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## *Invited Commentary*

# *n*-3 Fatty acid fortification: opportunities and obstacles

There is a growing recognition that low tissue levels of long-chain *n*-3 fatty acids (LC *n*-3 FA; EPA and DHA) are associated with increased risk for coronary heart disease (CHD) (Wang *et al.* 2006), and perhaps neuropsychological diseases (Hibbeln *et al.* 2006). The most direct approach to correcting this deficiency is, of course, to increase the dietary intake of foods rich in these FA, which typically means fish and shellfish. Indeed, the American Heart Association has recommended that adults without known CHD consume at least two preferably oily fish meals per week to reduce their risk for cardiac events (Kris-Etherton *et al.* 2002). Similar recommendations have been made by health authorities in the United Kingdom (Scientific Advisory Committee on Nutrition/Committee on Toxicology, 2004) and Australia (National Health & Medical Research Council, 2006). However, it is not clear whether the world's oceans could meet this demand. According to a recent report, we are witnessing an ever accelerating loss of ocean biodiversity which could lead to 'the global collapse of all taxa currently fished by the mid-21st century'(Worm *et al.* 2006). Whether this dire prediction will prove to be true or not, the strategy of providing *n*-3 FA via 'a fish in every pot' may not be realistic. However at present, there are few substitutes for the LC *n*-3 FA in seafood. So where can we turn in order to obtain these FA?

There are several options, including increased production of oil-rich but inedible fish species (e.g. menhaden), the use of single-celled organisms to biosynthesize EPA and DHA (Meyer *et al.* 2004), and the use of biotechnology to produce both plants (Ursin, 2003) and animals (Lai *et al.* 2006) enriched in LC *n*-3 FA. Each of these approaches will play a part in meeting the growing demand for EPA and DHA. But how will these FA actually reach the consumer if not in a fish fillet? It is here that the report by Murphy *et al.* (2007) in this issue of the *British Journal of Nutrition* provides us with a glimpse of the future: fortification of 'regular' foods with (tasteless!) LC *n*-3 FA. Based on the unquestioned success of fortification programmes with iodine, folic acid, vitamin D and B-vitamins, the surreptitious inclusion of these FA into the food supply is the best approach for raising LC *n*-3 FA levels in the entire population.

By using a wide variety of 'lightly' fortified foods (generally providing between 50 and 150 mg EPA + DHA per serving of cheese spread, chocolate, instant oats, milk, dips, biscuits, pancakes, muffins, breads, salad dressings, margarines, dry soup mixes, cereals, and eggs), these investigators were able to increase the daily LC *n*-3 FA intake from one typical of the Australian diet (100–200 mg/d) to 1000 mg/d. This is the intake recommended by the American Heart Association for patients with known CHD (Kris-Etherton *et al.* 2002). Over the 6-month study, erythrocyte levels of EPA and DHA (expressed as a % of total FA; the omega-3 index (Harris & von Schacky, 2004)) rose from about 4 % to over 7 %. Even at 6 months when steady state levels may still not have been reached, this level is quite close to the proposed target of 8 % associated with significantly reduced risk for death from CHD (Harris & von Schacky, 2004). For the most part, the fortified foods were well-received and could not be distinguished from their unfortified counterparts. Therefore, in confirmation of a previous study (Lovegrove *et al.* 1997), Murphy *et al.* demonstrate that heart-healthy tissue levels of LC *n*-3 FA may be achieved solely with fortified foods, without any fish or fish oil capsules.

Although the list of foods currently fortified with LC *n*-3 FA is growing (Whelan & Rust, 2006), why is it still so short? Why has the food industry been slow to respond? What are the obstacles preventing companies from rushing headlong into LC *n*-3 FA fortification? It is not the lack of high quality, deodorized and stabilized oils enriched with LC *n*-3 FA since these are currently available, and more will be produced as demand grows. What is lacking is the demand. Why? At least partly because of the inability of food manufacturers to make clear, direct and strong health claims for their products. Without a way to inform consumers that a product fortified with EPA and DHA provides a health benefit that more than justifies the slightly increased cost over the non-fortified product, the industry lacks the incentive to produce such foods.

### The Food and Drug Administration and label claims

In the US, the Food and Drug Administration (FDA) has three vehicles industry can use to communicate the healthfulness of their products to consumers (from strongest to weakest): health claims; nutrient content claims; and structure/function claims. The best of the best is an *unqualified* (i.e. no caveats or qualifiers needed) health claim because it reflects 'significant scientific agreement' that food/nutrient X reduces risk for disease Y. For example, soluble fibre has been shown to lower serum LDL cholesterol, and since cholesterol is an FDA-approved CHD risk factor, an oat-based cereal like Cheerios (General Mills, Minneapolis, MN, USA) can carry a formal health claim: 'Three grams of soluble fibre daily from whole grain oat foods, like Cheerios, in a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. Cheerios has 1 gram per cup.' And prominently displayed on its label is 'Cheerios Can Reduce Your Cholesterol!' Why is there no such claim for LC *n*-3 FA?

