Fish as a Functional Food?

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Definition: Functional Foods

“Functional Foods” are foods or dietary components that may provide a health benefit beyond basic nutrition: health promoting or disease preventing.

Examples can include whole foods such as fruits and vegetables, whole grains, fortified or enhanced foods and beverages, and some dietary supplements.

Biologically active components in functional foods may impart health benefits or desirable physiological effects.
Scientific Criteria

FDA regulates **food products** according to their intended use and the nature of claims made on the package. Five types of health-related statements or claims are allowed on food and dietary supplement labels:

- **Nutrient content claims** indicate the presence of a specific nutrient at a certain level.

- **Structure and function claims** describe the effect of dietary components on the normal structure or function of the body. These claims must also include the following statement on the label: *“This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent any disease”.*

- **Dietary guidance claims** describe the health benefits of broad categories of foods.

- **Qualified health claims** convey a developing relationship between components in the diet and risk of disease, as reviewed by the FDA and supported by the weight of credible scientific evidence available.

- **Health claims** confirm a relationship between components in the diet and risk of disease or health condition, as approved by FDA and supported by significant scientific agreement, i.e., long chain omega-3 fats on CVD.
N-6 and N-3 PUFAs

**Linoleic Acid (LA):** n-6 PUFA

\[
\text{HOOC} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{C}} - \overset{\text{N-6}}{\text{CH}_3}
\]

**Alpha-Linolenic Acid (ALA):** n-3 PUFA

\[
\text{HOOC} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{C}} - \overset{\text{N-3}}{\text{CH}_3}
\]

This end does not change
n-6 Family

Vegetable oils, meats, eggs

Specialty oils: i.e., borage and evening primrose oils

Meats, fish, eggs

Prostaglandins
Thromboxane
Prostacyclin

Cancer
CVD
Inflammation

n-3 Family

Vegetable oils: i.e., canola, soybean, flax

Fish & fish oil, Echium oil
Black current oil
GMO veg oils

Vegetable oils, meats, eggs

Specialty oils: i.e., canola, soybean, flax

Meats, fish, eggs

Cancer
CVD
Inflammation

Prostaglandins
Thromboxane
Prostacyclin

COX-1
COX-2

EPA
eicosapentaenoic acid

DPA
docosapentaenoic acid

DHA
docosahexaenoic acid

24:5 n-3

24:6 n-3

20:4 n-3

LA
linoleic acid

GLA

DGLA

AA
arachidonic acid

Stearidonic acid

DGLA

20:4 n-3

SDA

EPA
eicosapentaenoic acid

DPA
docosapentaenoic acid

DHA
docosahexaenoic acid

Whelan et al., 2005
FOOD SOURCES
Omega-3 Content (g/100g) of Selected Seafood (raw)

![Graph showing the omega-3 content (g/100g) of various seafood species.](image-url)
DHA is the known “biologically required” omega-3 PUFA

- Richest sources are in the brain and retina of the eye
- DHA comprises 60% of the rod outer segments of the eyes
- Only dietary DHA can change tissue DHA
Pooled odds ratios for age-related macular degeneration (AMD), comparing the highest with the lowest dietary intake of fish

(AMD is the leading cause of blindness in people >50 yo)

In September 2004, the FDA approved the use of EPA and DHA in the labeling of foods for a “healthy heart”.

“Supportive, but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.” (FDA, Sept 9, 2004)

This data was based on fish intake, not supplemented levels of pure EPA and DHA.
Impact of LC N-3 LCPUFA on Mortality Statistics

Calculation of the disease burden modifiable by n–3 long-chain fatty acids (LCFAs) (top panel).

Scattergram by country and best-fit regression curve for dose-response relation between the % n–3 fatty acids in tissue LCFAs and cardiovascular mortality (bottom).

Population size and differences in age distributions were adjusted for by using the rate of illness (per 100 000) age-adjusted to the European standard distribution.

MRFIT, Multiple Risk Factor Intervention Trial.

