Scientific Advisory Committee on Nutrition

Paper for discussion: Advice sought by FSA on the benefits of oily fish and fish oil consumption from SACN

Agenda Item 6

Please see attached paper for discussion. The following tables are also attached:

Table 1 Consumption of Fish by British Adults

Table 2 Reported Use of Cod Liver & Fish Oil Supplements for British Adults

Table 3 Consumption of Fish Oil Supplements by British Adults

Background

The Food Standards Agency invited SACN to comment on the health benefits of oily fish.

The Chairman in conjunction with Christine Williams with input from Professor Tom Sanders and Dr Philip Calder participated in a conference call on 13 May to discuss the issues. The Secretariat compiled the following paper as a result of this discussion.

Members are invited to comment on the conclusions reached.

Scientific **A**dvisory **C**ommittee on **N**utrition

Advice sought by FSA on the benefits of oily fish and fish oil consumption from SACN

Background

1. The FSA has asked SACN's advice on the health benefits of oily fish, fish oil and encapsulated fish oil consumption.

2. The Committee on Medical Aspects of Food Policy (COMA) recommended that 'people eat at least two portions of fish, of which one should be oily, weekly' (Department of Health. Nutritional Aspects of Cardiovascular Disease. Report on Health and Social Subjects No 46. S.3.7.3 p:17 London:HMSO 1994.).

Advice sought

3. Members and co-opted experts advised on whether the evidence on health benefits of oily fish, fish oil and encapsulated fish oil, has strengthened since COMA last commented on the area. In particular, advice was sought on the evidence in the following areas:
   - Health benefits in terms of primary disease prevention
   - Health benefits in terms of secondary disease prevention
   - The quantity or threshold of fish or oil required for health benefits and additional benefits of higher levels of consumption

Response

4. In this paper, n-3 polyunsaturated fatty acids (PUFA) refers to eicosapentaenoic (EPA), and docosahexaenoic acid (DHA). Also, the estimate used for n-3 PUFA content of oily fish is 2g/100g (one portion of fish is 100g); however, it should be noted that there is much seasonal variation within species and much variation between species.

Health benefits in terms of primary disease prevention

5. Since the mid 1990s a number of additional prospective studies have confirmed the data showing fish consumption to be inversely related to risk of CHD (Dolecek et al, 1992; Kromhout et al. 1985). Notably the Nurses Health Trial (Hu et al. 2002) conducted a 16 year follow-up of 84,688 women demonstrating that compared with women who rarely ate fish (<1 portion per month), those with a higher intake of fish had a lower risk of CHD. However, not all studies, have shown this association (for example Ascherio et al, 1995).

6. It has been suggested that the lack of benefits reported in some studies appears to be due to low prevalence of CHD in their study populations. A review by Marckmann and Grønbæk (1999) concluded that populations at low risk of CHD

and with healthy life-styles do not gain any additional protection from increased consumption of fish. More recent follow-ups, however, of the large studies that initially showed no association of fish consumption on CHD death in low risk populations, have, subsequently, demonstrated a protective effect (Hu *et al*. 2002; Albert *et al*. 2002). This may reflect the ageing of the study population and the concomitant increased risk of CHD.

7. The potential for CHD risk reduction, therefore, is likely to be greatest in those at the highest risk. 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 Grønbæk, 1999).

8. More evidence for the benefits of fish consumption comes from case control studies that have explored the relationship between intermediary markers of fish consumption and health. These studies have measured the fatty acid composition of cell membranes and blood (Siscovick *et al*. 1995; Albert *et al*. 2002). Cell membrane composition reflects fatty acid intake, however, the exact nature of the relationship is unknown. Siscovick *et al* measured red blood cell fatty acid composition in men at the time of sudden cardiac arrest and compared this with subjects with no history of CHD. They found lower levels EPA and DHA in cases who had suffered sudden cardiac death than in controls.

9. In a prospective, nested case-control study of healthy males (Physicians Health Study) 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.

10. There are no completed primary RCTs 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.

Health benefits in terms of secondary disease prevention

11. At the time the COMA recommendation was made the only secondary intervention study to have been published was the DART trial (Burr et al. 1989). In this study two year all cause mortality was reduced by 29% in survivors of first myocardial infarct who consumed 2 servings of oily fish (or equivalent fish oil capsules – 1g/d n-3 PUFA). Fish intake in this study was increased from an estimated 10-20g/d to 30-60g/d (0.7-1.3g/d n-3 PUFA).

12. More recently, the results from another study of survivors of myocardial infarcts have been reported (GISSI-Prevenzione Investigators, 1999). Subjects were

followed-up over 3.5 years and those who were supplemented with 1g/d n-3 PUFA had 20% reduction in all cause mortality, 30% reduction in cardiovascular death and 45% reduction in sudden cardiac death. The low dose (1g/d n-3 PUFA) at which these effects are observed is notable. It has been postulated that the likely mechanism of action is the stabilisation of arrhythmias (Marchioli *et al*. 2002).

13. 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.

14. 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 recognised 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).

15. 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 quantity or threshold of fish or oil required for health benefits and additional benefits of higher levels of consumption.

