

**THE RELATIONSHIP BETWEEN OMEGA-3
FATTY ACID INTAKE AND RISK OF
CARDIOVASCULAR DISEASE**

**A review of a diet-disease relationship prepared for
Food Standards Australia New Zealand**

by

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PREFACE

Purpose of this review

The purpose, as stated in a brief from FSANZ, was to undertake a rigorous and objective scientific review of the relationship between omega-3 fatty acids (ω 3) and the risk of cardiovascular disease (CVD). The findings of this review will be used to guide the development of any high level claim or claims recommended by FSANZ for pre-approval.

Approach

As specified in a template provided by FSANZ, a comprehensive review of all the available evidence was not intended; rather, a streamlined approach was to be undertaken building on an existing authoritative review prepared by USFDA in 2004. Relevant original research papers, reviews and selected consensus statements published subsequently have also been taken into consideration to provide a reappraisal of evidence on the relationship between ω 3 intake and CVD in accordance with the FSANZ template.

Scope

i) Fatty acids of interest

For the purposes of this review, ω 3 refers to two marine-derived polyunsaturated fatty acids (PUFA) in which the first double bond is three carbons away from the methyl end of the carbon chain, viz. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This is consistent with reviews conducted by the United States Food & Drug Administration (USFDA) around ω 3 and coronary heart disease (CHD), which were limited to EPA and DHA. The plant-derived ω 3 alpha-linolenic acid (ALA) is not included in these reviews or in the definition used herein.

ii) Form in which ω 3 are consumed

This review examines the relationship between ω 3 and CVD. The outcome will be considered in the context of ω 3 consumed via conventional foods, rather than dietary supplements. However, the review considers evidence for the diet disease relationship obtained through intake of EPA or DHA in any form. Evidence of this type was included in the reviews conducted by the USFDA.

iii) Disease endpoints

The starting point of this review is the USFDA response to a health claim petition regarding the relationship between ω 3 and reduced risk of CHD. The endpoints used by the USFDA to identify CHD risk reduction were: coronary events (myocardial infarction, ischemia), CV death, atherosclerosis, and high blood pressure (BP).

The scope of this review goes further than the USFDA response, and considers the relationship between ω 3 and CVD. Despite this, the US response is considered a valid starting point for this review. The term CHD is traditionally limited to atherosclerosis. FSANZ is seeking a rigorous assessment of the mechanisms by which ω 3 may benefit circulatory function and heart disease, and acknowledges that the mechanisms may be by means other than atherosclerosis. Therefore, this review also considers other forms of CVD, including sudden death, stroke and heart failure.

In this context, it is also necessary to extend the consideration of biomarkers of CV risk beyond those which the USFDA considered as valid risk factors for CHD, viz. LDL-cholesterol and BP. Thus evidence will also be considered for relationships between ω 3 intake and plasma triglycerides (TG), heart rate (HR), heart rate variability (HRV), atrial fibrillation (AF), arterial compliance, endothelial vasodilator function, intima-media thickness (IMT) and plaque stability.

PART 1: CRITICAL APPRAISAL OF A USFDA AUTHORITATIVE REVIEW

a) Appraisal of the selection and assessment of evidence by the USFDA

The USFDA has responded to a succession of petitions for health claims relating to ω 3 since it first introduced its policy of approving health claims for foods and supplements based on the weight of publicly available scientific evidence and on significant scientific agreement among experts that such evidence supported the health claim. Starting with a negative ruling published in 1991 (USFDA, 1991), it conducted a series of reviews of the accumulating scientific evidence for and against a relationship between ω 3 intake and risk of CHD. The most recent of these is the subject of this appraisal: a response published in 2004 to the 2003 Martek petition. It is 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.

The USFDA's 2004 review builds on its preceding responses to health claim petitions. The most comprehensive of these was a letter to Emord & Associates, Oct 31, 2000 (USFDA, 2000), in which, even though the USFDA concluded that there was "not significant scientific agreement for an *unqualified* claim about the relationship between EPA and DHA ω 3 and reduced risk of CHD", they allowed a *qualified* health claim for supplements based on the *weight* of scientific evidence.

The evidence considered by the USFDA in 2000 was both observational and experimental. Building once again on the body of preceding evidence from its 1991 review which it deemed inadequate to substantiate a health claim, it cited 13 new observational studies published since 1991 relating the consumption of ω 3 or fish to CHD outcomes. It also considered 4 new intervention trials assessing effects of ω 3 consumption on CHD outcomes and 23 intervention trials assessing effects on biomarkers.

A number of the intervention trials considered in the 2000 review had shown improvement of CV biomarkers, including TG and BP, with ω 3 supplementation. At that time, however, only LDL-cholesterol was considered by the USFDA to be a valid marker of CHD risk. As LDL-cholesterol is one of few major CV risk factors which is not improved and may even be worsened by high ω 3 intakes, it is not surprising that the USFDA found no biomarker evidence to support a benefit of ω 3 in CHD. In contrast, all 4 trials which had assessed effects of ω 3 on disease outcomes were positive. However, they were conducted in subjects with existing CHD and the USFDA argued that the benefit of ω 3 in reducing CHD risk may not necessarily be attained in a normal, healthy population (to whom health claims are directed).

Eight of the 13 epidemiological (observational) studies showed significant reductions of CHD risk with increased fish consumption in a normal population. In a few cases, the decreased risk correlated with blood ω 3 levels. In most cases, however, it was only related to fish consumption. Even though the intervention trials demonstrated that ω 3 intake reduces CHD risk, the USFDA argued that the benefit of a high fish consumption in the observational studies might be due to some other factor in the diet, even though no other candidate nutrient in fish has been identified.

The qualified health claim introduced by the USFDA in 2000 addressed these reservations as follows:- "*The scientific evidence about whether ω 3 may reduce the risk of CHD is suggestive, but not conclusive. Studies in the general population have looked at diets containing fish and it is not known whether diets or ω 3 in fish may have a possible effect on a reduced risk of CHD. It is not known what effect ω 3 may or may not have on risk of CHD in the general population.*"

In September 2004, in response to a petition by Martek, the USFDA updated its 2000 review and allowed the qualified health claim for ω 3 and CHD to be extended to foods in the following

simplified form:-“*Supportive but not conclusive research shows that consumption of EPA and DHA ω 3 may reduce the risk of CHD*”.

The September 2004 ruling had taken account of additional evidence to that reviewed in 2000, viz. two intervention trials and 8 observational studies, and included BP as a surrogate endpoint. The two intervention trials had examined BP as a primary outcome measure and found no effect of ω 3 supplementation. It is interesting that the USFDA was now prepared to consider BP as a valid biomarker for CHD, having discounted it in 2000, although they made no retrospective analysis of the numerous pre-2000 intervention trials in which BP was an outcome measure. There have been several meta-analyses based largely on pre-2000 studies that confirm an antihypertensive effect of ω 3 (see Part 4). Other intervention studies cited by the USFDA since 2000 showed that ω 3 supplementation improved plaque stability and angioplasty outcomes. However, as these were not deemed to be valid surrogate endpoints for CHD, they were not considered.

Of the 8 observational studies, 7 showed that reduced CHD risk could be attributed to ω 3 intakes based on blood levels or estimated from fish consumption. The ability to relate benefit directly to ω 3 rather than fish led to removal of the disclaimer in the earlier health claim. However, as observational studies cannot prove a causal relationship between ω 3 intake and risk reduction, this new evidence was not considered conclusive.

The conservative approach taken by the USFDA in considering evidence for a health claim is consistent with their responsibility to safeguard the public. It should be remembered that early petitions for an ω 3 health claim were supported by limited evidence which was often of poorer quality and encouraged by anecdotal or unsubstantiated claims of cholesterol lowering and other supposed benefits of fish oil. At the same time, concerns had been raised about the safety of high ω 3 intake levels, particularly with respect to possible increases in bleeding, blood glucose, LDL-cholesterol and LDL oxidation. Thus in their 1991 ruling, the USFDA recommended limiting ω 3 consumption to 1g/day but subsequently relaxed this to 3g/day based on further consideration of the evidence of risk to safety in their GRAS ruling for menhaden oil. Assuming that an individual may acquire up to 1g/day (90% intake percentile) from other sources, the USFDA has advised that ω 3 intakes from foods carrying the health claim should be limited to 2g/day.

The USFDA claim is the first evidence-based health claim for ω 3 in foods to be approved by a government agency and is based on a progressive review of cumulative evidence over 13 years, with consideration for the quality of evidence based on the USFDA’s own rigorous guidelines (“Interim Evidence-based Ranking System for Scientific Data”). **Thus one can have confidence in the validity of the claim which, as a *qualified claim*, states that the evidence is *supportive but not conclusive*.**

According to the rigorous policy framework proposed by FSANZ for consideration of high level health claims (as summarised in Fig 3.1 of their framework document), the fact that the USFDA’s authoritative review did not find ***convincing*** evidence for an ω 3/CHD relationship should have ended further consideration. The framework allows for further consideration of a review and any new evidence published subsequently *only* if the review has concluded that the evidence is convincing. Nevertheless, the template provided by FSANZ asks us to use the USFDA review as a starting point, to reconsider existing evidence in the broader context of CVD and to take account of new evidence. For this purpose, we have considered evidence published to the end of 2005.

b) Appraisal of evidence available at the time but beyond the scope of the USFDA review

A MEDLINE electronic database search was undertaken via *PubMed* to appraise the published evidence available at the time of the USFDA review and to capture relevant publications since that time. The results of the search and the search parameters employed appear in APPENDIX A. A total of 868 papers published from 2000-2005 were identified which related ω 3 to CV biomarkers or CVD. Over 300 of these were reviews or meta-analyses. However, 178 reports on clinical trials in adults were identified, together with another 376 original reports relating to humans. While many of these were either published since 2004 or not relevant, it is clear that the 10 new studies published since 2000 which were considered by the USFDA represents only a small proportion of the total body of evidence available but beyond the limited scope (*viz.* ω 3 and CHD risk) of the USFDA review.

The USFDA established a qualified health claim for ω 3 and CHD in 2000, based on the weight of existing scientific evidence, then reaffirmed their position in 2004. The process used to select and assess evidence was conservative and rigorous. Nevertheless, as noted above, there are gaps in the evidence considered by the USFDA which were within the scope of its review, *viz.* failure to retrospectively consider the earlier evidence relating to BP as a biomarker for CHD which had not been considered in its 2000 review. The current review not only addresses this deficiency but extends the scope from CHD, *i.e.* coronary artery disease or atherosclerosis, for which LDL-cholesterol and BP are surrogate endpoints, to CVD, which includes sudden death, stroke and heart failure (HF) and for which a variety of other surrogate endpoints, or biomarkers, might also be considered. The primary evidence linking increased ω 3 intake to reduced risk of sudden death and stroke was emerging during the course of the USFDA reviews and is considered below and in Parts 1(c) and 2. Evidence relating to BP and other biomarkers will be considered in Part 4, where evidence to justify other biomarkers to CVD risk is also presented.

Sudden Death

Sudden death (reflecting fatal ventricular arrhythmia) is widely regarded as the single most significant outcome of the landmark GISSI-P intervention trial, with a 53% reduction of risk attributable to ω 3 supplementation observed after 4 months of supplementation (Marchioli 2002). The USFDA repeatedly ignored the reduction of sudden death when considering this trial, presumably because their definition of CHD did not encompass sudden death, although this is not clear. The GISSI-P trial is considered more fully below. The strength of the sudden death outcome combined with a lack of evidence for prevention of subsequent myocardial infarction has prompted a shift in focus on possible protective mechanisms of ω 3 from atherosclerosis to arrhythmogenesis and has encouraged the establishment of trials to monitor the effects of ω 3 supplementation on the incidence of ventricular tachycardia or fibrillation in patients with implanted cardioverter/defibrillators. The outcomes of these recent trials are considered in Part 2.

Stroke

Evidence for a protective effect of ω 3 in ischaemic stroke was emerging at the time of the 2000 and 2004 USFDA reviews. Two large prospective cohort studies showed an inverse association between increasing ω 3 consumption and the risk of stroke, *viz.* the Nurses' Health Study in women (Iso 2001) and the Health Professionals Follow-up Study in men (He 2002). The positive findings of these cohort studies contrast with the non-significant trend for an increased risk of stroke reported in GISSI-P (1999).

Iso et al (2001) reported in a 14 year follow-up of 79,839 women in the Nurses Health Study that increased ω 3 consumption was associated with reduced risk of thrombotic stroke. Compared with women who ate fish less than once per month, those with a higher intake of fish had a lower risk of total stroke. The relative risks (RR) were: 0.93 for fish consumption 1-3 times per month, 0.78

for once per week, 0.73 for 2-4 times per week, and 0.48 for 5 or more times per week, in multivariate analyses adjusting for age, smoking and other CVD risk factors (P for trend = 0.06). Among stroke subtypes, a significantly reduced risk of thrombotic stroke was found in women who ate fish. Compared with those who ate fish less than once per month, the RR were: 0.77 for fish consumption 1-3 times per month, 0.61 for once per week, 0.52 for 2-4 times per week, and 0.30 for 5 or more times per week, in multivariate analyses adjusting for confounders (P=0.03). Women in the highest quintile of ω 3 intake (median intake of 0.48g/day), had a reduced risk of total and thrombotic stroke, with multivariate relative risks of 0.72 and 0.67, respectively, relative to those in the lowest quintile (median intake of 0.08 g/day). There was no association between either fish intake or ω 3 intake and the incidence of haemorrhagic stroke.

He et al (2002) showed a significant inverse association between fish intake and stroke in the Health Professional Follow-up Study, a US prospective cohort that examined 43,671 men aged 40-75 years who were initially free of cardiovascular disease. During 12 years of follow-up, 608 strokes were recorded. Compared with men eating fish less than once per month, the multivariate RR of ischemic stroke was significantly lower among those who ate fish 1-3 times per month (0.57). However, a higher frequency of fish intake was not associated with further risk reduction; the RR was 0.54 for consumption of fish 5 or more times per week. By dichotomized fish intake, the multivariate RR for men consuming fish at least once per month compared with those who ate fish less than once per month was 0.56 for ischemic stroke and 1.36 for hemorrhagic stroke. No significant associations were found between fish or ω 3 intake and risk of hemorrhagic stroke.

GISSI-P (1999) is the longest intervention trial (3.5 years) conducted in the largest sample (n = 11,324) to examine the effect of ω 3 on cardiovascular events. The findings from this study in relation to risk of stroke indicated that supplementation with 850-882 mg ω 3/day (ethyl esters of EPA and DHA in a 1:2 ratio) tended to increase the risk of combined fatal and non-fatal stroke (RR 1.21, 95%CI 0.91 – 1.63). This is not surprising, considering that almost all subjects were taking anti-platelet medication, thus heightening their risk of haemorrhagic stroke. The proportion suffering this outcome would likely be greater in the ω 3 treatment arm where cardiac death was substantially reduced. Nevertheless, the difference in stroke was not significant.

