European Food Safety Authority

The EFSA Journal (2009) 1000, 1-13

SCIENTIFIC OPINION

DHA and ARA and brain development

Scientific substantiation of a health claim related to docosahexaenoic acid (DHA) and arachidonic acid (ARA) and brain development pursuant to Article14 of Regulation (EC) No 1924/2006[1]

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

(Question No EFSA-Q-2008-212)

Adopted on 13 March 2009

PANEL MEMBERS

Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

SUMMARY

Following an application from Mead Johnson & Company 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 brain 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 brain 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 contribution to the normal development of the brain is beneficial for infants' and children's development and health.

The applicant identified a total 33 publications as being pertinent to the health claim for humans. A total of 13 full publications which report original data from RCTs on the effects of

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from Mead Johnson & Company on DHA and ARA and brain development. *The EFSA Journal* (2009) 1000, 1-13

DHA supplementation (with or without ARA) on brain development in physiologic conditions and in subjects born at term and have been presented, reporting the results from eight study designs. All these studies were conducted in term infant populations fed different formulas from birth through the first months of life up to 12 months at the maximum.

In two RCTs, formulas with less than 0.2% DHA (in various combinations with ARA) from birth through six or 12 months of age had no effect on neurodevelopmental indices measured with different methods as compared to standard, unsupplemented formulas. Two double-blind RCTs investigated the effects of formulas supplemented with DHA around 0.3% either alone or in combination with ARA at around the same level (ARA:DHA ratio = 1) form birth to 6-12 months of life on Bayley's Mental and Psychomotor Developmental Indices (MDI and PDI) at 12 and 24 months or at 18 months of age as compared to unsupplemented formulas. No differences in MDI or PDI scores were observed among the formula-fed groups. In another double-blind RCT, term infants allocated at birth to consume a formula supplemented with 0.15-0.25% DHA and 0.30-0.40% ARA (ARA:DHA ratio = 1.7:1 to 2:1) for four months had significantly more intentional solutions and higher intention scores at 10 months of age than infants who received the unsupplemented formula.

In the remaining three study designs, formulas supplemented with either 0.3 % DHA alone or in combination with ARA in higher dosages (ARA:DHA ratio from 1.4:1 to 2:1) were used in the intervention groups. These doses of DHA and the DHA:ARA ratio are in the range of those recommended by the applicant to obtain the claimed effect.

In the first study, term infants consuming a formula supplemented with 0.30% DHA and 0.44% ARA for four months scored significantly higher in the Brunet-Lézine test than infants in the control (unsupplemented) formula group at four months of age, but these differences were not sustained at 24 months of life. In the second study, healthy term infants consuming a formula supplemented with 0.3% DHA and 0.45% ARA (ARA:DHA ratio = 1.5) for two months had mildly abnormal GMs significantly less often than did infants receiving the unsupplemented formula. No differences between groups were found in clinical neurological condition, neurological optimality score, fluency score, or the Bayley's MDI or PDI at 18 months of life. The third study included 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. Infants supplemented with DHA and ARA yielded significantly higher MDI scores at 18 months than infants in the control group. No significant differences between groups were observed among the three groups regarding the PDI or the Behaviour Rating Scale. Infants were tested at four years of age for Intelligence Quotient (IQ). Verbal IQ in the control and DHA-supplemented formula groups was significantly lower than in the DHA plus ARA group. No differences were observed among groups regarding the full scale IQ or the performance IQ.

The Panel notes that none of the studies using formulas supplemented with doses of DHA and ARA lower than proposed in the conditions of use or 0.3% DHA and an ARA:DHA ratio of one show an effect of DHA and ARA supplementation on neurodevelopment indices infants as compared to unsupplemented formulas. The Panel also notes that the four studies using either slightly lower DHA doses or about 0.3% DHA and the ARA:DHA ratio proposed in the conditions of use (between 1.4:1 and 2:1) show a short-tem beneficial effect of DHA and ARA supplementation on different measures of neurodevelopment. However, the different testing ages and the use of different tests for assessment limit the comparability of the studies. Also, the predictive value of the neurodevelopment tests used is uncertain. Indeed, only two of the studies above show an effect beyond the supplementation period, and only one reports a sustained effect beyond the first year of life in a limited sample of subjects. In no case the

breastfed reference group showed lower developmental indices when compared to any formula-fed group.

On the basis of the data presented, the Panel concludes that the data presented are insufficient to establish a cause an effect relationship between the intake of infant and follow-on formula supplemented with DHA at levels around 0.3% of the fatty acids and a ratio ARA:DHA between 1.4:1 and 2:1 and the contribution to normal brain development in infants and young children from birth to three years of age.

