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Omega-3s Prove Their Worth from Infancy to Adulthood

The *PUFA Newsletter* is pleased to present a guest paper by Edward Emken, Midwest Research Consultants, Illinois, USA, summarizing some key issues in the conversion of alpha-linolenic acid to its long-chain omega-3 polyunsaturated fatty acid (n-3 LC-PUFA) derivatives. Understanding and measuring this conversion is crucial to assessing the adequacy of diets rich in alpha-linolenic acid, but low in n-3 LC-PUFAs, for fetal and infant development, cardiovascular health, immune function, and many other conditions affected by n-3 LC-PUFAs. Not surprisingly, the conversion is affected by many factors, including age, gender, and dietary fatty acid composition.

For the first time this year, we describe research on n-3 LC-PUFAs and immune function. In a dose-response study of n-3 LC-PUFAs in healthy adults, Trebble and colleagues at the University of Southampton, U.K., found that men consuming modest and increasing amounts of n-3 LC-PUFAs reduced their production of two cytokines—substances that mediate inflammation—in proportion to the amount consumed, up to one gram/day. Above that level, cytokine production tended to be less affected. In a separate report of this study, production of the pro-inflammatory substance, prostaglandin E$_2$, was also reduced. Production of interferon gamma, which fights infection, was increased. The authors discussed possible implications of this work and how it may explain some of the contradictory reports in the literature.

In infant development research, Bouwstra and colleagues at the University of Groningen, The Netherlands, compared the effect of LC-PUFA-supplemented formula with standard formula on the motor activity of three-month old healthy term infants. They used videotapes of the infants’ motor activities to assess the movement quality. Examples of these videotapes, by special courtesy of the authors, are included in our summary. Significantly fewer infants receiving the LC-PUFA-supplemented formula had “mildly abnormal” movements compared with those receiving the unsupplemented formula.

Finally, this issue includes a collection of the available dietary recommendations or guidelines for LC-PUFAs from international organizations and authoritative groups in different countries. The summary focuses on guidance for adults and does not include recommendations for LC-PUFAs in infant formulas. I am especially grateful to colleagues and friends around the world who provided information presented in this summary.

We welcome your comments, as always.

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Alpha-Linolenic Acid Conversion to n-3 LC-PUFAs

Alpha-linolenic acid is an essential omega-3 (n-3) fatty acid present at low levels in all tissues. It serves as a precursor for the synthesis of long-chain n-3 polyunsaturated fatty acids (n-3 LC-PUFAs), but it cannot substitute for eicosapentaenoic acid and docosahexaenoic acid. Interestingly, a high level of dietary alpha-linolenic acid does not substantially increase the accumulation of long-chain n-3 polyunsaturated fatty acids (n-3 LC-PUFAs) in tissues. In contrast, accumulation of eicosapentaenoic acid and docosahexaenoic acid in tissue lipids is significantly increased by modest amounts of dietary n-3 LC-PUFAs. This difference in accumulation suggests the presence of regulation or control mechanisms.

The n-3 LC-PUFAs are particularly important for the proper function of organs and tissues that transmit signals between cells. Examples are brain, retina, nerve fiber, and heart tissue. Various diseases and disorders, such as Alzheimer’s disease, heart arrhythmia, vision loss, and the development of infant brain and vision have been linked to inadequate levels of docosahexaenoic acid. In addition, n-3 LC-PUFAs lower serum triglyceride levels. These fatty acids appear to moderate inflammation-related disorders such as arthritis and asthma through their effects on eicosanoids, substances that mediate inflammation. In addition, n-3 LC-PUFAs displace arachidonic acid, the precursor fatty acid of these pro-inflammatory eicosanoids. Eicosanoids derived from n-3 LC-PUFAs oppose the action of eicosanoids derived from n-6 fatty acids that promote inflammation. The various health benefits of n-3 LC-PUFAs are generally associated with the 20- and 22-carbon n-3 PUFAs rather than with their 18-carbon fatty acid precursor, alpha-linolenic acid. For these reasons, estimating the percent conversion of alpha-linolenic acid has become an important question. It is not known if alpha-linolenic acid itself has significant physiological or health-related effects.

Many studies have shown that animals and humans are capable of converting alpha-linolenic acid to n-3 LC-PUFAs. For example, a whole-body balance study in rats reported 14% conversion of alpha-linolenic acid to docosahexaenoic acid. Carbon-13 isotope tracer studies in baboons showed that preformed docosahexaenoic acid had a seven to 20-fold higher bio-equivalence for incorporation in neonatal or fetal brain than docosahexaenoic acid derived from its dietary precursor, alpha-linolenic acid. Despite its lower bio-equivalence, 0.45 percent energy from dietary alpha-linolenic acid appeared sufficient to meet the n-3 LC-PUFA needs of the developing brain.

Reported results for percent alpha-linolenic acid conversion in humans are highly variable. In 10 groups of adult men or women, the average estimated conversion of isotope-labeled alpha-linolenic acid...
to n-3 LC-PUFA metabolites and docosahexaenoic acid was 17.3 ± 12.8 percent and 3.6 ± 3.8 percent, respectively (mean + sd). Reported conversion of labeled alpha-linolenic acid to docosahexaenoic acid in nine infant groups ranged from 1.8 to 18.4 percent (average 8.9 ± 5.7 percent).

An inherent problem with all human studies is that the results are based solely on plasma lipid data. Thus, the actual percent conversion may be higher or lower than the estimated percent conversion. Most likely, plasma data underestimate alpha-linolenic acid conversion because synthesized n-3 LC-PUFAs are removed from plasma to meet the n-3 LC-PUFA requirements of various tissues.

The wide variability in percent alpha-linolenic acid conversion data suggests that many factors may be involved in the regulation of alpha-linolenic acid conversion. Dietary alpha-linolenic acid, linoleic acid, and n-3 LC-PUFAs have been shown to inhibit alpha-linolenic acid conversion in human subjects. For example, our laboratory has shown that dietary docosahexaenoic acid reduced conversion of alpha-linolenic acid to n-3 LC-PUFAs and linoleic acid to arachidonic acid by 65-70% (Figure 1). This finding has a number of implications that are related to the health benefits associated with docosahexaenoic acid supplementation.

Docosahexaenoic acid also inhibits conversion of linoleic acid to arachidonic acid, which may be partly responsible for some of the health benefits associated with docosahexaenoic acid supplementation. A high dietary intake of alpha-linolenic acid also inhibits conversion and is part of the reason why diets containing high amounts of alpha-linolenic acid generally fail to increase the levels docosahexaenoic acid in blood lipids.