Table 1: Evidence on stroke available but not considered by the USFDA review in 2004

Reference	Study design			Outcomes	
	Source / intake	Population	Study duration	Relevant outcome measures	Effect
Iso et al (2001)	Omega-3 intake from fish. EPA+DHA 0.08-0.48 g/day	Prospective cohort. Female N=79,839	14 yr	Total stroke Ischemic stroke Hemorrhagic stroke	Highest vs lowest ω 3 intake Multivariate RR 0.72 (95%CI 0.53 – 0.99) Multivariate RR 0.71 (95%CI 0.46 – 1.10) Multivariate RR 0.76 (95%CI 0.43 – 1.37)
He et al (2002)	Fish intake. EPA+DHA <0.05– >0.6 g/day	Prospective cohort Male N=43,671	12 yr	Ischemic stroke Hemorrhagic stroke	Multivariate RR for fish intake 1-3/month compared to <1/month RR 0.57 (95%CI 0.35 – 0.95) RR 1.81 (95%CI 0.58 – 5.66)
GISSI-P (1999)	Capsules EPA+DHA 850-882 mg/d (2:1 ratio)	Patients who survived recent MI N=11,324	3.5 yr	Fatal + non-fatal stroke	RR 1.21 (0.91 – 1.63) (PUFA vs No PUFA)

Values shown as mean \pm SEM.

c) Re-analysis of pivotal studies cited by the USFDA

Intervention studies

The following two intervention studies were considered by the USFDA to be the only studies published since their 2000 review which were adequately designed to assess effects of DHA or EPA on CHD risk (Woodman 2002, Finnegan 2003). These studies were randomised controlled trials which were sufficiently controlled to allow for the determination of effects of EPA and DHA on risk factors for CVD, and should be accorded the highest weighting of all of the evidence provided. In the 2004 USFDA review, the only endpoints considered valid for identifying CHD risk reduction were coronary events (MI, ischemia), CV death, atherosclerosis and high BP, while the only surrogate markers for CHD which were considered valid were high BP, serum total cholesterol, serum LDL-cholesterol, and serum HDL-cholesterol. On this basis the 2004 USFDA review concluded that the studies by Woodman et al (2002) and Finnegan et al (2003) provided no evidence that EPA or DHA reduced the risk of CHD. However, the current review is assessing effects of EPA and DHA on *CVD risk* and is encompassing a broader range of biomarkers. Therefore, both Woodman et al (2002) and Finnegan et al (2002) will be re-reviewed in relation to ω 3 and CVD risk.

Woodman et al (2002)

Woodman et al supplemented 59 type 2 diabetes patients who had treated hypertension and moderately high serum TG levels with 4 g/day of EPA ethyl ester, DHA ethyl ester or olive oil for 6 weeks using a double-blind, parallel design. Supplementation with EPA and DHA did not have any effect on BP, serum total, LDL or HDL cholesterol, but did result in significant reductions (19% EPA, 15% DHA group) of serum TG.

Finnegan et al (2003)

Finnegan et al recruited 150 moderately hyperlipidemic subjects and randomly allocated them to one of five interventions, fish oil (0.8 or 1.7 g of EPA+DHA per day), rapeseed and linseed oil (4.5 or 9.5 g of ALA per day) or an n-6 PUFA control (sunflower and safflower oil) for 6 months. While EPA+DHA did not affect blood pressure or any other markers of CHD risk deemed acceptable by the USFDA during their 2004 review, as in the Woodman study, Finnegan and co-workers reported reductions in fasting plasma TG after 2 months in both the 0.8 g/day and 1.7 g/day groups (15% reduction), and at 4 months in the 0.8 g/day group. However, the changes in plasma TG concentrations in response to ω 3 supplementation were not different from the control group at any time during the study, and the values in both of these groups were no longer significantly different from baseline or control after 6 months.

Table 2: Intervention studies added by the USFDA in their 2004 review

Reference	Study design			Outcomes	
	Source / intake	Population	Study duration	Relevant outcome measures	Effect
Woodman et al (2002)	Capsules 4g EPA or 4g DHA	T2D Treated hypertension N = 59	6 wk	BP, HR TG LDL HDL ₂ HDL ₃	NS EPA ↓17% (P<0.05) DHA ↓17% (P< 0.05) NS EPA ↑ 14% (P< 0.05) DHA ↑19% (P< 0.05) EPA ↓ 9.5%L (P< 0.05) DHA ↓ 2.9% (NS)
Finnegan et al (2003)	Capsules 0.8g or 1.7g/day EPA + DHA	Hyperlipidaemic N = 150	6 mo	BP TG	NS NS

Values shown as mean ± SEM.

The studies by Woodman et al (2002) and Finnegan et al (2003) were well designed randomised controlled trials, and evidence from these trials should be weighted heavily in determining an effect of EPA or DHA on CV risk. However neither study showed reduction of BP or other markers of CV risk (other than TG) as a result of supplementation with EPA and DHA, and only one (Woodman 2002) found that serum TG was reduced significantly more with ω 3 than the control (Finnegan showed reduction, but not different from control). Hence, it is not possible to conclude from these two studies alone that EPA and DHA reduce the risk of CVD.

Observational studies

Of the 10 observational studies published during the period between the 2000 and 2004 reviews, only eight were included in the 2004 USFDA review because two (Gillum 2000, Osler 2003) had not provided detail of the type of fish consumed so it was not possible to estimate intakes of EPA and DHA. The remaining eight studies are re-reviewed here, but evidence from these studies should not be weighted as highly as the intervention studies because they can only provide information on associations between EPA and DHA and CVD risk. These studies have been chosen for re-review because they provide evidence of associations between EPA and DHA and risk factors for CVD that are relevant for the current review, but were not considered valid biomarkers of disease in the 2004 USFDA review, so were not discussed.

Rissanen (2000)

This study reported the results of an average 10 year follow-up of 1,871 men aged 42 – 60 years at baseline, from an ongoing prospective population-based cohort study investigating risk factors for CVD, atherosclerosis, and related outcomes in Eastern Finland. A 44% reduced risk of acute coronary events (acute MI, acute chest pain) was reported in men at the highest quintile of serum DHA+DPA concentration compared with men in the lowest quintile once age, BMI, examination years, maximal oxygen uptake, hair mercury content, serum ferritin, serum LDL-cholesterol, systolic blood pressure, serum insulin, ADP-induced platelet aggregation, socioeconomic status, ischemic findings in exercise test, smoking, place of residence, and dietary energy intake were controlled for. No separate analysis of effects of DHA alone were conducted, and no association was found between the proportion of EPA and the risk of acute coronary events. However, the study did report that men in the highest quintile of serum DHA+DPA also had an 8.9% higher serum HDL-cholesterol and 16.4% lower ADP-induced platelet aggregability than men in the lowest quintile. For the purposes of the present review, elevated serum HDL-cholesterol is considered to be a valid marker of reduced CVD risk, so this study provides evidence of an association between blood DHA+DPA concentrations and reduced risk of CVD.

Torres (2000)

This study compared the number of deaths from IHD per 100,000 men in a fishing village and a rural village on the Portugese island of Madeira, and related this to differences in fish consumption and serum n-3 PUFA concentrations in 50 men living in the fishing village and 37 men living in the rural village. Participants were aged 25 – 65 years and were randomly selected from electoral rolls for the two villages. Blood samples were collected for serum n-3 PUFA analysis and dietary intake was assessed by two nutritionists using an interviewer-administered food frequency questionnaire which asked how often, on average, during the last year a particular food had been consumed, including fish (and type of fish). Daily fish consumption and serum EPA and DHA concentrations were higher in the subjects from the fishing village compared with those from the farming village, and the mortality from IHD per 100,000 men, estimated from death certificate records, in the farming village was four-fold higher (1205 in rural village vs 310 in fishing village) over an 8 year period (1990 to 1997). Serum TG levels were 27.9% lower in subjects from the fishing village (mean \pm SD: 1.3 ± 0.6 vs 1.8 ± 1.1 mmol/l), and total serum cholesterol was 10% lower (4.8 ± 1.0 vs 5.4 ± 1.5 mmol/l), despite higher cholesterol intakes in

the fishing village (378.3 ± 166.2 vs 240.8 ± 166.7 g/day). Therefore, this study provides evidence of an association between fish consumption, serum EPA and DHA concentrations and reduced biomarkers of CVD risk (viz. TG and total cholesterol).

Hallgren (2001)

Hallgren reported on a population based prospective case-control study nested in the Västerbotten Intervention Programme (VIP) within Northern Sweden. Subjects were invited to a health survey when they reached 30, 40, 50 and 60 years of age during which fish intake was assessed by food frequency questionnaire (FFQ) and EPA and DHA concentrations in plasma phospholipids were determined. Data on 78 people who suffered a first-ever MI on average 18 months after a health survey were compared with 156 controls matched for sex, age (± 2 years), date of last health survey (± 1 year) and geographical region who had not suffered an acute MI or stroke. *The 2004 USFDA review indicated that this study showed no association between fish intake or blood EPA and DHA concentrations and acute MI. However, this interpretation, while strictly correct, may be somewhat misleading since a relationship between plasma phospholipid EPA and DHA concentrations and first ever MI was reported, and elevated plasma phospholipid n-3 PUFA is suggestive of an increased fish intake.* While there was no statistically significant association between first-ever MI and reported fish intake, univariate analyses indicated that the risk of a first-ever MI decreased with increasing plasma phospholipid EPA and DHA concentrations, with both EPA and DHA concentrations being significantly related to the risk of acute MI (EPA odds ratio 0.56; 95% CI 0.33 to 0.99, DHA odds ratio 0.74; 95% CI 0.55 to 0.99). The lack of a relationship between reported fish intake and first-ever MI, despite the association with plasma phospholipid n-3 concentrations, probably reflects the number of fish meals reported at baseline being a poor estimate of the amount of fish consumed. Subjects were asked to report the number of fat and lean fish meals they consumed per week, and subjects were divided into categories of consuming \geq one, or $<$ one meal of fat fish, lean fish or total fish per week. This level of discrimination between amount of fish consumed would not allow for a high level of discrimination between high and low n-3 PUFA consumers. The finding that the risk of a first-ever MI was reduced in subjects with high levels of plasma phospholipid EPA and DHA suggests a protective effect of a high n-3 intake against CHD. A weak negative correlation was also found between plasma phospholipid EPA and DHA concentrations and systolic blood pressure ($r = -0.15$, $P = 0.029$). This study provides evidence of an association between plasma phospholipid levels of EPA and DHA (a marker of EPA and DHA intake) and a reduced risk of first-ever MI and a reduction in systolic blood pressure which is a biomarker of CVD risk.

Albert (2002)

Albert reported on a prospective, case-control study which was nested in the U.S. Physician's Health Study. In the Physician's Health Study 22,071 male physicians who were aged between 40 and 84 years in 1982 and had no history of myocardial infarction, stroke, transient ischemic attacks or cancer provided baseline blood samples for analysis of whole blood EPA and DHA (combined serum phospholipid and erythrocyte membrane content) and were randomised to receive aspirin, beta carotene, or placebo. Dietary intake of fish was ascertained using a semi-quantitative food-frequency questionnaire at 12 months, and information on CV events was updated every six months during the first year, and then annually thereafter. Over 17 years of follow-up, data for 94 subjects who had been free of confirmed CVD before death, but suffered sudden death from cardiac causes, were matched with two control subjects (who were alive and free of confirmed CVD) on the basis of age, smoking status and length of time since randomisation. Baseline blood levels of long-chain n-3 PUFA were correlated with fish intake at 12 months ($r^2 = 0.24$, $P = 0.001$), and blood levels of EPA (1.84 ± 0.53 vs 1.72 ± 0.59 , mean \pm SD; $P = 0.06$) and DHA (2.38 ± 0.78 vs 2.12 ± 0.65 ; $P = 0.005$) were higher in the controls compared with those who suffered sudden cardiac death, although the difference in levels of EPA did not quite reach statistical significance. An inverse relationship was found between whole

blood long-chain n-3 PUFA concentrations (EPA, DHA and DPA) and sudden cardiac death both before and after adjustment for confounders, but the separate effects of EPA and DHA could not be determined because separate analyses of these PUFA were not conducted. This study therefore provides evidence of an association between fish intake and blood levels of EPA and DHA, which in turn was associated with a reduced risk of sudden cardiac death.

Hu et al (2002)

This study reported the results from a 16 year follow-up of the Nurse's Health Study which was a large prospective cohort study of 84,688 female registered nurses who were apparently free of CVD at baseline. Semi-quantitative food frequency questionnaires and health status questionnaires were administered at baseline, and then every two years, to estimate fish and n-3 PUFA (EPA+DHA) intake and incidence of CHD (defined as CHD deaths and non-fatal MI). Incidences of CHD death and non-fatal MI were confirmed by reference to medical records and death certificates. An inverse relationship was observed between fish intake and CHD, as well as between n-3 PUFA intake and CHD, with these associations being stronger for fatal CHD than for non-fatal MI. These patterns were evident when adjusted only for age, or for other risk factors. Therefore, this study provides evidence of an association between an increased intake of EPA and DHA and a reduced risk of death from CHD or the risk of suffering a non-fatal MI.

Hu et al (2003)

This study analysed data from a subgroup of 5,103 diabetic nurses from the Nurse's Health Study (see Hu 2002 above). There was an inverse relationship between CHD risk and fish consumption ($P = 0.002$). However, unlike in the earlier study, in this subgroup of diabetic patients, there was no significant relationship between CHD risk and estimated EPA and DHA intake ($P = 0.10$). This latter finding may be due to the smaller number of subjects analysed compared with the earlier study, since there was a trend toward reduced CHD risk and EPA/DHA intake.

Mozaffarian et al (2003)

This study reports results of a prospective cohort study (CV Health Study) with 3910 participants (male and female) aged ≥ 65 yrs and free of known CVD at baseline (assessed by questionnaires on health status and physical examination). Dietary intake was assessed by food frequency questionnaire. Fish intake from the FFQ was correlated with combined plasma phospholipid EPA and DHA concentrations for both tuna intake ($r = 0.35$, $P < 0.01$) and other fish intake ($r = 0.59$, $P < 0.001$), but not fried fish/fish sandwich intake ($r = 0.04$, $P = 0.78$). Primary outcomes were IHD death (fatal MI and CHD death). MI was classified using chest pain, cardiac enzymes and ECG. CHD death was classified as death not meeting all of the criteria of MI, but occurring within 72 hours of chest pain, or with an antecedent history of IHD. During 9.3 years of follow up there were 247 deaths from ischemic heart disease (IHD), and 363 non-fatal MIs. After adjustment for age, gender, education, diabetes, smoking, BMI, systolic blood pressure, serum lipids, C-reactive protein and dietary factors, estimated intake of EPA+DHA at baseline (0.55 g/day and 0.92 g/day respectively) was associated with a lower risk of fatal IHD, but there was no association between EPA+DHA and non-fatal MI. Increasing intake of EPA+DHA was also associated with increasing serum HDL-cholesterol concentration ($P < 0.05$) but was also associated with increasing serum LDL-cholesterol concentration ($P < 0.05$). Potential confounders were not controlled for to determine the independent effects of EPA+DHA on these parameters. Therefore, this study provides evidence of an association between an increased intake of EPA and DHA and increased serum HDL-cholesterol concentration, which might be expected to reduce CVD risk. The association with a concurrent increase in LDL-cholesterol, while expected to increase CVD risk, apparently did not impact too extensively as there was an overall association between increased intake of EPA and DHA and reduced risk of death from CHD.

