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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to beta-palmitate and contribution to softening of stools pursuant to Article 14 of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Specialised Nutrition Europe (formerly IDACE), submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to beta-palmitate and contribution to softening of stools. The food constituent, beta-palmitate, that is the subject of the health claim, is sufficiently characterised. Contribution to softening of stools is a beneficial physiological effect for infants. In weighing the evidence the Panel took into account that, out of two human intervention studies with important methodological limitations, one suggested a stool-softening effect of beta-palmitate whereas the second did not, that one animal study did not support a stool-softening effect of beta-palmitate, and that the evidence provided for a mechanism by which beta-palmitate could contribute to the softening of stools is weak. The Panel concludes that a cause and effect relationship has not been established between the consumption of beta-palmitate and softening of stools.

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KEY WORDS

beta-palmitate, stools, infant formula, health claims

¹ On request from the Competent Authority of France following an application by Specialised Nutrition Europe (formerly IDACE), Question No EFSA-Q-2008-174, adopted on 6 February 2014.

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SUMMARY

Following an application from Specialised Nutrition Europe (formerly IDACE), submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to beta-palmitate and contribution to softening of stools.

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

The food constituent that is the subject of the health claim is beta-palmitate, a structured triglyceride with ≥ 50 % of palmitic acid at the sn-2 (middle or beta) position of the glycerol backbone. The intended use of beta-palmitate is to partially replace conventional triglycerides from vegetable oils in infant formulae to the extent that at least 35 % of the total palmitic acid content, which is assumed to be 20–25 % of total fatty acids, is in the sn-2 position. The Panel considers that beta-palmitate is sufficiently characterised.

The claimed effect proposed by the applicant is “contributes to soften the stools, which helps to increase their frequency”. The target population proposed by the applicant is infants (from birth to 12 months of age). Upon a request by EFSA for clarification on the claimed effect, the applicant indicated that the claimed effect referred to stool consistency rather than to stool frequency. Contribution to softening of stools is a beneficial physiological effect for infants.

Eighteen publications were identified by the applicant and one by the Panel as being pertinent to the claim. Of these, three human studies and four non-human studies did not report on stool outcomes, and three human studies did not provide information about the effect of beta-palmitate on stool consistency. The Panel considers that no conclusions could be drawn from these publications for the scientific substantiation of the claim.

Three human studies reported on the effects of beta-palmitate on stool consistency. In one study, stool consistency was an unplanned observation, which did not allow conclusions to be drawn from that study on stool consistency for the scientific substantiation of the claim.

In a 12-week intervention study, the consumption of a formula containing 50 % of palmitate in the sn-2 position significantly increased the percentage of soft (runny/watery) stools compared with consumption of a formula with only 12 % of palmitate in the sn-2 position; the volume and frequency of stools were not different between the two formula groups. The effect on stool consistency with the beta-palmitate formula disappeared when solid complementary foods were added to the formula diet. This study was affected by a high drop-out rate, a high rate of non-compliance, and results were provided for completers only, without taking into account repeated measures. The Panel considers that this study with important methodological limitations suggests an effect of beta-palmitate in formula on softening of stools.

Another 12-week human intervention study found no difference in the consistency of stools between two groups of infants fed formulae with 44 % and 14 % of palmitate in the sn-2 position, respectively. The Panel considers that this study with important methodological limitations (i.e. high drop-out rate, analysis performed in completers without taking into account repeated measures or multiple comparisons) suggests no effect of beta-palmitate in formula on softening of stools.

In weighing the evidence the Panel took into account that, out of two human intervention studies with important methodological limitations, one suggested a stool-softening effect of beta-palmitate whereas the second did not, that one animal study did not support a stool-softening effect of

beta-palmitate, and that the evidence provided for a mechanism by which beta-palmitate could contribute to the softening of stools is weak.

The Panel concludes that a cause and effect relationship has not been established between the consumption of beta-palmitate and softening of stools.

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BACKGROUND

Regulation (EC) No 1924/2006⁴ 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 this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this 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 this Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the 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.
- On 26/03/2008, during the validation process of the application, EFSA sent a request to the applicant asking it to provide missing information.
- On 01/07/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 18/07/2013.
- On 25/09/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 04/10/2013 and was restarted on 24/10/2013, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- On 24/10/2013, EFSA received the requested information.
- During its meeting on 06/02/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to beta-palmitate and contribution to softening of stools.

