ABSTRACT

Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today’s Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects. In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2-3/1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences. These studies indicate that the optimal ratio may vary
with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries, that are being exported to the rest of the world.

Key Words: Omega-6/omega-3 fatty acid balance; genetic patterns; chronic disease; dietary recommendations.

INTRODUCTION

A number of anthropological, nutritional, and genetic studies indicate that overall human diet, including energy intake and energy expenditure, has changed over the past 10,000 years with major changes occurring during the past 150 years in the type and amount of fat and in vitamins C and E intake (Eaton and Konner, 1985; Eaton et al., 1988, 1998; Leaf and Weber, 1987; Simopoulos, 1991, 1995, 1995a, 1998a, 1999a, 1999b, 1999c, 1999d) (Fig. 1).

![Figure 1](image_url)  
*Figure 1.* Hypothetical scheme of fat, fatty acid (ω6, ω3, trans and total) intake (as percent of calories from fat), and intake of vitamins E and C (mg/day). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations, and from longitudinal observations and their putative changes during the preceding 100 years. (From Simopoulos (1999a).)
Whereas major changes have taken place in our diet over the past 10,000 years since the beginning of the Agricultural Revolution, our genes have not changed significantly. The spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. Therefore, over the past 10,000 years there has been time for very little change in our genes, perhaps 0.005%. In fact, our genes today are very similar to the genes of our ancestors during the Paleolithic period 40,000 years ago, at which time our genetic profile was established (Eaton and Konner, 1985). Genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected.

Eaton and Konner (1985) estimated higher intakes for protein, calcium, potassium, and ascorbic acid and lower sodium intakes for the diet of the late Paleolithic period than the current U.S. and Western diets. Most of our food is calorically concentrated in comparison with wild game and the uncultivated fruits and vegetables of the Paleolithic diet. Paleolithic man consumed fewer calories and drank water, whereas today most drinks to quench thirst contain calories. Today, industrialized societies are characterized by (1) an increase in energy intake and decrease in energy expenditure; (2) an increase in saturated fat, omega-6 fatty acids, and trans fatty acids, and a decrease in omega-3 fatty acid intake; (3) a decrease in complex carbohydrates and fiber; (4) an increase in cereal grains and a decrease in fruits and vegetables; and (5) a decrease in protein, antioxidants, and calcium intake (Eaton and Konner, 1985; Eaton et al., 1988, 1998; Simopoulos, 1998a, 1999b). The increase in trans fatty acids is detrimental to health (Simopoulos, 1995d). In addition, trans fatty acids interfere with the desaturation and elongation of both omega-6 and omega-3 fatty acids, thus further decreasing the amount of arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid availability for human metabolism (Simopoulos, 1995b). During evolution, the omega-6/omega-3 essential fatty acid ratio was 1–2/1, whereas today in Western societies it is between 10–20/1. Table 1 shows the omega-6/omega-3 ratio in various countries and compares them with the Paleolithic period (Eaton et al., 1998; Pella et al., 2003; Sanders, 2000; Simopoulos, 1998a; Sugano and Hirahara, 2000).

Table 1. Omega-6/omega-3 ratios in various populations.

<table>
<thead>
<tr>
<th>Population</th>
<th>ω6/ω3</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleolithic</td>
<td>0.79</td>
<td>Eaton et al. (1998)</td>
</tr>
<tr>
<td>Greece prior to 1960</td>
<td>1.00–2.00</td>
<td>Simopoulos (1998)</td>
</tr>
<tr>
<td>Current Japan</td>
<td>4.00</td>
<td>Sugano et al. (2000)</td>
</tr>
<tr>
<td>Current India, rural</td>
<td>5–6.1</td>
<td>Pella et al. (2003)</td>
</tr>
<tr>
<td>Current United Kingdom and Northern Europe</td>
<td>15.00</td>
<td>Sanders (2000)</td>
</tr>
<tr>
<td>Current United States</td>
<td>16.74</td>
<td>Eaton et al. (1998)</td>
</tr>
<tr>
<td>Current India, urban</td>
<td>38–50</td>
<td>Pella et al. (2003)</td>
</tr>
</tbody>
</table>
CLINICAL INTERVENTION STUDIES AND
THE OMEGA-6/OMEGA-3 BALANCE

