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**SCIENTIFIC OPINION**

# Scientific Opinion on the substantiation of a health claim related to Yestimun® and immune responses pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

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

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## ABSTRACT

Following an application from Leiber GmbH submitted 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 was asked to deliver an opinion on the scientific substantiation of a health claim related to Yestimun® and the initiation of appropriate innate and adaptive immune responses. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data. The Panel considers that the food, Yestimun®, which consists of (1,3)-(1,6)-β-D-glucans from brewer's yeast cell wall (100 % *Saccharomyces cerevisiae*), is sufficiently characterised. The target population is adults. The Panel considers that the initiation of appropriate innate and adaptive immune responses is a beneficial physiological effect. In weighing the evidence the Panel took into account that in the one human intervention study conducted with Yestimun® from which scientific conclusions could be drawn for the scientific substantiation of the claim, no effects of Yestimun® were observed on any outcome that could imply a beneficial effect on the initiation of appropriate innate and adaptive immune responses, and that the evidence provided in the animal and *in vitro* studies does not predict an effect of Yestimun® on the initiation of appropriate innate and adaptive immune responses in humans. The Panel concludes that a cause and effect relationship has not been established between the consumption of Yestimun® and the initiation of appropriate innate and adaptive immune responses.

## KEY WORDS

Yestimun®, beta-glucans, immune responses, health claims.

1 On request from Leiber GmbH, Question No EFSA-Q-2008-667, adopted on 30 April 2010.

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## SUMMARY

Following an application from Leiber GmbH submitted 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 was asked to deliver an opinion on the scientific substantiation of a health claim related to Yestimun® and the initiation of appropriate innate and adaptive immune responses.

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

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*) as "active" ingredient (about 90 % by weight). Beta-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. The Panel considers that the food, Yestimun®, which is the subject of the health claim, is sufficiently characterised.

The claimed effect is "reducing the risk for common cold infections by decreasing the susceptibility for common cold infections during the cold season by strengthening the body's natural defences and improving the body's immune defence against common cold viral infections during the cold season". The target population is adults. The Panel notes that a well-functioning immune system includes the initiation of appropriate innate and adaptive immune responses including defence against viral infections such as common colds. The Panel considers that the initiation of appropriate innate and adaptive immune responses is a beneficial physiological effect.

The applicant identified 17 references as being pertinent to the health claim. These references included 10 human studies, five animal studies and two *in vitro* studies.

Four human intervention studies addressed the effects of intravenously injected yeast beta-glucans. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect owing to the inappropriate route of exposure. Four human studies investigated the effects of oral administration of yeast beta-glucans on immune parameters. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect as the changes of immune parameters do not represent an improvement on the initiation of appropriate innate and adaptive immune responses.

One publication reported on a pilot double blind placebo-controlled randomised intervention on the effects of Wellmune®, a preparation derived from brewer's yeast cell wall (*Saccharomyces cerevisiae*) and containing beta-glucans, on multiple end points. The Panel notes the very small number of subjects recruited, the high drop out rate, the multiplicity of "primary outcomes", and the lack of adjustment for multiple testing. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

An unpublished study report presented the results of a multicentre randomised, double blind, placebo-controlled trial conducted in 100 healthy adult subjects over a period of 26 weeks with Biolex® Beta HP capsules (same as Yestimun®). The primary outcome of the study was the frequency of occurrence of cold episodes. The Panel considers the frequency of occurrence of cold episodes as an indirect measure of the function of the immune system. The difference between test and placebo groups was not statistically significant. Post-hoc analyses were performed based on episodes that occurred in the winter months using both the per-protocol and the intention-to-treat populations. The Panel notes that these post-hoc analyses were not statistically justified by the applicant. The quality of typical common cold symptoms (sore throat and/or difficulty swallowing, hoarseness and/or cough and watery nasal secretion) during the cold episodes was assessed as secondary outcome. The Panel considers that the evidence provided does not establish that changes in any of these secondary outcomes in relation to

the treatment of common cold imply a beneficial effect on the initiation of appropriate innate and adaptive immune responses.

The Panel notes that the evidence provided in animal and *in vitro* studies does not predict an effect of Yestimun® on the initiation of appropriate innate and adaptive immune responses in humans.

In weighing the evidence the Panel took into account that in the one human intervention study conducted with Yestimun® from which scientific conclusions could be drawn for the scientific substantiation of the claim, no effects of Yestimun® were observed on any outcome that could imply a beneficial effect on the initiation of appropriate innate and adaptive immune responses, and that the evidence provided in the animal and *in vitro* studies does not predict an effect of Yestimun® on the initiation of appropriate innate and adaptive immune responses in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Yestimun® and the initiation of appropriate innate and adaptive immune responses.

