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Omega-3 Fatty Acids:
Health Benefits and Dietary Recommendations

Council for Agricultural Science and Technology

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Council for Agricultural Science and Technology
4420 West Lincoln Way, Ames, IA 50014-3447, USA
Phone: (515) 292-2125
Email: cast@cast-science.org
Web: www.cast-science.org

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Task Force Members

Authors

Donald C. Beitz, Chair, Department of Biochemistry, Biophysics, and Molecular Biology, Iowa State University, Ames, Iowa

William J. Banz, Department of Animal Science, Food, and Nutrition, Southern Illinois University, Carbondale, Illinois

Tom Brenna, Dell Medical School, Dell Pediatric Research Institute, University of Texas at Austin, Austin, Texas, USA, and Division of Nutritional Sciences, Cornell University, Ithaca, New York

Philip C. Calder, Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

Contributors

Sandeep Bhale, Hi Growth Markets, Hill's Pet Nutrition, Topeka, Kansas

Emma Derbyshire, Nutrition and Physiology, Manchester Metropolitan University, Manchester, United Kingdom

Deborah A. Diersen-Schade, Global Scientific Affairs, Mead Johnson Nutrition, Evansville, Indiana

Daniel Goldstein, Medical Sciences and Outreach, Monsanto Company, St. Louis, Missouri

Carrie Ruxton, Nutrition Communications, Cupar, United Kingdom

Jay Whelan, Department of Nutrition, University of Tennessee, Knoxville

Reviewers

Ronald W. Hardy, Aquaculture Research Institute, University of Idaho, Hagerman

Artemis P. Simopoulos, The Center for Genetics, Nutrition and Health, Washington, D.C.

CAST Liaison

David Songstad, Research/Cell Biology, Cibus, San Diego, California

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Foreword

Recognizing the need for a guide to understanding differences in omega-3 fatty acids, potential new sources of omega-3s for increasing omega-3 intake, and the impact of functional differences and new sources on developing guidelines for food labeling, claims, and dietary intake recommendations, the CAST Board of Directors authorized preparation of this report.

An eminent group of ten experts was selected as the writing task force, led by Dr. Donald Beitz as project manager. Two highly qualified scientists were invited to serve as peer reviewers, and a member of the CAST Board of Representatives served as project liaison. The authors prepared an initial draft of this document and reviewed and revised all subsequent drafts based on reviewers' comments. The CAST Board of Directors reviewed the final draft, and all task force members reviewed the galley proofs. The CAST staff provided editorial and structural suggestions and published the document. The task force authors are responsible for the publication's scientific content.

On behalf of CAST, we thank the task force members who gave of their time and expertise to prepare this publication as a contribution by the scientific community to public understanding of the issue. We also thank the employers of the scientists, who made the time of these individuals available at no cost to CAST.

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Nancy Reichert
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Director of Council Operations

Interpretive Summary

Hippocrates, an ancient Greek physician considered to be the father of medicine, pronounced "Let food be thy medicine and medicine be thy food." Throughout the centuries, man has relied on foods and herbs to maintain health and treat disease. Over this time, causes of mortality have shifted from nutrient deficiencies, infectious agents, and accidents to mortality rates that are predominantly tied to lifestyle-associated chronic diseases. In 1920, pneumonia and influenza were the leading causes of death in the United States, followed by cardiovascular disease and tuberculosis, with cancer being number six on the list (NCHS 2016). Chronic diseases with a clear link to diet and lifestyle now dominate mortality statistics, i.e., obesity, cardio-cerebrovascular disease, cognitive and neurological function, cancer, and diabetes (NCHS 2016). As such, there has been a renewed interest in how diet can promote health and protect against modern excesses above and beyond the prevention of nutrient deficiencies.

One area of research that has attracted attention because of their broad health benefits has been omega-3 polyunsaturated fatty acids. Omega-3 fatty acids are not a single dietary entity, but rather a family of metabolically related compounds that are not necessarily interchangeable and do not necessarily have the same biological functions. As a result, understanding how each family member is metabolically related to one other and the biological consequences of each when consumed in the diet is critical. This publication focuses its attention on the health benefits of omega-3 fatty acids, food sources, and dietary recommendations.

To understand the potential health benefits, this publication provides a clear description of this unique family of bioactive nutrients, how they are metabolically interrelated, where in the diet they are predominantly found, how they can contribute to human health and well-being, and how much one needs to consume to realize potential health-promoting benefits. It is additionally important to understand guidelines governing labeling of foods, nutrient and health claims related to omega-3 fatty acids, and what these statements mean.

Like all dietary polyunsaturated fats, these fatty acids are incorporated into the membranes of virtually all cells. In doing so, their physiological effects can be felt systemically. Structure and function of cell membranes are modified, and, as such, how cells communicate externally and internally is affected by the type and amount of omega-3 fatty acids incorporated. All tissues and organs are potentially influenced, not only by modifications of their cell membranes, but also by how they respond to downstream metabolites of omega-3 fatty acids produced by one cell or tissue to influence an adjacent or distant cell or tissue. In addition, omega-3 fatty acids help to moderate tissue concentrations of arachidonic acid and its bioactive metabolites where the literature reports deleterious effects can occur when these compounds are produced chronically at high levels.

Inflammation is at the core of many health-related conditions, cancer, cardiovascular disease, and neurological pathologies. One unifying target of omega-3 fatty acids is to attenuate an overly active immune response by moderating the mediators of inflammation. In doing so, omega-3 fatty acids have a "ripple effect," impacting multiple processes. For example, inflammation is an important promotor of cancer. In cardiovascular disease, it is well known that the pathogenesis of atherosclerosis is mediated by a localized inflammatory response within the subendothelium of the vasculature. And the structural lipids in the brain have among the highest concentrations of docosahexaenoic acid, an omega-3 fatty acid that seems to have neuroprotective properties.

Critical to this review is identifying dietary sources and relative abundance of these fatty acids and discussing the latest changes in food production and manufacturing technologies that improve dietary access of these health-promoting nutrients. Critically, availability of the more biologically active omega-3 fatty acids (those that are highly unsaturated) is primarily limited to fish and fish products. Unfortunately, not everyone likes fish. Therefore, generating plant-derived sources rich in these kinds of omega-3 fatty acids has unique advantages, particularly when the availability of fresh fish is low. Furthermore, new production techniques have led to improved ways of enriching the tissues of poultry, livestock, eggs, and even fish with omega-3 fatty acids, expanding food choices and access.

In summary, this publication presents a robust narrative on the family of omega-3 polyunsaturated fatty acids—a narrative that not only includes their biochemistry, but also encompasses potential health effects, dietary sources, recommended intakes, and federal regulations regarding health and nutrient claims—so readers can make informed decisions on if and how they can better incorporate these nutrients in promoting a healthier lifestyle.

1 Introduction

Omega-3 (n-3) *fatty acids* are dietary constituents that have a major influence on human growth, development, function, and disease risk. Omega-3 fatty acids have received a great amount of research attention in the past decade as a nutritional food supplement because of their many demonstrated and putative benefits for human health. Hence it is important that people understand these potential benefits and how they can adjust their diets if necessary to reap these benefits. The objectives of this paper are to (1) define these unique nutrients, (2) indicate what foods are good sources, (3) summarize their health benefits, (4) describe how food production and processing can be and are being altered to increase omega-3 fatty acid content, and (5) summarize the relevant food policies.

Chemically speaking, omega-3 fatty acids are *polyunsaturated fatty acids*[1] (PUFAs) with a double bond (C=C) at the third carbon from the methyl end of the linear chain of carbons that make up a fatty acid structure. Nutritionists consider *linoleic acid* (LA) and *alpha-linolenic acid* (ALA) to be essential for life. Linoleic acid contains double bonds at carbons 9 and 12 of its 18 carbon chain; the double bond at carbon 12 makes LA an omega-6 (n-6) fatty acid. Many common plant oils like maize, sunflower, and soy oil are rich in LA. Alpha-linolenic acid contains double bonds at carbons 9, 12, and 15 of its 18 carbon chain. Hence ALA is an omega-3 fatty acid. It is found in flax seeds and chia and their oils. The other key omega-3 fatty acids are *eicosapentaenoic acid* (EPA) and *docosahexaenoic acid* (DHA), which are present in seafood—especially fatty fish—and in oils from fatty fish and selected algae. Marine algae are responsible for biosynthesis of EPA and DHA, which pass up through the food chain to fatty fish.

New techniques in food production and manufacturing have enabled the benefits of omega-3 fatty acids (usually as fish oil) to be present in nonfish food products. For example, eggs can be enriched with omega-3 fatty acids by feeding fish oil to laying hens. The content of omega-3 fatty acids in meats, milk, and plant-derived foods can be increased by selective breeding and manufacturing procedures. An important recent development is incorporation of the genes involved in DHA biosynthesis in marine algae into canola. Docosahexaenoic acid concentrations in excess of 3% of fatty acids in an oil matrix of canola/rapeseed may facilitate dramatically improved DHA intakes from a source equivalent on a molecular basis to most of the DHA synthesized on the planet (Walsh et al. 2016). In summary, there is much interest in increasing intake of omega-3 fatty acids by the general population through increased intake of omega-3 fatty acid-rich and -enriched foods.

Many authorities have made recommendations for intake of EPA and DHA because of their significant role in development, health and disease prevention. In theory, humans have the ability to convert dietary ALA to EPA and DHA. Because the conversion of ALA to DHA, and indeed of EPA to DHA, seems inefficient, EPA and DHA should be consumed in the diet, even though their absence is unlikely to lead to obvious clinical deficiencies. Table 1.1 provides a list of selected foods that contain the most common omega-3 fatty acids.

A plethora of clinical and epidemiological evidence relates to the beneficial effects of omega-3 fatty acids, as in fatty fish, and is especially strong in neurocognitive disease. Four meta-analyses to date demonstrate that EPA-rich oils decrease symptoms of major depression (Grosso et al. 2014; Hallahan et al. 2016; Mocking et al. 2016), including reduction of perinatal depression (Lin et al. 2017). Reduction of cardiovascular risk by decrease of platelet aggregation and of the tendency toward thrombosis has been known for decades (Dyerberg et al. 1978). The present publication documents, however, that omega-3 fatty acids have a broader positive role in human health than these limited examples. For example, some, but not all, studies suggest that dietary supplementation of omega-3 fatty acids lessens the risk of colorectal and breast cancers. More research on the effect of fish oil and omega-3 fatty acids on these and other cancers is critical.

Growing evidence is emerging that omega-3 fatty acids have immunomodulatory effects and thus may be useful in treating inflammatory conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, asthma, lupus, and cystic fibrosis. It is well recognized that the human nervous system contains a significant amount of DHA. Several animal experiments suggest that omega-3 fatty acids are required for proper function of neurotransmitters, which are crucial for optimal brain function. Feeding infants supplemental omega-3 fatty acids has produced consistent results on visual acuity (Morale et al. 2005) and cognitive development (Drover et al. 2009; Willatts et al. 1998). Some studies also suggest that supplemental omega-3 fatty acids decrease risk of cognitive impairment, cognitive decline, dementia,

[1] Italicized terms (except genus/species names, published material titles, and words in quoted material) are defined in the Glossary.

Table 1.1. Omega-3 fatty acid content of selected foods[a]

Food	ALA	EPA	DPA[b]	DHA
	grams/100 grams			
Beef, ground, 90% lean	0.048	0.004	0.000	0.001
Butter, salted	0.320	0.000	0.000	0.000
Cheese, cheddar	0.117	0.010	0.017	0.000
Chicken, dark meat	0.026	0.002	0.002	0.008
Egg, whole, raw, fresh	0.036	0.000	0.008	0.051
Fish, cod, Pacific, raw	0.001	0.034	0.004	0.091
Fish, salmon, pink, canned	0.048	0.334	0.089	0.740
Fish, tilapia, raw	0.033	0.005	0.043	0.080
Margarine-butter blend	2.638	0.000	0.000	0.000
Mollusk, oyster, eastern, wild	0.164	0.352	0.020	0.270
Nuts, almonds, dry roasted	0.006	0.000	0.000	0.000
Nuts, pistachio, dry roasted	0.212	0.000	0.000	0.000
Nuts, walnuts	2.677	0.000	0.000	0.000
Oil, canola	9.136	0.000	0.000	0.000
Oil, coconut	0.022	0.000	0.000	0.000
Oil, flaxseed	53.368	0.000	0.000	0.000
Oil, soybean	6.786	0.000	0.000	0.000
Peanuts, dry roasted	0.025	0.000	0.000	0.000
Pork, cured ham, lean only	0.025	0.000	0.000	0.000
Turkey breast, meat only	0.020	0.000	0.005	0.000
Vegetable juice cocktail	0.004	0.000	0.000	0.000

[a]Adapted from *National Nutrient Database for Standard Reference Release 27*, Software v. 2.06 (USDA 2014).

[b]DPA = *docosapentaenoic acid*.

and Alzheimer's disease in the elderly, but long-term studies are needed for verification of positive effects. No adverse effects are observed when effects of omega-3 fatty acids on specific human diseases and disorders are evaluated.

What follows these introductory comments is an elaboration of the nomenclature and synthesis, traditional dietary sources, and biological significance of the omega-3 fatty acids. Much of the text is devoted to current understanding of biological functions and potential health benefits of omega-3 fatty acids for humans. Because of the great interest in health benefits of omega-3 fatty acids, agricultural and manufacturing practices are becoming available to increase concentrations of these nutrients in common animal- and plant-derived foods. The final section describes public policy guidelines relative to claims of health, nutrient content, structural functions, and food labeling.

