EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to barley beta-glucan and lowering of blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006

EFSA Publication; Tetens, Inge

Link to article, DOI:
10.2903/j.efsa.2011.2470

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

European Food Safety Authority

EFSA Journal 2011;9(12):2470

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to barley beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 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 Cargill Incorporated submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to barley beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease, referring to disease risk reduction and including a request for the protection of proprietary data. The food constituent that is the subject of the health claim, barley beta-glucans, is sufficiently characterised. Lowering blood LDL-cholesterol concentration is a beneficial physiological effect by decreasing the risk of coronary heart disease. The applicant identified a total of 16 references as being pertinent to the health claim. These references comprised three meta-analyses, 10 human intervention studies, two animal studies and one mechanistic study. In weighing the evidence, the Panel took into account that one meta-analysis including 11 RCTs and one additional RCT which investigated the effects of barley beta-glucans at doses of at least 3 g/day showed a decrease in total and LDL-cholesterol concentrations in both normo- and hypercholesterolaemic subjects, and that the mechanism by which barley beta-glucans could exert the claimed effect is biologically plausible and supported by the animal studies provided. The Panel concludes that a cause and effect relationship has been established between the consumption of barley beta-glucans and the lowering of blood LDL-cholesterol concentrations. The following wording reflects the scientific evidence: "Barley beta-glucans have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease". At least 3 g of barley beta-glucans should be consumed per day in order to obtain the claimed effect. The target population is adults who want to lower their blood cholesterol concentrations.

KEY WORDS

Barley beta-glucans, fibre, blood cholesterol, LDL-cholesterol, health claims.

---

[1] On request from the Competent Authority of Belgium following an application by Cargill Incorporated, Question No EFSA-Q-2011-00798, adopted on 23 November 2011.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen for the preparatory work on this scientific opinion.

Suggested citation: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to barley beta-glucan and lowering of blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(12):2470. [14 pp.]. doi:10.2903/j.efsa.2011.2470. Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following an application from Cargill Incorporated submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to barley beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction and including a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is barley beta-glucans. Beta-glucans are non-starch polysaccharides composed of glucose molecules in long linear polymers. Beta-glucans occur naturally in barley and are measurable in foods by established methods. This opinion applies to barley beta-glucans naturally present in foods and to those forms added to foods. The Panel considers that the food constituent, barley beta-glucans, which is the subject of the health claim, is sufficiently characterised.

The claimed effect is "lowering/reduction of blood cholesterol, which may reduce the risk of (coronary) heart disease". The target population proposed by the applicant is adults with normal or mildly elevated blood cholesterol concentrations. The Panel considers that lowering blood LDL-cholesterol concentration is a beneficial physiological effect by decreasing the risk of coronary heart disease.

The Panel has already issued an opinion on beta-glucans from various sources, including barley, and maintenance of normal blood cholesterol concentrations, pursuant to Article 13(1) of Regulation (EC) No 1924/2006, with a favourable outcome. The Panel has also issued an opinion on barley beta-glucans and reduction of blood cholesterol concentrations, which may reduce the risk of (coronary) heart disease, pursuant to Article 14 of Regulation (EC) No 1924/2006, with a favourable outcome.

The applicant identified a total of 16 references as being pertinent to the health claim. These references comprised three meta-analyses, 10 human intervention studies, two animal studies and one mechanistic study.

The information provided for one of the studies was insufficient to allow a scientific evaluation by the Panel. The mechanistic study was an acute trial concerned with the production of short chain fatty acids following the consumption of cereal-based meals. The Panel considers that no conclusions can be drawn from these two studies for the scientific substantiation of the claim.

The first meta-analysis comprised 11 studies (17 treatment arms) which included a total of 591 subjects. Seven studies had a cross-over design and four had a parallel design. The duration of the intervention lasted from 4 to 12 weeks (mean 5.2 weeks) and 10–62 subjects were enrolled in the studies. Study populations were both normo- and hypercholesterolaemic, with mean blood cholesterol ranges from 3.6 to 8.6 mmol/L. The mean age ranged from 20 to 63 years. Mean baseline body mass index ranged from 19 to 35 kg/m^2. The estimated daily consumption of barley beta-glucans ranged from 3 to 12 g, with a median intervention dose of 5 g/day. The sources of barley beta-glucans included barley flour, barley flakes, pearled barley, and barley bran. Most control groups received comparable products based on wheat or rice. Overall, barley beta-glucans lowered total and LDL-cholesterol concentrations by 0.30 mmol/L (95 % CI: 0.39 to 0.21, $p<0.00001$) and 0.27 mmol/L (95 % CI: 0.34 to 0.20, $p<0.00001$), respectively. HDL-cholesterol concentrations were not affected.

