

SCIENTIFIC OPINION

DHA and ARA and visual development

Scientific substantiation of a health claim related to docosahexaenoic acid (DHA) and arachidonic acid (ARA) and visual development pursuant to Article 14 of Regulation (EC) No 1924/2006¹

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

(Question No EFSA-Q-2008-211)

Adopted on 22 January 2009

PANEL MEMBERS

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SUMMARY

Following an application from Mead Johnson Nutritionals submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, 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 visual development.

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

The food constituents that are the subject of the health claim are docosahexaenoic acid (DHA) and arachidonic acid (ARA), which are well characterised fatty acids that can be quantified in foods by established methods. The absorption of DHA and ARA is well documented. The Panel considers that the food constituents DHA and ARA are sufficiently characterised.

The claimed effect is the contribution to the optimal visual development of infants and young children. The target population proposed by the applicant is infants and young children (from birth to three years of age). The Panel considers that a normal visual function is beneficial for infants' and children's development and health.

The applicant identified a total of 43 publications as being pertinent to the health claim. A total of 12 publications which report original data from randomised controlled trials (RCTs) on the

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effects of DHA supplementation (with or without ARA) on visual development in physiological conditions and in infants born at term and one pooled analysis including four of the RCTs indicated above were considered as pertinent to substantiate the claimed effect. An additional RCT not included in the application also met these requirements.

Of the 13 full publications of RCTs, three include long term observations on subjects supplemented in the first months of life, while one publication reports complementary observations on visual function, so that the results from nine original study designs are available. Of these, six include term infant populations fed different formulas from birth through the first months of life up to 12 months at the maximum, while three included breastfed infants starting either a DHA plus ARA supplemented formula or DHA-enriched weaning foods at different time points (six weeks to six months) and continuing up to 12 months.

RCTs in term infants with randomisation at birth

Four of the RCTs presented found no effect of formula supplemented with either DHA or DHA and ARA on visual outcomes as compared to the unsupplemented formula. The doses of DHA and/or ARA used in three of these studies were significantly lower than those proposed by the applicant to obtain the claimed effect. The two other RCTs showed better results on visual outcomes through the first year of life in infants fed formulae supplemented with either DHA or DHA and ARA as compared to the unsupplemented formula group. In these two studies, the doses of DHA used were in the range of those proposed by the applicant to obtain the claimed effect and sample sizes were based on power calculations considering sweep visual evoked potential (VEP) acuity as primary outcome.

The Panel notes that none of the studies presented has shown a benefit of either DHA alone or DHA plus ARA on visual development as compared to the breast fed control group, that no studies have observed an additional benefit of DHA plus ARA supplementation over DHA alone on visual acuity in term infants, and that direct associations only between markers of DHA (but not ARA) status and visual outcomes have consistently been reported.

From the studies presented in term infants with randomisation at birth, the Panel considers that the consumption of infant formulae supplemented with DHA at around 0.36% of total fatty acids from birth up to 12 months is associated with better visual function in term infants as compared to the consumption of unsupplemented formulae, even if a dose-response relationship has not been directly tested and not all the studies performed at the recommended dose reach the same conclusion.

RCTs in term infants with randomisation after weaning

The three studies presented were conducted using doses of either DHA or DHA and ARA in the range proposed by the applicant to obtain the claimed effect, have power calculations performed considering sweep VEP acuity as primary outcome, find better visual acuity up to 12 months in infants fed supplemented formulae/weaning foods as compared to the unsupplemented group, and report direct associations between markers of DHA (but not ARA) status and visual outcomes.

One pooled analysis including data from four of the RCTs presented in the two sections above and including a total of 243 infants found a positive correlation between the duration of intake of either human milk or DHA and ARA via formulae (containing 0.36% DHA and 0.72% ARA) and better sweep VEP acuity at 52 weeks of age.

Taking into consideration both the studies with randomisation at birth and the studies with randomisation post-weaning, the Panel notes that supplementation with either DHA alone or with DHA plus ARA has shown no benefit on the visual development of term infants as compared to breast feeding. The Panel also notes that no studies investigating the effects of

both DHA and DHA plus ARA supplementation have observed an additional benefit of DHA plus ARA supplementation over DHA alone on visual acuity in term infants, and that direct associations between markers of DHA (but not ARA) status and visual outcomes have been consistently reported. The Panel considers that a role of ARA on visual development of term infants cannot be established on the basis of the data presented.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the intake of infant and follow-on formula supplemented with DHA at levels around 0.3% of total fatty acids and visual function at 12 months in formula-fed infants born at term from birth up to 12 months and in breastfed infants after weaning up to 12 months. The Panel could have not reached this conclusion without considering the studies claimed by the applicant as proprietary.

