Omega-3 fatty acids (n-3 polyunsaturated fatty acids) are dietary nutrients offering human health plus disease preventing/managing potential. Certain plant sources (and derived vegetable oils) such as flaxseed, canola oil, walnuts, etc. contain significant amounts of the plant-based omega-3 fatty acid known as a-linolenic acid (ALA, 18:3n-3). In contrast, fish/fish oils are enriched to varying degrees with the omega-3 fatty acids known as eicosapentaenoic acid (EPA, 20:5n-3) plus docosahexaenoic acid (DHA, 22:6n-3). Flaxseed and other plant-derived oils are totally lacking in DHA/EPA combined whereas DHA/EPA are found in fish/fish oils which contain very minor amounts of ALA. A typical North American diet provides approximately 2-3 g/day of ALA from mixed plant /animal sources whereas EPA and DHA are consumed at levels of approximately 50 mg and 80 mg/day, respectively, for an overall combined DHA/EPA intake per person of approximately 130-150 mg/day. The vast majority of the dietary DHA/EPA is consumed from fish /fish oil sources.

DHA is the omega-3 fatty acid that is now widely recognized as the physiologically-essential nutrient in the brain for normal functioning of neural tissue (including cognitive performance, learning ability, memory, etc) and in the retina of the eye for visual acuity. Almost all the omega-3 fatty acid found in brain tissue, where it is required for structure-function relationships, is in the form of DHA with other omega-3 fatty acids such as ALA being found only in trace amounts regardless of dietary intakes of ALA. DHA addition to infant formula containing ALA was found to improve the mental development index. In 1990, Health Canada established ALA as an essential fatty acid in the diet (at 0.5% of total dietary energy) based on considerations from previous animal studies (for the most part) that ALA can be converted into the physiologically-essential DHA for brain and retinal functioning. However, human studies during the last few years have indicated a very limited conversion efficiency from dietary ALA to DHA such that attention has been given to consideration that dietary DHA is a potentially essential dietary nutrient for many in the population who lack sufficient conversion capacity from ALA to DHA. Using deuterated ALA in controlled human trials coupled with GLC-mass spec analysis of newly formed DHA in human trials, conversion efficiencies ranging from 0 to 8% on average have been reported. Furthermore, a recent study has shown that the consumption of several grams of ALA per day failed to increase the low levels of DHA in human breast milk. These studies on the very limited conversion of ALA to DHA coupled with the recognition of DHA as a physiologically-essential nutrient for neuronal functioning has lead to the release of a number of commercial products containing DHA including infant formulae, cow's milk, omega-3 shell eggs, plus a wide variety of fortified foods containing DHA as an additive. This trend is expected to continue so that the current low intakes of DHA (in North America and elsewhere across all sectors) can be enhanced so that the nutritional gap between current intakes and targets for optimal health can be closed. In this regard, it should be noted that the average adult in North America consumes approximately 80 mg of DHA per day; whereas, the Workshop on the Essentiality of Recommended Dietary Intakes (RDIs) for omega-6 and omega-3 fatty acids as held at the NIH in Bethesda (1999) recommended that pregnant and lactating women should ensure an intake of at least 300 mg/day of DHA.
Considerable research activity (both epidemiological plus interventional studies) has focused on the relationship between increased omega-3 fatty acid intakes and the risk of coronary heart disease (CHD) and mortality. Interest in ALA as a cardioprotective fatty acid has arisen in part from reports on the Mediterranean diet wherein higher intakes of ALA as part of such dietary patterns have been associated with the secondary prevention of coronary heart disease. It should be noted that ALA is but one of many potential cardioprotective components of the so-called Mediterranean diet. The proposed mechanism(s) by which an ALA-enriched diet might protect against fatal coronary heart disease is proposed to be mediated by the metabolic conversion of ALA to the long-chain omega-3 fatty acids in the form of EPA plus DHA. A recent study seeing flaxseed oil rich in ALA has confirmed a moderate rise in circulating plasma lipid levels of EPA plus DPA (but not DHA); the authors suggest that this rise, although moderate, in EPA plus DPA might possibly mediate any beneficial effects towards cardiovascular health derived by the consumption of flaxseed oil. It should be noted herein that the published literature using deuterated ALA suggests conversion efficiencies of dietary ALA to EPA plus DHA (combined) ranging from 5-15% overall. Controlled studies wherein high levels of ALA had been fed in the presence of moderate or low levels of linoleic acid (LA, 18:2n-6), including the use of low-n-6:n-3 ratios, have indicated a moderate rise in EPA as well as docosapentaenoic acid (DPA, 22:5n-3) in circulating blood serum phospholipid (biomarker for status) upon increasing ALA intakes without any significant elevation in the measured levels of DHA.