16. 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 plasma triacylglycerol levels, blood pressure, platelet aggregation and inflammatory response. 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 recognised 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

17. 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.

18. 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).

Conclusions

19. An overview of the evidence on the health benefits of oily fish and fish oils strongly supports the COMA recommendation of 1994 that 'people eat at least two portions of fish, of which one should be oily, weekly'. The scientific evidence that increased fish consumption or fish oil supplementation would decrease the incidence of CHD in the UK population is stronger now than in 1994.

20. The evidence is mainly drawn from secondary prevention trials that provide good evidence that increased fish consumption or fish oil supplementation would decrease the incidence of CHD in an at risk group. Extrapolating to a 'healthy' population is difficult. However, the UK population should be viewed as a 'high risk' population because of the high prevalence of CVD.

21. The evidence from secondary prevention trial data demonstrates that a beneficial effect of fish consumption, and fish oil supplementation, on CHD risk can be achieved at a dose of 1g/d n-3 PUFA. The COMA recommendation was for n-3 PUFA intake to increase from 0.1g/d to 0.2g/d. It seems likely that if this recommendation were revisited, the strength of the current evidence would lead to the recommendation for a figure greater than 0.2g/d for the UK population.

Please find attached two review articles on primary and secondary prevention data as background.

References

1. Albert, C. M.; Campos, H.; Stampfer, M. J.; Ridker, P. M.; Manson, J. E.; Willett, W. C., and Ma, J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med. 2002; **346**(15):1113-8.

2. Albert, C. M.; Hennekens, C. H.; O'Donnell, C. J.; Ajani, U. A.; Carey, V. J.; Willett, W. C.; Ruskin, J. N., and Manson, J. E. Fish consumption and risk of sudden cardiac death. JAMA. 1998; **279**(1):23-8.

3. Ascherio, A.; Rimm, E. B.; Stampfer, M. J.; Giovannucci, E. L., and Willett, W. C. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med. 1995; **332**(15):977-82.

4. Bucher, H. C.; Hengstler, P.; Schindler, C., and Meier, G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta- analysis of randomized controlled trials. Am J Med. 2002; **112**(4):298-304.

5. Burr, M. L.; Fehily, A. M.; Gilbert, J. F.; Rogers, S.; Holliday, R. M.; Sweetnam, P. M.; Elwood, P. C., and Deadman, N. M. Effects of changes in fat, fish, and

fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet. 1989; **2**(8666):757-61.

6. Department of Health (1994) *Nutritional aspects of cardiovascular disease. Report of the Cardiovascular Review Group Committee on Medical Aspects of Food Policy. Reports on Health and Social Subjects* no. 46. London: H. M. Stationary Office.

7. Department of Health (1999) *Health Survey for England. Cardiovascular Disease '98.* London: H. M. Stationary Office.

8. Dolecek, T. A. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. Proc Soc Exp Biol Med. 1992; **200**(2):177-82.

9. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999; **354**(9177):447-55.

10. Harris, W. S. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr. 1997; **65**(5 Suppl):1645S-1654S.

11. Hu, F. B.; Bronner, L.; Willett, W. C.; Stampfer, M. J.; Rexrode, K. M.; Albert, C. M.; Hunter, D., and Manson, J. E. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA. 2002; **287**(14):1815-21.

12. Kromhout, D.; Bosschieter, E. B., and de Lezenne Coulander, C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med. 1985; **312**(19):1205-9.

13. Marchioli, R.; Barzi, F.; Bomba, E.; Chieffo, C.; Di Gregorio, D.; Di Mascio, R.; Franzosi, M. G.; Geraci, E.; Levantesi, G.; Maggioni, A. P.; Mantini, L.; Marfisi, R. M.; Mastrogiuseppe, G.; Mininni, N.; Nicolosi, G. L.; Santini, M.; Schweiger, C.; Tavazzi, L.; Tognoni, G.; Tucci, C., and Valagussa, F. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002; **105**(16):1897-903.

14. Marckmann, P. and Grønbæk, M. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. Eur J Clin Nutr. 1999; **53**(8):585-90.

15. Olsen, S. F. and Secher, N. J. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. BMJ. 2002; **324**(7335):447.

16. Simmer, K. Longchain polyunsaturated fatty acid supplementation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 2, 2002a. Oxford

17. Simmer, K. Longchain polyunsaturated fatty acid supplementation in infants born at term (Cochrane Review). In: The Cochrane Library, Issue 2, 2002b. Oxford

18. Siscovick, D. S.; Raghunathan, T. E.; King, I.; Weinmann, S.; Wicklund, K. G.; Albright, J.; Bovbjerg, V.; Arbogast, P.; Smith, H.; Kushi, L. H., and et, a. l. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA. 1995; **274**(17):1363-7.