Hibbeln et al. AJCN 83:S1483-S1493, 2006
CARDIOVASCULAR DISEASE
The Effect of EPA/DHA (fish & fish oil) Consumption on CVD Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>N-3 PUFA g/day</th>
<th>Effect on CVD Mortality (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascherio (1995)</td>
<td>70 mg/d vs 580 mg/d</td>
<td>NS (n=44,895)</td>
</tr>
<tr>
<td>Singh (1997)</td>
<td>+1.08 g/d (EPA)</td>
<td>↓ (n=122)</td>
</tr>
<tr>
<td>Albert (1998) (Physicians Health Study)</td>
<td>10 mg/d vs ≥247 mg/d</td>
<td>NS (n=20,551)</td>
</tr>
<tr>
<td>Marchioli (2002) (GISSI Prev. Trial)</td>
<td>+1 g/d (EPA+DHA)</td>
<td>↓ (n=11,323)</td>
</tr>
<tr>
<td>Hu (2002)</td>
<td>67 mg/d vs 533 mg/d</td>
<td>↓ (n=84,688)</td>
</tr>
<tr>
<td>Hu (2003) (Nurses Health Study)</td>
<td>40 mg/d vs ≥250 mg/d</td>
<td>↓ (n=5,103)</td>
</tr>
<tr>
<td>Mozaffarian (2005)</td>
<td>&lt;250 mg/d vs ≥250 mg/d</td>
<td>↓ (n=45,722)</td>
</tr>
<tr>
<td>Yzebe (2004)</td>
<td>Meta-Analysis</td>
<td>↓ (n=13,780)</td>
</tr>
</tbody>
</table>
**Myocardial Infarction (MI)** is where blood flow to the still-beating heart is interrupted causing damage to the heart (also called a “heart attack”)

**Cardiac Arrest** is the abrupt cessation of normal circulation of the blood due to failure of the heart to contract effectively (arrhythmia, tachycardia)

**Sudden Cardiac Death** is the *sudden*, abrupt loss of heart function in a person
SUDDEN DEATH

Plaque “cap” stabilization: (prevents atherothrombosis)

75% of coronary thrombi lead to MI and death
90% of carotid thrombi cause ischemic stroke

A major impact of n-3 LC PUFA is on sudden death
Inflammation’s Many Roles

INFLAMMATION—now recognized as a central player in atherosclerosis—occurs when certain white blood cells (those that normally constitute the first line of defense against infection) invade and become active in a tissue. These diagrams depict the growth of an atherosclerotic plaque in a coronary artery; the three close-up views highlight some of the inflammatory processes that can ensue when someone’s blood carries too much low-density lipoprotein (LDL).

**EPA and DHA**

**↑ cap stability**

Libby, P. Scientific American 2002
SUDDEN DEATH

A major portion of Sudden Death is due to ventricular fibrillation

Plaque “cap” stabilization: (prevents atherothrombosis)
75% of coronary thrombi lead to MI and death
90% of carotid thrombi cause ischemic stroke

• Anti-arrhythmic

A major impact of n-3 LC PUFA is on sudden death
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Omega-3 FA Infusion Prevents Ventricular Tachyarrhythmias in Dogs

Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels: *Physicians' Health Study*


90% reduction in risk

$p$ for trend = 0.001

Mean: 3.58, 4.76, 5.63, 6.87

Omega-3 Index

A measure of the amount of EPA+DHA in red blood cell membranes expressed as the percent of total fatty acids

There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

3/64 = 4.6%

Omega-3 Index = 4.6%

Risk for Primary Cardiac Arrest and Red Blood Cell EPA+DHA Level

- Mean RBC EPA+DHA by Quartile:
  - Quartile 1 (Q1): 3.3%
  - Quartile 2 (Q2): 4.3%
  - Quartile 3 (Q3): 5.0%
  - Quartile 4 (Q4): 6.5%

90% reduction in risk

* p<0.05 vs Q1

Adapted from Siscovick DS et al. *JAMA* 1995;274:1363-1367
Relationship Between Reported Intake of Tuna and Other Non-fried Fish and the Omega-3 Index (n=163)

Omega-3 Index (%)

Frequency of Intake (% of Population)

- <1/mon (13%)
- 1–3/mon (42%)
- 1/wk (18%)
- >1–2/wk (15%)
- >2/wk (12%)

INFLAMMATION

Inflammation is related to all chronic diseases including:

- heart disease
- cancer
Diseases and conditions with an inflammatory component in which LC n–3 PUFA might be of benefit

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Lupus</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Childhood asthma</td>
</tr>
<tr>
<td>Adult asthma</td>
</tr>
<tr>
<td>Allergic disease</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Neurodegenerative disease of aging</td>
</tr>
<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Acute cardiovascular events</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Systemic inflammatory response to surgery, trauma, and critical illness</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Cancer cachexia</td>
</tr>
</tbody>
</table>

P. Calder, AJCN 83:S1505-S1519, 2006
Inverse relation between the eicosapentaenoic acid (EPA) content of human mononuclear cells and the production of tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β).