The second meta-analysis included eight studies, seven of which were already included in the meta-analysis above. The additional study was a randomised, parallel, 30-day intervention trial in

79 hypercholesterolaemic subjects. The results from this meta-analysis were similar to those obtained in the first meta-analysis. Barley beta-glucans lowered total and LDL-cholesterol concentrations by 0.35 mmol/L (95 % CI: 0.48 to 0.21, $p<0.05$) and by 0.26 mmol/L (95 % CI: 0.36 to 0.16, $p<0.05$), respectively. Other blood lipid parameters were not affected. To address publication bias, visual inspection of funnel plots, Egger's weighted regression statistics, and the trim and fill method were applied. When potentially missing studies (i.e. unpublished negative studies) were taken into account, barley beta-glucans still had a significant, albeit reduced, effect on total and LDL-cholesterol concentrations.

The applicant submitted a third meta-analysis with a total of eight studies which were already taken into account in the first meta-analysis above. The Panel notes that this third meta-analysis does not provide additional information for the scientific substantiation of the claim.

In a randomised controlled cross-over trial, 24 mildly hypercholesterolaemic men consumed a barley beta-glucan enriched diet (6 g barley beta-glucans per day) or a rice bran-enriched control diet for 4 weeks each (with a 3-week washout in between) after a 3-week run-in period. Compared to the rice-bran diet, the barley beta-glucan diet induced a significant decrease in total and LDL-cholesterol concentrations of 0.34 mmol/L (95 % CI: 0.47 to 0.20, $p<0.001$) and 0.21 mmol/L (95 % CI: 0.40 to 0.02, $p=0.033$), respectively. No effects were observed on other blood lipid parameters.

Two animal studies in Syrian golden hamsters compared the efficiency of beta-glucans of different sources (barley and oat), and of barley beta-glucans of varying molecular weight (high and low MW), respectively. The studies found that irrespective of the source or the molecular weight, beta-glucans were effective in lowering blood total and LDL-cholesterol concentrations. Furthermore, both studies showed increases in the concentrations of faecal total neutral sterols following consumption of the various beta-glucans. The Panel considers that these studies are supportive of the effect of barley beta-glucans.

The cholesterol-lowering effect of barley beta-glucans is considered to depend on increased viscosity that reduces the reabsorption of bile acids and increases both the synthesis of bile acids from cholesterol as well as the faecal excretion of neutral sterols. Viscosity in the small intestine is determined by the concentration, molecular weight and solubility of the barley beta-glucans.

In weighing the evidence, the Panel took into account that one meta-analysis including 11 RCTs, and one additional RCT, which investigated the effects of barley beta-glucans at doses of at least 3 g/day showed a decrease in total and LDL-cholesterol concentrations in both normo- and hyper-cholesterolaemic subjects, and that the mechanism by which barley beta-glucans could exert the claimed effect is biologically plausible and supported by the animal studies provided.

The Panel concludes that a cause and effect relationship has been established between the consumption of barley beta-glucans and the lowering of blood LDL-cholesterol concentrations.

The Panel considers that the following wording reflects the scientific evidence: “Barley beta-glucans have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease”.

The Panel considers that at least 3 g of barley beta-glucans should be consumed per day in order to obtain the claimed effect. This amount can reasonably be consumed as part of a balanced diet. The target population is adults who want to lower their blood cholesterol concentrations.

TABLE OF CONTENTS

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, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of this Regulation, an application for authorisation 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 10/06/2011.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction and including a request for the protection of proprietary data.
- On 07/07/2011, during the validation process of the application, EFSA sent a request to the applicant to provide additional information.
- The applicant provided the requested information on 27/07/2011.
- The scientific evaluation procedure started on 10/08/2011.
- During its meeting on 23/11/2011, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to barley beta-glucans and the lowering of blood LDL-cholesterol concentrations.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 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: barley beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of barley beta-glucans, a positive assessment of its safety, nor a decision on whether barley beta-glucans are, or are 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 17 of Regulation (EC) No 1924/2006.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Cargill Incorporated, acting through Cargill Health and Nutrition, c/o Cargill R&D Centre Europe, Havenstraat 84, B-1800 Vilvoorde, Belgium.

