European Food Safety Authority

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SCIENTIFIC OPINION

I omega kids®/Pufan 3 kids® and concentration

Scientific substantiation of a health claim related to I omega kids®/Pufan 3 kids® and concentration 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-2008-094 and Question No EFSA-Q-2008-099)

Adopted on 24 October 2008 by written procedure

PANEL MEMBERS

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SUMMARY

Following two applications from Pharma Consulting & Industries submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to: I omega kids®/Pufan 3 kids® and concentration.

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

The foods that are the subject of the health claim are I omega kids® and Pufan 3 kids®, which contain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as active ingredients. The long-chain n-3 polyunsaturated fatty acids EPA and DHA are recognised nutrients and are measureable in foods by established methods. They are well absorbed when consumed in the form of triglycerides. This evaluation will apply to all appropriate sources of EPA and DHA in the specified amounts. The Panel considers that DHA and EPA are sufficiently characterised.

The claimed effect is to promote concentration. The target population for the health claim is children aged one year to 12 years and older. Concentration can be interpreted as attention, which is a well defined psychological construct. The Panel considers that promoting attention is beneficial to children's health.

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from Pharma Consulting & Industries related to the scientific substantiation of a health claim on I omega kids®/Pufan 3 kids® and concentration. *The EFSA Journal* (2008) 846, 1-10

The evidence presented to support the claim that consumption of EPA and DHA promotes concentration in children is based on six intervention studies which used a variety of markers/endpoints and were of variable quality. Results arising from these five placebo-controlled, double-blind and one single-arm studies can be described as conflicting. Two of the studies reported no improvement on primary analysis of a plethora of outcome measures after supplementation with n-3 long-chain polyunsaturated fatty acids. Differences between the active groups and placebo in the limited number of the total outcome measures that were significant in the remaining studies indicate that the beneficial effects of supplementation are modest. These interventions also suffer from small numbers of subjects, have used varying doses and ratios of EPA and DHA (and other polyunsaturated fatty acids) in the formulations for supplementation, were performed largely in children with clinically diagnosed or suspected attention deficit hyperactivity disorder (ADHD), with ADHD-related disorders, or with developmental coordination disorder, some of whom were on medication for these disorders, and used a large number of endpoints, some of which (for example, aggression and ADHD index) would be difficult to reconcile as direct relevant measures of attention.

On the basis of the data presented, the Panel considers that a cause and effect relationship has not been established between the consumption of DHA and EPA and promotion of concentration (interpreted as attention) in children aged one year to 12 years and older.

Key words: EPA, DHA, concentration, attention, 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 applications were received on 25/01/2008.
- The scope of the applications was proposed to fall under claims referring to children's development and health.
- During the check for completeness[3] of the applications, the applicant was requested to provide missing information on 07/02/2008 and on 03/04/2008.
- The applicant provided the missing information on 23/03/2008 and on 06/06/2008.
- The scientific evaluation procedure started on 15/06/2008.
- On 24/10/2008 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 I omega kids®/Pufan 3 kids® and concentration.

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: I omega kids®/Pufan 3 kids® and concentration.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of I omega kids® and Pufan 3 kids®, a positive assessment of its safety, nor a decision on whether I omega kids® and Pufan 3 kids® 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.

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

[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"

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: Pharma Consulting & Industries, Vlaschaard 2, 4529 PR Eede (Sluis), The Netherlands.

1.1. Food/constituent as stated by the applicant

I omega kids®/Pufan 3 kids®

1.2. Health relationship as claimed by the applicant

I omega kids®/Pufan 3 kids® contain fish oil which provide the necessary EPA and DHA and help to promote concentration.

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

Help to promote concentration

1.4 Specific conditions of use as proposed by the applicant

I omega kids®/Pufan 3 kids® contain fish oil with eicosapentaenoic acid (EPA as triglycerides) 18%, docosahexaenoic acid (DHA as triglycerides) 12% (EPA/DHA ratio 1.5/1), and D alpha tocopherol (Vitamin E) 0.65%. Tutti-frutti flavour. The doses recommended by the applicant are: a) children from 1 year old: 2.5 mL per day or as recommended by the physician, b) children from 12 years old: 15 mL per day.