## Daily values

One obstacle to obtaining an unqualified (or 'A' level) health claim for LC *n*-3 FA is the lack of an approved daily value, a target intake that, if consumed, could meaningfully impact CHD risk. An unqualified health claim must, by FDA rules, include a daily value (in the Cheerios example, 3 g soluble fibre). Although there is no official daily value for LC *n*-3 FA, a strong case can be made for choosing 500 mg/d. Health authorities in both the United Kingdom and in Australia have chosen approximately this level as a healthy target intake, and the consumption of two, preferably oily, fish meals per week would translate into about 500 mg/day if the 'oily fish' was salmon, sardines, or albacore tuna. Prospective, double-blind, randomized, controlled trials in the primary prevention setting will never be done to prove that this specific intake will significantly reduce cardiac events, and yet a wealth of circumstantial evidence supports such a target value (Jacobson, 2006; Psota *et al.* 2006). Even if a more conservative but evidence-based daily value of 250 mg/d were established (as suggested by the recent analysis by Mozaffarian & Rimm (2006)), it would be a tremendous step forward.

## Qualified health claims

Although there is no daily value, and thus no unqualified health claim for LC *n*-3 FA, there is an FDA-approved *qualified* (i.e. a claim containing caveats or qualifications) health claim that can be used for any food or dietary supplements containing LC *n*-3 FA: 'Supportive but not conclusive research shows that consumption of EPA and DHA *n*-3 fatty acids may reduce the risk of coronary heart disease. One serving of (name of food) provides (x) grams of EPA and DHA *n*-3 fatty acids.'

There are at least two problems with this claim that markedly diminish its value to the food industry. First, it is 'qualified,'(an unfortunate term since most people would consider a 'qualified' health claim to be superior to an 'unqualified' one, but in fact, the reverse is the case). Second, because it does not (indeed, cannot) include a daily value as discussed above, *any level* of LC *n*-3 FA in a food can warrant use of the claim. If essentially any product can carry the claim, it is useless for differentiating a truly good source of LC *n*-3 FA from a poor one.

## Official risk markers

Cherrios can carry an unqualified health claim because it contains an ingredient (soluble fibre) that has been shown to lower LDL cholesterol, an 'official' risk marker for CHD. Another major obstacle to LC *n*-3 FA obtaining an unqualified claim is the fact, well-illustrated by Murphy *et al.* (2007), that American Heart Association-recommended intakes of EPA and DHA do not materially impact any classic or emerging CHD risk factor used by government agencies as surrogate markers for disease risk. The only blood test that showed a marked change in Murphy *et al.* (2007) was the omega-3 index, i.e. erythrocyte EPA and DHA. There was no effect on systolic and diastolic blood pressure, arterial compliance, blood concentrations of glucose, insulin, lipoprotein lipids (total, HDL and LDL cholesterol and triacylglycerols), C-reactive protein or urinary 11-dehydro-thromboxane B2 (a marker of platelet aggregation). But a change in the omega-3 index (which has been shown to be a valid surrogate for human myocardial EPA and DHA; Harris *et al.* 2004) may in fact be a very relevant biomarker for CHD risk. Several studies have shown that increased tissue/serum levels of LC *n*-3 FA are associated with significantly reduced risk for CHD (Siscovick *et al.* 1995; Albert *et al.* 2002; Lemaitre *et al.* 2003), and it appears that it is their very presence in membranes that is responsible for reduced risk (Leaf *et al.* 2003; Ma *et al.* 2004). But since non-pharmacologic intakes of LC *n*-3 FA do not lower serum cholesterol or blood pressure (the only two biomarkers of CHD risk which a food can alter and thereby win an FDA health claim), they cannot obtain a CHD claim. The irony of this is that current data indicate that LC *n*-3 FA could reduce risk for *death*, a far greater enemy of health than hypercholesterolaemia! If federal agencies would allow a health claim for any food naturally containing or fortified with LC *n*-3 FA (or even stearidonic acid which can favourably impact the omega-3 index; James *et al.* 2003) that 'significantly' raised *n*-3 FA blood levels, then a wide variety of products could carry a meaningful health claim.

I look forward to the day when labels on LC *n*-3 FA-rich products, whether naturally rich (e.g. fish) or fortified (e.g. salad dressings, yoghurt, bread, margarine, ice cream, etc.) will contain the following statement: '500 milligrams of EPA and DHA *n*-3 fatty acids, in a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. Fisherman's French Dressing (fictitious name) has 200 milligrams per serving.' And prominently displayed on the label we would find: 'Fisherman's French Dressing Can Reduce Your Risk for Heart Disease!' This type of claim would be warmly embraced by the food industry, and the health benefits of fortification, so clearly promised by Murphy *et al.* (2007) would move closer to reality.

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