

Annex 2.

Nutritional considerations

1. The level of evidence presented in this paper has been restricted to human population studies with disease end points – essentially, prospective cohort studies and randomized controlled trials, although some case-control studies have also been included. A large body of literature exists investigating the effects of fish, fish oils and n-3 PUFA consumption on cardiovascular disease risk (CVD) – much mechanistic work, including culture work, animal and human studies, as well as many randomized controlled trials using CVD risk factors as end-points have been undertaken. These will not, however, be discussed in detail in this paper.

This paper is based on the advice sought by the FSA on the benefits of oily fish and fish oil consumption from SACN (<http://www.sacn.gov.uk/sacn0212.pdf>).

Fish consumption and cardiovascular disease

2. Several prospective cohort studies have investigated the relationship between fish consumption and the incidence of thrombotic stroke (Keli et al, 1994; Morris et al, 1995; Gillum et al, 1996; Orenca et al, 1996; Iso et al, 2001; He et al, 2002); however, the evidence remains equivocal and for the purposes of this paper the relationship between fish consumption and the incidence of coronary heart disease (CHD) will be discussed. All studies observed no association between consumption of fish or fish oil and haemorrhagic stroke.

Prospective epidemiological studies

3. An inverse relationship between fish consumption, and n-3 PUFA intake, and CHD mortality has been reported in several (Mozaffarian et al, 2003; Hu et al, 2002; Yuan et al, 2001; Oomen et al 2000; Kromhout et al, 1995, 1985; Rodriguez et al, 1996, Dolecek et al, 1991), although not all (Albert et al 1998; Kromhout et al, 1996; Asherio et al, 1995; Morris et al, 1995), prospective cohort studies.
4. In the Health Professionals Follow-up Study, (Ascherio et al, 1995) a non-significant trend (RR, 0.74 95% CI 0.44 – 1.23) for a lower risk of fatal CHD with increasing fish consumption was observed; and although no effect on CHD mortality was observed in the US Physicians' Health Study (Albert et al, 1998) there was a significant reduction in sudden cardiac death with increasing fish consumption – this effect was not observed after the initial follow-up period (Morris et al, 1995). In the Seven Countries Study (Kromhout et al, 1996) fish intakes were inversely related to 25-year mortality from CHD in univariate analyses, but these associations became non-significant when the confounding effects of saturated fatty acids, flavonoids (a confounder not considered in many earlier studies) and smoking were taken into account.
5. It has been suggested that the lack of benefit reported in some prospective studies may be due to low prevalence of CHD in their study populations, e.g. Ascherio et al, 1995. A systematic review of 11 prospective cohort studies by Marckmann

and Grønbaek (1999) concluded that populations at high risk of CHD benefited most from increased consumption of fish. Beneficial effects of fish consumption in populations with a lower CHD prevalence have subsequently been demonstrated, however, e.g. Shanghai, China (Yuan et al, 2001). The risk of CHD increases markedly with age, as does the prevalence of risk factors such as hypertension and hypercholesterolaemia. Where an association between fish intake or n-3 fatty acids derived from fish has been reported, this has been in middle-aged and elderly subjects. The potential for CHD risk reduction, therefore, is likely to be greatest for those at highest risk; however a small risk reduction for the whole population could have a large public health benefit.

