

# Scientific Advisory Committee on Nutrition

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## Nutritional considerations

1. The Committee reviewed the evidence on the health benefits of fish and fish oil consumption with specific reference to cardiovascular disease risk and pregnancy outcome. The Committee considered the UK recommendations on fish consumption and long chain n-3 polyunsaturated fatty acid intake (Department of Health, 1994) with regard to the evidence that had arisen since.

Current UK recommendations (Department of Health, 1994):

- ‘That people eat at least two portions of fish, of which one should be oily’
- ‘An increase in the population average consumption of long-chain n-3 PUFA from about 0.1g/d to about 0.2g/d.’

## *Fish consumption in the UK*

2. White fish have flesh that is very low in fat as these fish accumulate fat in their livers, e.g. cod. Oily, or fatty, fish have fat in their flesh – the amount is related to their breeding cycle, and after breeding the fat content falls considerably. Oily fish are 5-20% fat compared with 1-2% fat for white fish. Oily fish include, sardines, salmon, pilchards, mackerel, herring and trout, whether fresh, frozen or canned. Fresh tuna is also included; however unlike other canned oily fish, canned tuna is not regarded as oily, as processing of tuna during canning reduces the fat content of the fish to a low level. White fish include cod, haddock, turbot, bream, bass etc. Please see Annex 1, which lists in Table 1 oily and white fish and in Table 2 details of the commonly consumed fish in the UK taken from the 2000/2001 National Diet and Nutrition Survey (NDNS).
3. The UK population average total fish and fish products consumption was 143 grams/person/week in 2000 (National Food Survey). Of this total 36 grams was fresh, frozen or processed white fish and 20 grams was fresh and processed (other than canned) oily fish. Consumption of canned salmon was 6 grams/person/week and other canned or bottled fish (including tuna) 26 grams. The remainder of the total is accounted for by cooked fish and fish products and shellfish.
4. The latest NDNS (Henderson et al, 2002) of adults aged 19-64 years shows that mean consumption of white fish (including products and dishes) by adults was 103g/week and for oily fish (excluding canned tuna) 50g/week. Correspondingly, mean consumption of white fish and oily fish by consumers was 221g/week and 194g/week respectively. Details are given in Annex 1 Tables 3-6. Most people in the UK consume very little fish. For example, during the period of the NDNS survey 74% of the participants did not consume oily fish (excluding canned tuna),

65% did not consume coated and/or fried white fish and 82% did not consume other white fish and dishes (Henderson *et al.*, 2002).

5. Comparison of the National Food Survey data from 1979 and 1999 shows that consumption of total fish and fish products increased by 13% between 1979 and 1999. Within the total, consumption of fresh oily fish more than doubled since 1979 while processed canned and shellfish increased by over 60% and fish products by over 40%.
6. The mean consumption of oily fish by adults (Henderson et al, 2002) has increased from 34g to 53g/week (from about a quarter to a third of a portion) since the last survey of this age group in 1986/87. The mean consumption of oily fish (excluding tinned tuna) by consumers has increased correspondingly from 134g/week to 194g/week. This is mainly due to an increase in consumption by women, particularly older women. Increased salmon consumption largely accounts for the increase.
7. The average portion size for adults is 140g. Details of other age groups given in Annex 1 Table 7.
8. Long chain polyunsaturated fatty acids (LC PUFA) are defined as those fatty acids that comprise 20 or 22 carbon atoms. Eicosapentaenoic acid (20:5n-3; EPA) and docosapentaenoic acid (22:5n-3; DPA) and docosahexaenoic acids (22:6n-3; DHA) are collectively referred to as LC n-3 PUFA. The estimate used for LC n-3 PUFA content of an average oily fish is 2g/100g and for an average white fish 0.3g/100g (see Annex 1 Table 2).

### ***Defining LC n-3 PUFA status***

9. The LC n-3 PUFA content of different cell membranes and plasma constituents, as well as adipose stores, can be modified by dietary intake; however, the exact relationship between LC n-3 PUFA dietary intake and changes in the content of these different pools is not understood. Different pools may vary in their responsiveness to changes in dietary LC n-3 PUFA intake (Vidgren et al, 1997). Homeostatic regulation may diminish sensitively to dietary intake, e.g. membrane fluidity maybe maintained for functional reasons in red blood cells, membrane LC n-3 PUFA content may affect lymphocyte cell signalling.
10. As there is no agreed, clear definition of what is meant by LC n-3 PUFA status in this context, or how it is best measured or characterized, the term will only be used in the most general sense in this paper. It would be inappropriate to use the term where what is really meant is blood concentration, or some other single measure, which might or might not be taken to reflect overall status.