Lemaitre et al (2003)

In a case-control study nested within the CV Health Study, Lemaitre et al examined associations between plasma phospholipid concentrations of EPA and DHA and fatal IHD and non-fatal MI in 179 subjects who were ≥ 65 years of age and free of known CVD at baseline (assessed from

Table 3: Observational studies added by the USFDA in their 2004 review

Reference	Study design			Outcomes	
	Intake	Study description	Duration	Outcomes	Effect
Rissanen et al (2000)	Not applicable	Prospective cohort Male 42 - 60 yr N = 1,871	10 yr	Acute MI / angina HDL Platelet aggregation	\downarrow 44% (95% CI 11% - 65%) (adjusted for risk factors) \uparrow 8.9% (P < 0.001) \downarrow 16.4% (P < 0.018)
Torres et al (2000)	Fish intake EPA intake 218.1 mg/d vs 26.7 mg/d DHA intake 536.0 mg/d vs 55.9 mg/d	Cross-sectional Residents of fishing village compared with farming village Male 25 - 65 yr N = 87	N/A	Ischemic heart disease deaths (/100,000 men) TG	310 (fish) vs 1205 (farm) [†] 1.3 \pm 0.6 (fish) vs 1.8 \pm 1.1 mmol/L (farm) (P < 0.01) [‡]
Hallgren et al (2001)	Fish intake Plasma phospholipid EPA and DHA	Prospective case- control N=234	~18 mo	SBP Acute MI	Plasma EPA+DHA $r^2=-0.15$, (P=0.029) Plasma EPA (Odds Ratio 0.56; 95%CI 0.33 - 0.99) Plasma DHA (Odds Ratio 0.74; 95%CI 0.55 - 0.99) Fatty fish intake (Odds Ratio 0.85; 95%CI 0.45 - 1.62)
Albert et al (2002)	Fish intake	Prospective case- control Male physicians N=278	17 yr	Risk of sudden cardiac death	Inverse relationship with blood DHA+EPA+DPA (P=0.004) Highest quartile of blood DHA+EPA+DPA, adjusted for age and smoking RR 0.31 (95%CI 0.13 - 0.75)
Hu et al (2002)	Fish intake	Prospective cohort Female nurses N = 84688	16 yr	Non-fatal MI CHD deaths	RR 0.77 (95%CI 0.54 - 1.11) (adjusted for risk factors) RR 0.55 (95%CI 0.33 - 0.91) (adjusted for risk factors)
Hu et al (2003)	Fish intake EPA+DHA intake	Prospective cohort Female nurses Diabetic N = 5103	16 yr	Risk of CHD	Fish intake RR 0.36 (95%CI 0.20 - 0.66) (adjusted for risk factors) EPA+DHA intake RR 0.69 (95%CI 0.47 - 1.03) (adjusted for risk factors)
Mozaffarian et al (2003)	Fish intake	Prospective cohort ≥ 65 yr N=3910	9.3 yr	IHD death Non-fatal MI	RR 0.47 (95%CI 0.27 - 0.82)(adjusted for risk factors) RR 0.67 (95%CI 0.42 - 1.07)(adjusted for risk factors)
Lemaitre et al (2003)	Plasma phospholipid EPA+DHA	Prospective case- control ≥ 65 yr N=358	~2 yr	IHD death Non-fatal MI	OR 0.30 (95%CI 0.12 - 0.76) (adjusted for risk factors) OR 0.97 (95%CI 0.71 - 1.33) (adjusted for risk factors)

[†] deaths per 100,000 men estimated from death certificates in 1990-1997. [‡] Values are mean \pm SD

health status questionnaires and physical examination). Data were compared with 179 control subjects who were randomly selected from the CV Health Study participants who remained free of IHD. Control subjects were matched for gender, clinical site, entry cohort, and age and were followed up for at least as long as that of the investigational group. Blood samples were collected at baseline and in the third year of follow-up for analysis of plasma phospholipid concentrations of DHA, EPA, ALA and LA. Blood samples collected closest to (before) the IHD event were used for the analysis. Primary outcomes were IHD death (fatal MI or other IHD death) or non-fatal MI. MI was classified using chest pain, cardiac enzymes and ECG. CHD death was classified as death not meeting all of the criteria of MI, but occurring within 72 hours of chest pain, or with an antecedent history of IHD. Fifty four cases of fatal IHD and 125 cases of non-fatal MI were identified and matched with 179 controls. In preliminary analyses both DHA and EPA were associated with lower risk of fatal IHD, so the concentrations of EPA and DHA were summed to use a single variable for the analysis and revealed an association between higher plasma concentrations of EPA+DHA and lower risk of fatal MI/IHD, but no association between plasma EPA+DHA and risk of non-fatal MI. There was also no association between plasma concentrations of EPA+DHA and plasma concentrations of HDL cholesterol or TG.

Intervention studies from the 2000 USFDA review

The 2004 review followed on from the 2000 review, indicating acceptance of the interpretation of the studies in the earlier review. Given that the studies relied on by the USFDA in the 2000 review indirectly influenced the decision in the 2004 review, and the intervention studies considered in that review were accorded the most weight, a number of key intervention studies from the 2000 review are re-reviewed here. These studies were selected because they examined the effect of long-term (≥ 1 year) intake of $\omega 3$ on CVD risk in samples of >200 subjects and reported on risk factors for CVD which are relevant to the current review.

Burr et al (1994) (and Burr et al 1989)

The paper by Burr et al (1994) was based on a reanalysis of data from their original Diet and Reinfarction Trial (DART) (Burr 1989). In the DART study 2033 men who had recovered from a recent acute MI were randomly assigned to receive or not receive advice on three dietary factors, one of which was to increase intake of fatty fish. The subjects advised to eat fatty fish consumed 3 – 4 times the amount of EPA per week compared with those not so advised, and experienced a 29% reduction in overall mortality, with the reduction in mortality being entirely attributable to a reduction in death from IHD. There was no difference in non-fatal IHD events between the fish advice and no fish advice groups. However, in the fish advice group, by 6 months of follow-up 14% of subjects could not tolerate fish and were instead advised to consume 3 g/day of “Maxepa” fish oil capsules, and by 2 years of follow-up 22% of subjects in the fish advice group were consuming “Maxepa” fish oil capsules as a substitute for fish. This provided an opportunity for subsequent investigation of whether the benefits of fish consumption for mortality were due to the n-3 fatty acids contained in fish (and fish oil) or to some other component of fish. This issue was addressed in a subsequent study (Burr 1994) in which data for 227 subjects from the original DART study, who had been given fish oil capsules at some stage in the trial, were matched with data for controls from the ‘no fish advice’ group whose index MI had occurred at about the same time. This analysis revealed that, as had been the case in the original analysis of the DART study, deaths from all-causes (fish oil 4.4% vs control 10.1%, $P = 0.04$) and from IHD (fish oil 3.5% vs control 9.3%, $P = 0.03$) were significantly lower in the subjects who had taken the fish oil compared with those who received no fish advice. This was a particularly important study because, although there may have been some selection bias because the sample was not a random subset of the fish advice group from the original DART study, it indicated that fish oil was no less effective than fatty fish in reducing post-MI mortality, suggesting that it was probably the n-3 fatty acids rather than some other ingredient of fish that conferred the protection.

In a later analysis of DART-1, Ness et al (2002) reported an increased all-cause mortality in the fish group during the 3 years immediately following the trial (unadjusted Hazard Ratio 1.13, 95%CI 1.01 – 1.7). This increase in mortality relative to the non-fish advice group may relate to a loss of compliance following the conclusion of the original DART-1 study in the fish-advice group, and an increase in fish intake in the non-fish advice group following their being advised of the study outcomes at the conclusion of DART-1. Ness et al (2002) surveyed the dietary habits of former DART-1 participants 10 years after the conclusion of the original trial and found that reported fish intake was still higher in subjects who had been in the original fish advice group in DART-1 compared with the non-fish advice group. However, Ness et al were unable to survey the people who had died prior to the 10 year dietary follow-up, and it is possible that those who died during the 3 year period following the conclusion of DART-1 were those who were least compliant with continuing fish intake. If the fish intake during DART-1 had provided a protective benefit which had increased their longevity despite the presence of cardiovascular and/or other disease compared with the non-fish group, then it would be expected that once this benefit was removed due to a reduction in fish intake they would die at an accelerated rate. Interestingly the increase in all-cause mortality was largely due to an excess of deaths not-attributable to cardiovascular disease, suggesting a continuing protective cardiovascular benefit.

Eritsland et al (1996)

Eritsland et al (1996) recruited 610 patients due to undergo coronary artery bypass surgery. All patients receive a bolus dose of 15 mg of Warfarin on the first morning of the post-operative day. On the second post-operative day they were randomly allocated, using a 2 by 2 factorial design to either 300 mg/day of aspirin, to Warfarin (dose aimed at achieving an INR of 2.5 to 4.2), or to these treatments combined with 2 g/day of EPA and 1.3 g/day of DHA delivered in the form of ethyl esters for 1 year. The primary endpoint was graft patency, which was significantly improved in the patients consuming the n-3 PUFA as determined by a lower incidence of graft occlusion and an association between reduced graft occlusions with increasing relative change in serum phospholipid n-3 PUFA. Importantly however, this study also reported data on serum lipids and, while total cholesterol, HDL cholesterol and LDL cholesterol were all increased in both the n-3 and control groups, there was a statistically significant reduction (19%) in serum TG concentrations in subjects receiving the n-3 treatment only.

Sirtori et al (1998)

Sirtori et al (1998) recruited 935 patients with hypertriglyceridaemia and other risk factors for CVD (eg. Type 2 diabetes, glucose intolerance, hypertension). After a 4 week run in during which patients followed an isocaloric diet and maintained concomitant therapy (eg hypotensive/antidiabetic), subjects were randomised (double-blind) to consume either 1530 mg of EPA and 1050 mg of DHA for 2 months, or a placebo (olive oil) in addition to their conventional therapy. No hypolipidemic drugs were prescribed during the study. After the first 2 months the doses of n-3 PUFA (1020 mg EPA, 700 mg DHA) and placebo were reduced up to the end of the 6th month, after which all subjects were allocated to the consumption of 1020 mg EPA and 700 mg DHA. By the end of the initial 6 month double-blind period of the study there was a significant reduction in plasma TG concentrations (21.5%) in subjects taking the n-3 PUFA, with a further small reduction in these subjects by the end of the study (21.5% to 25.2% reduction). During the second 6 months of the study, when subjects who had previously been consuming the placebo were switched to n-3 PUFA, they also experienced a significant reduction in plasma TG concentration (19.5%), such that by the end of 12 months there was no difference in plasma TG concentrations between groups. No effects on total cholesterol, HDL cholesterol or glycemic control were observed. This study was important because it again provided evidence that EPA and DHA are effective in reducing plasma TG concentrations.

GISSI-P (1999)

The GISSI trial investigated the effects of EPA and DHA on relative risk of CHD (defined as death, non-fatal MI, non-fatal stroke). Patients who had survived a recent MI (≤ 3 months) were recruited for the study, with no age restrictions. Patients were randomly allocated to one of four treatment groups, supplementation with n-3 PUFA (850 – 882 mg/day of ethyl esters of EPA and DHA, in a 1:2 ratio), 300 mg/day of vitamin E (synthetic α -tocopherol), n-3 PUFA + vitamin E, or no supplement. Patients were advised to adhere to recommended preventative treatments, including aspirin, β -blockers, ACE inhibitors, but not statins (which were not supported by definitive data on efficacy when the study commenced). Assessments were undertaken at baseline, and after 6, 12, 18, 30 and 42 months. Assessments included the administration of a food frequency questionnaire and collection of a blood sample for determination of blood lipid concentrations. Primary end-points were cumulative rate of all-cause death, non-fatal MI, and non-fatal stroke, and the cumulative rate of CV death, non-fatal MI, and non-fatal stroke.

A two-way factorial analysis (n-3 PUFA vs no n-3 PUFA) on an intention-to-treat analysis revealed a 10% relative decrease in the risk of the combined primary end-point of all-cause death, non-fatal MI and non-fatal stroke ($P = 0.048$), but the 11% decrease in risk for the other combined end-point of CV death, non-fatal MI, and non-fatal stroke was not significant ($P = 0.053$). Four-way analysis of the data (n-3 PUFA vs Vitamin E vs n-3 PUFA+Vitamin E vs no supplement) demonstrated that supplementation with n-3 PUFA resulted in statistically significant reductions in both primary end-points, viz. all-cause death + non fatal MI + stroke (-15%, $P = 0.02$) and CV death + non-fatal MI+ stroke (20%, $P = 0.008$), and that these reductions were due entirely to decreases in mortality rather than non-fatal CV events which were not different across treatment groups. In particular there was a 45% reduction in mortality due to sudden death, which is consistent with studies which have demonstrated anti-arrhythmic properties of marine n-3 PUFA. The authors reported no clinically important changes in cholesterol (total, HDL and LDL), but there was a small, but statistically significant decrease in TG concentrations (3.4%) in patients receiving n-3 PUFA. This study is of particular importance because of its duration and large sample size and, as with previous studies (in particular Burr 1989), confirmed that supplementation with EPA and DHA reduced cardiovascular mortality, but had no effect on the incidence of non-fatal cardiovascular events. The study also demonstrated that supplementation with EPA and DHA significantly reduced blood TG concentrations, but the magnitude of the decrease was less than reported in most other trials.

Von Schacky et al (1999)

While 223 subjects commenced in this study, complete data on the primary outcome (coronary angiography) was only available for 162 subjects at the end of the study period. However, despite there being <200 subjects for the primary outcome, this study has been re-reviewed because data for >200 subjects was available for the secondary outcome measures, in particular data on blood lipids and blood pressure.