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: beta-palmitate and contribution to softening of stools.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of beta-palmitate, a positive assessment of its safety, nor a decision on whether

⁴ 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. OJ L 404, 30.12.2006, p. 9–25.

beta-palmitate is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

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.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Specialised Nutrition Europe (formerly IDACE), 9-31, Avenue des Nerviens 1040, Brussels, Belgium.

Food/constituent as stated by the applicant

According to the applicant, the food constituent for which the claim is made is beta-palmitate.

Health relationship as claimed by the applicant

According to the applicant, beta-palmitate contributes to soften the stools, which helps to increase their frequency in infants receiving a formula enriched with this lipid source.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Beta-palmitate enrichment contributes to soften stool consistency which helps to increase their frequency".

As equivalent alternative wordings, the applicant has also proposed: "Beta-palmitate contributes to soften stool consistency/contributes to increase stool frequency/is suitable to soften stool consistency/suitable to increase stool frequency".

Specific conditions of use as proposed by the applicant

According to the applicant, the target population is infants (from birth to 12 months of age) as defined in Directive 89/398/EEC on foodstuffs intended for particular nutritional uses, especially infant formulas as defined by 2006/141/EC, for which authorised claims and conditions of use are already fixed by the Annex IV of this directive, the follow-on formulas and the Foods for Special Medical Purposes (FSMP) as defined by Directive 1999/21/EC.

According to the applicant, in formulas supported by this claim, beta-palmitate will account for a minimum of 35 % of total palmitic acid when the palmitic acid content is between 20 and 25 % of total fatty acids.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is beta-palmitate.

Beta-palmitate is a structured triglyceride mixture with a high content of triglycerides esterified with palmitic acid at the sn-2 (middle or beta) position of the glycerol backbone. Beta-palmitate is produced by enzymatic esterification of unnamed vegetable oils after which 45 to 80 % of total palmitic acid are esterified at the sn-2 position. The sn-1 and sn-3 positions are predominantly occupied by unsaturated fatty acids, primarily oleic acid (C18:1). The main triglycerides present in beta-palmitate are 1,2-dipalmitoyl-3-oleyl triglyceride and 1,3-dioleoyl-2-palmitoyl triglyceride.

According to the specifications from two manufacturers, beta-palmitate contains > 98 % triglycerides; 28–60 % of total fatty acids are palmitic acid of which ≥ 50 % in the sn-2 position, 30–60 % are oleic acid, < 2 % are trans-fatty acids while < 0.1 % are free fatty acids. The peroxide value is ≤ 2.0 mEq O₂/kg. The ratio of saturated fatty acids (SFAs) to mono-unsaturated fatty acids and to

poly-unsaturated fatty acids measured in batches of beta-palmitate was 40–50: 45–50 : 5–7. Beta-palmitate is stabilised using antioxidants suitable for use in infant formula in the EU.

The intended use of beta-palmitate is to partially replace conventional triglycerides from vegetable oils in infant formulae to the extent that at least 35 % of the total palmitic acid content, which is assumed to be 20–25 % of total fatty acids, is in the sn-2 position, which means that the amount of beta-palmitate used in a formula would depend on both the total fat content and its fatty acid composition.

The fatty acid content and the positioning of fatty acids on the glycerol backbone can be measured by established methods.

The Panel notes that the term “beta-palmitate” is used in the application to denote both the structured triglyceride mixture with palmitate predominant at the sn-2 position of the glycerol backbone and the palmitate monoglyceride arising from digestion by lipases. In this opinion the term beta-palmitate will be used only for the structured triglyceride mixture, which is the subject of the health claim.

The Panel considers that the food constituent, beta-palmitate, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is “contributes to soften the stools, which helps to increase their frequency”. The target population proposed by the applicant is infants (from birth to 12 months of age). Upon a request by EFSA for clarification of the claimed effect, the applicant indicated that the claimed effect referred to stool consistency rather than to stool frequency.

Hard stools resulting from colonic retention, decreased propulsion and dehydration of intestinal contents is the predominant symptom of constipation in infants.

