Summary of a workshop on n–3 fatty acids: current status of recommendations and future directions1,2

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INTRODUCTION

The day after the conference “n–3 Fatty Acids: Recommendations for Therapeutics and Prevention,” a workshop was held at the Institute of Human Nutrition, Columbia University, New York, NY (22 May 2005). Present at the workshop were Sharon R Akabas, Jan Breslow, Yvon Carpentier, Richard J Deckelbaum, Esther Granot, Joseph Hibbeln, Craig Jensen, and Penny Kris-Etherton. Susan Carlson and Philip Calder submitted their summaries before the workshop but were not in attendance. All participants had been briefed before the workshop and apprised of the workshop goals and objectives. The workshop objectives were to consider and summarize the strength of the data on positive (or negative) effects of n–3 fatty acids as follows:

1) To assess which single n–3 fatty acids [α-linolenic acid (ALA), eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA)] or combinations might be responsible for specific biological effects in different areas of health and disease.

2) Where the data, studies, and consensus permit, to either corroborate or set a recommendation for specific intakes of n–3 fatty acids for each topic reviewed.

3) Wherever possible, to distinguish between prevention and treatment of the condition when making recommendations.

4) Where the data are insufficient or too disparate to permit setting a recommendation, to identify in general terms the studies needed for such recommendations to be set.

Each participant was supplied a grid for organizing and summarizing data on specific n–3 fatty acids; for pregnancy and infant development, we added arachidonic acid (AA). A sample empty grid is shown in Figure 1.

The workshop participants concluded that most work to date has not sufficiently distinguished between the specific n–3 fatty acids, especially between DHA and EPA, nor in many studies have background intakes of n–6 fatty acids been adequately controlled.

Each area was summarized by using 2 general categories: 1) current knowledge for which a general consensus exists, and 2) gaps and recommendations for research and policy. The workshop concluded with a summary of the general conclusions that are relevant to all areas of n–3 fatty acids and health. References for the summaries below can be found in the articles included in the supplement.

Gaps and recommendations for research and policy

- More work should be done to assess whether these doses are associated with any increased bleeding.
- More extensive dose-response studies should be conducted.
- Further assessment of specific effects of DHA and EPA should be conducted on neuropsychological function, immune response, and rates of infection in the infant.

INFANTS

Current knowledge for which a general consensus exists

- High intake ratios of EPA to DHA can lead to a decreased growth rate.
- Current levels of DHA:AA (1.4:1 to 2:1) are beneficial for the visual and cognitive development of low-birth-weight infants and likely also normal-birth-weight infants.

Gaps and recommendations for research and policy

- The role of ALA is poorly understood and should be further examined, but ALA likely cannot substitute for DHA.
- Dose responses of AA and DHA need to be more fully characterized.
- Whether DHA is beneficial for immune and allergic response in older infants should be examined.

CARDIOVASCULAR DISEASE

Current knowledge for which a general consensus on EPA and DHA exists

- Reduced overall mortality after onset of cardiovascular disease.
- Reduced sudden death and arrhythmias, primarily in secondary prevention trials.
- Reduced blood triacylglycerol concentrations with higher doses.
- May slightly increase LDL, but the increase is not clinically significant.
- Limited effect associated with increased ALA.

Gaps and recommendations for research and policy

- Dose-response data for EPA and DHA are limited and should be studied.

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Some data from small clinical trials suggest that DHA alone is similar to or better than a combination of EPA plus DHA; these studies should be replicated in larger trials.

A large trial on the effects of n-3 fatty acids in the primary prevention of cardiovascular disease should be conducted.

MENTAL HEALTH

Current knowledge for which a general consensus exists

- EPA plus DHA appear to have better efficacy than either alone.
- DHA alone has not been effective.
- n-3 Fatty acids are likely to improve psychotic, depressive, and aggressive symptoms in severe patients.

Gaps and recommendations for research and policy

- A clear body of treatment data on effects of EPA, DHA, or both has not yet been developed for either schizophrenia, depressive, or aggressive disorders; thus, recommendations should be cautious.
- Dose-response data and primary prevention trials are lacking.

AGING: DEMENTIA AND MACULAR DEGENERATION

Current knowledge for which a general consensus exists

- Increased fish and DHA intake are protective against cognitive decline.
- Fish consumption and DHA are associated with a reduced risk of developing Alzheimer disease.
- DHA may improve mental function and reduce aggression in patients with dementia.
- Consuming fish and low linoleic acid is associated with reduced risk of age-related macular degeneration.

Gaps and recommendations for research and policy

- Dose-response and primary prevention studies for both dementia and age-related macular degeneration are needed.

METABOLIC SYNDROME

Current knowledge for which a general consensus exists

- To improve insulin sensitivity, n-3 fatty acids are more useful in prevention than in treatment.
- EPA plus DHA effectively lowers blood triacylglycerol concentrations.
- High doses tend to decrease small, dense LDL concentrations and may improve insulin sensitivity.

Inclusion of n-3 fatty acids should be considered along with other lifestyle interventions such as exercise, diet, and medication.