Other factors that may be important in alpha-linolenic acid conversion are gender, age, genetics, and physiological characteristics. One group has reported the interesting observation that alpha-linolenic acid conversion appears to be much higher for women than men. Alpha-linolenic acid conversion by preterm infants appears to be two to three times higher than in adults (Figure 2). Men with an inherited visual disorder have lower conversion than normal controls. Stress and pregnancy are examples of various physiological factors that may increase alpha-linolenic acid conversion. Overall, it appears that alpha-linolenic acid conversion may increase or decrease in response to the body’s need for n-3 LC-PUFAs.

The U.S. National Academy of Sciences 2002 report on Dietary Reference Intakes for Macronutrients published in 2002 made a courageous effort to provide recommendations for n-3 PUFA intake. The report suggested adequate intake values for alpha-linolenic acid of 1.6 grams/day for men (19-50 yr), 1.1 grams/day for women (19-50 yr) and 0.5 grams/day for infants (0-6 months). Based on these intake values and the average estimated alpha-linolenic acid percent conversion data from stable isotope studies, we calculated that the total amount of n-3 LC-PUFAs synthesized would be 277 mg/d for men, 398 mg/d for women and 65 mg/d for infants. These calculated mg/day values are about 30 percent lower than estimates obtained by gastric
and parenteral infusion studies with alpha-linolenic acid-deficient patients. This difference is not unreasonable because alpha-linolenic acid conversion is expected to be higher in alpha-linolenic acid deficient subjects than non-deficient subjects.

The above are the best estimates that we can make based on available data. We do not know exactly how much alpha-linolenic acid is converted to eicosapentaenoic acid and docosahexaenoic acid, but the current levels of dietary alpha-linolenic acid in U.S. diets appear adequate to meet the nutritional needs of healthy individuals. However, it is not clear if conversion of alpha-linolenic acid to n-3 LC-PUFA is adequate to provide health benefits for individuals with specific health problems or those at high risk for certain diseases. The final resolution of this controversial issue remains an elusive goal.


Cardiovascular Health

Consumption of n-3 LC-PUFAs Reduces Risk of Death in Heart Disease Patients

In people with established coronary artery disease, the consumption of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) can significantly and markedly reduced cardiac mortality, especially from sudden death. These beneficial effects prompted the American Heart Association last year to recommend the consumption of one gram/day of these fatty acids by people with heart disease (see March newsletter article on AHA Recommendations). Those at risk of heart disease, but without clinical symptoms, are also urged by the Heart Association to consume fatty fish at least twice a week to obtain the cardioprotective benefits of n-3 LC-PUFAs.

A person’s usual consumption of n-3 LC-PUFAs, found mainly in fatty fish, is reflected in various biomarkers – usually tissue levels of eicosapentaenoic acid or docosahexaenoic acid, the major n-3 LC-PUFAs. Plasma phospholipid or red blood cell membrane levels are easily accessible and have been used to examine n-3 LC-PUFA status. Adipose tissue has also been used, but is less readily available. Measurement of tissue levels of n-3 LC-PUFAs provides a snapshot of an individual’s LC-PUFA status and can be related to profiles of disease risk or major health events such as cardiac arrest, stroke, and death.

Erkkila and colleagues at the University of Kuopio, Finland, examined the fatty acids in serum cholesteryl esters and phospholipids in 415 men and women with clinically established coronary artery disease, aged 33 to 74 years, who were enrolled in a secondary prevention program. Four-day food records and blood samples were collected at baseline and participants

![Figure 1. Relative risks of cardiac death or all-cause mortality by tertile of EPA or DHA in serum cholesteryl esters](image-url)
were followed for five years. The average age of study subjects was 61 years.

Over the five-year follow-up period 36 participants died, including 21 from events in the cardiovascular system. There were 72 other nonfatal cardiovascular events among survivors. Relative risks of cardiovascular events were calculated by category of fatty acids in serum phospholipids and cholesteryl esters and amount of fish consumption. The latter was divided into thirds above and below the median intake of 57 grams/day. These intake levels (tertiles) included 0, 1-57, and more than 57 grams of fish/day. Similarly, serum cholesteryl ester fatty acid levels were divided into thirds for the calculation of relative risks.

Higher levels of n-3 LC-PUFAs in serum cholesteryl esters were significantly related to lower risk of mortality from all causes and from coronary events (Figure 1). The level of eicosapentaenoic acid was significantly related to lower risk of coronary death and docosahexaenoic acid to deaths from all causes. Although fish consumption was related to levels of eicosapentaenoic and docosahexaenoic acids in cholesteryl esters, it was not by itself associated with reduced risk of mortality or coronary death. Alpha-linolenic acid, the precursor fatty acid of n-3 LC-PUFAs, did not have significant protective effects against death or cardiac events. The authors noted that subjects who died during the follow-up period were significantly older and had higher levels of total and low-density lipoprotein cholesterol and triglycerides than survivors.

These findings add to the literature showing that those with higher levels of n-3 LC-PUFAs in their blood lipids have significantly reduced risk of death from all causes and from heart disease. In this study, fish consumption itself was not associated with lower mortality, but it was the main source of n-3 LC-PUFAs that were protective. As other studies have reported, n-3 LC-PUFAs do not appear to provide significant protection against myocardial infarction or other cardiovascular events, but they have significant protective effects against mortality. No significant benefits were associated with alpha-linolenic acid. What remains to be clearly established, however, are benefits in subjects without clinical symptoms of cardiovascular disease.


Maternal and Infant Health

LC-PUFA Supplementation of Infants Improves Quality of General Movements

Long-chain polyunsaturated fatty acids (LC-PUFAs) are essential for healthy infant development, but there is doubt whether term and preterm infants obtain or synthesize sufficient LC-PUFAs to meet developmental needs in the first months of life. The fatty acids docosahexaenoic acid and arachidonic acid, members of the omega-3 and omega-6 fatty acid families, respectively, are present in breast milk and have recently been added to many infant formulas, especially in developed countries. Although the human brain requires these fatty acids for normal growth and development, effects on functional and behavioral outcomes, particularly in term infants, appear to be rather subtle. Furthermore, commonly used assessment tools may be unable to measure fine distinctions of potential importance.

