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Food and Drug Administration
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RE: Docket No. 2007N-0464 Submitted February 18, 2008
Weston A. Price Foundation reply to the Soy Nutrition Institute's comments

The following is the Weston A. Price Foundation's reply to the Soy Nutrition Institute's submission to the FDA entitled, "Response to claims about the harmful effects of soy cited in the December 17, 2014 Weston A. Price Foundation complaint in the U.S. District Court."

The Weston A. Price Foundation, a non-profit nutrition education foundation with offices in Washington DC (the "Foundation"), is pleased to submit these comments as a supplement to its petition Docket No. 2007N-0464 pursuant to the Federal Food, Drug and Cosmetic Act (FFDCA).

The Foundation urges the US Food and Drug Administration to amend the Final Rule Re Food Labeling: Health Claims; Soy Protein and Heart Disease, which became effective October 19, 1999, by removing Sec. 101.82 Health claims: Soy protein and risk of coronary heart disease (CHD). Foods containing soy protein should not carry a heart disease health claim.

Under section 403(4)(3)(B)(i) of the Federal Food, Drug and Cosmetic Act, FDA can authorize a health claim only if the standard of significant scientific agreement is met.

The data submitted with our February 18, 2008 petition established a lack of consensus among experts, qualified by scientific training and experience, about claims that soy protein prevents heart disease or even lowers cholesterol. Soy protein heart health claim "consumption of 25 grams of soy protein per day as part of a diet low in saturated fat and cholesterol may reduce the risk of heart disease" is not supported by significant scientific agreement.

Since that date, numerous other studies show a lack of consensus among experts, qualified by scientific training and experience, that soy protein can protect against heart disease; indeed, there is considerable evidence indicating that consumption of soy protein may increase the risk of heart disease.

Additional studies supporting the Weston A. Price position on soy heart health claims are listed in Attachment One. Also listed on Attachment One are several studies indicating adverse effects of soy on thyroid function, as low thyroid function has been associated with cardiovascular disease.

It should be noted that the European Food Safety Authority (EFSA) has refused to support a heart health claim for soy protein and the American Heart Association (AHA), reversing its previous position, sought repeal of the current FDA authorized soy heart healthy claims.

The European Food Safety Authority says "A cause and effect relationship has not been established between the consumption of ISP (isolated soy protein as defined by the applicant) and a reduction in blood LDL-cholesterol concentrations.".© EFSA, 2010 http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1688.pdf. The EFSA statement is attached as Attachment Two.

The American Heart Association has informed the FDA of its view that "at this time [2008, the year of the Foundation's petition] the totality of evidence linking soy protein consumption with reduced risk of coronary heart disease is not sufficient to meet the standards of significant scientific agreement (SSA). Thus, AHA strongly recommends that FDA revoke the soy protein and CHD health claim." http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_312848.pdf. The case for revocation of the soy heart health claims is stronger now than it was seven years ago. The AHA 2008 Letter to FDA is attached as Attachment Three.

The Soy Nutrition Institute's comments "on the harmful effects of soy" that it says were cited by the Weston A. Price Foundation are off point, irrelevant to and fail to address the issue before the court and the FDA in this case.

The issue raised by the Foundation's petition before the FDA and the court case addressing that petition concerns FDA-authorized references to soy protein as useful in reducing the risk of coronary disease. Specifically, the Foundation petitioned the FDA to remove any references to soy in the following currently authorized health claims:

(e) Model health claim. The following model health claims may be used in food labeling to describe the relationship between diets that are low in saturated fat and cholesterol and that include soy protein and reduced risk of heart disease:

(1) 25 grams of soy protein a day, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of food] supplies __ grams of soy protein.

(2) Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease. One serving of [name of food] provides __ grams of soy protein.

[64 FR 57732, Oct. 26, 1999]

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=101.82

The Soy Nutrition Institute document submitted to FDA to which this document responds makes two points:

First, This information continues to support the FDA's conclusion that significant scientific agreement exists for this diet-disease [soy/coronary disease] relationship.