2. Assessment

2.1. Characterisation of the food/constituent

The foods that are the subject of the health claim are I omega kids® and Pufan 3 kids®, which contain docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) as active ingredients.

The long-chain n-3 polyunsaturated fatty acids EPA and DHA are recognised nutrients and are measureable in foods by established methods. They are well absorbed when consumed in the form of triglycerides.

The applicant manufactures flavoured fish oil rich in EPA and DHA for which specifications, description of the manufacturing process and stability information are provided. The scientific evidence provided by the applicant to substantiate the health claim has been obtained using EPA and DHA from a variety of sources and not exclusively from the product manufactured by the applicant. This evaluation will apply to all appropriate sources of EPA and DHA in the specified amounts.

The Panel considers that DHA and EPA are sufficiently characterised.

2.2. Relevance of the claimed effect to human health

The claimed effect is to help to promote concentration. The target population for the health claim is children aged one year to 12 years and older.

Although "concentration" has not been defined by the applicant, the applicant has referred to studies which have considered a range of psychological constructs some of which can be measured with a questionnaire and could be considered as markers for attention, which is a well defined psychological construct.

The Panel considers that promoting attention is beneficial to children's health.

2.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Web of Science and Pubmed using the terms children, omega 3, highly unsaturated fatty acids (HUFA), EPA, DHA, attention deficit hyperactivity disorder (ADHD), infants, childhood, long-chain polyunsaturated fatty acids (LCPUFA), essential fatty acids, fish oil, attention, behaviour, behavioural problems, and learning difficulties in all possible combinations. Search dates are not reported. The applicant indicated that all human intervention trials and observational studies were reviewed and that non-human studies were not considered. A total of 19 publications were identified by the applicant, 6 of which were excluded. The 13 pertinent publications identified by the applicant were 6 intervention studies, one meta-analysis, three systematic reviews, and three other review publications. The Panel notes that the search strategy used does not contain a decision tree and it is unclear how the applicant identified the publications considered pertinent to the claim.

The evidence presented to support the claim that EPA and DHA promote concentration in children is based on six intervention studies in children which used a variety of markers/endpoints and were of variable quality. The markers/endpoints identified were changes in aggression, conduct disorder, inattention/cognitive problems, hyperactivity, oppositional/defiant behaviour, ADHD index, anxious/shy, restless/impulsive, reading, and spelling.

Two of the interventions report negative findings (Hirayama *et al.*, 2004; Voigt *et al.*, 2001). In the placebo-controlled, double-blind intervention study (Hirayama *et al*., 2004) conducted in Japan, there was no improvement in the performance of those children (n=20) who received foods containing DHA-rich fish oil (estimated intake of 3.6g DHA/week) compared with children in the placebo group (n=20) who received control foods containing olive oil for 8 weeks. The children, aged 6-12 years, suffered from ADHD (clinically diagnosed or suspected), were mostly without medication, and the endpoints which showed no improvements were ADHD-related symptoms according to DSM-IV criteria, aggression assessed by both parents and teachers, visual perception; visual and auditory short-term memory, development of visual-motor integration, continuous performance, and impatience. In the placebo-controlled, double-blind intervention study (Voigt *et al*., 2001) conducted in the United States, there was no improvement in performance of those children (n=32 at randomisation) who received algal-derived triglyceride capsules providing 0.345g DHA/day compared with children in the placebo group (n=31 at randomisation) who received a placebo capsule for 16 weeks. Children were aged 6-12 years, with diagnosis of ADHD, and were being treated successfully with stimulant medication. The endpoints which showed no improvement were scores on laboratory measures of inattention and impulsivity (test of variables of attention, children's colour trails test) while not taking stimulant medication, scores on the Conners Parents Rating Scale (CPRS) and scores on the child behaviour checklist (CBC).

Of the four remaining studies that were cited, one (Sorgi *et al*., 2007) was a small, one-arm study where 9 children aged 8-16 years were given 16.2g of EPA (10.8g) plus DHA (5.4g) concentrates/day (dosages adjusted dependent on arachidonic acid (ARA) to EPA ratio at week 4) and continued for 8 weeks. There were significant improvements in all categories of the ADHD Symptom Checklist IV and the CPRS. The Panel notes that the absence of a control group and the small sample size preclude any conclusions being drawn from this study.