More sensitive techniques for measuring the effects of LC-PUFAs on cognitive and motor development are emerging. In this study, Bouwstra and co-workers videotaped the spontaneous motor activities of healthy three-month-old infants born at term, and classified the quality of the infants’ general movements. Such movements are complex, involving head, trunk, arms, and legs. Quality is reflected in the fluency, variation, and complexity of the movements (Figures 1 and 2). These features can be scored and used to evaluate the quality of brain function in young infants. Quality of movement is classified into four groups: normal-optimal, normal-suboptimal, mildly abnormal, and definitely abnormal. Quality of general movements is a strong predictor of neurologic development, especially at the age of two to four months after term.
Bouwstra and colleagues assessed quality of movement in three-month-old term infants to evaluate the effect of LC-PUFA supplementation for two months in healthy infants. Using a randomized, controlled, double-blind study design, two groups of healthy term infants were fed formula with or without the addition of docosahexaenoic and arachidonic acids. A third group of healthy term breast-fed infants was used for reference. Arachidonic and docosahexaenoic acids were provided at the level of 0.45 percent and 0.30 percent by weight, respectively.

At three months of age the spontaneous motor behavior of the infants was videotaped for 15 minutes and the quality of the general movements were classified into the four categories described above. After controlling for confounding factors, multivariate regression analysis was conducted to determine the effect of type of feeding. Groups of infants included between 119 and 147 individuals. Assessments were performed on 397 infants.

None of the infants met the criteria for “definitely abnormal.” Significantly more infants receiving unsupplemented formula were categorized as having mildly abnormal movements than those fed formula with LC-PUFAs (31% vs. 19%, p=0.04), or breast milk (20%). Breast-fed infants had the highest proportion in the “normal-optimal” category (34% vs. 18% for the supplemented formula groups and 21% for the unsupplemented, respectively), a difference that reached statistical significance when the analysis corrected for confounding factors. The difference in the numbers of infants in the normal-optimal category for supplemented and unsupplemented formulas was not statistically significant. Figure 3 shows the percentage of infants in each treatment in the three movement behavior categories.

This study shows in a novel and clear way that the provision of LC-PUFAs to healthy term infants for two months significantly reduces the occurrence...
of mildly abnormal general movements at three months of age. These observations are believed to reflect improved neurological condition. The authors suggest that LC-PUFAs may affect the formation of synapses in the cortex which may be linked to signal transduction and hence, cortical function. The finding that fewer infants receiving LC-PUFAs had mildly abnormal general movements may be linked to the development of other developmental disorders such as attention deficit and clumsy motor behavior. Whether these differences are long-lasting remains to be determined.


**LC-PUFAs Consumed After Weaning Linked to More Mature Visual Acuity at 12 Months**

The long-chain omega-3 fatty acid (n-3 LC-PUFA) docosahexaenoic acid is concentrated in brain, especially in the cortex, retina, and photoreceptor membranes of the eye. The high level of docosahexaenoic acid in the retina is associated with the development of visual acuity in infants and age-related macular degeneration in adults.

What we consider “vision” comprises several distinct aspects such as, visual acuity—the ability to resolve fine spatial detail, sensitivity to contrast, and stereoacuity, which relates to depth perception. Visual acuity has been widely used to evaluate visual development in infants. One technique of assessing visual acuity in infants is to measure visually evoked potentials (VEPs). This is an electrophysiologic test that measures the responsiveness of the visual cortex to a changing visual stimulus. VEPs depend on the retina and the retinocortical pathway, so that if retinal dysfunction exists, a deficit in acuity will be observed.

Studies in preterm infants have shown that development of visual acuity in infants fed formula supplemented with n-3 LC-PUFAs is comparable to that of breast-fed infants who obtain n-3 LC-PUFAs from human milk. Preterm infants fed formula without n-3 LC-PUFAs have poorer visual acuity scores. Results in term infants are somewhat inconsistent and studies vary considerably in design, measurement tools, and composition of formulas. However, sufficient convincing evidence exists to support the addition of LC-PUFAs to infant formula.

At weaning, infants consume very little LC-PUFAs unless they are given LC-PUFA-supplemented foods such as docosahexaenoic acid-enriched eggs. It is not known whether provision of n-3 LC-PUFAs after weaning affects visual function. Hoffman and colleagues at the University of Texas Southwestern Medical Center, USA, explored this question by providing either LC-PUFA-supplemented or unsupplemented formula to healthy term infants who were weaned from breast-feeding at four to six months of age. The LC-PUFA-supplemented formula contained 0.36% of the total fatty acids as docosahexaenoic acid and 0.72% as arachidonic acid, both from single cell oils. Formulas were provided until the infants reached 12 months of age. Growth, red blood cell fatty acids, visual acuity and stereoacuity were measured at pre-weaning (4-6 months) and 12 months of age. Of the 68 infants randomly assigned to the study, 61 completed the trial.

At weaning there were no significant differences between the two groups of infants in demographics, weight, height, and parental variables, except that parental education level was significantly higher for the unsupplemented formula group. Visual function and fatty acid levels in red blood cells were similar in both groups at weaning. By the age of 12 months, however, there were significant differences between the two groups, independent of weaning age.

Red blood cell docosahexaenoic acid level was 2.5-fold higher in the infants fed LC-PUFA-supplemented formula compared with those receiving unsupplemented formula, whereas eicosapentaenoic acid and n-3 docosapentaenoic acid levels were significantly reduced. With the exception of arachidonic acid, n-6 LC-PUFA levels were also significantly reduced in the infants fed the supplemented formula.
A reduction in n-6 LC-PUFAs usually accompanies n-3 LC-PUFA supplementation.

At 12 months of age, infants receiving the LC-PUFA-supplemented formula maintained or increased their level of red cell arachidonic and docosahexaenoic acids, but infants fed the unsupplemented formula had a 50 percent reduction in docosahexaenoic acid. Arachidonic acid level was not significantly affected.

By one year of age, visual acuity improved in both formula groups, as reflected by lower VEP scores (Figure 1). Most importantly, visual acuity was significantly better in the LC-PUFA supplemented group. In multivariate analysis, red blood cell docosahexaenoic acid level was the only variable that contributed significantly to improved VEP acuity. In contrast, VEP acuity was positively – meaning adversely – associated with increased levels of linoleic and arachidonic acids in red blood cells. LC-PUFA supplementation had no significant effect on stereoacuity.

It is of interest to note that in the subgroup of infants weaned at four months of age, the difference in VEP acuity between those weaned to supplemented or unsupplemented formula was already statistically significant after just two months. Acuity scores of infants fed the LC-PUFA-supplemented formula did not differ from those of breast-fed infants.

