

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to a combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) and decreasing potentially pathogenic intestinal microorganisms pursuant to Article 14 of Regulation (EC) No 1924/2006¹

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

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ABSTRACT

Following an application from Töpfer GmbH submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) and decreasing potentially pathogenic intestinal microorganisms. 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 proposed claim, a combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, has not been sufficiently characterised. The claimed effect is "establishment of a natural, beneficial bifidobacterial dominance in the large intestine, which can lead to a suppression of harmful bacteria and thereby to a better health status". The target population is infants and children aged between 0 to 36 months. The Panel considers that decreasing potentially pathogenic intestinal microorganisms might be beneficial to human health. The applicant identified a total of 34 publications considered as being pertinent to the health claim. In weighing the evidence, the Panel notes that the strains that are the subject of the health claim have not been sufficiently characterised and that from the evidence provided it cannot be established that the strains used in the studies are the same strains that are the subject of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of the combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum* and decreasing potentially pathogenic intestinal microorganisms in infants and children aged between 0 and 36 months.

KEY WORDS

Bifidobacterium bifidum, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, bifidobacteriapotentially pathogenic intestinal microorganisms, health claims.

1 On request from Töpfer GmbH, Question No EFSA-Q-2009-00224, adopted on 4 December 2009.

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SUMMARY

Following an application from Töpfer GmbH submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) and decreasing potentially pathogenic intestinal microorganisms.

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 proposed claim is a combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*. The Panel considers that the food constituent, the combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, which is the subject of the health claim, has not been sufficiently characterised.

The claimed effect is "establishment of a natural, beneficial bifidobacterial dominance in the large intestine, which can lead to a suppression of harmful bacteria and thereby to a better health status". The target population is infants and children aged between 0 to 36 months. The Panel notes that aspects of the term "health status" are not sufficiently defined and do not allow an in depth scientific analysis of the claimed effect. The gastrointestinal tract is populated with a large number of microorganisms and it normally acts as an effective barrier against generalised systemic infections. It is not possible to provide the exact numbers of bacterial groups that would constitute a beneficial microbiota. However, the Panel considers that decreasing potentially pathogenic intestinal microorganisms might be beneficial to human health.

The applicant identified a total of 34 publications considered as being pertinent to the health claim: 13 randomised controlled trials, 6 observational studies, and 15 non-human studies.

The Panel notes that 11 randomised controlled trials provided insufficient identification of the bacterial strains used to establish that they were the same strains which are the subject of the health claim. In addition, the 6 human observational studies did not use the combination of bifidobacteria which is subject of the health claim. The Panel considers that no scientific conclusions can be drawn from these studies for substantiation of the claim.

Two randomised controlled trials were performed in infants with the combination of bifidobacteria which is the subject of the health claim. The Panel notes that the identity of the strains used in these studies cannot be ascertained and thus from the evidence provided it cannot be established that the strains used in these studies are the same strains that are the subject of the health claim. The Panel considers that no scientific conclusions can be drawn from these studies for the substantiation of the claim.

The applicant submitted 15 *in vitro* and animal studies performed with one or more of the following strains: *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis* and *Bifidobacterium longum*. These studies were related to pathogen adhesion, inhibition of adhesion, production of antibacterial substances and passive protection in mice. The Panel notes that from the evidence provided it cannot be established that the strains used in these studies are the same strains that are the subject of the health claim. Therefore no scientific conclusions can be drawn from these studies for the substantiation of the claim.

In weighing the evidence, the Panel notes that the strains that are the subject of the health claim have not been sufficiently characterised and that from the evidence provided it cannot be established that the strains used in the studies are the same strains that are the subject of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of

the combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum* and decreasing potentially pathogenic intestinal microorganisms in infants and children aged between 0 and 36 months.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

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 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 the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA:

- The application was received on 22/01/2009.
- The scope of the application was proposed to fall under a health claim referring to children's development and health.
- On 28/01/2009 and 23/04/2009, during the check for completeness⁵ of the application, the applicant was requested to provide missing information related to the format of the application and species identification and strains characterisation of the combination of bifidobacteria which are the subject of the health claim.
- The applicant provided the missing information on 24/03/2009 and 20/07/2009.
- The scientific evaluation procedure started on 15/08/2009.
- During the meeting on 4 December 2009, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to a combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) and decreasing potentially pathogenic intestinal microorganisms.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

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: combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) and decreasing potentially pathogenic intestinal microorganisms.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*,

⁴ 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.