Key words: Docosahexaenoic acid, arachidonic acid, brain development, infants, 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 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 completeness[3] 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 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 docosahexaenoic acid and arachidonic acid and brain 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 brain 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

The European Food Safety Authority wishes to thank Carlo Agostoni and the members of the Working Group for the preparation of this opinion: Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Hannu Korhonen, Ambroise Martin, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

1. Information provided by the applicant

Applicant's name and address: Mead Johnson & Company 3 rue Joseph Monier-BP 325, 92506 Rueil-Malmaison Cedex, France.

The application includes a request for the protection of 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 for brain development.

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

DHA and ARA contribute to the optimal brain 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 for which complete specifications, manufacturing process, bioavailability and stability information have been provided. DHA is derived from the alga *Crypthecodinium 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 sources with appropriate bioavailability 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 brain 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 contribution to the normal development of the brain is beneficial for infants' and children's 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 (RCTs) on the effects of formulae intended for infants and young children (from birth to 36 months) containing DHA and ARA on brain and cognitive development (as primary or secondary outcome) with the following search terms: DHA, ARA, infant, brain, cognitive, mental, long-chain polyunsaturated fatty acids, fatty acids, omega 3, omega 6, toddler milk and all combinations of terms. 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 33 publications as being pertinent to the health claim for humans (13 RCTs, one meta-analysis of RCTs, one observational cohort study, three postmortem studies, six reviews, seven expert recommendations and two abstracts containing unpublished data).

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 brain development in physiologic conditions are not suitable sources of data to support the claimed effect. The Panel also considers that the results of the meta-analysis presented assessing the effects of long-chain polyunsaturated fatty acid supplementation on developmental outcomes in term infants cannot be directly extrapolated for the substantiation of the claimed effect as the inclusion criteria used for trial selection do not match the conditions of use proposed by the applicant in the present application (Simmer et al., 2008).

A total of 13 full publications (Agostoni et al, 1995; Agostoni et al. 1997; Auestad et al., 2001; Auestad et al., 2003; Ben et al., 2004; Birch et al., 2000, proprietary data; Birch et al., 2007, proprietary data; Bouwstra et al., 2003; Bouwstra et al., 2005; Lucas et al., 1999 ; Makrides et al., 2000; Willatts et al. 1998a and 1998b) which report original data from RCTs on the effects of DHA supplementation (with or without ARA) on brain development in physiologic conditions and in subjects born at term and have been presented by the applicant.

The 13 publications above include long term observations on subjects supplemented in the first months of life (Agostoni et al., 1997; Auestad et al., 2003; Bouwstra et al., 2005; Birch et al., 2007) while one publication reports complementary observations on neurodevelopmental outcomes (Willatts et al., 1998b). Therefore, the results from eight original study designs are available. All these studies were conducted in term infant populations fed different formulas from birth through the first months of life up to 12 months at the maximum (Agostoni et al., 1995; Auestad et al., 2001; Ben et al., 2004; Birch et al., 2000; Bouwstra et al., 2003; Lucas et al., 1999; Makrides et al., 2000; Willatts et al., 1998a).

In two RCTs (Auestad et al, 2001; Ben et al, 2004), formulas with less than 0.2% DHA (in various combinations with ARA) from birth through six (Ben et al., 2004) or 12 months of age (Auestad et al., 2001; Auestad et al., 2003, follow-up) had no effect on neurodevelopmental indices measured with different methods as compared to standard, unsupplemented formulas. Only in one study the power calculations were reported (Auestad et al., 2001). The Panel notes that the doses of DHA (and ARA) used in these studies were lower than those proposed by the applicant to obtain the claimed effect.

Two publications report the results of double-blind RCTs investigating the effects of formulas supplemented with DHA around 0.3% either alone or in combination with ARA at around the same level (ARA:DHA ratio = 1) form birth to 6-12 months of life as compared to unsupplemented formulas (Lucas et al., 1999; Makrides et al., 2000). In the study by Lucas et al. (1999), 309 healthy term infants were randomly allocated at birth to receive either a DHA and ARA supplemented formula (n = 154) or a control (unsupplemented) formula (n = 155) for

six months. Breastfed infants for at least six weeks served as reference group (n = 138). Sample sizes were based on power calculations considering the Bayley's Mental and Psychomotor Developmental Indices (MDI, PDI) of infant development as primary outcomes. A total of 125, 125, and 104 infants in the intervention, control and reference groups were evaluated at 18 months for Bayley's MDI and PDI. No significant differences were observed at 18 months between the intervention and the control group, or between the formula-fed vs the breastfed groups, on either cognitive or motor development after adjustment for confunders. 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. A total of 61 infants could be investigated at 1 and 2 years of age. From a control group of 63 breast-fed infants, 46 completed the trial until two years of age. Sample sizes were based on power calculations considering sweep VEP acuity (and not Bayley's MDI and/or PDI scales) as primary outcome. No differences were observed between the three formula-fed groups at one or two years of age on Bayley's MDI or PDI. Breastfed infants had higher MDI scores than formula-fed infants at two years of age even after adjusting for environmental variables. The Panel notes that doses of DHA in these studies (but not the DHA:ARA ratio) are in the range of those recommended by the applicant to obtain the claimed effect.

