RESEARCH

Perspectives in Practice

The Content of Favorable and Unfavorable Polyunsaturated Fatty Acids Found in Commonly Eaten Fish

KELLY L. WEAVER, PhD; PRISCILLA IVESTER, MS; JOSHUA A. CHILTON; MARTHA D. WILSON, PhD; PRATIVA PANDEY; FLOYD H. CHILTON, PhD

ABSTRACT
Changes in diet during the past century have caused a marked increase in consumption of saturated fatty acids and n-6 polyunsaturated fatty acids (PUFAs) with a concomitant decrease in the intake of n-3 PUFAs. Increased fish consumption has been shown to be the only realistic way to increase dietary quantities of beneficial long-chain n-3 PUFAs such as eicosapentaenoic acid and docosahexaenoic acid and re-establish more balanced n-6:n-3 ratios in the diets of human beings. Our objective in this research was to characterize some of the relevant fatty acid chemistry of commonly consumed fish, with a particular focus on the four most commonly consumed farmed fish. To do this, 30 commonly consumed farmed and wild fish were collected from supermarkets and wholesalers throughout the United States. Fatty acid composition of samples from these fish was determined using gas chromatography. The 30 samples studied contained n-3 PUFAs ranging from fish having almost undetectable levels to fish having nearly 4.0 g n-3 PUFA per 100 g fish. The four most commonly farmed fish, Atlantic salmon, trout, tilapia, and catfish, were more closely examined. This analysis revealed that trout and Atlantic salmon contained relatively high concentrations of n-3 PUFA, low n-6:n-3 ratios, and favorable saturated fatty acid plus monounsaturated fatty acid to PUFA ratios. In contrast, tilapia (the fastest growing and most widely farmed fish) and catfish have much lower concentrations of n-3 PUFA, very high ratios of long chain n-6 to long chain n-3 PUFAs, and high saturated fatty acid plus monounsaturated fatty acid to PUFA ratios. Taken together, these data reveal that marked changes in the fishing industry during the past decade have produced widely eaten fish that have fatty acid characteristics that are generally accepted to be inflammatory by the health care community.


Compelling evidence demonstrating the health benefits of n-3 polyunsaturated fatty acids (PUFAs) in fish together with dwindling supplies of fish caught from the wild have spawned a dramatic expansion in aquaculture (an annual rate of increase of 9.2% compared with 1.4% for captured fish) (1-3). Although a great deal of attention has been focused on the contamination of farmed fish populations with methyl mercury, polychlorinated biphenyls, and other organic compounds (4), little has been published with regard to the effects of rapid changes in the fish industry on PUFA or saturated fatty acid (SFA) levels in emerging, intensively farmed species of fish. Our research reveals certain intensively farmed species of fish contain PUFA profiles that have been shown to be detrimental to human health.

In the United States, tilapia has shown the biggest gains in popularity among seafood and this trend is expected to continue as consumption is projected to increase from 1.5 million tons in 2003 to 2.5 million tons by 2010, with a sales value of more than $5 billion (5). Based on this growth, tilapia is now the second (to farmed Atlantic salmon) most widely farmed fish in the world. Catfish has also seen explosive growth, from 0.3 million metric tons in 1994 to 0.7 million metric tons in 2003 (6). In contrast to the dramatic increases in farmed fish, wild salmon capture and wild tilapia capture has remained unchanged for the past 10 years (6).

The health benefits of the n-3 PUFAs in fish have been well documented (7). A meta-analysis examining fish consumption and coronary heart disease (CHD) in 13 cohort studies revealed an inverse relationship between fish consumption and CHD as well as sudden cardiac death, where each 20 g/day increase in fish consumption was associated with a 7% lower risk of fatal CHD (8). Long-chain n-3 PUFAs such as eicosapentaenoic acid (EPA) (also referred to as 20:5) and docosahexaenoic acid (DHA) (also referred to as 22:6) found in oily fish are thought to
be critical bioactive components that account for many of the health benefits of fish. The mechanisms responsible for their effects on cardiovascular disease and other complex diseases are likely to be multifactorial. Based on a large body of evidence collected during the past three decades, the American Heart Association (AHA) recommends that the general public eat at least two servings of fish per week, cardiovascular disease patients consume 1 g EPA+DHA per day, and patients with hypertriglyceridemia consume 2 to 4 g EPA+DHA per day (9).

The ratio of arachidonic acid (AA) to very long-chain n-3 PUFAs (EPA and DHA) in diets of human beings appears to be an important factor that dictates the anti-inflammatory effects of fish oils. Ingestion of fish or fish oil diets leads to a marked increase of EPA in membrane phospholipids and in some cases, a concomitant decrease in arachidonic acid. Wada and colleagues (10) recently reported that increasing the ratio of EPA to arachidonic acid in cellular phospholipids likely dampens prostanoid signaling with its largest effects on cyclooxygenase-1 involving the production of prostaglandin D, E, and F. Biochemical data from the laboratory of Serhan and colleagues (11) also predict that changes in arachidonic acid to EPA or DHA ratios shift the balance towards proinflammatory prostaglandins, thromboxanes, and leukotrienes, to protective chemical mediators known as resolvins and protectins, which are proposed to play a pivotal role in resolving inflammatory response.

As discussed earlier, there have been dramatic changes in the fishing industry during the past decade, with fish virtually unknown 10 years ago now dominating the marketplace. Changes in fish consumption patterns raise important questions as to the effect of aquaculture on the quality and quantities of key very long-chain PUFAs that human beings ingest. Although there has been some evidence that aquaculture can cause modest changes in concentrations and ratios of PUFAs in Atlantic salmon, even that is not clearly established. For example, the US Department of Agriculture (USDA) database 20 reports that farm-raised Atlantic salmon contains more than 1 g dietary arachidonic acid per 100 g fish (12). If this is correct, farmed salmon is by far the richest source of arachidonic acid in most Western diets and raises important questions regarding its consumption, especially by vulnerable populations (12). The objective of this study was to determine the current status of the PUFA content in the most commonly eaten fish.

