European Food Safety Authority

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SCIENTIFIC OPINION

DHA and ARA and development of brain and eyes

Scientific substantiation of a health claim related to Docosahexaenoic Acid (DHA) and Arachidonic Acid (ARA) and support of the neural development of the brain and eyes 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-2008-120)

Adopted on 8 September 2008 by written procedure

PANEL MEMBERS

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SUMMARY

Following an application from Martek Biosciences Corporation submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to Docosahexaenoic acid and arachidonic acid and support of the neural development of the brain and eyes.

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

The food/constituent, which is the subject of the health claim is a combination of docosahexaenoic acid (DHA, 22:6 n-3), an omega-3 long chain polyunsaturated fatty acid (LCPUFA) and arachidonic acid (ARA, 20:4 n-6), an omega-6 LCPUFA. The applicant manufactures DHA-rich algal oil and ARA-rich fungal oil. However, the scientific evidence provided to substantiate the health claim has been obtained using DHA and ARA from a variety of sources. This evaluation applies to all appropriate sources of DHA and ARA in the specified amounts. The Panel considers that DHA and ARA are sufficiently characterised.

Supplementation with LCPUFA (including DHA and ARA) and neural development in newborn infants (preterm and term) has been extensively evaluated and reviewed. Most of the

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studies presented relate to the effect of LCPUFA supplementation during the first months of life on tissue LCPUFA status and/or neural development assessed at different ages during infancy or early childhood. The Panel considers that these studies are not pertinent to the claim as the study populations are not representative of the target population for which the proposed health claim is intended (six months to three years of age).

Only a few studies presented specifically address the effects of DHA and ARA supplementation on neural development in infants older than six months and these are considered by the Panel as pertinent to the health claim.

Two studies investigated the effects of dietary supplementation with DHA and ARA on visual maturation at 1 y of age. Term infants recruited for these studies were breastfed from birth until 4-6 months of age, and then randomised to consume either DHA and ARA-enriched formula or control formula. In the first study, infants (n=61) were randomly assigned to consume either a standard commercial infant formula or the same formula supplemented with DHA and ARA. In the second study, infants (n=51) consumed one jar/day of either standard commercial solid baby foods or baby foods containing DHA-enriched egg yolk. Breast feeding continued in the second trial up to about nine months of age. At one year of age, red blood cell (RBC)-DHA levels in the intervention groups were significantly higher than RBC-DHA levels in the control group, suggesting good availability of the supplementary DHA. Visual-evoked potential (VEP) acuity was significantly more mature in the intervention groups compared to controls. Both RBC- DHA levels and DHA intake were significantly correlated with VEP acuity at 12 months.

The applicant did not present any study investigating the effects of DHA and ARA supplementation starting at six months of age on visual maturation or on any other measure of brain development, e.g., cognitive function, in healthy infants fed unenriched formula during the first six months of life.

The consumption of baby foods/formula supplemented with DHA and ARA from six months to one year of age might have a beneficial effect on visual acuity maturation in infants breast-fed during the first 4-6 months of age.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of DHA and ARA starting at six months of age and the neural development of the brain and eyes in infants and young children up to the age of three years.

Key words: docosahexaenoic acid (DHA), arachidonic acid (ARA), long-chain polyunsaturated fatty acids, brain development, eye development

TABLE OF CONTENTS

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, Article 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 11/02/2008.
- The scope of the application was proposed to fall under claim referring to children's development and health.
- During the ckeck for completeness [3] of the application, the applicant was requested to provide missing information on 03/03/2008 and on 03/04/2008.
- The applicant provided the missing information on 19/03/2008 and on 14/04/2008.
- The application was considered valid by EFSA and the scientific evaluation procedure started on 15/04/2008.
- On 8 September 2008 the NDA Panel, after having evaluated the overall data submitted, adopted by written procedure an opinion on the scientific substantiation of a health claim related to Docosahexaenoic acid and arachidonic acid, and support neural development of the brain and eyes.

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: Docosahexaenoic acid and arachidonic acid, and support neural development of the brain and eyes.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of docosahexaenoic acid and/or arachidonic acid, a positive assessment of its safety, nor a decision on whether docosahexaenoic acid and/or arachidonic acid are, or are 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 for use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Articles 17 of Regulation (EC) No 1924/2006.

