Long chain Omega-3 fatty acids and cardiovascular disease – FSANZ consideration of a commissioned review

Review Title:
The relationship between omega-3 fatty acid intake and risk of cardiovascular disease

Reviewers:
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3.1 FSANZ review request

The specific question posed by FSANZ for this review was whether a claim about long chain omega-3 fatty acids and coronary heart disease (CHD) could be substantiated from the literature, and, if so, whether this result could be generalised to the Australian and New Zealand population. The reviewers were asked to draw on the findings of an existing authoritative review of this topic by the U.S. Food and Drug Administration (FDA) (FDA, 2003), to update its findings with any recent evidence and to consider the relevance of the review to Australia and New Zealand. FSANZ specifically directed that the review should focus on a relationship involving the marine-derived oils eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) with a secondary question as to whether there was any evidence for a relationship with docosapentaenoic acid (DPA). Alpha-linolenic acid (ALA) was specifically excluded from consideration.

3.2 Background

Omega-3 fatty acids are a class of polyunsaturated fatty acids with the double bond in the third carbon position from the methyl terminal. The most widely known omega-3 fatty acids are EPA and DHA found in oily fish but which ultimately derive from algae. Other omega-3 fatty acids are ALA which is found in plants and DPA which is found in red meat at concentrations that are dependent upon the diet of the animals. DPA may be converted into either EPA or DHA. The amount of DPA in the diet is debated and recent food analyses suggest the quantities may be much higher than previously thought. CHD is the most common form of heart disease and is usually the result of atherosclerosis, a thickening and hardening of the arteries that restricts the blood flow. CHD symptoms include chest pain (stable angina), heart attacks (myocardial infarction), and shortness of breath. CVD is a broader term that includes all diseases of the heart and arteries. CVD includes CHD, hypertension, cerebrovascular disease (stroke), and peripheral vascular disease.

The FDA reviewed the relationship between omega-3 fatty acid intake and CHD on a number of occasions since 1991. The FDA found "*supportive but **not conclusive** research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk CHD"*. Following the review, the FDA announced the availability of a qualified health claim for reduced risk of CHD on conventional foods that contain EPA and DHA omega-3 fatty acids. The outcome considered in the FDA review was CHD which is traditionally limited to atherosclerosis. Other mechanisms have been suggested as the means by which omega-3 may benefit circulatory function and heart disease. Following advice from Howe et al, the FSANZ review was expanded to cover a wider body of evidence examining a relationship between omega-3 fatty acid intake and CVD more generally rather than focusing only on CHD. For this

purpose it was appropriate to evaluate a wider range of physiological characteristics to determine whether any of these could be regarded as emerging biomarkers.

3.3 Assessment of the 2004 FDA Review

Howe et al considered the 2004 FDA review "*the most rigorous consideration of the cumulative scientific evidence relevant to this relationship to be undertaken by a government agency and is therefore an appropriate starting point for this review*". Nevertheless, some reservations were expressed because Howe et al regarded that the FDA reviews were based on a limited number of biomarkers that did not capture the full extent of the potential benefits of omega-3 fatty acid consumption. In the 2004 FDA review, blood pressure was included as a biomarker but the relationship between omega-3 fatty acid intake and blood pressure was only considered for studies that had been published since the previous review in 1991. Howe et al re-appraised studies that had been included in the FDA review to examine relationships that had been outside the scope of that review.

3.4 Expansion of the scope of the FDA review

Howe et al expanded the scope of the review to include CVD endpoints such as sudden death, heart failure and ischaemic stroke. Additional biomarkers of CVD risk including dyslipidaemia (high triacylglycerols and/or low HDL-cholesterol) were considered along with other characteristics thought to be indicative of CVD risk such as heart rate, heart rate variability, arterial compliance and endothelial dilatation.

3.5 Evidence published since the FDA review

Howe et al conducted a MEDLINE search over the period 2000 – 2005 which captured published reports that were not available for the 2004 FDA review. During that period 868 papers were identified relating to omega-3 fatty acids and CVD.