MATERIALS AND METHODS

Seafood Sources

Samples of a wide variety of fish were obtained in 2005 through seafood distributors on both the east and west coast (Poseidon Seafood, Atlanta, GA; Red Chamber Co, Vernon, CA; and Trident Seafoods Corp, Seattle, WA). Samples from these distributors are representative of fish that would be served in restaurants and available in supermarkets. In addition, farmed salmon were obtained directly from two Chilean companies, AquaChile and Camanchaca. This is particularly relevant because 60% of the farmed salmon obtained on the east coast is Chilean in origin (personal communication with Alex Trent, executive director, The Salmon of the Americas). Additional samples of farmed tilapia, catfish, trout, and salmon were obtained from farms in Wisconsin, Idaho, North Carolina, Ecuador, Honduras, Norway, New Zealand, western Canada, and Chile and from supermarkets (Harris Teeter, Fresh Market, Lowes, Publix, Wegman’s, and Winn Dixie) in Alabama, Florida, North Carolina, and Pennsylvania. Samples of canned fish were purchased from supermarkets locally (Winston-Salem, NC). The study was designed using availability sampling, as not all fish farms and fish distributors contacted were willing to provide samples for analysis. Because the availability of many fish is seasonal, restaurant distributors could only provide samples of fish currently in stock. All fish were shipped overnight on dry ice. To ensure the integrity of the tissue samples, all sections were immediately snap frozen in liquid nitrogen and stored at −80°C until analysis.

Study Design

An initial study was conducted to examine the fatty acid profile of 30 species of wild and farmed fish by gas chromatography–flame ionization detection (see Figure 1). Approximately 1 g sections of tissue were taken from each fish in duplicate and analyzed as described below. These fish were then analyzed based on their n-3 fatty acid content. For all fish species, n=1, except: mahi mahi, cod, halibut, sockeye salmon, where n=2; farmed tilapia, where n=11; farmed catfish, where n=8; farmed Atlantic salmon, where n=16; and farmed trout, where n=7. A second study was then conducted to more closely examine the fatty acid profile and ratios in the four most commonly farmed fish, Atlantic salmon (n=16), tilapia (n=11), catfish (n=8), and trout (n=7).

Fatty Acid Methyl Esters Analysis of Fish Samples

Approximately 1 g from each fish was weighed and homogenized in 10 mL/g deionized water at high speed for 60 seconds. An aliquot was taken for fatty acid methyl
ester analysis following a modification of the protocol by Metcalfe and colleagues (13). Tubes were prepared containing 25 μg triheptadecanoin (17:0) (Nu-Check Prep, Elsyian, MN) in hexane as an internal standard. Homogenates were saponified with ethanol and 50% potassium hydroxide at 60°C for 30 minutes. Following base hydrolysis, neutral lipids (ie, nonsaponifiable lipids) were extracted and discarded. A second hexane extraction resulted in isolation of the liberated fatty acids and fatty acid methyl esters were derived using 12% boron trifluoride in methanol. Fatty acid methyl esters were dissolved in isooctane.

Gas Chromatography–Flame Ionization Detection Conditions
The system consists of an HP 5890 Series II gas chromatograph (Agilent Technologies, Inc, Santa Clara, CA) with direct-on-column inlet, HP 7673 auto-injector (Agilent Technologies, Inc, Santa Clara, CA), FID, Varian Select for FAME (part no. CP7420, Varian, Inc, Palo Alto, CA) column (100 m × 0.25 mm id) with a 1 m × 0.53 mm id precolumn. Carrier gas (hydrogen) was at 20 psi head pressure, 1.25 mL/min at 90°C; carrier make-up gas (nitrogen) at 20 mL/min. Temperature program was 90°C for 0.5 minute; 10°C/min to 150°C; 2.5°C/min to 200°C; 1.5°C/min to 220°C, hold 20 minutes. Total run time was 60 minutes plus a 5-minute equilibration. Component peaks were identified by retention time comparison to purified standards and standard mixtures. Data were reported as milligrams fatty acid per gram fish.

Statistical Analysis
Descriptive statistics, such as means, were calculated using Excel (version 11.8211.8202, 2003, Microsoft Corp, Redmond, WA).

RESULTS
n-3 PUFA
Initial studies were carried out to survey the n-3 concentrations and n-6: n-3 ratio of 30 commonly eaten fish.

Statistical Analysis
Descriptive statistics, such as means, were calculated using Excel (version 11.8211.8202, 2003, Microsoft Corp, Redmond, WA).

RESULTS
n-3 PUFA
Initial studies were carried out to survey the n-3 concentrations and n-6: n-3 ratio of 30 commonly eaten fish.

Figure 1 shows the concentrations of n-3 PUFAs per 100 g (approximately 3.5 oz) portion in these fish. As expected, there are marked differences in the concentrations of n-3 PUFAs in different species of fish, with the salmon and trout species having the higher concentrations of n-3s. Based on these initial data, fish species were divided into three categories; those that contained >500 mg n-3 fatty acids/100 g fish (Category 1), those that contained between 150 and 500 mg n-3 fatty acids/100 g fish (Category 2), and those that contained <150 mg n-3 fatty acids per 100 g fish (Category 3).

Category 1 Fish
Figure 2 and Figure 3 show the percentage of n-3 PUFAs, n-6 PUFAs, monounsaturated fatty acids (MUFAs), and SFAs in a given fish. Fish in each category have been arranged from highest to lowest percentages of n-3 PUFAs. All fish within Category 1 (Figure 2) with the exception of bronzi contained high concentrations of n-3 PUFAs and low concentrations of n-6 PUFAs. It is noteworthy that sockeye salmon contained both high concentrations of n-3 PUFAs and low concentrations of n-6 PUFAs resulting in a very favorable n-3 to n-6 ratio. Coho salmon, Copper River salmon, and farmed rainbow trout also contained beneficial concentrations and ratios of n-3 PUFAs and n-6 PUFAs. Although farmed Atlantic salmon contained high concentrations of n-3 PUFAs, they also contained much higher concentrations of n-6 PUFAs.

