European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to soy protein and reduction of blood cholesterol concentrations pursuant to Article 14 of the Regulation (EC) No 1924/2006[1]

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from HarlandHall Ltd. on behalf of the Soya Protein Association (SPA), the European Vegetable Protein Federation (EUVEPRO), and the European Natural Soyfood Manufacturers Association (ENSA) submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific opinion on soy protein and reduction of blood cholesterol concentrations. The scope of the application was proposed to fall under a health claim referring to reduction of a disease risk. The food constituent that is the subject of the health claim is soy protein, i.e. the protein component of the soybean Glycine max. The Panel considers that soy protein is sufficiently characterised. The claimed effect is "reduces blood cholesterol and may therefore reduce the risk of (coronary) heart disease". The target population is healthy adults. The Panel considers that lowering LDL-cholesterol is a beneficial physiological effect by reducing the risk of coronary heart disease. In weighing the evidence, the Panel took into account that the results from the four human intervention studies identified by the applicant as being controlled for the macronutrient composition of the test products do not support an effect of the protein component of soy on LDL-cholesterol concentrations, and that the proposed mechanism by which the protein component of soy would exert the claimed effect is not supported by available scientific evidence. The Panel concludes that a cause and effect relationship has not been established between the consumption of soy protein and the reduction of LDL-cholesterol concentrations.

KEY WORDS

Soy protein, coronary heart disease, total cholesterol, LDL-cholesterol, health claim.

1 On request from HarlandHall Ltd, Question No EFSA-Q-2009-00672, adopted on 9 July 2010.

2 Panel members: Carlo Virginio 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 for the preparatory work on this scientific opinion: Carlo Virginio 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.

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SUMMARY

Following an application from HarlandHall Ltd. on behalf of the Soya Protein Association (SPA), the European Vegetable Protein Federation (EUVEPRO), and the European Natural Soyfood Manufacturers Association (ENSA) submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific opinion on soy protein and reduction of blood cholesterol concentrations.

The scope of the application was proposed to fall under a health claim referring to reduction of a disease risk.

The food constituent that is the subject of the health claim is soy protein, i.e. the protein component of the soybean Glycine max. Soy protein occurs in whole soy bean products that have undergone minimal processing such as toasting, roasting, boiling or soaking yielding products such as boiled soy bean, soy drink, soy cream, soy cheese, soy yoghurts, tofu, soy meat replacer and edamame. Alternatively, it is present in soy bean extracts such as soy protein isolate (SPI), soy protein concentrate (SPC) or soy protein flour (SPF) or textured soy protein derived from them. The starting material from which these three products derive is hulled, defatted soybean flake, which contains approximately 50 % protein by weight. The products typically contain the following amount of protein: SPF-hulled and defatted 52-54 %; SPC 65-72 %; SPI 90-92 %; textured soya protein 40-90 %; full fat soy flour (SF)-hulled full fat soybean 40 %. In addition to protein, SPI, SPC, SPF and soy foods contain other food constituents which might exert an effect on blood cholesterol (e.g., fat and fatty acids, including polyunsaturated fatty acids, fibre, isoflavones). The applicant has clarified that the protein component of soy is the food constituent which is proposed for the claimed effect. Protein can be measured in soy protein-containing products by established methods. The Panel considers that the food constituent, soy protein, which is the subject of the health claim, is sufficiently characterised.

The claimed effect is "reduces blood cholesterol and may therefore reduce the risk of (coronary) heart disease". The target population is healthy adults. The Panel considers that lowering LDL-cholesterol is a beneficial physiological effect by reducing the risk of coronary heart disease.

The applicant provided 40 studies in humans, 32 of which were randomised controlled trials and eight were observational studies. The applicant also provided 10 meta-analyses and a review of possible mechanisms by which soy protein might exert the claimed effect.

The Panel notes that most of the studies selected by the applicant were not appropriately designed to test the effect of soy protein *per se*, but were conducted using either soy protein isolate (SPI) or soy foods which contain, in addition to protein, other constituents which have been reported to exert an effect on blood cholesterol in human intervention studies (e.g., fat and fatty acids, including polyunsaturated fatty acids, soy fibre, soy isoflavones). This was the case for a meta-analysis of a subset, comprising 23 studies, of the 32 RCTs submitted by the applicant.

