European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms (ID 913, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

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

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a health claim pursuant to Article 13 of Regulation (EC) No 1924/2006 in the framework of further assessment related to *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms. The food constituent that is the subject of the health claim, *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079, is sufficiently characterised. The claimed effect, defence against pathogenic gastro-intestinal microorganisms, is a beneficial physiological effect. The proposed target population is the general population. The Panel notes that the evidence provided is not sufficient to establish that the strains *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and *Saccharomyces cerevisiae* var. *boulardii* Hansen CBS 5926, which were used in the studies provided, are identical, and considers that owing to the possibility that the effects are strain-specific, results obtained with one strain cannot be extrapolated to another strain. On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms.

KEY WORDS

Saccharomyces cerevisiae var. *boulardii*, CNCM-I-1079, gastro-intestinal, microorganism, health claims.

[1] On request from the European Commission, Question No EFSA-Q-2012-00127, adopted on 26 April 2012.

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SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. This opinion addresses the scientific substantiation of health claims in relation to *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms. The scientific substantiation is based on the information provided by the competent Authority of the United Kingdom for further assessment of this claim.

The food constituent that is the subject of the health claim is *Saccharomyces cerevisiae* var. *boulardii* CNCM-I-1079. The Panel considers that *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 is sufficiently characterised.

The claimed effect, which is proposed for further assessment, relates to defence against gastro-intestinal pathogens. The proposed target population is the general population. The Panel considers that defence against pathogenic gastro-intestinal microorganisms is a beneficial physiological effect.

The Panel notes that the evidence provided is not sufficient to establish that the strains *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and *Saccharomyces cerevisiae* var. *boulardii* Hansen CBS 5926, which were used in the studies provided, are identical, and that none of the studies provided for the substantiation of the claim was conducted with the strain that is the subject of the claim (i.e. *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079). The Panel considers that owing to the possibility that the effects are strain-specific, results obtained with one strain cannot be extrapolated to another strain.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms.

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INTRODUCTION

The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. These claims include already assessed claims related to micro-organisms which the Panel considered to be not sufficiently characterised and claims for which the NDA Panel concluded that there was insufficient evidence to establish a cause and effect relationship between the consumption of the food and the claimed effect.

Following an opinion of the NDA Panel on a health claim pursuant to Article 13 of Regulation (EC) No 1924/2006[4] in which the Panel concluded that the data available were not sufficient to characterise "*Saccharomyces cerevisiae* var. *boulardii*" (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009), EFSA received additional information from the competent Authority of the United Kingdom for further assessment of this claim. The information provided in the framework of further assessment for the health claims which are the subject of this opinion is tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent (ID 913)

The food constituent that is the subject of the health claim is *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 (hereafter *S. cerevisiae* var. *boulardii* CNCM I-1079). Data on phenotypic (morphological and biochemical analyses) and genotypic (RFLP analysis using a yeast DNA transposon probe for hybridisation, and PFGE and PCR delta sequence analysis) characterisation of *S. cerevisiae* var. *boulardii* CNCM I-1079 were provided in the application.

Three references were also provided in the application related to the molecular techniques used for the identification and genetic typing of *S. cerevisiae* strains (Hennequin et al., 2001; Mallié et al., 2001; van der Aa Kühle and Jespersen, 2003), but none of them provided data on the strain that is the subject of the health claim, *S. cerevisiae* var. *boulardii* CNCM I-1079.

For *S. cerevisiae* var. *boulardii* CNCM I-1079, a culture collection number from the Collection Nationale de Cultures de Microorganismes (CNCM) was provided. The CNCM is a restricted-access non-public collection, which has the status of an International Depositary Authority under the Budapest Treaty.

Data on the production and quality controls (identity, purity, and biological and chemical safety) of the strain culture and the encapsulation process of *S. cerevisiae* var. *boulardii* CNCM I-1079 were provided.

The Panel considers that the food constituent, *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health (ID 913)

The claimed effect, which is proposed for further assessment, relates to defence against gastro-intestinal pathogens. The proposed target population is the general population.

The presence of pathogenic micro-organisms in the gastro-intestinal tract (e.g. viruses and bacteria) may lead to the development of gastro-intestinal infections. Maintenance of defence against

[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.

pathogenic gastro-intestinal microorganisms may protect against gastro-intestinal infections and associated diarrhoea.

The Panel considers that defence against pathogenic gastro-intestinal microorganisms is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect (ID 913)

The references provided included human studies which addressed the effect of *S. cerevisiae* var. *boulardii* on incidence of antibiotic-associated diarrhoea related to *Clostridium difficile* (Can et al., 2006; Lewis et al., 1998; McFarland et al., 1995; Surawicz et al., 1989); on *Clostridium difficile* recurrent diarrhoea (Surawicz et al., 2000); on antibiotic-associated diarrhoea related to candidiasis (Adam et al., 1977); on side-effects of *Helicobacter pylori* eradication therapy (Cindoruk et al., 2007; Cremonini et al., 2002; Duman et al., 2005); on traveller's diarrhoea (Kirchhelle et al., 1996; Kollaritsch et al., 1989; Kollaritsch et al., 1993); on amoebiasis (Mansour-Ghanaei et al., 2003); on acute diarrhoea of unknown origin (Hochter et al., 1990); and four meta-analyses (D'Souza et al., 2002; McFarland, 2006, 2010; Szajewska and Mrukowicz, 2005). Animal studies, *in vitro* studies and a review paper were also provided. The Panel notes that the review submitted (Zanello et al., 2009) did not provide original data that can be used for the substantiation of the claim. The Panel also notes that in two animal studies (Girard et al., 2003; Sezer et al., 2009) models of diarrhoea of non-infectious origin were used, and that, therefore, they did not provide information that can be used for the scientific substantiation of a claim on defence against pathogens.