## **The effects of LC PUFA on early human growth and cognitive function.**

### ***Background***

11. DHA and arachidonic acid (AA) are essential for the development of the central nervous system in mammals. There is a growth spurt in the human fetal brain

during the last trimester of pregnancy and the first postnatal months when a large increase in the cerebral and retinal content of AA and DHA occurs. These two LC PUFA can be synthesized from precursor essential fatty acids by chain elongation and desaturation: AA from linoleic acid of the n-6 series, and DHA from alpha-linolenic acid (ALA) of the n-3 series. The same enzymes are utilized by the different series, resulting in competition between the n-6 and n-3 fatty acids. AA and DHA are preferentially incorporated in the cell membranes of neuronal cells, where they modulate the structure, fluidity and function of the membrane. DHA acyl chains promote the function of the G-protein-coupled system in photoreceptor cell membranes and enhance the signalling pathways of metarhodopsin II (see Larque et al, 2002).

12. Although glial cells, astrocytes and cerebral endothelium may elongate and desaturate the precursor essential fatty acids, the main source of the DHA and AA that accumulates in the brain is preformed. Neither the fetal retina nor brain initially synthesizes LC PUFA and the capacity of the fetal brain to synthesize LC PUFA is a function of gestational age (Clandinin 1999), making placental transfer of preformed LC PUFA crucial. During the last trimester of pregnancy fetal requirements for DHA and AA are especially high because of the rapid synthesis of brain tissue (Clandinin et al, 1980; Martinez, 1992). The fetus and newborn infant are depend on a maternal supply of DHA and AA.
13. As a consequence of the increased demand on maternal DHA supplies, it has been suggested that depletion of maternal DHA stores occurs over pregnancy, and successive pregnancies and periods of lactation may reduce levels further (Al et al, 2000; Otto et al, 2001).
14. In humans, the fetal and infant brain DHA content appears to be more affected by diet than the AA content, suggesting that the endogenous metabolic regulation of AA content is more effective than that of DHA (Makrides et al, 1994). In human breast milk the AA content is also tightly regulated; whereas, more than four-fold differences have been observed in the content of the n-3 PUFA series (ALA and DHA) (Rodriguez-Palmero et al, 1999).
15. Markers of maternal LC n-3 PUFA status vary with fish and/or LC n-3 PUFA consumption during pregnancy. Regular consumption of oily fish (Olsen et al, 1991; Sanjurjo et al, 1995) or supplementation with LC n-3 PUFA (van Houwelingen et al, 1995; Connor et al, 1996) results in increased circulating maternal DHA during pregnancy and at term. Maternal supplementation with ALA, however, was not shown to increase maternal and neonatal DHA plasma concentrations, despite increasing EPA and DPA concentrations (de Groot et al, 2004). A dose-dependent increases in the DHA content of human breast milk was observed with fish oil supplementation (Harris et al, 1984); and although ALA supplementation resulted in increased ALA and EPA content of human breast milk, DHA levels were unaffected (Francois et al, 2003).

### ***Maternal DHA requirements in pregnancy and lactation***

16. Using the information available an assessment was conducted of the demands placed on a mother during pregnancy and lactation for n-3 PUFA, and her likely ability to meet these demands, either from her dietary intake, from her tissue

reserves, or from *de novo* formation from precursors taken in the diet or mobilised from tissue reserves (see Annex 2 for details). Conservative estimates were used, based upon the limited data available, and it was assumed that all other nutrients were available in adequate amounts and no other factors operated to limit normal metabolic inter-conversions. The assessment concluded that for a significant proportion of women it is very likely that the demands of pregnancy and lactation are greater than can be readily achieved from the sum of current levels of dietary consumption, endogenous mobilisation and *de novo* formation. This would suggest that a significant proportion of women are potentially at risk of inadequate LC n-3 PUFA status; however, the data currently available from which to draw this conclusion are limited.

### ***Infant formula supplementation with LC PUFA***

17. In contrast to human milk, conventional milk infant formulas with fat derived from vegetable oils do not provide appreciable amounts of LC PUFA. A marked decrease in plasma and red blood cell AA and DHA content was observed in infant formula fed as compared with breast-fed infants (Makrides et al, 1995). Moreover, the proportion of DHA in the brain cortex of breast-fed infants was higher compared to those fed infant formula without LC-PUFA (Makrides et al, 1994).
18. Many studies have been undertaken to assess whether increasing LC PUFA dietary intake affects visual and cognitive functions in preterm and full-term infants. These are difficult studies since neuronal processes are complex and multi-factorial, and potential confounders include birth weight, parental education and socio-economic status, smoking, variability in the infants DHA levels at birth, different PUFA ratios among the infant formulas studied, samples size and different test methodology. These studies used doses of LC PUFA that were comparable with the concentrations found in human milk.
19. Possible adverse effects of supplementing infant formulas with LC PUFA have also been described. In preterm infants, postnatal growth was reduced by the feeding of infant formulas supplemented with fish oil rich in the LC n-3 PUFA eicosapentaenoic acid (EPA), but no appreciable amount of AA, thus inducing a reduction of plasma AA concentrations (Carlson et al, 1993b). In these studies plasma AA concentrations were positively correlated with postnatal growth.
20. Similarly, a high dietary supply of ALA, associated with a low dietary ratio of n-6:n-3 PUFA, concomitantly reduced both plasma AA and weight gain until the age of 120 d in healthy term infants (Jensen et al, 1997). In contrast, the provision of infant formulas with an adequate and balanced supply of dietary AA and DHA has not been shown to have adverse effects on growth (Koletzko et al, 2001).