2 Nomenclature/Interconversions

Nomenclature

The omega-3 fatty acids are one of the two major classes of polyunsaturated fatty acids required for human health. Only three omega-3 fatty acids have been studied extensively for their health effects. Despite this small number, there is much confusion over their nomenclature in the popular and technical literature. Nomenclature for the common omega-3 fatty acids is shown in Table 2.1.

For the purposes of this paper, all polyunsaturated fatty acids with the omega-3 fatty acid configuration are referred to as omega-3 fatty acids. From the perspective of traditional agriculture and foods, the main omega-3 fatty acids are ALA, EPA, and DHA. Alpha-linolenic acid is primarily of plant origin, but it is in animal foods when consumed by the animal, whereas EPA and DHA are of animal origin forms that are primarily found in marine foods—specifically fish, shellfish, and crustaceans—and beef from grass-fed cattle. Alpha linolenic acid is considered to be an essential fatty acid (EFA), though there are no known metabolic functions for which it is uniquely required.

In recent years, nutritional properties of a fourth member of the family, *docosapentaenoic acid* (DPA), have emerged. This omega-3 fatty acid has long been known to be a component of fish oils that contain EPA and DHA, but because there has been no DPA-concentrated oil until recently, it was not well studied. A fifth member of the family, *stearidonic acid* (SDA), recently has been developed for human use because of availability in an SDA-enriched soy oil.

Essential fatty acids are fatty acids that humans and other animals must consume because the body requires them for good health and cannot synthesize them. Linoleic acid (*omega-6 fatty acid*) and ALA (omega-3 fatty acid) are the two EFAs. These acids are necessary for skin integrity and serve as precursors for physiologically important eicosanoids.

Although the main food omega-3 fatty acids are ALA, EPA, and DHA, from time to time there has been an emphasis on developing foods and oils with omega-3 fatty acids other than these three principal fatty acids. The introduction of oil from soybeans modified to contain high amounts of SDA was promoted a few years ago. Stearidonic acid is a more efficient precursor for EPA than is ALA because it bypasses the first biochemical step in humans, that is, the introduction of a double bond into the 6–7 position in the fatty acid molecule that is thought to be a bottleneck, or rate-limiting step, in the synthesis of EPA. A large body of convincing data, however, shows that no amount of EPA or SDA can increase circulating DHA concentrations, making DHA the omega-3 fatty acid most vulnerable to metabolic deficiency. Normally, SDA is at trace amounts in foods, and there is no known direct function for it in humans. A basic understand-

Table 2.1. Nomenclature of omega-3 fatty acids

Carbon Number	Double Bonds	Common Name	Abbreviation(s)
16	3	Hexadecatrienoic acid	16:3omega-3, 16:3ω3[a], or 16:3n-3
18	3	Alpha-linolenic acid	18:3omega-3, 18:3ω3, or 18:3n-3 ALA, ALnA, or aLNA
18	4	Stearidonic acid	18:4omega-3, 18:4ω3, or 18:4n-3 SDA
20	4	Eicosatetraenoic acid	20:4omega-3, 20:4ω3, or 20:4n-3
20	5	Eicosapentaenoic acid	20:5omega-3, 20:5ω3, or 20:5n-3 EPA
22	5	Docosapentaenoic acid	22:5omega-3, 22:5ω3, or 22:5n-3 DPA or DPAω3
22	6	Docosahexaenoic acid	22:6omega-3, 22:6ω-3, or 22:6n-3 DHA

[a] ω = omega

ing of the relationships between the omega-3 fatty acids is thus necessary to appreciate the various omega-3 fatty acids of relevance to foods now and in the future.

The key feature of the omega-3 fatty acids is that a part of their structure designated by the omega-3 can be made only by plants and lower animals but not by mammals or birds. They are modified by human metabolism according to a specific pattern that is now understood in a number of respects. Table 2.1 shows seven omega-3 fatty acids of importance in foods and/or in mammalian metabolism. They are arranged in order of increasing carbon chain length and increasing number of double bonds, which is also the order in which they are synthesized by humans. See Table 2.2 for omega-3 fatty acid key points.

Alpha-linolenic acid is often referred to as the parent omega-3 fatty acid. It was identified as the key plant food omega-3 fatty acid via studies in rodents and other small animals in the 1960s. It is now known that ALA can be synthesized in humans from a minor omega-3 fatty acid hexadecatrienoic acid that is found at trace levels in leafy greens such as spinach (Cunnane et al. 1995). This conversion is not recognized as providing significant amounts of omega-3 fatty acid; however, in vegan diets rich in leafy greens it may become a significant source.

Table 2.2. Omega-3 fatty acid key points

ALA is
- The major plant-based omega-3 fatty acid in the food supply
- Called an EFA but is required only as a precursor for long-chain PUFAs, primarily EPA and DHA, although conversion to DHA appears to be limited in humans
- Rich in a few seed oils

EPA and DHA are
- The major marine and animal-based omega-3 fatty acids
- Long-chain PUFAs
- Required in human tissue for numerous metabolic functions, including structural components for neural tissue and signaling molecules for inflammatory processes
- Very low in farmed meat (beef, pork, chicken) and lower than they would otherwise be in farmed fish because of intentional feeding practices
- Predominantly synthesized on a global basis by marine microorganisms

Minor omega-3 fatty acids may be important for food and agriculture because
- SDA soy oil was developed as a more efficient precursor for EPA than ALA; there is clear evidence that it is not an efficient precursor for DHA
- Terrestrial plants do make some omega-3 fatty acids, especially bryophytes such as fiddleheads, which are eaten by humans

Interconversion of Omega-3 Fatty Acids

Omega-3 fatty acids are metabolically connected via an alternating series of desaturations and elongations that insert double bonds into the carbon chain and elongate the chain in two carbon units, respectively. The process is depicted in Figure 2.1.

The conversion of ALA to long-chain PUFAs (e.g., EPA and DHA) is widely regarded to be inefficient as determined by studies that supplement ALA and looked at blood levels of long-chain PUFAs (Brenna et al. 2009) and by isotopic tracer studies (Brenna 2002). Notably, these studies have all been done with participants consuming western diets known to be rich in LA.

Animal studies show unequivocally that diets high in LA make conversion of ALA to long-chain PUFAs inefficient because of competition (Holman 1998), and in this sense LA is an antagonist to omega-3 metabolism. This competition is normally discussed in terms of omega-6 to omega-3 "ratio," mathematically interpreted as depending on the

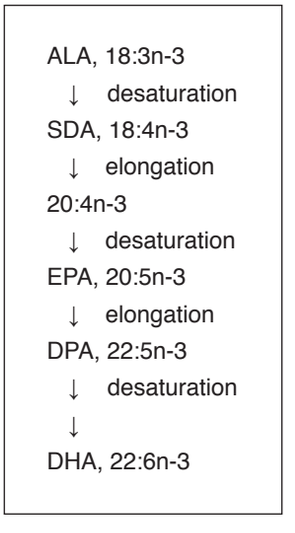

Figure 2.1. Pathway of desaturations and elongations for synthesis of DHA from ALA. (The conversion of DPA to DHA involves one or several reactions and thus is denoted by two arrows.)

concentrations of omega-6 per unit of omega-3, or the reciprocal. The original concept of ratio, however, was developed using only ALA and LA, and it implies that an increase of ALA would moderate the ratio and improve conversion. Whereas this occurs for conversion to EPA, many studies show only limited conversion to DHA (Baker et al. 2016). Good evidence shows that the total amount of dietary LA suppresses ALA conversion to long-chain PUFAs, as illustrated in a recent comprehensive study (Gibson et al. 2013). In particular, no amount of supplemental dietary ALA raises DHA in human blood pools, but lowering LA does increase DHA (Brenna 2011). These observations demonstrate that it is not the omega-6 to omega-3 ratio, but LA concentrations themselves independent of ALA that overwhelm omega-3 conversion to long-chain PUFAs.

Dietary LA concentrations more than tripled in the 20th century with the widespread adoption of seed oils rich in LA and poor in ALA (Blasbalg et al. 2011). Experimental animal studies also show that lower LA concentrations than common in western diets dominated by commodity soy oil cause substantial increases in tissue DHA. A limited number of recent human studies with high oleic oils shows that DHA rises by lowering LA (Taha et al. 2014). This finding was linked causally to reduction in time per day of severe headache (Ramsden et al. 2013), possibly linked to decreased production of pro-pain LA-derived signaling molecules and increased production of anti-pain omega-3-based signalling (Ramsden, Ringel, et al. 2016) molecules.

In contrast to ALA intake, dietary consumption of EPA and DHA sharply increases their respective statuses (Brenna et al. 2009). With respect to the current western food system, ALA consumption without EPA+DHA supports minimal omega-3 status to avoid frank deficiency and development within the normal range. Consumption of preformed EPA+DHA is far more effective as support for the most active metabolic functions of omega-3 fatty acids. As shown elsewhere in this report, preformed EPA+DHA consumption is associated with optimal function and reduction of chronic disease via mechanisms that are either now well known or are under active study.

An important development in recent years is the widespread introduction of high oleic oils derived from traditional breeding methods. High oleic oils are typically low in LA, as in the instance of high oleic safflower and soy oils. These oils closely resemble olive oil in their fatty acid profiles and are therefore expected to be much less antagonistic to production and tissue incorporation of EPA and DHA. High oleic oils have longer shelf lives and improved frying properties, thereby being very attractive for the food system, including restaurants and other establishments providing prepared meals. Thus, for nutritional and food system reasons, high oleic oils are highly desirable and are expanding into the market rapidly.

3 Traditional Dietary Sources of Omega-3 Fatty Acids

Alpha-linolenic acid is quantitatively by far the most important plant omega-3 fatty acid. As an approximate rule, ALA is richer in the leaves of plants than in the seeds. Alpha-linolenic acid is the predominant PUFA in leafy vegetables such as cabbage, brussels sprouts, spinach, and lettuce. Because leafy foods are not rich in fat, however, they carry relatively small amounts of ALA in total.

Alpha-linolenic acid is present in a limited number of seed oils, notably flax (also known as linseed), canola, and soy oils; of these, ALA is the predominant fatty acid only in flax. It is present at negligible concentrations in other common food oilseeds, such as maize, safflower, and sunflower, and is low in the main fruit oils, olive and palm. Alpha-linolenic acid is also negligible in peanuts and nuts with the notable exception of walnuts, which contain significant concentrations. It is also present in specialty oils such as hemp oil and perilla oil, the latter of which is more readily available outside the United States.

At present, the foods richest in EPA and DHA are fish and shellfish. The amounts of EPA and DHA vary widely in these marine sources, both in total amount and in the relative amounts of EPA and DHA. Wild freshwater fish have substantial amounts of EPA and DHA (Wang et al. 2016), though lean white farmed fish such as catfish have low total amounts of EPA and DHA because of feeding of high LA grains, as do some wild marine fish (e.g., orange roughy) and crustaceans (e.g., shrimp, lobster). Oily fish, particularly salmon, mackerel, and herring, are rich sources of EPA and DHA. Oysters and clams vary widely in their relative amounts of EPA and DHA.

A pervasive misconception is that the EPA and DHA content of wild fish is substantially different than that of farmed (or cultured) fish. The fatty acid profiles depend on the feeds and farming practices for the specific fish species. Some farmed species—e.g., salmon—are produced with high EPA+DHA feeds and have higher total EPA+DHA than do wild caught fish, though they also have much higher fat levels (Cladis et al. 2014).

The meat of marine mammals, including seal, walrus, and whale, is also rich in EPA and DHA, as well as DPA. With the exception of Alaskan natives, these meats are consumed by some coastal populations primarily outside the United States.

Ruminant meats and dairy foods are naturally low in PUFAs, particularly omega-3 fatty acids. Polyunsaturated fatty acids in the cow's diet are toxic to rumen bacteria. Rumen bacteria secrete enzymes that saturate double bonds of PUFAs, producing saturated fatty acids (SFAs), such as stearic acid, which are then absorbed from the small intestine and incorporated into tissues. Pasture-fed cattle have higher amounts of omega-3 fatty acids, though the total remains low.

Because of the large amount of beef consumed in western countries, variation in EPA and DHA in beef can translate into significant differences in total EPA and DHA intake (Ponnampalam, Mann, and Sinclair 2006). Milk, however, has only trace amounts of DHA and is low in EPA; these concentrations are not significantly modulated by feeding practice (O'Donnell-Megaro, Barbano, and Bauman 2011). Enrichment of milk with DHA can be achieved by administering DHA that is protected from ruminal biohydrogenation by proprietary means, and such milk is widely available in Ontario, Canada. We are not aware of similar products in the United States, though some milks are fortified with DHA. Consumption of foods from nonruminant animals such as eggs, poultry, and pork offer greater possibilities to increase the omega-3 fatty acid content of the human diet because agricultural practices can be used to produce eggs, poultry, and pork with greater concentrations of omega-3 fatty acids (Gonzalez-Esquerra and Leeson 2001). Methods to effect these changes are described later.