Following a request to provide studies which could show the effect of protein *per se*, the applicant re-assessed the results of the meta-analysis by considering only the studies performed using soy protein isolate and by taking into account study quality (high, medium and low quality). The Panel considers that the design of the studies on SPI rated by the applicant as having medium or low quality does not address the effects of the food constituent that is the subject of the health claim (the protein component of soy alone) on LDL-cholesterol concentrations.

Four intervention studies identified as high quality by the applicant were included in a new meta-analysis which aimed to address the effects of soy protein *per se* on blood cholesterol concentrations.

One randomised double blind controlled parallel study was designed to assess the effects of soy protein isolate with and without isoflavones on blood lipids. There was a statistically significant dose-response relationship between the intake of isoflavones and the decrease in total and LDL-cholesterol concentrations. The Panel notes that, in the context of this study, an effect of soy isoflavones on blood

cholesterol concentrations was observed and therefore considers that the inclusion of the three study arms receiving isoflavone-containing soy protein isolate in the new meta-analysis provided by the applicant is not appropriate. The Panel notes that this study does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

One study was designed to assess the effects of isoflavone-containing and of isoflavone-free soy protein isolate on markers of cardiovascular risk, including blood lipids. No significant differences were observed between the soy protein isolate with no isoflavones (or the soy protein isolate with isoflavones) and the control group with respect to changes in total or LDL-cholesterol concentrations during the study. The Panel notes that this study does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

One study was designed to assess the effects of soy protein isolate containing isoflavones versus cow's milk protein on blood lipids. No significant differences between the SPI and the control group were observed for changes in any of the cholesterol fractions during the study. The Panel notes that this study was not designed to assess the effects of the protein component of soy on LDL-cholesterol concentrations but, nevertheless, does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

Another randomised double blind controlled parallel study was designed to assess the effects of isoflavone-containing soy protein isolate on LDL-cholesterol concentrations. A statistically significant decrease in total and LDL-cholesterol concentrations was reported in the SPI group compared to placebo at week 6 but not at week 12. The Panel notes that this study was not designed to assess the effects of the protein component of soy on LDL-cholesterol concentrations but, nevertheless, does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

The Panel considers that results from these four intervention studies identified by the applicant as being controlled for the macronutrient composition of the test products do not support an effect of the protein component of soy on LDL-cholesterol concentrations.

In weighing the evidence, the Panel took into account that the results from the four human intervention studies identified by the applicant as being controlled for the macronutrient composition of the test products do not support an effect of the protein component of soy on LDL-cholesterol concentrations, and that the proposed mechanism by which the protein component of soy would exert the claimed effect is not supported by available scientific evidence.

The Panel concludes that a cause and effect relationship has not been established between the consumption of soy protein and the reduction of LDL-cholesterol concentrations.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1924/20064 establishes rules governing the Community authorisation of health claims made on foods. Health claims shall be 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 14 of that Regulation lays 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 that Regulation, an application for authorisation 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 European Food Safety Authority (EFSA).

Steps taken by EFSA:

- The application was received on 12/06/2009.
- The scope of the application falls under disease risk reduction claim.
- During the completeness check[5] of the application, the applicant was requested to provide missing information on 17/03/2009 and on 18/05/2009.
- The applicant provided the missing information on 15/05/2009 and on 08/06/2009.
- The application was considered valid by EFSA and the scientific evaluation procedure started on 15/07/2009.
- On 15/10/2009 the NDA Panel agreed on the List of Questions to request the applicant to supplement the particulars accompanying the application.
- The applicant submitted the responses to the NDA Panel List of Questions on 02/12/2009.
- During the meeting on 09/07/2010, the NDA Panel, in the light of the overall data submitted adopted an opinion on soy protein and reduction of blood 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 is requested to issue a scientific opinion on the information provided by the applicant concerning soy protein and "reduces blood cholesterol".

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of soy protein, a positive assessment of its safety, nor a decision on whether soy protein is, or is not, classified as a foodstuff. It should be noted that such an assessment or a decision are not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope and the proposed wording of the claim as considered by the EFSA in this opinion may be subject to changes pending the outcome of the authorisation procedure foreseen in Article 17 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.

[5] In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: HarlandHall Ltd (on behalf of SPA/EUVEPRO/ENSA), The Stables, Ranbury Ring, London Road, Poulton, Cirencester, GL7 5HN, England.

Food/constituent as stated by the applicant

Soy(a) protein, hereafter referred to as soy protein.

Health relationship as claimed by the applicant

"Soy protein" is the food constituent, "blood cholesterol" the risk factor and "coronary heart disease" (CHD) the human disease.