6. Furthermore some of the initial cohort reports showing no effect have been modified on subsequent follow ups. In the Honolulu Heart Program the initial report (Curb and Reed, 1985) suggested no relationship between fish intake and CHD risk and this led to the view at the time that a protective effect was only seen in populations with low fish intake. Later analysis, however, from the Honolulu Heart Program showed that fish intake and n-3 PUFA derived from fish were associated with a significantly reduced risk of CHD mortality with an interaction with smoking (Rodriguez et al, 1996).
7. The Nurses' Health Study (Hu et al., 2002) recently reported an inverse association between fish intake and n-3 PUFA and CHD mortality in women. Compared with women who rarely ate fish (less than once per month), the risk for CHD death was 21%, 29%, 31%, and 34% lower for fish consumption 1 to 3 times per month, once per week, 2 to 4 times per week, and >5 times per week, respectively (P for trend<0.001). Comparing the extreme quintiles of fish intake, the reduction in risk for CHD deaths seemed to be stronger for CHD death than for nonfatal MI (RR 0.55 versus 0.73).
8. In the Kuopio Ischaemic Heart Disease Risk Factor Study, a prospective population study in Eastern Finland (Rissanen et al, 2000), an observed beneficial effect of fish consumption on CHD mortality was shown to be attenuated by high mercury content in fish. More recently, the European Multi-Centre Case-Control Study (EURAMIC) (Guallar et al,2002) reported that DHA adipose levels (a measure of long-term fish consumption) were inversely associated with risk of myocardial infarction, but only after adjustment for mercury levels. A previous study by this group showed no association between DHA adipose levels and risk of reoccurrence of myocardial infarction, however, levels of mercury contamination were not determined (Guallar et al,1999). Although an association between mercury levels and CHD was observed in the EURAMIC analysis this was not observed in a nested case-control study of the US Health Professionals' cohort (Yoshizawa et al, 2002). Also, the studies suggesting that mercury attenuated the beneficial effects of n-3 PUFA, still reported a beneficial effect of fish consumption on CHD (Rissanen et al, 2000; Guallar et al,2002).
9. Overall, the prospective cohort studies suggest that those who consume fish have a lower risk of CHD than those who do not; and in high risk populations there appears to be a dose-dependent benefit of increasing fish consumption of up to 40-60g/d mixed type (corresponding to about 0.9g/d n-3 PUFA) (Marckmann and Grønbaek, 1999). This is borne out in a recent prospective cohort study in subjects

aged 65 years or older, but with no known cardiovascular disease at entry to the study (Mozaffarian et al, 2003). Five doses of fish consumption were assessed: less than once a month; once to thrice a month; once a week; twice a week; and more than three times a week (estimated at 0, 0.13, 0.27, 0.55 and 0.92 g/d n-3 PUFA respectively). Total CHD deaths, and especially arrhythmic CHD deaths, were sequentially reduced with increasing fish intake; there was a 49% and a 58% lower risk of total CHD and arrhythmic CHD respectively with fish consumption more than three times a week compared with less than once per month.

10. More evidence for the benefits of fish consumption comes from case-control studies of healthy males that have explored the relationship between intermediary markers of fish consumption and CHD. These studies have measured the fatty acid composition of cell membranes and blood.
11. In the Physicians' Health Study, (Guallar, 1995) concentrations of DHA and EPA in plasma cholesterol esters and phospholipids did not differ between subjects with CHD and controls; however, in a more recent analysis of the same cohort (Albert et al, 2002) whole blood levels of EPA and DHA were found to be lower at baseline in 94 men who subsequently died of sudden cardiac arrest, than in 184 controls matched for age and smoking (Albert et al. 2002). The relative risk of sudden death in subjects with levels of long chain n-3 PUFA in the highest quartile (ave. 6.87% total fatty acids) was 10% of those in the lowest quartile (ave. 3.58% total fatty acids) ($P < 0.001$). The threshold effect that was previously reported for protection against sudden death in relation to increased fish consumption (Albert et al, 1998) was not seen in this cohort for blood levels of n-3 PUFA. A prospective nested case-control analysis of the Multiple Risk Factor Intervention Trial (Smith et al, 1995) DHA (22:5) were inversely associated with CHD risk in 94 men with incident CHD and 94 men without incident CHD.
12. These prospective findings are very similar to those reported in a population-based case-control study involving 82 cases of sudden cardiac arrest (Siscovick et al, 1995). That study found a strong inverse association between red blood cell n-3 PUFA composition at the time of the arrest and the risk of sudden cardiac arrest among subjects with no history of clinically recognized cardiac disease (i.e., 5.5 g of n-3 PUFA/month, equivalent to two fatty fish meals per week, was associated with a 50% reduced risk of primary cardiac arrest). Taken together, these data support the hypothesis that long-chain n-3 fatty acids are responsible for the observed inverse association between fish consumption and sudden cardiac death.