### ***Visual function***

21. Many studies investigating the effect of nutritional factors on neurodevelopment have used visual functions as outcome measures because of the well documented increases in visual functions in the first years of life (Teller, 1997). Visual acuity tests measure the integrity of the neural pathway from the retina to the occipital cortex and provide a surrogate marker of central nervous system function; however the long-term significance of improved retinal and visual function on

later neurodevelopment has yet to be shown. For preterm infants various studies have shown that those who were breast-fed had better visual acuity at 2-4 months of age and more advanced retinal development than those who were infant formula fed (Birch et al 1992a, 1992b). In full-term infants, some evidence suggests that breast-feeding is associated with enhanced visual function at age 3.5 years (Williams et al, 2001), and children whose mothers ate oily fish during pregnancy, as compared with those who did not, tended to have better visual function.

### ***Effects of LC PUFA on visual function***

22. Preterm infants born with a birth weight of <1500g have a limited fat stores at birth, a possible insufficiency in the elongation/desaturation enzymatic pathways and an inadequate intake of LC PUFA provided by infant formula (Uauy et al, 2001). Randomized controlled trials (RCT) that have included infant formula feeding with or without LC PUFA and assessed visual function in preterm and full-term infants are summarized in Tables 1 and 2 respectively.

***Table 1. Effects of LC PUFA on visual function in preterm infants***

Reference	Experimental group (n)	Post-conceptual age assessment (wk)	Measure	Outcome
Uauy et al, 1990	10-12	36	ERG	Marine oil infant formula and breast milk improved VF
Birch et al, 1992a	Further follow-up	57	Teller, VEP	Marine oil infant formula and breast milk improved VF
Birch et al, 1992b	9-16	36 & 57	VEP, FPL	Marine oil infant formula and breast milk improved VF
Carlson et al, 1993	33	38, 48, 57, 68, 79 & 92	Teller	Marine oil infant formula improved VF upto 48 wk; VF was associated with DHA concentrations upto 48 wk
Carlson & Werkman, 1996a	33-34	68, 79 & 92	Fagan	Marine oil infant formula improved VF upto 48 wk
Werkman & Carlson, 1996	26-33	39, 48, 57, 68, 79 & 92	Teller	Marine oil infant formula improved VF upto 48 wk
Carlson et al, 1996b	12-15	92	Fagan	Marine oil infant formula improved VF
Fadella et al, 1996	12-25	52	Flash VEP, ERG, BAEP	Marine oil infant formula and breast milk improved VEP only

O'Connor et al, 2001	140-143	8, 16, 26, 36, 52	Teller, Fagan, sweep VEP,	Marine oil infant formula with either fungal or egg DHA infant formula improved VEP only
van Wezel-Meijler et al, 2002	22	23, 36, 62, 114	Teller Flash VEP	No effect; although. marine oil infant formula group showed non significant improvement in VF at 23 wk

VF, visual function; Teller, Teller acuity cards; FPL, forced-choice preferential looking; Fagan, Fagan novelty preference; VEP, visual evoked potentials; ERG, electroretinography; BAEP, brainstem acoustic evoked potentials.

23. These trials support the efficacy of LC PUFA intake on the early development of the visual system, which was not achieved to similar extents with infant formulas providing the precursor PUFA: linoleic acid or ALA. A meta-analysis by SanGiovanni et al (2000) concluded that LC PUFA supplemented infant formulas showed significant differences at two and four months of age. Similarly, a Cochrane review concluded that there is evidence that LC PUFA supplemented infant formula increases the early rate of visual maturation in preterm infants, although this did not take into account trials later than 1998 (Simmer, 2002).