Soy protein has been shown to reduce total and LDL cholesterol in healthy subjects with normal or mildly elevated blood cholesterol. Reduction of total and LDL cholesterol has been shown to reduce the risk of heart disease.

Wording of the health claim proposed by the applicant

Soy protein has been shown to lower/reduce blood cholesterol; blood cholesterol lowering may reduce the risk of (coronary) heart disease.

Specific conditions for use proposed by the applicant

The applicant claims that 12-25 g/d of soy protein are effective in reducing blood cholesterol and therefore the requirement per serving is prescribed as $\geq$3.75 g. Foods containing soy protein should be at least a source of protein as in the annex of Regulation (EC) 1924/2006.

Similar claims as proposed/authorised by other entities

The applicant lists the opinions of the following bodies in favour of authorising a health claim on soy protein products and the reduction of blood cholesterol concentrations: UK Joint Health Claims Initiative (JHCI), USA Food and Drug Administration (FDA), Japan Food for Specified Health Uses (FOSHU), Ministry of Health, Labour and Welfare. The applicant also states that in July 2006 Malaysia approved a health claim on the consumption of soy protein products and the reduction of blood cholesterol.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is soy protein, i.e. the protein component of the soybean Glycine max. Soy protein is largely comprised of storage protein, bound by a single membrane in the protein bodies in which there are two main types commonly known as β-conglycinin (7S globulin) and glycinin (11S globulin) (Liu, 1997). The soy protein may be consumed as part of whole soy bean products that have undergone minimal processing such as toasting, roasting, boiling or soaking yielding products such as boiled soy bean, soy drink, soy cream, soy cheese, soy yoghurts, tofu, soy meat replacer and edamame. Alternatively, it can be prepared from soybeans by various separation and extraction processes. Such products are covered by the CODEX General Standard for soy protein products (CODEX STAN 175-1989). The commonly produced concentrated forms of soy protein that are used as food ingredients are soy protein isolate (SPI), soy protein concentrate (SPC) or soy protein flour (SPF) or textured soy protein derived from them, which are then incorporated into a wide range of foods. The starting material from which these three products derive is hulled, defatted soybean flake, which contains approximately 50 % protein by weight. The products typically contain the following amount of protein: SPF-hulled and defatted 52-54 %; SPC 65-72 %; SPI 90-92 %; textured soya protein (SPF, SPC or SPI after thermoplastic extrusion or steam texturisation) 40-90 %; full fat soy flour (SF)-hulled full fat soybean 40 %.

SPI, SPC, SPF and soy foods contain other food constituents than soy protein which might exert an

effect on blood lipids (e.g., fat and fatty acids, including polyunsaturated fatty acids, fibre, isoflavones). The applicant has clarified that the protein component of soy is the food constituent which is proposed for the claimed effect.

Protein can be measured in soy protein-containing products by established methods.

The Panel considers that the food constituent, soy protein, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "reduces blood cholesterol and may therefore reduce the risk of (coronary) heart disease". The target population is healthy adults.

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 (Petersen et al., 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002).

It has been shown that blood cholesterol can be decreased by drugs and by dietary and lifestyle changes (Denke, 2005; Gordon, 2000; Katan et al., 2003; Law, 2000; Ornish et al., 1998; Pedersen et al., 2005; van Horn et al., 2008).

The Panel considers that lowering LDL-cholesterol is a beneficial physiological effect by reducing the risk of CHD.

3. Scientific substantiation of the claimed effect

The review of the human data undertaken by the applicant was considered comprehensive and pertinent data have been identified and included in the application. The literature search strategy is clearly described and was updated to 16 October 2008.

The applicant identified 40 studies in humans as pertinent to the claim; 32 of which were randomised controlled trials (RCT) and eight were observational studies. The applicant also identified 10 meta-analyses (one of which is unpublished and claimed as confidential) and a review of possible mechanisms by which soy protein could exert the claimed effect (Xiao et al., 2008) as pertinent to the claim.

Broadly, intervention studies in humans were included in the application if they were RCT conducted in healthy populations with normal to mild hypercholesterolaemia and the intervention (as the only change in the diet) was the consumption of about 25 g of soy protein/day ± 50 % (range 10-40 g) as soy protein isolates (SPI), either intact or water-washed, or from soy foods. A total of 142 studies were excluded by the applicant (140 interventions and two observational studies) as were two meta-analyses and seven review publications on the basis of the following exclusion criteria: inclusion of obese subjects (body mass index >35 kg/m^2) or diseased populations, intakes of soy protein >40 g/d, use of SPI depleted of isoflavones (alcohol-washed SPI), or not reporting on blood lipids.

