European Food Safety Authority

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SCIENTIFIC OPINION

DHA and support of the visual development of the unborn child and breastfed infant

Scientific substantiation of a health claim related to DHA and support of the visual development of the unborn child and breastfed infant pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2008-675)

Adopted on 13 March 2009

PANEL MEMBERS

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SUMMARY

Following an application from Merck Selbstmedikation GmbH submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to DHA and support of the visual development of the unborn child and breastfed infant.

The scope of the application was proposed to fall under a health claim referring to children's development and health.

The food constituent that is the subject of the proposed claim is docosahexaenoic acid derived from tuna oil which is presented in soft gel capsules which contain >200 mg DHA, >50 mg eicosapentaenoic acid (EPA) and between 11.4 and 14.4 mg d-α-tocopherol. The food supplement is intended for pregnant and lactating women.

DHA is a well characterised fatty acid the absorption of which is well documented. DHA can be quantified in foods by established methods. The Panel considers that the food constituent, DHA, for which the claim is made is sufficiently characterised.

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from Merck Selbstmedikation GmbH on DHA and support of the visual development of the unborn child and breastfed infant. *The EFSA Journal* (2009) 1006, 1-12.

The claimed effect is that DHA provided via the mother contributes to the child's visual development. The target population for the claimed effect is unborn children and breastfed infants. The target population for the supplementation with DHA is pregnant and lactating women.

The Panel considers that normal visual development is beneficial for children's development and health.

The applicant identified a total of 41 publications as being pertinent to the health claim (15 randomised controlled trials (RCT), one non-randomised controlled trial, two observational cohort studies, three meta-analyses of human intervention studies, five systematic reviews, four other review publications, three guidelines/consensus opinions and eight mechanistic human studies).

The Panel considers that for the substantiation of the claim under consideration only human intervention or cohort studies reporting effects on visual function development in offspring of mothers who were exposed to defined intakes of DHA, either through supplementation or diet during pregnancy and/or lactation, provide the necessary evidence.

Therefore, intervention studies which assessed visual acuity in children who had been either breastfed or fed formula enriched with DHA are not regarded as pertinent for the substantiation of the proposed health claim, nor are RCT which describe the effects of DHA supplementation of pregnant women on the DHA concentrations in maternal and umbilical cord blood and in placenta and RCT conducted with DHA in lactating women which assess the effect on breast-milk DHA content.

Five RCT of DHA supplementation in pregnant or lactating women which include endpoints related to visual function assessment and an observational cohort study on the effects of maternal oily fish consumption and/or breastfeeding on children's stereoacuity testing at age 3.5 years are considered pertinent to the claim under consideration.

DHA supplementation during pregnancy

Two RCT have assessed the effect of supplementation of women with DHA during pregnancy. In the first randomised double-blind placebo-controlled trial 100 healthy pregnant women consumed either fish oil capsules (200 mg DHA/day) or sunflower oil capsules (400 mg oleic acid/day) from week 15 of gestation until delivery. Visual evoked potential (VEP) recording, performed within the first five days of life and at 10 and 26 weeks of age showed no association of mean peak latency of the major components with DHA content in cord blood or postnatal breast milk. VEP recordings, done at 10 and 26 weeks of age, revealed no group difference. There was, however, a significant positive correlation between the DHA level in cord blood red blood cells (RBC) of infants and one index of earlier maturation of VEP. Retinal development, assessed during the first week of life, did not differ between the groups but was related to infant DHA status at birth. The Panel considers that no positive association between maternal DHA supplementation and visual development of the infants was established. In the second study pregnant women consumed approximately 200 mg DHA/day (n=16) or a placebo (n=14) from week 24 of pregnancy until term and visual acuity was measured in their infants at four months and six months of age. The Panel considers the study as inconclusive because of the small sample size and the non-consistency of a positive effect with increasing age of the infants.

DHA supplementation during lactation

Three RCT have assessed the effect of supplementation of breastfeeding women with DHA on visual development of the infants. In the first study 52 lactating women were randomised to consume either 0, 0.2, 0.4, 0.9 or 1.3 g DHA supplement/day starting 5 days postpartum and

