

# Docosahexaenoic Acid<sup>1,2</sup>

## Nutrient

DHA (22:6n-3) is a long-chain PUFA (LCPUFA)<sup>3</sup> of the  $\omega$ -3 (n-3) family with a 22-carbon chain and 6 *cis* double bonds (22:6n-3) (1). DHA is not an essential FA per se, because it can be metabolized to some extent from its essential precursor,  $\alpha$ -linolenic acid [ALA (18:3n-3)], via a series of desaturations and elongations (1). Although ALA can be converted metabolically into EPA (20:5n-3) and on to DHA, the conversion rate is considered to be low in humans (2). Consequently, plasma and tissue concentrations of DHA are determined mainly by dietary DHA intake, and the consumption of large amounts of ALA has been shown to have little effect on plasma DHA concentrations, except in those with a very low ALA intake (2). As a result, many organizations worldwide have issued a recommendation for dietary DHA intake (often combined with EPA) (3). However, the Institute of Medicine concluded in its 2002 report that there was insufficient evidence to set a specific DRI for DHA (3). Most of the evidence for the benefits of n-3 LCPUFAs is based on studies of fish consumption or of supplements (fish oils); therefore, relatively little is known about the unique effect of DHA (without EPA).

The strongest evidence for a benefit of DHA relates to its unique role in cognitive and visual development and function. DHA is found in high concentrations in neuronal cell membrane phospholipids, where it can exert many physiologic roles including regulation of membrane fluidity, neurotransmitter release, gene expression, myelination, and cell differentiation and growth (1). Considering the low rate of de novo DHA synthesis from ALA, many researchers agree that DHA is required in the diet in order to reach and maintain adequate brain and eye DHA concentrations and related neurologic and visual functions (1, 3). DHA is accumulated rapidly in the brain and eye during gestation and early infancy and is essential for the growth and maturation of the infant's brain and retina. Breast milk naturally contains substantial amounts of DHA: analysis of breast milk samples from >2400 women from around the globe gave a mean concentration of DHA in breast milk of 0.32 g/100 g FA, with a range of 0.06–1.4 (4). Evidence-based recommendations from randomized controlled studies suggest that infant formula should be enriched with DHA (generally between 0.2% and 0.35% of total FAs) for optimal brain and visual development in both preterm and full-term infants. Consumption of preformed DHA in the diet has been associated with many beneficial effects on cognitive functions throughout

the life course (1). Several observational studies have reported, among the potential beneficial effects in adults, a lower risk of dementia and cognitive decline with a higher intake of EPA plus DHA, although results from clinical studies are far less consistent (1).

A large body of evidence from epidemiologic and intervention studies has emerged on the cardioprotective effects of DHA and EPA (3). Meta-analyses of observational and prospective studies have reported that a higher intake of EPA plus DHA (or fish) is associated with a reduced risk of heart failure and mortality from coronary artery disease. Meta-analyses of intervention studies also have reported beneficial effects of EPA plus DHA supplementation (or fish intake) on the primary and secondary prevention of cardiovascular disease (CVD) (3). Several potential mechanisms could be responsible for this lower risk of mortality. Indeed, EPA plus DHA has been shown to reduce susceptibility to cardiac arrhythmias, stabilize atherosclerotic plaques, lower plasma TG concentrations, modestly reduce blood pressure, and decrease markers of systemic inflammation and oxidative stress (3, 5). It is now well established that inflammation is a key etiologic factor in the pathogenesis of chronic diseases such as CVD, and EPA plus DHA has been shown to exert anti-inflammatory effects. A higher intake of EPA plus DHA increases the n-3 LCPUFA content of cell membrane phospholipids, which in turn modulates several signaling pathways (1, 5). The incorporation of DHA into cell membranes leads to the generation of anti-inflammatory lipid mediators implicated in the resolution of inflammation, such as resolvins, protectins, and maresins (1, 5). However, observational and clinical trials have not always reported consistent results regarding the anti-inflammatory effects of EPA plus DHA (5). These LCPUFAs appear to efficiently lower inflammation in rheumatoid arthritis, whereas some suggestive but inconsistent results have been observed in inflammatory bowel disease and asthma (5). Among the potential beneficial effects on cancer, n-3 LCPUFAs have been shown to exert antineoplastic activity by inducing apoptotic cell death in human cancer cells and increasing the sensitivity of tumor cells to conventional therapies without affecting normal cells (6).

## Deficiencies

Dietary n-3 PUFA deficiency is very rare, and its consequences on health are not fully understood yet (1, 3). Because DHA can be synthesized from ALA, there is perhaps no frank deficiency in DHA. Moreover, the conversion from ALA to EPA and on to DHA has been shown to be increased in adults consuming no DHA. Frank deficiency of ALA has been observed in rare cases in patients receiving long-term parenteral or gastric feeding (1). Symptoms include numbness, paresthesia,

<sup>3</sup>Abbreviations used: ALA,  $\alpha$ -linolenic acid; CVD, cardiovascular disease; LCPUFA, long-chain PUFA.

weakness, an inability to walk, pain in the legs, blurring of vision, and flaky skin, together with low concentrations of EPA and DHA in the blood stream and tissues. The provision of ALA reverses biochemical and clinical symptoms (1). In the absence of ALA, it is likely that DHA would become essential.