The following wording reflects the scientific evidence: “DHA contributes to the visual development of infants”.

In order to bear the claim a formula should contain at least 0.3% of the total fatty acids as docosahexaenoic acid. Such amounts can be easily consumed as part of a balanced diet.

The target population is infants (formula-fed infants born at term from birth up to 12 months and breastfed infants after weaning up to 12 months).

Key words: Docosahexaenoic acid, arachidonic acid, visual development, visual function, visual acuity, visual evoked potential, infants

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BACKGROUND

Regulation (EC) No 1924/2006² 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 14/02/2008.
- The scope of the application was proposed to fall under a health claim referring to children's development and health.
- During the check for completeness³ of the application, the applicant was requested to provide missing information on 21/03/2008 and on 23/09/2008.
- The applicant provided the missing information on 31/08/2008 and on 06/10/2008.
- The scientific evaluation procedure started on 15/10/2008.
- During the meeting on 22/01/2009, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to docosahexaenoic acid and arachidonic acid and visual development.

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 visual development.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of docosahexaenoic acid and arachidonic acid, a positive assessment of its safety, nor a decision on whether docosahexaenoic acid and 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 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: Mead Johnson Nutritionals, 3 rue Joseph Monier-BP 325, 92506 Rueil-Malmaison Cedex, France.

The application includes proprietary data.

1.1. Food/constituent as stated by the applicant

Docosahexaenoic acid (DHA) and arachidonic acid (ARA)

1.2. Health relationship as claimed by the applicant

Docosahexaenoic Acid (DHA) and arachidonic acid (ARA) are important constituents of brain and retinal tissues. DHA and ARA contribute to the optimal visual development of infants and young children.

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

DHA and ARA contribute to the optimal visual development of infants and young children.

1.4. Specific conditions of use as proposed by the applicant

Condition of use for the claim: the formula contains at least 0.3% of the fatty acids as DHA and the ratio ARA:DHA is between 1.4:1 and 2.0:1.

2. Assessment

2.1. Characterisation of the food/constituent

The food constituents that are the subject of the health claim are docosahexaenoic acid (DHA) and arachidonic acid (ARA) derived from single cell oils manufactured by the applicant, for which complete specifications, manufacturing process, bio-availability and stability information have been provided. DHA is derived from the alga *Cryptocodinium cohnii* and ARA from the fungus *Mortierella alpina*. DHA and ARA from single cell oils are intended to be added to food for particular nutritional uses for infants and young children from birth to 3 years of age according to Directive 89/398/EEC at the concentration of at least 0.3% of the fatty acids as DHA and a ratio ARA:DHA between 1.4:1 and 2:1. This evaluation will apply to DHA and ARA from all appropriate sources in the specified amounts.

DHA and ARA are well characterised fatty acids the absorption of which is well documented and can be quantified in foods by established methods.

The Panel considers that the food constituents DHA and ARA are sufficiently characterised.

2.2. Relevance of the claimed effect to human health

The claimed effect is the contribution to the optimal visual development of infants and young children. The target population proposed by the applicant is infants and young children (from birth to three years of age).

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

2.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed and Scopus to identify randomised controlled trials (RCT) on the effects of formulae intended for infants and young children (from birth to 36 months) containing DHA and ARA on visual development (as primary or secondary outcome) using the search terms DHA, ARA, infant, visual development, visual acuity, visual, preterm, long-chain polyunsaturated fatty acids, weaning food, fatty acids, stereoacuity, visual evoked potential (VEP), Teller Card, omega-3, omega-6, and toddler milk. The snow ball method (search for additional references in the papers identified through the search) was used for hand searching.

The applicant identified a total of 41 publications as being pertinent to the health claim (18 RCTs of which only 12 were presented as full-text, one observational study, one pooled analysis of RCT, three meta-analyses of RCTs, one systematic review, nine review publications, six guidelines/consensus opinions and one other publication). The applicant also included one unpublished human study and one animal study in the pertinent literature.