According to the application, the studies provided for the substantiation of the claim were conducted with the strain *S. cerevisiae* var. *boulardii* Hansen CBS 5926 from Biocodex, except for four studies in which the strain used was not specified. In two out of these four studies, the commercial brand name was mentioned (Perenterol®), which according to the application is manufactured by the owner of *S. cerevisiae* var. *boulardii* Hansen CBS 5926 (Kirchhelle et al., 1996; Kollaritsch et al., 1993), while the other two studies were conducted or sponsored by the company which owns *S. cerevisiae* var. *boulardii* Hansen CBS 5926 (Hochter et al., 1990; Surawicz et al., 2000).

In the application it was stated that "the strain *S. cerevisiae* var. *boulardii* CNCM I-1079 is genetically equivalent to *S. boulardii* CBS 5926 (also named *S. cerevisiae* var. *boulardii* Hansen CBS 5926 or ATCC 74012)" based on the genotypic analyses previously described in the characterisation section (RFLP analysis using a yeast DNA transposon probe for hybridisation and PFGE analysis) and submitted in the application.

The Panel notes that the evidence provided is not sufficient to establish that the strains *S. cerevisiae* var. *boulardii* CNCM I-1079 and *S. cerevisiae* var. *boulardii* Hansen CBS 5926 are identical, and that none of the studies provided for the scientific substantiation of the claim were conducted with the strain that is the subject of the claim (i.e. *S. cerevisiae* var. *boulardii* CNCM I-1079). The Panel considers that owing to the possibility that the effects are strain-specific, results obtained with one strain cannot be extrapolated to another strain.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms.

CONCLUSIONS

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

- The food constituent, *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed for further assessment relates to defence against gastro-intestinal pathogens. The proposed target population is the general population. Defence against pathogenic gastro-intestinal microorganisms is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of *Saccharomyces cerevisiae* var. *boulardii* CNCM I-1079 and defence against pathogenic gastro-intestinal microorganisms.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 for further assessment (No: EFSA-Q-2012-00127). The scientific substantiation is based on the information provided by the competent Authority of the United Kingdom for further assessment of this claim (available at: http://www.efsa.europa.eu/en/topics/topic/article13.htm).

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APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[5] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[6]

Foods are commonly involved in many different functions[7] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[5] OJ L12, 18/01/2007

[6] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.

[7] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.

- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.

- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.
- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. 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 wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

APPENDIX C

Table 1. Health claims related to *Saccharomyces cerevisiae* var. *boulardii* CNCM-I-1079, including conditions of use, as proposed in the framework of further assessment.

ID	Food or Food constituent	Health Relationship	Proposed wording
913	*Saccharomyces boulardii* CNCM-I-1079	The food constituent helps to fight against gastro-intestinal (GI) pathogens. The presence of pathogenic microorganisms in the GI tract may lead to the development of GI infections like diarrhea from different etiology (antibiotic associated diarrhea, traveller's diarrhea, acute diarrhea). Indeed, antibiotic treatments, change in dietary habits when travelling, or hospitalization can lead to GI infections accompanied with diarrheas. Maintenance of the defence against pathogenic GI microorganisms may protect against the development of GI infections and has been found by the EFSA NDA Panel as being a beneficial physiological effect. (EFSA Journal 2011, 9(6):2167). Moreover, decreasing potentially pathogenic intestinal microorganisms might be beneficial to human health (EFSA Journal 2009, 7(9):1232 and 1242). Outcome measures used to assess the claimed effects in humans include incidence of diarrhea, stool frequency and consistency, and presence of *Clostridium difficile* in stools.	The food constituent is helping to maintain gut health by improving defence against pathogens in the gastro-intestinal tract, particularly in people with impaired gut health.
	Conditions of use A review of the scientific literature shows a broad range of daily dosages for *S. boulardii* (2*109 to $3*10^{10}$ CFU/day) for the intended use of protection against pathogens and the development of gastro-intestinal infections in adults. General population with impaired gut health, including people taking antibiotics (which are often associated with diarrhea) or travellers to developing countries, who are a high risk population for the development of diarrhea (traveller's diarrhea mainly caused by bacteria; *E. coli* is the pathogen most frequently isolated).		

GLOSSARY AND ABBREVIATIONS

CFU	Colony forming units
CNCM	Collection Nationale de Cultures de Microorganismes
DNA	Deoxyribonucleic acid
PCR	Polymerase chain reaction
PFGE	Pulsed field gel electrophoresis
RFLP	Reaction fragment length polymorphisms