Interest in the Mediterranean diet derives directly from the results of the Seven Countries Study, which began in 1958 (Keys et al., 1970). After 5 to 15 years of follow-up, the study demonstrated that the mortality rate from coronary heart disease in southern Europe was two- to three-fold lower than in northern Europe or the United States. The mortality from coronary heart disease and all causes in the cohort from Crete was much lower than that among the nine other cohorts from southern Europe. This findings suggested that the population of Crete could be considered to have the greatest life expectancy in the Western world, even though average serum cholesterol concentrations in the population of Crete were similar to those in the other Mediterranean cohorts. What are the components in the diet of Crete that are responsible for longer life expectancy? They certainly could not be those that influence serum cholesterol concentrations. Extensive studies on the traditional diet of Greece (the diet prior to 1960) indicate that the dietary pattern of Greeks consisted of a high intake of fruits, vegetables (particularly wild plants), legumes, nuts, cereals mostly in the form of sourdough bread rather than pasta, more olive oil and olives, less milk but more cheese, more fish, less meat, and moderate amounts of wine, more so than other Mediterranean countries (Simopoulos and Sidossis, 2000). Most important, because of consumption of wild plants, and eggs and meat from grazing poultry and animals, the omega-3 fatty acids were found throughout the food chain, giving an omega-6:omega-3 ratio of 1–2:1, similar to the ratio of the Paleolithic diet. Analyses of the dietary pattern of Crete shows a number of protective substances, such as selenium, glutathione, a balanced ratio of omega-6:omega-3 essential fatty acids, high amounts of fiber, antioxidants (especially resveratrol from wine and polyphenols from olive oil), and vitamins E and C, some of which have been shown to be beneficial in the secondary prevention of cardiovascular disease and decreasing the risk of cancer, including cancer of the breast. The traditional diet of Greece, or the diet of Crete and many other traditional diets, resembles nutritionally the composition of the Paleolithic diet on which the human’s genetic profile was programmed. Such diets are first and foremost balanced in the essential fatty acids, are high in monounsaturated fats, and are low in saturated fats and trans fatty acids, but high in fruits, vegetables, legumes, and nuts. The Lyon Heart Study based on a modified diet of Crete has clearly shown that the diet of Crete could decrease the death rate from coronary artery disease by 70% and is a diet that can be easily adapted to the French population and possibly other populations as well.

The Lyon Heart Study was a dietary intervention study in which a modified diet of Crete (the experimental diet) was compared with the prudent diet or Step I American Heart Association Diet (the control diet) (de Lorgeril and Salen, 2000; de Lorgeril et al., 1994; Renaud et al., 1995). The experimental diet provided a ratio of linoleic acid (LA) to alpha-linolenic acid (ALA) of 4/1. This ratio was achieved by substituting olive oil and canola (oil) margarine for corn oil. Because olive oil is low and corn oil is high in LA, 8% and 61% respectively, the ALA incorporation into cell membranes was increased. Cleland et al. (1992) showed that olive oil increases the incorporation of omega-3 fatty acids, whereas the LA from corn oil competes.
The ratio of 4/1 of LA/ALA led to a 70% decrease in total mortality at the end of 2 years (de Lorgeril et al., 1994).

The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI) Prevenzione Trial participants were on a traditional Italian diet plus 850 to 882 mg of omega-3 fatty acids at a ratio of 2/1 eicosapentanoic acid (EPA) to docosahexaenoic acid (DHA) (GISSI, 1999). The supplemented group had a decrease in sudden cardiac death by 45%. Although there are no dietary data on total intake for omega-6 and omega-3 fatty acids, the difference in sudden death is most likely due to the increase of EPA and DHA and a decrease of AA in cell membrane phospholipids. Prostaglandins derived from AA are proarrhythmic, whereas the corresponding prostaglandins from EPA are not (Li et al., 1997).

Coronary artery disease (CAD) in south Asian people has increased in the past 15 years. Furthermore, this increase is not explained by conventional risk factors. In view of the evidence obtained from the Lyon Heart Study, Singh et al. (2002) carried out a study in which the experimental group received a Mediterranean diet of Crete similar to the diet used in the Lyon Heart Study. They carried out a randomized, single-blind trial in 1,000 patients with angina pectoris, myocardial infarction, or surrogate risk factors for CAD. Of the patients, 499 were allocated to a diet rich in whole grains, fruits, vegetables, walnuts, and almonds—the modified diet of Crete or Indo-Mediterranean diet. The controls, the other 501, consumed a local diet similar to the Step I National Cholesterol Education Program (NCEP) prudent diet (Singh et al., 2002).