Edible oils are a key source of dietary PUFAs and vary widely in their composition. Table 3.1 shows the fatty-acid composition of many of the major oils in the U.S. food supply (Aladedunye and Przybylski 2013; Butzen and Schnebly 2007; Firestone 1999). The fats noted in the table are listed according to the predominant type of fatty acid present. Those edible fats rich in SFAs are essentially devoid of omega-3 fatty acids. Next is a group of edible fats that are rich in PUFAs, LA being the major one. These fats too are devoid of omega-3 fatty acids. The third group is those edible fats that are rich in ALA, which is an omega-3 fatty acid and one that can be metabolically converted to EPA and/or DHA by the consumer (Brenna 2002). Lipids of flaxseed contain approximately 50% ALA. The fourth group of fats are those that are relatively rich in oleic acid, a monounsaturated fatty acid. These fats contain low concentrations of omega-3 fatty acids. Oils rich in mono-unsaturated fatty acid used in the United States are olive and, to a limited degree, avocado. New high oleic varieties of oils that are now in the marketplace have compositions that closely resemble olive and are expected to have neutral, rather than antagonistic, effects on PUFA metabolism, especially omega-3 fatty acids.

Besides including seafood in the human diet to increase intake of omega-3 fatty acids, flaxseed oil, meal, or seeds and other linolenic acid-rich oils can be used to supplement the human diet with omega-3 fatty acids.

Table 3.1. Fatty acid composition of edible fats and oils

	SFA (Saturated Fatty Acid)[a]				MUFA (Monounsaturated Fatty Acid)[b]	PUFA (Polyunsaturated Fatty Acid)		Totals		
Fats rich in:	10:0+12:0	14:0	16:0	18:0	18:1ω[b]9	18:2ω6	18:3ω3	SFA	MUFA	PUFA
SFA										
Coconut	54	19	9	3	6	2	0	85	6	2
Palm Kernel	52	16	8	3	15	2	0	79	15	2
Palm	--	1	44	5	40	9	0	50	40	9
Cocoa	--	--	26	34	33	3	0	60	33	3
Butterfat (cow)	6	11	27	12	29	2	0	56	29	2
Beef Tallow	--	3	24	19	43	3	1	46	43	4
Lard (pork fat)	--	2	26	14	44	10	0	42	44	10
						Mean ± Standard Deviation		60±16	30±15	5±3
PUFA (Linoleic)										
Peanut	--	--	11	3	52	28	0	14	52	28
Sesame	--	--	9	5	39	45	0	14	39	45
Safflower (commodity)	--	--	7	2	19	75	0	9	19	75
Cottonseed	--	1	24	3	18	52	0	28	18	52
Sunflower (commodity)	--	--	7	5	26	61	0	12	26	61
Corn	--	--	13	2	31	53	1	15	31	54
Rice Bran	--	0.5	22	3	43	21	1	26	43	22
						Mean ± Standard Deviation		17±7	33±13	48±18
PUFA (Alpha-linolenic)										
Flaxseed (linseed)	--	--	6	3	20	17	53	9	20	70
Canola (rapeseed)	--	--	3	2	60	20	10	5	60	30
Soy (commodity)	--	--	11	4	23	54	7	15	23	61
Walnut	--	--	7	2	18	58	14	9	18	72
						Mean ± Standard Deviation		10±4	30±20	58±19
MUFA										
Olive	--	--	13	3	71	10	1	16	71	11
Avocado	--	--	14	--	65 (16:1, 6)	13	1	14	71	14
Sunflower (high oleic)	--	--	4.7	3.7	79	9.5	0.4	15	79	10
Soy (high oleic)	--	--	11	4	75	<9	3	15	75	<12
Peanut (high oleic)	--	--	7	3	76	4	0	10	76	4
						Mean ± Standard Deviation		14±2	74±3	10±4

[a]Expressed as percent fatty acid, weight-for-weight (%, w/w).

[b]ω=omega.

4 Biological Significance of Omega-3 Fatty Acids

Omega-3 fatty acids are among the most studied compounds in biomedicine, from molecular biology and human genetics to food production. A 2017 Pubmed search on "omega-3 fatty acids" yielded more than 24,000 citations, of which 4,300 are reviews. Omega-3 fatty acids are ubiquitous throughout body tissues where they function in structure and signaling. Studies on omega-3 fatty acids are normally focused on EPA and DHA specifically, and in studies, as well as in food, they are usually but not always administered together.

More studies have been conducted on omega-3 long-chain PUFA effects on neural tissue and on cardiovascular health than other outcomes. Their concentration is highest in the retina and brain, where they are associated with more rapid development during the perinatal period. In most other tissues, they are responsible for modulating inflammation and, most notably, reducing its intensity and enhancing its resolution. They accomplish this biological effect via conversion to oxygenated metabolites known as eicosanoids and docosanoids that act both local to their site of synthesis and systemically.

Omega-3 fatty acids are relevant to humans throughout the life cycle. Specific periods such as infancy, pregnancy, and aging seem to be vulnerable to low omega-3 fatty acid intake and status. Humans are sensitive to omega-3 fatty acid deficiency starting in fetal life. Scores of studies show that animals deprived of omega-3 fatty acids through gestation and lactation exhibit abnormalities in neurotransmitter levels, catecholamines, and signaling compounds compared to animals with a supply of omega-3 fatty acids. These diets consistently induce functional deficits in electroretinograms, reflex responses, reward- or avoidance-induced learning, maze learning, behavior, and motor development compared to omega-3 fatty acid replete groups (Brenna 2011). Studies show that DHA in the diets of human infants improves visual and cognitive development (Milte et al. 2012).

Recommendations to substitute fatty acid for SFA-rich fat have long been made for heart health. A reevaluation of human studies in support of that recommendation suggests that fatty acid effects on lowering risk of heart disease may be omega-3 fatty acid related (Ramsden, Hibbeln, and Majchrzak-Hong 2011; Ramsden et al. 2011, Ramsden, Zamora, et al. 2016). A 2014 meta-analysis of prospective cohort studies shows that intake and circulating EPA and DHA are independently protective for cardiovascular disease while providing no evidence that SFA, LA, or ALA are related to coronary heart disease (Chowdhury et al. 2014). A 2017 statement of the American Heart Association clarified that a shift from saturated to unsaturated fats is cardioprotective but not replacement of saturated fats with carbohydrates, and it emphasized an overall healthy dietary pattern (Sacks et al. 2017).

5 Cardiovascular Disease, Cancer, Inflammation, and the Brain

Introduction

Evidence for a role of long-chain omega-3 fatty acids (EPA and DHA) in human health originates in preclinical and clinical studies showing composition of tissue or specific functions such as clotting or inflammatory function. Medical data specifically on health or disease outcomes come from two different experimental approaches, one observational and the other interventional. The first of these is studies of the association between omega-3 fatty acid intake from the diet or omega-3 fatty acid concentration in a specific body pool (e.g., blood plasma, serum, or red blood cells) and biomarkers or clinical markers of disease risk or a disease manifestation. Such studies can involve comparisons between populations or subpopulations (called ecological studies; e.g., comparison between populations in Greenland and Denmark or between Japanese living in Japan and in the United States), comparisons between individuals with disease and those without (called case-control studies), or the tracking of a group of individuals over time to identify the likelihood of emergence of disease (called prospective cohort studies). Such studies typically involve long-term exposure to omega-3 fatty acids and often include large numbers of individuals.

The experimental approach (intervention) is the clinical trial, where individuals consume an increased amount of omega-3 fatty acids for a period of time and the effect on disease risk factors, disease manifestations, or disease occurrence is monitored. Such studies are typically relatively short and often involve relatively small numbers of individuals. A clinical trial is more robust if there is a control (placebo) group, allocation to the control or the omega-3 fatty acid group is random, and the participants and the researchers are "blind" to the group to which each participant is allocated. This design is termed a randomized controlled trial (RCT), and this design is considered to provide the highest level of experimental evidence available from a single study. Experimental results from several association studies or RCTs can be aggregated in meta-analyses that consequently include large numbers of participants and have great statistical power to identify effects. Meta-analyses also are regarded as a high level of medical evidence because they aggregate results of multiple studies, though they are commonly criticized for combining studies that are not similar in their details.

Omega-3 Fatty Acids and Cardiovascular Disease

Cardiovascular disease (CVD) includes heart disease, cerebrovascular disease, and peripheral vascular disease. Cardiovascular disease is a major source of morbidity (illness) and mortality and carries immense personal, societal, economic, and health care costs. The major causes of death as a result of CVD are myocardial infarction (MI; heart attack) and stroke. Heart disease is the number one cause of death in the United States, accounting for almost 600,000 deaths in 2010, with stroke being the number four cause of death, accounting for almost 130,000 deaths in 2010. Approximately one in three deaths among Americans each year is a result of CVD.

Native populations in Greenland, northern Canada, and Alaska consuming their traditional diet had much lower rates of death from CVD than predicted, despite their high dietary fat intake (Bjerregaard and Dyerberg 1988; Dyerberg et al. 1978; Kromann and Green 1980; Newman et al. 1993). Typically, the rate of mortality was less than 10% of that predicted. The protective component was suggested to be the omega-3 fatty acids consumed in very high amounts as a result of the regular intake of seal and whale meat, whale blubber, and oily fish (Bang, Dyerberg, and Hjorne 1976). Japanese consuming a traditional diet also exhibit a low cardiovascular mortality (Yano et al. 1988), and this diet is rich in seafood, including oily fish and sometimes marine mammals, which contain significant amounts of EPA and DHA. Substantial evidence from prospective and case-control studies has now accumulated indicating that consumption of omega-3 fatty acids decreases the risk of CVD outcomes in western populations, although not all studies agree. These studies have been summarized and discussed in detail elsewhere (Calder 2004; Kris-Etherton, Harris, and Appel 2002; London et al. 2007; von Schacky 2004; Wang et al. 2006).

The protective effect of omega-3 fatty acids toward CVD development most likely relates to beneficial modification of a broad range of risk factors. These include plasma triacylglycerol concentrations, blood pressure, and inflammation, which are all lowered by omega-3 fatty acids (Calder 2004; De Caterina 2011; Harris 1996; Kris-Etherton, Harris, and Appel 2002; Saravanan et al. 2010). The healthier risk factor profile would result in improved blood flow and lessened

Table 5.1. Factors involved in cardiovascular risk affected by omega-3 fatty acids

Factor	Effect of Omega-3 Fatty Acids
Plasma triacylglycerol concentration (fasting and postprandial)	↓
Production of chemoattractants	↓
Production of growth factors	↓
Cell surface expression of adhesion molecules	↓
Production of inflammatory eicosanoids and cytokines	↓
Blood pressure	↓
Endothelial relaxation	↑
Thrombosis	↓
Cardiac arrhythmias	-/↓
Heart-rate variability	↑
Atherosclerotic plaque stability	↑

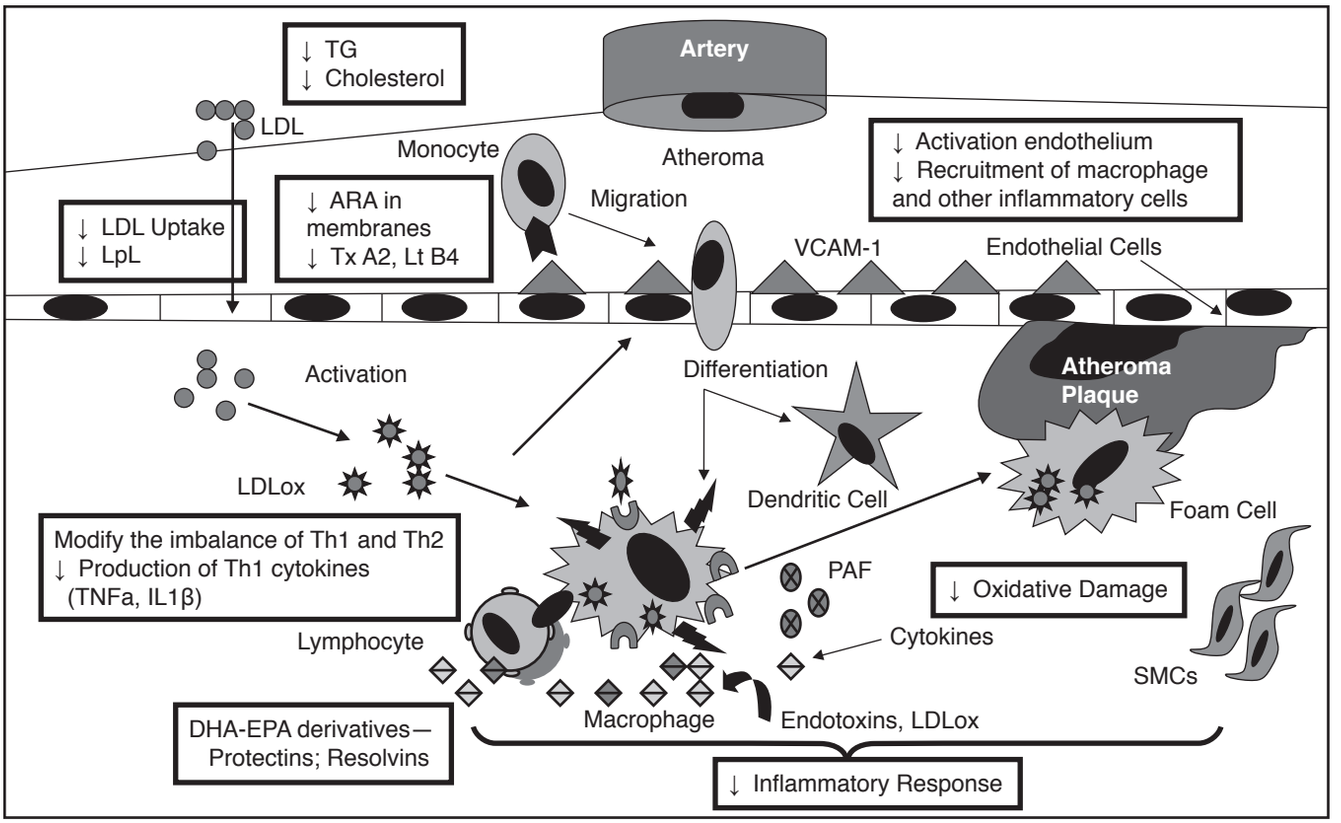

Figure 5.1. Roles of EPA and DHA in preventing atherogenesis (Deckelbaum and Torrejon 2012; permission from the American Society for Nutrition).

