



Scientific Opinion on the substantiation of a health claim related to Bifidobacterium bifidum CNCM I-3426 and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to *Bifidobacterium bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) 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 Lallemand Health Solutions, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to *Bifidobacterium bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract. The food constituent that is the subject of the claim is *B. bifidum* CNCM I-3426. The Panel considers that *B. bifidum* CNCM I-3426 is sufficiently characterised. The Panel considers that defence against pathogens in the upper respiratory tract is a beneficial physiological effect. The applicant provided one published human intervention study, one unpublished human intervention study (which was published during the evaluation of the claim) and one *in vitro* study as pertinent to the claimed effect. The Panel considers that no conclusions can be drawn from either of the human studies for the scientific substantiation of the claim. In the absence of evidence of an effect of *B. bifidum* CNCM I-3426 on defence against pathogens in the upper respiratory tract in humans, the results of the *in vitro* study submitted cannot be used as a source of data for the scientific substantiation of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

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KEY WORDS

Bifidobacterium bifidum CNCM I-3426, defence against pathogens, immune function, upper respiratory tract, health claim

¹ On request from the Competent Authority of France following an application by Lallemand Health Solutions, Question No EFSA-Q-2014-00673, adopted on 22 April 2015.

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SUMMARY

Following an application from Lallemand Health Solutions, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to *Bifidobacterium bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application includes a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is *B. bifidum* CNCM I-3426. The Panel considers that *B. bifidum* CNCM I-3426 is sufficiently characterised.

The claimed effect proposed by the applicant is that *B. bifidum* CNCM I-3426 can lead to an “increase of the proportion of healthy days (i.e. days without cold symptoms) by maintaining normal immune function in healthy adults during everyday life events such as moderate stress”. Upon a request from EFSA for clarification, the applicant explained that the claimed effect refers to defence against pathogens in the upper respiratory tract. The target population, as proposed by the applicant, is the general population. The Panel considers that defence against pathogens in the upper respiratory tract is a beneficial physiological effect.

The applicant provided one published human intervention study, one unpublished human intervention study (which was published during the evaluation of the claim) and one *in vitro* study as pertinent to the claimed effect.

One human intervention study was performed with a food which did not comply with the specifications provided for the food that is the subject of the health claim. The other human intervention study did not provide information on the effect of the food (i.e. *B. bifidum* CNCM I-3426) on clinical outcomes related to upper respiratory infections (e.g. incidence, severity and/or duration of symptoms) which could be used for the scientific substantiation of the claim of defence against pathogens in the upper respiratory tract. The Panel also notes that the post-hoc, between-arm statistical analyses provided for the primary outcome were not justified. The Panel considers that no conclusions can be drawn from either of the human studies for the scientific substantiation of the claim.

In the absence of evidence of an effect of *B. bifidum* CNCM I3426 on defence against pathogens in the upper respiratory tract in humans, the results of the *in vitro* study submitted cannot be used as a source of data for the scientific substantiation of the claim.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

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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, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) 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 19/09/2014.

- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- The scientific evaluation procedure started on 08/12/2014.
- On 21/01/2015, 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, and the clock was stopped on 16/02/2015, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 02/03/2015, EFSA received the applicant's reply as submitted by the applicant and the clock was restarted.
- During its meeting on 22/04/2015, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) 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 *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of *B. bifidum* CNCM I-3426, a positive assessment of its safety, nor a decision on whether *B. bifidum* CNCM I-3426 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 18(4) of Regulation (EC) No 1924/2006.

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.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address

Lallemand Health Solutions, 17975 rue des Gouverneurs, Mirabel, Quebec, Canada, J7J 2K7.

The application contains a request for the protection of proprietary data from an unpublished Langkamp-Henken and Dahl (2014) study report, in accordance with Article 21 of Regulation (EC) No 1924/2006.

Food as stated by the applicant

According to the applicant, the food for which this health claim is made is *Bifidobacterium bifidum* CNCM I-3426.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect refers to an increase of the proportion of healthy days (i.e. days without cold symptoms) by maintaining normal immune function in healthy adults during everyday life events such as moderate stress. The mechanisms of action of probiotics with regard to the management of upper respiratory tract infections, like cold and flu, have not yet been confirmed. Nevertheless, various potential mechanisms have been proposed, based on evidence from *in vitro*, animal and human studies, including an enhancement of barrier function, the production of antimicrobial substances and immunomodulatory effects. Upon a request from EFSA, the applicant explained that the claimed effect relates to defence against pathogens in the upper respiratory tract.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: “*Bifidobacterium bifidum* CNCM I-3426 increases the proportion of healthy days by maintaining normal immune function in healthy adults during everyday life events such as moderate stress”.