The 223 patients (18–75 years) recruited for the study had been hospitalised for diagnostic coronary angiography, had stenosis >20% in at least one vessel and had revascularisation planned or performed in the previous 6 months on no more than one vessel. Overweight patients ($BMI > 25 \text{ kg/m}^2$) were advised to restrict caloric intake, but no other dietary advice was given. Subjects were randomised to consume six 1g capsules per day for 3 months and then 3 capsules per day for 21 months of either a placebo oil which contained no marine n-3 PUFAs (and was similar to the fatty acid composition of the average European diet) or fish oil (35.4% EPA, 21.5% DHA) using a double-blind, stratified design. Each 1 g capsule contained 4 mg of α -tocopherol as an antioxidant. Stratification was on the basis of 1) percutaneous transluminal coronary angioplasty <6 months prior to randomisation, 2) current therapy with a lipid-lowering agent, 3) > 2 of high LDL ($> 3.88 \text{ mmol/L}$), smoking, history of MI in a first-degree relative, hypertension. Coronary angiography was performed at baseline and 24 months. Blood pressure was measured and blood

samples were collected at baseline, 1, 6, 12, 18 and 24 months, but only samples at baseline and 24 months were collected after an overnight fast. After 24 months of supplementation, coronary segments in the fish oil group showed less progression, and more regression of coronary artery disease than did coronary segments in the placebo group (P = 0.04).

There were no effects of fish oil on blood pressure, total cholesterol or HDL-cholesterol, but LDL-cholesterol was increased in the fish oil group compared with the placebo. Blood TG concentrations were decreased relative to controls from 1 – 18 months, but were not different at 24 months. This study is particularly important as it demonstrates an effect of n-3 PUFA on coronary artery disease, but the effect on TG lowering is inconclusive given that differences in TG concentrations were only evident from 1-18 months when non-fasted blood was collected, but there was no difference at 24 months when fasted blood was collected. It is possible to conclude from this study that fish oil supplementation may not lower fasting blood TG concentrations in the longer-term (≥ 2 years). However, the lower TG in the samples from 1-18 months may be indicative of the effect of fish oil in reducing elevated postprandial TG.

Table 4: Pivotal intervention studies considered by the USFDA in their 2000 review

Reference	Study design			Outcomes	
	Intake	Study description	Duration	Outcomes	Effect
Burr et al (1994)	Fish oil capsules (3g/day)	N=454	2 yr	IHD death	Fish oil group 3.5% Control group 9.3% (P=0.03)
Eritsland et al (1996)	4 g/day fish oil capsules 51% EPA 32% DHA	Patients due for coronary bypass surgery N=610	1 yr	1 yr graft patency HDL LDL TG	OR 0.72 (95%CI 0.51 – 1.01) (risk of ≥ 1 occluded graft) OR 0.77 (95%CI 0.60 – 0.99) (graft occlusion rate per distal anastomosis) Fish oil 9.7% increase (P<0.001 vs baseline) Control 5.1% increase (P<0.001 vs baseline) Fish oil 10% increase (P<0.001 vs baseline) Control 7.7% increase (P<0.001 vs baseline) Fish oil 19% decrease (P<0.001 vs Control)
Sirtori et al (1998)	Capsules up to: EPA 1530 mg/d DHA 1050 mg/d	Hypertriglyceridaemia (+ other CVD risk factors) N=935	12 mo	TG HDL	Decrease ~23% NS
GISSI-P (1999)	Capsules 850 – 882 mg/d EPA+DHA (2 :1 ratio)	Patients who survived recent MI, N=11,324	3.5 yr	All-cause death, non-fatal MI and non-fatal stroke CV death, non-fatal MI and non-fatal stroke	RR 0.85 (0.74 – 0.98) (PUFA vs No PUFA) RR 0.80 (0.68 – 0.95) (PUFA vs No PUFA)
Von Schacky et al (1999)	Capsules EPA 35.4%; DHA 21.5% (6g/d x 3 mo then 3g/day x 21 mo)	Hospitalised for coronary angiography 18 – 75 yr N=162	2 yr	Progression of coronary atherosclerosis BP HDL TG	P=0.041 vs control NS NS 21% diff vs control (P<0.01)

The intervention studies re-reviewed here tended to provide consistent findings relating to reduced risk of CHD death, but not non-fatal CV events, and consistent reductions in blood triglyceride concentrations. Given that these studies were intervention studies which were well designed, with relatively large sample sizes, they can be interpreted as providing convincing evidence that EPA and DHA reduce blood TG concentrations and risk of CHD death, but do not reduce the risk of suffering a non-fatal cardiovascular event.

Conclusions from this reappraisal

The majority of studies deemed eligible by the USFDA for consideration in their 2000 and 2004 reviews have been reappraised. They provide evidence that increasing ω 3 consumption can reduce the risk of CV death but may not necessarily reduce the risk of non-fatal CV events. This evidence formed the basis for approval by the USFDA of a qualified health claim relating EPA and DHA consumption to reduced risk of CHD. In the present reappraisal, however, it is apparent that the majority of these studies, particularly the intervention studies conducted prior to the 2000 USFDA review, showed that EPA and/or DHA reduce blood TG concentrations. However, elevated blood TG was not considered a valid risk factor for CHD by the USFDA during their reviews, even though there is considerable evidence which indicates that it is an independent risk factor for CVD (see Part 4). Therefore, based on the findings of the studies from the 2000 and 2004 USFDA reviews which have been reappraised, there is convincing evidence to indicate that ω 3 can reduce the risk of CVD by reducing blood TG concentrations. The reappraisal of these studies also provides evidence to suggest that ω 3 supplementation might increase blood levels of HDL-cholesterol. As the evidence for this was not as compelling as for effects on TG, it may only be concluded that effects on HDL-cholesterol are possible.

d) Consideration of the validity of the USFDA's conclusions

As stated in Part 1a, one can have confidence in the validity of the USFDA's conclusions, as expressed in the ensuing qualified health claim, which states that the evidence for CHD risk reduction by ω 3 is *supportive but not conclusive*.

The shortcoming of the USFDA's 2004 review is its limited scope due to lack of consideration of other CVD outcomes (viz. stroke, sudden death, HF) and other CV biomarkers (e.g. blood TG, HR, HRV, arterial compliance and endothelial vasodilation) and its failure to retrospectively review the extensive body of pre-2000 evidence for effects of ω 3 on BP. Nevertheless, it is a conservative and reliable starting point from which to consider supporting evidence for a broader health claim focus, viz. the ability of ω 3 to reduce the risk of CVD.

PART 2. REVIEW OF EVIDENCE RELEASED SINCE THE TIME OF THE USFDA REVIEW

As stated above, a MEDLINE electronic database search identified 868 papers published in 2000-2005 relating ω 3 to CVD. Numerous clinical, experimental and epidemiological studies provide overwhelming evidence that ω 3 from fish and fish oil protect against atherosclerotic heart disease and sudden coronary death (Schmidt 2005a, Schmidt 2005b). Since the release of the 2004 USFDA review, a number of publications of prospective population studies have confirmed a relationship between fish consumption and lower rates of CHD mortality and/or sudden death. As outlined in Part 1(b), this report also examines the relevance of ω 3 beyond CHD, namely coronary artery disease (CAD), stroke, antiarrhythmic effects (sudden death) and heart failure, and thus will provide data from studies not previously addressed by previous USFDA reviews. In accordance with the FSANZ framework, each of these will be assessed in relation to the level of certainty to which a relationship is substantiated. In addition, two meta-analyses (He 2004 and Whelton 2004), a Cochrane Review (Hooper 2004), a National Heart Foundation of Australia draft position paper (Colquhoun 2005) and a dossier of evidence (Baldwin & Rice, 2004) supporting the UK Joint Health Claims Initiative's ω 3 health claim appearing since the USFDA review will be discussed.

Coronary Artery Disease

An inverse association between fish consumption and CAD has been reported in two studies from Finland in patients with established coronary artery disease (Erkkila 2003, Erkkila 2004). Erkkila et al (2003) assessed 285 men and 130 women with CAD participating in EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events study). During the 5 year follow-up, 36 patients died, 21 had myocardial infarctions, and 12 had strokes. The relative risks (RR) of death adjusted for cardiovascular disease risk factors for subjects in the highest tertile of EPA and DHA in cholesterol esters compared with those in the lowest tertile were 0.33 for EPA and 0.31 for DHA (P =0.06 and 0.03, respectively). A high proportion of EPA in cholesterol esters was associated with a low risk of CAD death. Compared with no consumption, consumption of fish tended to be associated with a lower risk of death. Consumption of 1-57 g per day was associated with a 50% reduction (RR=0.5) and greater than 57 g per day was associated with a 63% reduction (RR=0.37) (P for trend=0.059).

Erkkila et al (2004) examined the association between fish intake and progression of coronary artery atherosclerosis in a prospective cohort study of 229 postmenopausal women with CAD participating in the Estrogen Replacement and Atherosclerosis trial. Usual fish intake was estimated at baseline by food-frequency questionnaire and quantitative coronary angiography was performed at baseline and after 3 years to evaluate changes in the mean minimum coronary artery diameter, the mean percentage of stenosis and the development of new coronary lesions. Compared with lower fish intakes, consumption of 2 or more fish meals or 1 or more serves of tuna or dark fish per week, was associated with significantly smaller increases in the percentage of stenosis (P<0.05) in diabetic women after adjusting for age, CVD risk factors and dietary intakes of fatty acids, cholesterol, fibre and alcohol. There were no significant associations in non-diabetic women. High fish consumption was also associated with smaller decreases in minimum coronary artery diameter and fewer new lesions. The authors concluded that consumption of fish was associated with significantly reduced progression of coronary artery atherosclerosis in women with overt CAD.

Overall the data from these two studies supports a possible benefit of ω 3 in CAD. One must bear in mind, however, that, in Erkkila et al (2004), fish prevented the progression of atherosclerosis but it did not prevent atherosclerosis. Furthermore, the benefits were confined to diabetic women.

Stroke

In addition to the Nurses' Health Study (Iso 2001) and the Health Professionals Follow-up Study (He 2002) cited above, another large prospective cohort study, viz. the Cardiovascular Health Study in the Elderly (Mozzaffarian 2005a) has now shown an inverse association between increasing ω 3 consumption and the risk of stroke. Once again, the benefit was observed for ischaemic but not haemorrhagic stroke.

In the Cardiovascular Health Study, Mozzaffarian et al (2005a) examined 4775 adults aged 65 years or older and free of known cerebrovascular disease at baseline. During 12 years of follow-up, there were 626 incident strokes, including 529 ischemic strokes. In multivariate analyses, tuna, broiled or baked fish consumption was inversely associated with total stroke ($P=0.04$) and ischemic stroke ($P=0.02$). There was a 13% lower risk of ischemic stroke with an intake of 1-3 times per week (RR 0.87), a 27% lower risk with an intake of 1-4 times per week (RR 0.73) and 30% lower risk with intake of 5 or more times per week (RR 0.70), compared with an intake of less than once per month. In contrast, fried fish/fish sandwich consumption was positively associated with total ($P=0.006$) and ischemic stroke ($P=0.003$); risk of ischemic stroke was 44% higher with fish consumption more than once per week (RR 1.44) compared with consumption less than once per month. Fish consumption was not associated with hemorrhagic stroke.

Overall the data from this recent prospective study, when taken into consideration with the earlier studies by Iso et al (2001) and He et al (2002), indicate a highly probable benefit of ω 3 in reducing the incidence of stroke, particularly ischemic stroke.

Atrial Fibrillation

Two studies have also reported that ω 3 can reduce the incidence of atrial fibrillation (AF), a primary risk factor for ischaemic stroke, in the elderly (Mozzaffarian 2004) and in patients undergoing coronary bypass surgery (Calo 2005).

In a prospective, population-based cohort of 4,815 adults aged 65 years or more, Mozzaffarian et al (2004) measured consumption of fish and incidence of AF. They reported that consumption of tuna, broiled or baked fish correlated with plasma phospholipid ω 3 fatty acids, whereas consumption of fried fish or fish sandwiches did not. During 12 years of follow-up, 980 cases of incident AF were diagnosed. In multivariate analyses, tuna, broiled or baked fish was inversely associated with the incidence of AF. There was a 28% lower risk with intake 1-4 times per week (RR=0.72, $P=0.005$), and 31% lower risk with intake of 5 or more times per week (RR=0.69, $P=0.008$), compared with less than once per month (P trend=0.004). The results were not different after adjustment for preceding myocardial infarction or congestive heart failure. In contrast, fried fish consumption was not associated with lower risk of AF.

Calo et al (2005) assessed the efficacy of preoperative and postoperative ω 3 treatment to prevent the occurrence of AF, which is a common complication in patients undergoing coronary artery bypass graft surgery (CABG). They found that ω 3 treatment substantially reduced the incidence of postoperative AF (54.4%) and resulted in shorter hospital stays. They randomized 160 patients to ω 3 or control treatment from at least 5 days before elective CABG until the day of discharge from the hospital. Postoperative AF developed in 33.3% of patients in the control group and in 15.2% of patients of the fish oil group ($P=0.013$). After CABG, the patients in the fish oil group were hospitalized for significantly fewer days than controls.

The data from these studies indicate a probable benefit of ω 3 for reducing the incidence of AF.

Antiarrhythmic Effects (Sudden Death)

The antiarrhythmic potential of ω 3 supplementation in humans was best demonstrated by the prevention of sudden death in the GISSI-P trial (GISSI-P 1999). Apart from prevention of AF evidenced in the observational studies described above, there have been recent attempts to evaluate potential benefits of ω 3 on surrogate endpoints of ventricular arrhythmia predisposing to sudden death in humans. One such endpoint is the occurrence of premature ventricular contractions (PVCs) recorded by continuous ECG (Holter) monitoring. PVCs are the result of electrical impulses arising from one of the cardiac ventricles before the next expected heart beat, that is, prematurely. As a result, the subsequent rhythm is irregular. Clinical symptoms depend on the frequency of the PVCs. Frequent PVCs are independent predictors of sudden cardiac death and mortality in survivors of myocardial infarction.

In a randomized, double-blind, placebo-controlled study of 65 patients with cardiac arrhythmias without coronary heart disease or heart failure, Singer et al (Singer 2004) supplemented patients with 3g daily fish oil or olive oil over 6 months. In the fish oil group, the incidence of atrial and ventricular premature complexes was reduced by 47% and 68%, respectively, couplets were reduced by 72% and triplets were entirely disappeared.

Geelen et al (Geelen 2005) investigated the effect of ω 3 fatty acids on heart rate and PVCs in 84 patients with frequent PVCs at baseline. Patients were randomly assigned to either ω 3 or placebo and 24h Holter recordings were made at baseline and after 14 weeks of intervention. Although PVCs were reduced by 6% more after fish oil treatment than after placebo, the groups were not statistically different. However, the 24h heart rate was significantly decreased in the fish-oil group by a mean of 2.1 beats per minute more than in the placebo group. The authors found that ω 3 did not substantially suppress the number of PVCs in patients with frequent PVCs, but significantly decreased HR, predicting a lower risk of sudden death.