ACKNOWLEDGEMENTS

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1. Information provided by the applicant

Applicant's name and address: Martek Biosciences Corporation, 6480 Dobbin Rd, Columbia, Maryland 21045, USA

1.1. Food/constituent as stated by the applicant

Docosahexaenoic Acid (DHA) as Docosahexaenoic Acid Single Cell Oil (DHASCO® Oil) and Arachidonic Acid (ARA) as Arachidonic Acid Single Cell Oil (ARASCO® Oil). Other sources of DHA and ARA, are available. It is the intention, therefore, that claims approved for DHA+ARA resulting from this application will apply to all appropriate DHA and ARA sources.

1.2. Health relationship as claimed by the applicant

DHA is an omega-3 long-chain polyunsaturated fatty acid (22:6 n-3) found in tissues throughout the body. ARA is an omega-6 long-chain polyunsaturated fatty acid (20:4 n-6) found in tissues throughout the body. DHA and ARA are major structural and functional components of all membranes, especially in the gray matter of the brain and the retina of the eye. DHA and ARA are important for brain and eye development in infants and have been shown to support brain and eye health in children by speeding maturation of early visual acuity and other measures of neural development. Benefits obtained from early supplementation appear to be maintained throughout childhood.

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

DHA and ARA support neural development of the brain and eyes.

1.4. Specific conditions of use as proposed by the applicant

The target population includes children fed weaning/complementary foods and formula, foods and food supplements containing LCPUFA six months to three years of age. The target population does not include infants fed infant formula where infant formula is the sole source of nutrition. Foods and supplements targeted toward children 6-12 months old should contribute to a minimum intake goal of 80 mg DHA and 105 mg ARA per day. Foods and food supplements that will be fed exclusively to children 1 year or older should contribute to a minimum intake goal of 80 mg of DHA per day. Dietary ARA sources increase in the complementary diet as additional foods are introduced. Therefore, foods and food supplements fed exclusively to children 1 year or older may provide a range of ARA from 0-105 mg.

2. Assessment

2.1. Characterisation of the food/constituent

DHA naturally occurs in fish, fish oil and in marine single cell microalgae. ARA naturally occurs in meat and egg products, and in a fungal oil source produced by the applicant.

The applicant manufactures DHA-rich algal oil and ARA-rich fungal oil for which complete specifications, full description of the manufacturing process and stability information are provided. The oils are intended to be used in milk and soy-based follow-on formulae as well as in complementary (weaning and post-weaning) foods and food supplements intended for children six months to three years of age. The scientific evidence provided by the applicant to substantiate the health claim has been obtained using DHA and ARA from a variety of sources

and not exclusively from the specific oils manufactured by the applicant. This evaluation will apply to all appropriate sources of DHA and ARA in the specified amounts.

The Panel considers that DHA and ARA are sufficiently characterised.

2.2. Relevance of the claimed effect to human health

DHA and ARA are components of lipids in the brain and retina and are incorporated into neural tissues during the brain growth spurt and throughout the first years of life. Between 50 and 60% of the brain's dry weight is lipid (Martinez, 1992), of which about half are PUFA, primarily LCPUFA, which are not available for energy production (Lauritzen et al., 2001). Endogenous synthesis of LCPUFA from precursors in newborn infants and the contribution of such synthesis to the overall availability of LCPUFA for tissue growth and development is limited. Endogenous synthesis decreases with postnatal age from birth to 7 months of age which explains that tissue LCPUFA status remains diet dependent in infants and young children, particularly after weaning, when human milk supplies are reduced and weaning foods are low and/or devoid in LCPUFA, especially DHA (Carnielli et al., 2007).

The claimed effect is the support of neural development of the brain and eyes. The target population is children six months to three years of age.

The Panel considers that normal neural development of the brain and eyes is beneficial for the development of infants and children.

2.3. Scientific substantiation of the claimed effect

The applicant searched all relevant databases for randomised controlled trials, observational studies, or meta-analyses published in English (or with an available English translation) in the last 10 years (between 1997 and 2007) which included healthy young children ≥ 6-month-old (including preterm delivery) receiving DHA and ARA supplementation during the complementary feeding period and reported either a neurologic endpoint or blood LCPUFA status as the primary outcome.

A total of 57 publications were initially identified. Of these, 32 were excluded by the applicant because of intervention periods less than four months, no introduction of solid food per study design, infant formula as sole food, no DHA-plus-ARA group, heterogeneous meta-analysis with regard to feeding duration or termination or no outcome measure of interest. The remaining 25 publications (14 publications reporting the results of 11 randomised controlled trials (RCTs), one meta-analysis of published studies and 10 guidelines, consensus opinions or textbook chapters) were considered by the applicant as pertinent to the health claim.