In the double-blind RCT by Willatts et al. (1998a), 44 term infants were randomly allocated at birth to consume either a formula supplemented with 0.15-0.25% DHA and 0.30-0.40% ARA (ARA:DHA ratio = 1.7:1 to 2:1, n = 21) or a standard (control, n = 23) unsupplemented formula for four months in order to investigate the effects of DHA and ARA supplementation on infant cognitive behaviour at 10 months of age by a means-end problem-solving test. A sample size of 24 subjects per group was calculated as being required to detect a difference of one intentional solution on the entire three-step problem with a power of 90% at P=0.05. Infants who received the DHA and ARA supplemented formula had significantly more intentional solutions and higher intention scores than infants who received the unsupplemented formula. The means-end problem-solving test is currently used to explore the function of specific associative areas in the prefrontal lobes, which are particularly rich in DHA. Significantly higher DHA content in these brain areas has been observed in breastfed infants vs (unsupplemented) formula-fed infants at four months of life in autoptic studies ("cot" death) presented by the applicant in the section of biological plausibility (Farquharson et al., 1993; Makrides et al., 1994). In anoher publication on the same infant population (Willatts et al., 1998b), a post-hoc analysis comparing infants with evidence of reduced growth parameters at birth and impaired attention control as manifested by a late peak fixation during infant habituation assessment at three months versus infants with early peak fixation within the supplemented (n = 11 vs n = 9, respectively) and the unsupplemented (n = 10 n = 10, respectively) formula groups showed that the number of solutions in the means-end problem-solving ability at nine months was significantly reduced in the late peak-fixation infants receiving the unsupplemented formula as compared to the other three groups. The Panel notes the small sample size on each of the groups and that the hypothesis tested in this post-hoc analysis falls beyond the primary outcome (number of solutions at the means-end problem solving test) for which the sample size required was initially identified (Willatts et al., 1998a). The Panel also notes that doses of DHA (but not the DHA:ARA ratio) reported in these studies were lower than those recommended by the applicant to obtain the claimed effect.

In the remaining three study designs (Agostoni et al, 1995; Bouwstra et al., 2003; Birch et al., 2000) formulas supplemented with either 0.3 % DHA alone or in combination with ARA in higher dosages (ARA:DHA ratio from 1.4:1 to 2:1) were used in the intervention groups. The

Panel also notes these doses of DHA and the DHA:ARA ratio are in the range of those recommended by the applicant to obtain the claimed effect.

In the double-blind RCT by Agostoni et al. (1995), healthy term infants were randomised at birth to consume either a formula supplemented with 0.30% DHA and 0.44% ARA (ARA:DHA ratio = 1.4:1, n = 29) or a control (unsupplemented) formula (n = 31) for four months. An exclusively breastfed group (n = 31) served as reference. Global neurodevelopmental performance was assessed by means of the Brunet-Lézine test as Developmental Quotient (DQ) at 4 months. A sample size of 24 subjects per group was calculated as being required to detect a clinically significant difference on DQ (10%) between groups with a power of 90% at P=0.05. Infants in the supplemented formula and in the breastfed groups scored significantly higher in the Brunet-Lézine test than infants in the control group at four months of age. No differences were observed between the supplemented formula and the breastfed groups. Differences between the formula-fed groups were not sustained when infants were re-evaluated with the Brunet-Lézine test at 24 months of life (Agostoni et al., 1997). The Panel notes that the Brunet-Lézine test (as well as the Griffith's scale and the Bayley's indices) ultimately derives from the Gesell's developmental schedules published in 1947 (Gesell and Amatruda, 1947), which were originary developed for the definition of mental handicap and not for the scoring of attitudes generally indicated as "intelligence" within the "normal" population of infants and children, in which their predictive value is doubtful.