Specific conditions of use as proposed by the applicant

The applicant has proposed that the quantity required to obtain the claimed effect is between 3×10^9 colony-forming units (CFU) and 7×10^9 CFU per day. This quantity can be obtained by the consumption of one capsule daily containing 5×10^9 CFU of *Bifidobacterium bifidum* CNCM I-3426. The proposed target population is the general population.

ASSESSMENT

1. Characterisation of the food

The applicant stated that the food that is the subject of the health claim is *Bifidobacterium bifidum* CNCM I-3426 (also named *B. bifidum* R0071). The bacterial strain was deposited in the “Collection Nationale de Cultures de Microorganismes” (CNCM) under the deposit number I-3426. The CNCM is a restricted-access non-public collection which has the status of International Depository Authority under the Budapest Treaty. Data on the phenotypic (morphology and biochemical test results) and genotypic characterisation of the species and strain, including 16S ribosomal DNA and *tuf* gene sequence analyses for species identification, and pulse field gel electrophoresis and random amplification of polymorphic DNA for strain typing, were provided.

Information about the manufacturing process and stability was also provided.

The Panel considers that the food, *B. bifidum* CNCM I-3426, 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 that *B. bifidum* CNCM I-3426 can lead to an “increase of the proportion of healthy days (i.e. days without cold symptoms) by maintaining normal immune function in healthy adults during everyday life events such as moderate stress”. The target population proposed by the applicant is the general population. In response to a request from EFSA, the applicant explained that the claimed effect refers to defence against pathogens in the upper respiratory tract.

Scientific evidence for the substantiation of health claims related to defence against pathogens in the respiratory tract can be obtained from human intervention studies showing an effect on clinical outcomes related to respiratory infections (e.g. incidence, severity and/or duration of symptoms), of either the upper respiratory tract (such as rhinitis, pharyngitis, sinusitis, otitis or the common cold) or the lower respiratory tract (such as pneumonia, bronchitis or bronchiolitis), or both (EFSA NDA Panel, 2015).

The Panel considers that defence against pathogens in the upper respiratory tract is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search using Medline and Google Scholar databases with the following search terms: “*Bifidobacterium bifidum* CNCM I-3426” OR “*Bifidobacterium bifidum* R0071” OR “*Bifidobacterium bifidum* R71” OR “*Bifidobacterium bifidum* Rosell-71”. One published human study (Cazzola et al., 2010), claimed by the applicant as pertinent to the health claim, was identified through the literature search. Additionally, one unpublished human intervention study (Langkamp-Henken and Dahl, unpublished) and one unpublished non-human study (MacPherson et al., unpublished) were submitted by the applicant as pertinent to the claim. The Panel notes that the results of one of these studies were published during the evaluation of the claim (Langkamp-Henken et al., 2015).

Cazzola et al. (2010), in a multi-centre, randomised, double-blind, placebo-controlled, parallel intervention study, assessed the effect of consuming a combination of three bacterial strains (*Lactobacillus helveticus* R0052, *Bifidobacterium infantis* R0033 and *B. bifidum* CNCM I-3426) plus fructo-oligosaccharides on the incidence of infections in 135 children. The Panel notes that this study was performed with a food which did not comply with the specifications provided for the food that is the subject of the health claim (see Section 1). The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In a single-centre, randomised, parallel, double-blind, four-arm, placebo-controlled study (Langkamp-Henken et al., 2015), the effects of three individual bacterial strains (*B. bifidum* CNCM I-3426, *Bifidobacterium longum* subsp. *infantis* R0033 and *Lactobacillus helveticus* R0052), given in capsules for six weeks (one capsule containing 3×10^9 CFU of the particular bacterial strain per day), were assessed against placebo capsules (magnesium stearate and potato starch) in a group of apparently healthy students (n = 581 randomised subjects, mean age 20 years, 371 females; 142 subjects in *B. bifidum* CNCM I-3426 group, 147 subjects in *B. longum* subsp. *infantis* R0033 group, 145 subjects in *L. helveticus* R0052 group and 147 subjects in placebo group) potentially under psychological stress during their autumn academic exams. The exams were held over a one-week period during the fourth or fifth week of the intervention. The percentage of subjects vaccinated against influenza varied from 28 to 38 % among the groups. Subjects who were taking medicines for allergic symptoms and had received antibiotic therapy in the two months prior to the study were excluded.

Online questionnaires were compiled daily by the subjects in order to gather information about cold and flu symptoms. The proportion of healthy days was evaluated using a modified Jackson scale which included nine questions about cold symptoms (running/congested nose, stiffness or chills, headache, cough, fatigue, fever, sore throat, achiness and ear discomfort) and symptom intensity (scores: 0 = no symptoms to 3 = severe symptoms). A day was considered as “healthy” if the sum of

the cold symptom intensity scores was ≤ 6 . Participants were asked not to record symptoms which could be attributed to allergy. The same questionnaire was also used to calculate the number of participants reporting at least one day with cold/flu symptoms (cold symptom intensity score > 6), the number of episodes of cold/flu and the duration of cold/flu.

