

# EPA & DHA Science Research Review

## EXECUTIVE SUMMARY

EPA and DHA are long-chain omega-3 fatty acids that are considered conditionally essential for health. Good sources of EPA and DHA in the diet include oily fish and fish oil products. Oils produced from microalgae are also emerging as beneficial sources of EPA and DHA. EPA and DHA act in the body by activating specific cellular receptors, through incorporation into cellular membranes, and through the generation of critical down-stream lipid mediators such as eicosanoids, and specialized pro-resolving mediators involved in inflammation resolution. Higher intakes of EPA and DHA have been shown to reduce plasma triglycerides (TG) and exert other positive effects on cardiovascular health. EPA and DHA have also been reported to support mood, as well as eye and cognitive health across the lifespan. The well-documented health benefits of EPA and DHA have led several expert working groups to set intake recommendations for clinical conditions.

## EPA & DHA

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long chain omega-3 polyunsaturated fatty acids (PUFAs) that have emerged as key biological regulators (Figure 1).<sup>1</sup> Although technically EPA and DHA can be synthesized from  $\alpha$ -linolenic acid (an omega-3 fatty acid abundant in many plant-based foods), and EPA can technically be converted to DHA, conversion can be extremely limited. This has led to the designation of EPA and DHA as "conditionally essential" nutrients that are required in the diet for optimal health.<sup>2</sup>

## GOOD SOURCES OF EPA & DHA

EPA and DHA are found in oily fish—such as salmon, herring, tuna, mackerel, and sardines—with EPA-DHA content of these foods ranging from 835 mg (sardines) to 1825 mg (Atlantic salmon) per 3-oz. serving.<sup>3</sup> Quality fish oil supplements are also rich sources of concentrated EPA and DHA.

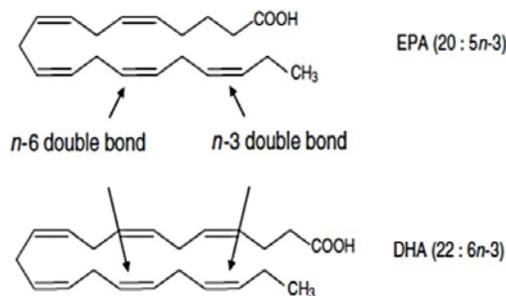
In recent years, oils produced from microalgae have become available to provide a concentrated sustainable source of EPA and DHA appropriate for vegetarians or consumers not wishing to consume fish or fish-based products. Algae, such as *Schizochytrium*, have the capacity to synthesize

omega-3 fatty acids that can subsequently be consumed by other marine life, and so can be considered the foundation of the oceanic food chain.

## DAILY INTAKE RECOMMENDATIONS

The recognized importance of EPA and DHA for health has led many expert bodies to recommend specific daily intakes of these fatty acids (Table 1). However, despite these recommendations, a significant nutrient gap exists, and current estimates of EPA and DHA from food sources in the US population fall short of these recommendations, totaling ~100 mg/day.<sup>4</sup> This highlights the need for continued education and promotion of EPA and DHA-rich sources in the daily diet.

As there have been concerns about the methylmercury (organic form of mercury) levels in finfish and shellfish, consumers can minimize health concerns by avoiding or limiting the consumption of fish containing high levels of methylmercury, such as King mackerel, shark, swordfish, and golden bass.<sup>5</sup> For most individuals the benefits of eating fish (with the exception of frequent intake of fish high in methylmercury) greatly exceed the magnitudes of possible risks caused by these contaminants.<sup>5,6</sup>



**Figure 1.** EPA and DHA are conditionally essential long-chain omega-3 PUFAs required for many biological processes within the body. Omega-3 fatty acids contain a C-C double bond at the third position from the methyl end.