Key: Boxes show the mechanisms of action where EPA and DHA may decrease the development of atherosclerosis.

LDLox—oxidized low-density lipoprotein; LpL—lipoprotein lipase; Lt—leukotriene; PAF—platelet activating factor; SMC—smooth muscle cell; TG—triglyceride; Th—T helper cell; Tx—thromboxane; VCAM-1—vascular cell adhesion molecule 1.

build-up of fatty deposits (plaques) within the blood vessel wall—this build-up is termed atherosclerosis. The effect of omega-3 fatty acids on cardiovascular risk factors is summarized in Table 5.1 and Figure 5.1.

Although improvement of the risk factor profile lowers the risk of developing CVD, a small number of studies has examined the effect of providing omega-3 fatty acids to patients with existing CVD. The outcome in these studies has most often been the occurrence of a major cardiovascular event (e.g., MI), including one that was fatal. Several studies published between 1989 and 2008 reported lower rates of death in patients receiving omega-3 fatty acids (Burr et al. 1989; GISSI-HF Investigators et al. 2008; GISSI-Prevenzione Investigators 1999; Marchioli et al. 2002; Yokoyama et al. 2007). Doses used in these studies were 500–900 mg EPA+DHA/day for 2 years (Burr et al. 1989); 885 milligram (mg) EPA+DHA/day for 1 (Marchioli et al. 2002), 3.5 (GISSI-Prevenzione Investigators 1999), or 3.9 (GISSI-HF Investigators et al. 2008) years; and 1.8 gram (g) EPA/day for 5 years (Yokoyama et al. 2007). As a result of these positive findings, several meta-analyses supported that omega-3 fatty acids result in lower mortality in patients with existing CVD (Bucher et al. 2002; Leon et al. 2009; Studer et al. 2005). It is probable that the mechanisms that lessen the likelihood of cardiovascular events and mortality in patients with established disease are different from the mechanisms that act to slow the development of atherosclerosis.

Three key mechanisms have been suggested to contribute to the therapeutic effect of omega-3 fatty acids. The first is altered cardiac electrophysiology seen as lower heart rate (Harris, Miller, et al. 2008), increased heart rate variability (Xin, Wei, and Li 2013), and fewer arrhythmias (Leaf and Xiao 2001). These effects make the heart more able to respond robustly to stress. The second is an anti-thrombotic action resulting from the altered pattern of production of chemical mediators that control platelet aggregation from *arachidonic acid* (ARA) and from EPA (von Schacky, Fisher, and Weber 1985). This effect would lower the likelihood of clot formation or would result in weaker clots less able to stop blood flow to affected organs. The third mechanism is the well-documented anti-inflammatory effect of omega-3 fatty acids, which would serve to stabilize atherosclerotic plaques, preventing their rupture (Cawood et al. 2010; Thies et al. 2003). This effect decreases the likelihood of a cardiovascular event (MI, stroke).

Despite the positive findings with omega-3 fatty acids, supported by meta-analyses and biologically plausible candidate mechanisms, a series of recent studies has failed to replicate the earlier findings (Galan et al. 2010; Kromhout, Giltay, and Geleijnse 2010; Rauch et al. 2010; Risk and Prevention Study Collaborative Group et al. 2013), and this has influenced the most recent meta-analyses that have concluded that there is little protective effect of omega-3 fatty acids on cardiovascular mortality (Kotwal et al. 2012; Kwak et al. 2012; Rizos et al. 2012). The most recent studies, however, have been criticized for various reasons related to small sample size (i.e., too few patients being studied), the low dose of omega-3 fatty acids used, and the too-short duration of follow-up (Calder and Yaqoob 2012).

Thus, there is significant literature gathered over more than 45 years—from association studies, from RCTs investigating the impact on risk factors, and from RCTs investigating the effect on hard clinical outcomes like mortality—that omega-3 fatty acids lower the risk of developing CVD and can be used successfully to treat people with CVD. Although the most recent RCTs in patients with CVD have produced findings that do not agree with the previously accumulated literature, it is too soon to discard the earlier evidence. The conclusion that omega-3 fatty acids have a role in decreasing CVD risk remains well supported (Calder 2017).

Omega-3 Fatty Acids and Cancer

Cancer is a major source of morbidity and mortality and carries immense personal, societal, economic, and health care costs. Cancer is the number two cause of mortality in the United States, accounting for approximately 575,000 deaths in 2010. More than one in four deaths among Americans each year is a result of cancer.

When taken orally, EPA and DHA are incorporated into blood lipids and into cell membranes, including those of tumor tissue. They exert a range of biological activities and influence cell membrane structure and function, cell signaling, gene expression, generation of lipid mediators, and oxidative stress. For example, DHA can promote tumor cell apoptosis, possibly through inducing oxidative stress. Eicosapentaenoic acid and DHA also replace the omega-6 fatty acid ARA in cell membranes, resulting in less production of mediators such as prostaglandin E_2, that drive tumor growth. Through these effects, EPA and DHA can directly influence cancer cells and the tumor environment and they can influence the host response to tumor bearing.

Anti-inflammatory actions of omega-3 fatty acids may also be important in preventing or slowing some steps in tumor initiation, particularly in some cancers such as colorectal cancer. Recent reviews provide excellent in-depth analysis of the mechanisms by which omega-3 fatty acids affect tumor cell proliferation, invasion, and metastasis (Gleissman, Johnsen, and Kogner 2010; Merendino et al. 2013); the ability of omega-3 fatty acids to enhance the effectiveness of anti-cancer treatments (Merendino et al. 2013; Murphy, Mourtzakis, and Mazurak 2012; Vaughan, Hassing, and Lewandowski 2013); and the current evidence of the efficacy

of omega-3 fatty acids in humans in the context of cancer and its treatment (Murphy, Mourtzakis, and Mazurak 2012; Vaughan, Hassing, and Lewandowski 2013).

The concentrations of omega-3 fatty acids are reported to be lower in some cancer patients than in controls, probably because of both dietary changes and altered metabolism (Murphy, Mourtzakis, and Mazurak 2012). Some prospective and case-control studies suggest that omega-3 fatty acids lower risk of colorectal, prostate, and breast cancers, but there is significant inconsistency in the findings from such studies (Gerber 2012). A recent systematic review concluded that omega-3 fatty acids are protective against breast cancer (Makarem et al. 2013).

In addition to effects that lower the risk of developing cancer, there seems to be a role for omega-3 fatty acids in patients with existing cancer. For example, quality of life and physical functioning can be improved in cancer patients with omega-3 fatty acids. A systematic review published by Elia and colleagues (2006) concluded that lung cancer patients receiving supplements containing EPA and DHA had improved appetite, energy intake, body weight, and quality of life. Alfano and colleagues (2012) reported lower inflammation and less physical fatigue in breast cancer patients with a higher concentration of omega-3 fatty acids in their bloodstream than in patients with a lower concentration. Cerchietti, Navigante, and Castro (2007) reported that lung cancer patients given 1.8 g EPA+DHA/day had improved appetite and less fatigue than did controls. Van der Meij and colleagues (2012) reported that 2.9 g EPA+DHA/day improved quality of life, physical function, cognitive function, and health status in patients with nonsmall-cell lung cancer. The patients receiving omega-3 fatty acids also tended to have higher physical activity compared with the control group.

Both EPA and DHA sensitize cultured tumor cells to chemotherapeutic agents, increasing the efficacy of those agents. The mechanism by which this sensitization occurs is not clear, but it might involve increased omega-3 fatty acid content of tumor cell membranes, resulting in increased lipid peroxidation in those membranes in the presence of the cancer therapeutic. This membrane change would result in improved efficacy of the therapy and perhaps lessened side effects. Murphy and colleagues (2011a) conducted a trial in patients with nonsmall-cell lung cancer and showed that 2.5 g EPA+DHA/day caused a twofold increase in response rate to the chemotherapy being used and prolonged the period over which patients could receive the chemotherapy. They also reported a trend toward improved survival with omega-3 fatty acids. Bougnoux and colleagues (2009) reported improved chemotherapy outcomes with 1.8 g DHA/day in breast cancer patients.

Cancer cachexia (loss of lean and fat tissue) is a complication that occurs in patients with advanced solid tumors; it greatly increases risk of mortality. Many of the factors involved in inducing and sustaining cachexia are targets for omega-3 fatty acids. Weed and colleagues (2011) reported that patients with squamous cell cancer of the head and neck taking 3.08 g EPA+DHA/day had increased lean body mass. Murphy and colleagues (2011b) conducted a trial in patients with nonsmall-cell lung cancer and showed that 2.2 g EPA+DHA/day was able to maintain body weight and muscle mass during chemotherapy. In other studies, omega-3 fatty acids increased body weight in cancer patients (Fearon et al. 2006; Guarcello et al. 2007).

Thus, there is considerable recent evidence from studies in humans, including a number of intervention trials, that omega-3 fatty acids have a range of benefits in patients with various types of cancer. Most intervention studies have used approximately 2 g EPA+DHA/day in cancer patients to demonstrate benefits. From their review of the literature, Vaughan, Hassing, and Lewandowski (2013) concluded that "there is now sufficient literature to suggest that the use of supplements containing EPA and DHA may have potential use as an effective adjuvant to chemotherapy treatment and may help ameliorate some of the secondary complications associated with cancer. Although this review was not exhaustive, our investigations indicate that supplementation with fish oil or EPA/DHA (> 1 g EPA and > 0.8 g DHA/day) is associated with positive clinical outcomes."

Omega-3 Fatty Acids and Inflammation

Inflammation is a key component of normal host defense mechanisms initiating the immune response and later playing a role in tissue repair. The inflammatory response is normally self-limiting to protect the host from damage. Of the fatty acids studied, omega-3 fatty acids seem to possess the most potent effects on the immune system and its inflammatory component (Calder 2011, 2013a,b). When continuously exposed to an inflammatory trigger, the loss of the normal mechanisms inducing tolerance or loss of resolving factors can allow inflammation to become chronic and in this state the damage done to host tissues may become pathological (Calder et al. 2009, 2013). As such, inflammation is the central adverse response seen in a range of inflammatory conditions, including rheumatoid arthritis (RA), inflammatory bowel diseases (IBDs), asthma, psoriasis, and atopic dermatitis (Calder et al. 2009, 2013). Furthermore, chronic low-grade inflammation is now recognized to be a contributor to CVD (Hansson and Hermansson 2011; Ross 1999) and to play a role in cardiometabolic diseases like obesity, type-2 diabetes, and nonalcoholic fatty liver disease (Calder et al. 2011).

The key link between fatty acids and inflammatory processes is that the omega-6 fatty acid ARA is the precursor for the production of a family of chemical mediators called eicosanoids, which are intimately involved in inflammation (Lewis, Austen, and Soberman 1990; Tilley, Coffman, and Koller 2001). Among these are the prostaglandins D_2 and E_2 formed by the cyclooxygenase pathway and the 4-series leukotrienes formed by the lipoxygenase pathways. Arachidonic acid metabolism is a long-recognized target for the pharmaceutical industry.

In contrast to the effects of ARA, the omega-3 fatty acids EPA and DHA give rise to mediators that are less proinflammatory, anti-inflammatory, or inflammation resolving (Calder 2011, 2013a,b). For example, the prostaglandins and leukotrienes produced from EPA are only weakly inflammatory, whereas in the last ten years new families of lipid mediators produced from the omega-3 fatty acids (both EPA and DHA) that play a role in resolving ("turning off") inflammation have been discovered. These mediators are called resolvins (produced from both EPA and DHA) and protectins and maresins (produced from DHA) (Serhan, Chiang, and van Dyke 2008; Serhan et al. 2002).

In addition to their effects on lipid mediators (prostaglandins, leukotrienes, resolvins, protectins, maresins), EPA and DHA influence several other aspects of inflammatory processes (Calder 2011, 2013a,b). These effects also seem to involve incorporation of EPA and DHA into the membranes of inflammatory cells from where they influence cell signaling and gene expression (Calder 2011, 2013a,b).

There is robust evidence that EPA and DHA given in combination at sufficient doses are anti-inflammatory. As a result they are suggested to have a therapeutic role in inflammatory diseases. This anti-inflammatory effect has been most widely studied in RA (Miles and Calder 2012), IBD (Calder 2009), and asthma (Calder 2006). Evidence of efficacy is strongest in RA, although high doses (up to 7 g/day of EPA+DHA) typically are used (Miles and Calder 2012).