Healthy male volunteers consumed various combinations of sunflower oil, flaxseed oil, and fish oil resulting in various EPA levels in blood mononuclear cells.

The mononuclear cells were isolated and stimulated ex vivo with endotoxin for 24 h.

The concentration of each inflammatory cytokine was inversely related to the EPA content of the mononuclear cells.

P. Calder AJCN 83:S1505-S1519, 2006
N-3 PUFA

↓ expression of adhesion molecules

↓ leukocyte chemotaxis

Anti-inflammatory eicosanoids

Resolvins (Resolution of inflammation)

↓ generation of reactive oxygen species

Arachidonic Acid

Proinflammatory eicosanoids (i.e., prostaglandins)

↓ inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8)

P. Calder AJCN 83:S1505-S1519, 2006
N-3 PUFA and the Brain
N-3 PUFA and the Brain

**DHA** is preferentially incorporated in the brain and retina

– The brain is 50% fat and ~15% of that is DHA
N-3 PUFA and Behavior
Relationship between per Capita Consumption of **Seafood** and **Homicides**

Hibbeln, JR  World Rev Nutr Diet, 2001; 88; 41-46

$p < 0.0006$
Elevated levels of corticotrophin-releasing hormone (CRF) increases fear and anxiety, components of defensive and violent behaviors.

\[ r = -0.67 \quad p < 0.006 \]

(CSF: cerebral spinal fluid)

Hibbeln et al, Biological Psychiatry, 2004
Neurological Disorders:
Depression and Biopolar Diseases
Seafood consumption and prevalence rates of postpartum depression.

Postpartum prevalence rates for Australia, New Zealand, Sweden and the United Kingdom, The United States were derived by meta-analysis. All other countries are represented by a single study. Apparent Seafood consumption lb/person/year is an economic measure of disappearance of all fish and seafood from the economy and is calculated by imports plus catch minus exports. A logarithmic regression was used for analysis ($r=-0.81$, $p<0.001$).

DHA contents of mothers’ milk and prevalence rates of postpartum depression

Postpartum prevalence rates for Australia, Sweden, the United Kingdom, The United States were derived by meta-analysis. All other countries are represented by a single study, see text. DHA content of mother’s milk is expressed as the weight percent of docosahexaenoic acid of mature milk. A simple Pearson’s product moment correlation was used for regression analysis ($r=-0.84$, $p<0.0001$).

Cross-National Comparison of the Relationship Between Seafood Consumption and Lifetime Prevalence Rates of Bipolar Disorders and Schizophrenia

Hibbeln et al., Am J. Psychiatry 160:2222, 2003
The Elderly and Dementia
Curves comparing cumulative mild cognitive impairment (MCI) incidence in subjects who were cognitively normal at the first evaluation by Mediterranean diet (MeDi) adherence.
Curves comparing cumulative Alzheimer disease (AD) incidence in subjects with mild cognitive impairment (MCI) at the first evaluation by Mediterranean diet (MeDi) adherence.
# Effect of N-3 PUFA on Dementia in Cohort Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings (RR)</th>
<th>Diet Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barberger-Gataeu 2002 (PAQUID Study)</td>
<td>↓ Dementia by 31%  ↓ AD by 34%</td>
<td>Fish consumption (at least 1/wk)</td>
</tr>
<tr>
<td>Kalmijn 1997 (Rotterdam Study) N&gt;3500</td>
<td>↓ Dementia by 60%  ↓ AD by 70% (w/o vascular complications)</td>
<td>Fish consumption Dose response with total n-3 PUFA (&lt;3 g/d - &gt;18.5 g/d)</td>
</tr>
<tr>
<td>Morris 2003 (Chicago Health and Aging Project)</td>
<td>↓ AD by 60-70%</td>
<td>Fish consumption Total n-3 PUFA (0.9 - 1.75 g/d) DHA (0.03 – 0.10 g/d) p&lt;0.02 EPA (0.0 – 0.3 g/d) NS (p&lt;0.40) ALA (0.72 – 1.46 g/d) NS (p&lt;0.10)</td>
</tr>
</tbody>
</table>