The Panel notes that the original Jackson scale (Jackson et al., 1958), which was validated for the diagnosis of common cold episodes, includes the rating of the following common cold symptoms on a 4-point scale: sneezing, headaches, malaise, chilliness, nasal discharge, nasal obstruction, sore throat and cough. A common cold episode is defined as a symptom score of 14 plus the subject's subjective feeling of illness or increased nasal discharge on three out of six days. For symptom scores < 14 , both the subject's subjective feeling of illness and an increased nasal discharge on three out of six days are required for diagnosis. The Panel also notes that the "modified" Jackson scale used in the study by Langkamp-Henken et al. (2015) includes one more symptom (fatigue), but defines a much lower threshold for the diagnosis of a common cold episode. Upon a request from EFSA for clarification on whether or not the modified Jackson scale used in the study had been validated for the diagnosis of the common cold, the applicant argued that the same questionnaire had been used in a previous study (Hughes et al., 2011). The Panel notes that this publication does not contain any information on the validation of the modified Jackson scale. The applicant also stated that the study population recruited by Langkamp-Henken et al. (2015) was different from the population studied by Jackson et al. (1958), and that "a validated questionnaire to assess cold and flu symptoms in healthy populations is absent". The Panel notes that the modified Jackson scale used by Langkamp-Henken et al. (2015) has not been validated for the diagnosis of the common cold. The Panel considers that no evidence was provided to confirm that the modified Jackson scale, as used in the study, is a valid tool for diagnosis of the incidence, severity and/or duration of common cold episodes, and therefore it is unclear how the outcome measures derived from this tool relate to the claimed effect on defence against pathogens.

Numerous primary outcomes, e.g. proportion of "healthy days" (days without cold symptoms), symptom intensity score, changes in faecal microbiota, various gastrointestinal symptoms and quality of life, were specified. Secondary outcomes comprised salivary immunoglobulin A (IgA), faecal IgA, bowel frequency and consistency, and salivary cortisol. In response to a request from EFSA, the applicant stated that the proportion of healthy days (i.e. days with a symptom score ≤ 6) was the only primary outcome of the study. The Panel notes that the outcome used to calculate the sample size was the proportion of days with a symptom score > 6 .

When the results for the primary outcome (i.e. the proportion of days with a symptom score ≤ 6) were analysed across all four study groups using a generalised linear model (GLM), no statistically significant differences among groups were found. Subsequent analyses, in which each study arm was compared with another, were performed by the applicant. The results of these post-hoc analyses were only presented for the *B. bifidum* CNCM I-3426 arm versus the placebo arm. In response to a request from EFSA to provide the full study report, the applicant did not provide the study report, but stated that only the information related to the intervention with *B. bifidum* CNCM I-3426 versus placebo was relevant for this application. The Panel notes that further between-arm analyses are not justified in the absence of a statistically significant difference among the study arms in the overall analysis using a GLM.

The Panel notes that this study does not provide information on the effect of the food (i.e. *B. bifidum* CNCM I-3426) on clinical outcomes related to upper respiratory tract infections (e.g. incidence, severity and/or duration of symptoms) which could be used for the scientific substantiation of a claim on defence against pathogens in the upper respiratory tract. The Panel also notes that the post-hoc, between-arm statistical analyses provided for the primary outcome were not justified. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

An *in vitro* study (MacPherson et al., unpublished) was also provided by the applicant in support of a mechanism by which *B. bifidum* CNCM I-3426 could exert the claimed effect. The Panel considers

that, in the absence of evidence of an effect of *B. bifidum* CNCM I3426 on defence against pathogens in the upper respiratory tract in humans, the results of this *in vitro* study cannot be used as a source of data for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

CONCLUSIONS

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

- The food product, *B. bifidum* CNCM I-3426, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “defence against pathogens in the upper respiratory tract”. The target population, as proposed by the applicant, is the general population. Defence against pathogens in the upper respiratory tract is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract.

DOCUMENTATION PROVIDED TO EFSA

1. Health claim application on *B. bifidum* CNCM I-3426 and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0429_FR). September 2014. Submitted by Lallemand Health Solutions.

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ABBREVIATIONS

CFU	colony-forming unit
CNCM	Collection Nationale de Cultures de Microorganismes
GLM	generalised linear model
IgA	immunoglobulin A
NDA	Dietetic Products, Nutrition and Allergies