**Table 1.** Recommended Daily Intakes of EPA & DHA

Expert Group	Target Population	Recommended Intake
Academy of Nutrition and Dietetics <sup>9</sup>	General adult population	500 mg EPA + DHA/day
American Psychiatric Association <sup>14</sup>	Patients with mood, impulse control, or psychotic disorders	1 g EPA + DHA/day
American Heart Association <sup>15</sup>	Patients with CVD	1 g EPA + DHA/day
	Patients with high triglycerides	2-4 g EPA + DHA/day
American Academy of Pediatrics <sup>16</sup>	Pregnant & nursing women	Additional 300 mg DHA/day

Additionally, supplemental sources of EPA and DHA, such as high quality, refined fish oil supplements, generally contain minimal levels of these contaminants. Companies that follow good manufacturing practices, conduct independent third party testing for contaminants, and adhere to the standards laid out by the Global Organization for EPA and DHA Omega-3s (GOED) Voluntary Monograph can assure the highest quality EPA- and DHA-rich marine oil products.

Supplemental sources of EPA and DHA through fish or algal oils are very well tolerated. A systematic review dealing with this topic reported that the most common adverse events associated with omega-3 fatty acids are gastrointestinal complaints: 6.6% of study participants who received omega-3 fatty acids and 4.3% of study participants who received placebo (the equivalent amounts of non-omega-3 fatty acids) reported gastrointestinal symptoms.<sup>7</sup>

Clinical bleeding with higher intakes of omega-3 fatty acids was reported almost solely in studies in which participants have a history of cardiovascular disease (CVD), and those who reported such an event took other medications such as warfarin or aspirin.<sup>7</sup>

#### **DIFFERENCES IN FATTY ACID FORMS**

Fish oil supplements provide EPA and DHA in different chemical forms and this has been the focus of both research and clinical attention. There have been conflicting research data on the bioavailability of EPA and DHA in various forms. Some researchers concluded that the triglyceride form is the most bioavailable,<sup>8-10</sup> while others reported equivalent

bioavailability in triglyceride and ethyl ester form.<sup>11,12</sup> In reality, many factors affect their bioavailability in humans, such as lipid intake from diet, EPA/DHA product dose and concentration, and frequency and length of EPA/DHA supplementation.

Regardless, both forms of EPA and DHA are good sources of omega-3 fatty acids, and both forms have been found to be effective in reducing plasma triglycerides (the pharmaceutical preparation of EPA and DHA approved by the FDA is in the ethyl ester form).<sup>13</sup>

#### **EPA & DHA FUNCTIONS IN THE BODY**

Various potential biological mechanisms of EPA and DHA have been proposed and studied, and EPA and DHA have been shown to have anti-inflammatory, anti-thrombotic, antihypertensive, hypo-triglyceridemic, and antiarrhythmic properties. EPA and DHA activate specific receptors within cells and so can directly act to induce changes in health and metabolism, and when incorporated into cell membranes, can influence membrane function. Additionally, downstream lipid mediators, including eicosanoids and specialized pro-resolving mediators, can be derived from EPA and DHA.

Eicosanoids (e.g., prostaglandins, thromboxanes, and leukotrienes) are hormone-like agents localized to tissues. Just as the specific biological functions of fatty acids depend on the structure of the fatty acid itself, the specific function of eicosanoids depend on the fatty acid from which it was produced. Higher concentrations of omega-3 fatty acids can lead to a greater production of eicosanoids from these fatty acids, reducing the eicosanoids from other fatty acid groups (such as omega-6 PUFAs).<sup>7</sup>

The balance between eicosanoids produced from omega-3 fatty acids and those produced from omega-6 fatty acids is important for many aspects of health, including cardiovascular health. Eicosanoids derived from the omega-6 fatty acid arachidonic acid have more potent and negative effects on blood pressure, inflammation, and platelet aggregation than those from the omega-3 fatty acid EPA, highlighting the requirement for balance between these fatty acids.<sup>2</sup>

#### **BENEFITS OF EPA & DHA**

##### Plasma Lipid Profile

According to the American Heart Association's Heart Disease and Stroke Statistics 2014 Update, 31.9 million (13.8%) of adults ≥ 20 years old have cholesterol levels ≥ 240 mg/dL.<sup>17</sup> Approximately 27%

of adults had a triglyceride level  $\geq 150$  mg/dL during 2007 and 2010; fewer than 3% of them received pharmacological treatment during 1999 and 2004.<sup>17</sup> Considering the significant negative effects that cardiovascular risk markers and disease have on patient morbidity and mortality, identifying safe and efficacious treatments is of paramount importance.