[RCT]
Effect of DHA supplementation on treatment of dementia using Hasegawa’s Dementia Rating Scale (HSD-R) and Mini-Mental State Examination (MMSE) Score in Nursing Home Patients

Multivariate linear regression analysis of 5-y cognitive decline in 210 elderly men in relation to fish consumption in 1990, showing the mean change in cognitive function between 1990 and 1995.
Fish oil DHA can be converted to Neuroprotectin D1 in the brain

Dietary DHA from Fish

Brain DHA

15-Lipoxygenase

Neuroprotectin D1 (NPD1)
CANCER
Effect of n-3 PUFA on tumor number in Apc\textsuperscript{Min/+}

(we added n-3 PUFA to a diet that already contained HED of ALA and LA)

Prostate Cancer

• Diagnosis of prostate cancer: elevated PSA, enlarged prostate, biopsy
• Prostatectomy: no PSA because no prostate epithelial cells
• Serum PSA increases: prostate cancer returns; metastasis to bone
• Hormone ablation therapy: removal of androgens reduces tumor and PSA
• Serum PSA increases: bone (prostate) cancer returns, independent of androgens
• Treatment: aggressive chemotherapy, prognosis is poor

Androgen-Ablation Therapy

Tumor Regression

Androgen-Dependent Growth

Androgen-Independent Growth

Migration to bone

Disease-Free Survival = Months to Years
RELAPSE to ANDROGEN-INDEPENDENT TUMOR GROWTH
Increasing Tumor Volume

LC N-3 PUFA Consumption and Prostate Cancer Risk

Risk based on stage of cancer

# Recommended Intakes of n-3 PUFA

<table>
<thead>
<tr>
<th>Year</th>
<th>Organization/individuals</th>
<th>Recommendations n-3 PUFA Intakes</th>
</tr>
</thead>
</table>
| 2006 | American Heart Association | Gen Rec: Eat fish (fatty fish) at least 2 times per week  
Documented CHD: 1 g/d n-3 LCPUFA (suppl may be required)  
Documented HyperTG: 2-4 g/d (see physician) |
| 2005 | US Dietary Guidelines | Two 4 oz servings high n-3 fish/wk; ~ 496 mg/d EPA+DHA |
| 2004 | ISSFAL  
Int’l Society for the Study of Fatty Acids and Lipids | ALA: 0.7% energy; EPA+DHA: ≥ 500 mg/d |
| 2004 | Wijendran and Hayes | ALA: 0.75% energy; EPA+DHA: 0.25 % energy (~0.56 g) |
| 2003 | World Health Organization | Total n-3 PUFA: 1-2% energy (1% en = 2.22g) |
| 2002 | Food and Nutrition Board (USA) | ALA: 1.1 g/d women of which 10% can be EPA+DHA  
ALA: 1.6 g/d men of which 10% can be EPA+DHA |
| 2002 | American Heart Association | Eat fish (fatty fish) at least 2 times per week |
| 2002 | Scientific Advisory Committee on Nutrition (UK) | Total n-3 PUFA: >0.2 g/d;  
Eat 2 portions of fish weekly (one being oily) |
| 2001 | Health Councils of the Netherlands | Total n-3 PUFA: 1% energy; DHA: 150-200 mg/d |
| 2000 | Simopoulos, Leaf, Salem | ALA: 2.22 g/d; EPA: ≥ 220 mg/d; DHA: ≥ 220 mg/d;  
EPA+DHA: 650 mg/d |
| 1999 | British Nutrition Foundation (UK) | ALA: 0.2% energy; Total n-3 PUFA: 1.25 g/d |
Take Home Messages

1. Dietary n-3 PUFA are essential nutrients and are important to maintain good health and prevent disease

2. Fish, in my opinion, has been shown to be a “functional food”

Because by definition:

“Functional Foods” are foods or dietary components that may provide a health benefit beyond basic nutrition: health promoting or disease preventing.
Your challenge:

1. Convince the public that your product is safer than ferel fish
2. Convince the public that your product is as nutritious as ferel fish
3. Provide a product where the health benefit is greater than the cost

How do you do this? Invest in research...publish, publish, publish
Fat content in the farmed trout was 5 times that of the wild trout.