The relationship between dietary intakes of ALA in relation to the incidence of fatal heart disease has been evaluated in five prospective epidemiological studies. The relative risk of fatal heart disease showed an apparent protective with higher intakes of ALA. There appeared to be a beneficial effect of ALA intakes in three trials, no effect in one, and a detrimental effect in one study. Overall, the relative risk of fatal heart disease for a high vs. low intake of ALA showed an approximate 20% lower relative risk (RR) when adjusting for various confounding factors. The clinical/interventional trials to date with increasing ALA intakes in relation to fatal coronary heart disease tend to support the aforementioned perspective studies and, overall, suggest that increasing the intake of ALA by 1.2 g/day may decrease the risk of fatal coronary heart disease by approximately 20%. Recently, a review of 9 cohort and case-control studies (analyzed by meta-analysis) have suggested that dietary ALA is associated with an increased prostate cancer risk; the authors of this study have indicated this relationship to be of concern and meritorious of further studies. However, the authors do point out in their discussion that even if the latter relationship were real, the protective effect on fatal or coronary heart disease with increasing consumption of ALA would probably outweigh the possible negative effects, especially for men with an increased risk of heart disease. It is of interest to note that a recent prospective study on a cohort of 48,000 men with no cancer history in 1986 followed for 14 years indicated that increased dietary intakes of ALA may increase the risk of advanced prostate cancer while, in contrast, increased intakes of DHA and EPA may reduce the risk of total and advanced prostate cancer. It has been pointed out that any potential relationship of increased dietary intakes of ALA and advanced prostate cancer should attempt to identify the specific food sources of ALA contributing to any such relationships since factors other than ALA...
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in such food sources may be contributing to such apparent relationships based on epidemiological (population) studies. Two recent studies (in the year 2005) have been published from the Harvard School of Public Health on the relationship between dietary ALA intake and the risk of sudden cardiac death and coronary heart disease in women as well as a separate study evaluating the potential beneficial effects of ALA consumption in men in relation to their background dietary intake of DHA plus EPA as derived from fish. The first study on 77,000 women participating in the nurses' health study over 18 years suggested that increased dietary intakes of ALA may reduce the risk of sudden cardiac death (by up to 40%) but not other types of fatal coronary heart disease or non-fatal myocardial infarctions. The second study involved 46,000 men initially free of known cardiovascular disease who were followed up over 14 years. Interestingly, the reduced risk of sudden cardiac death with higher intakes of omega-3 fatty acids did not appear to be significantly influenced by the background intake of omega-6 fatty acids or by the omega-6:omega-3 ratio in the diet. The omega-3 fatty acids from both seafood (DHA plus EPA) and plant sources (as ALA) appeared to significantly reduce the risk of coronary heart disease however the protective effects of increased ALA consumption were only observed when the intake of DHA plus EPA from seafood was low. Specifically, no apparent benefit of increasing the consumption of dietary ALA was observed for lowering the risk of non-fatal myocardial infarctions and total coronary heart disease as seen when the DHA plus EPA (combined) consumption surpassed 100 mg/day; when the background intake of DHA plus EPA was below 100 mg/day, an apparent beneficial effect of increasing the consumption of ALA was exhibited.

A number of review articles have appeared based on epidemiological studies from various countries indicating that higher intakes of fish/fish oils containing EPA plus DHA (combined) are associated with a reduced risk of cardiovascular disease and fatal coronary events. A very recently-published evaluation (via meta-analysis) on the basis of 11 eligible studies in 13 cohorts including 220,364 individuals with an average 11 years of follow-up indicated that fish consumption is inversely associated with fatal coronary heart disease and that mortality from coronary heart disease may be reduced by eating fish at least once per week or more (up to and including 5 servings/week). This latter meta-analysis is supportive of previous studies on omega-3 fatty acid intake as EPA plus DHA combined (where increasing intakes of DHA/EPA up to approximately 700 mg/day was associated with a reduction in cardiovascular disease-related mortality and all-caused mortality. The GISSI-Prevenzione study indicated that supplementation with DHA/EPA combined (to approximately 900 mg/day) in patients having experienced a heart attack (who were advised to consume a Mediterranean-type diet in addition to appropriate prescribed cardiovascular medications) exhibited an approximate reduction in follow-up sudden cardiac deaths as compared to placebo-treated controls. These findings have resulted in the American Heart Association (in their dietary guidelines) advising at least 2 servings of fish (particularly fatty fish) per week to reduce the risk of CHD and much higher intakes of fatty fish (one serving per day) to provide for intakes of DHA/EPA combined of approximately 900 mg/day for those with coronary disease. These recommended intakes are many-fold current mean daily intakes in North American adults (at 130-150 mg/day). The aforementioned ISSFAL workshop (Bethesda) has recommended 650 mg of DHA/EPA combined per day (at least one third of which should be either EPA or DHA) for health and
disease prevention in those without coronary heart disease.

Very recently, the group from the USDA Human Nutrition Research Centre on Aging at Tufts University has reported on relationships between dietary fatty acid (type) intake and age-related lens opacities associated with cataracts of the eye. In the female population study as part of the Nurses’ Health Study cohort, higher dietary intakes of both LA (n-6) and ALA (n-3) were associated with an increased risk of age-related nuclear opacity whereas no such significant relationships were found with respect to the increased consumption of the long-chain omega-3 polyunsaturated fatty acids from fish in the form of DHA plus EPA. These authors emphasize that further study is needed to clarify the relationships between the type of fatty acid consumed and cataract risk.