As can be seen in Table 2, the intervention group consumed more fruits, vegetables, legumes, walnuts, and almonds than the controls [573 g (SD 127) vs. 231 g (SD 19) per day p < 0.001]. The intervention group had an increased intake of whole grains and mustard or soybean oil. The mean intake of alpha-linolenic acid was two-fold greater in the intervention group [1.79 g (SD 0.4) vs. 0.78 g (SD 0.2) per day, p < 0.001]. In this study, the ratio of omega-6/omega-3 was 9.1 in the Indo Mediterranean group vs. 21 in the control group. A ratio of 9.1 is similar to the ratio of the control group in the Lyon Heart Study. If Singh et al. had decreased the ratio further, they would have had a significant difference in total mortality between the Indo-Mediterranean and control groups. Total cardiac endpoints were significantly reduced in the intervention group.

<table>
<thead>
<tr>
<th>Table 2. Indo-mediterranean diet heart study. a</th>
</tr>
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<tbody>
<tr>
<td>At 2 yr</td>
</tr>
<tr>
<td>o-6/o-3 at baseline</td>
</tr>
<tr>
<td>o-6/o-3 at 2 yr</td>
</tr>
<tr>
<td>ALA at 2 yr</td>
</tr>
<tr>
<td>Fruits, vegetables, legumes, walnuts, almonds (g/day)</td>
</tr>
<tr>
<td>Total cardiac endpoints</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
</tr>
</tbody>
</table>

aData from Singh et al., 2002
fewer in the intervention group than the controls (39 vs. 76 events, \( p < 0.001 \)). Sudden cardiac deaths were also reduced (6 vs. 16, \( p = 0.015 \)), as were nonfatal myocardial infarctions (21 vs. 43, \( p < 0.001 \)). In the treatment group, patients with preexisting CAD had significantly greater benefits compared with such patients in the control group. The authors concluded that an Indo-Mediterranean diet that is rich in alpha-linolenic acid might be more effective in primary and secondary prevention of CAD than the conventional Step I NCEP prudent diet (Singh et al., 2002).

Further support for the need to balance the omega-6/omega-3 EFA comes from the studies of Ge et al. (2002) and Kang et al. (2001). The study by Ge et al. clearly shows the ability of both normal rat cardiomyocytes and human breast cancer cells in culture to form all omega-3s from omega-6 fatty acids when fed the cDNA encoding omega-3 fatty acid desaturase obtained from the roundworm *Caenorhabditis elegans*. The omega-3 desaturase efficiently and quickly converted the omega-6 fatty acids that were fed to the cardiomyocytes in culture to the corresponding omega-3 fatty acids. Thus, omega-6 LA was converted to omega-3 ALA and AA was converted to EPA, so at equilibrium, the ratio of omega-6 to omega-3 PUFA was close to 1/1 (Kang et al., 2001). Further studies demonstrated that the cancer cells expressing the omega-3 desaturase underwent apoptotic death, whereas the control cancer cells with a higher omega-6/omega-3 ratio continued to proliferate (Ge et al., 2002).

Except for the Lyon Heart Study and the Indo-Mediterranean Diet Study, most of the cardiovascular disease omega-3 fatty acid supplementation trials did not attempt to modify the consumption of other fat components, and specifically did not seek to reduce the intake of omega-6 fatty acids, despite the fact that there is convincing support for such studies. However, James and Cleland (1997) report beneficial effects in patients with rheumatoid arthritis, and Broughton et al. (1997) showed beneficial effects in patients with asthma by changing the background diet. James and Cleland evaluated the potential use of omega-3 fatty acids within a dietary framework of an omega-6/omega-3 ratio of 3–4/1 by supplying 4 g of EPA+DHA and using flaxseed oil rich in ALA. In their studies, the addition of 4 g EPA and DHA in the diet produced a substantial inhibition of production of IL-1\( \beta \) and TNF when mononuclear cell levels of EPA were equal to or greater than 1.5% of total cell phospholipid fatty acids, which correlated with a plasma phospholipid EPA level equal to or greater than 3.2%. These studies suggest the potential for complementarity between drug therapy and dietary choices that increased intake of omega-3 fatty acids and decreased intake of omega-6 fatty acids may lead to drug-sparing effects. Therefore, future studies need to address the fat composition of the background diet, and the issue of concurrent drug use. A diet rich in omega-3 fatty acids and poor in omega-6 fatty acids provides the appropriate background biochemical environment in which drugs function.