### Diet Recommendations

There is currently no specific DRI for DHA. However, numerous organizations worldwide have issued a recommendation for DHA (often combined with EPA) intake and/or for fish intake. The 2015 Dietary Guidelines for Americans recommend that the general population and pregnant and breastfeeding women consume  $\geq 8$  ounces (227 g) seafood/wk, providing  $\geq 250$  mg/d EPA plus DHA (7). The Academy of Nutrition and Dietetics and the Dietitians of Canada recommend that people consume  $\geq 500$  mg/d EPA plus DHA provided by 2 servings fatty fish/wk for adults (3). The WHO recommends an intake of  $\geq 250$  mg EPA plus DHA/d for adults. The European Food Safety Authority also recommends the consumption of  $\geq 250$  mg EPA plus DHA/d for adults, as well as an additional intake of 100–200 mg DHA/d for pregnant and lactating women (3). The International Society for the Study of Fatty Acids and Lipids recommends that adults consume  $\geq 500$  mg EPA plus DHA/d and that pregnant and lactating women consume at least 300 mg DHA/d (3). There is also general agreement that infant formula should be enriched with DHA (with  $\geq 0.32\%$  of total FAs as DHA) (1).

### Food Sources

Seafood and fish are the major dietary source of DHA—especially cold-water fatty fish, including salmon, herring, tuna, anchovies, and sardines (3). These fatty fish are by far the richest dietary source of DHA, with each serving of 75 g providing between 750 and 1500 mg DHA. Breast milk also contains DHA for the infant. Nowadays, there is also a variety of food products fortified in fish oil–derived EPA and DHA, including eggs, yogurt, milk, juice, and spreads (3). Finally, many supplements exist on the market, including fish oil, krill oil, and algal oil.

### Clinical Uses

The AHA recommends that individuals with CVD take 1 g EPA plus DHA/d for the secondary prevention of CVD (3). The Institute of Medicine and the AHA both recommend that hyperlipidemic individuals consume 2–4 g EPA plus DHA/d under a physician's care to lower serum TG concentrations. These amounts of n–3 LCPUFA can be achieved with dietary fish oil supplements or prescription formulations that contain both EPA and DHA. There are 2 prescription formulations of n–3 LCPUFAs available in the United States: the  $\omega$ -3 acid ethyl esters (LOVAZA) and the icosapent ethyl (VASCEPA). Some

formulas designed for enteral or parenteral use contain n–3 LCPUFAs (1, 8).

### Toxicity and Adverse Outcomes

No Tolerable Upper Intake Level has been established yet for DHA. Although DHA intake generally is considered to be safe for most people, there are some minor concerns reported when high amounts of fish oil supplements are consumed ( $>3$  g/d EPA plus DHA) (3). Potential adverse effects reported include a fishy taste, nausea, intestinal gas, loose stools, belching, bruising, and an increased risk of bleeding (3). There is also a concern about mercury with fish consumption, and it is recommended that pregnant and lactating women, as well as young children, avoid certain types of fish high in mercury. DHA could interact with antihypertensive, anticoagulant, and antiplatelet drugs, and individuals are advised to consult a physician before taking large doses of EPA plus DHA ( $>3$  g/d) when on these medications.

### Recent Research

Emerging research has investigated the role of DHA independently of EPA on inflammation and CVD risk factors. The first results from the Comparing EPA to DHA Study were published recently and demonstrated for the first time, to our knowledge, that DHA is more effective than EPA in modulating specific markers of inflammation, as well as blood lipids (a greater reduction in TGs and a greater increase in HDL cholesterol) (9). Studies have shown that DHA supplementation in the maternal diet may have a favorable impact on the development of the infant's immune system and the risk of allergic or atopic diseases early in life (10). Recent studies also have identified polymorphisms in several genes that could partly explain the large interindividual variability observed in plasma TG concentrations in response to EPA plus DHA supplementation (11).

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## References

1. Weiser MJ, Butt CM, Mohajeri MH. Docosahexaenoic acid and cognition throughout the lifespan. *Nutrients* 2016;8.
2. Burdge GC, Calder PC. Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod Nutr Dev* 2005;45:581–97.
3. Flock MR, Harris WS, Kris-Etherton PM. Long-chain omega-3 fatty acids: time to establish a dietary reference intake. *Nutr Rev* 2013;71:692–707.
4. Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. *The Am J Clin Nutr* 2007;85(6):1457–64.
5. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim Biophys Acta* 2015;1851:469–84.
6. D'Eliseo D, Velotti F. Omega-3 fatty acids and cancer cell cytotoxicity: implications for multi-targeted cancer therapy. *J Clin Med* 2016;5.
7. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary guidelines for Americans. 8th Edition. December 2015 [cited 2016 Jul 7]. Available from: <http://health.gov/dietaryguidelines/2015/guidelines/>.
8. Calder PC. Rationale and use of n–3 fatty acids in artificial nutrition. *Proc Nutr Soc* 2010;69:565–73.
9. Allaire J, Couture P, Leclerc M, Charest A, Marin J, Lepine MC, Talbot D, Tchernof A, Lamarche B. Randomized, crossover, head-to-head comparison of EPA and DHA supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA Study. *The American Journal of Clinical Nutrition* 2016; 104:280–7.
10. Richard C, Lewis ED, Field CJ. Evidence for the essentiality of arachidonic and docosahexaenoic acid in the postnatal maternal and infant diet for the development of the infant's immune system early in life. *Appl Physiol Nutr Metab* 2016;41(5):461–75.
11. Vallee Marcotte B, Cormier H, Guenard F, Rudkowska I, Lemieux S, Couture P, Vohl MC. Novel Genetic Loci Associated with the Plasma Triglyceride Response to an Omega-3 Fatty Acid Supplementation. *J Nutrigenet Nutrigenomics* 2016;9(1):1–11.