One question of significant current interest is whether or not increased intake of omega-3 fatty acids by pregnant and breast-feeding women will lessen the risk of allergic disease in their babies (Calder 2013c; Calder, Kremmyda, et al. 2010). During pregnancy, omega-3 fatty acids are efficiently transferred from the mother to her fetus (Haggarty 2010), with the amount transferred being directly related to the mother's intake (Swanson, Block, and Mousa 2012). There is some evidence that increased intake of EPA and DHA during human pregnancy has an effect on the immune system of the baby (Dunstan et al. 2003a,b; Noakes et al. 2012) and that this effect may decrease allergic symptoms later in life (Calder 2013c; Calder, Kremmyda, et al. 2010; Dunstan et al. 2003b; Furuhjelm et al. 2009; Palmer et al. 2012). A recent study reported that fish oil consumption by pregnant women decreased risk of persistent wheeze and asthma in the offspring at ages three to five years (Bisgaard et al. 2016). Supplementing the diets of very young infants also has immune effects consistent with decreased likelihood of allergy (D'Vaz et al. 2012). This area of research has been reviewed recently (Miles and Calder 2017).

Thus, the anti-inflammatory actions of omega-3 fatty acids are extensively demonstrated, and the underlying mechanisms are increasingly understood (Calder 2015). High doses of omega-3 fatty acids can be used to treat frank inflammatory conditions, whereas lower doses likely have a role in protecting against low-grade inflammatory conditions.

Omega-3 Fatty Acids and the Brain

More than 50% of the dry weight of the brain is lipid, particularly structural lipid (i.e., phospholipids). The human brain and retina contain an especially high proportion of DHA relative to other tissues, but little EPA. Grey matter phosphatidylethanolamine contains 24% of its fatty acids as DHA, whereas grey matter phosphatidylserine contains 37% of its fatty acids as DHA. Docosahexaenoic acid contributes 50 to 70% of the fatty acids present in the rod outer segments of the retina. These rod outer segments contain the eyes' photoreceptors. Cellular DHA is important for neurotransmission, neuronal membrane stability, neuroplasticity, and signal transduction (Salem et al. 2001). The EPA that is present is likely to play a role in immunity and inflammation (Farooqui, Ong, and Horrocks 2006).

The human brain growth spurt occurs from approximately the beginning of the third trimester of pregnancy to 18 months after birth. The amount of DHA in the brain increases dramatically during the brain growth spurt. In humans, brain weight increases from approximately 100 g at 30 weeks of gestation to near 1,100 g at 18 months of age; during this time, there is a three- to fourfold increase in DHA concentration in the brain and a 35-fold increase to total brain DHA. This DHA is provided by the mother through the placenta during pregnancy and in breast milk after birth. An adequate supply of omega-3 fatty acids, especially DHA, is essential for optimal visual, neural, and behavioral development. Thus, it is important that pregnant and breast-feeding women and infants consuming formula instead of breast milk have adequate intakes of omega-3 fatty acids, especially DHA.

Omega-3 fatty acids have important roles in the brain beyond infancy and indeed may be important for brain function throughout the life course. Children with attention deficit hyperactivity disorder or autistic spectrum disorders have lower concentrations of omega-3 fatty acids in their bloodstream than do control children (LaChance et al. 2016; Rich-

ardson 2004), leading to the suggestion that these and other developmental disorders such as dyslexia and dyspraxia are related to some sort of fatty acid deficiency state. Therefore, normalization of omega-3 fatty acid concentrations might lead to clinical benefit in these conditions. This possibility has been examined in a number of trials, some showing some improvements (Bélanger et al. 2009; Gustafsson et al. 2010; Meguid et al. 2008; Milte et al. 2012; Perera et al. 2012; Richardson and Puri 2002; Sorgi et al. 2007; Stevens et al. 2003; Yui et al. 2012) and others having no effect (Amminger et al. 2007; Bent et al. 2011; Hirayama, Hamazaki, and Terasawa 2004; Johnson et al. 2009; Politi et al. 2008; Raz, Carasso, and Yehuda 2009; Voigt et al. 2001).

Rudin (1981) was the first to suggest that mental disorders might result from a deficiency in omega-3 fatty acids and might respond to provision of these fatty acids. Schizophrenic patients have lower concentrations of omega-3 fatty acids in their red blood cells than do controls (Glen et al. 1994; Peet et al. 1995; Rudin 1981; Yao, van Kammen, and Welker 1994). In a study of nine countries, Hibbeln (1998) demonstrated a significant correlation between high annual fish consumption and lower prevalence of major depression, an observation that is compatible with a proposed protective effect of omega-3 fatty acids. A small study using a very high dose of omega-3 fatty acids (9.6 g/day) reported a reduction in depressive symptoms (Su et al. 2003), whereas a study using a lower dose of DHA alone (2 g/day) did not see this effect (Marangell et al. 2003). Intervention with 6.2 g/day of EPA+DHA for four months in patients with bipolar manic depression resulted in significant improvements in nearly all outcomes, especially with respect to depressive symptoms (Stoll et al. 1999). Likewise, 2 g/day EPA improved symptoms in patients with unipolar depressive disorder after four weeks (Nemets, Stahl, and Belmaker 2002).

The first trial of omega-3 fatty acids in schizophrenia identified clinical improvement with EPA (2 g/day), but not with DHA (Peet et al. 2001), whereas subsequent trials also showed benefit with EPA (Fenton et al. 2001; Peet and Horrobin 2002), although not all studies have seen this (Emsley et al. 2002). Although these findings are encouraging, a Cochrane review concluded that omega-3 fatty acids should be regarded only as an experimental treatment for schizophrenia (Joy, Mumby-Croft, and Joy 2003). One study reported significant benefit from 1 g/day EPA in borderline personality disorder (Zanarini and Frankenburg 2003), whereas two studies report anti-aggressive effects of DHA (Hamazaki et al. 1996, 2002). Many of these studies suggest that EPA is superior to DHA, which may account for discrepancies between study findings.

Sublette and colleagues (2012) analyzed the findings from 15 RCTs investigating the effects of EPA, concluding that supplements containing ≥ 60% EPA in doses ranging from 0.2 to 2.2 g/day EPA, in excess of DHA, were effective against primary depression. There is also evidence from meta-analysis that depressive symptoms seen in bipolar disorder may be improved by the adjunctive use of omega-3 fatty acids (Sarris, Mischoulon, and Schweitzer 2012). In fact, four meta-analyses to date demonstrate that EPA-rich oils decrease symptoms of diagnosed major depression including reduction of perinatal depression (Grosso et al. 2014; Hallahan et al. 2016; Lin et al. 2017; Mocking et al. 2016). Previous studies failing to find evidence of effects of omega-3 fatty acids on depression used weak designs with strong placebo effects, and/or mood-based questionnaires rather than diagnoses by professionals. An initially surprising, though consistent, finding is that EPA-rich supplements are more effective than DHA-rich supplements against major depression, despite the increase in EPA with DHA supplementation. This observation suggests an independent requirement for EPA apart from DHA.

Postmortem studies showed that the brains of Alzheimer's disease sufferers contain less DHA than those without the disease (Cunnane et al. 2012; Prasad et al. 1998; Tully et al. 2003). Some studies have linked low concentrations of omega-3 fatty acids in blood to dementia (Soderberg et al. 1991) and cognitive impairment (Conquer et al. 2000). A Cochrane review of RCTs studying the role of omega-3 fatty acids in preventing cognitive decline in healthy older people, however, showed no benefits (Sydenham, Dangour, and Lim 2012). Sinn and colleagues (2012) reported that 1.8 g of EPA+DHA/day for six months lessened depressive symptoms and improved cognition in adults with mild cognitive impairment. Although Scheltens and colleagues (2012) reported that 1.5 g EPA+DHA/day for six months improved memory performance in subjects with mild Alzheimer's disease, a number of studies using several doses and ratios of EPA and DHA reported no effect on cognitive performance in people with Alzheimer's disease (Boston et al. 2004; Freund-Levi et al. 2006, 2008; Kotani et al. 2006; Quinn et al. 2010).

Thus, DHA is a key structural component of the brain and retina, where it plays particular, unique, functional roles. A supply of DHA is very important early in life, especially during the fetal and early infant periods when the eye and central nervous system are developing. Because the supply must come from maternal sources (via the placenta and breast milk), maternal DHA status is likely to be important in determining eye and brain development early in life. Thus, maintenance of maternal DHA status is the key to optimizing DHA supply to the developing fetus and newborn infant. A lack of omega-3 fatty acids results in poor visual development and in learning and behavioral abnormalities. Newly emerging questions of interest relate to the influence of omega-3 fatty acids on childhood developmental disorders,

adult psychiatric and psychological disorders, and neurodegenerative diseases of aging. These conditions seem associated with a lowered omega-3 fatty acid status.

Conclusions

Eicosapentaenoic acid and DHA have key roles in cell membrane structure and function and regulate cellular responses, including gene expression. Through these effects, EPA and DHA alter the ability of cells, tissues, and organs to respond to physiological and pathological stimuli and stresses in a way that seems to result in improvement in human health. In accordance with this observation, low intake or low status of omega-3 fatty acids is associated with increased risk of CVD and of some cancers, and perhaps of childhood developmental disorders, adult psychiatric and psychological disorders, and neurodegenerative diseases of aging. It is clear that, via effects on a range of risk factors, consumption of omega-3 fatty acids lowers the likelihood of developing CVD and protects against mortality from MI.

These fatty acids also exert anti-inflammatory actions that make them useful as therapeutic agents in diseases with an inflammatory component. They seem very effective at high doses in RA. Omega-3 fatty acids have special roles in the brain and visual systems. There is a very high content of DHA in grey matter of the brain and in the outer segment of the retinal rods of the eye. Docosahexaenoic acid is accumulated into these regions early in life, and a supply from the mother in utero and during the suckling period seems very important in determining optimal DHA accumulation and optimal brain and visual function. Emerging data suggest that omega-3 fatty acids may be beneficial in childhood developmental disorders, adult psychiatric and psychological disorders, and neurodegenerative diseases of aging. Thus, omega-3 fatty acids seem associated with improved health and well-being throughout the life course. Although it is evident that increased intake of these fatty acids should be encouraged in various population groups, it is clear that greater scientific evidence of protective effects is required in a number of conditions.

6 Agricultural and Manufacturing Practices to Increase Omega-3 Fatty Acids in the Human Food Supply

Introduction

The most important change in foods that will enhance omega-3 status is reduction in LA in foods and replacement with oleic acid, as is done with most high-oleic oils. High-oleic oils and foods are more stable to oxidative rancidity than commodity-high LA oils and foods, especially in frying and other high-temperature applications. Moreover, increases in ALA or other omega-3 fatty acids are a huge challenge to the food industry with respect to oxidative stability, decreasing shelf life dramatically. In fact, in large measure the increase in shelf life with low omega-3 fatty acid led to the current minimal omega-3 fatty acid state of the food supply. Additionally, opportunities for high DHA oils in cold applications such as salad dressings are now available with genetically modified oils. A recently described oil has more than 3% DHA in a canola oil base, having transferred the DHA synthetic genes from marine algae to the seed crop (Walsh et al. 2016). Lowering LA or raising DHA in the diet are the only ways to increase circulating DHA in humans (Brenna et al. 2009).

As previously discussed, an abundance of research has established the usefulness of marine-based omega-3 fatty acids, EPA, and DHA, in the prevention and management of chronic disease (Browning 2003; Hooper et al. 2006; Horrocks and Yeo 1999; Lombardo and Chicco 2006; Marik and Varon 2009; McEwen et al. 2010; Pedersen et al. 2010; Rudkowska 2010; Ruiz-Rodriguez, Reglero, and Ibanez 2010; Saravanan et al. 2010; Simopoulos 1999; Whelan and Rust 2006). On the other hand, frequent inconsistencies exist regarding the potential benefits of the shorter-chain (e.g., ALA) versus longer-chain (e.g., EPA and DHA) omega-3 fatty acids.

The amount and ratio of various fatty acids may alter the overall response of an individual to specific omega-3 fatty acids (Burdge and Calder 2005). Although ALA can be metabolically converted to the biologically active omega-3 fatty acids (Arterburn, Hall, and Oken 2006), the efficiency of the enzymatic conversion of ALA to EPA and on to DHA may vary considerably and seems inefficient in many individuals (Arterburn, Hall, and Oken 2006; Baker et al. 2016). For example, the conversion of ALA to the omega-3 fatty acids is greater in women compared to men, possibly an important factor for meeting the DHA demands of the fetus and neonate (Burdge and Calder 2005; Childs et al. 2010). It has been noted that, on the average, individuals in the United States consume ALA as the primary omega-3 fatty acid. Furthermore, the dietary intakes of EPA and DHA often fall well below the recommendations; thus, many individuals must rely on limited conversion of ALA to more biologically active omega-3 fatty acids (Arterburn, Hall, and Oken 2006; Burdge and Calder 2005; Calder, Dangour, et al. 2010; Das 2005, 2007, 2010; Whelan 2009).

For some time, *Δ6-desaturase* has been considered the rate-limiting enzyme involved in the conversion of ALA and LA to the longer-chained biologically active omega-3 and omega-6 fatty acids (Burdge and Calder 2005) (Figure 6.1). This same enzyme has been implicated as a pivotal step in the formation of DHA from EPA (Burdge and Calder 2005), and all Δ6-desaturase precursors (e.g., LA and ALA) may compete for the same enzyme (Arterburn, Hall, and Oken 2006; Burdge and Calder 2005; Calder, Dangour, et al. 2010; Das 2005, 2007, 2010; Whelan 2009). In addition, it has been shown that long-chain PUFAs (e.g., DHA, EPA, ARA) may compete for incorporation into membrane phospholipids and other biologically active lipids (Das 2005, 2007, 2010; Horrobin 1993). Factors such as genetics, disease, sex, and the type and amount of individual fatty acids can impact ALA conversion to EPA/DHA and can also impact Δ6-desaturase activity (Burdge and Calder 2005; Childs et al. 2010; Das 2005, 2007, 2010; Gerster 1998; Portolesi, Powell, and Gibson 2007; Zhao et al. 2011).