3.6 Relevance to Australia and New Zealand

Although much of the observational data were derived from US cohorts, Howe et al considered that similarities between US and Australian/New Zealand cardiovascular health statistics were sufficient to be able to generalize the findings among the countries. They did comment that Australian fish tends to have a lower fat content than fish commonly consumed in the northern hemisphere.

3.7 Conclusion

Howe et al concluded that in its totality the existing evidence for CVD risk reduction by omega-3 intakes from food is **convincing**.

3.8 FSANZ consideration of the Howe et al review

Howe et al considered omega-3 fatty acid intake in relationship to several established risk factors for CVD including total and LDL-cholesterol, HDL-cholesterol, and blood pressure. Howe et al concluded that there was unequivocal evidence for a blood pressure lowering effect of omega-3 intake, with an effect size estimated to be 0.66/0.35 mmHg per g/d. The

current omega-3 intake by Australians is estimated to average around 170 mg/d (Howe *et al*., 2006). A doubling or tripling of omega-3 from food sources would increase intake by around 200 – 400 mg and would involve substantial changes in dietary habits. If increases of omega-3 intake of this magnitude could be achieved, the predicted effect on blood pressure reduction would be extremely small.

Howe et al concluded that omega-3 intake had little impact on total cholesterol but may elicit a small transient rise in LDL-cholesterol. This suggestion of an LDL-cholesterol raising effect albeit "small and transient" is of concern because LDL-cholesterol is an established risk factor for CVD. Any evidence for a rise in this index with omega-3 intake needs to be thoroughly investigated. Citing four supporting articles, Howe et al suggested that the raising of LDL-cholesterol may not necessarily represent a bad outcome because omega-3 supplementation has been associated with a modest increase in the LDL particle size. In two of the studies, DHA but not EPA supplementation was associated with an increase in LDL particle size (Mori *et al*., 2000; Woodman *et al*., 2003). In another study, fish oil supplementation increased LDL particle size in one group, but had no effect in two other groups (Contacos *et al*., 1993), and in the fourth study fish oil supplementation was associated with increasing the susceptibility of LDL to copper-induced and macrophage-mediated oxidation (Suzukawa *et al*., 1995). Whether a modest increase in LDL particle size is associated with a reduction in risk of CHD is unknown. The US National Cholesterol Education Program (NCEP) expert panel regard small LDL particles to be one component of atherogenic dyslipidaemia but consider it unresolved as to whether LDL particle size predicts CHD independently of other risk factors (NCEP, 2002).

A meta-analysis of human trials cited by Howe et al found that the effect of omega-3 on HDL-cholesterol was minimal (Harris, 1996). However, Howe et al suggested that there may be a beneficial redistribution of HDL subfractions. The expert panel of the NCEP list HDL subfractions as possible emerging risk factors for CHD that may warrant future appraisal. However, at present the NCEP panel consider that a superiority in predictive power of HDL subfractions over total HDL cholesterol has not been demonstrated in large, prospective studies (NCEP, 2002).

Howe et al presented evidence indicating a triglyceride-lowering effect of omega-3. Whether elevated triglycerides constitute an independent risk factor for CHD is questionable. The NCEP expert panel regard elevated triglycerides as a marker for CHD risk factors rather than as a risk factor *per se* because of close associations between triglycerides and other established risk factors (NCEP, 2002). A more recent report that includes the results of two large prospective studies (Reykjavik and EPIC-Norfolk) described moderately strong independent associations between triglycerides and CHD risk (Sarwar *et al*., 2006). Odds ratios adjusted for other CHD risk factors were 1.76 (95% CI: 1.39, 2.21) and 1.57 (95% CI: 1.10, 2.24) in the Reykjavic and the EPIC-Norfolk studies, respectively, comparing people in the top and bottom thirds of usual triglyceride concentrations. In the EPIC-Norfolk trial, adjusting for HDL-cholesterol gave an odds ratio of 1.31 (1.06, 1.62). Differentials in the triglyceride tertiles were around 33% in both studies (1.28 and 0.87 mmol/L Reykjavic; 2.00 and 1.33 mmol/L EPIC-Norfolk). From their literature search, Howe et al reported consistent reductions in triglyceride concentrations of around 20 – 30%, a magnitude of reduction similar to that found from a systematic review of studies on the effects of omega-3 fatty acids on serum lipoproteins (Harris, 1997). The dose of supplemental omega-3 in the studies included by Harris averaged around 3 – 4 g/d or 10 – 12 MaxEPA capsules. To obtain this amount of omega-3 from food, Harris estimated it would require daily consumption of 4