This study demonstrates the benefit to VEP acuity of providing supplementary docosahexaenoic acid beyond four months of age and up to one year of age in formula-fed infants. Those fed unsupplemented commercial formula experienced a 50 percent decrease in red blood cell docosahexaenoic acid and had significantly poorer VEP acuity scores. This observation suggests that conversion of the precursor was inadequate to meet the infant’s demand for docosahexaenoic acid. The authors noted that the changes in red cell docosahexaenoic acid level and VEP acuity occurred in spite of providing the essential fatty acids, linoleic acid and alpha-linolenic acid in the ratio of ten to one, as currently recommended in the United States. These findings underscore the importance of n-3 LC-PUFA supplementation in infancy and the need to define the optimal period for providing LC-PUFAs to healthy infants. The study also suggests that recommended intake levels are open to question.


Are There Benefits of Docosahexaenoic Acid Supplementation in Pregnancy?

During pregnancy, the developing fetus relies on the mother for its supply of nutrients, including essential fatty acids. Many women consuming western
diets eat little fatty fish, the main food source of long chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs). The fetus must rely on maternal fatty acid stores and conversion of alpha-linolenic acid to the long-chain form, docosahexaenoic acid, an important constituent of the brain and retina of the eye. It is important to know whether increasing the consumption of n-3 LC-PUFAs during pregnancy benefits or otherwise affects the infant or the mother.

There is some concern whether a pregnant woman or young infant can synthesize an adequate amount of docosahexaenoic acid from alpha-linolenic acid, its 18-carbon precursor. On the other hand, does increasing maternal consumption of n-3 LC-PUFAs, particularly docosahexaenoic acid, make a difference to infant development, particularly in term infants? Colette Montgomery, Cari Malcolm and their colleagues at the University of Glasgow, Scotland, tackled that question. They examined blood lipids in maternal and cord blood along with tests of retinal function in term infants born to women randomly assigned at 15 weeks gestation to consume either fish oil or high-oleic acid placebo until delivery. In this double-blind, placebo-controlled study, fish oil supplements provided 200 mg/day of docosahexaenoic acid and about 40 mg/day of eicosapentaenoic acid. The placebo provided 400 mg/day of oleic acid.

Originally, 100 women were enrolled in the study, but at delivery 38 mothers withdrew from it for reasons of nausea, loss of contact, prematurity, or low birthweight. Because blood samples were not available for several participants at all sampling times of 15 and 28 weeks and delivery, the sample sizes differed in each group for measurements taken at different times. Maternal and umbilical cord blood was obtained at delivery from 59 and 56 pregnancies, respectively.

Outcome measures included dietary assessment of fish consumption and other lifestyle variables, fatty acid concentrations in total lipids of red blood cells, and plasma, in maternal and cord blood, as well as electroretinograms in infants within the first week of life. Parity was similar in both groups of women and had no effect on docosahexaenoic acid status during gestation or at birth. However, docosahexaenoic acid level in the cord plasma of women with no previous pregnancy was greater compared with those who had had a previous pregnancy. At 15 weeks gestation, when supplementation began, women who consumed fish once or more per week had a greater proportion of DHA in plasma and red blood cells than women not eating fish. Once supplementation began, weekly fish consumption was not associated with docosahexaenoic acid status at 28 weeks or birth.

Supplemented and unsupplemented mothers did not differ in PUFA status at the 15-week baseline measurement. At 28 weeks and term, mothers consuming fish oil had a higher docosahexaenoic acid concentration in plasma and red blood cells than unsupplemented...
mothers (Figure 1). Even though the level of docosahexaenoic acid declined between 28 weeks and term, docosahexaenoic acid in red blood cells at term was significantly greater in supplemented than unsupplemented mothers.

In cord blood, however, there were no significant differences between the groups in the proportion or concentration of docosahexaenoic acid. As has been observed in previous studies, the concentration of docosahexaenoic acid in cord blood at birth exceeded that in maternal blood. The accretion of LC-PUFAs in cord blood at term was highly specific for docosahexaenoic and arachidonic acids and was not observed for eicosapentaenoic acid or other LC-PUFAs.

The authors noted that gestational age, gender ratio, birth weight and length were similar in the fish oil and placebo groups. But infants in the highest quartile of cord plasma docosahexaenoic acid had significantly longer gestation times—8 additional days—than those in the lowest quartile (283.5 days vs. 275.1 days, p<0.05). Results were not significant when docosahexaenoic acid quartiles were based on red blood cell levels.

Infant retinal development was assessed by two different electroretinographic measurements. Rod photoreceptor function was measured using blue filter electroretinograms in response to increasingly bright flashes. As the light intensity increases, cone function intrudes on rod responses and corrections were made for this phenomenon. A second set of electroretinograms was recorded under conditions of dark adaptation in response to a bright white flash. These responses reflected a mixed rod and cone response. Recordings were also made in 11 adults to confirm the equivalence of neonatal and adult measurements. Of 60 infants eligible for these studies, 41 and 44 satisfactory electroretinograms were obtained for rod function and rod and cone function, respectively. Each group had 19 infants from placebo mothers.

Results from the electroretinograms indicated that photoreceptor rod function—that is, greater retinal sensitivity—was significantly associated with increased docosahexaenoic acid level in cord red blood cells. The association also held for arachidonic acid and total n-3 LC-PUFAs. Electroretinograms measuring mixed rod and cone activity did not differ with docosahexaenoic acid status at birth. There were no differences between infants of supplemented and placebo mothers. Thus, maternal supplementation with docosahexaenoic acid from the 15th week of pregnancy until term was not associated with enhanced retinal development in their infants. However, infants with higher retinal sensitivity, reflecting more mature electroretinograms, had significantly more docosahexaenoic acid in cord red blood cells.

This is the first randomized controlled study of healthy term infants to evaluate retinal function using electroretinograms. Its findings are similar to those in preterm infants whose visual function was assessed using different methods. The results are consistent with other reports that the maturity of various neurodevelopmental responses is greater in infants with higher docosahexaenoic acid status. These studies provide additional evidence of the importance of docosahexaenoic acid in fetal development.