The Panel considers that contribution to softening of stools is a beneficial physiological effect for infants.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Medline based on unspecified search criteria to identify publications which evaluated the effects of beta-palmitate in infants and young children. Studies carried out with other lipid constituents or in other population groups were excluded. The period which was covered by the literature search was not specified.

The applicant identified 18 references as pertinent to the claim. One systematic review which addressed the effects of formulae with different lipid structures on calcium absorption and bone mineralisation (Koo et al., 2006) and two intervention studies which investigated the effects of beta-palmitate on the absorption of lipids and on the structure of plasma lipids in infants (Innis et al., 1994; Nelson and Innis, 1999) did not report on stool outcomes. The Panel considers that no conclusions can be drawn from these publications for the scientific substantiation of the claim.

Of the remaining references, six referred to human (Carnielli et al., 1996; Kennedy et al., 1999; Miró et al., 2001; Bongers et al., 2007; Chevallier et al., 2009) and animal (Enzymotec, unpublished) intervention studies conducted with beta-palmitate and which report on stool consistency, whereas four human studies (Quinlan et al., 1995; Carnielli et al., 1995; Lucas et al., 1997; Lopez-Lopez et al., 2001) and five non-human studies (de Fouw et al., 1994; Innis et al., 1997; Innis and Dyer, 1997; Lien et al., 1997; Sanders et al., 2001) addressed the mechanisms by which beta-palmitate could exert the claimed effect.

3.1. Studies on stool consistency

Five human intervention studies reported on stool consistency as an outcome. One study was a single-arm intervention with no control group (Chevallier et al., 2009); the composition of the control formula was not specified in another study (Miró et al., 2001, unpublished); and in a third study (Bongers et al., 2007) the intervention and control formulas did not differ only in their beta-palmitate content, but also in the content of other ingredients (e.g. galacto-oligosaccharides and long-chain fructo-oligosaccharides), which may have an effect on stool consistency. The Panel notes that these studies do not provide information about the effect of beta-palmitate on stool consistency and considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

One intervention study investigated the effects of beta-palmitate on stool consistency in healthy infants (Kennedy et al., 1999). A second intervention study, which addressed the effects of beta-palmitate on the intestinal absorption and faecal excretion of calcium and fatty acids, reported on stool consistency as an unplanned observation (Carnielli et al., 1996). The Panel is aware of one additional study by Litmanovitz et al. (2013; 2013-unpublished) which investigated the effects of beta-palmitate on bone health and reported on stool consistency as a secondary outcome.

The study by Carnielli et al. (1996) was a balance study designed to investigate the effect of the structural position of palmitic acid in the triglyceride on the intestinal absorption and the faecal excretion of fat and calcium. Data on stool consistency were collected when differences in the first faecal samples were noted, but systematic scoring of the degree of stool hardness and colour was not part of the original protocol and was not undertaken for all subjects. The Panel considers that no conclusions can be drawn from this unplanned observation for the scientific substantiation of the claim.

Kennedy et al. (1999) conducted a randomised, double-blind, controlled, parallel intervention study to investigate the effects of beta-palmitate on skeletal mineral deposition and stool consistency in 203 formula-fed healthy term-born infants (119 males). Subjects were enrolled within the first eight days of life and randomised to receive either a formula with beta-palmitate ($n = 100$) or a control formula without beta-palmitate ($n = 103$) for 12 weeks. One hundred and twenty breast-fed infants were also studied from 10 to 12 weeks of age (reference group). The beta-palmitate and control formulae were similar in percentage of fatty acids as palmitic acid (about 20 %), but differed in the percentage of palmitate in the sn-2 position (50 % in the beta-palmitate formula vs. 12 % in the control formula). The beta-palmitate formula also had a 4 % higher energy and 7 % higher fat content than the control formula. Sample size calculations (120 per group) were based on differences in stool hardness and constipation between the groups at 5 % significance and 80 % power.

Stool consistency, frequency and volume were reported by mothers of formula-fed infants in 7-day diaries at 6 and 12 weeks. Each stool passed by an infant was coded for consistency and volume by using previously validated colour photos for stool consistency (runny, mushy, formed, or hard) and diagrams for stool volume. Mothers of breast-fed infants completed the stool diary and questionnaire at 12 weeks only. Differences in stool consistency (per cent of subjects with hard or formed stools, with mushy stools, and with runny or watery stools) and in the stool consistency score between the beta-palmitate formula and the control formula at weeks 6 and 12 were analysed using the Mann-Whitney *U*-test. The Kruskal–Wallis test was used to assess differences in these variables among the three study groups at week 12. Analysis of variance was used to examine differences in total stool volume per week and volume per stool among the three groups with post-hoc pairwise comparisons by Bonferroni tests. The Panel notes that repeated measures were not taken into account in data analyses.

