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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to Yestimun® and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Leiber GmbH, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, 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 Yestimun® and defence against pathogens in the upper respiratory tract. The food that is the subject of the health claim, Yestimun®, which consists of (1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall, is sufficiently characterised. The claimed effect, defence against pathogens in the upper respiratory tract, is a beneficial physiological effect. No human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant. The Panel concludes that a cause and effect relationship has not been established between the consumption of Yestimun® ((1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall) and defence against pathogens in the upper respiratory tract.

KEY WORDS

Yestimun®, beta-glucans, brewer's yeast, pathogens, upper respiratory tract, health claims

[1] On request from the Competent Authority of Germany following an application by Leiber GmbH, Question EFSA-Q-2012-00761, adopted on 21 March 2013.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from Leiber GmbH, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, 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 Yestimun® 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 that is the subject of the health claim is Yestimun®, which consists of (1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall. The Panel considers that Yestimun® is sufficiently characterised.

The claimed effect proposed by the applicant is related to the defence against pathogens in the upper respiratory tract. The target population proposed by the applicant is adults in the general population. The Panel considers that defence against pathogens in the upper respiratory tract is a beneficial physiological effect.

The applicant performed a literature search in Medline for publications in English and German using keywords, "like yeast beta-glucan, immune system, oral, human, study, trial". As directly pertinent to the claim, the applicant identified through the literature search one published randomised controlled trial (RCT) and provided two unpublished RCTs.

These studies investigated the effect of Yestimun® on the frequency of occurrence of common cold episodes or upper respiratory tract infections, on the duration of the infection and on symptom severity scores.

The Panel notes that the evidence provided by the applicant does not establish the validity of the questionnaires and the criteria used in these studies to assess the incidence, duration or the severity of common cold episodes. The Panel also notes the limitations in the statistical analyses of these studies (e.g. exclusion of one study site from statistical analysis without appropriate justification and the requested re-analysis of the data was not presented for one of the studies, the multi-centre design was not taken into account in the statistical analyses of two of the studies and no account was taken for multiplicity of "primary outcomes" in one of the studies).

The Panel considers that no conclusions can be drawn for the scientific substantiation of the claim from any of the human intervention studies provided by the applicant.

The Panel notes that in the absence of an effect of Yestimun® in humans on defence against pathogens in the upper respiratory tract the submitted human, animal and *in vitro* studies pertaining to a possible mechanism by which Yestimun® could exert the claimed effect do not provide any scientific evidence for the substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Yestimun® ((1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall) and defence against pathogens in the upper respiratory tract.

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BACKGROUND

Regulation (EC) No 1924/2006[4] 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 20/08/2012.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and includes a request for the protection of proprietary data.
- On 04/10/2012, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 22/10/2012, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 25/10/2012.
- On 14/12/2012, 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 18/12/2012 and restarted on 02/01/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 08/01/2013, EFSA received the requested information (which was made available to EFSA in electronic format on 07/01/2013).
- During its meeting on 21/03/2013, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to Yestimun® 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: Yestimun® 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 Yestimun®, a positive assessment of its safety, nor a decision on whether Yestimun® is,

[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.

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.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Leiber GmbH, Hafenstraße 24, 49565 Bramsche, Germany.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006 (manufacturing process).

Food/constituent as stated by the applicant

According to the applicant, the food, which is the subject of the claim, is Yestimun®, which is (1,3)-(1,6)-β-D-glucan of brewer's yeast cell wall (100 % *Saccharomyces cerevisiae*).

Health relationship as claimed by the applicant

According to the applicant, β-glucans of the yeast cell wall are dietary fibres that have been shown to induce immunostimulating responses in animals and humans after oral administration. Yestimun® causes a reduction of the number of common cold episodes during the cold season in normal subjects, which was shown in two independent studies. Common colds are caused by viruses, which are pathogens that are eliminated by the body's defence mechanisms. The interaction of yeast β-glucan particles, like Yestimun®, with the Peyer's patches in the intestine alerts the immune system resulting in reduced numbers of common cold episodes and, thus, helps maintaining the body's defence against pathogens.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Daily administration of Yestimun® helps to maintain the body´s defence against pathogens".

Specific conditions of use as proposed by the applicant

According to the applicant, 0.45 g of Yestimun® should be administered twice daily in order to obtain the claimed effect. The target population proposed by the applicant is adults in the general population.

ASSESSMENT

1. Characterisation of the food/constituent

The food that is the subject of the health claim is Yestimun®.

Yestimun® consists of (1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall (100 % *Saccharomyces cerevisiae*) (about 90 % by weight). β-Glucans are polysaccharides consisting of a backbone of D-glucose subunits linked by (1,3)-β-glucosidic bonds with irregular β-(1,6)-linked glucosidic side chains of various length. Information about the stability of the product, about the batch-to-batch variability of the (1,3)-(1,6)-β-D-glucan content in different batches of Yestimun® and about the manufacturing process has been provided by the applicant. β-Glucans are measureable in foods by established methods.