teaspoons cod liver oil, 250 g salmon, or 1.2 kg snapper. Among the papers cited by Howe et al the least amount of omega-3 shown to lower triglycerides from food was around 1 g/d derived from a fish diet (Weber and Raederstorff, 2000). The magnitude of triglyceride reduction with fish consumption is usually less than that typically reported for high dose omega-3 supplementation. Fehily et al found a 6.7% reduction in triglycerides when people consumed 200 – 600 g per week oily fish compared with a control diet, but oily fish tended to displace meat, white fish and cheese, so it would not be possible to ascribe the triglyceride-lowering to oily fish or omega-3 oils alone (Fehily *et al*., 1983). Indeed, dietary intervention with fish has not been shown to reduce triglycerides in all studies (Atkinson *et al*., 1987; Jacques *et al*., 1992; Tidwell *et al*., 1993). Although there is good evidence that high dose supplementation with purified fish oils lowers triglyceride concentrations, there is uncertainty as to whether triglycerides constitute an independent risk factor for CHD and to what extent triglycerides can be lowered using food as the means to increase omega-3 fatty acid intake.

Howe et al also reviewed evidence for an effect of omega-3 on possible or emerging risk factors for CVD. These factors included endothelial function, arterial compliance, heart rate, heart rate variability, arrythmogenesis and atrial fibrillation, atherosclerosis progression and plaque stability. It is not clear whether any or all of these characteristics are independent modifiable risk factors for CVD or whether they represent manifestations of the disease. Much of the evidence presented was related to a treatment effect in people with established CVD having been given doses of omega-3 well in excess of those practically obtainable by dietary means. FSANZ consider that a dose-response causal effect of omega-3 on these possible or emerging risk factors for CVD has not been established.

An important benefit ascribed to omega-3 is reduced risk of recurrence of a myocardial infarction. In support of this, Howe et al cited a meta-analysis of randomized controlled trials carried out in patients with CHD (Bucher *et al*., 2002). Bucher et al reported a beneficial risk ratio of omega-3 intake on fatal myocardial infarction 0.7 (95% CI: 0.6, 0.8), sudden death 0.7 (0.6, 0.9), and overall mortality 0.8 (0.7, 0.9). A more recent meta-analysis (Hooper *et al*., 2006) included the results of trials published since the Bucher meta-analysis. Hooper et al found that the relative risk of death in people randomized to omega-3 was weak (RR 0.87, 95% CI: 0.73, 1.03) and inconsistency among studies was moderate (I^2 = 42%). When the results of a study by RB Singh whose trials have been questioned, was excluded, and the analysis was restricted to studies at low risk of bias, inconsistency among studies was low (I^2 = 0%) and the relative risk of death was 0.98 (0.70, 1.36). There was no definite effect of omega-3 on CVD events (RR 0.95, 95% CI: 0.82, 1.12).

A proposed mechanism whereby omega-3 might affect CHD outcome is ventricular arrhythmia. Howe et al suggest that the anti-arrhythmic potential of omega-3 was best demonstrated by the prevention of sudden death in the GISSI-P trial (GISSI-P, 1999). Smaller intervention trials cited by Howe et al have shown encouraging findings on endpoints related to arrhythmia (Singer and Wirth, 2004; Leaf *et al*., 2005; Raitt *et al*., 2005; Geelen *et al*., 2005), but another large well designed randomized controlled trial is needed to confirm the benefit of omega-3 supplementation on sudden death in patients being treated for CHD. Raitt et al found an increased risk of ventricular tachycardia or fibrillation in patients with implantable cardioverter defribrillator devices (ICDs) receiving omega-3 and suggested that fish oil supplementation for people with ICDs and recurrent ventricular arrhythmias should be avoided (Raitt *et al.,* 2005).