**Table 2. Effects of LC PUFA on visual function in full-term infants**

Reference	Experimental group (n)	Assessment age (mth)	Measure	Outcome
Makrides et al, 1995	13-23	4, 7	VEP	Marine oil infant formula and breast milk improved VF
Carlson et al, 1996c	19-20	2, 4, 6, 9 & 12	Teller	Marine oil infant formula improved VF at 2 mth only
Auestad et al, 1997	26-28	2, 4, 6, 9 & 12	Sweep VEP, FPL	No effect
Jorgensen et al, 1998	11-25	4	Sweep VEP	Only breast milk improved VF; although. marine oil infant formula group showed non significant improvement
Birch et al, 1998	22-23	1.5, 4, 6, 12	Sweep VEP, FPL	Marine oil infant formula and breast milk improved VEP only
Hoffman et al, 2000	29	1.5, 4, 12	ERG, VEP	Marine oil infant formula and breast milk improved VF

Makrides et al, 2000	21-46	4, 8	Flash VEP	No effect of marine infant formula, but breast-fed infants had better VEP acuity at 34 weeks of age, but not at 16 weeks.
Auestad et al, 2001	119-120	12	VEP, Teller	No effect of either breast-feeding or Marine oil infant formula
Auestad et al, 2003	Follow-up	39	VMF, Teller	No effect of either breast-feeding or Marine oil infant formula

VMF, visual-motor function.

24. Some of the trials in healthy term infants show that LC PUFA improved visual acuity during the first year of life, but others found no significant effect. None of the trials reported negative effects on visual acuity. Differences among the results may be due to differences in the methodology and in supplementation strategies (Larque et al, 2002).
25. Two recent RCTs where the infants were weaned from breast-feeding at 1.5 and 4-6 mths respectively are summarized in Table 3.

**Table 3. Effects of LC PUFA on visual function in full-term infants post weaning**

Reference	Experimental group n number	Assessment age (mth)	Measure	Outcome
Birch et al, 2002	32-33	1.5, 4, 6, 12	Sweep VEP, stereoacuity	Marine oil infant formula improved VEP only at 4, 6 and 12 mth
Hoffman et al, 2003	30-31	12	Sweep VEP, stereoacuity	Marine oil infant formula improved VEP

26. Beneficial effects of LC-PUFA supplementation on visual function were observed. The first of these two trials (Birch et al, 2002) provide evidence for a continued need for DHA in the infant diet beyond six weeks, while the latter (Hoffman et al, 2003) extends this age to beyond four months.

### ***Effects of LC PUFA on behavioural development***

27. Different tests have been used to examine the effects of postnatal dietary LC-PUFA on neurodevelopment (Carlson, 2000). At present, it remains unclear which tests are most sensitive to detect any potential effects of LC PUFA. RCTs that have included infant formula feeding with or without LC PUFA and assessed behavioural development in preterm and full-term infants are summarized in Tables 4 and 5 respectively.

**Table 4. Effects of LC PUFA on behavioural development in preterm infants**

Reference	Experimental group n number	Post-conceptual age assessment (wk)	Measure	Outcome
O'Connor et al, 2001	140-143	36, 52, 78	BMD, MacA	No overall effect of marine oil infant formula; however in infants with birth weight < 1250g marine oil infant formula group showed higher PDI for BMD
Lucas et al, 2001	65-116	49, 88	KP&S, BMD	No effect of either breast milk or marine oil infant formula
Fewtrell et al, 2002	78-81	49, 88	BMD PDI	Breast milk, but not marine oil infant formula improved scores
Wezel-Meijler et al, 2002	22	23, 36, 62, 114	BMD, PDI	No effect of marine oil infant formula

BMD, Bayley Mental Development Index; MacA, MacArthur Communicative Development Inventory; PDI, psychomotor developmental index; KP&S, Knobloch, Passamanick and Sherrards' developmental screening inventory.

**Table 5. Effects of LC PUFA on behavioural development in full-term infants**

Reference	Experimental group n number	age (mth)	Measure	Outcome
Agostoni et al, 1995	27-30	4	B-L	Marine oil infant formula and breast milk improved
Agostoni et al, 1997	25-30	24	B-L	No effect, although developmental quotients were still positively correlated with to both AA and DHA levels at 4 mth
Willatts et al, 1998	21-22	10	Problem solving	Marine oil infant formula improved problem solving
Scott et al, 1998	33-60	12, 14	MacA BMD	No effect of either breast-feeding or marine oil infant formula
Lucas et al, 1999	138-155		BMD	No effect of either breast-feeding or marine oil infant formula
Birch et al, 2000	17-20	18	BMD	No effect of marine oil infant formula
Makrides et al, 2000	21-46	4, 8	BMD	No effect of either breast-feeding or marine oil infant formula

Auestad et al, 2001	119-120	12	MacA BMD	No effect of either breast-feeding or marine oil infant formula
Auestad et al, 2003	Follow-up	39	IQ, Peabody	No effect of either breast-feeding or marine oil infant formula
Bouwstra et al, 2003	119-131	3	GM	Beneficial effect of marine oil infant formula and, more so, breast-feeding

B-L, Brunet-Lézine test; IQ, Stanford Binet IQ; Peabody, Peabody picture vocabulary test-revised; GM, general movements.