Category 2 Fish
Examination of Category 2 fish (containing between 150 and 500 mg n-3 per 100 g fish) revealed that most fish in this category also had favorable n-3 to n-6 ratios with two notable exceptions (Figure 3). Both farm-raised tilapia and farm-raised catfish had considerably higher concentrations of n-6 PUFAs when compared to n-3 PUFAs. In both cases, this resulted in n-6 to n-3 ratios >2.
The ratios of n-6:n-3 PUFAs are shown in Figure 5C. As anticipated from results shown in Figure 2, both farm-raised Atlantic salmon and trout have ratios well below 1, whereas both tilapia and catfish have ratios >2. Total n-3 and n-6 PUFAs are often reported when assessing the health benefits of a fish. However, 18 carbon n-3 or n-6 PUFAs such as α-linolenic acid and linoleic acid, respectively, are poorly converted to very long-chain n-3 or n-6 PUFAs by human beings (17). Because 20 to 22 carbon very long-chain fatty acids are likely responsible for most of the biological activities attributed to fish, determining concentrations of very long-chain n-3 and n-6 PUFAs is most critical when considering the health benefits of fatty acids in given fish (11,18). Consequently, the ratios of the two primary 20 carbon n-6 and n-3 eicosanoid pathway substrates, arachidonic acid and EPA, were determined (Figure 5D). Both farmed tilapia and catfish contained high arachidonic acid:EPA. Although there was a great deal of variability in the arachidonic acid:EPA ratio in farm-raised tilapia, the average ratio was approximately 11:1, with two fish samples harvested in Central America containing more than 20 times more arachidonic acid than EPA. The ratio of PUFAs in these fish is high predominantly because they contain high quantities of arachidonic acid, with an average of 134 mg and 67 mg arachidonic acid for tilapia and catfish, respectively, with some tilapia samples from Central America containing >300 mg arachidonic acid per 100-g portion. To put this into perspective, a 100-g portion of hamburger (80% lean) contains 34 mg arachidonic acid, whereas a doughnut contains 4 mg arachidonic acid and 100 g pork bacon contains 191 mg arachidonic acid (19). For individuals who are eating fish as a method to control inflammatory diseases such as heart disease, it is clear from these numbers that tilapia is not a good choice. All other nutritional content aside, the inflammatory potential of hamburger and pork bacon is lower than the average serving of farmed tilapia. In contrast to tilapia and catfish, farm-raised salmon and trout contained low ratios of arachidonic acid to EPA (approximately 0.2), largely due to their high concentrations of EPA. These data with farmed salmon are consistent with a recent study by Hamilton and colleagues (12) and are in contrast to those reported by the USDA (19), which states that farm-raised Atlantic salmon contains much higher levels of arachidonic acid (1.152 mg/100g) and an arachidonic acid to EPA ratio of 1.9:1.

**DISCUSSION**

Taken together, these data raise important questions regarding the influence of aquaculture in changing the pattern of consumption of key fatty acids known to affect the health of human beings. The most rapidly expanding fish in terms of world and US consumption, tilapia, as well as farmed catfish, have several fatty acid characteristics that would generally be considered by the scientific community as detrimental. First, they have much higher SFA+MUFA:PUFA ratios with atherosclerosis progression and increased risk of cardiac events (14-16). Figure 5B shows this ratio in farmed salmon, tilapia, catfish, and trout. Whereas trout and salmon contain favorable ratios of ~<2, tilapia and catfish contain ratios of SFA+MUFA:PUFA of approximately 4.

Epidemiologic studies and clinical trials in both human beings and nonhuman primates have correlated SFA+MUFA:PUFA ratios with atherosclerosis progression and increased risk of cardiac events (14-16). Figure 5B shows this ratio in farmed salmon, tilapia, catfish, and trout. Whereas trout and salmon contain favorable ratios of ~<2, tilapia and catfish contain ratios of SFA+MUFA:PUFA of approximately 4.
associated with atherosclerosis, recent studies suggest
that the desaturation of saturated fats such as stearate to
oleic acid by stearoyl-coenzyme A desaturase appears to
be an essential step in mediating the induction of obesity,
insulin resistance, and dyslipidemia (20-23). Conse-
quently, ratios this high would be predicted to induce, not
protect from, diseases such as atherosclerosis.

**Concerns Regarding Dietary Arachidonic Acid**

The concentrations of n-6 PUFA arachidonic acid in farmed tila-
pia and catfish are very high. In fact, these fish contain
some of the highest levels of arachidonic acid found in
human beings’ food chain. There is a controversy among
scientists in this field as to the importance of arachidonic
acid or n-6:n-3 ratios vs the concentration of long-chain
n-3 alone with regard to their effects in human biology
(24,25). Harris and colleagues (26) have published several
articles indicating that dietary arachidonic acid or n-6:
n-3 ratios have no influence on CHD. This tenet is based
on several lines of reasoning. First, an earlier study in 10
healthy male volunteers showed no proaggregation ef-
teffects of high doses of dietary arachidonic acid and no
effects on what the authors termed immune function (26).
Second, a recent study showed that supplementation of a
Japanese diet with 840 mg arachidonic acid had no effects
on platelet function (27). Given the limitations of these
studies, it is difficult to understand how either of these
studies speaks to the issue of whether or not dietary
arachidonic acid or ratios of long-chain n-6:n-3 fatty acids
have an effect on disease progression in vulnerable pop-
ulations. In the former study, dietary arachidonic acid
caused more than four-fold increase in the ex vivo capac-
ity of peripheral blood mononuclear cells from these vol-
tunteers to produce leukotriene B4. Given the central role
that leukotrienes play in the pathology of disease in hu-
man beings, especially inflammatory disease, this cer-
tainly questions the conclusion that there was no effect
of arachidonic acid. In the latter study, arachidonic acid was
fed to a Japanese population and fatty acid measure-
ments of platelets in phospholipids or triglycerides were
taken. The Japanese population consumes huge quanti-
ties of n-3 fatty acids each day from birth (>800 mg/day
normally and >800 mg/day EPA+DHA in the study diet).
Consequently, it would be predicted that the high concen-
trations of EPA already in platelet phospholipids would
prevent a marked change in the arachidonic acid:EPA
ratio or in platelet aggregation as a result of an increase
in arachidonic acid. However, without platelet phospho-
lipid data, it is not possible to make that determination.