Twenty infants in the beta-palmitate group and 23 infants in the control-formula group stopped receiving the study formula before the end of week 12 because of “hunger”, severe constipation (two in the beta-palmitate and one in the control formula group), vomiting and unknown reasons. Of the

80 infants in both formula groups who completed 12 weeks of study formula feeding, 20 infants in the beta-palmitate group and 17 in the control formula group (together > 20%) received complementary food at a median age of 10 weeks, leaving 60 infants in the beta-palmitate group and 63 infants in the control formula group who were exclusively fed with either study formula for 12 weeks (a total of 61 % of the randomised infants). Data on stool consistency, volume and frequency were analysed for 84 and 75 infants in the beta-palmitate group and for 87 and 73 infants in the control formula group at weeks 6 and 12, respectively. No intention-to-treat analyses were performed. Upon a request by EFSA for clarification of the number of infants included in the statistical analyses, the applicant indicated that data on stool characteristics at 12 weeks were available for only 75 and 73 infants out of the 80 infants per group who completed the 12 weeks of formula feeding.

Infants consuming the beta-palmitate formula passed a significantly higher percentage of runny/watery stools than infants consuming the control formula at six [median (interquartile range) = 14 (0, 50) and 0 (0, 0), respectively] and 12 weeks [7 (0,29) and (0, 0), respectively], and a significantly lower percentage of hard or formed stools at week 6 [0 (0, 35) and 33 (0, 73), respectively]. No significant differences between the two formula groups were observed for the percentage of hard or formed stools at week 12, or for the percentage of mushy stools at any time point. Differences in stool consistency between the formula groups were no longer significant, however, when infants received solids in addition to formula. Breast-fed infants passed significantly lower percentages of hard/formed and mushy stools and a significantly higher percentage of runny/watery stools than either formula group. There were no differences between the formula groups in the number of stools per week or the mothers' estimation of total stool volume per week or volume per stool.

The Panel notes that in this intervention trial of 12 weeks' duration conducted in healthy term infants, consumption of a formula in which 50 % of the palmitic acid is esterified to the sn-2 position of the glycerol backbone increased the percentage of soft (runny/watery) stools compared with consumption of a formula with the same palmitic acid content but with only 12 % in the sn-2 position, and that volume and frequency of stools were not different between the two formula groups. The effect on stool consistency with the beta-palmitate formula disappeared when solid complementary foods were added to the formula diet. The Panel also notes that this study was affected by a high drop-out rate (20 %) and a high rate of non-compliance (39 %), that results were provided for completers only (i.e. subjects who received the study formula during 12 weeks and provided complete data sets), and that repeated measures were not taken into account in data analysis.

The Panel considers that this study with important methodological limitations suggests a stool softening effect of a formula containing 20 % of fatty acids as palmitic acid and 50 % of palmitate in the sn-2 position compared with a similar formula with only 12 % of palmitate in the sn-2 position.

A randomised, double-blind, controlled, parallel intervention study by Litmanovitz et al. (2013; 2013, unpublished) enrolled 83 healthy, term-born infants within the first two weeks of life. Formula-fed infants (n = 58) were randomised to receive either a formula with beta-palmitate (44 % of total palmitic acid in the sn-2 position of the glycerol backbone, n = 30) or a regular formula (14 % of total palmitic acid in the sn-2 position, n = 28) for 12 weeks. The composition of the two formulas was similar (about 20 % of fatty acids as palmitic acid) except for the percentage of palmitate in the sn-2 position. A reference group of infants exclusively breast-fed (n = 25) was also included in the study. The primary outcome (used for power calculations) was changes in bone speed of sound (Litmanovitz et al., 2013). Secondary outcomes were "infant comfort", crying patterns and stool consistency (Litmanovitz et al., 2013, unpublished).