**Immune and Inflammatory Function**

**Low Dose n-3 LC-PUFAs Linked to Reduced Cytokines and Enhanced Immunity**

The body defends itself against external pathogens and internal metabolic mischief using a variety of cells, chemical agents, and regulatory pathways that are part of immune function. Inflammatory
responses, which are part of the immune system, are involved in many clinical disorders not usually thought of as “immune” conditions—for example, cardiovascular disease. Studying the inflammatory component of diseases has provided additional insight into complex health conditions.

Inflammatory and immune responses can be modulated by different types of fatty acids. For example, omega-3 (n-3) polyunsaturated fatty acids (PUFAs) tend to dampen these responses, while n-6 PUFAs may exacerbate them. Immune system cells, such as peripheral blood mononuclear cells (white blood cells) release substances that mediate inflammatory responses. These substances or cytokines can serve as markers of inflammatory responses. Levels of some important cytokines such as tumor necrosis factor-alpha and interleukin-6 are elevated in response to immune and inflammatory conditions. Some reports indicate that the consumption of n-3 long-chain (LC)-PUFAs reduces the production of these cytokines.

Consumption of n-3 LC-PUFAs via fish oil is associated with the incorporation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into the phospholipids of plasma red blood cells and peripheral blood mononuclear cells. It is also thought to increase the production of lipid peroxides, metabolites with potentially pro-inflammatory and other damaging effects on cells. Another effect is to alter the production of eicosanoids, substances also involved in inflammatory responses. Inconsistent findings on the effects of n-3 LC-PUFAs on peripheral blood mononuclear cell composition and function and the production of lipid peroxides have cast doubt on the value of n-3 LC-PUFA consumption in immune and inflammatory conditions.

To clarify the effects of n-3 LC-PUFAs on peripheral blood mononuclear cell function, Trebble and colleagues at the University of Southampton, United Kingdom, designed a dose-response study in 16 healthy men of an average age of 30 years, supplying three levels of n-3 LC-PUFAs as fish oil capsules in successive increasing amounts for four-week periods each. The amount of EPA and DHA (ratio 2:1) provided in each four-week period were 0.3, 1.0 and 2.0 grams/day. Subjects were randomly assigned to consume fish oil with or without a mixed antioxidant preparation. Blood samples were taken at baseline and after each four-week period. Phospholipid fatty acid analysis was performed on plasma and red blood cells. Cytokines, eicosanoids, lipid peroxides, and lymphocyte proliferation were measured in preparations made from peripheral blood mononuclear cells.

As the amount of fish oil consumed increased the level of EPA and DHA in the phospholipids of
plasma and red blood cells increased in a linear fashion (Figure 1). Uptake of EPA approximately doubled at the highest level of n-3 LC-PUFA consumption. Uptake of DHA followed the same trend but was less pronounced. The addition of antioxidants consistently increased the uptake of these fatty acids, but the increase was statistically significant only for EPA in one red cell phospholipid class. Production of lipid peroxides, as reflected in the measurement of plasma malonaldehyde, was not significantly affected by the consumption of antioxidants or of n-3 LC-PUFAs up to 2.0 grams/day.

Consumption of n-3 LC-PUFAs significantly reduced the production of tumor necrosis factor-alpha and interleukin-6 in both the antioxidant supplemented and unsupplemented groups (Figures 2 and 3). The greatest reduction in cytokine production occurred at the level of 1.0 gram/day of n-3 LC-PUFAs, but significant reductions occurred at 0.3 grams/day. At 2.0 grams/day of n-3 LC-PUFAs, cytokine production tended to be higher than that observed at 1.0 gram/day.

In a separate paper describing results from this study, Trebble and colleagues showed that increasing intakes of n-3 LC-PUFAs significantly reduced the production of prostaglandin $E_2$, a pro-inflammatory substance. At the same time, production of interferon-gamma, a cytokine that combats infections, was increased along with the proliferation of peripheral blood mononuclear cells. Reduction in prostaglandin $E_2$ is consistent with human studies, but increased proliferation of peripheral blood mononuclear cells and enhanced interferon-gamma production conflict with previous reports. These findings may relate to the low dose of n-3 PUFAs used in the present study and the possibility that higher intakes may have inhibited cell proliferation and the production of certain cytokines.

These studies from Calder’s laboratory have clarified questions about the effects of n-3 LC-PUFA consumption on phospholipid composition, cytokine production, lipid peroxide formation, and the effect of simultaneously increasing antioxidant intake. They have shown that:

- consumption of modest amounts of fish oil n-3 LC-PUFAs increased the incorporation of EPA and DHA in plasma and red blood cell phospholipids;
- doses of n-3 LC-PUFAs up to one gram/day markedly and significantly reduced the production of tumor necrosis factor-alpha, interleukin-6, and prostaglandin $E_2$ by peripheral blood mononuclear cells in healthy men;
- production of tumor necrosis factor-alpha and interleukin-6 was not reduced further at intakes above 1 gram/day and tends to increase;
- consumption of low levels of n-3 LC-PUFAs increased proliferation of peripheral blood mononuclear cells and production of interferon-gamma which would enhance immune activity;
- simultaneous supplementation with antioxidants significantly increased the uptake of n-3 LC-PUFAs.
into plasma and red cell phospholipids, but had no significant effect on cytokine production;

- consumption of n-3 LC-PUFAs up to 2 grams/day with or without antioxidants did not increase lipid peroxide formation as reflected by malonaldehyde level; and

- production of tumor necrosis factor-alpha and interleukin-6 was negatively correlated with the concentration of eicosapentaenoic acid in plasma and red blood cell phospholipid pools over a range of n-3 LC-PUFA consumption up to 2 grams/day.

These studies may also explain some of the inconsistencies among studies in which larger doses of n-3 LC-PUFAs were used, and are a reminder that the beneficial effects of n-3 LC-PUFAs may be realized with modest consumption. The latter suggests that dietary recommendations to consume fatty fish twice a week are likely to be effective under diverse health conditions.


Dietary LC-PUFAs Associated with Lower Levels of Inflammatory Markers in Healthy Subjects

Findings from studies examining the effect of dietary polyunsaturated fatty acids (PUFAs) on markers of inflammation and immunity have been inconsistent. This is true in spite of evidence of beneficial effects of long-chain omega-3 PUFAs (n-3 LC-PUFAs) in patients with chronic inflammatory conditions such as rheumatoid arthritis. In this report, researchers from the Harvard Schools of Public Health and Medicine, Boston, Mass., USA, examined the status of several markers of immunity in relation to the consumption of n-3 LC-PUFAs in samples selected from two large groups of healthy subjects participating in long-term health surveys.