The real question is whether or not dietary arachidonic
acid affects disease progression in vulnerable popula-
tions. In this regard, several studies, including Neilson
and colleagues (28-31), indicate that there is a strong in
vivo correlation between arachidonic acid consumption
and eicosanoid production. The first reported study of
oral administration of highly enriched esterified arachi-
donic acid to human beings was carried out in 1975 at
Vanderbilt University in John Oats’ laboratory and dem-
onstrated a marked increase in urinary prostaglandin E
metabolites as well as a significant reduction in the
threshold necessary to induce secondary, irreversible ag-

![Diagram of fatty acid concentrations in farmed fish](image-url)
gregation of platelets (30). Most disturbingly, several individuals were removed from that study due to concerns regarding platelet reactivity. Other vulnerable populations markedly overproduce eicosanoids. For example, several polymorphisms related to leukotriene generation have been identified in asthmatic populations and a large proportion of asthmatics overproduce leukotrienes (32,33). Interestingly, these patients are 11 times more likely to respond to cysteinyl leukotriene blockers than asthmatics who do not overproduce leukotrienes (34,35).

A more recent study by Dwyer and colleagues (36) demonstrated a strong association between a polymorphism in the 5-lipoxygenase gene promoter and an increase in intima-media thickness (a common measurement of cardiovascular risk). Interestingly, dietary arachidonic acid was associated with enhanced atherogenesis in this genotype. In contrast, increased dietary intake of EPA and DHA blunted this effect. The diet–gene interactions observed in these studies were specific to these fatty acids. Consequently, with respect to individual diseases, increases in arachidonic acid likely have different effects depending on the specific eicosanoids produced, the cell type that is activated, the disease in question and, as more recent studies are informing us, on the genotype of the individual afflicted.

Concerns Regarding the Use of Nutrition Databases to Assess Risk

A second argument that has been used to support the contention that dietary arachidonic acid or n-6 to n-3 ratios have little relevance are studies that have examined the relationship of either the fatty acid composition of various tissues acquired in the course of a number of studies or the fatty acid composition of food ingested from food frequency questionnaires to cardiovascular risk. In regard to the latter, the USDA National Nutrition Database is most frequently used to determine the fatty acid composition of foods. With regard to fish, if one scans the most recent version (Release 20) and examines farm-raised Atlantic salmon or tilapia, there were two and three data points, respectively, used to obtain the fatty acid quantities in the nutrient chart. It is not clear if these are analyses from one, two, or three fish. Most troubling is that farm-raised salmon is listed as having 1,150 mg arachidonic acid and 618 mg EPA per 100 mg portion. Our study taking duplicate samples from 28 fish throughout North America and the study by Hamilton and colleagues (12) that measured 459 farm-raised Atlantic salmon indicate that there is approximate five times more EPA than arachidonic acid in current stocks of farm-raised salmon and arachidonic acid concentrations are several-fold lower than indicated in Database 20. Indeed, this is good news for consumers who are ingesting farm-raised Atlantic salmon. The news is not so good with tilapia; here, Database 20 states there is 30 mg arachidonic acid per 100 mg in tilapia. However, our study shows that the amount of arachidonic acid depends largely on where the fish is obtained, with Central American tilapia containing as much as 10 times the 30 mg suggested by the USDA database. Because farm-raised Atlantic salmon and tilapia are major sources of fish for many individuals in the United States, using databases such as Database 20 to determine relationships of arachidonic acid to disease will likely lead to wrong conclusions. For example, using this database in a population that eats large amounts of farm-raised Atlantic salmon with resulting cardiovascular benefit will give the false impression that dietary arachidonic acid is beneficial in cardiovascular disease.

Metabolism of Cellular and Tissue Arachidonic Acid and EPA

Similarly, meta-analyses examining the relationship between tissue arachidonic acid levels and cardiovascular risk have been interpreted to show no relationship. However, the tissues analyzed have arachidonic acid ranges from <5% of total fatty acids to >25% of fatty acids. Even worse is the fact that some of the analyzed tissues are highly enriched in triglycerides and others in phospholipids. Biochemical studies have established that arachidonic acid is incorporated into triglycerides (via de novo glycerolipid biosynthesis) (37) and phospholipids (via arachidonic acid-phospholipid remodeling) by different mechanisms depending on the concentration of arachidonic acid presented to cells (38). In addition, arachidonic acid in different glycerolipids is located in different cellular pools and locations. Arachidonic acid in remodeled phospholipids is mobilized for eicosanoids (39) whereas arachidonic acid in triglycerides is not (40). Thus it is unlikely that simple analyses that place all arachidonic acid pools together will be able to predict with any precision whether dietary arachidonic acid is an important risk factor for disease in human beings.

Although the effect of altering the dietary ratio of arachidonic acid:EPA has yet to be determined, it is known that increasing EPA relative to arachidonic acid both in vitro and in vivo blocks prostaglandin formation from arachidonic acid by inhibiting cyclooxygenase-1 (41-43). In addition, cells such as platelets can convert EPA to thromboxane A₃ via cyclooxygenase-1 (44,45). EPA may also increase production of prostacyclin, which has been shown to diminish platelet aggregation (46). Another critical effect of increasing EPA:arachidonic acid is that it enhances the formation of prostaglandin E₃ (PGE₃) from EPA utilizing cyclooxygenase-2 (47,48). PGE₃ is thought to block inflammation, whereas arachidonic acid derived PGE₂ may promote inflammation. More recently, both EPA and DHA have been shown to be converted into anti-inflammatory mediators known as resolvins and protectins (11,18). Consequently, the ratio of arachidonic acid to long-chain n-3 PUFAs in diets of human beings is likely to be an important factor that regulates the balance of arachidonic acid and fish oil-derived eicosanoids produced.

How Did We Get Here?