The applicant claimed proprietary rights for the meta-analysis conducted by Harland JI (2011, unpublished) and for information pertaining to the production process of barley betafiber (Barliv^{TM}).

Food/constituent as stated by the applicant

According to the applicant, barley beta-glucans, which are soluble cereal fibres.

Health relationship as claimed by the applicant

According to the applicant, consuming at least 3 g of barley beta-glucans per day helps reduce LDL- and total cholesterol. LDL-cholesterol is a risk factor for coronary heart disease (CHD), so reducing this risk factor within a healthy diet and lifestyle can help to lower the overall risk of developing heart disease.

Wording of the health claim as proposed by the applicant

The applicant proposed the following wording for the health claim: "Barley beta-glucan has been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of (coronary) heart disease".

Specific conditions of use as proposed by the applicant

According to the applicant, to bear the claim:

- Foods should provide at least 3 g/day of beta-glucans from barley, barley bran, or from mixtures of non-processed or minimally processed barley beta-glucans in one or more servings.
- A minimum of 0.75 g of beta-glucans per serving is recommended, or one-fourth of the 3 g daily amount specified above, to assist consumers to choose foods to suit their diet.
- The weight-average molecular weight of the barley beta-glucans that are the subject of this application varies between 100 and 2000 kDa.
- The label ingredient list should refer to its barley origin in compliance with Commission Directive relating to the labelling, presentation and advertising of foodstuffs (2000/13/EC and, as amended by 2007/68/EC).

The target population proposed by the applicant is adults with normal or mildly elevated blood cholesterol concentrations.

Similar claims as proposed/authorised by other entities

The US Food and Drug Administration (FDA, 2005, 2008) has already approved a health claim for barley beta-glucans which is similar to the one proposed in this application. Barley beta-fiber was included as an eligible source in 2008, based on the evidence provided by Keenan et al. (2007).

In 2006, the Swedish Code of Practice extended its claim about certain types of dietary fibre and cholesterol-lowering effects to barley fibres (Åman, 2006).

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is barley beta-glucans, which are soluble fibres present in barley (*Hordeum vulgare* L.). Beta-glucans are non-starch polysaccharides composed of glucose molecules in long linear polymers consisting in blocks of 2-4 glucose units linked by β-(1→4) bonds, separated generally by a single glucose molecule with a β-(1→3) link, leading to an approximate distribution of 70 % to 30 % for the two types of linkages. The molecular weight (MW) varies between 50 and 2000 kDa. The mixed linkages are important for the physical properties, such as solubility and viscosity. Viscosity is a function of the concentration of dissolved beta-glucans and of its molecular weight (Wood et al., 2000), and further depends on differences in raw materials, processing and methods of determination. Beta-glucans occur naturally in barley (4-7 %) and are measurable in foods by established methods. This opinion applies to barley beta-glucans naturally present in foods, and to those forms added to foods.

The Panel considers that the food constituent, barley beta-glucans, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "lowering/reduction of blood cholesterol, which may reduce the risk of (coronary) heart disease". The target population proposed by the applicant is adults with normal or mildly elevated blood cholesterol concentrations.

Coronary heart disease (CHD) is a leading cause of mortality and morbidity in European populations, with over 1.9 million deaths in the European Union and over 4.35 million deaths in Europe each year (Pedersen et al., 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002a, b).

It has been shown that blood cholesterol concentrations can be decreased by drugs, and by dietary and lifestyle changes (Denke, 2005; Gordon, 2000; Ornish et al., 1998; van Horn et al., 2008).

The Panel considers that lowering blood LDL-cholesterol concentrations is a beneficial physiological effect by decreasing the risk of coronary heart disease.

