Scientific Advisory Committee on Nutrition

The effects of long chain polyunsaturated fatty acids on early human growth and cognitive function.

1. This draft report has been compiled using recent reviews, meta-analyses and papers published since.

Background

2. Docosahexaenoic acid (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 long-chain polyunsaturated fatty acids (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).

3. Although glial cells, astrocytes and cerebral endothelium may elongate and desaturate the precursor essential fatty acids, the accumulation of preformed DHA and AA in the brain is far more efficient. Neither the fetal retina nor brain initially synthesize 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. The fetus and newborn infant depend on a maternal supply of DHA and AA.

4. 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 (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).

5. Maternal n-3 PUFA status varies with fish and/or n-3 PUFA consumption during pregnancy. Regular consumption of oily fish (Olsen et al, 1991; Sanjurjo et al, 1995) or supplementation with n-3 PUFA (van Houwelingen et al, 1995; Connor et al, 1996) results in increased circulating maternal DHA status during pregnancy and at term. 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 content of human breast milk, DHA levels were unaffected (Francois et al, 2003).

6. In contrast to human milk, conventional milk 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 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 formula without LC PUFA (Makrides et al, 1994).

7. Many studies have been undertaken to assess whether improving LC PUFA status affects visual and cognitive functions in preterm and full-term infants. These are difficult studies since neuronal processes are complex and multifactorial, and potential confounders include birth weight, parental education and socio-economic status, smoking, variability in the infants DHA status at birth, different PUFA ratios among the 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.

Visual function

8. 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 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

9. Preterm infants born with a birth weight of <1500g have a virtual absence of adipose tissue at birth, a possible insufficiency in the elongation/desaturation enzymatic pathways and an inadequate intake of LC-PUFA provided by formula (Uauy et al, 2001). Randomized controlled trials (RCT) that have included 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-conceptional age assessment (wk)	Measure	Outcome
Uauy et al, 1990	10-12	36	ERG	Marine oil formula and breast milk improved VF
Birch et al, 1992a	Further follow-up	57	Teller, VEP	Marine oil formula and breast milk improved VF
Birch et al, 1992b	9-16	36 & 57	VEP, FPL	Marine oil formula and breast milk improved VF
Carlson et al, 1993	33	38, 48, 57, 68, 79 & 92	Teller	Marine oil formula improved VF upto 48 wk; VF was associated with DHA status upto 48 wk
Carlson & Werkman, 1996a	33-34	68, 79 & 92	Fagan	Marine oil formula improved VF upto 48 wk
Werkman & Carlson, 1996	26-33	39, 48, 57, 68, 79 & 92	Teller	Marine oil formula improved VF upto 48 wk
Carlson et al, 1996b	12-15	92	Fagan	Marine oil formula improved VF
Fadella et al, 1996	12-25	52	Flash VEP, ERG, BAEP	Marine oil 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 formula with either fungal or egg DHA formula improved VEP only
van Wezel-Meijler et al, 2002	22	23, 36, 62, 114	Teller Flash VEP	No effect; although. marine oil 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.

10. In summary, 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 formulas providing the precursor PUFA: linoleic acid or ALA. A meta-analysis by SanGiovanni et al (2000) concluded that LC-PUFA supplemented formulas showed

significant differences at two and four months of age. Similarly, a Cochrane review concluded that there is evidence that LC-PUFA supplemented formula increases the early rate of visual maturation in preterm infants (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 formula and breast milk improved VF
Carlson et al, 1996c	19-20	2, 4, 6, 9 & 12	Teller	Marine oil 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 formula group showed non significant improvement
Birch et al, 1998	22-23	1.5, 4, 6, 12	Sweep VEP, FPL	Marine oil formula and breast milk improved VEP only
Hoffman et al, 2000	29	1.5, 4, 12	ERG, VEP	Marine oil formula and breast milk improved VF
Makrides et al, 2000	21-46	4, 8	Flash VEP	No effect of marine formula, but breastfed 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 breastfeeding or Marine oil formula
Auestad et al, 2003	Follow-up	39	VMF, Teller	No effect of either breastfeeding or Marine oil formula

VMF, visual-motor function.

11. To summarize, 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 strtegies (Larque et al, 2002).

12. 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 formula improved VEP only at 4, 6 and 12 mth
Hoffman et al, 2003	30-31	12	Sweep VEP, stereoacuity	Marine oil formula improved VEP

13. 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) extents this age to beyond four months.