EPA and DHA have been shown to have positive effects on several cardiovascular risk factors, although a strong effect of lowering triglycerides has been most consistently demonstrated. The majority of EPA/DHA intervention studies report a net decrease of about 10% to 33% in plasma triglycerides.<sup>7</sup> Studies have shown that on average, for every 1 g of EPA/DHA consumed, there is an estimated 5% to 10% reduction in triglycerides. These effects have been shown to be dose-dependent and consistently overall among healthy participants and patients with cardiovascular risk factors or disease—although meta-regression analysis demonstrates that, regardless of the dose of EPA/DHA or study size, the average net decrease in triglyceride level was larger in studies conducted with patients who had higher baseline triglycerides.<sup>7</sup>

The efficacy of EPA and DHA for lowering triglycerides has led to the development of several high concentrated EPA and DHA pharmaceutical products like Lovaza. Lovaza (generally taken at a dose of 4 g/day) is a combination of EPA/DHA ethyl esters, indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia (i.e., triglycerides  $\geq 500$  mg/dL). In this group, Lovaza intervention reduced triglycerides by 45%. Positive increases in HDL-cholesterol were also seen with Lovaza treatment, although increases in LDL-cholesterol also occurred.<sup>18,19</sup>

In relation to other components of the plasma lipid profile, most studies report small, non-significant increases in total cholesterol and HDL- and LDL-cholesterol after supplementation with EPA and DHA.<sup>7</sup> However, the effect of omega-3 fatty acids on LDL-cholesterol was weaker and inconsistent (compared with the effects on triglycerides), with many studies reporting net increases of LDL-cholesterol  $\leq 10$  mg/dL.<sup>7</sup> In patients with severe hypertriglyceridemia, Lovaza (4 g/day) significantly increased LDL-cholesterol, although the LDL-cholesterol concentration was still within the desirable range.<sup>18,19</sup> The Lovaza investigators deduced that the rise in LDL-cholesterol levels probably reflected more of an increase in LDL particle size rather than an

increase in LDL particle number. Data suggest that omega-3 fatty acids increase LDL particle size by decreasing small density LDL (pattern B) and increasing the levels of the larger LDL (pattern A).<sup>20,21</sup> (Compared with LDL pattern B, LDL pattern A is considered less atherogenic.)

A number of studies have evaluated the specific effect of purified EPA or DHA alone. A systematic review including 10 randomized controlled trials (RCTs) of EPA monotherapy, 17 RCTs of DHA monotherapy, and 6 RCTs comparing EPA and DHA report that although both EPA and DHA decrease triglycerides, DHA increases LDL-cholesterol, whereas EPA does not (**Table 2**).<sup>22</sup>

**Table 2.** Summary of EPA vs. DHA on Plasma Lipid Profile

	EPA vs. Placebo	DHA vs. Placebo	EPA vs. DHA
Triglycerides	↓ 7.74-109.5 mg/dL Avg. ↓ 45.8 mg/dL*	↓ 2.43-56.4 mg/dL Avg. ↓ 25.1 mg/dL*	Greater ↓ by DHA than EPA by a mean of 6.14 mg/dL*
LDL-Cholesterol	Avg. ↓ 1.76 mg/dL	Avg. ↑ 7.23 mg/dL*	Greater ↑ by DHA than EPA by a mean of 4.63 mg/dL*
HDL-Cholesterol	Avg. ↑ 0.20 mg/dL	Avg. ↑ 4.49 mg/dL*	Greater ↑ by DHA than EPA by a mean of 2.15 mg/dL