It has been speculated that a defect in Δ6-desaturase may be an important factor in the initiation and progression of many disease states (e.g., metabolic syndrome, diabetes mellitus, and CVD) (Botelho et al. 2013; Casey et al. 2013; Das 2005, 2007, 2010, 2013; Kavanagh et al. 2013; Kuhnt et al. 2014). Increased consumption of LA also decreases the conversion of ALA to long-chain PUFAs (Arterburn, Hall, and Oken 2006). Diets high in ALA seem to limit its accumulation in plasma and decrease its conversion rate to EPA and DHA (Arterburn, Hall, and Oken 2006). This observation suggests that ALA cannot reliably replace EPA and DHA and that most American diets contain modest ALA and high LA content, thus having even a more profound effect on the ALA to omega-3 fatty acid conversion rate.

In recent times, an increased consumption of LA and decreased consumption of omega-3 fatty acid, coupled with the inefficient conversion of ALA to biologically active omega-3 fatty acid, has contributed to low tissue EPA and DHA content. Collectively, the limited supply of omega-3

Table 6.1. Compositional comparison of SDA soybean oil, echium oil, and common vegetable-derived food oils

Fatty Acid	Soybean[a]	SDA Soybean[b]	Flax-seed[c]	Canola[d]	Corn[d]	Cotton-seed[d]	Olive[d]	Echium[e]	Peanut[d]	Safflower[d]	Sunflower[d]
					— Percent total fatty acids by weight —						
14:0 (myristic)	<0.5	<0.5	<1	<1	<1	1	<1	<1	<1	<1	<1
16:0 (palmitic)	7.0–12	9–13	9 (total sat)	4	11	22	13	<1	11	7	7
18:0 (stearic)	2.0–5.5	2.0–5.5		2	2	3	3	3.7	2	2	5
18:1 omega-9 (oleic)	19–30	10–20	18	62	28	19	71	15.9	48	13	19
18:2 omega-6 (linoleic)	48–65	15–30	16	22	58	54	10	18.8	32	78	68
18:3 omega-3 (alpha-linolenic)	5–10	9–12	57	10	1	1	1	28.4	<1	<1	<1
18:3 omega-6 (gamma-linolenic)	na	5–8	na	na	na	na	na	11	na	na	na
18:4 omega-3 (stearidonic)	na	15–30	na	na	na	na	na	12.5	na	na	na

na = not available

[a]United States Pharmacopeial Convention (2010)

[b]Monsanto Company (2009)

[c]Flax Council of Canada (2011)

[d]Strayer et al. (2006)

[e]Surette et al. (2004)

(Adapted from Banz et al. 2012.)

fatty acids and the inefficient conversion of ALA to biologically active omega-3 fatty acids (Banz et al. 2012; Calder and Deckelbaum 2011; Casey et al. 2013; Deckelbaum et al. 2012; Decker, Akoh, and Wilkes 2012) highlights the attractiveness of agricultural-based substitutes that could represent a sustainable and efficient alternative to marine-based omega-3 fatty acids.

In humans, Δ6-desaturase is considered the rate-limiting step in converting ALA to EPA, though more recent evidence indicates almost any step can be limiting depending on genetics (Zhang, Kothapalli, and Brenna 2016). The type and amount of dietary omega-3 or omega-6 fatty acids can decrease the activity of Δ6-desaturase and thus impair interconversion of EPA and DHA in vivo. This activity is especially apparent in subjects provided diets with high ALA or LA content. The efficiency of Δ6-desaturase is also highly variable in humans. In addition, the severity of metabolic dysfunction within diabetic individuals is reported to negatively impact Δ6-desaturase activity and decrease interconversion of omega-3 fatty acids. To bypass the compromised desaturase genes, transgenic soybean plants (SDA-enriched soybean) were recently generated through targeted incorporation of Δ6-desaturase and Δ*15 desaturase* genes. The resulting soybeans produce oil markedly higher in SDA and gamma-linolenic acid (GLA) and lower in LA and ALA. It may be possible that SDA and GLA consumption, individually or in combination with each other, could elicit marked anti-inflammatory properties.

Plant-derived Foods

Most common food oils contain a blend of fatty acids (Table 6.1). Alpha-linolenic acid is the major omega-3 fatty acid in the diet (Burdge and Calder 2005; Whelan 2009; Whelan and Rust 2006). The richest dietary source of ALA is flaxseed oil, although many other vegetable oils contain modest amounts of ALA such as soy and canola oils (Table 6.1) (Banz et al. 2012; Casey et al. 2013; Deckelbaum et al. 2012; Decker, Akoh, and Wilkes 2012). In a typical westernized diet, high consumption of maize and soy oils can contribute to an increased intake of omega-6 and decreased intake of omega-3 fatty acids (Arterburn, Hall, and Oken 2006). Furthermore, minimal amounts of ALA can be converted to EPA and DHA following consumption (Burdge and Calder

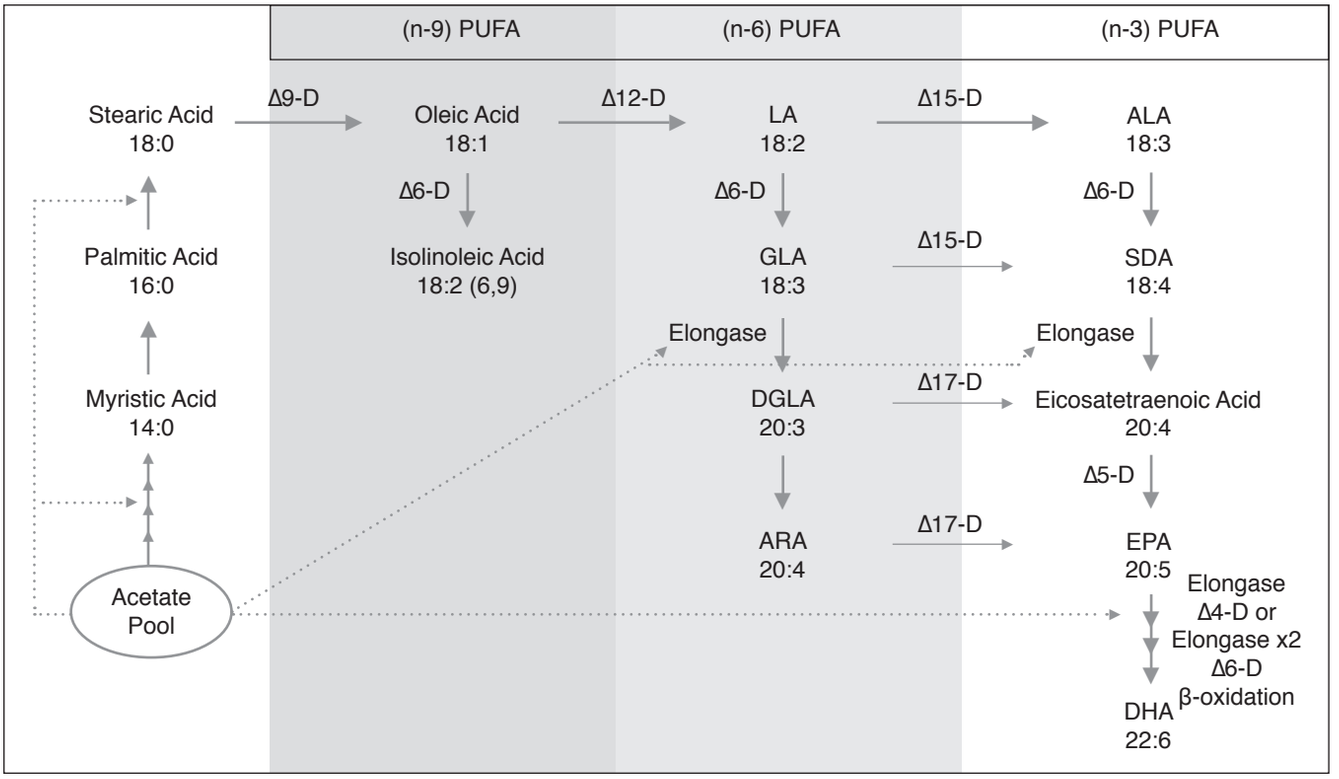

Figure 6.1. Metabolism of PUFA and key interconversion of *omega-9* (n-9), omega-6 (n-6), and omega-3 (n-3) fatty acids. Plants and some animals, but not humans or other mammals, can convert the n-6 to n-3 fatty acids. GLA=gamma-linolenic acid; DGLA=dihomo-gamma-linolenic acid. (Adapted from Banz et al. 2012.)

2005; Whelan 2009; Whelan and Rust 2006). In fact, the major metabolic fate of ALA, in a high-ALA diet, seems to be oxidation and not synthesis of omega-3 fatty acids (Burdge and Calder 2005; Whelan 2009; Whelan and Rust 2006).

Presently, the main dietary sources for the omega-3 fatty acids are fish and other seafood, and/or commercially available fish-oil supplements (Cheng et al. 2010). The sustainability of these marine sources is questionable as globally over-fishing becomes a problem and aquaculture is unable to compensate for the shortage (Cheng et al. 2010). The imbalance of omega-6 and omega-3 fatty acid intake, coupled with the inefficient conversion of ALA to biologically active omega-3 fatty acids (Burdge and Calder 2005), has stimulated the search for plant-based substitutes that could represent a sustainable and efficient alternative to marine-based omega-3 fatty acids (Banz et al. 2012; Casey et al. 2013; Deckelbaum et al. 2012; Decker, Akoh, and Wilkes 2012).

The omega-3 index (the sum of EPA and DHA in red blood cells) has been found to strongly correlate with a lower risk of CVD such as sudden cardiac death (Harris 2010; Harris, Assaad, and Poston 2006; Harris, Lemke, et al. 2008). Several studies (Guichardant et al. 1993; Hammond et al. 2008; Harris et al. 2007; Harris, Lemke, et al. 2008; Ishihara et al. 2002; James, Ursin, and Cleland 2003; Lemke et al. 2010; Miles, Banerjee, and Calder 2004; Miles et al. 2004; Surette et al. 2004; Whelan 2009; Yang and O'Shea 2009; Zhang et al. 2008) have examined the impact of high SDA oil consumption on the several risk factors for the development of CVD and/or its related pathologies. These studies have demonstrated that dietary SDA elicited an improvement in the omega-3 index, a decrease in serum triacylglycerols/very low-density lipoproteins, and a significant hepatoprotective effect. Several studies also have shown a marked anti-inflammatory property of these high SDA oils (James, Ursin, and Cleland 2003; Miles, Banerjee, and Calder 2004; Miles et al. 2004).

More recently, it has been demonstrated that high SDA oil also has anti-atherogenic properties in a preclinical model (Forrest et al. 2011). These findings demonstrate the potential importance of SDA-enriched oils as a more sustainable alternative to marine-based EPA in the human diet (Miller et al. 2008). Moreover, SDA-enriched soy oil currently is positioned to help meet the consumer demand for omega-3 fatty acids because of its established manufacturing process,

GRAS (generally recognized as safe) approval, and more efficient conversion to omega-3 fatty acids than current commodity oils.

At present, the most readily available sources of EPA and DHA are oily fish such as salmon (Sayanova and Napier 2011; Venegas-Caleron, Sayanova, and Napier 2010). Although SDA modestly increases concentrations of EPA in tissues, it has limited impact on concentrations of DHA in tissues and is not as efficient as omega-3 fatty acids in changing concentrations of omega-3 fatty acids in tissues (Harris et al. 2007; James, Ursin, and Cleland 2003). Consequently, enhancing the omega-3 fatty acid content of several common commodity oils has become a research focus that could be applicable for human and livestock applications (Cheng et al. 2010; Clemente and Cahoon 2009; Kinney 2006; Kinney, Cahoon, and Hitz 2002). Substantial advancements have been made in the production of omega-3 fatty acids, such as EPA and DHA, in plant systems (Abbadi et al. 2004; Damude and Kinney 2007, 2008; Hoffman et al. 2008; Sayanova and Napier 2011; Venegas-Caleron, Sayanova, and Napier 2010; Walsh et al. 2016).

Although promising, disadvantages of plants containing high concentrations of EPA and DHA exist (Teichert and Akoh 2011a,b). For example, oxidative instability of omega-3 fatty acids could promote lipid peroxidation, ultimately limiting the potential applications of such oils (Husveth et al. 2000) because of a decrease in shelf life (Kouba and Mourot 2011). Innate antioxidants and/or the addition of antioxidant products could ameliorate some of the deleterious effects associated with the oxidative instability of omega-3 fatty acids. In addition, and unlike SDA soy oil, potential regulatory approval may be complicated by the requirements for multiple transgenes for EPA and DHA synthesis (Clemente and Cahoon 2009; Eckert et al. 2006; Lu et al. 2011). The success of these biotechnological efforts will depend on the practical and economic viability in the production of high EPA and DHA oilseeds. If successful, commercial production focused on enhancing the omega-3 fatty acids in plants could provide a sustainable source. Limited availability of high omega-3 fatty acid sources could make efforts targeted at the enrichment of omega-3 fatty acids or biosynthetic precursors (e.g., SDA) in common commodity oils appealing for the food and feed industries (Kawabata et al. 2013; Lemke et al. 2013; Lenihan-Geels, Bishop, and Ferguson 2013; Surette 2013; Walker, Jebb, and Calder 2013).