The Panel considers that the food, Yestimun® ((1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall), 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 related to the defence against pathogens in the upper respiratory tract. The target population proposed by the applicant is adults in the general population.

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 in Medline for publications in English and German using keywords, "like yeast beta-glucan, immune system, oral, human, study, trial". Studies were included if they used insoluble yeast β-glucans and investigated the incidence of common cold infections in humans or immunological parameters in animal and in *ex vivo* models. Exclusion criteria comprised studies using β-glucans other than *S. cerevisiae*-derived β-glucans and studies with parenteral administration.

As directly pertinent to the claim, the applicant identified through the literature search one published randomised controlled trial (RCT) (Feldman et al., 2009) and provided two unpublished RCTs (Graubaum, 2007, unpublished; Bothe, 2011, unpublished).

In the randomised, double-blind, placebo-controlled, seven-centre study by Bothe (2011, unpublished), 224 subjects (mean age: 46.0±15.7 years; 146 female) with recurrent upper respiratory tract infections were randomised to consume daily either 900 mg (2 x 450 mg) Yestimun® (n=112) or placebo (maltodextrin, n=112) for 16 weeks (from October 2010 to May 2011). The primary endpoint of the study was the reduction in the number of common cold episodes per subject during the study period. Secondary outcomes were the severity of an entire common cold episode, the severity of an episode in the first two days, the severity of the episode at the "Episode Visit" (at the fifth day of each common cold episode), the duration of a cold episode and the use of antibiotics and analgesics.

Subjects rated daily the severity of 10 pre-defined symptoms (headache, joint pain, sore throat, feeling of lump in the throat/difficulty swallowing, hoarseness, cough, running nose, nasal congestion, cold-related sleeping difficulties, "fever" (not defined)) on a 4-level Likert item (symptom-free, mild, moderate and severe symptoms, except for "fever" which was always rated as severe) in diaries.

A common cold episode was defined by the occurrence of at least two of the following symptoms rated at least as mild (2 on the 4-point item): sore throat, feeling of lump in the throat/difficulty swallowing, hoarseness, cough, running nose and nasal obstruction. Upon occurrence of a common cold episode, a composite score was calculated to assess the severity of the common cold episode.

Following a request from EFSA to provide a rationale for the use of this questionnaire to assess the incidence, duration and severity of common cold episodes, the applicant referred to the Jackson criteria. These criteria include the rating of the following common cold symptoms on a 4-point item: sneezing, headache, 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 (Jackson et al., 1958).

The Panel notes that both the questionnaire and the criteria used in the study by Bothe (2011, unpublished) to assess the incidence, duration and severity of common cold episodes differ from those developed by Jackson et al. (1958). The Panel considers that the evidence provided by the applicant does not establish the validity of the questionnaire and the criteria used in the study to assess the incidence, duration or the severity of common cold episodes.

Data were analysed by the Mann Whitney U test or by the χ^2 test if proportions were analysed. In one study site, the average number of common cold episodes was statistically significantly different from the other study sites and lower than the expected number of common cold episodes per subject. Data from this study site (60 subjects) were removed from data analyses. Upon a request from EFSA to re-analyse the data taking into account this study site, the applicant explained that this centre was excluded from analysis owing to possible underreporting of the outcome but did not provide the requested re-analysis of the data.

The Panel notes that the evidence provided by the applicant does not establish the validity of the questionnaire and the criteria used in the study to assess the incidence, duration or the severity of common cold episodes. The Panel also notes that removing one centre from data analysis owing to possible underreporting which might have occurred in this site is not an appropriate justification for removing the site from the statistical analysis, that the results of the requested re-analysis of the data including this centre were not presented and that the statistical analysis did not account for the multi-centre design of the study. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

In the randomised, double-blind, placebo-controlled, five-centre study by Graubaum (2007, unpublished), 100 healthy adult subjects (median age: 46.3 years, 58 women) with recurrent upper respiratory tract infections were randomised to consume daily either 900 mg (2 x 450 mg, n=50) Biolex® Beta HP capsules (identical to Yestimun®) or placebo (micro-crystalline cellulose, n=50) for 26 weeks (from November 2006 until June 2007). Doses of Biolex® Beta HP or placebo had to be doubled upon occurrence of a common cold episode for the duration of the episode. The primary outcome of the study was the frequency of occurrence of common cold episodes. Secondary outcomes included the frequency of occurrence of individual common cold symptoms on the first day of the episode, severity of common cold symptoms expressed as composite common cold scores on days 1 to 5 of the episode, relative changes in severity of common cold symptoms expressed as composite common cold scores from day 1 to day 3 and from day 1 to day 5, and the "therapeutic success" of doubling the dose of Biolex® Beta HP or placebo upon occurrence of a common cold episode (=necessary intervention period until the first symptom free day of individual common cold symptoms). The Panel notes that for the present evaluation only outcomes related to the single dose of Biolex® Beta HP were considered further and not those outcomes which were the target for treatment by doubling the dose of the intervention.