3. Scientific substantiation of the claimed effect

The Panel has already issued an opinion on beta-glucans from various sources, including barley, and maintenance of normal blood cholesterol concentrations, pursuant to Article 13(1) of Regulation (EC) No 1924/2006 (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009). On the basis of the studies provided for oat beta-glucans, and of eight studies provided for barley beta-glucans (Behall et al., 2004a, b; Biörklund et al., 2005; Keenan et al., 2007; Keogh et al., 2003; McIntosh et al., 1991; Newman et al., 1989; Shimizu et al., 2008), the Panel concluded that a cause and effect relationship had been established between the consumption of beta-glucans and the maintenance of normal blood cholesterol concentrations. Six of the studies conducted with barley beta-glucans (Behall et al., 2004a, b; Keenan et al., 2007; McIntosh et al., 1991; Newman et al., 1989; Shimizu et al., 2008) showed significant lowering of LDL-cholesterol concentrations, whereas two studies did not (Biörklund et al., 2005; Keogh et al., 2003).

The Panel has also issued an opinion on barley beta-glucans and reduction of blood cholesterol concentrations, which may reduce the risk of (coronary) heart disease, pursuant to Article 14 of Regulation (EC) No 1924/2006, with a favourable outcome (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011).

The applicant performed a literature search in Medline and Embase (from 1990 until February 2011) using the search terms "barley beta-glucan" and "cholesterol or blood lipids". The search was confined to human studies and was complemented by hand searching using reference lists in identified publications. Studies were included if they were well designed (i.e. suitable controls, no significant weight gain/loss during the study, no significant differences in primary outcome measures at baseline between intervention and control groups), were conducted in healthy populations with normal or mildly elevated blood cholesterol concentrations, and used at least 3 g of barley beta-glucans per day for the intervention.

The applicant identified a total of 16 references as being pertinent to the health claim. These references comprised three meta-analyses (including one unpublished meta-analysis claimed as proprietary by the applicant), 10 human intervention studies (including one unpublished human study), two animal studies and one mechanistic study.

The information provided for one of the studies (Pins et al., unpublished, abstract only) was insufficient to allow a scientific evaluation by the Panel. The mechanistic study (Nilsson et al., 2010) was an acute trial concerned with the production of short chain fatty acids following the consumption of cereal-based meals. The Panel considers that no conclusions can be drawn from these two studies for the scientific substantiation of the claim.

The three meta-analyses (AbuMweis et al., 2010; Talati et al., 2009; Harland, 2011, unpublished and claimed as proprietary by the applicant) considered all but one (Rondanelli et al., 2011) of the remaining individual randomised controlled trials (RCTs) which the applicant provided for the scientific substantiation of the claim.

The first meta-analysis (AbuMweis et al., 2010) comprised 11 studies (17 treatment arms) published between 1989 and 2008, and which included a total of 591 subjects (Behall et al., 2004a, b; Biörklund et al., 2005; Keenan et al., 2007; Keogh et al., 2003; Li et al., 2003; McIntosh et al., 1991; Newman et al., 1989; No authors listed, 2005, unpublished clinical study report; Shimizu et al., 2008; Sundberg, 2008). Seven studies had a cross-over design and four had a parallel design. The duration of the intervention lasted from 4 to 12 weeks (mean 5.2 weeks) and study size ranged from 10 to 62 subjects. Study populations were both normo- and hypercholesterolaemic (mean blood cholesterol concentrations 3.6 to 8.6 mmol/L), the mean age ranged from 20-63 years and the mean body mass index (BMI) from 19-35 kg/m^2. Five studies recruited only males and one study recruited only females. The estimated daily consumption of barley beta-glucans ranged from 3 to 12 g, with a median intervention dose of 5 g/day. The sources of barley beta-glucans included barley flour, barley flakes, pearled barley and barley bran which were consumed as breakfast cereals, biscuits, bread, pancakes, muffins, tabbouleh, steamed grains, powders, juice/drinks and a low MW gelled form. Most control groups received comparable products based on wheat or rice. In five studies, subjects consumed their habitual diet, and in two studies, an American Heart Association Step I diet. Two other studies were controlled feeding trials with typical Japanese and Western diets. In one study subjects were given instructions to follow a low saturated and low *trans* fat diet. The primary outcome of this meta-analysis was to quantify the effect of beta-glucans from barley on total and LDL-cholesterol concentrations. Estimates of the pooled treatment effect size and 95 % confidence intervals (CI) were calculated using both fixed effect and random effects models. Overall, barley beta-glucans lowered total and LDL-cholesterol concentrations by 0.30 mmol/L (95 % CI: 0.39 to 0.21, $p<0.00001$) and by 0.27 mmol/L (95 % CI: 0.34 to 0.20, $p<0.00001$), respectively. The ingestion of barley beta-glucans did not affect HDL-cholesterol concentrations. The cholesterol-lowering effect of beta-glucans from barley was apparently independent of baseline cholesterol concentrations, type of intervention and food matrix. High doses of barley beta-glucans (>7 g/day) did not appear to have a greater effect on blood cholesterol than modest consumption (3-5 g/day). In one study, consumption of either high or low MW barley beta-glucans at doses of 3 and 5 g/day for six weeks significantly decreased LDL-cholesterol concentrations relative to control (Keenan et al., 2007). However, the MW of beta-glucans was not reported in the majority of studies and therefore it was not possible to assess