Howe et al proposed that there was a highly probable benefit of omega-3 in reducing the incidence of stroke, particularly ischaemic stroke. In a meta-analysis of cohort studies it was found that the frequency of fish consumption was inversely associated with the relative risk of stroke (He *et al*., 2004). A more recent study was consistent with the meta-analysis except that the fish preparation was an important determinant of the relationship (Mozaffarian *et al*., 2005). Fried/sandwich fish consumption was positively associated with stroke whereas tuna, broiled or baked fish was inversely associated with total and ischaemic, but not haemorrhagic stroke. In contrast, in the EPIC-Norfolk cohort (n = 24312) there were no significant relationships between total fish, shellfish or fish roe consumption and incident stroke over 8.5 y follow-up (Myint *et al*., 2006). However, oily fish intake was lower in women who subsequently had a stroke with an odds ratio comparing consumers with non-consumers of 0.69 (95% CI: 0.51, 0.94). The association with oily fish consumption was not found in the men despite a similar frequency of intake to that of the women. The proportion of people using cod liver oil supplements was not different between those who had a stroke and those who did not. Results of these cohort trials are inconsistent in that associations may or may not be dependent upon type of fish, fish preparation, gender, and type of stroke. The cohort studies provide interesting findings that should be tested in randomized controlled intervention trials.

FSANZ convened a meeting via teleconference of the "FSANZ Scientific Advisory Group" (SAG) for the development of the substantiation framework for nutrition, health and related claims to discuss the findings of the Howe et al review and the conclusion reached by the reviewers. Members of the SAG included nutritional academics from leading universities in Australia and New Zealand and FSANZ staff. Key points arising from the 22nd November 2006 teleconference are presented below:

- There are insufficient randomised controlled trials with consistent findings in favour of omega-3 fatty acids and reduced CVD risk.

- From the available evidence considerable weight is placed on the GISSI-P trial (GISSI-P 1999), particularly where this appears in meta-analyses. The GISSI-P trial, however, despite its positive finding, has been criticised because of the lack of blinding and loss to follow up.

- Despite the value of the intervention trials, they are secondary prevention studies. A positive effect may not translate to a primary prevention effect.

- Whilst there are several observational studies linking high fish intake to reduced CVD events and mortality, these could be influenced by many confounding factors including a 'lifestyle' effect.

- A major biological mechanism proposed to link omega-3 fatty acids and CVD is an anti-arrhythmic effect, but this has not translated to reduced CVD events when investigated further.

- There is convincing evidence that supplemental omega-3 fatty acids in relatively high doses of about 1 g per day modestly reduce blood pressure and triglycerides but, to date, this has not resulted in a consistent reduction in CVD risk in well designed randomised controlled trials.

- There is insufficient evidence that other physiological parameters, such as heart rate variability, considered in the Howe et al review are established biomarkers for CVD risk. Therefore studies showing that they can be changed using omega-3 fats do not necessarily indicate that there would be a downstream effect on CVD.

- Three systematic reviews published since the Howe *et al*. review was finalised (Balk *et al*., 2006; Mozaffarian and Rimm, 2006; Wang *et al*., 2006) do not alter the opinion of the scientific advisory group.

3.9 FSANZ summation

After a careful review of the evidence presented by Howe et al and relevant papers published since their review was completed, FSANZ considers that the evidence for a benefit of long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on CVD morbidity and mortality can be rated as **'probable'** but cannot be rated as 'convincing**'**. The publication of the review and the subsequent opinion by FSANZ is sufficient evidence to support a general level health claim based on the diet-disease relationship between long-chain omega-3 fatty acids and cardiovascular health.

Sources of isolated DPA are not readily available and there has been little evaluation of its health effects, therefore no comment can be made in this regard. The 2004 FDA review (the starting point for the Howe et al review) did not include all available observational studies on fish consumption and CHD because some of the studies provided no details of fish type or portion sizes and omega-3 intakes could not be estimated. Because only a subset of the literature on fish consumption was used FSANZ can make no conclusion regarding fish intake and CHD or CVD. Hence the FSANZ position on omega-3 intakes from food is not contrary to dietary guidelines recommending fish intake or general level health claims around the value of fish.

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