continuing until 12 weeks. Breast milk DHA content was related to infant plasma and RBC phospholipids DHA. VEP acuity of infants, assessed at 12 and 16 weeks of age did not differ between the dosage groups. In the second study 122 lactating women with habitual low fish consumption were randomised to consume a fish oil preparation containing 1.5 g n-3 Long chain polyunsaturated fatty acids (n-3 LCPUFA) or an olive oil preparation starting within a week of delivery and continuing for four months. There was no effect of fish-oil supplementation on the visual acuity of infants at either two or four months of age. The Panel notes that a maternal DHA dose around 1.0 g/day did not promote better visual acuity in young infants than no maternal supplementation. In the third study 114 breastfeeding mothers were assigned to capsules with high-DHA algal oil (200 mg DHA/day) and 113 mothers to capsules with DHA-free vegetable oil for four months after delivery. Apart from a significantly lower transient VEP amplitude in the infant group whose mothers were supplemented with DHA there were no significant differences between groups of visual acuity measured at four and eight months of age. The Panel considers that the positive association between maternal DHA supplementation and one out of four infantile visual parameters measured at eight months of age is insufficient to establish a relationship between maternal DHA supplementation and visual development of the infant.

A cohort study in a subset of 435 full-term children from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) related stereoacuity data collected at the age of 3.5 years to breastfeeding duration, mother's antenatal blood DHA content and oily fish consumption. Maternal oily fish consumption was associated with maternal blood DHA content and children whose mothers ate oily fish while pregnant were more likely to achieve high-grade stereopsis than were children whose mothers did not eat fish. The Panel considers that these data do not permit to establish a causal relationship between maternal DHA intake during pregnancy and stereoacuity development of their children.

The Panel concludes that there is insufficient evidence to establish a cause and effect relationship between the consumption of supplementary DHA during pregnancy and lactation and visual development in unborn children or breastfed infants.

Key words: docosahexaenoic acid, fish oil, visual development, children

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BACKGROUND

Regulation (EC) No 1924/2006[2] harmonises the provisions that relate to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of that Regulation and are authorised in accordance with this Regulation and included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of that Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of that Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to European Food Safety Authority (EFSA).

Steps taken by EFSA:

- The application was received on 19/08/2008.
- The scope of the application was proposed to fall under a health claim referring to children's development and health.
- During the check for completeness[3] of the application, the applicant was requested to provide missing information on 26/09/2008.
- The applicant provided the missing information on 02/10/2008.
- The scientific evaluation procedure started on 15/10/2008.
- During the meeting on 13/03/2009, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to DHA and support of the visual development of the unborn child and breastfed infant.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to DHA and support of the visual development of the unborn child and breastfed infant.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of DHA, a positive assessment of its safety, nor a decision on whether DHA is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

[2] European Parliament and Council (2006). Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

[3] In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

It should also be highlighted that the scope, the proposed wording of the claim and the conditions of use as proposed by the applicant may be subject to changes pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

ACKNOWLEDGEMENTS

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1. Information provided by the applicant

Applicant's name and address: Merck Selbstmedikation GmbH, Roesslerstrasse 96, 64293 Darmstadt, Germany

1.1. Food/constituent as stated by the applicant

DHA (docosahexaenoic acid; 22:6n-3)

1.2. Health relationship as claimed by the applicant

The applicant claims that DHA supports visual development of the foetus (unborn child) and infant.

1.3. Wording of the health claim as proposed by the applicant

DHA is important for early development of the eyes in the foetus (unborn child) and infant. Maternal DHA supply contributes to the child's visual development.

1.4. Specific conditions of use as proposed by the applicant

Pregnant and lactating women should aim to achieve an average intake of 200 mg DHA per day.

2. Assessment

2.1. Characterisation of the food/constituent

The food constituent that is the subject of the proposed claim is docosahexaenoic acid derived from tuna oil which is concentrated and purified by transesterification, molecular distillation and chromatography and presented in soft gel capsules which contain >200 mg DHA, >50 mg eicosapentaenoic acid (EPA) and between 11.4 and 14.4 mg d-α-tocopherol. Complete specifications, manufacturing process, bioavailability and stability informations have been provided. The food supplement is intended for pregnant and lactating women.

DHA is a well characterised fatty acid the absorption of which is well documented. DHA can be quantified in foods by established methods. The Panel considers that the food constituent, DHA, for which the claim is made is sufficiently characterised and that the present assessment applies to all products supplying a similar amount of DHA.

2.2. Relevance of the claimed effect to human health

The claimed effect is that DHA provided via the mother contributes to the child's visual development. The target population for the claimed effect is unborn children and breastfed infants. The target population for the supplementation with DHA is pregnant and lactating women.

The Panel considers that normal visual development is beneficial for children's development and health.