There are several factors that may contribute to the marked differences observed in the fatty acid profiles of tilapia. Tilapia is a very hardy fish that grows rapidly on formulated feeds that contain lower protein levels, higher carbohydrate levels, and a wide range of fat sources compared with many other carnivorous farmed species (5). They are easy to breed and can be cultured intensively and economically in systems ranging from rural ponds to situations where the nutrition is exclusively dependent

July 2008 ● Journal of the AMERICAN DIETETIC ASSOCIATION 1183
on commercially formulated diets. Fish from the most intensively farmed system are typically fed higher levels of the 18 carbon n-6 fatty acid linoleic acid from vegetable oils as part of the feed (49). This, in turn, is efficiently converted through two desaturation steps and an elongation step to arachidonic acid that is found in tissues. Tilapia appears to represent an important example where an intensely farmed fish has a much higher content of SFA, MUFA, and linoleic acid leading to high concentrations of arachidonic acid and high n-6:n-3 ratios. Unfortunately, aquaculture, which holds such promise as a PUFA source from fish, can give rise to detrimental and potentially harmful PUFAs when fatty acid precursors of those PUFAs fed to fish are not taken into account.

Numerous clinical studies have been conducted with the conclusion that increased fish consumption reduces the risk of CHD (50). In addition, the AHA recommends that individuals consume fish at least twice per week. Although the AHA does specify fatty or oily fish as preferable, specific types of fish are not highlighted as especially healthful or especially unhealthful. Without being given certain fish to either look for or avoid, the general population is likely to purchase the fish that is most readily available at the supermarket, or the fish that costs the least. Farmed tilapia certainly fits into both categories. Since 2000, shipments of frozen tilapia fillets from China to the United States (representing 66% of imports) have risen from 4 million to 140 million lb. Chinese frozen tilapia fillets averaged $1.38 per lb in 2006, about even with the previous 2 years (51). Although convenience and price will clearly be important drivers in the marketplace, our study shows that the drastically different nutrition profiles must be taken into account when deciding on or recommending fish to consume. This study has several limitations. First, although fish were sampled from a wide variety of sources throughout the United States and other countries, it would be impossible to sample fish from every source worldwide. Notably absent from this study are fish from Asian and European sources. In addition, the analyses focus on fish that are commonly eaten in the United States, whereas fish often eaten in other parts of the world may have been neglected from the study. A final limitation of this study is that the sampling of fish was not random. The sampling was based on which species were available and which distributors were willing to provide samples for analysis. Although every effort was made to sample fish from a wide variety of geographical locations, it was not possible to sample all locations and fish species equally.

Can Tilapia Offer Public Health Benefits or Harm?

Despite recommendations from organizations such as the AHA to increase fish consumption in general, this study shows that not all fish are created equal. The initial overview of fish alone shows that there is a range of n-3 fatty acid content from practically none to nearly 4,000 mg per 100 g fish. Closer inspection of the four most commonly farmed fish, Atlantic salmon, tilapia, catfish, and trout, reveals yet another discrepancy in the general ideal that it is healthful to eat fish. Whereas farmed Atlantic salmon and farmed trout have some of the highest levels of n-3 fatty acids, combined with low levels of arachidonic acid, farmed tilapia and catfish have low levels n-3 fatty acids along with levels of arachidonic acid so high they can be considered detrimental. Taken together with tilapia’s explosive growth and its relatively inexpensive price at best gives vulnerable populations a false sense of security in their dietary choices and at worst renders them more vulnerable. Clearly it is necessary to educate the population on the health differences between species of fish to negate the widely held belief that eating any fish is beneficial.

This research was funded by National Institutes of Health (NIH) Grant P50 AT0027820 from the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements (ODS). Funding was also provided by the NIH Molecular Medicine Training Grant No. T32 GM63485.

The authors thank Monica Pace for her administrative assistance.

References

15. Ma J, Folsom AR, Lewis L, Eckfeldt JH. Relation of plasma phospholipid and cholesterol ester fatty acid composition to carotid artery


50. Sinclair AJ, Mann NJ. Short-term diets rich in arachidonic acid influence plasma phospholipid polyunsaturated fatty acid levels and prostacyclin and thromboxane production in humans. J Nutr. 1996;126(suppl):1110S-1114S.


Research Editorial

You Are What You Eat Applies to Fish, Too

WILLIAM S. HARRIS, PhD

The health benefits of fish have long been touted based on their low fat content, excellent protein quality, and available micronutrients. Recently, calls for increased “oily fish” intake have been on the rise. Several large epidemiological investigations, as well as randomized clinical trials (1,2), have underscored the cardiovascular benefits of n-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), nutrients found almost exclusively in seafood. The 2007 recommendations from the American Dietetic Association (ADA) and the Dietitians of Canada (DC) are the latest to join in a growing international chorus (3) specifying a healthful diet. The ADA/DC (which mirrors that of the American Heart Association [AHA]) to consume “two servings per week, preferably of fatty fish” (1). Pertinent to these recommendations is the report from Weaver and colleagues in this issue of the Journal (4).

Weaver and colleagues (4) make the important point that not all fish are n-3—rich. Certain popular species, such as farmed catfish and tilapia, are very low in fat and therefore in n-3 fatty acids. The American public—despite the best efforts of groups like the AHA and the ADA/DC to specifically promote “oily” or “fatty” fish—may assume that all fish provide heart-healthy n-3 and end up consuming species that provide essentially none. Besides tilapia and catfish, species like cod, mahi-mahi, and shrimp all fall into this category. Although when baked or broiled these types of seafood remain good choices relative to most terrestrial meats, they become decidedly bad choices when breaded and fried. Contrary to popular opinion, deep-fried fish sticks are not what we mean by fatty fish! It is incumbent upon food and nutrition professionals to continue to be vigilant in explaining to clients and the public which fish are good sources of n-3 fatty acids, and which provide no more benefit than a bologna sandwich. Weaver and colleagues are helping in this educational effort.

W. S. Harris is director, Metabolism and Nutrition Research Center, Sanford Research, University of South Dakota, Sioux Falls.