28. Overall, the results are equivocal, with some trials showing an effect of LC PUFA supplementation on the tests of behaviour employed while others not. Interestingly, in nearly all trials that observed no effect of marine oil infant formula, no effect of breast-feeding was observed.
29. Interestingly, a follow-up of the Willatts et al trial (1998), which also included other centres that participated in the original safety and tolerance studies, examined blood pressure at age six in relation to the trial interventions (Forsyth et al, 2003). Children who had received either breast milk or LC PUFA supplemented infant formula had significantly lower blood pressure than those who received the non-supplemented infant formula.

### ***Summary of the infant formula LC PUFA supplementation trials***

30. The trials investigating an effect of LC n-3 PUFA on visual function in preterm infants consistently demonstrate a short-term beneficial effect on VEP. This effect however, is observed to be transient.
31. The trials investigating an effect of LC n-3 PUFA on visual function in term infants are less consistent: the majority of trials demonstrate a beneficial effect, particularly on VEP, but others, including the largest trial (Auestad et al, 2001, 2003), failed to demonstrate an effect.
32. The majority of trials investigating an effect of LC n-3 PUFA on behavioural measures in both preterm and term infants failed to demonstrate an effect.
33. No adverse effect was observed in any of the trials investigating an effect of LC n-3 PUFA on behavioural and visual function measures in preterm and term infants.

### ***Effects of maternal LC n-3 PUFA dietary intake on infant neurodevelopment and growth***

34. Williams et al (2001) observed in a prospective cohort study of 435 children, whose mothers ate oily fish during pregnancy, as compared with those who did not, tended to have better visual function (stereoacuity) when assessed at age 3.5 years.
35. A cross-sectional study of 39 four month old breast-fed term infants (Jorgensen et al, 2001) suggested a cause-effect relationship between infant human milk DHA intake and visual acuity (VEP).
36. Two recent prospective cohort studies have investigated the relationship between umbilical venous plasma DHA and AA levels and cognitive function in 128 four year olds (Ghys et al, 2002) and 306 seven year olds (Bakker et al, 2003); however, no significant association was found.
37. RCTs that have supplemented pregnant women with LC n-3 PUFA and assessed infant neurodevelopment are summarized in Table 6. It should be noted that those studied by Helland et al represent only a small subgroup of offspring from the 590 pregnancies recruited.

***Table 6. Effects of maternal LC n-3 PUFA supplementation on infant neurodevelopment***

Reference	Population	Dose <sup>%</sup> (g/d)	Start <sup>^</sup> (wk)	Outcome
Helland et al, 2003	Fish oil 48 Control 36	2	18 until 3 months post-partum	Marine oil supplementation improved mental processing composite of the K-ABC tests a four years of age (106 [7.4] vs 102.3 [11.3]; P=0.049); a tendency for higher scores for the sequential processing scale, simultaneous processing scale and non-verbal scale was also observed.
Malcolm et al, 2003a & b	Fish oil 28 Control 27	0.2 DHA	15 until birth	No effect on VEP or ERG, although, an association between the infants DHA levels and VEP and ERG was observed.

<sup>^</sup> week of pregnancy supplement started; <sup>%</sup> LC n-3 PUFA.

### ***Effects of maternal LC n-3 PUFA dietary intake on gestation length and fetal growth***

38. Olsen et al (1995) suggested that higher DHA and EPA intake from fish in Faroe Islanders compared with Danes was the reason for longer gestation in Faroe Islanders. A recent prospective cohort study (Olsen & Secher, 2002) of 8729 pregnant women found that low consumption of fish was a strong risk factor for preterm delivery and low birth weight. This relation was strongest below an estimated daily intake of 0.15g LC n-3 PUFA or 15g fish. RCTs that have supplemented pregnant with LC n-3 PUFA during the third trimester and assessed gestation length and infant growth are summarized in Table 7.

**Table 7. Effects of maternal LC n-3 PUFA supplementation on gestation length and fetal growth**

Reference	Population	Dose <sup>%</sup> (g/d)	Start ^	Birth weight (g)	Gestation length (d)	Outcome
Olsen et al, 1992	Intervention 266 Control 136 Control (no oil) 131	2.7	30	3571 (528) 3445 (510) 3504 (531)	283.3 (11.1) 279.4 (13.1) 281.7 (11.6)	Fish oil increased gestation length
Olsen et al, 2000	Intervention 110 Control 122 Women who had previous preterm deliveries	2.7	20	3169 (674) 2960 (707)	269.2 (19.7) 260.7 (29.5)	Fish oil reduced recurrence of preterm delivery
Helland et al, 2001	Intervention 175 Control 166	2.0	18	3609 (493) 3618 (527)	279.6 (9.2) 279.2 (9.3)	No effect
Malcolm et al, 2003a	Intervention 31 Control 29	0.2	15	3507 (500) 3645 (495)	279.7 (9.5) 279.6 (8.5)	No effect
Smuts et al, 2003	Intervention 142 Control 149	0.13* DHA only	26	3209 (533) 3106 (551)	274.1 (13.5) 271.6 (15.6)	High-DHA eggs increased gestation length #