Effects of LC-PUFA on behavioural development

14. 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 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-conceptional age assessment (wk)	Measure	Outcome
O'Connor et al, 2001	140-143	36, 52, 78	BMD, MacA	No overall effect of marine oil formula; however in infants with birth weight < 1250g marine oil 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 formula
Fewtrell et al, 2002	78-81	49, 88	BMD PDI	Breast milk, but not marine oil formula improved scores
Wezel-Meijler et al, 2002	22	23, 36, 62, 114	BMD, PDI	No effect of marine oil 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 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 formula improved problem solving
Scott et al, 1998	33-60	12, 14	MacA BMD	No effect of either breastfeeding or marine oil formula
Lucas et al, 1999	138-155		BMD	No effect of either breastfeeding or marine oil formula
Birch et al, 2000	17-20	18	BMD	No effect of marine oil formula
Makrides et al, 2000	21-46	4, 8	BMD	No effect of either breastfeeding or marine oil formula
Auestad et al, 2001	119-120	12	MacA BMD	No effect of either breastfeeding or marine oil formula
Auestad et al, 2003	Follow-up	39	IQ, Peabody	No effect of either breastfeeding or marine oil formula

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

15. 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 formula, no effect of breast-feeding was observed.

Effects of maternal n-3 PUFA status on infant neurodevelopment

16. 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.

17. 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).

18. 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.

19. RCTs that have supplemented pregnant women with n-3 PUFA and assessed infant neurodevelopment are summarized in table 6.

Table 6.Effects of LC-PUFA on infant neurodevelopment

Reference	(n)	Dose n-3 PUFA (g/d)	Supplement started (wk)	Outcome
Helland et al, 2003	48	2	18 until 3 months post-partum	Marine oil supplementation improved mental processing composite of the K-ABC tests a four years of age; a tendency for higher scores for the sequential processing scale, simultaneous processing scale and nonverbal scale was also observed.
Malcolm et al, 2003	50	0.2 DHA	15 until parturition	No effect on infant retinal development (ERG that included a scotopic blue intensity series and a bright white flash). Although, an association between the DHA status of term infants and retinal sensitivity was observed.

Effects of maternal n-3 PUFA status on gestation length and fetal growth

20. 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 long chain n-3 PUFA or 15g fish. RCTs that have supplemented pregnant with n-3 PUFA during the third trimester and assessed gestation length and infant growth are summarized in table 7.

Table 7.Effects of LC-PUFA on gestation length and fetal growth

Reference	Experimental group n number	Dose n-3 PUFA (g/d)	Supplement started (wk)	Outcome
Olsen et al, 1992	266	2.7	30	Gestation in the fish-oil group was on average 4.0 (CI 1.5-6.4) days longer; the difference in birth weight was 107 (1-214) g.
Olsen et al, 2000	450 women who had previous preterm deliveries	2.7	20	Fish oil supplementation reduced the recurrence risk of pre-term delivery – an 8.5 day increase in gestation and a 209gincrease in average birth weight

Helland et al, 2001	170	2	18	No effect, although the average birth weight and gestation in the control group were already high: 3600g and >279d
Malcolm et al, 2003	50	0.2	15	No effect
Smuts et al, 2003	142-149	High-DHA eggs 0.133	26	Gestation increased 6.0 days on average and a non significant increase in birth weight, length and head circumference were observed.

The effects of long chain polyunsaturated fatty acids on cognitive decline

21. Although, as yet, no RCTs have been completed in this area, several studies suggest an association between n-3 PUFA status and cognitive decline.

22. A cross-sectional study in patients with Alzheimer disease (AD), other types of dementia and cognitive impairment compared with controls, observed that low plasma concentrations of n-3 PUFA appeared to be risk factors for cognitive impairment and dementia (Conquer et al, 2000).

23. A prospective cohort study (Morris et al, 2003) found that subjects who consumed fish once per week or more had a 60% less risk of AD compared with those who never ate fish. Total intake of n-3 PUFA and DHA intake, but not EPA, were associated with reduced risk of AD. A recent case-control study (Tully et al, 2003) observed lower serum cholesteryl ester-DHA levels in AD patient and that these were progressively reduced with severity of clinical dementia.

24. Heude et al (2003) assessed erythrocyte membrane fatty acid composition in a prospective cohort study where cognitive abilities were determined over a four year follow-up period. A higher proportion of total n-3 PUFA was associated with a lower risk of cognitive decline.

25. It remains to be determined whether low n-3 PUFA status in AD is a causal factor in the pathogenesis and progression of AD.

Accompanying recent reviews and meta-analyses:

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