\* Statistically significant; ↓ = decrease; ↑ = increase

### Blood Pressure

In several large population-based studies, red blood cell concentrations of EPA and DHA have been shown to be inversely associated with blood pressure.<sup>23</sup> A recent systematic review and meta-analysis indicated that supplementation with fish oil rich in EPA and DHA has a blood pressure reducing effect in hypertensive patients, decreasing systolic blood pressure by  $\sim 2.56$  mmHg and diastolic blood pressure by 1.47 mmHg.<sup>24</sup> This follows from results of an earlier meta-analysis that reported that omega-3 fatty acids EPA and DHA in doses of over 3 g/day reduced diastolic and systolic blood pressure, with these reductions reaching significance in hypertensive subjects only.<sup>7,25</sup>

### Heart Rate

Some studies suggest that a higher intake of omega-3 fatty acids, especially of DHA, may contribute to the maintenance of healthy heart rhythm. In 3 separate

large prospective cohort studies, an increased concentration of omega-3 fatty acids in serum was shown to reduce the risk of developing atrial fibrillation, with DHA showing the strongest association.<sup>26,27</sup> A meta-analysis of fish oil intervention studies reported that in randomized controlled trials, fish oil supplementation reduces heart rate, particularly in those with higher baseline heart rate.<sup>28</sup>

### CVD & Cardiac Mortality

Prospective cohort studies have consistently shown that higher intakes of EPA and DHA are associated with a reduced risk of CVD. In a systematic review of cohort studies, the consumption of  $\geq 250$  mg/day of EPA and DHA was associated with a significant 36% reduction in fatal heart disease.<sup>29</sup>

Large meta-analyses of randomized controlled trials of EPA and DHA supplementation have reported reductions in risk of cardiac mortality and CVD secondary prevention.<sup>30,31</sup> However, not all published systematic reviews and meta-analyses have yielded similar conclusions. For example, 1 review found that omega-3 fatty acid might protect against vascular disease (relative risk = 0.86; 95% CI: 0.75-0.99) but not coronary events.<sup>32</sup> But another review did not find any association between omega-3 supplementation and myocardial infarction or stroke.<sup>33</sup> A recent meta-analysis reported no beneficial effect of EPA and DHA supplementation for reduction of cardiac mortality in patients at higher risk of cardiovascular events.<sup>34</sup>

Clinical trials are generally of short duration, and those trials investigating cardiac endpoints tend to include patients with advanced disease. Even considering the variable effects of EPA and DHA supplementation trials on cardiac endpoints such as mortality, the American Heart Association retained the recommended intake of 1 g EPA and DHA daily for individuals with existing CVD.<sup>15</sup>

### Adult Cognitive Function & Mood

Higher intakes of omega-3 fatty acids, particularly DHA, have been shown to support maintenance of healthy cognitive function:

- In the Zutphen Elderly Study, a prospective cohort study of elderly participants aged 70-89 years, fish consumption was associated with a reduced level of cognitive decline than non-fish consumption.<sup>35</sup>
- In participants of the Framingham Heart Study and the Prospective Investigation of the Vasculature in Uppsala Sension Study, higher EPA and DHA status were positively associated with indices of

cognitive performance, and scores on tests of visual memory, executive function, and abstract thinking, with DHA showing a stronger association.<sup>36,37</sup>

- In an RCT of 132 mg EPA plus 880 mg DHA or placebo in healthy adults, omega-3 fatty acid supplementation led to beneficial changes in executive functioning compared with placebo control.<sup>38</sup>
- In a meta-analysis examining the effects of omega-3 fatty acid supplementation on indices of cognitive function in a group of adults with mild cognitive impairment free of dementia and Alzheimer's disease, a DHA-driven effect on memory, immediate recall, attention, and processing speed was reported.<sup>39</sup>