In the double-blind RCT by Bouwstra et al. (2003), healthy term infants were randomised at birth to consume either a formula supplemented with 0.3% DHA and 0.45% ARA (ARA:DHA ratio = 1.5:1, n = 119) or a control (unsupplemented) formula (n = 131) for two months. A breastfed group (n = 147), of which 73 infants stopped breasfeeding before the 2-month intervention and were subsequently assigned to the supplemented formula, served as reference. The quality of general movements (GMs) based on the observations of videotapes recording the infants' movements was assessed 3 months of age. The quality of GMs was classified as normal-optimal, normal-suboptimal and midly abnormal. This test appears to have a predictive value for the neurological development (not intelligence) later in life. No power calculations are reported. Infants in the control group had mildly abnormal GMs significantly more often than did infants in the supplemented formula and breastfed groups (31% compared with 19% and 20%, respectively). Infants in the breastfed group had normal-optimal GMs more frequently than did infants in the supplemented formula and control groups (34% compared with 18% and 21%, respectively). No differences between the supplemented formula, the control formula and the breastfeed groups were found in clinical neurological condition, neurological optimality score, fluency score, or the Bayley's MDI or PDI when the infants were re-tested at 18 months of life (Bouwstra et al., 2005).

The double-blind RCT by Birch 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. 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. A sample size of 16 subjects per group was calculated as being required to detect mean differences in the MDI of the Bayley scales of 1SD or greater at 18 months between groups. At that age, 20 subjects in the control formula group, 17 in the DHA-supplemented formula group and 19 in the DHA plus ARA formula groups were tested with the Bayley scales of infant development. Infants supplemented with DHA and ARA yielded significantly higher MDI scores (mean = 7 points) than infants in the control group. Both the cognitive and motor subscales of the MDI showed a significant developmental age advantage for the groups supplemented with DHA and with DHA plus ARA as compared to controls. No significant differences between groups were observed among the three groups regarding the PDI or the Behaviour Rating Scale. Significant correlations were observed between DHA

concentrations in red blood cells (but not between ARA, linoleic acid, α-linolenic acid or eicosapentaenoic acid) at four months (but not at 12 months) and the MDI scores at 18 months of age. Infants in the formula-fed and breastfed groups were tested at four years of age for Intelligence Quotient (IQ). Verbal IQ in the control and DHA-supplemented formula groups was significantly lower than in the DHA plus ARA and the breastfed groups. No differences were observed among all four groups regarding the full scale IQ or the performance IQ (Birch et al., 2007).

The Panel notes that none of the studies using formulas supplemented with doses of DHA and ARA lower than proposed in the conditions of use or 0.3% DHA and an ARA:DHA ratio of one show an effect of DHA and ARA supplementation on neurodevelopment indices infants as compared to unsupplemented formulas (Auestad et al., 2001; Auestad et al., 2003; Ben et al., 2004; Lucas et al., 1999; Makrides et al., 2000). The Panel also notes that the four studies using either slightly lower DHA doses (Willatts et al., 1998a) or about 0.3% DHA (Agostoni et al, 1995; Birch et al, 2000; Bouwstra et al., 2003) and the ARA:DHA ratio proposed in the conditions of use (between 1.4:1 and 2:1) show a short-tem beneficial effect of DHA and ARA supplementation on different measures of neurodevelopment. However, the different testing ages and the use of different tests for assessment limit the comparability of the studies. Also, the predictive value of the neurodevelopment tests used is uncertain. Indeed, only two of the studies above show an effect beyond the supplementation period (Willatts et al., 1998a; Birch et al., 2007), and only one reports a sustained effect beyond the first year of life in a limited sample of subjects (Birch et al., 2007). In no case the breastfed reference group showed lower developmental indices when compared to any formula-fed group.

Although the Panel acknowledges that there is some evidence supporting a short-tem effect of DHA and ARA supplementation starting at birth on brain development in non-breastfed infants, the Panel considers that the data available is inconsistent and does not support an effect beyond the supplementation period or beyond the first year of life.

The Panel concludes that the data presented are insufficient to establish a cause an effect relationship between the intake of infant and follow-on formula supplemented with DHA at levels around 0.3% of the fatty acids and a ratio ARA:DHA between 1.4:1 and 2:1 and the contribution to normal brain development in infants and young children from birth to three years of age.

CONCLUSIONS

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

- The food constituents DHA and ARA are sufficiently characterised.
- The claimed effects is the contribution to the optimal brain 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). Contribution to the normal development of the brain is beneficial for infants' and children's development and health.
- The data presented are insufficient to establish a cause an effect relationship between the intake of infant and follow-on formula supplemented with DHA at levels around 0.3% of the fatty acids and a ratio ARA:DHA between 1.4:1 and 2:1 and the contribution to normal brain development in infants and young children (from birth to three years of age).

DOCUMENTATION PROVIDED TO EFSA

Health claim application on DHA and ARA and brain development pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No:0131a-FR). October 2008. Submitted by Mead Johnson & Company.

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GLOSSARY / ABBREVIATIONS

ARA	Arachidonic acid
DHA	Docosahexaenoic acid
GMs	General movements
DQ	Developmental Quotient
IQ	Intelligence Quotient
MDI	Mental Developmental Index
PDI	Psychomotor Developmental Index
RCTs	Randomised controlled trials