the impact of MW on the cholesterol-lowering effect of barley beta-glucans in these studies. Funnel plots were used to assess publication bias. Their slightly asymmetrical appearance indicated that small negative studies might have remained unpublished. The Panel notes that nine out of the 11 studies considered in the meta-analysis reported a significant effect of barley-beta glucans on total and LDL-cholesterol concentrations.

The second meta-analysis (Talati et al., 2009) included eight studies (13 treatment arms, 391 subjects), seven of which (Biörklund et al., 2005; Keenan et al., 2007; Keogh et al., 2003; Li et al., 2003; McIntosh et al., 1991; Newman et al., 1989; Shimizu et al., 2008) were already included in the meta-analysis by AbuMweis et al. (2010). The additional study (Lupton et al., 1994) was a randomised, parallel, 30-day intervention in 79 hypercholesterolaemic subjects. The results from this meta-analysis were similar to those obtained by AbuMweis et al. (2010). Barley beta-glucans lowered total and LDL-cholesterol concentrations by 0.35 mmol/L (95 % CI: 0.48 to 0.21, $p<0.05$) and by 0.26 mmol/L (95 % CI: 0.36 to 0.16, $p<0.05$), respectively. Other blood lipid parameters (HDL-cholesterol, triglycerides) were not affected. To address publication bias, visual inspection of funnel plots, Egger's weighted regression statistics, and the trim and fill method were applied. When potentially missing studies (i.e. unpublished negative studies) were taken into account, barley beta-glucans still had a significant, albeit reduced, effect on total and LDL-cholesterol concentrations.

The applicant submitted a third meta-analysis (Harland, 2011, unpublished and claimed as proprietary by the applicant) which considered eight studies (Behall et al., 2004a, b; Keenan et al., 2007; Keogh et al., 2003; Li et al., 2003; McIntosh et al., 1991; Newman et al., 1989; Shimizu et al., 2008) already taken into account in the meta-analysis by AbuMweis et al. (2010). The Panel notes that this meta-analysis does not provide additional information to the meta-analysis by AbuMweis et al. (2010) for the scientific substantiation of the claim.

One human intervention study (Rondanelli et al., 2011) which was not available at the time the three meta-analyses above were conducted was also provided by the applicant. In this randomised controlled cross-over trial, 24 mildly hypercholesterolaemic men (mean age 50.3±5.3 years) consumed a barley beta-glucan-enriched diet or a rice bran-enriched control diet for four weeks each (with a three-week wash-out in between) after a three-week run-in period on a Step 1 American Heart Association diet containing rice bran enriched foods (providing 19.7 g/day total dietary fibre, including 7 g/day soluble fibre). The barley beta-glucan diet provided 39.3 g/day total dietary fibre, of which 13.7 g/day was soluble fibre and 6 g/day of this was barley beta-glucans from a dry, processed, "high" (but undeclared) molecular weight concentrate included in various foods. The rice bran-enriched control diet provided 45.7 g/day total fibre, of which 10.4 g/day was soluble fibre. A significant decrease in total cholesterol (-0.54 mmol/L, 95 % CI: -0.75 to -0.33, $p<0.001$) and LDL-cholesterol (-0.53 mmol/L, 95 % CI: -0.79 to -0.26, $p<0.001$) was observed during the run-in period. The treatment effect of the barley beta-glucan and the rice diets was presented as the mean difference between final values (95 % CI) adjusted for the baseline values of each period and for period effect. Compared to the rice-bran diet, the barley beta-glucan diet induced a significant decrease in total and LDL-cholesterol concentrations of 0.34 mmol/L (95 % CI: 0.47 to 0.20, $p<0.001$) and 0.21 mmol/L (95 % CI: 0.40 to 0.02, $p=0.033$), respectively. No effects were observed on other blood lipid parameters (HDL-cholesterol, apolipoprotein A-I and B, triglycerides, or various calculated ratios).