2.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in MEDLINE (until November 2007) using the search terms "pregnancy, lactation, DHA, DHA supplementation, LCPUFA, fish oil, omega-3, vision, visual acuity, retina, breast milk, development, infant" in various combinations. In addition, reference lists of relevant publications and conference proceedings were searched. Inclusion criteria to identify pertinent publications were randomised trials which compared DHA supplementation during pregnancy and/or lactation with placebo and cohort studies in which maternal seafood consumption during pregnancy and/or lactation was related to measures of visual function in the offspring. Studies which reported only on brain and cognitive development or which concerned only LCPUFA-enriched baby food were excluded.

The applicant identified a total of 41 publications as being pertinent to the health claim (15 randomised controlled trials (RCT), one non-randomised controlled trial, two observational cohort studies, three meta-analyses of human intervention studies, five systematic reviews, four other review publications, three guidelines/consensus opinions and eight mechanistic human studies).

The Panel notes that the majority of the references considered pertinent by the applicant provide evidence that DHA and ARA are major structural and functional LCPUFA in the brain and retina and are readily incorporated into neural tissues during the brain growth spurt and throughout the first years of life. Consistent with early preferential accumulation of LCPUFA in certain tissues is the correlation between these fatty acids and visual function development. Whilst DHA can be synthesised in the human body from its precursor essential fatty acid alpha-linolenic acid (ALA) to a certain extent which may be determined by polymorphisms of the fatty acid desaturases, the human foetus appears to be largely dependent on placental transfer of DHA from the mother, derived either from her diet, from synthesis or from stores in adipose tissue. Placental transport specifically enriches DHA in foetal blood. After birth most DHA is provided to the infant via breast milk, in which the DHA concentration is dependent both on maternal dietary DHA intake and on maternal DHA stores, whilst the contribution by synthesis is low (Koletzko *et al*., 2007, 2008; IoM, 2007).

Visual development i.e. retinal and visual pathway maturation can be estimated by different methods: visual evoked potential (VEP) acuity testing, electroretinogram (ERG) and, subjective, behavioural measures such as the Teller Acuity Card procedure.

The Panel considers that for the substantiation of the claim under consideration only human intervention or cohort studies reporting effects on visual function development in offspring of mothers who were exposed to defined intakes of DHA either through supplementation or diet during pregnancy and/or lactation provide the necessary evidence.

Therefore, an intervention study which compared visual acuity at the age of four years in children who had been either breastfed or fed un-enriched formula or formula enriched with DHA or both DHA and arachidonic acid (ARA) for the first 17 weeks of life (Birch *et al*., 2007) is not regarded as pertinent, nor is an RCT in women of child-bearing age who were neither pregnant nor lactating and which compared the effects on plasma fatty acid composition of a supplement consisting of a blend of DHA, EPA, ARA and γ-linolenic acid (GLA) to the effects of a placebo (Geppert *et al*., 2008).

Also five RCT which describe the effects of DHA supplementation of pregnant women on the DHA concentrations in maternal and umbilical cord blood and in placenta (Connor *et al*., 1996; Sanjurjo *et al.*, 2004; Montgomery *et al*., 2003; Larqué *et al*., 2006; Krauss-Etschmann *et al.*, 2007) and two of five RCT conducted with DHA either in the form of the acid or as fish or fish oil or egg in lactating women starting from five days to two weeks postpartum (Jensen *et al.*, 2000; Fidler *et al.*, 2000) are considered as not pertinent for the proposed health claim.

Another double-blind placebo-controlled study in pregnant women used doses of DHA much higher than proposed by the applicant (2.2 g compared to 200 mg) and did not directly measure parameters of visual function but eye hand coordination (Dunstan *et al.*, 2006), and was, therefore, not considered pertinent.

Five RCT of DHA supplementation in pregnant or lactating women which include endpoints related to visual function assessment and an observational cohort study on the effects of maternal oily fish consumption and/or breastfeeding on children's stereoacuity testing at age 3.5 years are considered pertinent to the claim under consideration (Gibson *et al.*, 1997; Williams *et al.*, 2001; Malcolm *et al.*, 2003a and b; Lauritzen *et al.*, 2004; Judge *et al.*, 2007; Jensen *et al.*, 2005).

DHA supplementation during pregnancy

Two RCT have assessed the effect of supplementation of women with DHA during pregnancy.