Study samples were randomly selected from 18,225 male participants in the Health Professionals Follow-up Study and more than 29,000 women in the Nurses’ Health Study II on the basis of self-reported alcohol consumption and absence of major diseases. Additional exclusions occurred in participants with incomplete descriptive information, rheumatoid arthritis, or ulcerative colitis. The final sample included 859 subjects, 405 men and 454 women. Tumor necrosis factor receptors, the cytokine interleukin-6, and C-reactive protein were measured in plasma. Fatty acid intake was computed from food frequency questionnaire data.

Intake of eicosapentaenoic acid plus docosahexaenoic acid was divided into quintiles ranging in women...
from 0.02 to 0.47 and in men from 0.06 to 1.12 grams/day. In both men and women, levels of tumor necrosis factor receptors 1 and 2 were lower with higher consumption of n-3 LC-PUFAs (p=0.03 and <0.001, respectively). Levels of interleukin-6 and C-reactive protein were not related to the consumption of LC-PUFAs. Levels of inflammatory markers were not related to the consumption of alpha-linolenic acid, the 18-carbon precursor of n-3 LC-PUFAs or linoleic acid, the major dietary n-6 PUFA and precursor of arachidonic acid.

However, findings also related to the level of linoleic acid consumption, because the lowest levels of tumor necrosis factor receptors were observed in those with the highest intake of both n-3 LC-PUFAs and linoleic acid. The highest levels of tumor necrosis factor receptors occurred in those with the lowest consumption of n-3 LC-PUFAs and highest intake of linoleic acid. Thus, the relative amounts of these fatty acids in the diet appear to influence whether certain markers of immune responses will be increased or reduced. This study presents an interesting snapshot of the relationship between various markers of inflammation and dietary intake of PUFAs in healthy subjects and illustrates the complex relationship between different intakes of n-3 and n-6 PUFAs.


### Mental Health

#### Fish Consumption and Docosahexaenoic Acid Reduce Risk of Alzheimer's Disease

Numerous animal studies have shown that long-chain polyunsaturated fatty acids (LC-PUFAs), particularly the omega-3 (n-3) fatty acid docosahexaenoic acid, are concentrated in specific regions of the brain. In humans, increased brain content of n-3 fatty acids has been associated with neurodevelopment and improved visual and behavioral function. Recent studies have strongly suggested that n-3 LC-PUFAs may inhibit the onset of certain behavioral conditions such as Alzheimer’s disease and depression. Alzheimer’s disease, a disease of aging, is the leading cause of dementia, afflicting more than four million people in the United States alone. As more people live longer, the number of people affected worldwide is expected to surge.

Two prospective studies have reported that Alzheimer’s disease is less prevalent among those who consume fish. Other reports have linked low levels of n-3 LC-PUFAs in plasma phospholipids with the incidence of Alzheimer’s disease. In the epidemiological study described here, Morris and colleagues in Chicago Ill., USA, reported that the incidence of Alzheimer’s disease was 60% lower in people who consumed fish once a week compared with those who rarely or never ate fish. These findings are part of a large study of the risk factors for Alzheimer’s disease in a biracial population of men and women 65 years and older.

A sample of 4320 subjects who were free of Alzheimer’s and other diseases, were given a baseline interview and cognitive function tests and followed for three years. From these, a stratified sample was selected for clinical evaluation and dietary assessment by food frequency questionnaire. Complete data were obtained for 815 subjects aged 65 to 94 years over an average follow-up period of 3.9 years. Fresh fish was consumed by 39.2% of participants at

**Table 1. Relative risk of Alzheimer’s disease by fish consumption in 815 older subjects over 3.9 years**

<table>
<thead>
<tr>
<th>Frequency of fish intake</th>
<th>Never</th>
<th>1-3/mo</th>
<th>1/wk</th>
<th>&gt;2/wk</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>121</td>
<td>250</td>
<td>296</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Alzheimer cases</td>
<td>23</td>
<td>39</td>
<td>43</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Multivariate Relative Risk (95% confidence interval)</td>
<td>1.0</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**PUFA Newsletter September 2003**
least weekly, while 13.9% consumed tuna fish sandwiches, 8.5% ate fish sticks or cakes and 2.4% consumed shellfish. At the end of follow-up, 131 persons were diagnosed with Alzheimer’s disease. with the observation of abundant docosahexaenoic acid in cerebral gray matter. The presence of docosahexaenoic acid in cell membranes affects the transmission of nerve signals which relates to brain function. The lack of an effect of eicosapentaenoic acid may be related to the low range of reported intake.

This study provides evidence that fish consumption may delay or help prevent the onset of Alzheimer’s disease in aging. Added to its known cardioprotective effects, regular fish consumption may improve quality of life and health, particularly in middle and late age.


The chance of developing Alzheimer’s disease was inversely related to the frequency of eating fish (Table 1). Those who ate fish once a week or more had a 60% reduction in the likelihood of developing Alzheimer’s disease compared with those who never ate fish.

When n-3 LC-PUFA intake was calculated from the dietary data, multivariate analysis showed a significant inverse association with total n-3 LC-PUFA and docosahexaenoic acid consumption (60% to 70% risk reduction), but not with eicosapentaenoic or alpha-linolenic acid intake (Figure 1). Further analysis, however, showed a significant protective effect of alpha-linolenic acid consumption in subjects with the apolipoprotein E-4 genotype, a genetic characteristic known to increase the risk of Alzheimer’s disease.

Finding a beneficial association between docosahexaenoic acid consumption and the risk of developing Alzheimer’s disease is consistent

LC-PUFA Levels in Plasma Phospholipids Linked to Depression in Elderly Dutch

The Rotterdam Study is an ongoing study of risk factors and health involving nearly 8000 people aged 55 and older, living in Rotterdam, The Netherlands. Participants are interviewed and clinically evaluated periodically. Every three years dietary assessments and blood samples are obtained. In a previous report from this study, investigators found no association between dietary consumption of total fat, fatty acids, or cholesterol and any type of dementia. On the other hand, other studies—mostly involving small numbers of psychiatric patients—have reported lower levels of long-chain omega-3 fatty acids (n-3 LC-PUFAs) in blood samples of patients with various psychiatric disorders compared with subjects without psychiatric illness. Now, data are available from the Rotterdam Study that include fatty acid measurements in plasma phospholipids from patients who had depression or subclinical depressive symptoms.