⁵ In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

Bifidobacterium infantis, *Bifidobacterium longum*), a positive assessment of its safety, nor a decision on whether the combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) 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: Töpfer GmbH, Heisinger Straße 6, 87463 Dietmannsried, Germany.

Food/constituent as stated by the applicant

Mixture of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum* in foods for particular nutritional uses for infants and children from birth to 3 years of age as referred to in Dir. 89/398/EEC.

Health relationship as claimed by the applicant

According to the applicant, the supply of living *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, the typical bifidobacterial species found in the infant intestine, with paps, infant and follow-on formulae allows even under adverse conditions (caesarian section, antibiotic therapy, hospitalization, no breast-feeding) the establishment of a natural, beneficial bifidobacterial dominance in the large intestine, which can lead to a suppression of harmful bacteria and thereby to a better health status.

Wording of the health claim as proposed by the applicant

Probiotic bifidobacteria lead to a healthy intestinal flora comparable to the composition of the intestinal flora of breast-fed infants intestine.

Specific conditions of use as proposed by the applicant

The target population is infants (from birth onwards) and young children (until 3 years of age).

Those foods are exclusively intended for the category of infants and young children and in line with the composition laid down in the specific directives.

The average daily intake of infant formulae (IF) is assumed to be 700 mL, the normal daily intake of follow-on formulae (FOF) is estimated to range from 500–750 mL depending on the age of the infant and the amount of the weaning food in the diet. Cereals are assumed to be consumed in quantities of one or two portion with 50 g powder each. Therefore the quantities of consumed food are 100 g for IF, 75–100 g for FOF and 50–100 g for cereals. All mentioned foods are containing at the end of shelf life 4×10^6 CFU bifidobacteria/g; thus the daily probiotic intake lies between 3×10^8 CFU and 4×10^8 CFU, which is in accordance with the daily intake of 2×10^8 CFU to 1×10^9 CFU recommended by the BgVV (BgVV Working Group, 1999).

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is a combination of *Bifidobacterium bifidum* NIZO3804, *Bifidobacterium breve* NIZO3676, *Bifidobacterium infantis* Reuter ATCC15697, and *Bifidobacterium longum* NIZO3694. Each strain constitutes 25% of the total bacterial concentration of the mixture, giving a minimum total concentration of 25×10^9 cfu/g freeze-dried bacteria with maltodextrin and starch as carrier.

The bacterial mixture is added to infant formulae or processed cereals. At the end of the shelf life, total bifidobacteria concentration in infant paps, formulae or follow-on formulae is 4×10^6 cfu/g

powder. Presuming a daily amount of 100 g infant formulae, 75-100 g of follow-on formulae and 50-100 g of pap powder, the daily dose of probiotics ranges from 2×10^8 to 1×10^9 cfu. Data on stability of the freeze-dried bifidobacterial mixture and infant formulae containing bifidobacteria are provided in the application. The carbohydrate content of the ready to drink infant formulae and of the cereal preparations is not given in the application. The shelf life under these conditions is 18 months.

Survival data of the different bifidobacterial strains during passage through an *in vitro* simulated model for the gastrointestinal tract are also provided.

No data on species identification and characterisation of the strains *Bifidobacterium bifidum* NIZO3804, *Bifidobacterium breve* NIZO3676, *Bifidobacterium infantis* Reuter ATCC15697, and *Bifidobacterium longum* NIZO3694 are included in the application or in the references provided, even after having requested supplementary information to the applicant.

The Panel considers that the food constituent, a combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, which is the subject of the health claim, has not been sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is “establishment of a natural, beneficial bifidobacterial dominance in the large intestine, which can lead to a suppression of harmful bacteria and thereby to a better health status”. The target population is infants and children aged between 0 to 36 months.