Address correspondence to: William S. Harris, PhD, Metabolism and Nutrition Research Center, Sanford Research, University of South Dakota, 1100 E. 21st St, Suite 700, Sioux Falls, SD 57105. E-mail: Bill.harris@usd.edu

Manuscript accepted: March 31, 2008.

Copyright © 2008 by the American Dietetic Association.

0002-8223/08/10807-0019$34.00/0

TILAPIA

Tilapia is a primary focus of Weaver and colleagues (4). According to National Fisheries Institute statistics (5), the top five fish/seafood consumed in America during the last 7 years have been, in decreasing order, shrimp, tuna, salmon, pollock, and catfish. In 2001, tilapia was not even in the top 10, but by 2006 it had displaced catfish in the number 5 position. It is clearly a fish on the rise. Based on data from the Nutrition Data Laboratory at the US Department of Agriculture (USDA), tilapia, like catfish, is very low in n-3 fatty acid, providing about 120 mg EPA+DHA/100 g (6), about 1/20th of that provided by farmed salmon. In this regard, the data presented in Figure 1 in the article by Weaver and colleagues (4), which show the n-3 fatty acid content of various fish, should be considered only as very rough estimates. This is partly because the sample sizes were so small (typically one fish) and partly because some values are in stark disagreement with USDA data. For example, “tuna” (presumably chunk light tuna) is listed as the lowest in n-3 fatty acids of all species tested. The Nutrient Data Laboratory value for canned light chunk tuna packed in water is 270 mg EPA+DHA per 100 g. Cod, on the other hand, has 184 mg EPA+DHA per 100 g according to the USDA, and yet it is far up the list from tuna in this Weaver and colleagues’ figure. Farmed catfish is listed above swordfish, and yet USDA values for these two fish are 177 and 819 mg/100 g, respectively. These concerns raise questions about the validity of the other fatty acid compositions reported in Weaver and colleagues’ article. On the other hand, it must be appreciated that most USDA data on fish composition are based on no more than 12 samples, and for some nutrients these samples are pooled (into between 6 and 1 blended samples) before analysis. Hence, the full variability of fatty acid content cannot be discerned from the USDA tables.

ARACHIDONIC ACID

But Weaver and colleagues (4) are not just concerned about the lack of n-3 fatty acids in low-fat fish like tilapia and catfish, they also focus on the presence of n-6 fatty acids, specifically arachidonic acid. Arachidonic acid is the metabolic product of linoleic acid, the classic “essential fatty acid” found in abundance in the American diet. Current linoleic acid intakes are about 6% to 7% of energy (7), far higher than the presumed nutritional requirement of about 0.5% to 1% of energy. Weaver and colleagues propose that arachidonic acid and linoleic acid are proinflammatory, proaggregatatory, and ultimately proatherogenic components of foods and thus should be minimized. Here is the fundamental issue raised by this article: Are current intakes of n-6 fatty acids, especially arachidonic acid, “bad” for us? Is a fish like tilapia a net
nutritional negative? Indeed, Weaver and colleagues assert that “the inflammatory potential of hamburger or pork bacon is lower than the average serving of farmed tilapia.” If increased arachidonic acid intakes are harmful, as these authors argue, then their points may, depending on exact intakes, have merit; but if arachidonic acid is not harmful, then the issues raised here may be much ado about nothing. What is the evidence regarding the health effects of arachidonic acid (and linoleic acid)? Is our current intake detrimental? Would heart health be served by reducing our n-6 fatty acid intake?

Arachidonic acid is the precursor to a wide variety of highly bioactive molecules called “eicosanoids” (eicosa-20, the number of carbons in arachidonic acid and in these metabolites). Some are proinflammatory, vasoconstrictive, and/or proaggregatory, such as prostaglandin E2, thromboxane A2, and leukotriene B4. However, others are antiinflammatory/antiaggregatory, such as prostacyclin, lipoxin A4, and epoxyeicosatrienoic acids (6). The latter are fatty acid epoxides produced from arachidonic acid by a cytochrome P450 epoxygenase. Epoxyeicosatrienoic acids also have vasodilator properties, causing relaxation of vascular smooth muscle cells (7). Production of arachidonic acid from linoleic acid is tightly regulated (8), which explains why wide variations in dietary arachidonic acid (above minimal essential intakes) do not materially alter tissue arachidonic acid content (9).

Hence, higher linoleic acid consumption does not translate into higher membrane arachidonic acid levels, as is widely assumed. In human studies, higher plasma levels of n-6 polyunsaturated fatty acids, mainly arachidonic acid, were associated with decreased plasma levels of serum proinflammatory markers, particularly interleukin-6 and interleukin-1 receptor antagonist, and increased levels of antiinflammatory markers, particularly transforming growth factor-β (10). Observational studies agree; higher n-6 polyunsaturated fatty acid consumption is associated with unchanged or lower levels of inflammatory markers (11).