The Panel notes that most of the studies selected by the applicant have been conducted using either SPI or soy foods containing, in addition to soy protein, other food constituents which have been reported to exert an effect on blood lipids in intervention studies (e.g., fat and fatty acids, including polyunsaturated fatty acids, soy fibre, soy isoflavones).

The applicant justifies the exclusion of studies using alcohol-washed SPI as the soy protein intervention by claiming that, in addition to isoflavones in SPI, it is possible that relevant (active) peptides with cholesterol-lowering properties from the protein fraction could also be removed from SPI using such a treatment. The Panel notes that no evidence has been provided by the applicant to establish that peptides with cholesterol-lowering properties are removed from SPI by alcohol washing. On request, the applicant has identified three RCT on the effects of alcohol-washed SPI on LDL-cholesterol

concentrations under the proposed conditions of use (25 g/d) (Crouse et al., 1999; Steinberg et al., 2003; Santo et al., 2008).

The Panel also notes that most of the intervention studies considered as pertinent by the applicant used animal protein from different sources (e.g., milk, meat, egg) as control. The Panel considers that, although a hypercholesterolaemic effect of animal protein has been described in some animal species, this effect is generally not observed in humans and mechanisms by which animal protein could exert a hypercholesterolaemic effect in humans have not been established (Sacks et al., 2006; Blachier et al., 2010). Therefore, the Panel considers that animal protein can be considered as neutral regarding its effects on blood cholesterol in humans and consequently an appropriate comparator to assess the effects of soy protein on blood cholesterol concentrations.

The applicant conducted a meta-analysis (fixed effect models) of a subset of the 32 RCTs, comprising 23 studies with a soy protein intake of 12-25 g (i.e., under the proposed conditions of use for the claim). All 23 studies were randomised, of which 13 were double blinded, 12 were of parallel design and 10 had a crossover design. The main source of soy protein was SPI in 25 treatment arms and soy foods in nine treatment arms. The age range of the study population was 27 to 61 years and included men and pre-, peri- and post- menopausal women. Average baseline cholesterol was in the range of 4.32-7.03 mmol/L and average protein intake across all studies was 22.7 g/day. Study duration was four weeks to six months.

The Panel notes that a large number of the studies included in the meta-analysis were not appropriately designed to test the effects of soy protein *per se*, but rather the effects, compared to similar amounts of animal protein as isolates or from food, of SPI or of soy foods standardised by their protein content which, in addition to soy protein, also contain other food constituents for which a significant LDL-cholesterol lowering effect has been reported in some humans intervention studies (e.g., soy fibre, soy isoflavones, poly-unsaturated fatty acids). The applicant was requested to provide reasons for the inclusion of such intervention studies in the meta-analysis.

The applicant states that, on the basis of two recent meta-analyses of randomised controlled trials addressing the effects of isolated soy isoflavones (given in capsules) on blood cholesterol concentrations, no significant effects of soy isoflavones on blood cholesterol concentrations can be expected (Yeung et al., 2003; Taku et al., 2008). Similarly, no significant effects of soy isoflavones on blood cholesterol concentrations have been observed in single RCTs published after the meta-analyses (Atteritsno et al., 2007; Aubertin-Leheudre et al., 2007; Ho et al., 2007; Nestel et al., 2007; Rios et al., 2008). However, available meta-analyses of RCTs which assessed the effects of soy isoflavones in soy protein (i.e., by comparing the effects of isoflavone-rich soy protein to those of isoflavone-depleted soy protein) on LDL-cholesterol concentrations lead to conflicting results; whereas some meta-analyses found no effect of isoflavones in soy protein (Weggemans and Trautwein, 2003; Solae et al., 2008, unpublished, claimed as proprietary by the applicant), others report a reduction in LDL-cholesterol with isoflavone-containing (versus isoflavone-depleted) soy protein isolates (Zhuo et al., 2004; Taku et al., 2007). The Panel considers that the available evidence is conflicting with regard to a possible effect of soy isoflavones in SPI on blood LDL-cholesterol concentrations.

The Panel notes that the applicant has selected the studies to be included in the meta-analysis on the unfounded (see above) assumption that soy isoflavones in SPI have no effect on blood cholesterol concentrations.