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## BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

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 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, Article 13(5) of that Regulation lays down provisions for 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 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 that Regulation, an application for authorisation or inclusion in the Community list of permitted claims referred to in Art 13(3) 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 4 December 2009.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.
- The scientific evaluation procedure started on 20 December 2009.
- On 24 March 2010, the NDA Panel agreed on the List of Questions which requests the applicant to submit supplementary information to accompany the application by 13 April 2010.
- The applicant submitted the responses to the NDA Panel List of Questions on 13 April 2010.
- During the meeting on 30 April 2010, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to Yestimun® and initiation of appropriate innate and adaptive immune responses.

## 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(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 the initiation of appropriate innate and adaptive immune responses.

## EFSA DISCLAIMER

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

[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.

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.

### Food/constituent as stated by the applicant

Yestimun® (1,3)-(1,6)-β-D-glucans of brewer's yeast cell wall (100 % *Saccharomyces cerevisiae*).

### Health relationship as claimed by the applicant

According to the applicant beta-glucans of the yeast cell wall are dietary fibres that have been shown to induce immune stimulating responses in animals and humans after oral administration. The applicant states that daily administration of Yestimun® caused a reduction of the number of common cold episodes during the cold season in normal subjects. Hence, the applicant claims that consumption of Yestimun® reduces the risk for common cold infections and, thus, decreases the susceptibility for common cold infections during the cold season by strengthening the body's natural defences.

### Wording of the health claim as proposed by the applicant

"Daily administration of Yestimun® strengthens the body's defence during the cold season."
"Daily administration of Yestimun® strengthens the body's immune defence by reducing the susceptibility for common cold infections during the cold season."
"Daily administration of Yestimun® improves the body's immune defence against common cold viral infections during the cold season."

### Specific conditions of use as proposed by the applicant

0,45 g of Yestimun® should be consumed twice daily.

## 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*) as "active" ingredient (about 90 % by weight). Beta-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. Complete specifications and manufacturing process, composition and stability information have been provided by the applicant.

The Panel considers that the food, Yestimun®, which is the subject of the health claim, is sufficiently characterised.

### 2. Relevance of the claimed effect to human health

The claimed effect is "reducing the risk for common cold infections by decreasing the susceptibility for common cold infections during the cold season by strengthening the body's natural defences and

improving the body's immune defence against common cold viral infections during the cold season". The target population is adults.

The Panel notes that a well-functioning immune system includes the initiation of appropriate innate and adaptive immune responses including defence against viral infections such as common colds. The Panel also notes that the susceptibility to common cold infections as assessed by, e.g., the frequency of occurrence of common cold episodes, may reflect the initiation of appropriate innate and adaptive immune responses.

The Panel considers that the initiation of appropriate innate and adaptive immune responses is a beneficial physiological effect.

## 3. Scientific substantiation of the claimed effect

The applicant performed a literature search in Medline using search terms like "yeast, beta-glucan, immune system, oral, human, study, trial" to identify publications in the English and German languages which reported on studies conducted in healthy subjects or in "patients with different clinical indications". No other details on the search strategy or decision tree for study selection were provided by the applicant.

The applicant identified 17 references as being pertinent to the health claim. These references included 10 human studies, five animal studies and two *in vitro* studies.

Four human intervention studies addressed the effects of intravenously injected yeast beta-glucans (Babineau et al., 1994a and 1994b; Dellinger et al., 1999; De Felippe et al., 1993). The Panel considers that this route of exposure is inappropriate to assess the health effects of a food. Four human studies investigated the effects of oral administration of yeast beta-glucans on immune parameters, such as the Th1/Th2 balance, salivary IgA concentrations, serum concentrations of neopterin and b-defensin synthesis, and/or gingivitis (Kirmaz et al., 2005; Lehne et al., 2006; Döll et al., 2005; Preus et al., 2008). The Panel notes that the evidence provided does not establish that changes in any of these markers represent an improvement on the initiation of appropriate innate and adaptive immune responses. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect.

One publication reported on a pilot double blind placebo-controlled randomised intervention on the effects of Wellmune® on multiple end points including the number of colds, average duration of a cold, number of symptomatic respiratory infections, number of flu or cold episodes, and the number of missed school/work days (Feldman et al., 2009). The applicant states that Wellmune® is a preparation derived from brewer's yeast cell wall (*Saccharomyces cerevisiae*) containing 70 % beta-glucans. A total of 40 healthy adults (28 females) were randomised to consume either 500 mg/day of Wellmune® (n = 21) or identical placebo tablets (rice flour; n = 19) for 90 days. A total of 12 subjects dropped from the study and one subject was not compliant with the study protocol, leading to a total of 27 subjects (14 in the intervention group) entering per-protocol data analysis. Intention-to-treat analyses were presented for 33 subjects only (17 in the intervention group). It is also unclear which was/were the primary outcome(s) of the study. The Panel notes the very small number of subjects recruited, the high drop out rate, the multiplicity of "primary outcomes", and the lack of adjustment for multiple testing. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