The Panel considers that publications/reports presented in summary form only and/or investigating the effects of DHA and ARA in pre-term infants and/or addressing clinical outcomes other than visual development are not suitable sources of data to support the claimed effect. The Panel also considers that the results of the meta-analyses presented assessing the effects of long-chain polyunsaturated fatty acid supplementation on visual outcomes in infants cannot be directly extrapolated to support the claimed effect as the inclusion criteria used for trial selection do not match the scope of the present evaluation (San Giovanni et al., 2000; Uauy et al., 2003; Simmer et al., 2008).

A total of 13 publications (Birch et al., 2000, proprietary data; Auestad et al., 2003; Birch et al., 2007, proprietary data; Hoffman et al., 2000, proprietary data; Carlson et al., 1996; Auestad et al., 1997; Birch et al., 1998, proprietary data; Auestad et al., 2001; Birch et al., 2005, proprietary data; Birch et al., 2002, proprietary data; Hoffman et al., 2003, proprietary data; Hoffman et al., 2004;) which report original data from RCTs on the effects of DHA supplementation (with or without ARA) on visual development in physiological conditions and in infants born at term and one pooled analysis including four of the RCTs indicated above (Morale et al., 2005, proprietary data) have been presented by the applicant as pertinent to substantiate the claimed effect. The Panel notes that an additional study not included in the application also meets the requirements and is considered as a pertinent source of data (Makrides et al., 2000) for the present evaluation.

The 13 full publications of RCT come from four groups of investigators. Three publications include long term observations on subjects supplemented in the first months of life (Birch et al., 2000; Auestad et al., 2003; Birch et al., 2007) while one publication reports complementary observations on visual functions (Hoffman et al., 2000), so that the results from nine original study designs are available. Of these, six include term infant populations fed different formulas from birth through the first months of life up to 12 months at the maximum (Carlson et al., 1996; Auestad et al., 1997; Birch et al., 1998; Auestad et al., 2001; Birch et al., 2005; Makrides et al., 2000), while three included breastfed infants starting either a DHA plus ARA supplemented formula (Birch et al., 2002; Hoffman et al., 2003) or DHA-enriched weaning foods (Hoffman et al., 2004) at different time points (six weeks to six months) and continuing up to 12 months.

RCTs in term infants with randomisation at birth

Two studies using formulae with either DHA 0.1%+ARA 0.4% or DHA 0.2% alone (Auestad et al., 1997; Auestad et al., 2001) did not find significant effects on vision in the supplemented group as compared to the unsupplemented group at either short (12 months) or long term

(39 months, Auestad et al., 2003). In the study reporting data both at short and long term (Auestad et al., 1997; Auestad et al., 2003), power calculations were not performed. The Panel notes that the doses of DHA (and ARA) used in these studies were significantly lower than those proposed by the applicant to obtain the claimed effect.

Carlson et al. (1996) studied term infants randomly assigned either to a standard formula (n = 20) or to the same formula (n = 19) containing egg yolk lecithin to provide 0.1% DHA and 0.43% ARA. A third group of infants breastfed for \geq three months served as non-randomised controls (n = 19). Grating visual acuity (Teller Acuity Card procedure) was determined at corrected ages of two, four, six, nine and 12 months past term. The breastfed and supplemented formula groups had higher grating visual acuity than the unsupplemented formula group at 2 months of age, but this difference was not sustained at four, six, nine and 12 months of life. The Panel notes the small sample size of the study, and that the dose of DHA used was lower and the ARA:DHA ratio higher than those proposed by the applicant to obtain the claimed effect.

In the study by Makrides et al. (2000), 83 healthy full-term infants were randomly allocated at the age of one week to receive one of three formulae (placebo formula, formula with 0.35 % of total fatty acids as DHA or 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. A total of 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. Breastfed infants had better VEP acuity at 34 weeks of age compared with all formula-fed infants, but not at 16 weeks. The Panel notes that doses of DHA in this study (but not the DHA:ARA ratio) are in the range of those recommended by the applicant to obtain the claimed effect.