Parents filled in three-day reports prior to the clinical visits (at baseline, and 6 and 12 weeks) on crying patterns, behaviour, formula consumption and stool characteristics, including colour (yellow, green, brown, black) and consistency (hard, mushy, watery). Statistical analyses were conducted using

pairwise *t*-tests for scale outcomes and pairwise chi-square tests for nominal outcomes for comparisons between the formula groups and between the formula groups and the breast-fed group.

Stool diaries were available from 61 infants (73 % of enrolled infants) after 12 weeks (beta-palmitate formula, $n = 21$; regular formula, $n = 21$; breast-fed, $n = 19$). Stool frequency was significantly higher and stool consistency significantly lower ($p < 0.05$) in the breast-fed infants compared to the formula groups at both 6 and 12 weeks, but was not significantly different between the two formula groups. At six weeks, hard stools were reported for 23.1 %, 16.7 %, and 5.0 % of infants consuming the beta-palmitate formula, the regular formula, and breast milk, respectively, whereas the percentage of infants with hard stools at 12 weeks was 14.3 %, 23.8 %, and 0.0 % for the beta-palmitate formula, the regular formula, and breast milk groups, respectively. No significant differences between groups were observed at six weeks. At 12 weeks, the percentage of infants with hard stools was significantly higher in the regular formula group than in the breast-fed group ($p < 0.05$), whereas no significant differences were observed between the beta-palmitate formula group and the breast-fed group or between the two formula groups.

The Panel notes that this controlled randomised trial of 12 weeks' duration found no difference in the consistency of stools between two groups of infants fed formulae with 44 % and 14 % of the palmitic acid content in the sn-2 position of the glycerol backbone, respectively. The Panel also notes that this study was affected by a high drop-out rate (28 %, reasons not specified) and that the results were analysed in completers only without taking into account repeated measures or multiple comparisons.

The Panel considers that this study with important methodological limitations suggests no stool softening effect of a formula containing 44 % of palmitate in the sn-2 position compared with a similar formula with 14 % of palmitate in the sn-2 position.

An animal study conducted in rats reported on stool consistency (Enzymotec, unpublished). A total of 100 rats (25 per group) were assigned to consume for three days a fat-free (control) diet or one of three diets containing 22 % of palmitic acid, of which 20 %, 40 % or 50 % was in the sn-2 position, but otherwise comparable regarding nutrient composition and fatty acid profile. No significant differences were observed among the three groups fed the fat-containing diets regarding stool consistency or faecal weight. The Panel considers that this study does not support a stool softening effect of beta-palmitate.

The Panel notes that one human intervention study reported stool-softening effects of a formula containing 50 % of palmitate in the sn-2 position compared with a formula containing 12 % only with exclusive formula feeding and only in infants ≤ 2 weeks of age at baseline (Kennedy et al., 1999), whereas another human intervention study reported no stool-softening effects of a formula containing 44 % of palmitate in the sn-2 position compared with a formula containing 14 % and one animal study did not support a stool-softening effect of beta-palmitate. The Panel also notes that the two human intervention studies from which conclusions could be drawn with respect to the effects of beta-palmitate on stool consistency suffer from important methodological limitations and are at high risk of bias.

3.2. Studies on mechanisms by which beta-palmitate could exert the claimed effect

Regarding the mechanism by which beta-palmitate could exert the claimed effect, the applicant claims that stool consistency correlates with the amount of calcium soaps (salts) in the stools, which are formed in the gut from unabsorbed calcium and SFAs and are solid at body temperature. An increased absorption of dietary calcium and/or of SFAs (including palmitic acid) would decrease the formation of calcium soaps in the gut and, thus, the consistency of stools. The applicant indicates that palmitate in the sn-2 position is more readily hydrolysed and absorbed in the gut than palmitate in the extreme positions of the glycerol backbone.

A claim on beta-palmitate and increased calcium absorption in infants has been already evaluated by the Panel with a negative outcome (EFSA NDA Panel, 2011). In that opinion, the Panel evaluated the studies by Carnielli et al. (1995, 1996) and by Lucas et al. (1997) and noted that one short-term human intervention study in term newborn infants (Carnielli et al., 1996) provided evidence that a high degree of palmitate in the sn-2 position could increase calcium absorption and decrease faecal fat and calcium excretion, whilst two other studies in pre-term infants did not show an effect on calcium absorption but rather on faecal calcium excretion as calcium soaps (Carnielli et al., 1995; Lucas et al., 1997).