Poultry-, Livestock- and Marine-derived Foods

In modern times, agricultural practices have focused on increasing omega-3 fatty acids in poultry-, livestock-, and marine-derived foods. The fatty acid composition of terrestrial and marine life reflects a combination of lipid biosynthesis and lipid consumption (Kouba and Mourot 2011; Kouba et al. 2003). For example, feeding poultry or livestock diets containing high omega-3 fatty acid fish products can lead to an enhancement of tissue EPA and DHA contents (Kouba et al. 2003). Increasing concerns regarding the sustainability and cost of fish products in animal feeds, however, seems to make this dietary procedure a nonviable approach (Kouba and Mourot 2011). On the other hand, increasing the omega-3 fatty acid content of some animal products can be achieved by the addition of high-ALA oil seeds to the diet.

It has been demonstrated that, under the best conditions, feeding animals diets rich in ALA grain extracts increases the concentration of ALA approximately twofold in beef, sixfold in pork, tenfold in chicken, and fortyfold in eggs. Feeding ALA to these animals, however, has a minimal effect on tissue EPA content and virtually no effect on DHA content (Bourre 2005a,b; Kouba and Mourot 2011). With the limited availability of high omega-3 fish (Sayanova and Napier 2011; Venegas-Caleron, Sayanova, and Napier 2010) and the modest effect of ALA on concentrations of omega-3 fatty acids, especially DHA, in tissues, current attempts at the enrichment of omega-3 fatty acids or pro-EPA precursors in common commodity oils may have possible applications in poultry, livestock, and marine diets (Cheng et al. 2010; Clemente and Cahoon 2009; Kinney 2006; Kinney, Cahoon, and Hitz 2002).

Poultry

Currently, the most success of enhancing omega-3 fatty acid via dietary means has been achieved in poultry meat and eggs (Bourre 2005a,b). In chickens, the composition of fatty acids stored in adipose tissues largely reflects that of ingested lipids (Kouba and Mourot 2011). It has been demonstrated that feeding a diet enriched with ALA has a direct consequence on poultry tissue and egg overall omega-3 fatty acid content. For example, the overall omega-3 fatty acid content of chicken meat may be enhanced by increasing the dietary intake of grains rich in ALA (Cherian 2008; Cherian and Goeger 2004; Cherian and Hayat 2009; Cherian and Sim 1993; Cherian, Bautista-Ortega, and Goeger 2009; Cherian et al. 2007; Gonzalez-Esquerra and Leeson 2001). Also, egg yolk omega-3 fatty acid content can be enhanced robustly with the addition of omega-3 fatty acids to the poultry diet (Ansenberger et al. 2010; Cherian et al. 2007; Hargis, Van Elswyk, and Hargis 1991; Lewis, Seburg, and Flanagan 2000; Poureslami et al. 2011; Trebunova et al. 2007).

Because of the limited conversion of ALA to omega-3 fatty acids, the potential use of the pro-EPA precursor, SDA, in poultry rations has been targeted at enriching poultry meat with omega-3 fatty acids (Kitessa and Young 2009; Rymer,

Hartnell, and Givens 2011). In one study (Rymer, Hartnell, and Givens 2011), it was demonstrated that supplementing broiler diets with SDA-rich soy oil increased the overall omega-3 fatty acid content of the meat compared with a lower omega-3 fatty acid vegetable oil, but not as robustly as an omega-3 fatty acid-rich fish oil diet.

Kitessa and Young (2009) found that an SDA-rich oil was better than an ALA-rich oil at enriching poultry meat with short- and long-chain omega-3 fatty acids. In fact, the concentrations of most of the individual omega-3 fatty acids were higher in the SDA than in the ALA group. Differences in DHA concentrations, however, were significant in breast but not thigh muscle meat. The total omega-3 fatty acid concentration of thigh muscle was higher with the SDA treatment versus the ALA treatment. These preliminary SDA oil studies support further research on the potential use of high omega-3 fatty acids-engineered oilseed (e.g., SDA, EPA, or DHA) utilization in poultry rations as a potential option to increase omega-3 fatty acids in meat and egg products.

Livestock

The success of enhancing omega-3 fatty acid content via dietary means in livestock has been less successful than in poultry (Bourre 2005a,b), although dietary-induced omega-3 fatty acid enhancement has been achieved in pork and in cattle (Bourre 2005a,b; Kouba and Mourot 2011). In monogastric animals, the tissue fatty acids composition essentially reflects ingested lipids and lipid biosynthesis, whereas in ruminants the milk and meat omega-3 fatty acid content is influenced greatly by the rumen microflora (Kouba and Mourot 2011). For example, it has been confirmed in swine that a diet rich in ALA can enhance content of omega-3 fatty acids in tissues and decrease the omega-6 to omega-3 ratio. Consequently, it has been proposed that the inclusion of flaxseed in swine diets is a valid method of improving the nutritional value of pork without deleteriously affecting organoleptic characteristics, oxidation, or color stability (Guillevic, Kouba, and Mourot 2008; Kouba et al. 2003, 2008; Matthews et al. 2000).

The overall omega-3 fatty acid content of muscle and adipose tissue in beef cattle also can be enhanced (typically about twofold) when given a grass-based diet or fed an ALA-rich diet (Daley et al. 2010; He et al. 2011; Scollan et al. 2001). In parallel, it has been shown that cow milk ALA concentration can be increased with flaxseed (ALA)-supplemented diets (Chilliard and Ferlay 2004; Chilliard et al. 2009; Daley et al. 2010; He et al. 2011; Kouba et al. 2003, 2008; Scollan et al. 2001; Shingfield et al. 2008; Weill et al. 2002). It has also been demonstrated that the meat from cattle fed a linseed meal-containing diet has a significantly higher proportion of ALA versus animals fed an LA-rich diet (Chilliard and Ferlay 2004; Chilliard et al. 2009; Daley et al. 2010; He et al. 2011; Kouba et al. 2003, 2008; Scollan et al. 2001; Shingfield et al. 2008; Weill et al. 2002).

More recently, it has been demonstrated that the omega-3 fatty acid content in milk fat of dairy cows can be enhanced by using SDA-enriched soy oil from genetically modified soybeans. It was concluded that SDA-enhanced oil from genetically modified soybeans combined with proper ruminal protection may achieve impressive increases in the milk fat content of omega-3 fatty acids (Bernal-Santos et al. 2010). On the other hand, it was found that when balanced for precursor fatty acid supply, a high SDA (echium) oil was not superior to a high ALA (linseed) oil at enriching lamb tissues with omega-3 fatty acids (Kitessa et al. 2011). With the growing consumer demand for high omega-3 fatty acid foods, more research investigating the potential use of omega-3 fatty acid-rich engineered oilseeds (e.g., SDA, EPA, or DHA) in livestock feed is warranted.

Fish

As previously mentioned, the most readily available present-day sources of EPA and DHA are oily fish such as salmon (Sayanova and Napier 2011; Venegas-Caleron, Sayanova, and Napier 2010). With an increased demand for omega-3 fatty acids, wild-caught marine-based sources are considered unsustainable; therefore, efficient alternatives that could provide omega-3 fatty acids have become an industry priority (Bharadwaj et al. 2010; Codabaccus et al. 2011). Furthermore, most fish do not readily synthesize omega-3 fatty acids; they actually obtain them from consumption of other organisms that contain significant amounts of the omega-3 fatty acids (Miller et al. 2008).

Consequently, alternative omega-3 fatty acids have drawn increased attention in the aquaculture industry. As discussed previously, several sources of nonmarine omega-3 fatty acids could be used in aquafeeds. For example, shorter-chain EPA precursors, such as SDA, may have useful applications in aquafeeds to promote the production of the omega-3 fatty acids (Bharadwaj et al. 2010; Codabaccus et al. 2011; Miller, Nichols, and Carter 2007, 2008; Miller et al. 2008). Common oilseed plants that may be engineered to produce EPA and/or DHA could provide a direct source of omega-3 fatty acids for the aquaculture industry (Abbadi et al. 2004; Damude and Kinney 2007, 2008; Hoffmann et al. 2008).

It was demonstrated, however, that replacement of dietary fish oil with SDA-containing oil had no effect on omega-3 fatty acid concentrations in Atlantic salmon (Miller, Nichols, and Carter 2007; Miller et al. 2008). Dietary SDA, however, can promote higher muscle DHA concentrations than ALA in hybrid striped bass (Bharadwaj et al. 2010). Although more research is needed, it seems that feeding an SDA-rich diet is questionable as a replacement regarding the need for wild-caught marine-based feeds in the aquaculture industry

(Miller, Nichols, and Carter 2008). Consequently, agricultural practices targeted at increasing EPA and DHA in oilseed crops may represent a more suitable alternative to marine-based omega-3 fatty acids in the aquaculture industry.

Conclusion

The low consumption of marine-based omega-3 fatty acid in the United States, along with a low efficiency to convert ALA to EPA and DHA in humans, has amplified the need to find alternative dietary sources or precursors of EPA and DHA (Arterburn, Hall, and Oken 2006; Burdge and Calder 2005; Calder and Yaqoob 2009; Calder, Dangour, et al. 2010; Das 2005, 2007, 2010; Whelan 2009). As discussed previously, several sources of nonmarine omega-3 fatty acid could be used in the food and feed industries (Banz et al. 2012; Casey et al. 2013; Deckelbaum et al. 2012; Decker, Akoh, and Wilkes 2012). Shorter-chain precursors, such as SDA, may have direct applications in the human diet and further applications at promoting the production of the omega-3 fatty acids in poultry, livestock, and fish (Kawabata et al. 2013; Lemke et al. 2013; Lenihan-Geels, Bishop, and Ferguson 2013; Surette 2013; Walker, Jebb, and Calder 2013).

Further, common oilseeds engineered to produce EPA and DHA could provide a direct source of omega-3 fatty acids for the food and feed industry. The American Heart Association recommends that healthy individuals consume oily fish (i.e., salmon, tuna, mackerel, herring, and trout) at least twice a week (AHA 2018), while individuals with a history of CVD are advised to visit with their doctor about supplements. This goal will likely not be met by the typical westernized diet. Therefore, agricultural practices targeted at increasing the omega-3 fatty acid content of animal-derived foods may represent a sustainable and efficient alternative to marine-based omega-3 fatty acids.

7 Guidelines for Labeling Related to Omega-3 Fatty Acids

Introduction

The area of labeling and claims related to omega-3 fatty acids is arguably even more complex than the potential health benefits and the science underlying those benefits. Although the metabolism and functions of the omega-3 fatty acids are quite universal among human populations across the globe (albeit with some differences related to, among other things, background diet, gender, and genetic factors), regulations related to labeling and types of claims vary widely from one country or region to another, from one age group or subpopulation to another (e.g., infant vs. adult and healthy vs. specific disease conditions), and from one type of product to another (e.g., food vs. dietary supplement vs. drug). In addition, regulations related to claims associated with health benefits of nutrients and other dietary components are in a significant state of flux in many countries. Whereas the focus of this document is omega-3 fatty acids within foods, more concentrated sources are available as dietary supplements and as drugs. This discussion will include only claims related to the omega-3 fatty acids for foods and dietary supplements in the United States.

The major omega-3 fatty acids ALA, EPA, and DHA have distinct functional effects. Although they are metabolically related, research has made it abundantly clear they are not as freely interconvertible in humans as was once thought, and they do not have identical effects. They should be listed separately on labels and no implication made that one can substitute for another.

Another aspect not covered herein is allowance for inclusion of various sources of the omega-3 fatty acids in the diet, especially for new or novel sources that have not historically been normal components of the diets within a given country. For example, in the United States, adding a new food component or source to the food supply would typically involve a GRAS determination, whereas in some other countries or regions such as Australia, Canada, or the European Union, this would involve obtaining a novel food ingredient approval. In addition, there are other regulatory requirements that must be met before marketing new or reformulated products in other categories, such as infant formulas and, of course, drugs.

The U.S. Food and Drug Administration (FDA) allows five types of claims for foods and dietary supplements: three categories of health claims (summarized below), nutrient content claims, and structure/function claims (USFDA 2013).

Health Claims

As defined by the FDA, "health claims describe a relationship between a food substance (a food, food component, or dietary supplement ingredient), and reduced risk of a disease or health-related condition" (USFDA 2013). Categories of health claims include the following (USFDA 2013):

1. Nutrition Labeling and Education Act of 1990 (NLEA)-authorized health claims, which are health claims that meet the standard of significant scientific agreement, in which the nutrient/disease relationship is well established
2. 1997 FDA Modernization Act (FDAMA) health and nutrient content claims, which are based on authoritative statements from a scientific body of the U.S. government or the National Academy of Sciences
3. Qualified health claims, based on the FDA's 2003 *Consumer Health Information for Better Nutrition Initiative* (USFDA 2003), in which there is emerging evidence of a relationship between a food component or supplement and decreased risk of a disease or health-related condition

There are currently no approved NLEA health claims meeting the criteria of significant scientific agreement specifically related to omega-3 fatty acids. Similarly, there are no approved FDAMA health claims specifically related to omega-3 fatty acids, although there is an approved claim related to substitution of SFAs with unsaturated (mono- and polyunsaturated) fatty acids and risk of heart disease.