In a double-blind, placebo-controlled trial, Raitt et al (Raitt 2005) randomised 200 patients with an implantable cardioverter /defibrillator (ICD) and a recent episode of sustained VT or VF, to receive fish oil or placebo. Patients were monitored monthly for the first 3 months and every 3 months thereafter for up to 2 years. ICD memory was checked for episodes of ICD therapy at each visit and classified as tachycardia, fibrillation, or other types of arrhythmia. Only episodes of tachycardia and fibrillation were considered end points. The primary endpoint was the time until the first episode of tachycardia or fibrillation that triggered ICD therapy. After 6, 12, and 24 months, 46%, 51% and 65% of patients randomized to receive fish oil had ICD therapy for VT/VF compared with 36%, 41% and 59% for patients randomized to placebo (P=0.19). In a subset of 133 patients whose qualifying arrhythmia was VT, 61%, 66% and 79% of patients in the fish oil group had VT/VF at 6, 12, and 24 months compared with 37%, 43% and 65% of patients in the control group (P=0.007). Recurrent VT/VF events were more common in patients taking fish oil (P<0.001). The authors concluded that in patients with a recent episode of sustained ventricular arrhythmia and an ICD, fish oil does not reduce the risk of VT/VF and may be proarrhythmic in some patients. There are reasons for the discordant data between this trial and other studies. Firstly, the patients had a history of sustained ventricular arrhythmia and seriously impaired ventricular function. These characteristics, highlighted by the need for an implanted defibrillator, put them at very high risk for sudden cardiac death. The authors also suggested that patients with ICDs and no history of recent myocardial infarction might experience arrhythmias in which interference with sodium ion channels exacerbates arrhythmia.

Leaf et al (Leaf 2005) examined 402 patients with ICDs and randomly assigned them double-blind to either fish oil or olive oil daily supplementation for 12 months. The primary end point was time to first ICD event for ventricular tachycardia or fibrillation (VT or VF) confirmed by electrograms

or death from any cause. Fish oil treatment showed a trend toward a prolonged time to the first ICD event (VT or VF) or of death from any cause (risk reduction of 28%; $P=0.057$). When therapies for probable episodes of VT or VF were included, the risk reduction was significant at 31% ($P=0.03$). Furthermore, in those patients that stayed on the protocol for at least 11 months, the antiarrhythmic benefit of fish oil was improved for those with confirmed events (risk reduction of 38%; $P=0.03$). The interpretation of these findings, however, was complicated by the relatively low compliance (65%) with the treatment protocol and the difficulty in obtaining electrocardiograms for all arrhythmic events. Overall, the findings might be viewed as providing qualified support for an $\omega 3$ benefit in patients with ICDs, as mortality did not differ between fish oil and control groups. Although it did not prevent mortality, the calculated hazard ratios favoured fish oil treatment.

Christensen et al (2005) studied the relationship between $\omega 3$ in serum and the incidence of ventricular arrhythmias in 98 patients with ischaemic heart disease and an ICD over a 12-month period. The numbers of VF and VT events were assessed. During the study period, 22 patients (25%) incurred a total of 71 ventricular events (39 ventricular tachycardia and 32 fibrillation events). Patients with more than one arrhythmic event had significantly lower $\omega 3$ than those without arrhythmias (7.1% vs 9.2%, $P<0.01$). In addition, the association was strongest for serum DHA. When patients were divided into quintiles according to their $\omega 3$ levels, those with the highest $\omega 3$ concentration had significantly fewer ventricular arrhythmias than patients with the lowest $\omega 3$ concentration (0.2 event vs 1.3 event, $P<0.05$). These data suggest that in patients who have ischemic heart disease and disturbed ventricular arrhythmias that require an ICD, protection against subsequent ventricular arrhythmias was associated with having a higher serum $\omega 3$ level.

Taken together, the abovementioned studies support a preventive effect of $\omega 3$ in arrhythmias and sudden death.

Heart Failure

In the Cardiovascular Health Study, which previously described an inverse association between fish consumption (tuna, broiled or baked fish, but not fried fish or fish sandwiches) and fatal ischaemic heart disease in an elderly population (Lemaitre 2003, Mozaffarian 2003), Mozaffarian et al (2005b) examined the relationship between fish consumption and incidence of congestive heart failure (HF) in 4,738 adults aged 65 years or more and free of HF at baseline. During 12 years of follow-up, 955 patients developed HF. In multivariate-adjusted analyses, tuna/other fish consumption was inversely associated with incident HF. The risk was 20% lower with 1-2 fish meals per week ($RR=0.80$), 31% lower with 3-4 meals per week ($RR=0.69$) and 32% lower with 5 or more meals per week ($RR=0.68$), compared with less than one fish meal per month (P trend=0.009). In contrast, fried fish consumption was positively associated with HF (P trend =0.01). Dietary $\omega 3$ intake was also inversely associated with HF (P trend =0.009), with 37% lower risk in the highest quintile of intake ($RR =0.73$) compared with the lowest.

While the data from the study by Mozaffarian et al (2005b) support a preventive effect of $\omega 3$ in HF, additional studies are required for confirmation.

Meta-Analyses

Two recent meta-analyses by He et al (2004) and Whelton et al (2004) further support an inverse association between $\omega 3$ and CHD. He et al assessed 11 eligible studies and 13 cohorts, including 222,364 individuals with an average 11.8 years of follow-up. Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled multivariate RRs for CHD mortality were 0.89 for fish intake 1-3 times per month, 0.85 for once per week, 0.77 for 2-4 times per week and 0.62 for 5 or more

times per week. The authors calculated that each 20g/day increase in fish intake related to a 7% lower risk of CHD mortality (P for trend=0.03). Whelton et al (2004) conducted a meta-analysis of 19 observational studies (14 cohort and 5 case-control). Fish consumption versus little to no fish consumption was associated with a relative risk of 0.83 (p <0.005) for fatal CHD and 0.86 (p <0.005) for total CHD.

Not all studies have shown associations between fish consumption and CV events, possibly due to the uncertainty of estimation of usual dietary fish consumption, failure to distinguish fatty- from low-fat fish, and the complex correlation between diet and other lifestyle factors. Markmann et al (1999) suggested that discrepancies between studies may relate to differences in study populations, with only high-risk individuals benefiting from increasing their fish consumption. The authors proposed that 40-60 g daily fish intake would provide a 50% reduction in death from CHD in high-risk populations. These findings were supported in a meta-analysis by Bucher et al (2002).

Cochrane Review

In a recent Cochrane Review, Hooper et al (Hooper 2004a) reviewed 48 randomised controlled trials and 41 cohort studies, and reported no benefit of ω 3 in relation to total or CV mortality. This somewhat surprising result was due in large part to inclusion of the Diet and Reinfarction Trial-2 (DART-2, Burr 2003), which contributed substantial heterogeneity to the meta-analyses. As meta-analyses provide averaged results which cannot reflect the circumstances of individual trials, the authors cautioned that the outcomes may not be meaningful. The main source of heterogeneity between the outcomes of the DART-2 trial and other trials is the increase in sudden death with fish and fish oil intake in DART-2. The results are also at variance with DART-1, in which the same authors showed that fish or fish oil supplementation decreased mortality by 29% over a two year period (Burr 1989). Some of the concerns with interpretation of data from the DART-2 trial relate to the small absolute numbers of CHD mortality and sudden death and to issues of compliance and recruitment. Moreover, a recent report by the US Department of Health and Human Services advised that DART-2 was of a poor methodological standard.

Notwithstanding the authors' negative conclusions, the Cochrane meta-analysis of the intervention trials found a *near* significant reduction in total mortality with ω 3 consumption (RR=0.87; CI=0.73-1.03), even when DART-2 was included. The omission of the DART-2 trial from the analysis provided an overall relative risk of death of 0.83 (CI 0.75-0.91) with no significant heterogeneity. The Cochrane meta-analysis of cohort studies, however, showed significantly reduced risk of both total (RR=0.65, CI=0.48-0.88) and CV (RR=0.79, CI=0.63-0.99) mortality with high versus low ω 3 intakes. These indications of reduced risk are encouraging; they hardly warrant the unsubstantiated concern about potential harmful effects of ω 3 implied by the authors.

While the Cochrane review provides a comprehensive cover of published evidence on the relationship of ω 3 to CVD, it has a number of limitations (apart from heterogeneity) which impact on its interpretations of the evidence. In particular, it combines data relating to ω 3 intakes from both plant and marine sources, even though there is abundant evidence that the health benefits are primarily attributable to the marine ω 3, EPA and DHA, and that there is minimal conversion of the plant ω 3, ALA, to EPA or DHA. Sub-analyses separating effects of EPA and DHA from those of ALA were undertaken for the two primary outcomes but not for the numerous secondary outcome measures. It also combines primary with secondary interventions and fatal with non-fatal events in its outcome measures. It limits the selection of studies for inclusion in its analyses to those of >6 months duration. A long time frame may be necessary for the assessment of hard end points but it will exclude most of the shorter term trials designed to assess the effects of ω 3 intake on biomarkers such as plasma lipids and BP, thus compromising their evaluation. Another

limitation is the use of a hierarchical system to choose outcome measures for inclusion, such that, for a study reporting individual effects of EPA and DHA, only the outcome related to EPA would have been included in the meta-analysis. As much of the experimental evidence points to DHA as the primary mediator of the CV benefits of ω 3, this is of particular concern. Finally, in conducting the analysis, it compares relative risks of the lowest and highest ω 3 intakes, without considering the potential impact of moderate, intermediate intakes. In the case of the stroke data, for example, this converted the positive outcome reported by He et al (2002) into a negative outcome.

The subsequent publication of the Cochrane review in the British Medical Journal (Hooper, 2006) has attracted an unprecedented editorial response, with numerous criticisms from leading authorities in the field (see <http://bmj.bmjournals.com/cgi/eletters/332/7544/752#138148>, Rapid Responses for Hooper et al). A number of subsequent publications, e.g. von Schacky & Harris, 2006, have since discredited the negative conclusions of the Cochrane review.

It is of interest that Hooper, first author of the Cochrane review, was first author of another 2004 publication on behalf of UK Heart Health and the British Dietetic Association which promoted ω 3 intake as the foremost dietary strategy for secondary prevention of CVD (Hooper 2004b).

National Heart Foundation of Australia Draft Position Paper (2005)

Colquhoun and Ferreira-Jardim (Colquhoun 2005), have recently prepared a draft paper to the National Heart Foundation of Australia (NHFA) on Fish, Fish Oils and Long Chain Omega-3 Fatty Acids. The authors conclude that data from epidemiological and randomised clinical trials convincingly show that ω 3 reduce cardiovascular disease. The report adds that ω 3 fortification of foods is likely to play an important role in facilitating an adequate ω 3 intake in the general population and a therapeutic ω 3 intake for patients with CHD or hypertriglyceridaemia.

The report recommends ω 3 intake consistent with the recommendations of the American Heart Association (Grundey 2003, Kris-Etherton 2003a, 2003b), the NIH expert group (The National Academies Press) and the World Health Organisation (Knapp 1997). Adults with documented CHD should consume approximately 1g of combined EPA+DHA per day, as 2-3 serves of fish (preferably oily fish) per week, as well as fish oil capsule supplements. For patients with elevated triglycerides, ω 3 fortified foods and drinks and/or capsules are an alternative therapy to drugs and should be taken at a starting dose of 1.2 g of EPA+DHA increasing up to 4 g per day. To lower the risk of CHD in the general population the report recommends adults consume 500 mg per day of marine ω 3, achieved by consuming 2-3 serves of fish (preferably oily fish) per week. If low ω 3 fish is consumed or if individuals do not wish to eat fish, alternative sources of ω 3 include marine ω 3 fortified foods and drinks as well as fish oil capsules.

UK Joint Health Claims Initiative (2005)

In 2005, the following health claim for ω 3 was introduced in the UK:

Eating 3g weekly, or 0.45g daily, long chain omega-3 polyunsaturated fatty acids, as part of a healthy lifestyle, helps maintain heart health.

This differs from the USFDA health claim in that it is a health maintenance claim, as opposed to a risk reduction claim (the latter is prohibited in the UK). Nevertheless, this message might be expected to have a similar impact on consumers. Moreover, it recommends a daily ω 3 intake of 450mg/day to attain the benefit.

The JHCI health claim and recommended intake was based on a detailed submission by Baldwin and Rice (2004), containing a systematic review of evidence and possible mechanisms of action. It summarised the evidence as follows:-

1.4.3 Overall Summary of RCT and Non-RCT Data.

Secondary prevention. The reduction in risk of death from a myocardial infarction following enhanced intake of long chain omega-3 polyunsaturates is consistently shown by the available data from randomised controlled trials, as reported by Bucher et al (2002). From these studies, it can be shown that increasing daily intake of long chain omega-3 polyunsaturates by around 1g reduces subsequent death risk quickly and sustainably, in those people who have already survived one or more myocardial infarctions.

Primary prevention. In people who have not experienced a myocardial infarction, there is also evidence from epidemiological and case-control studies that indicates a lower subsequent risk of myocardial death in those with increased intakes of the long chain omega-3 polyunsaturates.

1.6 Summary of Evidence Review

The Scientific Question posed in paragraph 1.2 is thus answered by the evidence reviewed in section 1.4. In addition, information on the probable mechanism(s) involved in this effect is presented. Though this aspect of the relationship between long chain omega-3 polyunsaturated fatty acids and coronary heart disease is not yet fully established, there is no doubt that the long chain omega-3 polyunsaturated fatty acids do act in a beneficial manner on a number of established risk factors for coronary heart disease.

This is also apparent from the recent (Jan 2004) comments made by Sir John Krebs, head of the Food Standards Agency. In advising consumers to continue to eat farmed salmon, Krebs is quoted in national media (Independent, Jan 13th 2004) as saying “Our advice is that people should consume at least two portions of fish weekly, one of which should be oily fish like salmon. There is good evidence that eating oily fish reduces the risk of death from recurrent heart attacks and that there is a similar effect in relation to first heart attacks.” A similar statement was also published at that time on the FSA website at www.foodstandards.gov/news/newsarchive/. A statement by the head of the UK Food Standards Agency, to the effect that there is good evidence that omega-3 polyunsaturates can reduce risk of heart death would seem to be a good place to end this review of the evidence available to support the claim being sought in this dossier.

PART 3: RELEVANCE OF THE RELATIONSHIP TO AUSTRALIA & NEW ZEALAND

a) Relevance of the review to the population characteristics in Australia and New Zealand

Much of the data relating ω 3 intakes to health outcomes in a typically “healthy” population has been obtained from observational studies conducted in the US, where CV health status and morbidity/mortality statistics are similar to those of Australia and New Zealand (ANZ). Hence it is reasonable to draw parallels between the demonstrated relationship of ω 3 intake to CV health status, especially as reflected by the larger meta-analyses, and the likely relationship of ω 3 intake to CV health status in ANZ.