A prospective randomised double-blind placebo-controlled trial was performed in 100 healthy pregnant women who consumed either fish oil capsules (200 mg DHA/day) or sunflower oil capsules (400 mg oleic acid/day) from week 15 of gestation until delivery. Fatty acid patterns, including DHA were measured in maternal venous blood at three time points (15, 28 weeks and term) and in venous umbilical cord blood (both plasma and red blood cells [RBC]) and in breast-milk when infants were breastfed immediately postpartum and at approximately 10 weeks and 26 weeks of age. Sample size calculations based on expected changes of maternal DHA status and of VEP P100 peak latency time by one standard deviation (SD) (α 0.05 and power β of 90%) gave the required number of participants as 21. Owing to maternal drop-outs and the exclusion of some infants (born before 36 weeks of gestation, birth weight below the 3rd percentile, Apgar score <7 at five minutes, medical problems), 56 mother-infant pairs could finally be analysed who had provided all samples: fish-oil group 30, placebo group 26. Whilst there was no difference at the start of the supplementation between the groups with regard to maternal DHA status (DHA concentration and as percentage of total fatty acids in plasma and RBC), the increase to a maximum concentration in plasma and RBC was up to 20% higher in the verum group than in the placebo group, and the physiological decline until term was slower with supplementation than with placebo. At term the DHA content of maternal RBC was significantly higher in the supplemented group both as concentration (by 20%) and as proportion (by 42%). Participants' fish consumption, both habitual and recent, did not influence the DHA content of plasma and RBC after 15 weeks of gestation when supplementation started. Notably there was no significant difference in DHA levels (both absolute and proportional) in cord blood and neonatal breast-milk samples from the two groups. VEP recording to flash stimuli was performed within the first five days of life and at 10 and 26 weeks of age and showed no association of mean peak latency of the major components with DHA content in cord blood or postnatal breast milk. VEP recordings to pattern-reversal stimuli were done at 10 and 26 weeks of age and revealed no group difference of the P100 component peak latency nor in the pattern-reversal VEP threshold check size. There was, however, a significant negative correlation between the DHA level in cord blood RBC of infants and pattern-reversal VEP peak latencies, indicating earlier maturation of VEP with higher DHA status. Retinal development was assessed during the first week of life with full-field ERGs that included a scotopic blue intensity series (rod photoreceptor function; n=41) and a bright white flash (mixed rod and cone signals; n=46) and found not to differ between groups. There was a relationship between infant DHA status at birth and maturity of the retina at birth, regardless of maternal supplementation. Infants in the highest quartile for cord blood DHA had higher retinal sensitivity (measured as log σ) compared with infants in the lowest quartile (Malcolm *et al.*, 2003a and b; Montgomery *et al.*, 2003). The Panel considers that no positive

association between maternal DHA supplementation and visual development of the infants was established.

In a small prospective randomised double-blind placebo-controlled trial, in which 16 pregnant women consumed a low-EPA fish-oil containing cereal bar providing approximately 200 mg DHA/day and 14 other women consumed a placebo cereal bar from week 24 of pregnancy until term, significantly better visual acuity measured by the acuity card procedure at four months ($p=0.018$ after adjustment for potential confounding variables) but not at six months of age was found in the DHA-supplemented group than in the placebo group (Judge *et al.*, 2007). The Panel considers the study to be inconclusive because of the small sample size and the non-consistency of a positive effect with increasing age of the infants.

DHA supplementation during lactation

Three RCT have assessed the effect of supplementation of breastfeeding women with DHA.

Fifty-two lactating women were randomised to consume either of five supplements (0, 0.2, 0.4, 0.9 or 1.3 g DHA/day) starting 5 days postpartum and continuing until 12 weeks. Breast milk DHA content ranged from 0.1 to 1.7% of total fatty acids and was related to infant plasma ($r=0.89$, $p<0.001$) and RBC ($r=0.88$, $p<0.001$) phospholipids DHA in a saturable curvilinear manner so that milk DHA above 0.8% of fatty acids resulted in little further increase in infant plasma or RBC DHA levels. VEP acuity was assessed at 12 and 16 weeks of age in the infants and did not differ between the dosage groups (Gibson *et al.*, 1997). The Panel notes that DHA doses between 0.2 g/day and six times that amount during lactation had no measurable positive influence on VEP acuity in young infants.

