Attachment 5

TECHNICAL REPORT: DIET-DISEASE RELATIONSHIPS

Background

The Initial Assessment Report canvassed opinion as to which possible high level health claims might be of interest to stakeholders. Seven were selected and investigating these allowed the proposed substantiation framework to be tested. Details of the substantiation of four of the potential claims were released in the Draft Assessment Report. Details of the outcome of the substantiation process for the remaining three are described below.

1. Fruit, vegetables and coronary heart disease

Review Title:
Dietary fruit and vegetable intake and risk of coronary heart disease.

Reviewers:
Ms Elisabeth Winkler, Associate Professor Carla Patterson, Professor Beth Newman, Queensland University of Technology.

The specific question posed for this review was whether a claim about fruit and vegetables and coronary heart diseases could be substantiated from the literature, and, if so, whether this result could be generalised to the Australian and New Zealand population.

The starting point for the review was the 2003 draft Canadian report entitled 'Short Literature Review for Fruits, Vegetables and Grain Products that Contain Fibre, Particularly Soluble Fibre, and Coronary Heart Disease', which examined the relationship between dietary fibre and risk of coronary heart disease. This included grains and grain products, fruits and vegetables. The overall conclusion was: "*Diets low in saturated fat and cholesterol and rich in high-fibre, intact foods, such as whole grains, fresh fruits and vegetables, may reduce the risk of heart disease, a disease associated with many factors.*"

The focus of the Canadian report was on dietary fibre, including grain products as well as fruits and vegetables, and on soluble fibre in particular. In the context of the fruit and vegetable relationship, the conclusions of the Canadian report and many of the included studies are of limited utility, because any beneficial effect of fruit and vegetable consumption in relation to coronary heart disease outcomes may be due to mechanisms unrelated to dietary fibre. Most of the early studies included in the Canadian report, in which associations with intake of fruit and vegetables were addressed separately, showed inverse relationships with coronary heart disease morbidity or mortality and to a lesser extent lipid levels.

1.1 Evidence published since the Canadian review

Seven new cohort studies reported on intake of fruit and vegetables and incidence or mortality from coronary heart disease, an eighth cohort study on fruit alone and a ninth study on vegetables alone. These cohort studies included between 500 and 84,000 subjects each with follow-up times ranging between 5 and 24 years. In addition, four case-control studies were found, three of which reported that higher intakes of fruit and vegetables combined, fruit alone or vegetables alone were protective against coronary heart disease. The recent results were consistent with the results of nine cohort studies reported in the Health Canada review.

However the magnitude of the inverse association varied substantially, from less than 10% to more than 50% reduction in risk. A major contributor to this range of results is the variability in the way that dietary intake was used in statistical analysis. Specifically, studies that divided dietary intake into tertiles would report a smaller reduction in risk than studies that divide intake into a larger number of groupings such as quintiles or deciles even when the underlying association is the same. This makes combining the results of the studies to derive an average risk reduction very difficult and so an overall summary figure was not calculated in the review. Of the studies that divided intake into more than two categories, six indicated that there was a progressive decrease in risk with increase in consumption and four indicated a plateauing of risk reduction above the second or third quintile of intake.

Most studies described their dietary intakes in quantitative terms but these were often not very comparable. One set of studies describe the effect of very low intakes. Three studies found that daily versus less-than-daily intake of fruit and vegetables was protective (Appleby et al., 2002, Liu et al., 2001, Yusuf et al., 2004), another that consumption two times per day was protective compared to less than daily (Bazzano et al., 2002) and another that 7.5 or more serves of vegetables per week was protective compared to less than 7.5 serves per week. A study using a 4-day record reported a plateau effect above 215 grams of fruit, berries and vegetables per day (Rissanen et al., 2003). Four American studies used different food frequency questionnaires and report relationships for a wider range of intakes. Two reported a plateau at the second quintile of intake (greater than either 1.61 (Genkinger et al., 2004) or 2.5 (Steffan et al., 2003) serves of fruit and vegetables per day). Although the other two reported a dose-response from the lowest to the highest quintile of intake, one study reported a range of <2.5 to >9 serves of fruit and vegetables (Joshipura et al, 2001) whereas the other reported a range of <1 to>2.5 serves of vegetables per day (Liu et al., 2001). One American study using a 7-day record reported an effect per serve of fruit and vegetables but did not describe the range measured in the study (Tucker et al., 2005). Although it is not possible to compare the absolute levels of intake between studies owing to the different methods used, it is clear that increasing intake from a low level to a moderate level is associated with a lower risk of coronary heart disease. Whether or not further risk reduction occurs when intakes are increased to higher levels is less clear.

In general these studies adjusted for a range of important confounders. In some cases, it could be argued that adjustment was inappropriate because it adjusted for factors on the causal pathway between the food and disease – in this case, the size of the relative risk would have been underestimated. However, there may be a range of other differences in food intake pattern among those with high or low intakes of fruit and vegetables. Therefore it is not possible to be certain whether the effect on coronary heart disease related to fruit and vegetables themselves or to some difference in intake among those with a diet rich in fruit and vegetables, such as difference in fat intakes.