Since blood levels (including serum phospholipid levels) of long-chain omega-3 fatty acids reflect the physiological status of the human body with respect to the n-3 polyunsaturates, correlations and comparative studies have been performed wherein blood levels of individual omega-3 fatty acids have been studied in relation to the risk of sudden death and fatal ischemic heart disease. In the former case, the strongest inverse relationship between blood levels of omega-3 fatty acids and those experiencing sudden death from cardiac causes was exhibited by DHA (P<0.005) followed by total long-chain omega-3 fatty acids (sum of DHA/EPA/DPA, P<0.01) and subsequently followed by EPA (P=0.06). However, the short-chain n-3 PUFA, namely ALA, showed no significant relationship in regard to the risk of sudden death from cardiac causes (P=0.28). In the Cardiovascular Health Study, a higher level of combined EPA plus DHA in plasma phospholipid was highly inversely correlated with the risk of fatal ischemic heart disease (odds ratio 0.30 with a P value of 0.01) whereas a significant but less inverse relationship was found in the case of ALA (odds ratio of 0.48 with a P value of 0.04).

The numerous interventional trials (controlled human trials) as published allow an overall perspective on the relative efficacy of ALA vs. DHA/EPA (combined) in favorably modifying various risk factors for cardiovascular disease (both conventional and non-conventional). The cardiovascular-protective effects of DHA/EPA have been attributed to their ability to favorably affect several risk factors for cardiovascular disease including anti-thrombotic, anti-arrhythmic, lipid-lowering (blood triglyceride-lowering), plus endothelial/vascular and other risk factors. Direct evaluation (gram vs. gram) for ALA vs. DHA/EPA (combined) is, in general, not possible for the most part since parallel studies using identical/comparative doses have not been conducted in controlled parallel/simultaneous studies by the same research group at the same time. Nonetheless, the published literature and reviews thereof indicate that, for the most part, ALA does not offer the same beneficial effects (or even portions thereof) for most of the cardiovascular risk parameters which have been evaluated and favorably influenced with DHA/EPA. It should also be noted that, in many of the controlled human trials, higher levels of ALA (omega-3) have been employed relative to DHA/EPA (combined). In general, the
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Anti-thrombotic effects (including inhibition of blood platelet aggregation) have been very week or non-existent when ALA is compared to DHA/EPA. This overall perspective should not be surprising upon consideration that ALA likely requires conversion to DHA/EPA via desaturation/elongation reactions if it were to provide similar cardioprotective effects to that of pre-formed DHA/EPA. As mentioned previously, the conversion efficiency of ALA to DHA/EPA is very limited in humans. Controlled human studies using deuterated ALA coupled to GC-mass spec analysis have indicated conversion efficiencies of ALA to DHA/EPA (combined) ranging from 8-30%. Whereas DHA/EPA has a well-established blood triglyceride-lowering effect with a trend towards increasing HDL-cholesterol levels, ALA has no such effects. In some isolated animal studies, there is evidence that ALA may have similar anti-arrhythmic actions as compared to DHA/EPA.

Although most risk variables for cardiovascular disease/mortality which have been evaluated to date suggest that ALA is inactive or more weakly active than DHA/EPA, measures of vascular reactivity with omega-3 fatty acids in controlled human studies is one target area where ALA (example as flaxseed oil) in some studies appears to exhibit similar beneficial effects to that of DHA/EPA (from fish oils) based on improving arterial compliance. This might possibly reflect immediate postprandial benefits on blood properties/endothelial interactions within a few an hours after consuming a meal enriched with omega-3 fatty acids (where efficient conversion of ALA to DHA/EPA in subsequent accumulation of the latter two fatty acids in membrane phospholipid may not be essential in this particular regard).

In summary and conclusion, DHA is the physiologically-essential nutrient needed in the brain and retina for cognitive functioning and visual acuity, respectively. DHA supplementation of infant formula (containing ALA) has been found to enhance cognitive performance in term infants. Conversion efficiencies of ALA to DHA in human trials have been determined to range from 0-9%. Higher dietary intakes of ALA (increasing intakes by 1,200 mg/day) have been associated with an approximate 20% lower risk of fatal heart disease whereas higher fish intakes (up to and including 5 servings/week providing approximately 650 mg DHA/EPA combined/day) have been associated with an approximate 40% lowering of CHD mortality based on epidemiological studies. In general, stronger inverse relations between blood levels of EPA plus DHA and fatal cardiac events have been found than for ALA. Most of the favorable effects of DHA/EPA ingestion on various risk factors for cardiovascular disease (via controlled interventional trials) including blood triglyceride-lowering are not found or matched by equivalent intakes of ALA. In contrast to ALA intakes, current dietary intakes of DHA/EPA in North America appear to be very much below target intakes for optimal human health and the prevention/management of cardiovascular disease and associated risk factors.


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