The effects of supplementation with LCPUFA (including DHA and ARA) on neural development in newborn infants (preterm and term) has been extensively evaluated and reviewed (Eilander et al., 2007; Simmer et al., 2008a and 2008b). Most of the studies presented by the applicant relate to the effect of LCPUFA supplementation during the first months of life on tissue LCPUFA status and/or neural development assessed at different ages during infancy or early childhood. Combined DHA and ARA supplementation of formula-fed infants can maintain blood and tissue LCPUFA levels to the same extent as human milk consumption. The feeding of formula enriched with DHA and ARA in amounts leading to daily intakes of about 100 and 200 mg, respectively, might benefit visual development of infants when compared to infants fed unenriched formulae (Eilander et al., 2007). However, a recent meta-analysis of 14 randomised intervention studies including 1719 infants with a variable duration of intervention (two months to one year), variable doses of LCPUFA from different sources, and a follow-up to three years showed inconsistent effects on visual acuity (Simmer et al., 2008b).

The Panel considers that the majority of these studies are not pertinent to the claim as the study populations are not representative of the target population for which the proposed health claim is intended (six months to three years of age).

When the combined DHA and ARA supplementation is continued into the second half of the first year of life, LCPUFA levels in blood phospholipids and blood cells can be maintained, which otherwise, owing to the low LCPUFA content of most weaning foods, would decrease (Auestad et al., 2001, 2003; Birch et al., 2005; Hoffman et al., 2003 and 2004; Makrides et al., 2000). There are few studies which compare the effect of the continued consumption of formulae differing in LCPUFA content by healthy term infants during the second half of the first year of life on growth, blood fatty acid content, visual function or other developmental parameters.

A total of 83 healthy full-term infants were randomly allocated at the age of one week to receive one of three formulae (28 placebo formula; 27 formula with 0.35 % of total fatty acids as DHA; 28 formula with both DHA 0.34 % and ARA 0.34 %) to be consumed throughout the first year of life. Both parents and assessors were unaware of the type of formula consumed by each participant. Some 68 infants could be investigated at 34 weeks of age, and 61 at two years of age. From a control group of 63 breast-fed infants, 46 completed the trial until two years of age. There were no differences in visual-evoked potential (VEP) acuity, which is used as an index of maturation of the retina and the visual cortex, between the formula groups at either 16 or 34 weeks of age. The MDI and PDI values of the Bayley Scales of Childhood Development at one and two years of age also did not differ among formula-fed groups (Makrides et al., 2000).

In three other double-blind, randomised controlled trials with healthy term infants consuming formula without LCPUFA or formulae supplemented with either DHA only (0.2 or 0.23 %) or with both DHA (0.12-0.14 %) and ARA (0.45-0.46 %) throughout the first year of life, no benefit on neural development (visual or cognitive) up to age 39 months could be demonstrated (Auestad et al., 1997; 2001; 2003).

A total of 103 healthy term infants were double-blind randomised at the age of five days to receive either a control formula devoid of DHA and ARA or a LCPUFA formula supplemented with DHA and ARA (0.36 and 0.72 % of total fatty acids, respectively) which they were to consume throughout the first year of life. Sweep VEP acuity was the primary outcome assessed at 6, 17, 39 and 52 weeks. Random dot stereoacuity, blood lipid profiles, growth and tolerance were secondary outcomes. Some 42 (LCPUFA) and 44 (control) infants completed the trial. VEP acuity was significantly better in the LCPUFA group than in the control group at all ages, while stereoacuity was only better at age 17 weeks. RBC-DHA concentrations at ages 17 and 39 weeks were more than twice and more than three times, respectively, the values of the control group. There were no differences in growth between the groups (Birch et al., 2005).

Two of the studies presented by the applicant specifically address the effects of DHA and ARA supplementation from six months of age on neural development in breast-fed infants and are considered by the Panel as pertinent to the health claim (Hoffman et al., 2003, Hoffman et al., 2004).