In addition, the assertion that consumption of higher amounts of arachidonic acid is harmful fails to consider relevant human experimental evidence. In the mid-1990s, an ambitious study was undertaken at the Western Human Nutrition Research Center in San Francisco. Nelson and colleagues sought to examine the effects of high but achievable intakes of arachidonic acid on a wide variety of physiological factors and biochemical markers (12-15). The study was undertaken because of concerns that remained after an earlier arachidonic acid feeding study of four men, in which ex vivo platelet reactivity was found to increase after feeding 6 g/day of arachidonic acid ethyl esters (16). Considering that 6 g/day was physiologically irrelevant, Nelson and colleagues recruited 10 healthy male volunteers and subjected them to 100 days of completely controlled feeding. For the first 50 days, half of the men consumed the control diet that provided typical amounts of arachidonic acid (about 200 mg/day), and the other half ate a diet providing 1,500 additional mg of arachidonic acid per day. During the second 50-day period, the diets were switched. At the end of each period the investigators measured the fatty acid composition of a variety of tissues: they assessed platelet function, measured serum lipids and production of proaggregation and antiaggregation eicosanoids, and examined several aspects of the immune response. Interestingly, bleeding times tended (P=0.06) to be longer, not shorter, with higher arachidonic acid intake (14). Their conclusion after all these studies was that “... results from this study suggest that dietary arachidonic acid fed at 1.5 g/d is not harmful to humans, nor does it affect blood lipid levels or platelet function while only having minimal effects on the normal immune response” (17). Likewise, in a recent study from Japan, arachidonic acid supplementation (840 mg/day for 4 weeks) had no effect on any metabolic parameter or platelet function (18). Finally, Dwyer and colleagues reported that 6% of subjects in a cohort of ostensibly healthy individuals had dual defects in the gene that codes for 5-lipoxygenase, an enzyme that converts arachidonic acid into inflammation-mediating leukotrienes (19). In this subset, dietary arachidonic acid was directly associated with carotid intimal-medial thickness, a marker of atherosclerosis. Although cause-and-effect relations cannot be deduced from cross-sectional studies, these findings do suggest, as Weaver and colleagues (4) note, that there are certain individuals in whom higher intakes of arachidonic acid could be of concern. Nevertheless, in this reviewer’s opinion, evidence from relevant human studies that a higher consumption of arachidonic acid promotes atherosclerosis and coronary heart disease is quite weak, and the assertion that because a serving of tilapia contains more arachidonic acid than hamburger or bacon it has greater “inflammatory potential,” is based on a potentially flawed conception of the physiological impact of dietary arachidonic acid.

Similarly, Weaver and colleagues (4) refer to the arachidonic acid/EPA ratio as a valid marker of inflammatory potential of foods. To the extent that this ratio is elevated because of increased arachidonic acid levels, the studies described here would argue that this may not be a problem. To the extent that this ratio is elevated because of a low intake of EPA, there may be validity to it, but the problem would be corrected by eating more n-3 fatty acid, not being less arachidonic acid. Not only is the arachidonic acid/EPA ratio a metric of dubious utility, there is even more doubt regarding the value of the n-6 to n-3 ratio. Use of this ratio has been rejected by UK Food Standards Agency (20), and no recommendations from governmental or professional organizations (including the ADA/DC) published in the last 6 years have embraced the ratio concept. The problems with this metric have been discussed in detail previously (21), and may be summarized briefly as follows:

1. Long-chain n-6 and n-3 fatty acids have markedly different physiological properties compared to their shorter-chain cousins (ie, EPA and DHA vs alphalino- leic acid [ALA], and arachidonic acid vs linoleic acid). Without defining which n-6 and which n-3 fatty acids comprise the ratio, there is no way of knowing the mix of long- and short-chain fatty acids included.
2. Ratios are mathematically problematic because the same numerical value can be achieved with frankly deficient or vastly excessive values for both the numerator and the denominator. Thus, setting target ra-
tios—whether for diets or for use as biomarkers of disease risk—provides no meaningful guidance.

3. Ratios can be manipulated by altering the numerator, the denominator, or both. There is an infinite number of intakes of both n-3 and n-6 fatty acids that will give the same ratio.

4. Lowering the ratio by eating more long-chain n-3 fatty acids will bring health benefits, whereas lowering the ratio by eating less n-6 fatty acids will not. In fact, considerable evidence suggests that doing the latter can actually increase risk for coronary heart disease (22,23).

Reliance on ratios to guide food decisions is ill-conceived. It distracts from the simple message endorsed by the AHA, the ADA/DC, and a growing number of governmental agencies around the world (24)—increase the intake of long-chain n-3 fatty acids—and leads the uninformed consumer to assume that eschewing vegetable oil is equivalent to taking fish oil. This is clearly not the case. Weaver and colleagues (4) are right on target in pointing out that some fish are far better sources of n-3 fatty acids than others and, sadly, that it is the cheaper fish that tend to provide lower amounts. Their call for organizations like the AHA to be specific in recommending certain fish as heart-healthy is well-taken, and the more recent ADA/DC position paper does just that. To conclude, the n-6 fatty acids, whether linoleic acid or arachidonic acid, are not the enemy—the problem is the American proclivity for foods low in n-3 fatty acids (including tilapia and catfish), and it is one that food and nutrition professionals are uniquely positioned to correct.

References
Regarding Favorable and Unfavorable PUFA in Fish

To the Editor:

We would like to thank Dr Harris for his thoughtful comments regarding our paper on favorable and unfavorable polyunsaturated fatty acids found in commonly eaten fish in the July 2008 issue of the Journal (1). Harris is a world-recognized and respected nutritionist, and his thoughts in the form of a Research Editorial (2) are greatly appreciated.

We feel it would be unproductive to issue a point-by-point response to his critique—many of these points were covered in the discussion of the manuscript. As we stated in our introduction of our paper, the objective of our study was “to determine the current status of the polyunsaturated fatty acid (PUFA) content in the most commonly eaten fish.” We feel this objective was accomplished with scientific rigor. We concluded simply, and without controversy, that “these data raise important questions regarding the impact of aquaculture in changing the pattern of consumption of key fatty acids known to affect human health.” Following this we concluded, “While convenience and price will clearly be important drivers in the marketplace, the current study shows that the drastically different nutritional profiles must be taken into account when deciding or recommending fish to consume.” It would appear that Harris has no major issues with these salient points of our study, so we are tempted to leave it at that. However, we found within the editorial other substantive issues worthy of additional mention.

First, Harris questions the analytical aspects of our study and admonishes the readers that our “n-3 fatty acid content of various fish should be considered only as very rough estimates.” In fact, the data in Table 1 are not rough estimates, but precise measurements, using state-of-the-art biochemical chromatographic techniques. The data describe the precise fatty acid composition of the fish we obtained from the common sources delineated in the methods. It is not feasible to do these types of costly measurements on fish obtained from all major fish markets and fish farms throughout the world, so of course, the data in Table 1 are not meant to provide precise information on the lipid content of the fish that you may eat tonight for dinner. This, we should think, is an obvious and therefore implicit caveat of our study.