Subjects rated daily the severity of six pre-defined symptoms (general feeling of illness, headache and/or joint pain, sore throat and/or difficulty in swallowing, hoarseness and/or coughing, watery nasal discharge and cold related sleeping difficulties) on a 3-level Likert item (no symptoms, mild symptoms, severe symptoms).

A common cold episode was defined by the occurrence of at least one of the following symptoms: headache and/or joint pain; sore throat and/or difficulty swallowing; hoarseness and/or cough; rhinorrhoea; cold related sleep difficulty. Upon occurrence of a common cold episode, subjects also had to present themselves to the investigator, who documented the symptoms experienced by subjects at the beginning of the episode and five days thereafter. A composite score was calculated to assess the severity of the common cold episode.

As for the study by Bothe (2011, unpublished), the Panel considers that the evidence provided by the applicant does not establish the validity of the questionnaire and the criteria used in the study to assess the incidence or the severity of common cold episodes.

Data were analysed using the Mann-Whitney U test. The χ^2 test was used when proportions were analysed. A non-parametric, multivariate analysis for repeated measures was used in the longitudinal analysis of secondary outcomes. *Post-hoc* analyses were performed based on episodes that occurred in the winter months (November to March, first half of the study) to avoid error that might have arisen

owing to possible misdiagnosis of allergic rhinitis as common cold infections during the summer months.

The Panel notes that the evidence provided by the applicant does not establish the validity of the questionnaire and the criteria used in the study to assess the incidence or the severity of common cold episodes. The Panel also notes that the statistical analysis did not account for the multi-centre design of the study and that avoidance of possible misdiagnosis is not an appropriate justification for conducing *post-hoc* analyses. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

A double-blind, placebo-controlled, randomised intervention (Feldman et al., 2009) in 40 healthy adults investigated the effects of consuming 500 mg/day Wellmune® (70 % yeast beta-glucan; n=21) for 90 days *vs.* placebo (rice flour; n=19) on symptomatic respiratory tract infections. Upon occurrence of a respiratory symptom, subjects were asked to present themselves to the investigators for diagnosis and were provided with symptom diaries. No information was provided about the criteria used in the diagnosis of respiratory tract infections or about the symptom diaries used.

Endpoints included the number of, and total days with, symptomatic respiratory tract infections (defined as common cold, influenza, pharyngitis), the average duration of a symptomatic respiratory tract infection, symptom severity of 13 pre-defined symptoms, and the number of missed school/work days. A total of 12 subjects dropped out from the study. Changes from baseline were analysed using repeated measures analysis of variance (RM-ANOVA) without correcting for multiple comparisons made.

The Panel notes that the criteria used to diagnose respiratory tract infections are unclear and that information about the symptom diaries used in the study is missing. The Panel also notes the small sample size of the study, the high drop-out rate and that the statistical analysis did not take into account the multiplicity of "primary outcomes". The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The Panel notes that no human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

With respect to the potential mechanism by which Yestimun® could exert the claimed effect the applicant provided two human studies (Döll et al., 2005; Lehne et al., 2006), seven animal studies (Fleischer et al., 2000; Fleischer et al., 2001; Vetvicka et al., 2002; Hong et al., 2004; Li et al., 2005; Małaczewska et al., 2010; Wójcik, 2010), four *in vitro* studies (Seljelid et al., 1981; Sandula et al., 1995; Kankkunen et al., 2010; Goodridge et al., 2011) and seven review publications (Bohn and BeMiller, 1995; Kogan, 2000; Tzianabos, 2000; Brown and Gordon, 2005; Zekovic et al., 2005; Akramiene et al., 2007; Volman et al., 2008).

The Panel notes that in the absence of an effect of Yestimun® in humans on defence against pathogens in the upper respiratory tract the submitted human, animal and *in vitro* studies pertaining to a possible mechanism by which Yestimun® could exert the claimed effect do not provide any scientific evidence for the substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Yestimun® ((1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall) and defence against pathogens in the upper respiratory tract.

CONCLUSIONS

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

- The food, Yestimun® ((1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall) which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is related to the defence against pathogens in the upper respiratory tract. The target population proposed by the applicant is adults in 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 Yestimun® ((1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall) and defence against pathogens in the upper respiratory tract.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Yestimun® and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0364_DE). October 2012. Submitted by Leiber GmbH.

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GLOSSARY AND ABBREVIATIONS

RM-ANOVA Repeated measures analysis of variance

RCT Randomised controlled trial