Asthma is a mediator-driven, inflammatory process in the lungs and the most common chronic condition in childhood. The leukotrienes and prostaglandins are implicated in the inflammatory cascade that occurs in asthmatic airways. There is evidence of airway inflammation even in newly diagnosed asthma patients within 2 to 12 months after their first symptoms (Laitinen et al., 1993). Among the cells involved in asthma are mast cells, macrophages, eosinophils, and lymphocytes. The
inflammatory mediators include cytokines and growth factors (peptide mediators) as well as the eicosanoids, which are products of AA metabolism and are important mediators in the underlying inflammatory mechanisms of asthma. Leukotrienes and prostaglandins appear to have the greatest relevance to the pathogenesis of asthma. The leukotrienes are potent inducers of bronchospasm, airway edema, mucus secretion, and inflammatory cell migration, all of which are important to the asthmatic symptomatology. Broughton et al. (1997) studied the effect of omega-3 fatty acids at a ratio of omega-6/omega-3 of 10/1 to 5/1 in an asthmatic population in ameliorating methacholine-induced respiratory distress. With low omega-3 ingestion, methacholine-induced respiratory distress increased. With high omega-3 fatty acid ingestion, alterations in urinary 5-series leukotriene excretion predicted treatment efficacy and a dose change in > 40% of the test subjects (responders), whereas the nonresponders had a further loss in respiratory capacity. A urinary ratio of 4-series to 5-series of < 1 induced by omega-3 fatty acid ingestion may predict respiratory benefit.

Bartram et al. (1993, 1995) carried out two human studies in which fish oil supplementation was given to suppress rectal epithelial cell proliferation and PGE2 biosynthesis. This was achieved when the dietary omega-6/omega-3 ratio was 2.5/1, but not with the same absolute level of fish oil intake and an omega-6/omega-3 ratio of 4/1. More recently, Maillard et al. (2002) reported their results on a case control study. They determined omega-3 and omega-6 fatty acids in breast adipose tissue and relative risk of breast cancer. They concluded, “our data based on fatty acid levels in breast adipose tissue (which reflect dietary intake) suggest a protective effect of omega-3 fatty acids on breast cancer risk and support the hypothesis that the balance between omega-3 and omega-6 fatty acids plays a role in breast cancer.”

Psychological stress in humans induces the production of proinflammatory cytokines, such as interferon gamma, tumor necrosis factor-\(\alpha\) (TNF\(\alpha\)), IL-6, and IL-10. An imbalance of omega-6 and omega-3 polyunsaturated fatty acid (PUFA) in the peripheral blood causes an overproduction of proinflammatory cytokines. There is evidence that changes in fatty acid composition are involved in the pathophysiology of major depression. Changes in serotonin (5-HT) receptor number and function caused by changes in PUFA provide the theoretical rationale connecting fatty acids with the current receptor and neurotransmitter theories of depression (Maes et al., 1996; Maes et al., 1997; Peet et al., 1998). The increased C20:4\(\omega6\)/C20:5\(\omega3\) ratio and the imbalance in the omega-6/omega-3 PUFA ratio in major depression may be related to the increased production of proinflammatory cytokines and eicosanoids in that illness (Maes et al., 1996). There are numerous studies evaluating the therapeutic effect of EPA and DHA in major depression. Stoll and colleagues (Locke and Stoll, 2001; Stoll et al., 1999) showed that EPA and DHA prolong remission, that is, reduce the risk of relapse in patients with bipolar disorder.

Tiemeier et al. (2003) showed that plasma fatty acid composition is associated with depression in the elderly. Subjects with depressive disorders had a higher ratio of omega-6 to omega-3 PUFA, 7.2 compared with 6.6 (\(P = 0.01\)). They concluded that, “Because this relation was not secondary to inflammation, atherosclerosis, or possible confounders, it suggests a direct effect of fatty acid composition on mood.”
These clinical studies in patients with cardiovascular disease, arthritis, asthma, cancer, and mental illness clearly indicate the need to balance the omega-6/omega-3 fatty acid intake for prevention, and during treatment, of disease. The scientific evidence is strong for decreasing the omega-6 and increasing the omega-3 intake to improve health throughout the life cycle (Simopoulos and Cleland, 2003). The scientific basis for the development of a public policy to develop dietary recommendations for essential fatty acids, including a balanced omega-6/omega-3 ratio is robust (Simopoulos, 1998, 2001). What is needed is a scientific consensus, education of professionals and the public, the establishment of an agency on nutrition and food policy at the national level, and willingness of governments to institute changes. Education of the public is essential to demand changes in the food supply.