Following a request to provide studies which could show the effect of protein *per se*, the applicant re-assessed the results of their meta-analysis of 23 intervention studies with a soy protein intake of 12-25 g/d by considering only the studies performed using SPI and by taking into account study quality (high, medium and low quality). Study quality was assessed on the basis of the JADAD scale (which relates to factors like randomisation and double-blinding) and by considering the degree to which control and treatment interventions were controlled for macronutrient content (especially for fibre, PUFA and saturated fatty acids (SFA)) and had reported on overall macronutrient intakes. The applicant identified a total of four high quality intervention studies, which included a total of eight intervention

arms (Allen et al., 2007; Crouse et al., 1999; Steinberg et al., 2003; West et al., 2005). Two of these studies were designed to test the effects of isoflavones contained in SPI and included one intervention arm receiving isoflavone-depleted SPI (Crouse et al., 1999; Steinberg et al., 2003). These intervention studies were included by the applicant in a new meta-analysis which aimed to address the effects of soy protein *per se* on blood cholesterol concentrations.

The randomised double blind controlled parallel study by Crouse et al. (1999) was designed to assess the effects of SPI with and without isoflavones on blood lipids. A total of 156 men and women (20-70 years of age) with LDL cholesterol concentrations between 3.62 mmol/L (140 mg/dL) and 5.17 mmol/L (200 mg/dL) were randomised to consume 25 g/d of SPI with either 3, 27, 37, or 62 mg of isoflavones or 25 g/d of casein (control) for 9 weeks after a one-month run-in period during which all subjects consumed 25 g/d of casein in the context of a NCEP Step I low-fat, low-cholesterol diet consisting of 30 % of energy as fat (polyunsaturated-monounsaturated- saturated fat ratio, 1:1:1) and 300 mg of cholesterol daily. Only the SPI providing 62 mg/d of isoflavones significantly reduced total (by 4 %) and LDL-cholesterol concentrations (by 6 %) compared to casein when all subjects were considered together, whereas both the SPI providing 37 mg/d and 62 mg/d of isoflavones showed significant reductions in total and LDL-cholesterol concentrations in subjects with high cholesterol concentrations at baseline. There was a statistically significant dose-response relationship between the intake of isoflavones and the decrease in total and LDL cholesterol concentrations ($p=0.01$ and $p=0.02$ for the trends for total and for LDL-cholesterol concentrations, respectively). No effect on either total or LDL-cholesterol concentrations was observed for SPI providing 3 mg or 27 mg of isoflavones per day. The Panel notes that, in the context of this study, an effect of soy isoflavones in SPI on blood cholesterol concentrations was observed and therefore considers that the inclusion of the three study arms receiving isoflavone-containing SPI in the meta-analysis provided by the applicant (which aimed to address the effects of soy protein *per se* on blood cholesterol concentrations) is not appropriate. Therefore, the Panel considers that no scientific conclusions can be drawn from the meta-analysis provided by the applicant for the scientific substantiation of the claim. The Panel notes that this study does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

The study by Steinberg et al. (2003) was designed to assess the effects of isoflavone-containing and of isoflavone-free SPI on markers of cardiovascular risk, including blood lipids. Following a randomised, double-blind, three phase cross-over design, 28 healthy postmenopausal women consumed 25 g/d of SPI with no isoflavones, 25 g/d of SPI with 108 mg isoflavones as aglycone units, and 25 g/d of total milk protein (control) for 6 weeks each, with 4-week washout period in between. Changes from baseline in the intervention and control groups were reported for total and LDL-cholesterol (-3.59 and -1.12 mg/dL in the SPI with isoflavones, +0.22 and - 0.64 mg/dL in the SPI without isoflavones, and +3.25 and +1.73 mmol/L in the control group for total and LDL-cholesterol, respectively). No significant differences were observed between the SPI with no isoflavones (or the SPI with isoflavones) and the control group with respect to changes in total or LDL-cholesterol concentrations during the study. The Panel notes that this study does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

The study by West et al. (2005) was designed to assess the effects of 25 g/d of SPI containing isoflavones (90 mg/d) vs 25 g/d of cow's milk protein on blood lipids in the context of a NCEP Step I low-fat, low-cholesterol diet in a randomised, double blind, two-phase cross-over design following a 3-week run-in period. A total of 32 hypercholesterolemic men (n=14) and post-menopausal women with LDL-cholesterol concentrations >50th percentile and total cholesterol >200 mg/dL (5.27 mml/L) consumed the intervention and control products for 6 weeks each with a 2-week washout in between. No significant differences between the SPI and the control group were observed for changes in any of the cholesterol fractions during the study. The Panel notes that this study was not designed to assess the effects of the protein component of soy alone on LDL-cholesterol concentrations but, nevertheless, does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