Research on biomarkers related to coronary heart disease risk provide early support for some of the hypothetical mechanisms underlying a reduction in coronary heart disease risk associated with consumption of fruits and vegetables.

- Lipid levels are consistently, inversely associated with fruit and vegetable intake in observational studies, but findings from four randomised, controlled trials are less consistent, showing null to moderate improvements.
- All four trials found a reduction in diastolic blood pressure but only three also found a reduction in systolic blood pressure.

- Several of these four trials had important dietary difference between control and intervention groups and so their consistent finding that systolic and diastolic blood pressure was reduced might be attributable to other differences in some trials.
- The study reporting the largest effect on blood pressure had a high proportion of African Americans who have a higher prevalence of hypertension than Caucasians.

Overall, the general consistency of findings across studies showing that higher intakes of fruit and vegetables reduced coronary heart disease morbidity and mortality is noteworthy. Irrespective of study design and specific outcome, and similarly for study populations differing by age, gender, or nationality, inverse associations were generally reported for fruit and/or vegetable intake and risk of coronary heart disease. Because most of the studies were not designed specifically to assess the relationship between fruit and vegetable consumption and coronary heart disease risk, many lacked sufficient statistical power to test the observed results. Therefore the consistency of the direction of the relationship overall was considered to be more important than the statistical significance, or otherwise, of individual studies.

It is noted that three large randomised controlled trials in persons with prior cardiovascular disease have shown that altering homocysteine levels by administering folic acid fails to alter recurrent cardiovascular disease incidence (O'Toole et al., 2004, Lonn et al 2006, Bonaa et al. 2006). Hence there is insufficient evidence to support the use of homocysteine as a biomarker for coronary heart disease.

There is insufficient evidence to support C-reactive protein as a biomarker as there is only one observational study in an elderly population.

1.2 Relevance to Australia and New Zealand

Total intakes in Australia and New Zealand are higher than in some European and American nations and lower than others. Therefore the studies, which were mostly conducted in Europe and America, can reasonably be generalised to Australia and New Zealand based on the incidence/mortality from coronary heart disease, the types of fruits and vegetables consumed, the quantities of intake, and the general, westernised lifestyle characteristic of participants in most of the studies.

The food intake questionnaires were inconsistent in including or excluding potatoes and juice from their list of fruit and vegetables. In addition, most studies assessed the intake of fruit and vegetables in general rather than the intake of raw fruit and vegetables. Some studies present analyses for sub-categories such as green leaves or cruciferous vegetables. Therefore, the association is for fruit and vegetables as a group, rather than fresh or raw fruit and vegetables. Some studies excluded pulses from their definition of vegetables.

Consideration of the appropriate individual fruits and vegetables eligible to carry the claim was drawn from the evidence base even though it was not definitive or consistent with respect to the types of fruit and vegetables included in studies. It was determined that a broad range of raw and processed fruit and vegetables and foods comprising at least 90% fruit and/or vegetables would be eligible. This included potato and other starchy roots, and green peas and beans that were generally marketed and consumed as vegetable. On the other hand, fruit juices, but not vegetable juices, were excluded on the basis of national dietary guidance advising only limited consumption of these liquid forms of fruit. The proposed nutrient

profiling model would apply to these foods, thus excluding any high saturated fatty acid, high salt or high sugar versions.

1.3 Conclusion

FSANZ considers that there is a convincing inverse relationship between a diet containing vegetables and fruit, and coronary heart disease.

- Overall, the general consistency of findings across studies showing that higher intakes of fruit and vegetables reduced coronary heart disease morbidity and mortality is noteworthy.

- Studies agreed that intakes in the middle of the population range were protective compared to low intakes. Only some studies showed that high intakes conferred additional protection compared to intakes in the middle of the population range.

- Most studies did not examine fruit separately from vegetables or sub-groups within these classes. Food intake methods generally did not distinguish between fresh and processed fruit and vegetables. Some studies included potatoes and/or juice while other studies excluded these from the definition of fruit and vegetables. Therefore the results apply to a broad group of raw and processed fruit and vegetables, and foods containing at least 90% fruit and/or vegetable, but excluding fruit juice.

2. Wholegrains and coronary heart disease

Review Title:
Relationship between wholegrain intake and risk of coronary heart disease

Reviewer:
Dr David Topping, CSIRO, Adelaide

The definition of wholegrain in the Australian New Zealand food regulations is "*the intact grain or the dehulled, ground, milled, cracked or flaked grain where the constituents – endosperm, germ and bran – are present in such proportions that represent the typical ration of those fractions occurring in the whole cereal, and includes wholemeal*".