An unpublished study report by Graubaum (claimed to be confidential by the applicant) presented the results of a multicentre randomised, double blind, placebo-controlled trial conducted in 100 healthy adult subjects (58 women, 42 men, age = 18-78 years old) who had experienced at least three cold episodes in the six months prior to enrollment. Subjects were randomly assigned to consume either Biolex® Beta HP capsules (same as Yestimun®, 0.45 g per capsule ) twice daily (0.9 g/day) or placebo (identical capsules containing micro-crystalline cellulose in the same amounts) for 26 weeks (from

November 2006 until June 2007). Six subjects (five in the test group, one in placebo) dropped out from the study for personal reasons, and nine additional subjects (four in the test group, five in placebo) did not comply with the study protocol. Data from the remaining 85 subjects (41 in the test group) were considered for per-protocol statistical analyses, whereas data from 94 subjects (excluding drop outs) were considered for intention-to-treat analyses.

The primary outcome of the study was the frequency of occurrence of cold episodes. The Panel considers the frequency of occurrence of cold episodes as an indirect measure of the function of the immune system. A total of 149 cold episodes were recorded among the 85 subjects considered for per-protocol analyses. The difference between test and placebo groups in the frequency of occurrence of cold episodes was not statistically significant. Similarly, a total of 171 cold episodes were recorded in the 94 subjects considered for intention-to-treat analyses. The difference between test and placebo groups was not statistically significant. Post-hoc analyses were performed based on episodes that occurred in the winter months (November to March, first half of the study) using both the per-protocol and the intention-to-treat populations. The Panel notes that these post-hoc analyses were not statistically justified by the applicant.

The quality of typical common cold symptoms (sore throat and/or difficulty swallowing, hoarseness and/or cough and watery nasal secretion) during the cold episodes was assessed as secondary outcome. Upon occurrence of cold episodes, subjects received a double dosage of four capsules daily (1.8 g/day) of either Biolex® Beta HP (Yestimun®) or placebo over a period of 5 days, then returning to the consumption of two capsules per day as per protocol. The Panel considers that the evidence provided does not establish that changes in any of these secondary outcomes in relation to the treatment of common cold imply a beneficial effect on the initiation of appropriate innate and adaptive immune responses.

The applicant identified five animal and two *in vitro* studies as being pertinent to the claim. The cell culture studies submitted by the applicant investigated the ability of yeast beta-glucans to stimulate and activate immune mouse and rat cells like macrophages and thymocytes (Seljelid et al., 1981; Sandula et al., 1995). The animal study by Vetvicka et al. (2002) investigated the oral administration of yeast beta-glucan as a prophylactic treatment to reduce the mortality of anthrax infection in mice and the inhibition of the growth of cancer cells *in vivo*. The study by Fleischer et al. (2000) investigated the effects of beta-glucans and fluochinolone enrofloxacin on red and white blood cells and plasma proteins of growing chickens. The humoral immune response (immunoglobulin production) was investigated in the study by Fleischer et al. (2001) in pigs. The study by Li et al. (2005) investigated the variation of pro-inflammatory cytokines in pigs after a diet supplemented with beta-glucans. The study by Hong et al. (2004) investigated the mechanism by which orally administered beta-glucans could enhance the tumoricidal activity of antitumor monoclonal antibodies in murine tumor models. The Panel notes that the evidence provided in animal and *in vitro* studies does not predict an effect of Yestimun® on the initiation of appropriate innate and adaptive immune responses in humans.

In weighing the evidence the Panel took into account that in the one human intervention study conducted with Yestimun® from which scientific conclusions could be drawn for the scientific substantiation of the claim, no effects of Yestimun® were observed on any outcome that could imply a beneficial effect on the initiation of appropriate innate and adaptive immune responses, and that the evidence provided in the animal and *in vitro* studies does not predict an effect of Yestimun® on the initiation of appropriate innate and adaptive immune responses in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Yestimun® and the initiation of appropriate innate and adaptive immune responses.

## CONCLUSIONS

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

- Yestimun®, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "reducing the risk for common cold infections by decreasing the susceptibility for common cold infections during the cold season by strengthening the body's natural defences and improving the body's immune defence against common cold viral infections during the cold season". The target population is adults. The initiation of appropriate innate and adaptive immune responses is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of Yestimun® and the initiation of appropriate innate and adaptive immune responses.

## DOCUMENTATION PROVIDED TO EFSA

Health claim application on Yestimun® and the initiation of appropriate innate and adaptive immune responses pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0215_DE). December 2009. Submitted by Leiber GmbH.

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