However, EPA and DHA supplementation trials in populations with more advanced diseases such as dementia often fail to show beneficial effect. For example, a Cochrane review of omega-3 fatty acid supplementation trials (intervention periods ranging from 6 to 40 months) showed no effect on incident dementia, word learning, digit spans, or verbal fluency.<sup>40</sup> (The lack of results seen in RCTs may be related to already advanced disease stage, in addition to relatively short intervention periods; it is recognized that longer duration, high quality studies are required before definitive recommendations can be made.<sup>40,41</sup>)

Omega-3 fatty acids, particularly DHA, have been shown to support the maintenance of healthy brain and gray matter volume and brain structure. In several large cohort studies, including the Framingham Heart Study, lower omega-3 status was associated with lower total brain, hippocampal, and gray matter volume and higher white matter hyperintensity, with DHA showing the greatest effect.<sup>36-38,42,43</sup>

Relating to mood disorders, recent evidence suggests that omega-3 fatty acids may be of clinical benefit. Several meta-analyses of trials conducted in patients with diagnosed depression or with depressive symptomatology report positive effects of omega-3 fatty acids on symptoms.<sup>44-47</sup> The positive effects appear to be driven by EPA.<sup>44,45,48</sup>

### Eye Health

Some studies have shown that higher intakes of omega-3 fatty acids are beneficial for several aspects of eye health. Omega-3 fatty acids, particularly EPA and DHA, help maintain the natural lubrication of the eye. A double blind RCT supplementing with 1245 mg EPA and 540 mg DHA daily for 12 weeks in adults

with symptoms of dry eye syndrome showed that subjective measures of pain associated with dry eye was significantly reduced and significant improvements were seen in tear film breakup time compared with placebo.<sup>49</sup> In another double-blind randomized controlled trial of 350 mg EPA and 350 mg DHA daily in 265 adults and 254 controls with dry eye syndrome, again subjective measures of pain associated with dry eye were reduced in the omega-3 group and tear film breakup time was improved.<sup>50</sup>

Omega-3 fatty acids, particularly DHA, help maintain retinal health and the health and integrity of the macula. Age-related macular degeneration (AMD) is the leading cause of blindness in developing countries and the third leading cause of global blindness. Meta-analyses of cohort studies indicate that higher dietary intakes of omega-3 fatty acids such as EPA and DHA help reduce the risk of developing AMD, with DHA generally more strongly associated, and so may be beneficial for the primary prevention of AMD.<sup>51</sup> Cohort studies published after this meta-analysis also highlight that higher circulating plasma concentrations of omega-3 and particularly DHA are associated with reduced incidence and progression of AMD.<sup>52-55</sup>

#### Child & Maternal Health

Some studies suggest that higher intakes of omega-3 fatty acids, particularly DHA, taken when pregnant and breastfeeding, help support brain development in infants:

- In a study of 341 pregnant women supplemented with fish oil containing DHA and EPA or placebo from 18 weeks of pregnancy to 3 months post-delivery, children born to the EPA/DHA supplemented mothers scored higher on the Mental Processing Composite at 4 years compared with children born to the placebo group mothers.<sup>56</sup>
- In another intervention of fish oil versus placebo from 20 weeks gestation to delivery, children of mothers supplemented with fish oil displayed increased eye-hand coordination at 2.5 years of age compared with the placebo group.<sup>57</sup>
- In a study of breastfeeding mothers receiving an algal oil rich in DHA (200 mg/day) for 4 months, infants from DHA-supplemented mothers scored higher on the Bayley Psychomotor Development index at 30 months of age compared with infants from the placebo group mothers.<sup>58</sup>
- When mothers were supplemented with DHA during pregnancy (300 mg daily from enriched bars), infants from the supplemented mothers performed better in problem-solving tasks than infants in the placebo group.<sup>59</sup>

- Additionally, DHA status at delivery (as assessed by cord blood DHA concentrations) was associated with greater odds of having a maximal neurological optimality score at 5.5 years of age.<sup>60</sup>

When taken during pregnancy, DHA helps to support the development and the maturation of the vision system in infants:

- Infants of women supplemented with DHA during pregnancy showed greater visual acuity scores at 4 months compared with placebo group; however, these differences did not persist at 6 months.<sup>59</sup>
- In a meta-analysis of trials of DHA-supplemented infant formula versus DHA-free formula for pre-term infants, DHA was seen to confer benefits to the early vision system development.<sup>61</sup>
- In a group of infants with DHA measured in cord blood at birth, higher DHA status was seen to be associated with earlier development of the P100 component of the pattern-reversal visually evoked potentials (VEP).<sup>62</sup>

#### Inflammation

EPA and DHA can impact several aspects of the inflammatory response. In a systematic review of 35 EPA/DHA intervention studies, decreased circulating C-reactive protein (CRP, an acute-phase response protein) and interleukin 6 (IL-6, a pro-inflammatory cytokine) were observed in some studies.<sup>63</sup> In a group of 454 healthy women and 405 healthy men, higher intakes of omega-3 fatty acids were associated with reduced plasma tumor necrosis factor-receptor 1 and 2 (sTNF-R1 and sTNF-R2).<sup>64</sup> In a supplementation study in 138 overweight adults, supplementation with 2.5 g omega-3 fatty acids per day reduced serum IL-6 and tumor necrosis factor alpha (TNF- $\alpha$ ).<sup>65</sup>

EPA can act as a direct competitor with arachidonic acid, reducing the synthesis of the more potent prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>).<sup>66</sup> In stimulated *ex vivo* neutrophils isolated from a group of adults supplemented with 3.2 g EPA and 2.2 g DHA daily for 6 weeks, arachidonic acid production and 5-lipoxygenase pathway production was significantly reduced.<sup>67</sup>

EPA and DHA can influence the inflammatory response in multiple ways, and have been shown to be beneficial for individuals suffering from inflammatory conditions, such as rheumatoid arthritis and inflammatory bowel disease:

- A systematic review and meta-analysis of randomized controlled trials supplementing patients

with rheumatic arthritis or joint pain secondary to other medical conditions with omega-3 fatty acids (mean daily EPA plus DHA dose of 2.745 g for average of 27 weeks) reported that supplementation with omega-3 fatty acids reduced patient reports of joint pain intensity, minutes of morning stiffness, number of painful and tender joints, and non-steroidal anti-inflammatory drug (NSAID) usage.<sup>68</sup>

- In a later systematic review and meta-analysis of RCTs, only including trials of 3-month duration or longer, a mean daily dose of 2.7 g omega-3 fatty acids reduced NSAID use.<sup>69</sup>
- In a cross-sectional study of patients with RA and healthy controls, concentrations of omega-3 fatty acids (omega-3 index) was significantly lower in RA patients.<sup>70</sup>
- In patients with Crohn's disease supplementing their diets with 2.7 g of omega-3 fatty acids for 1 year, a significantly greater number of patients in the fish oil group remained in remission, although this increase in remission rates was not seen in all studies.<sup>71,72</sup> A meta-analysis aiming to clarify this reported a significant benefit for omega-3 fatty acids in Crohn's disease (RR 0.77; 95% CI: 0.61-0.98), although studies were notably heterogeneous in outcome.<sup>73</sup>

## CONCLUSION

The omega-3 fatty acids EPA and DHA are important nutrients at various stages of life. Data from good-quality randomized controlled trials have demonstrated their effects in reducing cardiovascular risk markers and some cardiovascular outcomes as secondary prevention. EPA and DHA also have reported benefits for cognitive function, mental health, maternal and child health, and certain inflammatory diseases.

Furthermore, omega-3 fatty acid supplementation has been found to be well-tolerated with minimal adverse events in most situations. Considering the positive health benefits of omega-3 fatty acids, particularly EPA and DHA, many expert working groups, including the American Heart Association and the American Academy of Pediatrics, have recommended specific EPA and DHA intakes to confer clinical benefit.

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