The other three interventions (Richardson and Puri, 2002; Richardson and Montgomery, 2005; Sinn and Bryan, 2007) cited by the applicant reported improvements in some of the markers/endpoints measured.

In the Northern Ireland placebo-controlled double-blind study (Richardson and Puri, 2002), a range of behavioural and learning problems associated with ADHD was assessed in children (n=32 on randomisation) who received capsules containing 0.186g EPA, 0.480g DHA together with a mix of other n-6 polyunsaturated fatty acids (0.096g gamma-linolenic acid, (GLA); 0.864g linoleic acid (LA); 0.042g ARA/day) or in children (n=19 at randomisation) who received control capsules containing olive oil for 12 weeks. The children, aged 8-12 years, who had learning difficulties, coordination disorder and also exhibited ADHD-like features, were assessed using the CPRS. The endpoints which showed significant improvement in the active treatment group compared with placebo were two out of 7 CPRS subscales (cognitive problems; anxious/shy) and one out of 7 CPRS global scales (Conners Index). The Panel notes that the small sample size, the relatively low number of significant endpoints compared to the total tested, the small size of the effects, the uncertain relevance of these tests to the claimed effect and the employment of a clinical sample of children with learning difficulties who exhibited ADHD-like features, and the fact that the intervention was conducted with a mix of n-6 LCPUFA in addition to EPA and DHA, limit the conclusions that can be drawn form this study in relation to the health claim under evaluation.

In the UK Oxford-Durham placebo-controlled, double-blind study (Richardson and Montgomery, 2005), motor function assessed with the Movement Assessment Battery for Children, reading and spelling achievement assessed with the Wechsler Objective Reading Dimensions, and ADHD-related symptoms assessed with the Conners Teachers Rating Scale (CTRS) were assessed in children (n=60 at randomisation) who received capsules containing 80% fish oil and 20% evening primrose oil (daily dose of 0.558g EPA, 0.174g DHA and 0.06g GLA) and in children (n=57 at randomisation) who received control capsules containing olive oil for 12 weeks followed by a one-way cross-over (placebo to active treatment) for an additional 12 weeks. The children, aged 5-12 years, met DSM-IV criteria for developmental coordination disorder (DCD) but were not receiving any treatment for this condition. The endpoints which showed significant improvement in the active treatment group compared with placebo were reading and spelling achievement, 4 out of 6 CTRS subscales (opposition, cognitive problems, hyperactivity, anxious/shy) and all 7 global scales (ADHD index, global restless-impulsive, global emotional lability, global index and DSM-IV inattentive, hyperactivity, total ADHD) with similar improvements observed in the original control group after the one-way cross-over. The Panel notes that the intervention was conducted with GLA in addition to EPA and DHA, and that, although some of the significant end-points might be relevant to the claimed effect, children with DCD cannot be considered representative of the target population for which the claim is intended, thereby limiting the degree to which conclusions can be drawn from this study in relation to the health claim under evaluation.

In the Australia placebo-controlled, double-blind intervention study (Sinn and Bryan, 2007), parent (CPRS) and teacher (CTRS) ratings of ADHD symptoms were assessed in children (n=41 on randomisation) who received capsules containing 80% fish oil and 20% evening primrose oil (daily dose of 0.093g EPA, 0.029g DHA and 0.01g GLA) together with a multivitamin/mineral supplement, in children (n=36 on randomisation) who received capsules containing the PUFA alone, or in children (n=27 on randomisation) who received control capsules containing palm oil for 15 weeks followed by a one-way cross-over (placebo to both active treatments) for further 15 weeks. The children, aged 7-12 years, exhibited ADHD-like features. The endpoints which showed significant improvement in both active groups compared with placebo were two out of 7 CPRS subscales (cognitive problems/inattention, oppositional) and 5 out of 7 global scales (ADHD index, global index, restless-impulsive, DSM-IV inattentive, hyperactive/impulsive), with similar improvements observed in the original control group after the one-way cross-over. None of the 14 CTRS endpoints improved in the active groups compared with placebo or after the one-way cross-over. The Panel notes that the small

sample size, the fact that the intervention was conducted with GLA in addition to EPA and DHA, the small size of the effects, the relatively low number of significant endpoints compared to the total tested, and the uncertain relevance of some of these tests to the claimed effect in children who exhibited ADHD-like features limit the conclusions that can be drawn from this study in relation to the health claim under evaluation.