Two animal studies (Delaney et al., 2003; Wilson et al., 2004) were also provided. In the study by Delaney et al., (2003), Syrian golden hamsters were fed a hypercholesterolaemic diet for two weeks. After this lead-in period, the control hamsters continued to receive the same diet whereas experimental hamsters were fed the same diet containing 2, 4 or 8 g beta-glucans from barley or oats per 100 g diet at the expense of cellulose, for a total of nine weeks. At weeks 3, 6 and 9, dose dependent decreases in total and LDL-cholesterol concentrations were observed, irrespective of the source of the beta-glucans. At week 9, a reduction in liver cholesterol was noted for the hamsters consuming the highest dose of oat or barley beta-glucans, as well as an increase in faecal total neutral sterols concentrations. A second animal study (Wilson et al., 2004) used the same model and design

to compare the effects of low MW barley beta-glucans (ca. 175 kDa) to those of high MW barley beta-glucans (ca. 1000 kDa). As compared to the control hamsters, both the low and the high MW barley beta-glucans (8 g/100 g diet) equally decreased blood total and LDL-cholesterol concentrations, and increased concentrations of faecal total neutral sterols and coprostanol, a cholesterol derivative. The Panel notes that in these animal studies no differences were observed between the effects of barley and oat beta-glucans on total and LDL-cholesterol concentrations, and that the low MW barley beta-glucans exerted similar effects to the high MW barley beta-glucans. The Panel considers that these studies are supportive of the claimed effect of barley beta-glucans.

The cholesterol-lowering effect of barley beta-glucans is considered to depend on increased viscosity that reduces the reabsorption of bile acids and increases both the synthesis of bile acids from cholesterol as well as the faecal excretion of neutral sterols (Delaney et al., 2003; Wilson et al., 2004). Viscosity in the small intestine is determined by the concentration, molecular weight and solubility of the barley beta-glucans. Barley beta-glucans may be degraded during the purification and manufacturing of foods by factors such as shear, heat and the action of enzymes, and its cholesterol-lowering effect may be weakened or even disappear. Differences in viscosity are thought to explain, at least in part, the large variation between the LDL-cholesterol lowering effects found in individual studies (EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009, 2010).

In weighing the evidence, the Panel took into account that one meta-analysis including 11 RCTs, and one additional RCT, which investigated the effects of barley beta-glucans at doses of at least 3 g/day showed a decrease in total and LDL-cholesterol concentrations in both normo- and hyper-cholesterolaemic subjects, and that the mechanism by which barley beta-glucans could exert the claimed effect is biologically plausible and supported by the animal studies provided.

The Panel concludes that a cause and effect relationship has been established between the consumption of barley beta-glucans and the lowering of blood LDL-cholesterol concentrations.

The Panel could have reached this conclusion without considering the meta-analysis claimed as proprietary by the applicant.

4. Panel's comments on the proposed wording

The Panel considers that the following wording reflects the scientific evidence: "Barley beta-glucans have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease".

5. Conditions and restrictions of use

The Panel considers that at least 3 g of barley beta-glucans should be consumed per day in order to obtain the claimed effect. This amount can reasonably be consumed as part of a balanced diet. The target population is adults who want to lower their blood cholesterol concentrations.

CONCLUSIONS

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

- The food constituent, barley beta-glucans, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "lowering/reduction of blood cholesterol, which may reduce the risk of (coronary) heart disease". The target population proposed by the applicant is adults with normal or mildly elevated blood cholesterol concentrations. Lowering blood LDL-cholesterol

concentrations is a beneficial physiological effect by decreasing the risk of coronary heart disease.