Mean (SD); ^ week of pregnancy supplement started; % LC n-3 PUFA; \* from high-DHA eggs; # after controlling for maternal BMI and number of previous pregnancies (276.5d versus 270.5d).

39. Olsen et al (2000) also examined the effect of maternal LC n-3 PUFA supplementation on women who had previously experienced intrauterine growth retardation or pregnancy induced hypertension respectively; however, no effect was observed. Another trial, also on women who had previously experienced intrauterine growth retardation or pregnancy induced hypertension, also observed no effect of fish oil supplementation (Onwude et al, 1995).

***Summary of the trails investigating maternal LC n-3 PUFA dietary intake on infant neurodevelopment and growth***

40. There is some evidence that increased maternal LC n-3 PUFA supply produced beneficial effects, especially in lower birth weight populations, and this may be more relevant in populations that tended to have a lower background intake of LC n-3 PUFA. No adverse effects of maternal LC n-3 PUFA supplementation were observed, even at relatively high doses.
41. In the trials that observed no effect of maternal LC n-3 PUFA supplementation on infant birth weight or gestation length the control group had birth weights greater than 3600g.

## **Fish consumption and cardiovascular disease**

30. 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 LC n-3 PUFA consumption on cardiovascular disease risk (CVD) factors and much mechanistic work, including cell culture, animal and human studies, 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>).
31. 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 significant association between consumption of fish or fish oil and haemorrhagic stroke.

### ***Prospective epidemiological studies***

32. An inverse relationship between fish consumption, and LC 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 (Osler et al, 2003; Albert et al, 1998; Kromhout et al, 1996; Asherio et al, 1995; Morris et al, 1995), prospective cohort studies.
33. 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 association with 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 association 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.
34. A study in middle-aged Danish adults, however, found no inverse association between fish consumption and risk of CHD mortality or overall mortality (Osler et al, 2003).
35. It has been suggested that the lack of benefit reported in some prospective studies may to be due to low prevalence of CHD in their study populations, e.g. Ascherio et al, 1995; Osler et al, 2003. 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. However, more recent

studies have demonstrated an association of fish consumption with a reduced risk of CHD in populations with a lower CHD incidence, 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.

36. Furthermore some of the initial cohort reports showing no association on initial follow up have produced positive findings for fish consumption on longer term 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. However, later analysis from the Honolulu Heart Program showed that fish intake and LC 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).
37. The Nurses' Health Study (Hu et al., 2002) recently reported an inverse association between fish intake and LC 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).
38. In the Kuopio Ischaemic Heart Disease Risk Factor Study, a prospective population study in Eastern Finland (Rissanen et al, 2000), an observed beneficial association 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, but not significantly, associated with risk of myocardial infarction, but that this inverse relation became stronger and statistically significant after adjustment for mercury levels. A previous study by this group showed no association between DHA adipose levels and risk of recurrence 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 association of LC n-3 PUFA, still reported a beneficial effect of fish consumption on CHD (Rissanen et al, 2000; Guallar et al, 2002).
39. 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 LC 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 LC 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.

40. 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.
41. In the first follow up 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 LC 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) ( $P < 0.001$ ). A threshold effect that was observed in a prospective cohort study for protection against sudden death in relation to increased fish consumption (Albert et al, 1998) was not seen in a nested case-control study within this cohort for blood levels of LC n-3 PUFA. A prospective nested case-control analysis of the Multiple Risk Factor Intervention Trial (Simon et al, 1995) observed that serum DHA levels were inversely associated with CHD risk in 94 men with incident CHD and 94 men without incident CHD.
42. 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 LC 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 LC 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 LC n-3 PUFA are responsible for the observed inverse association between fish consumption and sudden cardiac death.

### ***Randomized controlled trials***

43. 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 2004.
44. Three secondary prevention trials – the Diet and Reinfarction Trial (DART) (Burr et al, 1989, 1994), Singh et al, 1997 and the GISSI-Prevenzione trial (GISSI-

Prevenzione Investigators, 1999) – have shown 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, patients who received advice to eat more fish had a significantly lower (29%) total mortality during 2 years of follow-up. There was also a non-significant trend toward a reduction in recurrent ischemic heart disease events with increased fatty fish consumption. A smaller trial (Singh et al, 1997), which included 240 MI patients, also demonstrated a significant reduction in all cause mortality when patient were supplemented with 2g/d LC n-3 PUFA.