Second, In addition, the evidence supports the safety of consuming soy protein and soyfoods.

The comments by the Soy Nutrition Institute provide no support for its first point--asserting a soy coronary disease relationship. They merely make the conclusory statement quoted above. Thus, concerning the point of these proceedings – the lack of significant scientific agreement that soy protein may reduce the risk of heart disease - the Soy Nutrition Institute's comments offer nothing.

Concerning the second Institute point, the safety of soy, the Institute document contains comments on thirteen statements about soy risk selected from the Weston A. Price Foundation federal court complaint. These comments avoid the question of support for the soy/coronary disease relationship claim and at best show differing opinions about various problems that the Weston A. Price Foundation has raised about soy safety under certain conditions.

Nothing contained in the Soy Nutrition Institute's comments supports the soy/coronary disease relationship. At best, these comments suggest scientific controversy—rather than significant scientific agreement--over various issues of soy safety. For this reason these comments are irrelevant to the proceeding before the FDA and the Federal court since they offer no support for the soy/coronary disease relationship.

The information available to FDA at this time establishes that there is not a significant scientific agreement supporting a soy/coronary disease relationship.

For this reason, we believe that the FDA has an obligation to amend the Final Rule to remove authorization for a heart disease prevention health claim for foods containing soy protein.

Respectfully submitted,

Sally Fallon Morell

Sally Fallon Morell
President

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ATTACHMENT I
STUDIES SHOWING ADVERSE EFFECTS OF SOY ON CARDIOVASCULAR DISEASE

Below find listed some scientific studies since 2008—the filing date of the Weston A. Price Foundation petition seeking revocation of the FDA-permitted soy/coronary health claims—which support the Foundation's position that significant scientific agreement supporting the soy health claims does not exist and therefore support the Foundation's petition for revocation of the soy heart health claims.

2015 Danxia Y. Dietary isoflavones, urinary isoflavonoids, and risk of ischemic stroke in women. Danxia Y et al. *AJCN* 2015; 102(3):680-686.

"A habitually **high intake of soy isoflavones may be associated with a modest but significant increase in the risk of ischemic stroke** in women."

2015 *Harvard Men's Health Watch* May 2015; 19(10)10.

"Add soy to your diet, but don't subtract other healthy foods. Soy foods can help you build a healthy diet, but **their ability to prevent heart disease and cancer remain unproven**."

2015 Konhilas, JP et al. Diet and sex modify exercise and cardiac adaptation in the mouse. *Am J Phy-Heart Circul Phy* 2015; 308 (2): H135-H145.

"The heart adapts to exercise stimuli in a sex-related manner when mice are fed soy chow. Females exercise more voluntarily than males and show more cardiac hypertrophy per kilometer run. Male mice fed a casein-based, soy-free diet **increased daily running distance over soy-fed counterparts**."

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2015 Harvey PA, Leinwand, LA. Dietary phytoestrogens present in soy dramatically increase cardiotoxicity in male mice receiving a chemotherapeutic tyrosine kinase inhibitor *Mol Cell Endocrin* 2015; 399(Issue C) : 330-335.

"Genistein, the most prevalent phytoestrogen in soy, is a potent endocrine disruptor and tyrosine kinase inhibitor (TK) that causes apoptosis in many cells types. TKIs such as Sunitinib cause cardiotoxicity in a significant number of patients. Significant lethality occurred in mice treated with Sunitinib and fed a phytoestrogen-supplemented diet. Isolated cardiomyocytes co-treated with genistein and Sunitinib exhibited additive inhibition of signaling molecules important for normal cardiac function and increased apoptosis compared with Sunitinib alone. Thus, **dietary soy supplementation should be avoided during administration of Sunitinib due to exacerbated cardiotoxicity**. "

2015 Campbell SC et al. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. *Menopause*. 2010 May-Jun;17(3):587-93.

"Data indicate that **1-year soy protein supplementation did not confer cardiovascular benefits**, in terms of favorable alterations in the lipid profile, in this cohort of postmenopausal women. These findings, as well as those from other studies, lend credence to the decision of the Food and Drug Administration to reevaluate the soy protein health claim issued a decade ago."