- A cause and effect relationship has been established between the consumption of barley beta-glucans and the lowering of blood LDL-cholesterol concentrations.
- The following wording reflects the scientific evidence: "Barley beta-glucans have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease".
- At least 3 g of barley beta-glucans should be consumed per day in order to obtain the claimed effect. This amount can reasonably be consumed as part of a balanced diet. The target population is adults who want to lower their blood cholesterol concentrations.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on barley beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0305_BE). June 2011. Submitted by Cargill Incorporated.

REFERENCES

AbuMweis SS, Jew S and Ames NP, 2010. Beta-glucan from barley and its lipid lowering capacity: a meta-analysis of randomized, controlled trials. European Journal of Clinical Nutrition, 64, 1472-1480.

Åman P, 2006. Cholesterol-lowering effects of barley dietary fibre in humans: scientific support for a generic health claim. Scandinavian Journal of Food and Nutrition, 50, 173-176.

Behall KM, Scholfield DJ and Hallfrisch J, 2004a. Diets containing barley significantly reduce lipids in mildly hypercholesterolemic men and women. The American Journal of Clinical Nutrition, 80, 1185-1193.

Behall KM, Scholfield DJ and Hallfrisch J, 2004b. Lipids significantly reduced by diets containing barley in moderately hypercholesterolemic men. Journal of the American College of Nutrition, 23, 55-62.

Biörklund M, van Rees A, Mensink RP and Önning G, 2005. Changes in serum lipids and postprandial glucose and insulin concentrations after consumption of beverages with beta-glucans from oats or barley: a randomized dose-controlled trial. European Journal of Clinical Nutrition, 59, 1272-1281.

Delaney B, Nicolosi RJ, Wilson TA, Carlson T, Frazer S, Zheng GH, Hess R, Ostergren K, Haworth J and Knutson N, 2003. Beta-glucan fractions from barley and oats are similarly antiatherogenic in hypercholesterolemic Syrian golden hamsters. Journal of Nutrition, 133, 468-475.

Denke MA, 2005. Diet, lifestyle, and nonstatin trials: review of time to benefit. American Journal of Cardiology, 96, 3-10.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2009. Scientific Opinion on the substantiation of health claims related to beta-glucans and maintenance of normal blood cholesterol concentrations (ID 754, 755, 757, 801, 1465, 2934) and maintenance or achievement of a normal body weight (ID 820, 823) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 7(9):1254, 18 pp.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2010. Scientific Opinion on the substantiation of a health claim related to oat beta-glucan and lowering blood cholesterol and

reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal, 8(12):1885, 15 pp.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. Scientific Opinion on the substantiation of a health claim related to barley beta-glucans and lowering of blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal, 9(12):2471, 12 pp.

FDA (US Food and Drug Administration), 2005. Food Labeling: Health Claims; Soluble Dietary Fiber From Certain Foods and Coronary Heart Disease. [Docket No. 2004P–0512]

FDA (US Food and Drug Administration), 2008. Food Labeling: Health Claims; Soluble Dietary Fiber From Certain Foods and Coronary Heart Disease. (Final Rule) [Docket No. FDA-2008-P-0090] (formerly Docket No. 2006P-0393)

Gordon DJ, 2000. Cholesterol lowering reduces mortality. The Statins. In: Cholesterol-Lowering Therapy. Evaluation of Clinical Trial Evidence. Ed Grundy SM. Marcel Dekker Inc., New York, USA, 299-311.

Harland JI, 2011 (unpublished, claimed as proprietary by the applicant). Meta-analysis of the effects of barley beta-glucan on blood lipids.

Keenan JM, Goulson M, Shamliyan T, Knutson N, Kolberg L and Curry L, 2007. The effects of concentrated barley β-glucan on blood lipids and other CVD risk factors in a population of hypercholesterolaemic men and women. British Journal of Nutrition, 97, 1162-1168.

Keogh GF, Cooper GJ, Mulvey TB, McArdle BH, Coles GD, Monro JA and Poppitt SD, 2003. Randomized controlled crossover study of the effect of a highly beta-glucan-enriched barley on cardiovascular disease risk factors in mildly hypercholesterolemic men. The American Journal of Clinical Nutrition, 78, 711-718.

Li J, Kaneko T, Qin LQ, Wang J and Wang Y, 2003. Effects of barley intake on glucose tolerance, lipid metabolism, and bowel function in women. Nutrition, 19, 926-929.