Randomized controlled trials

13. There are no completed primary randomized controlled trials (RCT) linking fish consumption or fish oil supplementation with primary prevention of CHD, although a number are on going or planned. The subjects in these trials will be healthy, but with increased risk of CHD. The earliest any of these trials will report is 2003.
14. Two secondary prevention trials – the Diet and Reinfarction Trial (DART) (Burr et al, 1989, 1994) and the GISSI-Prevenzione trial (GISSI-Prevenzione Investigators, 1999) – showed that fish consumption or fish oil supplementation

reduces coronary mortality among patients after MI. In the DART, which included 2033 men allocated to 3 dietary interventions, subjects who received advice to eat more fish had a significantly lower (29%) total mortality during 2 years of follow-up. There was also a nonsignificant trend toward a reduction in recurrent ischemic heart disease events with increased fatty fish consumption.

15. In the more recent GISSI-Prevenzione trial, which included 11 324 MI patients (primarily men), daily supplementation (1 g/d) of n-3 PUFA for 2 years reduced occurrence of the main cardiovascular end points (cardiovascular death, nonfatal MI, and stroke) by 20%, cardiovascular death (including coronary or cardiac deaths and sudden deaths) by 30%, and all fatal events by 20%. Survival curves for n-3 PUFA treatment diverged early after randomisation: total mortality was significantly lower after three months and risk of sudden death was significantly reduced after four months. This early effect of n-3 PUFA supports the hypothesis that the likely mechanism of action is the stabilisation of arrhythmias (Marchioli *et al.* 2002).
16. A recent meta-analysis of RCTs (Bucher *et al.* 2002) using disease end-points concluded that dietary and supplemental intake of n-3 PUFA reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with CHD.
17. The secondary prevention trials, therefore, provide good evidence that increased fish consumption or fish oil supplementation would decrease the incidence of CHD in the UK population. Extrapolating evidence to a 'healthy' population is difficult e.g. dose levels may not be appropriate. This was previously recognized by COMA (Department of Health. Nutritional Aspects of Cardiovascular Disease. Report on Health and Social Subjects No 46. 1.5.16 p:32 London:HMSO 1994).
18. The UK population, however, is a 'high risk' population with regard to CHD: almost 30% of the English population have some form of cardiovascular disease (Dept of Health, 1999).

The dose-response effect

19. The beneficial effect observed in the secondary prevention studies are observed in the order of 1g/d n-3 PUFA and the prospective epidemiological evidence is suggestive of a threshold effect, in high-risk populations, occurring at this level also (about 0.9g/d). This is below the dose however that is required for a demonstrable effect on cardiovascular risk factors, such as a reduction of plasma triacylglycerol levels (Sacks & Katan, 2002), blood pressure (Geleijnse *et al.*, 2002), platelet aggregation (Hornstra, 2001) and the inflammatory response (Calder, 2001). At least 1.5 g/d n-3 PUFA supplementation is required to produce beneficial effects on these factors. For example, to achieve increases in bleeding time, due to reductions in platelet aggregation, subjects need to be supplemented with 3g/d n-3 PUFA. At these levels of intake, the well recognized LDL raising effect of fish oil, that are observed in approximately 20% of subjects (Harris, 1997), are more likely. The most probable mechanism for the effect 1g/d n-3

PUFA on secondary CHD prevention is the stabilisation of arrhythmias (Marchioli *et al.* 2002).

