus 600 mg/day DHA or more for long periods/months) might reduce immune function due to their anti-inflammatory properties. Doses of 2–15g/day EPA and/or DHA might

also increase bleeding time by reducing platelet aggregation.[55] However, the European Food Safety Authority (EFSA) states that long-term consumption of EPA and DHA supplements at combined doses of up to about 5gm/day appears to be safe. Further, the EFSA stated that these doses have not been shown to cause bleeding problems or affect immune function, glucose homeostasis, or lipid peroxidation.[336] The FDA recommends not exceeding 3gm/day of EPA and DHA combined, with up to 2gm/day from dietary supplements unless prescribed by qualified physician.[262,311]

Summary

Purpose

When diet alone is the delivery, the majority of the US population and other western developed nations for various reasons, fall short of the recommended amounts of the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), established by The World Health Organization (WHO) and other experts including those suggesting persons achieve an omega-3 index (O3I) score >8%, and therefore should supplement the deficit. Just as vitamins and essential minerals daily intake recommendations (DRIs) are established for best overall health, the daily recommendation for each life-stage, including children, of EPA and DHA has been established to properly support the areas where these molecules participate in creating and maintaining their respective target organ/tissue structure and functions such as the heart/cardiovascular system, brain, eye, etc. Chronic dietary shortages of these critically important fatty acids compromise all areas of the body that are EPA and DHA dependent. For those not regularly consuming (cannot or will not) appropriate fatty fish (at least 2-4servings/week) or certain uncommon plant foods, the SuperOmega-3 supplement would provide a corrective amount and ratio of EPA and DHA omega-3 fatty acids in a mercury-free, easy-to-ingest form to meet recommendations that are associated with healthier outcomes at all life-stages through supporting the structure and function of the cardiovascular, brain and vision systems conveying a potential prophylactic effect. Additionally, the SuperOmega-3 ingredients are obtained from a certified sustainable source.

Unique Feature Combination of dotFIT SuperOmega-3

- Less expensive than any 3rd party NSF Certified for Sport tested comparable product.
- Omega-3 fish oil complex starts from wild-caught Alaska Pollock oil from the cold, pure waters of Alaska's Bering Sea. The final dotFIT SuperOmega-3 product delivers the two desired long chain omega-3 fatty acids, EPA and DHA in the recommended amounts of >500 mg/d with a 1.5:1 ratio of EPA to DHA.
- MSC-certified. Concentrates in the SuperOmega-3 Fish Oils are certified Sustainable and Traceable by the Marine Stewardship Council (MSC), the first omega-3 concentrate to achieve this distinction.
- NSF Certified for Sport
- Produced by AlaskOmega®. Their superior manufacturing process produces the market leading "fresher oil," which translates into better product stability, longer shelf life, and optimal sensory characteristics – i.e. no fish burps.[337]
- Omega-3 fish oil complex is mercury-free and contains no PCBs.
- Formula considers use of other dotFIT products to help the user maintain a safe and optimal range of total nutrient intake.
- Organic Technologies, producer of AlaskOmega® omega-3 fish oil concentrates and natural oils, has among the industry's lowest product specification limits for oil oxidation and environmental contaminants[338]
- Manufactured in a regularly inspected NSF certified facility, in compliance with Good Manufacturing Practices (GMPs) exclusively for dotFIT, LLC

Supplement Facts

Supplement Facts

Serving Size: 1 Softgel
Servings Per Container: 60

Amount Per Serving	% Daily Value*
Calories	10
Calories from Fat	10
Total Fat	1 g 2%*
Fish Oil - AlaskOmega®	1000mg **
EPA (Eicosapentaenoic acid) (360 mg)	
DHA (Docosahexaenoic acid) (240 mg)	

* Percent Daily Values are based on a 2,000 calorie diet.
** Daily Value not established.

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