Lupton JR, Robinson MC and Morin JL, 1994. Cholesterol-lowering effect of barley bran flour and oil. Journal of the American Dietetic Association, 94, 65-70.

McIntosh GH, Whyte J, MvArthur R and Nestel PJ, 1991. Barley and wheat foods: Influence on plasma cholesterol concentrations in hypercholesterolemic men. The American Journal of Clinical Nutrition, 53, 1205-1209.

Newman RK, Lewis SE, Newman CW, Boik RJ and Ramage RT, 1989. Hypocholesterolemic effect of barley foods on healthy men. Nutrition Reports International, 39, 749-760.

Nilsson AC, Östman EM, Bach Knudsen KE, Holst JJ and Björck IME, 2010. A cereal-based evening meal rich in indigestible carbohydrates increases plasma butyrate the next morning. The Journal of Nutrition, 140, 1932-1936.

No authors listed, 2005, clinical study report, unpublished. Effects of boiled, flaked, milled barley powder product (Aktiv) on LDL-, HDL- and total cholesterol, triglycerides, glucose, insulin and HS-CRP levels in healthy hypercholesterolemic men and women. Centre for Human Studies of Foodstuffs (KPL), Uppsala.

Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, Sparler S, Armstrong WT, Ports TA, Kirkeeide RL, Hogeboom C and Brand RJ, 1998, erratum in 1999. Intensive lifestyle changes for reversal of coronary heart disease. Journal of the American Medical Association, 280, 2001-2007, erratum 281, 1380.

Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M and Tsai J, 2005. High-dose atorvastatin vs usual-dose simvastatin for

secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA, 294, 2437-2445.

Pins JJ, Shamliyan T, Knutson N, Goulson M and Keenan JM, unpublished, no year given. A pilot trial of concentrated barley beta-glucan on blood lipids in hypercholesterolemic men and women.

Rondanelli M, Opizzi A, Monteferrario F, Klersy C, Cazzola R and Cestaro B, 2011. Beta-glucan- or rice bran-enriched foods: a comparative crossover clinical trial on lipidic pattern in mildly hypercholesterolemic men. European Journal of Clinical Nutrition, 65, 864–871.

Shimizu C, Kihara M, Aoe S, Araki S, Ito K, Hayashi K, Watari J, Sakata Y and Ikegami S, 2008. Effect of high β-glucan barley on serum cholesterol concentrations and visceral fat area in Japanese men – a randomized, double-blinded, placebo-controlled trial. Plant Foods for Human Nutrition, 63, 21-25.

Sundberg B, 2008. Cholesterol lowering effects of a barley fibre flake product. Agro Food Industry Hi-Tech, 19, 14-17.

Talati R, Baker WL, Pabilonia MS, White CM and Coleman CI, 2009. The Effects of Barley-Derived Soluble Fiber on Serum Lipids. Annals of Family Medicine, 7, 157-163.

Van Horn L, McCoin M, Kris-Etherton PM, Burke F, Carson JA, Champagne CM, Karmally W and Sikand G, 2008. The evidence for dietary prevention and treatment of cardiovascular disease. Journal of the American Dietetic Association, 108, 287-331.

WHO (World Health Organization), 2002a. Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO expert consultation, Geneva 28 January-1 February 2002. WHO Technical Report Series 916.

WHO (World Health Organisation), 2002b. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Available from http://www.who.int/whr/2002/en/

Wilson TA, Nicolosi RJ, Delaney B, Chadwell K, Moolchandani V, Kotyla T, Ponduru S, Zheng GH, Hess R, Knutson N, Curry L, Kolberg L, Goulson M and Ostergren K, 2004. Reduced and High Molecular Weight Barley Beta-Glucans Decrease Plasma Total and Non-HDL-Cholesterol in Hypercholesterolemic Syrian Golden Hamsters. Journal of Nutrition, 134, 2617–2622.

Wood PJ, Beer MU and Butler G, 2000. Evaluation of role of concentration and molecular weight of oat ß-glucan in determining effect of viscosity on plasma glucose and insulin following an oral glucose load. British Journal of Nutrition, 84, 19-23.

GLOSSARY / ABBREVIATIONS

BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MW	Molecular weight
RCT	Randomised controlled trial