Non Cardiac Benefits

20. Fish oils may also be of benefit to non-cardiac conditions. RCTs in rheumatoid arthritis patients, supplementation with fish oil, containing on average 3.8 g/d n-3 PUFA, has been shown to ameliorate symptoms and spare NSAID use (Calder, 2001).
21. Fish consumption and fish oil supplementation have also been suggested to extend gestational length, most particularly in low consumers (Olsen and Secher, 2002). In preterm infants inclusion of long chain n3-PUFA in formulae has been claimed to improve visual acuity in early post natal life; however, meta-analyses demonstrate only small early benefits with no evidence of sustained long term advantage (Simmer, 2002a). There is no conclusive proof that n-3 PUFA supplementation is beneficial to cognitive outcome either in infants born preterm (Simmer, 2002a) or at term (Simmer, 2002b).
22. Fish consumption has also been suggested to be beneficial to the development of a number of conditions – cognitive function and decline (e.g. schizophrenia, Alzheimer's), cancer (e.g. colo-rectal, prostate), atopic disease (e.g. asthma) – however, current evidence is insufficient to draw any firm conclusions.

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Table 1: Fish consumption, n-3 PUFA and CHD prospective cohort and specific case-control studies disease outcome

Reference	Type of Study	Intake* [EPA+DHA or FO or n-3 FA or Fish -- g/d] (Source of estimated intake)	Study Duration ⁺	Population [∇] [no & characteristics]	Disease Outcome [♦]
Mozaffarian et al, 2003 Cardiovascular Health Study	Prospective cohort	Fish <1 serving/mo to ≥3 serving/wk, FFQ	9 yr	3910 General [∞] aged ≥ 65 yr	↓ CHD mortality, especially ↓ arrhythmic IHD death
Guallar, et al., 2002 EURAMIC Study	Case-control	(DHA in adipose tissue) toenail mercury levels		684 cases, 724 controls M	↓ first MI – high mercury content in fish attenuated this protective effect
Hu, et al., 2002 Nurses' Health Study	Prospective cohort	Fish (0.03- 0.24 % energy/d n-3 FA) 0 to 5 serving/wk, FFQ	16 yr	84 688 F General	↓ CHD mortality
Albert, et al., 2002 Physicians' Health Study	Nested, Case-control	(Blood samples EPA+DHA)	17 yr	94 cases and 184 controls, among 14916, M General	↓ sudden cardiac death
Yuan, et al., 2001 Shanghai, China	Prospective cohort	Fish 50 → ≥ 200 g/wk , FFQ, n-3 FA	10yr	18244, M General	↓ fatal MI
Oomen, et al., 2000 Seven Countries Study - Finnish, Italian & Dutch subset	Prospective cohort	Lean and fatty fish (FFQ)	20 yr	2738 General	↓ CHD mortality for fatty fish only

Rissanen, et al., 2000 Kuopio Ischaemic Heart Disease Risk Factor Study	Prospective cohort	serum DPA+DHA hair mercury levels	10 yr	1871, M General	↓ MI – high mercury content in fish attenuated this protective effect
Guallar, et al., 1999 EURAMIC Study	Case control	(DHA in adipose tissue)		639 case, 700 control M	NS MI
Albert, et al., 1998 Physicians' Health Study	Prospective cohort	Fish (0→4x/wk) FFQ	12 yr.	14916, M General	↓ sudden cardiac death, NS MI & CHD mortality
Daviglus, et al., 1997 Western Electric	Prospective cohort	Fish 0 → ≥ 35 g/d, FFQ [0; 1-17; 18-34; ≥35g/d]	30 yr.	1822, M General	↓ non-sudden death from MI
Kromhout, et al., 1996 Seven Countries Study	Prospective Longitudinal Health survey	Fish (FFQ)	25 yr.	12783, General	NS CHD mortality
Rodriguez, et al., 1996 Honolulu Heart	Prospective cohort	Fish (0→>1x/d) (FFQ)	23 yr.	8006, General	↓ CHD mortality ^Φ High fish could attenuate this negative effect of smoking
Ascherio, et al., 1995 US Health Professionals' Follow-up Study	Prospective cohort	Fish (0.07→0.58g/d, <i>n</i> -3 FA) 0 to 5 serving/wk, FFQ	6 yr.	44895, M General	NS CHD
Guallar, et al., 1995 US Physicians' Health Study	Nested, Case-control	(Blood samples EPA+DHA)	5 yr.	14916, M General	NS first MI
Kromhout, et al., 1995 Rotterdam, the Netherlands	Prospective cohort	Fish (+/-) (diet record)	17 yr.	272, MF General	↓ CHD death
Morris, et al., 1995 US Physicians' Health Study	Prospective cohort	Fish (1→>5x/wk)	4 yr.	21185, M General	NS CVD, MI