The study by Birch et al. (1998) and Hoffman et al. (2000) included 112 infants randomised at the age of five days to consume either a formula with DHA 0.35% alone, a formula with DHA 0.36% plus ARA 0.72%, or a control formula devoid of DHA and ARA for 17 weeks. Separate cohorts were used to assess electroretinography (ERG, 33 subjects) and visual evoked potential (VEP, 79 infants) for ethical reasons (to avoid infant overtesting). An additional group of term infants (n=29) exclusively breastfed for at least the first 17 weeks of life served as non-randomised control group for blood fatty acid and VEP data. Major outcome measures included growth, blood fatty acid analyses (six, 17, 26, 52 weeks), VEPs analyses (six, 17, 26, 52 weeks) in the VEP arm only (Birch et al., 1998), and ERG responses (six, 17 weeks) in the ERG arm only (Hoffman et al., 2000). Sample sizes were based on power calculations considering sweep VEP acuity as primary outcome. Supplementation with infant formula containing either DHA or DHA plus ARA yielded better VEP acuity at six, 17, and 52 weeks of age but not at 26 weeks, when visual acuity development reaches a plateau. Infants receiving either enriched formula had more mature ERG responses at 6 weeks of age. Infants receiving the DHA formula had higher DHA and lower ARA levels in red blood cells (RBCs) compared to infants fed the DHA plus ARA formula. DHA (but not ARA) concentrations in RBCs at 17 weeks significantly correlated with visual function at 52 weeks in both studies. Fifty-two out of the 79 infants randomised to the VEP arm were re-evaluated at 4 years of age for visual acuity (Birch et al., 2007), which yielded significantly greater visual acuity in both the DHA and DHA plus ARA supplemented formula groups (with no significant differences between them) compared to the unsupplemented formula group. None of the supplemented formula groups had better visual acuity than the reference human milk-fed group. The Panel notes that doses of DHA in

this study are in the range of those proposed by the applicant in the conditions of use to obtain the claimed effect.

The study by Birch et al. (2005) included a total of 103 healthy term infants double-blind randomised at the age of five days to receive either a control formula devoid of DHA and ARA or a formula supplemented with DHA and ARA (0.36 and 0.72 % of total fatty acids, respectively) for the first year of life. Sample sizes were based on power calculations considering sweep VEP acuity as primary outcome. Sweep VEP acuity was assessed at six, 17, 39 and 52 weeks. Random dot stereo-acuity, blood lipid profiles, growth and tolerance were secondary outcomes. A total of 42 (DHA and ARA supplemented group) and 44 (control) infants completed the trial. VEP acuity was significantly better in the DHA and ARA group than in controls at all ages tested, while stereo-acuity 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, and significantly correlated with visual acuity at all ages tested. There were no differences in growth between groups. The Panel notes that doses of DHA in this study are in the range of those recommended by the applicant to obtain the claimed effect.

The Panel notes that none of the studies presented has shown a benefit of either DHA alone or DHA plus ARA on visual development as compared to the breast-fed control group, that no studies have observed an additional benefit of DHA plus ARA supplementation over DHA alone on visual acuity in term infants, and that direct associations only between markers of DHA (but not ARA) status and visual outcomes have consistently been reported.

Taking into account the studies above, the Panel considers that the consumption of infant formulae supplemented with DHA at around 0.36% of total fatty acids from birth up to 12 months is associated with better visual function in term infants as compared to the consumption of unsupplemented formulae (Birch et al., 1998; Hoffman et al., 2000; Birch et al., 2007; Birch et al., 2005), even if a dose-response relationship has not been directly tested and not all the studies performed at the recommended dose reach the same conclusion (Makrides et al., 2000).

RCTs in term infants with randomisation after weaning

Birch et al. (2002) investigated the effects of post-weaning dietary supplementation with DHA and ARA on visual maturation at 17, 26, and 52 weeks of age in term infants that were breast fed from birth until 6 weeks of life. A total of 65 infants were randomly (block randomisation schedule) assigned to consume either a standard commercial infant formula (controls, n = 32) or the same formula supplemented with 0.36% and 0.72% of total fatty acids as DHA and ARA respectively (intervention, n = 33) until the age of 52 weeks. Sample sizes were based on power calculations considering sweep VEP acuity as primary outcome. Infants who were weaned to formula containing DHA plus ARA had significantly better visual acuity at 17, 26, and 52 weeks of age and significantly better stereo-acuity at 17 weeks of age than did infants who were weaned to the unsupplemented formula. Better visual acuity and stereo-acuity at 17 weeks was correlated with higher concentrations of DHA in plasma. Better visual acuity at 52 weeks was correlated with higher concentrations of DHA in plasma and RBC. No significant effects of diet on growth were found.