In addition, three human studies have been provided by the applicant in relation to the mechanism by which beta-palmitate could exert an effect on stool consistency (Quinlan et al., 1995; Kennedy et al., 1999; Lopez-Lopez, 2001).

One observational study in breast-fed infants and formula-fed infants reported a significant relationship between stool hardness and the content of calcium and of calcium fatty acid soaps in the faeces (Quinlan et al., 1995). In the study by Kennedy et al. (1999) described above, total fatty acids and SFA soaps in faeces were significantly lower in the beta-palmitate formula group than in the control group. In the study by Lopez-Lopez et al. (2001), fatty acids and palmitic acid in faeces, but not faecal calcium, were significantly lower in infants consuming a formula with 45 % of palmitic acid in the sn-2 position compared to a formula with 19 % in the sn-2 position.

Out of the six animal studies provided by the applicant, only two conducted in rats reported on the composition of stools following consumption of beta-palmitate (Lien et al., 1997; Enzymotec, unpublished). Both studies showed an inverse relationship between the amount of palmitate in the triglyceride sn-2 position in the animal's diet and faecal excretion of fatty acids (including palmitic acid) and fatty acid soaps. However, lower faecal excretion of SFAs and fatty acid soaps following consumption of diets with high percentages of palmitate in the sn-2 position did not result in softer stools in the only study which investigated this outcome (Enzymotec, unpublished).

The Panel considers that the evidence provided for a mechanism by which beta-palmitate could contribute to the softening of stools is weak.

In weighing the evidence the Panel took into account that, out of two human intervention studies with important methodological limitations, one suggested a stool-softening effect of beta-palmitate whereas the second did not, that one animal study did not support a stool-softening effect of beta-palmitate, and that the evidence provided for a mechanism by which beta-palmitate could contribute to the softening of stools is weak.

The Panel concludes that a cause and effect relationship has not been established between the consumption of beta-palmitate and softening of stools.

CONCLUSIONS

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

- The food constituent, beta-palmitate, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is “contributes to soften the stools, which helps to increase their frequency”. The target population proposed by the applicant is infants (from birth to 12 months of age). Contribution to softening of stools is a beneficial physiological effect for infants.

- A cause and effect relationship has not been established between the consumption of beta-palmitate and softening of stools.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on beta-palmitate and contribution to softening of stools pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0094_FR). February 2008. Submitted by Specialised Nutrition Europe (formerly IDACE).

REFERENCES

- Bongers ME, de Lorijn F, Reitsma JB, Groeneweg M, Taminau JA and Benninga MA, 2007. The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial. *Nutrition Journal*, 6, 8.
- Carnielli VP, Luijendijk IH, van Goudoever JB, Sulkers EJ, Boerlage AA, Degenhart HJ and Sauer PJ, 1995. Feeding premature newborn infants palmitic acid in amounts and stereoisomeric position similar to that of human milk: effects on fat and mineral balance. *American Journal of Clinical Nutrition*, 61, 1037-1042.
- Carnielli VP, Luijendijk IH, Van Goudoever JB, Sulkers EJ, Boerlage AA, Degenhart HJ and Sauer PJ, 1996. Structural position and amount of palmitic acid in infant formulas: effects on fat, fatty acid, and mineral balance. *Journal of Pediatric Gastroenterology and Nutrition*, 23, 553-560.
- Chevallier B, Fournier V, Logre B, Beck L, Ceccato F, Hui Bon Hoa G, Lachambre E, Van Egroo LD and Sznajder M, 2009. Intérêt d'une nouvelle préparation infantile dans la prise en charge des régurgitations du nourrisson: Value of a new thickened formula in infants with regurgitations. *Archives de Pédiatrie*, 16, 343-352.
- EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. Scientific Opinion on the substantiation of a health claim related to beta-palmitate and increased calcium absorption pursuant to Article 14 of Regulation (EC) No 1924/2006. *EFSA Journal* 2011;9(7):2289,16 pp. doi:10.2903/j.efsa.2011.2289
- Enzymotec Ltd, unpublished. Comparative study of synthetically structured triglycerides efficacy on fatty acid absorption in weanling rats.
- de Fouw NJ, Kivits GA, Quinlan PT and van Nielen WG, 1994. Absorption of isomeric, palmitic acid-containing triacylglycerols resembling human milk fat in the adult rat. *Lipids*, 29, 765-770.
- Innis SM and Dyer R, 1997. Dietary triacylglycerols with palmitic acid (16:0) in the 2-position increase 16:0 in the 2-position of plasma and chylomicron triacylglycerols, but reduce phospholipid arachidonic and docosahexaenoic acids, and alter cholesteryl ester metabolism in formula-fed piglets. *Journal of Nutrition*, 127, 1311-1319.
- Innis SM, Dyer R and Nelson CM, 1994. Evidence that palmitic acid is absorbed as sn-2 monoacylglycerol from human milk by breast-fed infants. *Lipids*, 29, 541-545.
- Innis SM, Dyer RA and Lien EL, 1997. Formula containing randomized fats with palmitic acid (16:0) in the 2-position increases 16:0 in the 2-position of plasma and chylomicron triglycerides in formula-fed piglets to levels approaching those of piglets fed sow's milk. *Journal of Nutrition*, 127, 1362-1370.
- Kennedy K, Fewtrell MS, Morley R, Abbott R, Quinlan PT, Wells JC, Bindels JG and Lucas A, 1999. Double-blind, randomized trial of a synthetic triacylglycerol in formula-fed term infants: effects on stool biochemistry, stool characteristics, and bone mineralization. *American Journal of Clinical Nutrition*, 70, 920-927.