**CONCLUSION**

In conclusion

- Humans evolved on a diet in which the ratio of omega-6/omega-3 EFA was about 1, whereas in Western diets the ratio is 15/1 to 16.7/1. Such evidence comes from studies on the evolutionary aspects of diet, modern-day hunter-gatherers, and traditional diets. Agribusiness and modern agriculture have led to decreases in omega-3 fatty acids and increases in omega-6 fatty acids. Such practices have led to excessive amounts of omega-6 fatty acids, upsetting the balance that was characteristic during evolution when our genes were programmed to respond to diet and other aspects of the environment.
- LA and ALA are not interconvertible and compete for the rate-limiting Δ6-desaturase in the synthesis of long-chain PUFA.
- AA (omega-6) and EPA (omega-3) are the parent compounds for the production of eicosanoids. Eicosanoids from AA have opposing properties from those of EPA. An increase in the dietary intake of omega-6 EFA changes the physiological state to prothrombotic, proconstrictive, and proinflammatory.
- Many of the chronic conditions—cardiovascular disease, diabetes, cancer, obesity, autoimmune diseases, rheumatoid arthritis, asthma, and depression—are associated with increased production of thromboxane A2, leukotriene B4, IL-1β, IL-6, TNF, and C-reactive protein. These factors increase by increases in omega-6 fatty acid intake and decrease by increases in omega-3 fatty acid intake, either ALA or EPA and DHA. EPA and DHA are more potent than ALA, and most studies have been carried out using EPA and DHA.
- The optimal dose or ratio of omega-6/omega-3 varies from 1/1 to 4/1, depending on the disease under consideration. Because many chronic diseases prevalent in Western cultures are multigenic and multifactorial, it is not surprising that the dose or the ratio differs.
- Studies show that the background diet, when balanced in omega-6/omega-3, decreases the drug dose. It is therefore essential to decrease the omega-6
intake while increasing the omega-3 in the prevention and management of chronic disease. Furthermore, the balance of omega-6 and omega-3 fatty acids is very important for homeostasis and normal development. The ratio of omega-6 to omega-3 EFA is an important determinant of health. Therefore, appropriate amounts of dietary omega-6 and omega-3 fatty acids at a ratio of about 1–2/1 consistent with the recommended adequate intake (AI) found in Tables A-1 and A-2 of Appendix A, need to be considered in making dietary recommendations, and these two classes of PUFA should be distinguished in food labels because they are metabolically and functionally distinct.

Table A-1. AI\(^a\) for adults.

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>g/day (2,000 kcal diet)</th>
<th>Energy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>4.44</td>
<td>2.0</td>
</tr>
<tr>
<td>(Upper limit)(^b)</td>
<td>6.67</td>
<td>3.0</td>
</tr>
<tr>
<td>ALA</td>
<td>2.22</td>
<td>1.0</td>
</tr>
<tr>
<td>DHA + EPA</td>
<td>0.65</td>
<td>0.3</td>
</tr>
<tr>
<td>DHA to be at least(^c)</td>
<td>0.22</td>
<td>0.1</td>
</tr>
<tr>
<td>EPA to be at least</td>
<td>0.22</td>
<td>0.1</td>
</tr>
<tr>
<td>TRANS-FA</td>
<td>(Upper limit)(^d)</td>
<td>2.00</td>
</tr>
<tr>
<td>SAT</td>
<td>—</td>
<td>&lt; 8.0</td>
</tr>
<tr>
<td>(Upper limit)(^e)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MONOs(^f)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)AI, adequate intake. If sufficient scientific evidence is not available to calculate an estimated average requirement, a reference intake called on adequate intake is used instead of a recommended dietary allowance. The AI is a value based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group (or groups) of healthy people. The AI for children and adults is expected to meet or exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific healthy population: LA, linoleic acid; ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TRANS-FA, trans fatty acids; SAT, saturated fatty acids; MONOs, monounsaturated fatty acids.

\(^b\)Although the recommendation is for AI, the Working Group believed that there is enough scientific evidence to also state an upper limit for LA of 6.67 g/day based on a 2,000 kcal diet or 3.0% of energy.

\(^c\)For pregnant and lactating women, ensure 300 mg/day of DHA.

\(^d\)Except for dairy products, other foods under natural conditions do not contain trans-FA. Therefore, the Working Group does not recommend trans-FA to be in the food supply as a result of hydrogenation of unsaturated fatty acids or high-temperature cooking (reused frying oils).