Gaps and recommendations for research and policy

- Dose-response studies should be examined, especially because different individuals seem to be affected differently by n-3 fatty acids.
- An upper level of intake for benefit needs to be established.
- A primary intervention or prevention trial should be conducted.

INFLAMMATORY AND IMMUNE RESPONSE

Current knowledge for which a general consensus exists

- For rheumatoid arthritis, there is a proven therapeutic benefit of EPA plus DHA. All studies that monitored use of nonsteroidal antiinflammatory agents reported a significant reduction in use, and n-3 fatty acids reduce requirements for corticosteroids.
- Although evidence is weaker for treatment of Crohn disease and psoriasis, n-3 fatty acids prolong remission in Crohn disease and reduce the requirement for corticosteroids in both conditions.
- α-Linolenic acid is not antiinflammatory at intakes <10 g/d.

Gaps and recommendations for research and policy

- Dose-response and primary prevention studies are needed in all areas of inflammatory and immune response.
- Some evidence exists that n-3 fatty acids are therapeutic for childhood asthma; more studies are needed.
- There is contradictory or no evidence that n-3 fatty acids are therapeutic in the treatment of ulcerative colitis, systemic lupus erythematosus, or adult asthma; more studies are needed.

GENERAL CONCLUSIONS RELEVANT TO ALL AREAS

Current knowledge for which a general consensus exists

- Preformed long-chain n-3 fatty acids, derived from marine or algal sources, are more efficient biologically than are plant-derived n-3 ALA.
- The efficiency of conversion of plant-derived ALA to EPA and DHA, where it has been shown to be beneficial, is dependent in large part on the n-6 fatty acid content of the diet.

Gaps and recommendations for research advancing policy

- In almost every area, data are insufficient to make recommendations for intake of specific n-3 fatty acids, eg, EPA versus DHA versus EPA + DHA combined.
- To develop more specific recommendations, more data will be needed that compare dose-response relations for both EPA and DHA.
- Biological effects of n-3 fatty acids will be better elucidated when tissue concentrations of each n-3 fatty acid are measured. Wherever possible, tissue concentrations should
be used to develop dose-response curves. Determining the appropriate tissue still requires more research, but at this time, plasma concentrations can be used as a reliable surrogate when the specific tissue level of interest cannot be obtained.

- The intake of n−6 fatty acids may markedly affect the n−3 fatty acid intake required to achieve a desirable tissue n−3 fatty acid level. Future studies should consider that higher n−6 fatty acid intakes may lead to higher n−3 fatty acid requirements to achieve desired biological effects.
- Intervention trials at a given dosage or form of an n−3 fatty acid are not necessarily going to have the same effect as more prolonged or lifelong intakes of n−3 fatty acids. Therefore, intakes required to prevent a specific disease may be different from intakes required to treat a disease, and research data should be interpreted with this in mind.
- Data are lacking for primary prevention in almost every health area, and secondary prevention trials do not necessarily predict the usefulness of n−3 fatty acids for primary prevention.
- National public health initiatives to increase n−3 fatty acid consumption are needed; the working group believes that data are currently sufficient to indicate that intake of n−3 fatty acids is suboptimal, and a national and international initiative should be launched to shift n−3 fatty acid intake upward.
- Cross-disciplinary initiatives should be encouraged when studying the effects of n−3 fatty acids (eg, if a mental health study is being performed, include endpoints relevant to cardiovascular disease).
Erratum

Deckelbaum RJ, Worgall TS, Seo T. n-3 Fatty acids and gene expression. Am J Clin Nutr 2006;83(suppl):1520S–5S.

Because of errors during the publishing process, the reference numbers in Figure 2 and its legend are incorrect. The corrected figure and legend appear below. In addition, in the fourth sentence in the Conclusion, reference 31 should be reference 3.

**FIGURE 2.** Genes influenced by n-3 fatty acids and by glitazones. Key representative genes critical for inflammation and lipid metabolism are listed. In general, proinflammatory genes (left column) are suppressed by n-3 fatty acids, while genes critical for lipid peroxidation, energy utilization, and lipid homeostasis are increased by n-3 fatty acids (right column). Note that many genes indicated by italic letters are activated or suppressed by n-3 fatty acids and glitazones in the same direction. This figure is based on data in references 14 and 31–76. COX2, cyclooxygenase 2; CRP, C-reactive protein; GLUT4, glucose transporter 4; ICAM, intercellular adhesion molecule; IL, interleukin; MMP9, matrix metalloproteinase 9; PDK4, pyruvate dehydrogenase kinase 4; UCP, uncoupling protein; VCAM, vascular cell adhesion molecule; vWF, von Willebrand factor. Other abbreviations are as defined in the legend to Figure 1.

Erratum


Under the heading “INFANTS” on page 1536S, the second bulleted point should read as follows: “Current levels of AA:DHA (1.4:1 to 2:1) are beneficial for the visual and cognitive development of low-birth-weight infants and likely also normal-birth-weight infants.”