Table 1 – Consumption of Fish[1] by British adults[2]

Age/sex & Base no.	Total fish excluding shellfish					Oily fish					White fish				
	Consumption (g/day)					Consumption (g/day)					Consumption (g/day)				
	Mean	Median	97.5%ile	Consumers over 7 days (%)	Mean (popl)[3]	Mean	Median	97.5 %ile	Consumers over 7 days (%)	Mean (popl)[3]	Mean	Median	97.5 %ile	Consumers over 7 days (%)	Mean (popl)[3]
	Consumers					Consumers					Consumers				
19-24 yrs/M (61)	35.4	27.1	98.8	46	16.3	17.9	12.9	46.3	21	3.8	34.5	27.1	88.9	36	12.4
19-24 yrs/F (77)	30.7	26.6	81.5	57	17.6	24.7	18.1	88.2	39	9.6	25.4	23.5	65.3	31	7.9
25-34 yrs/M (159)	36.9	28.1	120.7	60	22.3	29.3	22.9	98.2	33	9.8	32.7	25.7	85.7	38	12.5
25-34 yrs/F (211)	29.1	24.4	82.6	58	16.8	23.8	17.1	70.2	36	8.6	23.1	24.3	53.0	35	8.2
35-49 yrs/M (304)	40.5	34.6	131.6	69	28.0	30.3	21.4	91.9	47	14.2	30.5	24.3	86.7	45	13.8
35-49 yrs/F (379)	36.2	28.9	98.0	69	25.0	26.2	18.5	82.8	45	11.9	29.3	24.3	78.4	45	13.1
50-64 yrs/M (242)	47.2	36.3	142.9	81	38.1	28.8	20.7	79.5	52	15.0	38.4	28.2	128.2	60	23.0
50-64 yrs/F (291)	44.8	36.4	123.0	80	35.8	30.3	22.2	103.5	58	17.5	31.2	25.0	71.4	59	18.3
All Males (766)	42.1	33.6	136.2	69	29.1	29.1	20.6	89.7	44	12.7	34.2	25.7	94.3	48	16.4
All Females (958)	37.6	29.5	105.4	69	25.9	27.3	19.4	87.8	47	12.7	28.8	24.3	77.9	46	13.2

[1] Excludes fish in recipe dishes
[2] National Diet and Nutrition Survey of British Adults aged 19-64 years 2000-1. Preliminary un-weighted data.
[3] Mean consumption including non-consumers

Table 2 – Reported use of cod liver and fish oil supplements for British adults[4]

Age/sex & Base no.	% who reported taking fish oil supplements in the interview
19-24 yrs/M (142)	1
19-24 yrs/F (136)	4
25-34 yrs/M (287)	12
25-34 yrs/F (275)	3
35-49 yrs/M (330	12
35-49 yrs/F (414)	11
50-64 yrs/M (330)	19
50-64 yrs/F (337)	26
All Males (1089)	13
All Females (1162)	13

[4] National Diet and Nutrition Survey of British Adults aged 19-64 years 2000-1. Preliminary un-weighted data.

Table 3 – Consumption of fish oil supplements for British adults[5, 6]

Age/sex & Base no.	Total fish oil supplements					Fish oil capsules					Fish oil Liquid				
	Intake of Fat (g/day) consumers					Intake of Fat (g/day) consumers			Consumers over 7 days		Intake of Fat (g/day) consumers			Consumers over 7 days	
	Mean	Median	97.5 %ile	%	N	Mean	Median	97.5 %ile	%	N	Mean	Median	97.5 %ile	%	N
19-24 yrs/M (61)	[0.2]	[0.2]	[0.3]	3	2	[0.2]	[0.2]	[0.3]	3	2	-	-	-	-	-
19-24 yrs/F (77)	[2.0]	[2.0]	[2.0]	1	1	[2.0]	[2.0]	[2.0]	1	1	-	-	-	-	-
25-34 yrs/M (159)	0.4	0.3	0.9	6	10	0.4	0.3	0.9	6	10	-	-	-	-	-
25-34 yrs/F (211)	[0.3]	[0.3]	[0.5]	1	3	[0.3]	[0.3]	[0.5]	1	3	-	-	-	-	-
35-49 yrs/M (304)	1.0	0.4	5.3	7	20	0.5	0.3	1.0	6	18	[5.3]	[5.3]	[7.6]	1	2
35-49 yrs/F (379)	0.5	0.3	1.1	7	28	0.5	0.3	1.1	7	28	-	-	-	-	-
50-64 yrs/M (242)	1.0	0.4	5.6	13	31	0.4	0.3	1.0	11	27	[4.4]	[4.9]	[6.4]	2	4
50-64 yrs/F (291)	0.8	0.5	4.4	14	42	0.6	0.5	1.0	14	40	[5.3]	[5.3]	[5.8]	…	2
All Males (766)	0.8	0.3	5.8	8	63	0.4	0.3	1.0	7	57	[4.7]	[4.9]	[7.7]	1	6
All Females (958)	0.7	0.4	2.4	8	74	0.5	0.4	1.1	8	72	[5.3]	[5.3]	[5.8]	…	2

Key [*] = Data based on less than 10 consumers
- = No consumers
… = Negligible percentage of consumers

[5] National Diet and Nutrition Survey of British Adults aged 19-64 years 2000-1. Preliminary un-weighted data.
[6] Fat intake, from supplements, has been used as a proxy for consumption (g/day).