The randomised double blind controlled parallel study by Allen et al. (2007) was designed to assess the effects of isoflavone-containing SPI on LDL-cholesterol concentrations. A total of 216 post-menopausal women with LDL cholesterol concentrations between 3.37 mmol/L (130 mg/dL) and 4.92 mmol/L

(190 mg/dL) or triglycerides >1.7 nmol/L (150 mg/dL) were randomised to consume 20 g/d of SPI containing 160 mg total isoflavones (96 mg aglycones) or 20 g/d of whole milk protein (control) for 12 weeks after a one-month single-blinded run-in period to select women with high (>80 %) compliance with the study products. A total of 25 women dropped out during the study. Only absolute values for blood lipids at baseline, 6 and 12 weeks per group are provided in the publication. Authors report a statistically significant decrease in total and LDL-cholesterol concentrations, after controlling for associated variables, in the SPI group compared to placebo at week 6 but not at week 12. The Panel notes that this study was not designed to assess the effects of the protein component of soy on LDL-cholesterol concentrations but, nevertheless, does not support an effect of the protein component of soy on LDL-cholesterol concentrations.

The Panel considers that results from these four intervention studies identified by the applicant as being controlled for the macronutrient composition of the test products do not support an effect of the protein component of soy on LDL-cholesterol concentrations (Crouse et al., 1999; Steinberg et al., 2003; Allen et al., 2007; West et al., 2005).

The Panel also considers that the design of the studies on SPI rated by the applicant as having medium or low quality and the studies on soy foods do not address the effects of the food constituent that is the subject of the health claim (the protein component of soy alone) on LDL-cholesterol concentrations. The same argument applies to the nine published (Anderson et al., 1995; Weggemans and Trautwein, 2003; Zhuo et al., 2004; Balk et al., 2005; Zhan and Ho, 2005; Reynolds et al., 2006; Taku et al., 2007; Harland and Haffner, 2008; Hooper et al., 2008) and two unpublished (Solae, 2008, claimed as proprietary by the applicant; a meta-analysis provided with the application which includes the 32 RCTs identified by the applicant with doses of 10-40 g/d of soy protein) meta-analyses provided by the applicant which aimed to address the relationship between soy protein consumption and blood lipids.

The Panel notes that the proposed mechanisms by which the protein component of soy could exert the claimed effect relate to the capacity of soy proteins/peptides to bind bile acids which would increase bile acid excretion in the gut, leading to reduced bile acid resorption and biliary cholesterol absorption. In addition, peptides derived from intestinal digestion of soy protein would enter the circulation and exert direct effects on the hepatic metabolism of cholesterol and increase the expression of the hepatic LDL receptor (Xiao et al., 2008). The Panel considers that such mechanisms have not been corroborated by available scientific evidence.

In weighing the evidence, the Panel took into account that the results from the four human intervention studies identified by the applicant as being controlled for the macronutrient composition of the test products do not support an effect of the protein component of soy on LDL-cholesterol concentrations, and that the proposed mechanism by which the protein component of soy would exert the claimed effect is not supported by available scientific evidence.

The Panel concludes that a cause and effect relationship has not been established between the consumption of soy protein and the reduction of LDL-cholesterol concentrations.

CONCLUSIONS

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

- The food constituent, soy protein, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “reduces blood cholesterol and may therefore reduce the risk of (coronary) heart disease”. The target population is healthy adults. Lowering LDL-cholesterol is a beneficial physiological effect by reducing the risk of coronary heart disease.
- A cause and effect relationship has not been established between the consumption of soy protein and the reduction of LDL-cholesterol concentrations.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on soy protein and "reduces blood cholesterol" pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0256_UK). July 2009. Submitted by HarlandHall Ltd. on behalf of the Soya Protein Association (SPA), the European Vegetable Protein Federation (EUVEPRO), and the European Natural Soyfood Manufacturers Association (ENSA).

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GLOSSARY / ABBREVIATIONS

CHD	Coronary heart disease
PUFA	Polyunsaturated fatty acids
SFA	Saturated fatty acids
SPC	Soy protein concentrate
SPF	Soy protein flour
SPI	Soy protein isolate
RCT	Randomised controlled trials