In 2000, CVD accounted for 39% of total mortality in Australia, of which 21% was attributed to CHD, 9% to stroke, and 9% to other diseases of the heart and blood vessels, e.g. sudden death and HF (Australian Institute of Health & Welfare, 2002). Similar figures were reported for New Zealand during the same period, with CVD accounting for 40% of total mortality, of which 22% was attributed to CHD, 10% to stroke, and 8% to other diseases of the heart and blood vessels (Hay & NZ Heart Foundation, 2004). The estimated economic burden of CVD in Australia is greater than any other disease (Mathers & Penm AIHW, 1999). Government authorities and the Heart Foundations strongly advocate diet and lifestyle approaches to reduce the risk of CVD. The current review demonstrates that there is substantial evidence that increasing dietary ω 3 intake through consumption of seafoods or other foods or supplements rich in EPA and DHA may decrease the risk of CVD, particularly in individuals with habitually low ω 3 intakes. However, in terms of extent of likely benefit, the importance of initial intakes is evident from the lack of effect or attenuation of effect seen in high fish-eating populations, such as the Japanese, Scandinavians or Alaskan Eskimos, and also from consideration of the relationship between LC ω 3 contents of erythrocytes and CV risk (Omega-3 Index), as reported by Harris and von Schacky (2004).

Using the NNS95 database, dietary intakes of EPA+DHA in Australia are estimated to average 170mg/day (Howe 2006), which is similar to estimates in the US of ~150mg/day but far less than estimates around 1600mg/day in Japan or 700mg/day in Norway (Dolecek, 1992). A considerable proportion of the long chain ω 3 consumed in Australia is DPA, an intermediate between EPA and DHA, derived predominantly from red meat. Sources of isolated DPA are not readily available, hence there has been little evaluation of its health benefits. It is reasonable to expect that it will have a health potential similar to that of EPA and DHA, as it can be readily converted to either. The total intake of EPA+DPA+DHA in Australia averages ~250mg/day, although the median intake (~120mg/day) is less than half of this (Howe 2006). The NHMRC, in its recent draft revision of Nutrient Reference Values, recommends maximum ω 3 intakes for optimal health of 430mg/day for women and 610mg/day for men (Baghurst, 2004). The NHFA, in its draft position paper, recommends an EPA+DHA intake of 500mg/day (Colquhoun 2005). These recommendations are consistent with that of the UK JHCI health claim, viz. 450mg/day.

Hence the average ω 3 intake in ANZ is about half the recommended level, while the median intake is only half again and an order of magnitude less than that of high fish-eating populations. It is therefore both possible and desirable to increase the ω 3 intake of the ANZ population.

Thus implementation of a CVD health claim in the ANZ population is likely to be effective in reducing CV risk, depending on the extent of increase in LC ω 3 consumption recommended. It should be noted that although the US health claim requires the LC ω 3 content/serving of the food to be stated, it does not stipulate an intake requirement. Being a qualified claim, it does not consider that the intake necessary to derive the health benefit has been established. Moreover, the USA has no official daily recommended intake value (DRV) for EPA and DHA, even though the Food & Nutrition Board of the Institute of Medicine recently determined a DRV for ALA.

Although the NHMRC and other organizations have now nominated ω 3 intake recommendations for optimal health, these cannot necessarily be interpreted as adequate intakes to reduce the risk of a specific disease condition such as CVD. Such information would ideally be obtained from long term intervention trials in a healthy population. Such a trial for ω 3, however, is unrealistic. The GISSI-P trial indicated substantial benefit in secondary prevention of CVD with 850mg/day (GISSI, 1999). An early observation trial, MRFIT, showed significantly lower CVD risk with ω 3 intakes at or above 650g/d (Dolecek, 1992). Recent meta-analyses cited above in Part 2 indicate that eating 1-2 serves/week of fatty fish (~200-400 mg/day of ω 3) can reduce CVD risk. A recent dietary intervention trial conducted in Australia with 80 healthy volunteers showed that the EPA+DHA content of erythrocytes could be increased from ~4% to ~7% by consuming 0.7g/day of ω 3 in processed foods (Murphy 2004). The analysis by Harris and von Schacky (2004) indicates that this level of increase would result in a significant decrease in CVD.

Whilst not definitive, it appears that ω 3 intakes consistent with the upper level of the Acceptable Macronutrient Distribution Range quoted by the NHMRC in its recent draft recommendation (Baghurst, 2004), viz. 430 mg/day for women and 610 mg/day for men, would be likely to achieve the anticipated reduction of CVD risk in ANZ. There is evidence suggesting that both EPA and DHA may improve specific CVD risk factors, which may occur by independent mechanisms. However, there is insufficient evidence at this stage to attribute any of these specific benefits to the individual ω 3 fatty acids, viz. EPA, DHA or DPA. Therefore it would be appropriate to adopt the NHMRC's generic inclusion of EPA+DPA+DHA for ω 3 in its Nutrient Reference Values, when considering a suitable intake recommendation for a CVD risk reduction claim in ANZ.

This intake can be relatively easily achieved by choosing fish such as salmon or tuna, either fresh or canned. The NHFA report (Colquhoun 2005) confirms that Australians are, on average, approaching the recommended consumption rate of 2 serves of fish/week. However, Australian fish tends to have lower fat content than common fish in the Northern hemisphere. Hence it is important to promote greater consumption of seafoods with high ω 3 content, as identified by Nichols et al (1998). On the other hand, we are no longer dependent on seafood as the primary source of ω 3 in the diet. Studies conducted in Australia by Metcalfe et al (2003) and Murphy et al (2004) have demonstrated that the recommended ω 3 intake can be achieved and sustained for at least 6 months by choosing from a variety of ω 3 enriched foods other than fish. Introduction of an ω 3 health claim would be expected to further stimulate development and local supply of alternative food sources of ω 3, including meat and eggs enriched with tuna fishmeal (Howe 2002), which is currently a waste product of Australia's tuna industry (personal communication). Development of such products may also help to offset concern about declining global availability of edible seafood, as much of the fishmeal derived from inedible pelagic fish or waste product of fish processing is used in less strategic stages of livestock production.

In summary, the relationship between ω 3 consumption and reduced risk of CVD is highly relevant to the ANZ population. Introduction of a health claim for foods could adopt the upper end of the AMDR in the NHMRC's draft NRV report as the recommended intake to reduce risk of CVD. Although there is insufficient evidence to justify this intake specifically for CVD risk reduction (as opposed to a general dietary recommendation), we consider that it is both feasible (double the average intake of Australian adults in 1995 (Howe et al, 2006)) and attainable by consumption of seafoods as well as a variety of alternative ω 3 enriched products. Increased availability of the latter is a likely outcome from the introduction of a CVD risk reduction claim for ω 3 in foods.

PART 4. RELATIONSHIP OF OMEGA-3 FATTY ACID INTAKE WITH RELEVANT BIOMARKERS OF DISEASE OUTCOME

a) Validation of Biomarkers for CVD Risk

There are several accepted biomarkers for CVD risk, including age, gender, total, LDL- and HDL-cholesterol, BP and smoking (National Cholesterol Education Program ATP III, 2002) but other biomarkers are emerging as CVD risk factors which are also influenced by ω 3 intake. These include TG, heart rate (HR), heart rate variability (HRV), atrial fibrillation (AF), arterial compliance, endothelial vasodilator function, intima-media thickness (IMT) and plaque stability.

In the Prospective Cardiovascular Münster (PROCAM) study (Assman 1998), which enrolled 19,698 people aged 16–65 years, participants were examined for lipid profile and CV risk factors at study entry and then observed for occurrence of fatal or non-fatal MI and sudden cardiac death. In an 8 year follow-up elevated TG emerged as an independent risk factor for major coronary events after controlling for LDL, HDL, age, SBP, smoking, diabetes mellitus, family history of MI and angina. Similarly, the Copenhagen Male study (Jeppesen 1998), which was an 8 year follow-up of 3,000 middle-aged and elderly Danish men who were free of CVD at enrolment, also identified an independent association of TG with the relative risk of CHD after adjustment for confounders. Prior to this, a meta-analysis of 17 population-based prospective studies including 46,413 men and 10,864 women had also supported a role for TG as an independent risk factor for CVD, reporting a 30% increase in relative risk of CVD in men and 75% in women for every 1 mmol/L increase in plasma TG (Hokanson & Austin, 1996). Based on the evidence from these studies there is a clear association between TG and CVD risk, but given that the studies were not interventions it is not possible to conclude that there is a cause and effect relationship. No controlled trials have demonstrated benefits of TG reduction alone on clinical or CV outcomes, primarily because it is difficult to lower TG without affecting other lipid and/or lipoprotein concentrations. Therefore, based on the current evidence available from observational studies, we conclude that it is highly probable that elevations in TG present an increased risk of CVD and that TG should be considered a valid biomarker of CVD risk. This is in line with the reduction of the upper limit for normal TG to <1.7 mmol/L in the American Heart Association's ATP III guidelines, indicating increased emphasis on TG reduction.

Sudden cardiac death (SCD) is responsible for approximately 50% of the mortality from CVD in Western countries. A number of studies have shown that increased HR (Dyer 1980, Kannel 1987, Shaper 1993, Wannamethee 1995, Palatini 1999, Jouven 2001, Palatini 2002) is a major independent risk factor for cardiovascular death, particularly SCD. Similarly, decreased HR variability (HRV) has been shown to be a powerful predictor of SCD and arrhythmic events in post-myocardial infarction patients (Hartikainen 1996). These studies suggest that HR and HRV are valid biomarkers of CVD risk, but again, the fact that they were observational studies only permits demonstration of an association between HR/HRV and CVD risk, so the evidence cannot be regarded as convincing (as it might be for an intervention trial), and it can only be concluded that it is probable that HR/HRV are valid biomarkers of CVD risk.

Carotid artery IMT is a predictor of stroke (Bots 1997; O'Leary 1999) and stenosis of internal carotid arteries with >60% lumen narrowing plays a causal role in a large percentage of strokes (Barnett 2000). Furthermore, progression in carotid IMT predicts risk for coronary events beyond that predicted by coronary measures of atherosclerosis (Hodis 1998). While plaque progression is an important risk factor for CVD, vulnerability of the atherosclerotic plaque to rupture is the primary determinant of thrombosis-mediated acute myocardial events (Plutzky 1999) and is therefore also an important determinant of CVD risk. Thus carotid IMT and atherosclerotic plaque stability should also be considered as valid markers of CVD risk.

Arterial dysfunction, in terms of decreased compliance (elasticity) or altered vasomotor reactivity, is an early indicator of increased CVD risk which may precede elevated BP and/or arterial stenosis. Arterial compliance is abnormal in subjects with, or at high risk of developing, arterial disease (Blacher 1999) and can be abnormal well before overt CVD develops (Simons 1999). Blacher et al (1999) studied the relationship between arterial compliance (using pulse wave velocity) and CV risk (from Framingham equations) in 710 volunteers with essential hypertension and found that arterial compliance was the primary predictor of the extent of atherosclerosis. Simons et al (1999) investigated cross-sectionally whether IMT and arterial compliance were associated with CV risk in 537 patients with vascular disease or atherosclerotic risk and found that risk of CVD (Framingham scores) increased nearly linearly with decreasing arterial compliance, indicating a close association between arterial compliance and CVD risk.

Similarly, abnormalities in endothelial function have been associated with a number of risk factors for CVD. The endothelium plays an integral role in maintaining arterial vasomotor tone and modulating vasoconstrictor, inflammatory, chemotactic and proliferative processes in the artery wall. Abnormalities of endothelial function have been associated with a number of CV risk factors. The non-invasive technique of flow-mediated dilatation (FMD) in the brachial artery (a marker of endothelium-mediated dilatory function) has shown strong correlations with coronary artery FMD (Takase 1998), suggesting that it might also provide a non-invasive method for assessing the extent of coronary artery disease (CAD). Celermajer et al (Celermajer 1994) reported that impaired FMD was associated with CVD risk factors (smoking, diabetes mellitus, age, hypercholesterolemia) in a sample of >500 healthy individuals who were free of CVD, and Enderle et al (Enderle 1998) reported that impaired brachial artery FMD was nearly as sensitive as exercise electrocardiography (ECG) in the detection of CAD and was more specific for the diagnosis of CAD than exercise ECG or angina pectoris, with FMD <4.5% predicting the diagnosis of CAD in 95% of cases. Therefore, there appears to be a strong relationship between FMD and risk of CVD, suggesting that both arterial compliance and FMD are predictive of CVD and are therefore valid biomarkers of CVD risk. However, given that the relationship between FMD and CVD risk has only been established in observational studies, it may only be concluded that it is probable that FMD is a valid biomarker of CVD.

b) Effects of ω 3 intake on biomarkers for CVD risk

There is extensive evidence for beneficial effects of ω 3 on a multiplicity of CV biomarkers and risk factors. They reduce BP (Appel 1993, Morris 1993, Howe 1998, Geleijnse 2002, Beilin 2003), and improve blood lipids (Harris 1996, Harris 1997), cardiac function (Leaf 2003), arterial compliance (McVeigh 1994, Nestel 2002), endothelial function and vascular reactivity (Mori 2000a, Chin 1994a). They also provide anti-inflammatory (Mori 2004, Calder 2001) and antiplatelet (Knapp 1997) effects. More recent data suggests that EPA and DHA have differential effects on lipids (Mori 2000b, Woodman 2002, Grimsgaard 1997), BP (Mori 1999a), HR (Mori 1999a), and vascular reactivity (Mori 2000a) in humans. The evidence for antihypertensive, antiplatelet and triglyceride lowering effects of ω 3 is long-standing and convincing. While the case for other biomarkers, particularly those that have been recognised only recently, may not yet be convincing when considered individually, it is important to consider the collective impact of improving multiple biomarkers on overall CVD risk, as ω 3 may be acting via several mechanisms to improve, for example, arterial vasodilator function.

Cholesterol and LDL-Cholesterol

In agreement with the USFDA report, ω 3 have very little impact on total cholesterol but may elicit a small, transient rise in LDL-C. Moreover, any increase in LDL-C has been associated with an increase in the LDL-particle size (Contacos 1993, Suzukawa 1995, Mori 2000b, Woodman 2003), a finding which might be expected to contribute to a reduction in atherogenic risk. LDL particle size is also regarded as a CV risk factor (Hulthe 2000) and correlates with sub-clinical

atherosclerosis as measured by intima-media thickening (Lahdenpera 1996). Small dense LDL particles are associated with an increased risk of CAD (Campos 1992).

Triglycerides and HDL-Cholesterol

Elevated fasting blood TG is consistently reduced ~20-30% by fish or fish oil consumption in humans (Harris 1989, Harris 1996, Harris 1997, Weber 2000). Moreover, supplementation with purified EPA reduced TG by 21% (Nestel 2002) and 23% (Mori 2000b) in mildly hyperlipidaemic subjects, by 19% in Type 2 diabetic individuals (Woodman 2002) and by 12% in healthy subjects (Grimsgaard 1997). Purified DHA supplementation has reduced TG in most controlled studies by approximately 17-33% (Woodman 2002; Nestel 2002; Mori 2000b; Grimsgaard 1997). The extent of decrease is dependent on baseline TG elevation (Mori 2000b).