\(^e\)Saturated fats should not comprise more than 8% of energy.

\(^f\)The Working Group recommended that the majority of fatty acids are obtained from monounsaturates. The total amount of fat in the diet is determined by the culture and dietary habits of people around the world (total fat ranges from 15% to 40% of energy), but with special attention to the importance of weight control and reduction of obesity.
APPENDIX A

Table A-2.  AIa for infant formula/diet.

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Percent of fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAb</td>
<td>10.00</td>
</tr>
<tr>
<td>ALA</td>
<td>1.50</td>
</tr>
<tr>
<td>AAc</td>
<td>0.50</td>
</tr>
<tr>
<td>DHA</td>
<td>0.35</td>
</tr>
<tr>
<td>EPAd</td>
<td>(Upper limit) &lt; 0.10</td>
</tr>
</tbody>
</table>

aAI, adequate intake. If sufficient scientific evidence is not available to calculate an estimated average requirement, a reference intake called on adequate intake is used instead of a recommended dietary allowance. The AI is a value based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group (or groups) of healthy people. The AI for children and adults is expected to meet or exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific healthy population: LA, linoleic acid; ALA, alpha-linolenic acid; AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; TRANS-FA, trans fatty acids; SAT, saturated fatty acids; MONOs, monounsaturated fatty acids.

bThe Working Group recognizes that in countries like Japan, the breast milk content of LA is 6% to 10% of fatty acids and the DHA is higher, about 0.6%. The formula/diet composition described here is patterned on infant formula studies in Western countries.

cThe Working Group endorsed the addition of the principal long chain polyunsaturates, AA and DHA, to all infant formulas.

dEPA is a natural constituent of breast milk, but in amounts more than 0.1% in infant formula it may antagonize AA and interfere with infant growth.

APPENDIX A

Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids

On April 7–9, 1999, an international working group of scientists met at the National Institutes of Health in Bethesda, Maryland (USA), to discuss the scientific evidence relative to dietary recommendations of omega-6 and omega-3 fatty acids (Simopoulos et al., 1999a). The latest scientific evidence based on controlled intervention trials in infant nutrition, cardiovascular disease, and mental health was extensively discussed. Tables A-1 and A-2 include the adequate intake (AI) for omega-6 and omega-3 essential fatty acids for adults and infant formula/diet, respectively.

**Adults.** The working group recognized that there were not enough data to determine dietary reference intake (DRI), but there were good data to make recommendations for AI for adults, as shown in Table A-1.

**Pregnancy and Lactation.** For pregnancy and lactation, the recommendations are the same as those for adults with the additional recommendation seen in footnote 1 (Table A-2), that during pregnancy and lactation women must ensure a DHA intake of 300 mg/d.

**Composition of Infant Formula/Diet** It was believed of utmost importance to focus on the composition of the infant formula, considering the large number of
premature infants around the world, the low number of women who breastfeed, and the need for proper nutrition of the sick infant. The composition of the infant formula/diet was based on studies that demonstrated support for both the growth and neural development of infants in a manner similar to that of the breastfed infant (Table A-2).

One recommendation deserves explanation here. After much discussion, consensus was reached on the importance of reducing the omega-6 polyunsaturated fatty acids (PUFAs), even as the omega-3 PUFAs are increased in the diet of adults and newborns for optimal brain and cardiovascular health and function. This is necessary to reduce adverse effects of excesses of arachidonic acid and its eicosanoid products. Such excesses can occur when too much LA and AA are present in the diet and an adequate supply of dietary omega-3 fatty acids is not available. The adverse effects of too much arachidonic acid and its eicosanoids can be avoided by two interdependent dietary changes. First, the amount of plant oils rich in LA, the parent compound of the omega-6 class, which is converted to AA, needs to be reduced. Second, simultaneously, the omega-3 PUFAs need to be increased in the diet. LA can be converted to arachidonic acid and the enzyme, Δ6 desaturase, necessary to desaturate it, is the same one necessary to desaturate ALA, the parent compound of the omega-3 class; each competes with the other for this desaturase. The presence of ALA in the diet can inhibit the conversion of the large amounts of LA in the diets of Western industrialized countries, which contain too much dietary plant oils rich in omega-6 PUFAs (e.g., corn, safflower, soybean oils). The increase of ALA, together with EPA and DHA, and reduction of vegetable oils with high LA content, are necessary to achieve a healthier diet in these countries.

REFERENCES