The starting point for the review was the 2003 draft Canadian report entitled 'Short Literature Review for Fruits, Vegetables and Grain Products that Contain Fibre, Particularly Soluble Fibre, and Coronary Heart Disease' examining the relationship between dietary fibre and risk of coronary heart disease. This included grains and grain products, fruits and vegetables. The overall conclusion was: "*Diets low in saturated fat and cholesterol and rich in high-fibre, intact foods, such as whole grains, fresh fruits and vegetables, may reduce the risk of heart disease, a disease associated with many factors.*"

With respect to the subject of wholegrain, the Health Canada review included studies of wholegrains and brans, including oat bran, and excluded secondary prevention studies or studies which should have been confounded by other dietary differences, such as fat intake. With respect to experimental studies, reductions in total cholesterol and LDL-cholesterol were the biomarkers considered and studies of oat bran gave favourable results. A number of these

studies used wheat bran as the control arm to keep total fibre intake constant between the groups. When reviewing cohort studies, three out of four studies using the definition of wholegrain as a food containing greater than 25% of wholegrain in the product found a protective effect with higher consumption.

2.1 Evidence published since the Canadian review

A range of intake descriptors were used among the six new cohort studies that examined coronary heart disease rather than all cardiovascular disease or stroke. Of the six, two studies measured fibre - cereal fibre in one and total fibre in the other – and so did not assess wholegrain intake. In another two studies, only part of the possible wholegrain intake was assessed: one measured only wholegrain breakfast cereal while the other included dark bread as well as wholegrain breakfast cereal. The remaining two studies calculated wholegrain intake by including partially wholegrain foods on a proportional basis. Among the last four, a range of important confounders were adjusted for, but aspects of diet (e.g. saturated fat intake), and sometimes elevated blood pressure were not included. Therefore, although four studies found a beneficial effect on coronary heart disease, it is unclear whether many of them measured wholegrain intake sufficiently well to be sure that the results were due to wholegrain intake. Only in the Norwegian study did the highest intake group consume more than three serves per day.

There have been five new intervention studies examining effects of wholegrains on plasma lipids: one study compared rye bread to wheat bread, one study compared oats to wheat cereals, one study compared oats to corn cereal, one study compared barley to wheat and brown rice and the fifth study compared barley enriched with B-glucan to a glucose substitute. Of the first three studies, rye bread and oats reduced total and/or LDL-cholesterol levels compared to the wheat or corn controls. Wheat bread had no effect on total and/or LDL-cholesterol levels and the wheat cereals increased them non-significantly. Only one of the barley studies found an effect on cholesterol levels after barley consumption.

2.2 Relevance to Australia and New Zealand

The evidence for wheat alone conferring a protective effect against coronary heart disease is inconclusive. It is clear that wheat consumption does not reduce total or LDL-cholesterol. Wheat is the primary cereal consumed in Australia and so any potential health claim about wholegrains would appear predominantly on wheat-based products. There is also mismatch between the types of foods examined in a number of the studies and the predominant wholegrain consumed in Australia.

FSANZ also notes that the evidence cited in the Australian Dietary Guidelines for Adults (NHMRC, 2003) for the recommendation of ‘eat plenty of cereals … preferably wholegrains’ references studies examining cancer, diverticular disease, diabetes and weight control with a specific reference to oats and psyllium and cholesterol lowering, and dietary fibre and constipation. Given that the current review examined a specific type of both the dietary components and the diseases mentioned in the guideline, it would not necessarily have expected to find a convincing relationship and so the conclusion is not necessarily at odds with the more general guideline.

2.3 Conclusion

FSANZ considers that the relationship between a higher intake of wholegrains and a reduction in coronary heart disease is not convincing and therefore a health claim has not been substantiated.

- The focus of the requested review was on wholegrains and bran, not on fibre.
- The definition of wholegrain in available studies was inconsistent and often vague.
- Some of the available studies measured intake of fibre rather than wholegrain and so may have included intake from other non-wholegrain sources. As intake of wholegrains is often very low in many studies it was unclear whether the results could be attributed to intake of wholegrains as such.
- There was inadequate control for confounding by a range of other lifestyle factors. The evidence supports a general trend for a relationship between coronary heart disease and a 'healthy' diet rather than a relationship specific to wholegrain intake.
- Results from the subset of studies on oats and barley, which are high in soluble fibre, could not be generalised to wheat, which is low in soluble fibre and the primary type of wholegrain that would be eaten in Australia and New Zealand. It is clear that the non-soluble fibre found in wheat does not lower cholesterol levels.
- Therefore there was an insufficient number and range of study types to form an adequate evidence base to examine the possible relationship between wholegrain, as consumed in Australia and New Zealand, and coronary heart disease.

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3. Long chain Omega-3 fatty acids and cardiovascular disease

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

Reviewers:
Professor Peter Howe[1], Dr Trevor Mori[2], Associate Professor Jon Buckley[1],
[1]University of South Australia, [2]University of Western Australia

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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