In a meta-analysis of human trials, Harris (1996) concluded that ω 3 had minimal effect on HDL-C. However, others have shown that fish oils increased HDL-C, due primarily to a significant increase in the cardioprotective HDL₂-C subfraction. (Mori 1992; Mori 1994; Dunstan 1997; Mori 1999b). In studies utilising purified oils, EPA or DHA supplementation had little effect on HDL-C levels in mildly hyperlipidaemic individuals (Mori 2000b) or in Type 2 diabetic patients (Woodman 2002). However, DHA supplementation significantly increased HDL₂-C by 37% in dyslipidaemic patients (Mori 2000b) and by 12% in Type 2 diabetic patients (Woodman 2002), while EPA increased HDL₂-C by 16% in Type 2 diabetic patients (Woodman 2002).

Blood Pressure

Randomised controlled trials of fish oils or dietary fish provide unequivocal evidence for a BP lowering effect of ω 3, particularly in hypertensives or individuals with mildly elevated BP (Appel 1993, Morris 1993, Geleijnse 2002). Morris et al (1993), in a meta analysis of 31 placebo controlled trials of effects of fish oils on BP, showed an overall reduction of -3.0/-1.5 mmHg with a significant dose response effect estimated at -0.66/-0.35 mmHg per g of ω 3/day. The hypotensive effect was greatest in hypertensive (treated and untreated) individuals (-3.4/-2.0 mmHg). Appel et al (1993), determined BP fell 1.0/0.5 mmHg in normotensives (in 11 trials) and 5.5/3.5 mmHg in untreated hypertensives (in 6 trials), with the average intake being more than 3g/day of ω 3. Geleijnse et al (2002), in a meta-analysis of 36 trials, showed that ω 3 reduced BP by -2.1/-1.6 mmHg. BP lowering effects tended to be greater in older (>45 years) (-3.5/-2.4) and hypertensive (\geq 140/90 mmHg) (-4.0/-2.5) individuals.

A population based study by Bonna et al (1990) in untreated mildly hypertensives randomised to 6g per day of purified EPA and DHA or corn oil for 10 weeks is the most conclusive BP trial. Relative to the corn oil, BP fell -6.4/-2.8 mmHg with fish oil. Other placebo-controlled studies have reported significant benefits of ω 3 on BP in hypertensives (Knapp 1989, Radack 1991, Norris 1986, Singer 1986, Levinson 1990). Prisco et al (1998) showed that in mild essential hypertensive, normolipidaemic men, 24 hour ambulatory BP was reduced by 6/5 mmHg after taking 3.4g per day ω 3 for 2 months. Toft et al (1995) confirmed that in essential hypertensives, BP fell by 3.8/2.0 mmHg after 16 weeks of 4g/day fish oil containing 85% EPA+DHA.

Bao et al (1998) conducted a factorial design study in which 63 overweight treated hypertensives were randomised to weight loss alone, given ω 3 as a daily fish meal, both combined or a control diet for 4 months. 24-hour ambulatory BP monitoring showed significant independent and additive effects of dietary fish and weight loss. Relative to controls, daytime BP fell 6.0/3.0 mmHg in the fish group, 5.5/2.2 in the weight loss group and 13.0/9.3 with the combination.

BP-lowering effects of ω 3 are potentiated by sodium restriction (Cobiac 1992) and concomitant antihypertensive drugs. Fish oils also amplify the hypotensive action of β -adrenergic receptor blockade in mild-to-moderate hypertensives (Singer 1990), but there is no additional benefit in

hypertensives on ACE inhibition (Howe 1994). Lungershausen et al (1994) also showed that ω 3 reduced BP by 3.1/1.8 mmHg in treated hypertensives taking either β -blockers or diuretics.

There is now evidence that purified EPA and DHA have differential effects on BP. Mori et al (1999a) showed that DHA, but not EPA, significantly reduced 24-hour (-5.8/-3.3 mmHg) and daytime (-3.5/-2.0 mmHg) BP relative to placebo in overweight, mildly-hypercholesterolaemic subjects. Patients were given 4g of highly purified EPA, DHA or olive oil daily while continuing their usual diets for 6 weeks. The BP-lowering effects were accompanied by significant improvements in endothelial and smooth muscle function in the forearm microcirculation with DHA but not EPA, as well as reduced vasoconstrictor responses (Mori 2000). In contrast, Woodman et al (2002) in a trial of similar design did not show a BP-lowering effect following purified EPA or DHA supplementation in Type 2 diabetic patients. Failure to detect changes in BP in the latter trial (Woodman 2002), is most likely due to concomitant use of pharmacological agents and/or increased BP variability resulting in inadequate statistical power.

Endothelial Function

Benefits on BP following dietary ω 3 are most likely associated with improvements in endothelial function and arterial compliance as evidenced from small animal and human studies (Beilin 2003). In humans ω 3 reduced forearm vascular reactivity to angiotensin II and noradrenaline (Lorenz 1983, Yoshimura 1987, Chin 1993a). Furthermore, the blunting effect of ω 3 on these responses was antagonised by oral administration of indomethacin, suggesting that ω 3 was exerting its beneficial effect, at least in part, by modifying cyclooxygenase-derived prostanoids (Chin 1993b).

Fish oils had a minimal effect on acetylcholine- or reactive hyperaemia- induced vasodilation in forearm resistance arteries of healthy subjects (Chin 1993b). However, ω 3 restored impaired responses to endothelium-dependent vasodilators in patients with CHD (Vekshtein 1989, Fleischhauer 1993). Chin et al (1994b) showed that vasodilatory responses to acetylcholine in hypercholesterolaemics were enhanced by dietary fish oil without changes in total cholesterol. Individuals with Type 2 diabetes supplemented ω 3 showed improved forearm vasodilator responses to acetylcholine, but not to glyceryl trinitrate, suggesting that fish oils protect against vasospasm and thrombosis by enhancing nitric oxide (NO) release and suppressing thromboxane (McVeigh 1993). ω 3 may also improve endothelial function in systemic large arteries in humans. In this regard, Goodfellow et al (2000), showed a significant improvement in flow-mediated dilatation of the brachial artery following a 4-months with 4g daily of ω 3, in subjects with hyperlipidaemia. The improvement was confined to endothelial-dependent responses.

Recent data by Mori et al (2000a), suggests that EPA and DHA have differential effects on vascular function in human arteries. The authors reported that DHA, but not EPA, improved vasodilator responses to endogenous and exogenous NO donors and attenuated vasoconstrictor response to noradrenaline in the forearm microcirculation of overweight subjects with hyperlipidaemia. The mechanisms were predominantly endothelium-independent, although the data did not preclude an endothelial component in the dilatory responses associated with DHA. The changes in arterial function were associated with a reduction in BP in these patients following supplementation with DHA, but not EPA (Mori 1999a).

The favourable effects of ω 3 on vasoreactivity are attributable to direct and indirect effects on the arterial wall (Beilin 2003). Incorporating ω 3 into endothelial membranes can increase membrane fluidity, calcium influx and endogenous synthesis and release of NO. Additional mechanisms may include direct effects on receptor-stimulated NO release, enhanced release of vasodilator prostanoids and/or endothelial-derived hyperpolarizing factor. Enhanced vasodilator responses to sodium nitroprusside may be due increased biotransformation to NO or increased reactivity of smooth muscle cells to vasorelaxation as a result of decreased calcium influx (Chin 1995).

Vasodilator effects could also be due to increased basal production of NO in smooth muscle as a consequence of decreased release of platelet-derived growth factor (PDGF) (Fox 1988), since NOS induction in vascular smooth muscle cells is inhibited by PDGF (Schini 1992).

Arterial Compliance

BP is strongly influenced by arterial compliance, which in turn is influenced by endothelial function. In this regard, McVeigh et al (1994) showed that compliance in the large arteries and more peripheral vasculature, as measured by pulse-contour analysis, improved significantly after 6 weeks of ω 3 compared with olive oil, in Type 2 diabetic individuals. In patients with dyslipidaemia, EPA and DHA supplementation improved arterial compliance by 35% and 27%, respectively (Nestel 2002). There was no significant difference in effect between EPA and DHA.

Heart Rate

HR reduction in humans (Vandongen 1993, Bao 1998, Dallongeville 2003) following dietary ω 3 suggests a significant cardiac component associated with the antihypertensive effects, possibly mediated by effects on autonomic nerve function or β -adrenoreceptor activity. Alternatively it may be a reflex response to a reduction in afterload resulting from increased aortic compliance and reduced total peripheral resistance. Bao et al (1998), in study with overweight treated hypertensives randomised for 4 months to a) weight loss alone, b) ω 3 given as a daily fish meal, c) the two modalities combined or d) a control diet, showed that ω 3 intakes were associated with HR reductions of 3-4 beats per minute. In a recent meta-analysis of 30 studies, Mozzaffarian (2005c) showed that ω 3 reduce HR overall by -1.6 bpm, with greater reductions in trials with baseline HR \geq 69 bpm (-2.5 bpm) and in trials of \geq 12 weeks duration (-2.5 bpm).

A differential effect of purified EPA and DHA on HR has been demonstrated in humans. Mori et al (1999a) reported that HR was reduced using DHA, but not EPA in overweight, mildly hyperlipidaemic, but otherwise healthy men given 4g daily EPA, DHA or olive oil for 6 weeks. Ambulatory 24-hour, awake and asleep HR fell 3.5, 3.7 and 2.8 bpm, respectively, following DHA. These differential effects of EPA and DHA on HR were substantiated by Grimsgaard et al (1998). Similarly, Woodman et al (2002) showed that DHA, but not EPA, significantly reduced clinic standing and supine HRs (-5.8 and -3.9 bpm, respectively) compared with placebo.

Heart Rate Variability

Sudden death is responsible for approximately 50% of the mortality from CVD in Western countries. Decreased HRV is a powerful predictor of mortality, sudden death and arrhythmic events in post-myocardial infarction patients (Hartikainen 1996). Data from human studies strongly suggest that ω 3 increase HRV in patients at high risk of sudden cardiac death and in healthy individuals (Christensen 2001a, Christensen 2003), supporting an antiarrhythmic effect of ω 3. Christensen et al reported that a high dose of ω 3 (5.2 g/day) significantly increased HRV in human survivors of myocardial infarction (Christensen 1996) and correlated directly with the DHA content of their platelet membranes (Christensen 1997). The same authors demonstrated a beneficial dose-dependent effect of ω 3 (2.0g vs 6.6g daily), on HRV in healthy men and women (Christensen 1999). Basal DHA levels in granulocytes and platelets were also positively associated with all indices of HRV in men. Others have shown that increased HRV is associated with ω 3 in platelets of Type 1 diabetic patients (Christensen 2001b), in granulocytes of patients referred for coronary angiography (Christensen 2001c) or with chronic renal failure (Christensen 1998), and in plasma cholesterol-esters in healthy men and women (Brouwer 2002).

Arrhythmogenesis and atrial fibrillation

In the GISSI-Prevenzione trial (GISSI-P 1999), 1g ω 3/d decreased sudden cardiac death by 45%. The anti-arrhythmic effects of ω 3 are most likely related to their incorporation in myocardial cells altering electrophysiological function to reduce the vulnerability to ventricular fibrillation, most

likely by inhibiting the fast, voltage-dependent sodium current and the L-type calcium currents, although evidence exists that they may also modulate potassium channels (Leaf 2003).

Effects On Atherosclerosis Progression and Plaque Stability

Intake of ω 3 has been regarded as beneficial in the prevention of atherosclerosis. In this regard, there is a high incidence of stroke in patients with carotid atherosclerosis. Carotid artery intima-media thickness (IMT) predicts stroke (Bots 1997; O'Leary 1999) and stenosis of internal carotid arteries with greater than 60% lumen narrowing plays a causal role in a large percentage of strokes (Barnett 2000). Furthermore, progression in carotid IMT predicts risk for coronary events beyond that predicted by coronary arterial measures of atherosclerosis (Hodis 1998). Hino et al (Hino 2004) showed that in 1920 Japanese aged over 40 years, ω 3 were significantly inversely related to carotid IMT. In contrast, supplementation with 1.65g per day ω 3 for 2 years had no effect on slowing progression of atherosclerosis in carotid arteries in 233 patients with coronary artery disease (Angerer 2002). Interestingly, the same patients showed improvements in coronary atherosclerosis as determined by ultrasonography (von Schacky 1999). Patients supplemented ω 3 had less progression and greater regression of coronary atherosclerosis, significantly less loss of luminal diameter and fewer CV events (von Schacky 1999).

Vulnerability of the atherosclerotic plaque to rupture is the primary determinant of thrombosis-mediated acute myocardial events (Plutzky 1999). In this regard, Thies et al (2003) showed that ω 3 were incorporated into plaque lipid fractions following supplementation to patients undergoing carotid endarterectomy. Furthermore, patients had atherosclerotic plaques that had thick fibrous caps and less inflammation, suggestive of plaque stabilisation.

Table 5: Effects of ω 3 intake on biomarkers of CVD risk

	Study Population	Duration (weeks)	Dose	Change
Triglycerides				
Harris 1997	Cross-Over design N=535	2-52	1.6-7.0g	-25%
Meta-analysis	Subjects with TG <2.0mmol/L			-34%
	Subjects with TG \geq 2.0mmol/L			
	Parallel design n=2343	3-52	1.1-7.0g	-25%
	Subjects with TG <2.0mmol/L			-25%
	Subjects with TG \geq 2.0mmol/L			
Grimsgaard 1997	Healthy individuals N=234	7	EPA 3.8g	-0.15 mmol/L (-0.06, -0.24) (21%)
			DHA 3.8g	-0.22 mmol/L (-0.15, -0.29) (26%)
Mori 2000b	Dyslipidaemic men N=56	6	EPA 4g	-0.37 mmol/L (\pm 0.14) (23%)
			DHA 3.8g	-0.45mmol/L (\pm 0.15) (20%)
Nestel 2002	Dyslipidaemic individuals N=56	7	EPA 3g	-0.36 mmol/L (21%)
			DHA 3.8g	-0.63 mmol/L (31%)
Woodman 2002	Hypertensive Type 2 DM N=51	6	EPA 4g	-0.25 mmol/L (\pm 0.09) (19%)
			DHA 3.8g	-0.24 mmol/L (\pm 0.09) (15%)
Blood Pressure				
Morris 1993	31 studies (overall)	3-24	1.7-15.0g	-3.0 mmHg (-4.5, -1.5) (systolic) -1.5 mmHg (-2.2, -0.8) (diastolic)
Meta-analysis	9 studies (hypertensives)	4-12	3.0-15.0g	-3.4 mmHg (-5.9, -0.9) (systolic) -2.0 mmHg (-3.3, -0.7) (diastolic)
	6 studies (hypercholesterolaemic)	4-12	1.7-6.0g	-4.4 mmHg (-6.6, -2.2) (systolic) -1.1 mmHg (-2.7, -0.5) (diastolic)
	9 studies (healthy individuals)	3-24	2.4-6.5g	-0.4 mmHg (-1.6, -0.8) (systolic) (NS) -0.7 mmHg (-1.5, 0.1) (diastolic) (NS)