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 four-six 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/six 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.

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 one 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 one year. Breast-feeding continued in both groups up to an age of about nine 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 notes that the three studies above (Birch et al., 2002; Hoffman et al., 2003 and 2004) were conducted using doses of either DHA or DHA and ARA in the range proposed by the applicant to obtain the claimed effect, had power calculations performed considering sweep VEP acuity as primary outcome, find better visual acuity up to 12 months in infants fed supplemented formulae/weaning foods as compared to the unsupplemented group and report direct associations between markers of DHA (but not ARA) status and visual outcomes.

One pooled analysis (Morale et al., 2005) including data from 4 of the RCTs described in the two sections above (Birch et al., 1998; Birch et al., 2002, Birch et al., 2005; Hoffman et al., 2003) and including a total of 243 infants found a positive correlation between the duration of intake of either human milk or DHA and ARA via formulae (containing 0.36% DHA and 0.72% ARA) and better sweep VEP acuity at 52 weeks of age.

No studies have been presented investigating the effects of DHA and ARA supplementation on visual function starting at six months of age in infants receiving unsupplemented formula from birth

Taking into consideration both the studies with randomisation at birth and the studies with randomisation post-weaning, the Panel notes that supplementation with either DHA alone or with DHA plus ARA has shown no benefit on the visual development of term infants as compared to breast-feeding. The Panel also notes that no studies investigating the effects of both DHA and DHA plus ARA supplementation have observed an additional benefit of DHA plus ARA supplementation over DHA alone on visual acuity in term infants, and that direct associations between markers of DHA (but not ARA) status and visual outcomes have been

consistently reported. The Panel considers that a role of ARA on visual development of term infants cannot be established on the basis of the data presented.

No studies have been presented investigating the effects of DHA and ARA supplementation on visual function in infants starting the supplemented formula after a period of unsupplemented formula feeding (EFSA, 2008).

The Panel concludes that a cause and effect relationship has been established between the intake of infant and follow-on formula supplemented with DHA at levels around 0.3% of total fatty acids and visual function at 12 months in formula-fed infants born at term from birth up to 12 months and in breastfed infants after weaning up to 12 months.

The Panel could have not reached this conclusion without considering the studies claimed by the applicant as proprietary (Birch et al., 2000; Birch et al., 2007; Hoffman et al., 2000; Birch et al., 1998; Birch et al., 2005; Birch et al., 2002; Hoffman et al., 2003)

2.4 Panel's comments on the proposed wording

Taking into account the scientific evidence presented, the Panel considers that the following wording reflects the scientific evidence:

“DHA contributes to the visual development of infants”.

2.5 Conditions and restrictions of use

The Panel considers that, in order to bear the claim, a formula should contain at least 0.3% of the total fatty acids as docosahexaenoic acid. Such amounts can be easily consumed as part of a balanced diet. The target population is infants (formula-fed infants from birth up to 12 months and breastfed infants after weaning up to 12 months).

CONCLUSIONS AND RECOMMENDATIONS

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

- The food constituents DHA and ARA are sufficiently characterised.
- The claimed effect is the contribution to the optimal visual development of infants and young children. The target population proposed by the applicant is infants and young children (from birth to three years of age). Normal visual function is beneficial for infants' and children' development and health.
- A cause and effect relationship has been established between the intake of infant and follow-on formula supplemented with DHA and visual function at 12 months in formula-fed infants born at term from birth up to 12 months and in breastfed infants after weaning up to 12 months.
- The following wording reflects the scientific evidence: “DHA contributes to the visual development of infants”.
- In order to bear the claim a formula should contain at least 0.3% of the total fatty acids as docosahexaenoic acid. Such amounts can be easily consumed as part of a balanced diet.
- The target population is infants (formula-fed infants born at term from birth up to 12 months and breastfed infants after weaning up to 12 months).

DOCUMENTATION PROVIDED TO EFSA

Health claim application on DHA and ARA and visual development pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0130a-FR). October 2008. Submitted by Mead Johnson Nutritionals.

