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 intake of EPA and DHA, now set at 500 mg/day. Achieving that intake will require following the recommendation of 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 (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.

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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/100 g, whereas, on the other hand, has 184 mg EPA+DHA/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, proaggregatory, 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 (5), 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 linoleic 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 be eating 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 alphalinoleic 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-
Ratios can be manipulated by altering the numerator, the denominator, or both. There is an infinite number of ratios of both n-3 and n-6 fatty acids that will give the same ratio.

3. 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 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