In summary, results arising from the five placebo-controlled, double-blind studies outlined above can be described as conflicting. Two of the studies (Hirayama *et al*., 2004; Voigt *et al*., 2001) reported no improvement on primary analysis of a plethora of outcome measures after supplementation with n-3 long-chain polyunsaturated fatty acids. Differences between the intervention and placebo groups in the limited number of the total outcome measures that were significant in the other studies indicate that the beneficial effects of supplementation are modest (Richardson and Puri, 2002; Sinn and Bryan, 2007). In the remaining study, the magnitude of the difference between the placebo and active groups is not as large as that suggested by the very small p values reported (Richardson and Montgomery, 2005). Possible reasons for the latter are discussed in a review (Ross *et al.*, 2007), which also states that the effects of intervention with n-3 LCPUFA in children with ADHD are inconclusive. These interventions also suffer from small numbers of subjects, used varying doses and ratios of DHA to EPA (and some included n-6 LCPUFA) in the formulations for supplementation, were performed largely in children with clinically diagnosed or suspected ADHD, with ADHD-related disorders, or with DCD. Some of the children were on medication for these disorders, and some studies used a large number of endpoints, some of which (for example aggression or ADHD index) would be difficult to reconcile as direct relevant measures of attention.

The Panel considers that a cause and effect relationship has not been established between the consumption of DHA and EPA and promotion of concentration (interpreted as attention) in children aged one year to 12 years and older.

CONCLUSIONS

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

- The long-chain n-3 polyunsaturated fatty acids EPA and DHA which are the subject of the health claim are sufficiently characterised.
- The claimed effect is to promote concentration. The target population for the health claim is children aged one year to 12 years and older. Concentration can be interpreted as attention, which is a well defined psychological construct. Promoting attention is beneficial to children's health.
- A cause and effect relationship has not been established between the consumption of DHA and EPA and promotion of concentration (interpreted as attention) in children aged one year to 12 years and older.

DOCUMENTATION PROVIDED TO EFSA

Health claim applications on I omega kids®/Pufan 3 kids® and concentration pursuant to Article 14 of the Regulation (EC) No 1924/2006 (Claim serial No: 0014-NL and 0019-NL). June 2008. Submitted by the Pharma Consulting & Industries.

REFERENCES

Hirayama S, Hamazaki T, Terasawa K, 2004. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder – a placebo-controlled double-blind study. *Eur. J. Clin. Nutr.* 58, 467-473.

Richardson AJ and Puri BK, 2002. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Prog. Neuropsychopharm. Biol. Psychiatry* 26, 233-239.

Richardson AJ and Montgomery P, 2005. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 115, 1360-1366.

Ross BM, Seguin J, Sieswerda LE, 2007. Omega-3 fatty acids as treatment for mental illness: which disorder and which fatty acid? *Lipids Health Dis.* 6, 21

Sinn N and Bryan J, 2007. Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. *J. Dev. Behav. Pediatr*. 28, 82-91.

Sorgi PJ, Hallowell EM, Hutchins HL, Sears B, 2007. Effects of an open-label study with high-dose EPA/DHA concentrates on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder. *Nutr. J.* 6, 16.

Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC, 2001. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J. Pediatr.* 139, 189-196.

GLOSSARY / ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ARA	Arachidonic acid
CBC	Child behaviour checklist
CPRS	Conners Parents Rating Scale
CTRS	Conners Teachers Rating Scale
DCD	Developmental coordination disorder
DHA	Docosahexaenoic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EPA	Eicosapentaenoic acid
HUFA	Highly unsaturated fatty acids
GLA	Gamma-linolenic acid
LA	Linoleic acid
LCPUFA	Long-chain polyunsaturated fatty acids
PUFA	Polyunsaturated fatty acids