Study subjects included 106 with depressive disorders, 264 with depressive symptoms and 461 randomly selected reference subjects aged 60 years or more.
Those with depressive symptoms had positive ratings on the Center for Epidemiologic Studies depression scale, but did not meet the criteria for depression from the professional diagnostic manual for mental disorders. Plasma phospholipid values were available for 115 of the 264 subjects with depressive symptoms. Results showed that those with depressive disorders had significantly higher levels of arachidonic acid, an n-6 fatty LC-PUFA, and significantly lower levels of docosahexaenoic acid, an n-3 LC-PUFA than reference subjects (p<0.05) (Figure 1). Differences in the ratio of total n-6 to n-3 fatty acids also reached statistical significance. These findings were based on analysis that controlled for age, sex, smoking status, blood pressure, and daily activities score. Adjustments for concentration of C-reactive protein, a marker of inflammation, and intima-media thickness, a blood vessel marker for atherosclerosis, did not change the results. Thus, depression in these subjects did not appear to be related to atherosclerosis or the immune marker, C-reactive protein.

Subjects with depressive disorders included a significant number of women with a history of stroke and with lower cognitive scores. There were no significant differences in plasma phospholipid fatty acids between reference subjects and those with subclinical depressive symptoms.

While other potentially confounding variables cannot be ruled out, this study suggests that depressive disorders may be linked to the consequences of altered fatty acid composition of tissue membranes. In particular, low levels of n-3 LC-PUFAs, especially of docosahexaenoic acid, which concentrates in specific regions of the brain, may directly affect brain function. It remains to be clearly established, however, whether increases in the n-3 LC-PUFA content of membranes can affect psychiatric or behavioral function.


Supplementary n-3 LC-PUFAs Improve Depression in Adults

Several studies have reported clinical improvements in patients with depression who consume long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) (see Low Dose EPA Study in March issue). In some reports, only eicosapentaenoic acid has been effective, while in others, benefits were observed following the consumption of fish oils or purified eicosapentaenoic acid and docosahexaenoic acid, the two major n-3 LC-PUFAs in fish oil. Studies have differed in design, length of treatment, and dose and therefore, are difficult to compare.

Some reports have indicated that subjects with various psychiatric disorders have lower levels of n-3 LC-PUFAs in their red blood cells or serum phospholipids compared with control subjects. Because LC-PUFAs are constituents of neural membranes and are involved in the transmission of nerve signals, reduced membrane levels of LC-PUFAs may be
involved in psychiatric disorders. Su and colleagues at the China Medical College Hospital in Taipei, Taiwan, undertook a controlled study of the effectiveness of n-3 LC-PUFAs in 28 patients with major clinical depression. Researchers also measured red blood cell fatty acids in several subjects before and after treatment.

After excluding subjects who responded to placebo after a one-week run-in period, 28 patients with a Hamilton Rating Score of 18 or more were randomized to receive either 10 capsules/day of n-3 LC-PUFAs or olive oil ethyl esters in addition to their regular medications. Treatment provided a total of 6.6 grams/day of n-3 LC-PUFAs. Clinical evaluation was determined using the Hamilton Rating Scale for Depression and all subjects except one in each of the treatment and placebo groups remained on their pre-study medications. A total of 22 subjects aged 18 to 60 years completed the eight-week study, 12 in the n-3 LC-PUFA group and 10 receiving the olive oil placebo. Red blood cell fatty acids were measured in seven treatment and six placebo subjects.

At the end of eight weeks, depressive patients treated with n-3 LC-PUFAs had significantly more reduced scores on the Hamilton Rating Scale for Depression compared with patients receiving the placebo capsules (Figure 1, score change of 13.6 vs 5.4 points p=0.001). Red blood cell docosahexaenoic acid level increased significantly in the treated subjects from 2.4 ± 2.6 to 5.8 ± 3.4 percent of fatty acids (p=0.03) and did not change significantly in the placebo group. By contrast, eicosapentaenoic acid levels in red blood cells did not change significantly in either group. Thus, these findings contrast with reports of beneficial effects from eicosapentaenoic acid consumption in depressive and schizophrenic patients. Increased levels of docosahexaenoic acid in red cell membranes might lead to increased content in neuronal membranes, though this can not be measured directly.

It is noteworthy that significant improvements in the Hamilton Rating Scale for Depression were observed after just four weeks of treatment and that improvement continued for the subsequent four weeks of treatment. The amount of n-3 LC-PUFAs used in this study was relatively large and may be responsible in part for the rapid response in these subjects. Larger, carefully controlled clinical trials using a range of doses are required to establish the effectiveness of n-3 LC-PUFAs in subjects with depression.


**Omega-3 LC-PUFAs and Schizophrenia: Effective Adjunct Treatment?**

Clinical improvements in patients with schizophrenia who consume omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) have been widely reported. There is also evidence that serum or red blood cell n-3 LC-PUFAs are significantly reduced in schizophrenic subjects. Several studies have reported that consumption of eicosapentaenoic acid, but not docosahexaenoic acid, is associated with significant clinical improvements in schizophrenic patients receiving medication.
However, data from well controlled clinical trials remain scarce.

Arvindakshan and colleagues studied the effectiveness of providing a low dose of n-3 LC-PUFAs, 600 mg/day, along with the antioxidant vitamins C (500 mg/day) and E (400 International Units) to 28 male and female patients with schizophrenia who were also taking medication. Patients received outpatient treatment at private hospitals in Pune, India. A control group of 45 healthy volunteers with no history of psychosis or mood disorders who did not use any medication was studied for comparison. Subjects in the patient and control groups were aged on average 31 and 30 years, respectively. Patients were treated for four months and evaluated clinically using seven psychopathology assessment ratings before and after treatment and four months after the end of treatment.

At the pretreatment assessment, patients had significantly lower levels of eicosapentaenoic and docosahexaenoic acids in their red blood cell membranes compared with normal controls. After four months of consuming n-3 LC-PUFAs, patients had significantly improved psychiatric rating scores and significant improvements in their quality of life ratings. Red blood cell membrane n-3 LC-PUFAs increased significantly at the end of treatment when compared with normal controls and with pretreatment values. After the four-month washout period, red cell n-3 LC-PUFAs returned to pretreatment levels, but several measures of psychopathology remained improved at the end of the washout period. However, the authors noted that the medications of patients may have changed during this time and would confound the observation.