45. In the more recent GISSI-Prevenzione trial, which included 11 324 MI patients (primarily men), daily supplementation (1 g/d) of LC 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 LC 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 LC n-3 PUFA supports the hypothesis that the likely mechanism of action is the stabilisation of arrhythmias (Marchioli *et al.* 2002).
46. A recent RCT (Burr et al, 2003) investigating the effect in men with angina of dietary advice to increase fish consumption (MaxEPA fish oil was given to those men who found fish unpalatable) found an adverse effect of fish consumption (particularly for those given fish oil supplements) on total mortality. The trial design, however, suffered from an interruption, due to funding problems; also, the assessment of compliance was only conducted in a very small subgroup.
47. The secondary prevention trials, therefore, provide evidence that increased fish consumption or fish oil supplementation would decrease mortality among patients who have suffered a myocardial infarction. 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).
48. 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***

49. The beneficial effect observed in the secondary prevention trials is observed in the order of 1g/d LC n-3 PUFA. It is not known whether doses above this level have any greater benefit. The prospective epidemiological evidence is suggestive of a plateau effect, in high-risk populations, at levels of about 0.9g/d; however, where fatty acid composition analyses of blood or blood compartments are determined, a positive relationship, with no plateau, is observed.
50. The dose of LC n-3 PUFA 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) is greater than 1g/d. At least 1.5 g/d LC 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 LC 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 LC n-3 PUFA on secondary CHD prevention is the stabilisation of arrhythmias (Marchioli *et al.* 2002).

51. The nature of the evidence provided by the RCTs is suggestive of beneficial effects occurring within a short time scale, with benefit becoming apparent within a few months to 2 years; however, evidence provided from prospective studies is suggestive of increasing impact of benefit with increasing time (e.g. effects of high fish consumption become evident after 5-10 years of follow up but not in the early years). The dose-response nature of the relationship between fish consumption and risk of CVD may be different in populations of differing risk of CVD, and although the UK population is, relative to other countries, at high risk of CVD, sub-population within the UK may exhibit differing degrees of risk.

### **Summary**

52. The vast majority of the evidence base shows that fish consumption and dietary intake of LC n-3 PUFA reduce risk from CVD. Three out of four of the RCTs conducted demonstrate a beneficial effect in people at risk of CVD. The largest of these, the GISSI-Prevenzione trial, which included 11 324 MI patients, confirmed the effect of LC n-3 PUFA in reducing risk from CVD. The recently published DART 2 (Burr *et al.*, 2003) reported an adverse effect of fish oil supplementation on CVD risk; however, there is no observational evidence to support this.

### **Conclusions**

53. The Committee recommended that the population guideline to eat at least two portions of fish a week of which one should be oily should equally apply to pregnant women. It was noted that this based on nutritional considerations and was still subject to toxicological considerations.
54. There are no grounds to alter the current dietary recommendation for the UK population to consume at least two portions of fish per week of which one should be oily.
55. The recommendation states 'at least...' as this signified a minimal achievable objective for a population average, and some evidence supports a beneficial effect of higher levels of fish consumption.
56. To discourage fish consumption of levels higher than the dietary recommendation would be inappropriate, unless there was an upper limit beyond which people should not consume.

57. The Committee revised the previous recommendation concerning LC n-3 PUFA to make it consistent with the recommendation for fish consumption by raising it to 0.45g/d from 0.2g/d.

***Research recommendations***

58. For dose-response studies to examine the response of different body pools, with sufficient doses and fat stores/cells/plasma constituents examined, to LC n-3 PUFA dietary intake.
59. To determine to what extent maternal LC n-3 PUFA dietary intake affects pregnancy outcomes, e.g. gestation length and birth weight, and follow-up measures.

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**Table 1: Fish consumption, LC 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 <sup>+</sup>	Population <sup>∇</sup> [no & characteristics]	Disease Outcome <sup>♦</sup>
Osler et al, 2003 Danish cohorts	Prospective cohort	Fish <1 serving/mo to ≥2 serving/wk, (FFQ)	5-18 yr	7540 General <sup>∞</sup> aged 30-70 yr	No association observed
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	No association observed
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	No association observed
Rodriguez, et al., 1996 Honolulu Heart	Prospective cohort	Fish (0→ >1x/d) (FFQ)	23 yr.	8006, General	↓ CHD mortality <sup>Φ</sup> 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, n-3 FA) 0 to 5 serving/wk , FFQ	6 yr.	44895, M General	No association observed
Guallar, et al., 1995 US Physicians' Health Study	Nested, Case-control	(Blood samples EPA+DHA)	5 yr.	14916, M General	No association observed
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	No association observed

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	No association observed
Kromhout, et al., 1985 Dutch subset of seven countries study	Prospective cohort	Fish 0 → ≥ 30 g/d , FFQ	20 yr	852, General	↓ CHD mortality

\***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.