The first study (Hoffman et al., 2003) investigated the effects of post-weaning dietary supplementation with DHA and ARA on visual maturation at one year of age in term infants that were breast-fed from birth until 4-6 months. A total of 61 infants were randomly (block randomisation schedule) assigned to consume either a standard commercial infant formula (controls, n = 31) or the same formula supplemented with 0.36% and 0.72% of total fatty acids as DHA and ARA respectively (intervention, n = 30) until the age of one year. The supply of DHA was estimated to be about 0.2–0.4 g DHA/6 months in the control group (primarily owing to endogenous DHA synthesis from α-linolenic acid) and about 22 g DHA/6 months in the

intervention group. Dietary intake of solid foods was neither controlled nor assessed throughout the study. Sample sizes were based on power calculations considering sweep VEP acuity as primary outcome. At one year of age, RBC-DHA concentrations in the intervention group were similar to those at baseline and significantly higher than RBC-DHA concentrations in the control group which significantly decreased from baseline (by around 50%), suggesting good availability of the supplementary DHA and compliance (not reported) with the dietary protocol; RBC-ARA concentrations did not change significantly in any group throughout the study. VEP acuity was significantly better in the intervention group compared to controls at one year. By linear regression analysis, infants with higher RBC DHA concentrations were found to have more mature visual cortical function ($r = -0.4$; $p<0.0005$).

The second study (Hoffman et al., 2004) investigated the effects of solid baby food supplementation with DHA on visual maturation at one year of age in term infants exclusively breastfed from birth until four months and likely to have breast milk as the only source of milk until one year of age. A total of 51 infants were randomly assigned at six months of age (random sequence generation) to consume daily 1 jar of either standard commercial solid baby foods (controls, n = 26) or baby foods containing DHA-enriched egg yolk and providing approximately 83 mg DHA/d (intervention, n = 25) until the age of 1 year. Breast feeding continued in both groups up to an age of about 9 months. Thus, for the entire 6-months trial period, the intervention group received an average of 108 mg DHA/day (13 mg/kg body weight/day) from baby foods and breast milk compared with 38 mg DHA/day (4.5 mg/kg body weight/day) in control infants from breast milk only. Infants in the intervention group were estimated to have consumed about 56 mg/d supplementary ARA and controls 0.3 mg/d supplementary ARA during the study. Sample sizes were based on power calculations considering sweep VEP acuity as primary outcome. In DHA-supplemented infants, VEP acuity was significantly more mature at 12 months of age than in controls. Both RBC-DHA levels and DHA intake were significantly correlated with VEP acuity at 12 months.

The Panel considers that the consumption of baby foods/formula supplemented with DHA and ARA from the age of six months to one year might have a beneficial effect on visual acuity maturation in infants breast-fed during the first 4-6 months of life.

No studies have been presented investigating the effects of DHA and ARA supplementation starting at six months of age on visual maturation or on any other measure of brain development, e.g., cognitive function, in healthy infants fed unenriched formula during the first six months of life (Makrides et al., 2002).

The Panel concludes that a cause and effect relationship has not been established between the consumption of DHA and ARA starting at six months of age and the neural development of the brain and eyes in infants and young children up to the age of three years.

CONCLUSIONS

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

- The food/constituents which are the subject of the health claim are sufficiently characterised.
- The claimed effect is to support neural development of the brain and eyes in infants and young children from six months and up to three years of age. Normal neural development of the brain and eyes is beneficial for the development of infants and children.
- The consumption of baby foods/formula supplemented with DHA and ARA from six months to one year of age might have a beneficial effect on visual acuity maturation in infants breast-fed until the age of 4-6 months; no evidence has been presented on the

effects of DHA and ARA supplementation starting at six months of age on visual maturation in healthy infants fed unenriched formula during the first six months of life.

- No evidence has been presented on the effects of DHA and ARA supplementation starting at six months of age on any other measure of brain development, e.g., cognitive function.
- A cause and effect relationship has not been established between the consumption of the food/constituent (DHA and ARA) starting at six months of age and the functional development of the brain and eyes in infants and young children up to the age of three years.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on "Docosahexaenoic Acid (DHA) and Arachidonic Acid (ARA)" and "support neural development of the brain and eyes" pursuant to Article 14 of Regulation (EC) No 1924/2006. Claim serial No: 0040-UK. April 2008. Submitted by Martek Biosciences Corporation.

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GLOSSARY / ABBREVIATIONS

ARA	Arachidonic Acid
DHA	Docosahexaenoic Acid
LCPUFA	Long Chain Polyunsaturated Fatty Acids
PUFA	Polyunsaturated Fatty Acids
VEP	Visual Evoked Potential
RBC	Red blood cells
MDI	Mental Development Index
PDI	Psychomotor Development lndex (of the Bayley Scales of Infant Development)