REFERENCES

- Auestad N, Montalvo MB, Hall RT, Fitzgerald KM, Wheeler RE, Connor WE, Neuringer M, Connor SL, Taylor JA, Hartmann EE, 1997. Visual acuity, erythrocyte fatty acid composition, and growth in term infants fed formulae with long chain polyunsaturated fatty acids for one year. *Pediatr. Res.* 41,1-10.
- Auestad N, Halter R, Hall RT, Blatter M, Bogle ML, Burks W, Erickson JR, Fitzgerald KM, Dobson V, Innis SM, Singer LT, Montalto MB, Jacobs JR, Qiu W, Bornstein MH, 2001. Growth and development in term infants fed long-chain polyunsaturated fatty acids: a double-masked, randomized, parallel, prospective, multivariate study. *Pediatrics* 108, 372-381.
- Auestad N, Scott DT, Janowsky JS, Jacobsen C, Carroll RE, Montalto MB, Halter R, Qiu W, Jacobs JR, Connor WE, Connor SL, Taylor JA, Neuringer M, Fitzgerald KM, Hall RT, 2003. Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulae containing long-chain polyunsaturated fatty acids to 1 year of age. *Pediatrics* 112, e177-e183.
- Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C, 1998. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. *Pediatr. Res.* 44, 201-209.
- Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG, 2000. A randomized trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev. Med. Child Neurol.* 42, 174-181.
- Birch EE, Hoffman DR, Castaneda YS, Fawcett SL, Birch DG, Uauy R, 2002. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. *Am. J. Clin. Nutr.* 75, 570-580.
- Birch EE, Castaneda YS, Wheaton DH, et al. 2005. Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. *Am. J. Clin. Nutr.* 81, 871-879.
- Birch EE, Garfield S, Castaneda Y, Birch DG, Uauy R, Hoffman DR, 2007. Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Human Dev.* 83, 279-284
- Carlson SE, Ford AJ, Werkman SH, Peeples JM, Koo WW, 1996. Visual acuity and fatty acid status of term infants fed human milk and formulae with and without docosahexaenoate and arachidonate from egg yolk lecithin. *Pediatr. Res.* 39, 882-888.
- EFSA (European Food Safety Authority), 2008. Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from Martek Biosciences Corporation 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 EFSA Journal* (2008) 794, 1-14

- Hoffman DR, Birch EE, Birch DG, Uauy R, Castaneda Y, Lapus MG, Wheaton DH, 2000. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. *J. Pediatr. Gastroenterol. Nutr.* 31, 540-553
- Hoffman DR, Birch EE, Castaneda YS, Fawcett SL, Wheaton DH, Birch DG, Uauy R, 2003. Visual function in breast-fed term infants weaned to formula with or without long-chain polyunsaturated at 4 to 6 months: a randomized clinical trial. *J. Pediatr.* 142, 669-677.
- Hoffman DR, Theuer R, Castaneda YS, Wheaton DH, Bosworth RG, O'Connor AR, Morale SE, Wiedemann LE, Birch EE, 2004. Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk. *J. Nutr.* 134, 2307-2313.
- Makrides M, Neumann MS, Simmer K and Gibson RA, 2000. A critical appraisal of the role of dietary long-chain polyunsaturated fatty acids on neural indices of term infants: a randomized, controlled trial. *Pediatrics* 105, 32-38
- Morale SE, Hoffman DR, Castaneda YS, Wheaton DH, Burns RA, Birch EE, 2005. Duration of long-chain polyunsaturated fatty acids availability in the diet and visual acuity. *Early Human Development* 81, 197-203
- Sangiovanni JP, Parra-Cabrera S, Colditz GA, Berkey CS, Dwyer JT, 2000. Meta-analysis of dietary essential fatty acids and long-chain polyunsaturated fatty acids as they relate to visual resolution acuity in healthy preterm infants. *Pediatrics* 105, 1292-1298.
- Simmer K, Patole SK, Rao SC, 2008. Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD000376. DOI: 10.1002/14651858.CD000376.pub2.
- Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE, 2003. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *J. Pediatr.* 143, S17-S25.

GLOSSARY / ABBREVIATIONS

ARA	Arachidonic acid
DHA	Docosahexaenoic acid
RBCs	Red blood cells
RCTs	Randomised controlled trials
VEP	Visual evoked potential