What is interesting in this study is that a low dose of n-3 LC-PUFAs administered for a relatively long time—four months—led to measurable improvement in the psychopathology of schizophrenic patients consuming other medications. Previous studies have used gram quantities of n-3 LC-PUFAs for up to three months. This study gives no indication whether treatment was related to one or both of the n-3 LC-PUFAs consumed. The study also provided antioxidant vitamins, which may be related to the effectiveness of n-3 LC-PUFA supplementation. Because the study lacked a placebo-treated group of patients, the results should be viewed with caution. Carefully controlled trials are needed to answer the important questions that remain about the usefulness of n-3 LC-PUFAs in treating schizophrenia.

<table>
<thead>
<tr>
<th>Country</th>
<th>Authority</th>
<th>Date</th>
<th>Target Group</th>
<th>Recommendation</th>
<th>Under Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>International</td>
<td>World Health Organization&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2003</td>
<td>General adult population</td>
<td><em>Percent daily energy</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>PUFAs: 6-10%</td>
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<td>n-6 PUFAs: 5-8%</td>
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<td>n-3 PUFAs: 1-2%</td>
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</tr>
<tr>
<td>International</td>
<td>WHO/FAO Joint Expert Consultation on Fats and Oils&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1994</td>
<td>Healthy adults</td>
<td>Ratio of LA:ALA in the diet should be between 5:1 and 10:1. Individuals with a ratio of LA:ALA in excess of 10:1 should be encouraged to consume more n-3 rich foods such as green leafy vegetables, legumes, fish, and other seafood. Particular attention must be paid to promoting adequate maternal intakes of essential fatty acids throughout pregnancy and lactation to meet the requirements of fetal and infant development.</td>
<td>No</td>
</tr>
<tr>
<td>International</td>
<td>Workshop on the Essentiality of and Recommended Dietary Intakes from Omega-6 and Omega-3 Fatty Acids&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2000</td>
<td>General adult population</td>
<td><em>/day/2000 kcal</em></td>
<td>No</td>
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<td>LA: 4.44</td>
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<td>ALA: 2.22</td>
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<td></td>
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<td>DHA+EPA: 0.65</td>
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<td>DHA at least 0.22</td>
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<td></td>
<td></td>
<td></td>
<td>EPA at least 0.22</td>
<td>--------------</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnant/nursing women</td>
<td>DHA: 300 mg/day</td>
<td>--------------</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>National Heart Foundation of Australia&lt;sup&gt;4, 5&lt;/sup&gt;</td>
<td>1999, 2001</td>
<td>General adult population and heart patients</td>
<td>Have fish (fresh or canned) at least twice a week; consume at least 2 g/day ALA</td>
<td>Yes</td>
</tr>
<tr>
<td>Canada</td>
<td>Health and Welfare, Canada&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1990</td>
<td>General adult population</td>
<td>1.1-1.6 g/day total n-3 PUFAs (ALA, EPA, DHA)</td>
<td>Yes</td>
</tr>
<tr>
<td>Japan</td>
<td>Ministry of Health, Labor and Welfare&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1999</td>
<td>General adult population</td>
<td>Ratio of n-6:n-3 PUFAs: 4:1</td>
<td>No</td>
</tr>
<tr>
<td>Scandinavia (Denmark, Finland, Norway, Sweden)</td>
<td>Nordic Council of Ministers&lt;sup&gt;8&lt;/sup&gt;</td>
<td>1996</td>
<td>Adults and children over 3 yrs</td>
<td><em>Percent daily energy</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Essential PUFAs: at least 3%</td>
<td>--------------</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>n-3 PUFAs: a minimum of 0.5%</td>
<td>--------------</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>British Nutrition Foundation&lt;sup&gt;9&lt;/sup&gt;</td>
<td>1999</td>
<td>Adults, 19-50 yrs</td>
<td><em>Percent daily energy</em></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LA: minimum 1.0%</td>
<td>--------------</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>ALA: 0.2%</td>
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<tr>
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<td></td>
<td></td>
<td>EPA+DHA: 1.25 g/day</td>
<td>--------------</td>
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</tbody>
</table>
## Collected Recommendations for LC-PUFA Intake

<table>
<thead>
<tr>
<th>Country</th>
<th>Authority</th>
<th>Date</th>
<th>Target Group</th>
<th>Recommendation</th>
<th>Under Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>Committee on the Medical Aspects of Food and Nutrition Policy (COMA)¹⁰</td>
<td>1994</td>
<td>Adults</td>
<td>Eat at least two portions of fish, of which one should be oily, weekly n-3 PUFAs: &gt; 0.2 g/day</td>
<td>No</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Scientific Advisory Committee on Nutrition¹¹</td>
<td>2002</td>
<td>Adults</td>
<td>Strongly supported 1994 COMA recommendation (above).</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Secondary prevention</td>
<td>Reported that recommendation of &gt;0.2 g/day would likely increase if reviewed.</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Health Council of the Netherlands¹²</td>
<td>2001</td>
<td>0-5 months</td>
<td>Total n-3 PUFAs: 80 mg/kg/day DHA: 20 mg/kg/day</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adults</td>
<td>Total n-3 PUFAs: 1% of energy DHA: 150-200 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnant/lactating women</td>
<td>Total n-3 PUFAs: 1% of energy DHA: 200 mg/day</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>Institute of Medicine¹³</td>
<td>2002</td>
<td>Adult men 19 yrs and older</td>
<td>ALA :1.6 g/day of which 10% can be EPA+DHA</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adult women 19 yrs and older</td>
<td>ALA: 1.1 g/day of which 10% can be EPA+DHA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnancy &amp; lactation</td>
<td>ALA: 1.4 and 1.3 g/day, respectively</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>National Heart, Lung, and Blood Institute, National Cholesterol Education Program¹⁴</td>
<td>2002</td>
<td>Persons with CHD or multiple risk factors for CHD</td>
<td>Supported AHA recommendation to include fish as part of a CHD risk-reduction diet. Higher dietary intakes of n-3 PUFAs are an option for reducing CHD risk</td>
<td>No</td>
</tr>
<tr>
<td>American Heart Association¹⁵</td>
<td></td>
<td>2002</td>
<td>All adults without CHD</td>
<td>Eat fish (particularly fatty fish) at least two times a week; include oils and foods rich in ALA.</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients with CHD</td>
<td>Consume approximately 1 g/day of EPA+DHA preferably from oily fish.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients with high triglycerides</td>
<td>2-4 g/day EPA+DHA as capsules under a physician’s care.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PUFA, polyunsaturated fatty acids; LA, linolenic acid; ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; CHD, coronary heart disease.
References


