A combination of beta-sitosterol and beta-sitosterol glucoside and normal function of the immune system: evaluation of a health claim pursuant to article 13(5) of regulation (ec) no 1924/2006

Dominique Turck, Jacqueline Castenmiller, Stefaan de Henauw, Karen Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J. Mcardle, Androniki Naska, et al.

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A combination of beta-sitosterol and beta-sitosterol glucoside and normal function of the immune system: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Jacqueline Castenmiller, Stefaan De Henauw, Karen Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Frank Thies, Sophia Tsabouri, Marco Vinceti, Jean-Louis Bresson and Alfonso Siani

Abstract

Following an application from Essential Sterolin Products (Pty) Ltd., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of beta-sitosterol and beta-sitosterol glucoside and normal function of the immune system. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The food proposed by the applicant as the subject of the health claim is a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1. The Panel considers that a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1 is sufficiently characterised. The claimed effect proposed by the applicant is 'normal function of the immune system by restoring balance between T_H1-T_H2 mediated immunity'. The Panel notes that the claimed effect 'normal function of the immune system by restoring balance between T_H1- and T_H2-mediated immunity' does not refer to a specific function of the body which can be assessed *in vivo* in humans by generally accepted methods, but rather to a mechanism of action by which the food/constituent could exert the claimed effect. The Panel considers that the claimed effect does not refer to any specific health claim as required by Regulation (EC) No 1924/2006. The Panel concludes that a cause and effect relationship cannot be established between the consumption of a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1 and a beneficial physiological effect.

Keywords: beta-sitosterol, beta-sitosterol glucoside, immune system, health claim

Requestor: Competent Authority of the Netherlands following an application by Essential Sterolin Products (Pty) Ltd.

Question number: EFSA-Q-2018-00701

Correspondence: nda@efsa.europa.eu

Panel members: Dominique Turck, Jacqueline Castenmiller, Stefaan De Henauw, Karen Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri, Marco Vinceti.

Competing interests: In accordance with Article 21 of the Decision of the Executive Director on Competing Interest Management (http://www.efsa.europa.eu/en/corporate/pub/policyonindependence), a waiver was granted to an expert of the working group, Jean-Louis Bresson. Pursuant to Article 21(6) of the afore-mentioned Decision, the concerned expert was allowed to take part in the discussion and in the drafting phase of the scientific output.

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Summary

Following an application from Essential Sterolin Products (Pty) Ltd., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of beta-sitosterol and beta-sitosterol glucoside and immune defence against pathogens.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications and the guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms.

The food proposed by the applicant as the subject of the health claim is a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1. The Panel considers that a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1, which is the subject of the health claim, is sufficiently characterised.

The claimed effect proposed by the applicant is 'contribution to the normal function of the immune system by restoring balance between T_H1-T_H2 mediated immunity'. The proposed target population is 'adults and children older than 6 years'.

The Panel notes that the claimed effect 'contribution to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity' does not refer to a specific function of the body which can be assessed *in vivo* in humans by generally accepted methods, but rather to a mechanism of action by which the food/constituent could exert the claimed effect.

The Panel considers that the claimed effect does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

On the basis of the data provided, the Panel concludes that a cause and effect relationship cannot be established between the consumption of a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1 and a beneficial physiological effect.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006[1] 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).

1.2. Interpretation of the Terms of Reference

European Food Safety Authority (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: a combination of beta-sitosterol (BSS) and beta-sitosterol glucoside (BSSG) and normal function of the immune system.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of a combination of BSS and BSSG, a positive assessment of its safety, nor a decision on whether a combination of BSS and BSSG 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.