In the second study 122 lactating women with a habitual low fish consumption were randomised to consume a fish oil preparation integrated into a muesli bar or cookies which contained 1.5 g n-3 LCPUFA (DHA-EPA ratio 2; n=62) or an olive oil preparation (n=60) starting within a week of delivery and continuing for four months. Ninety-seven of their infants completed the trial, 53 from the fish-oil and 44 from the olive-oil group. Their data were compared to those of 47 reference infants born to mothers with habitual high fish consumption. The primary outcome measures were DHA content of milk samples (0, 2 and 4 months after birth), and of infant RBC membranes (4 months after birth) and infant visual acuity at ages two and four months measured by sweep VEP. Fish oil supplementation led to a threefold increase in DHA content of the 4-month breast-milk samples ($p<0.001$) and the infant RBC DHA content reflected DHA concentrations in breast-milk ($r=0.564$, $p<0.001$). DHA breast-milk concentrations in the fish-oil group at two and four months were almost twice those in the reference group who had high fish consumption. There was no effect of fish-oil supplementation on the visual acuity of infants at either two or four months of age and there was no significant difference between groups in the increase in visual acuity from two to four months. Univariate analysis showed no association between visual acuity and maternal n-3 LCPUFA intake, DHA concentration in breast-milk and maternal or infant RBC DHA content at four months, but multiple regression analysis showed that infant RBC DHA levels were a major determinant of visual acuity in the two randomised groups ($p=0.008$) (Lauritzen *et al.*, 2004). The Panel notes that a maternal DHA dose around 1.0 g/day did not promote better visual acuity in young infants than no maternal supplementation.

In the third study 114 breastfeeding mothers were assigned to capsules with high-DHA algal oil (200 mg DHA/day) and 113 mothers to capsules with DHA-free vegetable oil for four months after delivery. Outcome measures were fatty acid patterns of maternal plasma phospholipids and milk lipids four months postpartum, the fatty acid pattern of infant plasma phospholipids, visual function of infants at four and eight months of age (Teller Acuity Card procedure, sweep and transient VEPs). The DHA content of milk lipids was significantly greater in the DHA

group than in the control group ($p<0.0001$) and the infant plasma phospholipid fatty acid pattern at four months of age mirrored that of milk lipid. There were no significant differences in the plasma phospholipid fatty acid pattern between groups at eight months of age. There were no significant differences between groups of visual acuity measured by either method at four and eight months of age. Transient VEP latency at four and eight months did not differ between groups, but the transient VEP amplitude was significantly lower in the group whose mothers were supplemented with DHA than in the control group, which is considered as a sign of greater maturity (Jensen *et al.*, 2005). The Panel considers that the positive association between maternal DHA supplementation and one out of four infantile visual parameters measured at eight months of age is insufficient to establish a relationship between maternal DHA supplementation and visual development of the infant.

A cohort study involved a randomly selected subset of 435 full-term children born during the last six months of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) in whom stereoacuity data collected at the age of 3.5 years were related to breastfeeding duration, mother's antenatal blood DHA content and oily fish consumption. Children who had been breastfed for more than four months were more likely to achieve high-grade stereopsis or stereoscopic vision than children who had not been breastfed (adjusted odds ratio 2.77; 95% CI 1.54, 4.97). Maternal oily fish consumption was associated with maternal blood DHA content ($p<0.0001$) and children whose mothers ate oily fish while pregnant were more likely to achieve high-grade stereopsis than were children whose mothers did not eat fish (adjusted odds ratio 1.57; 95% CI 1.00, 2.45) (Williams *et al*., 2001). The Panel considers that these data do not permit to establish a causal relationship between maternal DHA intake during pregnancy and stereoacuity development of their children.

The Panel concludes that there is insufficient evidence to establish a cause and effect relationship between the consumption of supplementary DHA during pregnancy and lactation and visual development in unborn children or breastfed infants.

CONCLUSIONS

On the basis of the data presented, the Panel concludes the following:

- The food constituent, DHA, for which the health claim is made is sufficiently characterised.

- The claimed effect is that maternal supplementation with DHA supports visual development of the unborn child and infant. The target population for the claimed effect is unborn children and breastfed infants. The target population for the supplementation with DHA is pregnant and lactating women. Normal visual development is beneficial for children's development and health.

- There is insufficient evidence to establish a cause and effect relationship between the consumption of supplementary DHA during pregnancy and lactation and visual development in unborn children or breastfed infants.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on DHA and support of the visual development of the unborn child and breastfed infant pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0218a_DE). August 2008. Submitted by Merck Selbstmedikation GmbH.

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GLOSSARY / ABBREVIATIONS

ALA	Alpha-linolenic acid
ALSPAC	Avon Longitudinal Study on Parents and Children
ARA	Arachidonic acid
EPA	Eicosapentaenoic acid
ERG	Electroretinogram
DHA	Docosahexaenoic acid
GLA	Gamma-linolenic acid
LCPUFA	Long chain polyunsaturated fatty acids
RBC	Red blood cells
RCT	Randomised controlled trial
VEP	Visual evoked potential