The Panel notes that aspects of the term “health status” are not sufficiently defined and do not allow an *in depth* scientific analysis of the claimed effect.

The gastrointestinal tract is populated with a large number of microorganisms and it normally acts as an effective barrier against generalised systemic infections. It is not possible to provide the exact number of bacterial groups that would constitute a beneficial microbiota.

However, the Panel considers that decreasing potentially pathogenic intestinal microorganisms might be beneficial to human health.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search using the following databases: PubMed of National Center for Biotechnology Information, BioInfoBank Library of BioInfoBank Institute and Google Scholar. The search terms which had been used were *Bifidobacterium*, probiotic, *breve*, *infantis*, *longum*, *bifidum*, intestinal, gut, clinical trial, infant, microflora, human in different combinations. The literature search concerned publications from 1997 onwards.

The applicant identified a total of 34 publications considered as being pertinent to the health claim: 13 randomised controlled trials, 6 observational studies, and 15 non-human studies.

Eleven references out of the 13 references cited by the applicant as randomised controlled trials (Canani et al., 2007; Hotta et al., 1987; Indrio et al., 2007; Kitajima et al., 1997; Knol et al., 2005; Kok et al., 1996; Langhendries et al., 1995; Mullié et al., 2004; Puccio et al., 2007; Saavedra et al., 1994; Uhlemann et al., 1999) provided insufficient identification of the bacterial strains used to establish that they were the same strains which are the subject of the health claim. The applicant has submitted 6 human observational studies (Duffy et al., 1986; Howie et al., 1990; Matsuki et al., 1999; Penders et al., 2006; Stark and Lee, 1982; Yoshioka et al., 1983) which address the development of bifidobacteria under different feeding regimens including breast feeding, bottle feeding and formula feeds combined with oligosaccharides. The Panel notes that these observational studies do not use the

combination of bifidobacteria which is subject of the health claim. The Panel considers that no scientific conclusions can be drawn from these studies for substantiation of the claim.

Two randomised controlled trials were performed in infants with the combination of bifidobacteria which is the subject of the health claim (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) (Mayer and Keschawarzi, 1970; Kaloud and Stögmann, 1968). The Panel notes that the identity of the strains used in these studies cannot be ascertained and thus from the evidence provided it cannot be established that the strains used in these studies are the same strains that are the subject of the health claim. The Panel considers that no scientific conclusions can be drawn from these studies for the substantiation of the claim.

The applicant submitted 15 *in vitro* and animal studies performed with one or more of the following strains: *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis* and *Bifidobacterium longum*. These studies were related to pathogen adhesion, inhibition of adhesion, production of antibacterial substances and passive protection in mice. The Panel notes that from the evidence provided it cannot be established that the strains used in these studies are the same strains that are the subject of the health claim. Therefore no scientific conclusions can be drawn from these studies for the substantiation of the claim.

In weighing the evidence, the Panel notes that the strains that are the subject of the health claim have not been sufficiently characterised and that from the evidence provided it cannot be established that the strains used in the studies are the same strains that are the subject of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of the combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum* and decreasing potentially pathogenic intestinal microorganisms in infants and children aged between 0 and 36 months.

CONCLUSIONS

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

- The food constituent, the combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*, which is the subject of the health claim, has not been sufficiently characterised.
- The claimed effect is “establishment of a natural, beneficial bifidobacterial dominance in the large intestine, which can lead to a suppression of harmful bacteria and thereby to a better health status”. The target population is infants and children aged between 0 to 36 months. Decreasing potentially pathogenic intestinal microorganisms might be beneficial to human health.
- A cause and effect relationship has not been established between the consumption of the combination of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum* and decreasing potentially pathogenic intestinal microorganisms in infants and children aged between 0 and 36 months.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on combination of bifidobacteria (*Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium longum*) and decreasing potentially pathogenic intestinal microorganisms pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 00234_DE). July 2009. Submitted by Töpfer GmbH.

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GLOSSARY / ABBREVIATIONS

FOF follow-on formulae

IF infant formulae