2. Data and methodologies

2.1. Data

Information provided by the applicant

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is 'a combination of beta-sitosterol and beta-sitosterol glucoside (100:1)'.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect relates to: 'contributes to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity'.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

The applicant claims that 'the combination of beta-sitosterol and beta-sitosterol glucoside (100:1) has been shown to influence the T-lymphocytes. After oral intake, the number of T_H1 cells was increased whereas T_H2 cells were inhibited or remained unchanged. Furthermore, the BSS/BSSG mixture stimulated the production of interleukin (IL)-2 and interferon (INF)-gamma but inhibited the secretion of IL-4. Therefore, BSS/BSSG could have a modulatory effect in a number of infectious diseases and also help to reinstate the balance in autoimmune diseases and in patients with allergic reactions'.

[1] 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.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'contributes to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity'.

Specific conditions of use as proposed by the applicant

According to the applicant, the target population for the intended health claim is 'adults and children older than 6 years'. The daily consumption of one capsule (containing BSS 20 mg and BSSG 0.20 mg) three times a day is recommended for adults and children older than 17 years, one capsule twice a day for children 11–16 years old and one capsule one or two times a day for children 6–10 years old.

Data provided by the applicant

Health claim application on a combination of BSS and BSSG and immune defence against pathogens pursuant to Article 13.5 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of a health claim application.[2]

As outlined in the General guidance for stakeholders on health claim applications,[3] it is the responsibility of the applicant to provide the totality of the available evidence.

2.2. Methodologies

The general approach of the Nutrition, Novel Foods and Food Allergens (NDA) Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016a).

The scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms are outlined in a specific EFSA guidance (EFSA NDA Panel, 2016b).

The application does not contain data claimed as confidential and as proprietary.

3. Assessment

The approach used by the NDA panel for the evaluation of health claims is explained in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016a).

In assessing each specific food/health relationship which forms the basis of a health claim, the Panel considers the following key questions:

i) the food/constituent is defined and characterised;
ii) the claimed effect is based on the essentiality of a nutrient; OR
the claimed effect is defined and is a beneficial physiological effect for the target population, and can be measured *in vivo* in humans;
iii) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Each of these three questions needs to be assessed by the Panel with a favourable outcome for a claim to be substantiated. In addition, an unfavourable outcome of the assessment of questions (i) and/or (ii) precludes the scientific assessment of question (iii).

3.1. Characterisation of the food/constituent

The food proposed by the applicant as the subject of the health claim is 'a fixed combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1'.

Beta-sitosterol and beta-sitosterol glucoside are plant sterols with molecular weights of 414.72 and 576.86 g/mol, respectively.

[2] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhauser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Sjodin A, Stern M, Tome D, Van Loveren H, Vinceti M, Willatts P, Martin A, Strain JJ, Heng L, Valtuena Martınez S and Siani A, 2017. Scientific and technical guidance for the preparation and presentation of a health claim application (Revision 2). EFSA Journal 2017;15(1):4680, 31 pp. https://doi.org/10.2903/j.efsa.2017.4680

[3] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 38 pp. https://doi.org/10.2903/j.efsa.2016.4367

Upon a request from EFSA, the applicant clarified that the food/constituent, which is the subject of the claim, is a fixed combination of BSS and BSSG from any source in a ratio of 100:1 on a weight basis.

The details related to manufacturing process and stability information were provided in the application. Plant sterols can be assessed in food by well-established methods.

The Panel considers that a fixed combination of BSS and BSSG in a ratio 100:1, which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is 'contributes to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity'. The proposed target population is 'adults and children older than 6 years'.

It is stated in the application that 'the function of the body that is subject to the claim for the targeted population is the immune system' and that the food/constituent 'could have a modulatory effect in a number of infectious diseases and also help to reinstate the balance in auto-immune diseases and in patients with allergic reactions'.

The Panel considers that 'contributes to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity' is not sufficiently defined for a scientific evaluation (EFSA NDA Panel, 2016b).