Second, Harris would appear to have a problem with our statement: “Several studies indicate that there is a strong in vivo correlation between AA [arachidonic acid] consumption and eicosanoid production.” It is worth noting that this is not controversial among experts in the field and we supported this declarative sentence by citing four studies published in prestigious journals. Note that our statement does not mention anything about disease states as these studies, for ethical reasons, are typically carried out on healthy human volunteers. What we in the field have ascertained, with some degree of certainty, is that high levels of dietary arachidonic acid is associated with an elevation in eicosanoid production. In addition, new ground-breaking studies indicate that another primary means by which polyunsaturated fatty acids such as arachidonic acid affect human disease is their influence on gene expression through Toll-like receptors and nuclear receptors such as PPARα, PPARγ, and more indirectly NFKβ. With respect to diseases, increases in eicosanoid production or changes in gene expression may have beneficial or harmful effects depending on the specific eicosanoid and gene product, the cell type that is activated, the disease in question and, as more recent studies are informing us, on the genotype of the individual afflicted. It is therefore left to the reader to use basic syllogistic logic to draw conclusions regarding potential pathophysiological consequences of the noted changes in eicosanoids and gene expression.

However, it would seem to us to be rather cavalier, if not naive, to conclude that the increased eicosanoid production and changes in gene expression associated with increases in dietary arachidonic acid is irrelevant to human health, based on one study with a small number of healthy human volunteers (3), and another with a healthy population that consumes very high concentrations of long-chain n-3’s each day (4), as Harris seems to want to do.

In fact, this is exactly what Harris has cautioned us not to do in his comment in the Journal of the American Medical Association (5) last year. Here, Harris stated that, “The rate of CHD [coronary heart disease] death among Japanese individuals is very low, and their intake of EPA [eicosapentaenoic acid] and DHA [docosahexaenoic acid] is very high compared with Western populations, but it seems inappropriate to include those cohorts in this analysis because of the marked differences between overall Western and Japanese diets.” We believe Harris is exactly right with regard to different study populations consuming dissimilar diets but also different patient populations. Moreover, we must be especially careful stating that dietary arachidonic acid has no effects on human health when there is a study in the scientific literature that shows a disturbing diet–gene interaction with dietary arachidonic acid in a vulnerable population (6).

We are all familiar with the classical Hippocratic admonition, Primum non nocere “First, do no harm.” I think it behooves us to consider this critical directive when making dietary prescriptions for the sake of health. With this thought in mind, we may have to reconsider advising, unqualifyingly, that those with cardiovascular disease (and other inflammatory diseases) should increase their dietary intake of fish. In the mid-1970s, we began turning to aquaculture for our dietary fish. Our paper, as well as others (7), reveals that farmed Atlantic salmon and trout are rich sources of n-3 fatty acids and have acceptable ratios of long-chain n-6 to n-3 polyunsaturated fatty acids. However, we have pointed out in our paper that farmed tilapia and catfish have levels
of long-chain n-6's and ratios of long-chain n-6 to n-3's as well as saturated + monounsaturated to polyunsaturated fatty acid ratios that might cautiously be deemed as unhealthy by many scientists who have been working in this field.

These points can and should be debated, but in the face of controversy, our first responsibility is to do no harm. If our hypothesis is incorrect and dietary arachidonic acid has no pro-inflammatory potential and altering n-6 to n-3 ratios is irrelevant with regard to human health, then we have published a paper that simply points out that the fastest growing fish in terms of fish production and consumption is, from a nutritional perspective, less than optimal. However, if dietary arachidonic acid is important, especially in vulnerable populations, as current literature suggests, then the ingestion of an additional 200 to 400 mg arachidonic acid in a fish that contains an arachidonic acid to eicosapentaenoic acid ratio ranging between 10 and 25 on a regular basis could have negative consequences regarding the incidence and severity of inflammatory disease.

Author’s Response:
I appreciate the opportunity to comment on Dr Chilton’s comments about my Research Editorial. He indicates that I disagreed with the statement that: “Several studies indicate that there is a strong in vivo correlation between AA [arachidonic acid] consumption and eicosanoid production.” In fact, I do not dispute that higher arachidonic acid intakes lead to higher production levels of eicosanoids. The Ferretti study (1) confirms this. What I dispute is the assumption that this is harmful. An increase in “vasoactive” eicosanoids can mean vaso-constrictive (adverse) and/or vaso-dilatory (beneficial) species. In this study, the balance between these two types of eicosanoids did not change with arachidonic acid feeding. No actual harm was observed.

Chilton further notes that there is a “disturbing” (pro-atherogenic) genetic interaction with dietary arachidonic acid in a population with a mutation in the 5-lipoxygenase gene (2). Unfortunately, more recent studies were unable to demonstrate that these mutations actually increased risk for coronary heart disease (CHD) (3.4). Hence, a relationship between arachidonic acid intake and CHD, which is unsupported by direct evidence, is even less plausible in light of these new data.

“First, do no harm.” No one disagrees with this dictum. I simply disagree that current evidence demonstrates that a higher-than-usual intake of arachidonic acid is actually harmful. I also disagree that the American Heart Association (or any health agency [5]) “unqualifyingly” recommends fish for CHD risk reduction; all clearly focus on “oily” fish. Tilapia or catfish are not on anybody’s short list of high n-3 fish, but compared to hamburger or bacon, they win hands down.

I completely agree with Chilton that the public needs to be better educated as to which fish are best for heart health. I simply object to the vilification of low n-3 fish (even if they might contain higher amounts of arachidonic acid) as “pro-inflammatory” and “pro-atherogenic.” Such allegations require more than a theoretical foundation.

William S. Harris, PhD
Director
Metabolism and Nutrition Research Center
Sanford Research/USD
Sioux Falls, SD

References

doi: 10.1016/j.jada.2008.08.025

Concern over Ready-to-Eat Breakfast Cereals

To the Editor:
The Research and Professional Brief published in the April 2008 issue of the Journal entitled “Examining the Nutritional Quality of Breakfast Cereals Marketed to Children” (1) is of concern. The authors concluded that “the majority of children’s cereals failed to meet national nutrition standards, particularly with respect to sugar content.” Thus, they recommend that “dietary advice for children to increase consumption of ready-to-eat breakfast ce-