Simon, et al., 1995 Multiple Risk Factor Intervention Trial	Nested Case-control	(Blood, DHA & EPA)	3.5 yr.	188, General	↓ CHD risk
Siscovick, et al., 1995 Seattle, WA	Case-control	(Blood), (FFQ) (5.5 g/mo., <i>n</i> -3 FA)		334 case 493 control, General	↓ first MI
Dolecek, et al., 1991 MRFIT	Prospective cohort	Multiple 24hr recalls	6-8yr	6258, M General	↓ CHD mortality
Lapidus, et al., 1986 Gothenburg, Sweden	Population	Fish FFQ	12 yr	1462 F General	NS CHD
Kromhout, et al., 1985 Dutch subset of seven countries study	Prospective cohort	Fish 0 → ≥ 30 g/d , FFQ	20 yr	852, General	↓ CHD mortality

Footnote: Abbreviations and notations Table 1

***Symbols for intake in g/d include:** FO - Fish Oil; *n*-3 - omega-3 fatty acids; FA -- fatty acid; DHA - docosahexaenoic acid; EPA- eicosapentaenoic acid; DHA + EPA (FO) - amount of DHA and EPA from fish oil; g -- grams; d -- day; FFQ -- Food frequency questionnaire.

[†]**Symbols for study duration include:** yr. -- year, mo. -- month.

[∇]**Symbols for description of population at time of enrollment:** MI - Myocardial Infarction; CHD - Coronary Heart Disease; CVD - Cardiovascular Disease. [∞] General is defined as free of indications of CHD; M – male only, F – female only.

[♦]**Symbol for intervention effect measures:** NS -- non-significant; ↑- increase in risk of CHD or CVD; ↓-decrease in risk of CHD or CVD.

^xIncrease in risk CHD using multivariate analysis and highest level of intake of omega-3 fatty acids derived from fish.

[Ⓞ] Decrease in risk of sudden cardiac death and/or CHD mortality associated with highest level of fish intake.

**Table 2: fish consumption, n-3 PUFA and CHD
Intervention Studies
Disease Outcome**

Reference	Intake* [EPA+DHA FO or n-3 FA- g/d] or	Study Duration ⁺	Population [∇] [no. & characteristics]	Disease Outcome [♦]
GISSI, et al., 1999	0.850-0.882 g/d EPA+ DHA (Ethyl esters)	3.5 yr.	11,324, MI	↓CVD death, non-fatal MI
Burr, et al., 1989	3 g/d FO or 2 or 3 portions oily fish/wk	2 yr.	2033, MI	↓CHD deaths

Footnote : Abbreviations and notations Table 2

* Symbols for intake in g/d include: FO - Fish Oil; FA -- fatty acid; DHA - docosahexaenoic acid; EPA- eicosapentaenoic acid; DHA + DPA (FO) - amount of DHA and EPA from fish oil; g-- grams; d -- day.

⁺**Symbols for study durations include:** yr. -- year, mo. -- month; d -- day.

[∇]**Symbols for description of population at time of enrollment:** MI - Myocardial Infarction; CVD - Cardiovascular Disease; CHD - Coronary Heart Disease. Representative of CHD disease patients.

[♦]**Symbol for intervention effect measures:** NS -- non-significant; ↑-- increase in risk of CHD or CVD; ↓-- decrease in risk of CHD or CVD.