The Panel notes that the outcome variables assessed in the human studies provided for the scientific substantiation of the claim include human lymphocyte proliferation, killing ability of natural killer (NK) cells against a target cancer cell line, number of CD4 cells of the T_H1 phenotype (Bouic et al., 1996); T_H1 in allergic individuals (Myers and Bouic, 1998); IL-6 and Tumour Necrosis Factor (TNF)-α in patients with rheumatoid arthritis (Louw et al., 2002); T_H1:T_H2 ratio in individuals with Human Immunodeficiency Virus (HIV) infection (Breytenbach et al., 2001), haematological parameters, inflammatory cytokines, CD3 and CD4, cortisol and IL-6 concentration and the cortisol: dehydroepiandrosterone (DHEA) ratio in a group of marathon runners (Bouic et al., 1999).

The Panel considers that these outcome variable(s), which can be measured *in vivo* in humans by generally accepted methods but do not refer to a benefit on specific functions of the body (i.e. changes in immune markers, e.g. numbers of various lymphoid subpopulations in the circulation, proliferative responses of lymphocytes, phagocytic activity of phagocytes, lytic activity of NK cells and cytolytic T cells, production of cellular mediators, serum and secretory immunoglobulin levels, delayed-type hypersensitivity responses), cannot constitute the only basis for the scientific substantiation of a health claim (EFSA NDA Panel, 2016a; EFSA NDA Panel, 2016b). Changes in these outcome variables should be accompanied by evidence of a beneficial physiological effect or clinical outcome in the application (EFSA NDA Panel, 2016b).

Upon a request from EFSA to define the claimed effect and to indicate the outcome variable(s) and the methods of measurement which could be appropriate to assess the claimed effect in human studies, the applicant replied as follows: 'The fixed combination of phytosterols (beta-sitosterol and beta-sitosterol glucoside) selectively enhances T_H1 and the production of IL-2 while reducing T_H2 and IL-6. That is, the fixed combination of phytosterols (beta-sitosterol and beta-sitosterol glucoside) targets the abnormality and corrects the immune dysfunction. In other words, the fixed combination of phytosterols (beta-sitosterol and beta-sitosterol glucoside) keeps the immune system in a healthy state of balance'.

The Panel notes that the claimed effect 'contribution to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity' does not refer to a specific function of the body which can be assessed *in vivo* in humans by generally accepted methods, but rather to a mechanism by which the food/constituent could exert the claimed effect.

The Panel considers that the claimed effect does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

The Panel concludes that a cause and effect relationship cannot be established between the consumption of a combination of BSS and BSSG in a ratio 100:1 and a beneficial physiological effect.

4. Conclusions

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

- The food/constituent, a combination of BSS and BSSG in a ratio 100:1, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is 'contribution to the normal function of the immune system by restoring balance between T_H1- and T_H2- mediated immunity'. The target

population proposed by the applicant is 'adults and children older than 6 years'. The claimed effect does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.
- A cause and effect relationship cannot be established between the consumption of a combination of BSS and BSSG in a ratio 100:1 and a beneficial physiological effect.

Steps taken by EFSA

Health claim application on 'a combination of beta-sitosterol and beta-sitosterol glucoside' and 'normal function of the immune system' pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0478_NL). Submitted by Essential Sterolin Products (Pty) Ltd., P.O. Box 958, Halfway House 1685, South Africa.

1) This application was received by EFSA on 11/09/2018.
2) The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
3) The scientific evaluation procedure started on 23/04/2019.
4) On 17/05/2019, 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 scientific evaluation was suspended on 27/05/2019 and was restarted on 12/06/2019, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
5) During its meeting on 03/07/2019, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to a combination of beta-sitosterol and beta-sitosterol glucoside in a ratio 100:1 and normal function of the immune system.

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Abbreviations

BSS	beta-sitosterol
BSSG	beta-sitosterol glucoside
DHEA	dehydroepiandrosterone
HIV	Human Immunodeficiency Virus
IL	Interleukin
INF	Interferon
NDA	Nutrition, Novel Foods and Food Allergens
NK	Natural Killer
T_H	T Helper
TNF-α	Tumour Necrosis Factor-α