<sup>†</sup>**Symbols for study duration include:** yr. -- year, mo. -- month.

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

<sup>♦</sup>**Symbol for intervention effect measures:** ↑ - increase in risk of CHD or CVD; ↓ - decrease in risk of CHD or CVD.

<sup>x</sup> Increase in risk CHD using multivariate analysis and highest level of intake of omega-3 fatty acids derived from fish.

<sup>Φ</sup> Decrease in risk of sudden cardiac death and/or CHD mortality associated with highest level of fish intake.

**Table 2: fish consumption, LC n-3 PUFA and CHD  
intervention studies  
disease outcome**

Reference	Intake* [EPA+DHA or FO or n-3 FA- g/d]	Study duration <sup>+</sup>	Population [number and characteristics <sup>v</sup> ]	Number of events and relative risk (95% confidence interval)			Outcome and comments <sup>†</sup>
				All deaths	Cardiac deaths	Sudden deaths	
Burr, et al., 2003	3 g/d FO or 2 portions oily fish/wk	3-9yr	Intervention 1571 Control 1543  Men with angina	283; 1.1 (0.9-1.3) 242	180; 1.2 (1.0-1.5) 139	73; 1.5 (1.0-2.2) 47	↑ CHD deaths, especially with fish oil. F&V groups were combined with fish groups to give fish vs no fish groups, as very low compliance in F&V groups.
GISSI, et al., 1999	0.85-0.88 g/d EPA+ DHA (Ethyl esters)	3.5 yr	Intervention 5666 Control 5658  MI	472; 0.8 (0.7-0.9) 545	214; 0.8 (0.7-0.9) 265	122; 0.7 (0.6-0.9) 164	↓ CHD deaths Relative risk for non fatal MI 0.9
Burr, et al., 1989	3 g/d FO or 2 or 3 portions oily fish/wk	2 yr	Intervention 1015 Control 1018  MI	94; 0.7 (0.6-0.9) 130	78; 0.7 (0.5-0.9) 116		↓ CHD deaths Relative risk for non fatal MI 1.5
Singh, et al., 1997	1.08g/d EPA 0.72 g/d DHA	1 yr	Intervention 122 Control 118  MI	14; 0.5 (0.3-0.9) 26	12; 0.6 (0.3-1.3) 18	2; 0.2 (0.1-1.1) 8	↓ CHD deaths.

The RCTs below investigated an effect of fish oil supplementation on coronary atherosclerosis regression in patients with extensive coronary atherosclerosis, and also recorded disease outcomes. These RCTs were not considered in the formal analysis of the outcome data because the small numbers of subjects involved precluded statistical analysis of the data. In most cases high doses of fish oils were used that achieved levels of intake of EPA and DHA that could not be achieved by normal diet. A recent meta-analysis of RCTs (Bucher *et al.* 2002), which included the trials below, concluded that dietary and supplemental intake of LC n-3 PUFA reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with CHD.

Leaf, et al., 1994	4.1 g/d EPA 2.8 g/d DHA	6 mo	Intervention Control	253 250	0; 0.2 (0.0-5.4) 2	0; 0.5 (0.0-14.6) 1	0; 0.5 (0.0-14.6) 1	A supplement of 8 g/d of omega-3 fatty acids failed to prevent the usual high rate of restenosis after PTCA.
Sacks, et al., 1995	2.9 g/d EPA, 1.9 g/d DHA	2 yr	Intervention Control	31 28	0; 0.4 (0.0-12.5) 1	0; 0.4 (0.0-12.5) 1		No effect on the progression of coronary atherosclerosis
Johansen, et al., 1999	2.7 g/d EPA, 2.3 g/d DHA	6 mo	Intervention Control	196 192	1; 0.3 (0.0-3.1) 3	0; 0.2 (0.0-5.4) 1	1; 1.0 (0.1-15.5) 1	No effect on the incidence of restenosis
Von Schacky	1.06 g/d EPA, 0.65 g/d DHA	2 yr	Intervention Control	111 112	1; 0.5 (0.0-5.5) 2	0; 0.5 (0.0-14.7) 1		A modest effect on the progression of coronary atherosclerosis was observed

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

<sup>+</sup>Symbols for study durations include: yr. – year, mo. – month; d – day.

<sup>∇</sup>Symbols for description of population at time of enrollment: MI – Myocardial Infarction.

• Symbols for intervention effect measures: ↑ – increase in risk; ↓ – decrease in risk.