Docosahexaenoic acid (DHA)

Nutrient:

Docosahexaenoic acid (DHA) is a long chain polyunsaturated fatty acid (LCPUFA) of the omega-3 (n-3) family with a 22-carbon chain and six *cis* double bonds (22:6n-3) (1). DHA is not an essential fatty acid *per se* since it can be metabolized to some extent from its essential precursor α-linolenic acid (ALA, 18:3n-3) via a series of desaturations and elongations (1). Although ALA can be metabolically converted into eicosapentaenoic acid (EPA, 20:5n-3) and on to DHA, the conversion rate is considered to be low in humans (2). Consequently, plasma and tissue levels of DHA are determined mainly by dietary DHA intake and consumption of large amounts of ALA has been shown to have little effect on plasma DHA concentrations, except in those with very low ALA intakes (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 dietary reference intake (DRI) for DHA (3). Most of the evidence for benefits of n-3 LCPUFAs is based on studies of fish consumption or of supplements ("fish oils") and 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 physiological roles including regulating 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 neurological and visual functions (1, 3). DHA is rapidly accumulated 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 significant amounts of DHA: analysis of breast milk samples from over 2400 women from around the globe gave a mean concentration of DHA in breast milk of 0.32 g/100 g fatty acid with a range of 0.06 to 1.4 (4). Evidence based recommendations from randomized controlled studies suggest that infant formula should be enriched in DHA (generally between 0.2-0.35% of total fatty acids) 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). Among the potential beneficial effects in adults, several observational studies have reported a lower risk of dementia and cognitive decline with higher intake of EPA+DHA, although results from clinical studies are far less consistent (1).

A large body of evidence from epidemiological and intervention studies has emerged on the cardioprotective effects of DHA and EPA (3). Meta-analyses of observational and prospective studies have reported that higher intake of EPA+DHA (or fish) is associated with a reduced risk of heart failure and mortality from coronary heart disease. Meta-analyses of intervention studies have also reported beneficial effects of EPA+DHA supplementation (or fish intake) on primary and secondary prevention of CVD (3). Several potential mechanisms could be responsible for this lower risk of mortality. Indeed, EPA+DHA has been shown to reduce susceptibility to cardiac arrhythmias, stabilize atherosclerotic plaques, lower plasma triglyceride (TG) levels, 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 etiological factor in the pathogenesis of chronic diseases like CVD and EPA+DHA has been shown to exert anti-inflammatory effects. Higher intake of EPA+DHA increases the n-3 LCPUFA content of cell membrane phospholipids which in turn modulates several signaling pathways (1, 5). 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+DHA (5). They 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 anti-neoplastic 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). Since 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 in ALA has been observed in rare cases in patients receiving long term parental or gastric feeding (1). Symptoms included numbness, paresthesia, weakness, inability to walk, pain in the legs, blurring of vision and flakey skin together with low levels of EPA and DHA in the blood stream and tissues. Provision of

ALA reversed 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 recommends that the general population and pregnant and breastfeeding women should consume at least 8 ounces of seafood per week providing ≥ 250 mg/day of EPA+DHA (7). The Academy of Nutrition and Dietetics and the Dietitians of Canada recommend to consume ≥ 500 mg/day of EPA+DHA provided by two servings of fatty fish/week for adults (reviewed in (3)). The World Health Organization recommends an intake of ≥ 250 mg/day of EPA+DHA for adults. The European Food Safety Authority also recommends consuming ≥ 250 mg/day of EPA+DHA for adults, as well as an additional intake of 100-200 mg/day of DHA for pregnant and lactating women (3). The International Society for the Study of Fatty Acids and Lipids recommends that adults should consume ≥ 500 mg/day of EPA+DHA and that pregnant and lactating women consume at least 300 mg/day of DHA (3). There is also a general agreement that infant formula should be enriched in DHA (at least 0.32% of total fatty acids as DHA) (1).

Food sources:

Seafood and fish are the major dietary source of DHA and 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 750-1500 mg of 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 including fish oil, krill oil and algal oil exist on the market.

Clinical uses:

The American Heart Association (AHA) recommends that individuals with CVD should take 1 g/day of EPA+DHA for secondary prevention of CVD (3). The Institute of Medicine and the AHA both recommend consumption of 2-4 g/day of EPA+DHA to lower serum TG levels in hyperlipidemic individuals under a physician's care. 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 two prescription formulations of n-3 LCPUFAs available in the U.S., the omega-3 acid ethyl esters (OM-3-A EEs, Lovaza) and the icosapent ethyl (IPE, 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 is generally considered safe for most people there are some minor concerns reported when high amounts of fish oil supplements are consumed (> 3g/day EPA+DHA) (3). Among the potential adverse effects reported there is a fishy taste, nausea, intestinal gas, loose stools, belching, bruising, and increased risk for bleeding (3). There is also a concern about mercury with fish consumption, and pregnant and lactating women as well as young children are recommended to

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+DHA (>3 g/day) when on these medications.

Recent research:

Emerging research has investigated the role of DHA independently of EPA on inflammation and cardiovascular risk factors. The first results from the Comparing EPA to DHA (ComparED) Study have recently been published and demonstrated for the first time that DHA is more effective than EPA in modulating specific markers of inflammation as well as blood lipids (greater reduction in TG and greater increase in HDL-cholesterol). There is still numerous ongoing studies assessing the impact of DHA during the pre- and post-natal period on infant development and on cognition in later life. Studies showed 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/atopic diseases early in life. Recent studies have also identified polymorphisms in several genes that could partly explain the large interindividual variability observed in plasma TG levels in response to EPA+DHA supplementation.

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[2]Abbreviations used: ALA, alpha-linolenic acid; CVD, cardiovascular disease; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DRI, dietary reference intake; LCPUFA, long chain polyunsaturated fatty acid; TG, triglyceride;

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