Appel 1993 Meta-analysis	31 studies (overall)	3-34	1.1-15.0g	-1.5 mmHg (-2.4, 0.6) (systolic) -1.0 mmHg (-1.6, -0.4) (diastolic)
	11 studies N=728 (normotensives)	3-24	1.5-6.5g	-1.0 mmHg (-2.0, 0.0) (systolic) -0.5 mmHg (-1.2, -0.2) (diastolic) (NS)
	6 studies n=291 (hypertensives)	4-34	1.1-15.0g	-5.5 mmHg (-8.1, -2.9) (systolic) -3.5 mmHg (-5.0, -2.1) (diastolic)
Geleijnse 2002 Meta-analysis	Meta-analysis of 36 studies N=2114 (overall) (hypertensives)	3-52	1.0-15.0g	-2.1 mmHg (-3.0, 1.0) (systolic) -1.6 mmHg (-2.2, -1.0) (diastolic) -4.0 mmHg (-5.7, -2.2) (systolic) -2.5 mmHg (-3.4, -0.5) (diastolic)
Bao et al 1998	Hypertensives N=63	16	3.6g 3.6g + weight loss	-6.0 mmHg (\pm 2.2) (24hr systolic) -3.0 mmHg (\pm 1.4) (24hr diastolic) -13.0 mmHg (\pm 2.4) (24hr systolic) -9.3 mmHg (\pm 1.4) (24hr diastolic)
Mori 1999a	Overweight hypertensives N=56	6	EPA 4g DHA 3.8g	-5.8 mmHg (\pm 2.1) (24hr systolic) -3.3 mmHg (\pm 1.3) (24hr diastolic) -3.5 mmHg (\pm 2.9) (24hr systolic) -2.0 mmHg (\pm 1.1) (24hr diastolic)
Woodman 2002	Hypertensive Type 2 DM N=51	6	EPA 4g DHA 3.8g	1.3 mmHg (\pm 3.5) (24hr systolic) (NS) 0.6 mmHg (\pm 1.7) (24hr diastolic) (NS) 6.0 mmHg (\pm 3.5) (24hr systolic) (NS) 0.9 mmHg (\pm 1.7) (24hr diastolic) (NS)
Heart Rate				
Mozzaffarian 2005c Meta-analysis	30 studies n=1678 (overall) Subjects with baseline HR >69bpm Studies >12 wks duration	4-52	0.8-15.0g	-1.6 bpm (-0.6, -2.5) -2.5 bpm (-1.4, -3.5) -2.5 bpm (-1.1, -4.0)
Bao et al 1998	Hypertensives N=63	16	3.6g	-3.1 bpm (\pm 1.4) (24hr) -4.2 bpm (\pm 1.6) (awake)
Grimsgaard 1998	Healthy individuals N=234	7	EPA 3.8g DHA 3.8g	1.9 bpm (\pm 5.1) (Seated) -2.2 bpm (\pm 4.6) (Seated)
Mori 1999a	Overweight hypertensives N=56	6	EPA 4g DHA 4g	2.0 bpm (\pm 1.4) (24hr) (NS) 2.7 bpm (\pm 1.7) (awake) (NS) 2.3 bpm (\pm 1.5) (asleep) (NS) -3.5 bpm (\pm 0.8) (24hr) -3.7 bpm (\pm 1.2) (awake) -2.8 bpm (\pm 1.2) (asleep)
Woodman 2002	Hypertensive Type 2 DM N=51	6	EPA 4g DHA 4g EPA 4g DHA 4g EPA 4g DHA 4g	-0.9 bpm (\pm 2.6) (24hr) (NS) -1.5 bpm (\pm 2.6) (24hr) (NS) -3.4 bpm (\pm 2.0) (Standing) (NS) -5.8 bpm (\pm 1.9) (Standing) -0.5 bpm (\pm 1.9) (Supine) (NS) -3.9 bpm (\pm 1.8) (Supine)

Data presented as mean \pm standard deviation (SD) or 95% confidence intervals

PART 5. OVERALL CONCLUSIONS

Introduction and scope of this review

The pioneering epidemiological studies of Bang and Dyerberg (1972) in Greenland Inuits in the 1960s first drew attention to the possibility that the ω 3 of marine origin may be cardioprotective. They attributed the Inuits' exceptionally low CV mortality rate to their high consumption of fatty seafood and, in particular, their ω 3 intake. This observation stimulated a steady stream of studies potential health benefits of fish and LC ω 3 consumption, which has increased exponentially over the last two decades.

Since its introduction of a health claims policy for foods, the USFDA has progressively monitored the growing body of evidence relating ω 3 intake to reduced risk of CHD. The *quality* as well as *quantity* of evidence is a critical determinant of the *weight* of available evidence for validating a health claim. In a succession of reviews over the last 15 years, the USFDA has employed rigorous standards to evaluate the evidence for this relationship and has excluded publications of dubious quality, e.g. where the study design or the conclusions drawn may have been flawed, thus ensuring the reliability of their conclusions.

In 2000, the USFDA ruled that the weight of evidence for a relationship between ω 3 and CHD, whilst *supportive*, was not *conclusive*. This decision was based on the following:-

- the majority of supporting evidence from observational studies in normal populations related fish consumption, rather than ω 3 intake, to reduced CHD risk;
- these observational studies, although supportive, do not prove a causal relationship;
- the smaller proportion of properly controlled intervention trials assessing CHD morbidity or mortality as endpoints provided direct evidence of a relationship between ω 3 intake and reduction of CHD risk. However, they were undertaken in most cases with subjects who had pre-existing CHD and may not, therefore, be indicative of outcomes in a normal population.
- Other intervention trials undertaken in subjects without pre-existing CHD assessed surrogate endpoints, of which only LDL-cholesterol was considered a valid marker of CHD risk. As ω 3 is known not to lower LDL-cholesterol, all of these trials were deemed negative.

Nevertheless, they USFDA allowed a *qualified* health claim for ω 3 *supplements*. Moreover, they reaffirmed that position in 2004 by allowing a *qualified* health claim for ω 3 in *foods*, based on a review of additional evidence published since 2000. Their 2004 review represents a starting point for the current review.

FSANZ have requested us to extend the scope of the current review from CHD to CVD, recognising that, while various nutrients such as polyunsaturated fats, fibre, soy protein and plant sterols have been accredited with reducing CHD risk by lowering LDL-cholesterol, ω 3 fatty acids do not lower LDL cholesterol but may possibly reduce CVD mortality by improving CV risk factors other than CHD.

Evidence considered

The USFDA evaluated evidence relating ω 3 to CHD from both observational (cohort) studies and intervention trials. However, they focused on mortality and morbidity outcomes. Even BP was not considered a valid biomarker in their 2000 review. In extending the scope to CVD, we have reappraised the evidence considered by the USFDA, taking particular account of effects of ω 3 on BP, sudden death, ischaemic stroke and heart failure. We have also reviewed other evidence on this broader relationship, identified by a Medline search for relevant papers published between 2000 and 2005.

Consideration of CVD risk necessitated inclusion of a broader range of biomarkers (viz. TG, BP, HR, HRV, AF, arterial compliance, endothelial vasodilator function, IMT and plaque stability) in addition to the hard end points (sudden death, stroke, HF). Whilst some of these biomarkers may not be used routinely in clinical practice as diagnostic *risk factors*, e.g. HR or HRV, a case has been made for their importance as outcome measures in scientific evaluations of the effects of ω 3 intake on CVD.

Interpretation of the evidence

The USFDA finds that the weight of existing evidence *supports* a relationship between ω 3 and reduced risk of CHD. Additional publications since the USFDA's 2004 review as well as those relating to broader role of CVD risk reduction have substantially strengthened the evidence for a benefit of ω 3 intake. In particular, meta-analyses showing an inverse relationship between ω 3 intake and ischaemic stroke afford strong evidence of CVD risk reduction. With the further inclusion of evidence based on a range of biomarkers in intervention trials conducted with healthy volunteers, a causal relationship is clear. It is likely that the benefit of ω 3 in CVD reduction may be attributable to the integral effect of ω 3 acting on multiple physiological mechanisms rather than through a single mechanism. Hence the evidence in relation to multiple CVD biomarkers and disease end points should be interpreted collectively. Using this approach, we find that, in its totality, the evidence for CVD risk reduction by ω 3 in foods is *convincing*. Indeed, the only major study to contradict this position is DART-2. This was the primary source of heterogeneity in the Cochrane review of ω 3 and CVD and negated an otherwise positive outcome. DART-2 and its inclusion in the Cochrane review have been widely criticised and discredited.

Potential application

The evidence for CVD benefit is still not *conclusive*, in that intake requirements of specific ω 3 fatty acids to deliver specific CVD benefits have not yet been established. Given the enormity of such a task, with dose-response relationships to be determined for effects of EPA and DHA on multiple mechanisms in various population sectors, it is unreasonable to delay actions which may benefit overall population health status whilst acquiring this evidence, especially considering that there is general agreement on safety considerations and an upper limit for ω 3 consumption. We consider that the ω 3 intake recommendations in the NHMRC draft NRV report (NHMRC 2004), viz. 610mg/d for men and 430mg/d for women, are appropriate for the ANZ population and may be expected to reduce CVD risk in ANZ. They are consistent with the NHFA's draft recommendation of 500mg/day for CVD risk reduction and the UK JHCI's recommendation of 450mg/day in its heart health claim.

Summary

In this review, we have

- appraised the USFDA's 2004 review on the relationship between ω 3 intake and CHD,
- considered additional publications providing evidence for and against that relationship, including relevant research published since 2004,
- considered publications providing evidence for and against an expanded relationship, viz. the relationship of ω 3 intake to CVD, including CAD, sudden death, stroke and heart failure.
- considered additional biomarkers as risk factors for CVD and evaluated evidence for a relationship between these biomarkers and ω 3 intake.

In regard to the USFDA's review, we find that

- the USFDA have used a rigorous approach in their progressive review of all available publications over a long time frame, which also affords a useful historical perspective on the development and refinement of knowledge in this field;

- they considered both *quantity* and *quality* in weighing the evidence;
- they correctly concluded in 2004 that, while the available evidence is *supportive* of a relationship between ω 3 intake and reduced risk of CHD, it is *not conclusive*;
- research published since that time has not significantly altered support for this relationship;
- the resultant health claim for foods based on this relationship is valid and applicable to the ANZ population.

With respect to the scope of the USFDA review, we consider that

- the definition of CHD is too limiting to fully capture the extensive CV health benefits which have been attributed to dietary ω 3;
- further supportive evidence is available relating ω 3 to reduced risk of sudden death, heart failure and, in particular, ischaemic stroke;
- evidence for the latter, however, while well established, originates from observational studies which are, by design, less convincing than intervention studies;
- nevertheless, the proposed expanded relationship between ω 3 and reduced risk of CVD is stronger than the relationship between ω 3 and reduced risk of CHD;
- the relationship is further strengthened if *additional* biomarkers of CVD risk are considered.

With respect to biomarkers, we find that

- most intervention trials to assess benefits of ω 3 in a normal population use biomarkers as outcome measures;
- the advice on biomarkers for CHD adopted by the USFDA for their reviews was too limited;
- having accepted BP as an additional biomarker for CHD risk in their 2004 review, they failed to retrospectively consider a large body of early (pre-2000) evidence for effects of ω 3 on BP;
- the virtual exclusion of biomarkers other than LDL-cholesterol by USFDA in their evaluation of intervention trials was a significant factor limiting the strength of available evidence to support the relationship between ω 3 and CHD;
- dyslipidaemia (high TG and/or low HDL-cholesterol in fasting blood) is also regarded as a valid biomarker for CHD;
- had the well established effects of ω 3 on TG been considered in the USFDA review, it would have strengthened the evidence in support of the relationship;
- several additional biomarkers are indicative of CVD risk including HR, HRV, arterial compliance and endothelial dilatation;
- there are many publications showing positive effects of ω 3 on these biomarkers, with very few showing lack of effect or negative effects;
- notwithstanding publication bias, collective consideration of the effects of ω 3 on these biomarkers further strengthens the relationship between ω 3 and reduced CVD risk.

In conclusion,

- in its totality, the existing evidence for CVD risk reduction by ω 3 in foods is *convincing*;
- the weight of evidence to support a health claim relating ω 3 to reduced risk of CVD is greater than that supporting the USFDA's qualified health claim for ω 3 and CHD;
- this position is consistent with the NHFA's draft position paper and the UK's ω 3 heart health claim;
- a negative finding from a Cochrane review on the relationship of ω 3 to CVD is questionable;
- while the evidence needed to establish an ω 3 intake requirement for CVD risk reduction in ANZ is still limited, an ω 3 intake consistent with recommendations by the NHMRC and NHFA, viz. ~500mg/day from foods, might be expected to reduce the risk of CVD in the ANZ population.

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APPENDIX A: BIBLIOGRAPHY

A PubMed search of relevant scientific literature published from 2000 – 2005 was conducted on 7th March. The search criteria and results are summarised in the table. The aim was to identify papers describing long-chain omega-3 fatty acids and some aspect of cardiovascular disease or a relevant biomarker in the title or abstract. The search identified a total of 178 papers describing **clinical trials** in adults. There were 376 **other papers (not including reviews)** of which 12 were **meta-analyses**. The references are listed alphabetically in those categories below.

Note: this search did not detect the Cochrane review by Hooper et al, 2004. Nor does it include certain references which have been cited in this review, in particular those which preceded the starting date for the search.

#1	Search cardiovascular disease OR CVD OR CHD OR coronary heart disease OR stroke OR atherosclerosis OR arrhythmia OR heart rate OR platelet aggregation OR blood pressure OR hypertension OR antithrombotic OR thromboxane OR triglyceride OR triacylglycerol OR cholesterol OR HDL OR arterial compliance OR FMD OR endothelial function Field: Title/Abstract, Limits: Publication Date from 2000 to 2006	204622
#2	Search fish OR omega-3 OR n3 OR EPA OR DHA Field: Title/Abstract, Limits: Publication Date from 2000 to 2006	29096
#3	Search #1 AND #2 Field: Title/Abstract, Limits: Publication Date from 2000 to 2005/12/31, English, Humans	868
#4	Search #1 AND #2 Field: Title/Abstract, Limits: All Adult: 19+ years, Publication Date from 2000 to 2005/12/31, only items with abstracts, English, Clinical Trial, Humans, MEDLINE Sort by: Author	178
#5	Search #1 AND #2 Field: Title/Abstract, Limits: Publication Date from 2000 to 2005/12/31, only items with abstracts, English, Meta-Analysis, Humans, MEDLINE	12
#6	Search #1 AND #2 Field: Title/Abstract, Limits: Publication Date from 2000 to 2005/12/31, only items with abstracts, English, Review, Humans, MEDLINE	295
#7	Search #1 AND #2 NOT #3 NOT #4 NOT #5 Field: Title/Abstract, Limits: Publication Date from 2000 to 2005/12/31, only items with abstracts, English, Humans, MEDLINE Sort by: Author	376

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