- Koo WW, Hockman EM and Dow M, 2006. Palm olein in the fat blend of infant formulas: effect on the intestinal absorption of calcium and fat, and bone mineralization. *Journal of the American College of Nutrition*, 25, 117-122.
- Lien EL, Boyle FG, Yuhas R, Tomarelli RM and Quinlan P, 1997. The effect of triglyceride positional distribution on fatty acid absorption in rats. *Journal of Pediatric Gastroenterology and Nutrition*, 25, 167-174.
- Litmanovitz I, Bar-Yoseph F, Lifshitz Y, Davidson K, Eliakim A, Regev RH, and Nemet D, 2013 (unpublished). Reduced crying in term infants fed with sn-2-palmitate infant-formula: a double-blind, randomised, clinical trial.
- Litmanovitz I, Davidson K, Eliakim A, Regev RH, Dolfin T, Arnon S, Bar-Yoseph F, Goren A, Lifshitz Y and Nemet D, 2013. High Beta-palmitate formula and bone strength in term infants: a randomized, double-blind, controlled trial. *Calcified Tissue International*, 92, 35-41.
- Lopez-Lopez A, Castellote-Bargallo AI, Campoy-Folgozo C, Rivero-Urgel M, Tormo-Carnice R, Infante-Pina D and Lopez-Sabater MC, 2001. The influence of dietary palmitic acid triacylglyceride position on the fatty acid, calcium and magnesium contents of at term newborn faeces. *Early Human Development*, 65 Suppl, S83-94.
- Lucas A, Quinlan P, Abrams S, Ryan S, Meah S and Lucas PJ, 1997. Randomised controlled trial of a synthetic triglyceride milk formula for preterm infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, 77, F178-184.
- Miró F, Santamaría A, Soriano V, Maseguer X, Prandi F and Rivero M, 2001. Poster based in a clinical observational trial: effectiveness of beta-palmitate on the improvement of constipation in infants. XV National Congress of Extra-hospital Paediatric Society of the Spanish Paediatric Association (AEP), Zaragoza, Spain.
- Nelson CM and Innis SM, 1999. Plasma lipoprotein fatty acids are altered by the positional distribution of fatty acids in infant formula triacylglycerols and human milk. *American Journal of Clinical Nutrition*, 70, 62-69.
- Quinlan PT, Lockton S, Irwin J and Lucas AL, 1995. The relationship between stool hardness and stool composition in breast- and formula-fed infants. *Journal of Pediatric Gastroenterology and Nutrition*, 20, 81-90.
- Sanders DJ, Howes D and Earl LK, 2001. The absorption, distribution and excretion of 1- and 2-[14C]palmitoyl triacylglycerols in the rat. *Food and Chemical Toxicology*, 39, 709-716.

ABBREVIATIONS

SFAs Saturated fatty acids