A qualified health claim related to coronary heart disease was approved in 2004 for conventional foods and dietary supplements that contain EPA and DHA; specifically, the claim statement is as follows (USFDA 2004):

> Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of (Name of the food) provides ( ) g of EPA and DHA omega-3 fatty acids. (See nutrition information for total fat, saturated fat, and cholesterol content.)

Dietary supplements may declare the amounts of EPA and DHA per serving in the "Supplement Facts" box on the label

instead of stating the amount in the claim itself. Also, dietary supplements should not recommend or suggest a daily intake of more than 2 g of EPA plus DHA. For foods (and supplements that are more than 5 g per serving) to use this claim, there are limits that must be met for amounts of total fat, saturated fat, cholesterol, and sodium per serving.

There is also an approved qualified health claim for unsaturated fatty acids from canola oil (which includes the omega-3 fatty acid ALA at ~9 g/100 g oil) and reduced risk of coronary heart disease, specifically (USFDA 2006):

> Limited and not conclusive scientific evidence suggests that eating about 1½ tablespoons (19 grams) of canola oil daily may reduce the risk of coronary heart disease due to the unsaturated fat content in canola oil. To achieve this possible benefit, canola oil is to replace a similar amount of saturated fat and not increase the total number of calories you eat in a day. One serving of this product contains (x) grams of canola oil.

This claim can be used for vegetable oil spreads, salad dressings, shortenings, and canola oil-containing foods that meet specific nutrient requirements, in addition to canola oil per se. Similar claims exist for olive oil and corn oil based on the replacement of saturated fats with monounsaturated and unsaturated fats, respectively. The claimed benefits are not established to be due solely to ALA content.

In addition, there is an approved qualified health claim for nuts (restricted to almonds, hazelnuts, peanuts, pecans, some pine nuts, pistachio nuts, and walnuts) and heart disease, and also a second, similar one specifically for walnuts and heart disease. Some types of nuts are sources of ALA, and walnuts are an especially rich source of this omega-3 fatty acid, with English walnuts providing ~9 g ALA/100 g, butternuts (white walnuts) ~8.7 g/100 g, and black walnuts ~2 g/100 g. The claim, however, is not predicated on ALA content, and benefits may relate in part or in toto to other components. The claim for nuts is as follows (USFDA 2004):

> Scientific evidence suggests but does not prove that eating 1.5 ounces per day of most nuts (such as 'name of specific nut') as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease. (See nutrition information for fat content.)

The specific claim for walnuts is the following (USFDA 2004):

> Supportive but not conclusive research shows that eating 1.5 ounces per day of walnuts, as part of a low saturated fat and low cholesterol diet and not resulting in increased caloric intake, may reduce the risk of coronary heart disease. See nutrition information for fat [and calorie] content.

Nutrient Content Claims

Nutrient content claims, which also were authorized by the NLEA, are label claims that, directly or by implication, characterize the level of a nutrient in a food. As defined by the FDA (USFDA 2013), "Nutrient content claims describe the level of a nutrient or dietary substance in the product, using terms such as *free, high*, and *low*, or they compare the level of a nutrient in a food to that of another food, using terms such as *more, reduced*, and *lite*."

In addition, nutrient content claims provide the specific amount of a given nutrient, or the percentage of the daily value (DV) for the nutrient, in a serving of the food. Daily values were established by the FDA in 1993 for use in labeling, based on the reference daily intake (RDI) or daily reference value (DRV), depending on the nutrient and population. A food can be said to be a "good source" of (or alternately, "contains" or "provides," which are considered synonymous with "good source") a given nutrient if it contains 10–19% of the DV and an "excellent source" of, or "high" in, a nutrient if it contains at least 20% of the DV. In general, information on the amount of a nutrient without a DV can be included on a label, but it is limited to and must include the specific amount and cannot characterize or compare the level. Because the FDA did not establish a DV for the omega-3 fatty acids, an acceptable nutrient content claim would be "contains/provides x g of omega-3 fatty acids (or of a specific omega-3 fatty acid)." A statement "contains/provides omega-3 fatty acids" without the specific amount, however, was not initially permitted because such a claim would be a synonym for "good source."

Beginning in 2004, additional nutrient content claims were thought to be acceptable for the specific omega-3 fatty acids ALA, EPA, and DHA, when the FDA made no objections to three petitions that cited the Institute of Medicine

Table 7.1. Nutrient claims

Nutrient Content Claim for ALA	Conditions for Making the Claim
High	≥ 320 mg of ALA per RACC[a] (≥ 20% of 1.6 g/day)
Good source	≥ 160 mg of ALA per RACC (≥ 10% of 1.6 g/day)
More	≥ 160 mg of ALA more per RACC than an appropriate reference food (≥ 10% of 1.6 g/day)

[a]RACC is the reference amount customarily consumed, a presumed usual serving size

RDIs for fatty acids, initially available in 2002, as DRVs for the fatty acids. As a result of the petitions, claims including "high" and "excellent source" for ALA, EPA, and DHA; "good source," "contains," and "provides" for ALA; and "more," "fortified with," and "plus" for ALA, all based on proposed reference values cited in the petitions of 1.3 to 1.6 g for ALA and 130 to 160 mg for DHA and/or EPA, were in use. In November 2007, the FDA published a proposed rulemaking that would prohibit these additional nutrient content claims for the omega-3 fatty acids (except those based on a proposed DV of 1.6 g for ALA). The Final Rule published in April of 2014 (USFDA 2014) limits nutrient content claims in foods and supplements to those based on ALA content and provides the guidance in Table 7.1.

Structure/Function Claims

A structure/function claim is one that describes the role of a nutrient or dietary ingredient in affecting normal structure or function in humans; a common example is "calcium helps build strong bones." Whereas this type of claim has long been used for dietary supplements and food as well as drugs, the Dietary Supplement Health and Education Act of 1994 provided additional regulatory procedures for these claims for dietary supplements. Unlike the health claims noted above, structure/function claims do not require preapproval by the FDA. The manufacturer is responsible for ensuring the claims are truthful and not misleading and must have the information to support the accuracy of the claim.

A dietary supplement using a structure/function claim must also carry the disclaimer that the FDA has not evaluated the claim, and that the product is not intended to diagnose, treat, cure, or prevent any disease; the latter claims would define the product as a drug rather than a dietary supplement. The manufacturer of a dietary supplement with a structure/function claim is required to submit a notification containing the text of the claim to the FDA within 30 days of marketing the product, but no notification or disclaimer is required when using a structure/function claim for a conventional food. A few examples of structure/function claims for omega-3 fatty acids include the following:

- Docosahexaenoic acid supports brain and eye development and function.
- Docosahexaenoic acid is the most abundant omega-3 fatty acid in the brain.
- Omega-3 fatty acids support a healthy heart.
- Omega-3 fatty acids are converted to eicosanoids, which have numerous functions in the body, including the brain, heart, blood vessels, and joints.
- Eicosapentaenoic acid and DHA are precursors of eicosanoids that have many well-documented health benefits.

Labeling of Meat and Poultry Products

The Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture, rather than the FDA, has labeling responsibility for meat and poultry products. In an interim policy statement of July 11, 2007, the FSIS stated that "factual statements of the amount of omega-3 fatty acids per serving are acceptable" on labeling for meat and poultry products, as are similar statements for omega-6 fatty acids or for specific omega-3 or omega-6 fatty acids (USDA–FSIS 2014). Further claims or implied claims related to the fatty acids, however, are not permitted. This includes claims characterizing the amounts of omega-3 fatty acids (or other nutrients), such as "good source of," "excellent source of," "fortified with," "contains," or "provides" (with the latter two, as noted earlier, considered synonyms for "good source"). All labels for meat and poultry products that include a statement about the level of omega-3 fatty acids must be provided to FSIS for approval before use.

8 Conclusions

This document provides the reader with important information on omega-3 fatty acids, which have gained much public attention because of their implications for positive human health benefits. The following conclusions regarding the science of omega-3 fatty acids for human health can be made on the basis of the previous discussion.

1. The most common omega-3 fatty acids are 18 to 22 carbons in length and contain three to six double bonds. Alpha-linolenic acid (C-18:3; ALA), eicosapentaenoic acid (C-20:5; EPA), and docosahexaenoic acid (C-22:6; DHA) are the most prevalent omega-3 fatty acids in the human diet.
2. Alpha-linolenic acid is required in the diet of humans for normal development. Human endogenous synthesis of EPA and DHA from dietary ALA is limited especially with modern intakes of omega-6 LA, and therefore EPA and DHA are likely to be essential for proper neurocognitive development and general health.
3. Foods rich in omega-3 fatty acids include flax and chia (ALA) and seafood, especially oily fish, fish oils, and algae (EPA and DHA).
4. Supplementation of the human diet with omega-3 fatty acids is safe and seems beneficial for several diseases and disorders.
5. Docosahexaenoic acid supports optimal neurocognitive development in infants and EPA and DHA support neurocognitive health in adults.
6. Association of omega-3 fatty acids (e.g., EPA and DHA) with lower risk cardiovascular disease is well known; EPA and DHA beneficially modify several risk factors such as blood triacylglycerols, blood pressure, and inflammatory markers. Effective use of EPA and DHA for treatment of patients with existing cardiovascular disease is more uncertain.
7. Because of variations among many studies, benefits of supplemental dietary omega-3 fatty acids for prevention and/or treatment of several cancers (e.g., breast, prostate, colon) remain unconfirmed but probable.
8. Current research is focused on confirming benefits on immunity and is highly probable based on ongoing results.
9. Feeding food-producing animals such as laying hens EPA- and DHA-enriched diets or ALA-enriched diets results in foods with greater content of the omega-3 fatty acids.
10. Plants can be modified to increase content of EPA and DHA for use in the human diet.
11. Many authorities have made recommendations for intake of EPA and DHA.
12. Federal guidelines are supportive of increasing the intake of omega-3 fatty acids by humans.

Appendix A: Abbreviations and Acronyms

ALA	Alpha-linolenic acid
ARA	Arachidonic acid
CVD	Cardiovascular disease
DGLA	Dihomo-gamma-linolenic acid
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
DRV	Daily reference value
DV	Daily value
EFA	Essential fatty acid
EPA	Eicosapentaenoic acid
FDA	U.S. Food and Drug Administration
FDAMA	1997 FDA Modernization Act
FSIS	Food Safety and Inspection Service
g	Grams
GLA	Gamma-linolenic acid
GRAS	Generally recognized as safe
IBD	Inflammatory bowel disease
LA	Linoleic acid
LDLox	Oxidized low-density lipoprotein
LpL	Lipoprotein lipase
Lt	Leukotrien
mg	Milligram
MI	Myocardial infarction
MUFA	Monounsaturated fatty acid
n-3	Omega-3
NLEA	Nutrition Labeling and Education Act of 1990
PAF	Platelet activating factor
PUFA	Polyunsaturated fatty acid
RA	Rheumatoid arthritis
RACC	Reference amount customarily consumed
RCT	Randomized controlled trial
RDI	Reference daily intake
SDA	Stearidonic acid
SFA	Saturated fatty acid
SMC	Smooth muscle cell
TG	Triglyceride; Triacylglycerol
Th	T helper cell
Tx	Thromboxane
VCAM-1	Vascular cell adhesion molecule 1

Appendix B: Glossary

Alpha-linolenic acid. An omega-3 fatty acid that contains 18 carbon atoms and 3 cis double bonds. The first double bond is located at the third carbon from the omega end. Alpha-linolenic acid is an essential dietary fatty acid for animals and humans.

Arachidonic acid. A polyunsaturated omega-6 fatty acid found in meats, eggs, and dairy products.

Delta-6 desaturase. Enzyme of a lipid metabolic pathway that converts linoleate (an anionic form of linoleic acid) and alpha-linolenate into long-chain fatty acids (generates delta-6 double bond).

Delta-15 desaturase. Enzyme of a metabolic pathway that converts linoleic acid to alpha-linolenic acid (generates delta-15 double bond).

Docosahexaenoic acid. An omega-3 fatty acid that contains 22 carbon atoms and 6 cis double bonds. The first double bond is located at the third carbon from the omega end.

Docosapentaenoic acid. An omega-3 fatty acid that contains 22 carbon atoms and 5 cis double bonds. The first double bond is located at the third carbon from the omega end.

Eicosapentaenoic acid. An omega-3 fatty acid that contains 20 carbon atoms and 5 cis double bonds. The first double bond is located at the third carbon from the omega end.

Linoleic acid. An omega-6 fatty acid that contains 18 carbon atoms and 2 cis double bonds. The first double bond is located at the sixth carbon from the omega end. Linoleic acid is an essential dietary fatty acid for animals and humans.

Omega-3 fatty acid. A fatty acid with a double bond (C=C) that is three carbon atoms from the methyl (omega) end of the fatty acid. Common omega-3 fatty acids found in foods are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA).

Omega-6 fatty acid. A fatty acid with a double bond (C=C) that is six carbon atoms from the methyl (omega) end of the fatty acid. A common omega-6 fatty acid found in foods is linoleic acid (LA), which is an essential fatty acid for animals and humans.

Omega-9 fatty acid. A fatty acid with a double bond (C=C) that is nine carbon atoms from the methyl (omega) end of the fatty acid. A common omega-9 fatty acid found in foods is oleic acid.

Polyunsaturated fatty acid. A fatty acid that contains 2 or more double bonds (C=C) in the carbon chain.

Stearidonic acid. An omega-3 fatty acid that contains 18 carbon atoms and 4 double bonds and that is biosynthesized from alpha-linolenic acid (ALA).

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