2014 Talaei M et al. Dietary soy intake is not associated with risk of cardiovascular disease mortality in Singapore Chinese adults. *J Nutr.* 2014 Jun;144(6):921-8.

"Soy intake was not significantly associated with risk of cardiovascular disease mortality in the Chinese population. However, a **slightly increased risk associated with high soy protein intake in men cannot be excluded** and requires further investigation."

2014 Yu D et al. Association of soy food intake with risk and biomarkers of coronary heart disease in Chinese men. *International J Cardiology* Mar 2014; 72(2): e285–e287.

"This study is the first to focus on soy foods and the risk of CHD in men and provide the evidence that **habitual high soy intake may have adverse effects on the development of CHD in men.** Habitual high soy food intake may be associated with increased risk of incident CHD in middle-aged and older Chinese men; elevated plasma IL-8 and PAI-1 might be potential contributing factors."

2014 Carmignani LO et al. The effect of soy dietary supplement and low dose of hormone therapy on main cardiovascular health biomarkers: a randomized controlled trial. *Rev Bras Ginecol Obstet.* 2014 Jun;36(6):251-8.

"The use of dietary **soy supplement did not show any significant favorable effect on cardiovascular health biomarkers** compared with HT (low dose hormone therapy)."

2013 Mangano KM et al. Soy proteins and isoflavones reduce interleukin-6 but not serum lipids in older women: a randomized controlled trial. *Nutr Res.* 2013 Dec;33(12):1026-33.

"**Soy protein and isoflavone (either alone or together) did not impact serum lipids or inflammatory markers.** Therefore, they should not be considered an effective intervention to prevent cardiovascular disease because of lipid modification in healthy late postmenopausal women lacking the ability to produce equol."

2013
Harland JI et al. *Soy: nutrition consumption and heart health.* In A. Ahmad (Ed.), Soy, nutrition, consumption and health (1-40) Nova Science Publishers, Inc.

"**Isolated isoflavones do not lower cholesterol.**"

2013 Girgih AT et al. Is category 'A' status assigned to soy protein and coronary heart disease risk reduction health claim by the United States Food and Drug Administration still justifiable? *Trends in Food Science & Technology*, Apr 2013; 30(2) :121-132.

"One objective of this review is to highlight some studies that were key evidence in the soy protein health claim approval, comparing these to emerging divergent scientific data, indicating modest lipid-lowering effects from soy proteins. Furthermore, the current US FDA health claim ranking system is reviewed, with a suggestion to use our modified ranking transient scale that will assist in appropriate ranking of all future health claims. **This review challenges the justification for soy protein to have a coronary heart risk reduction health claim** based on data on soy protein and cholesterol-lowering generated since the soy protein heart health claim was approved in 1999 which show modest to no effect and the fact that the FDA announced that it would re-evaluate the soy protein and heart health claim in December 2007."

2013 Qin Y et al. Isoflavones for hypercholesterolaemia in adults. *Cochrane Database Syst Rev.* 2013 Jun 6;6

"**We found no evidence for effects of isoflavones on patient-important outcomes or lowering of cholesterol levels in people with hypercholesterolaemia.**"

2012 European Food Safety Authority (EFSA). Scientific Opinion on the substantiation of a health claim related to isolated soy protein and reduction of blood LDL-cholesterol concentrations pursuant to Article 14 of Regulation (EC) No 1924/20061 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA).), Parma, Italy. *EFSA Journal* 2012; 10(2) 2555.

"Following an application from the European Natural Soyfood Manufacturers Association (ENSA), the Panel on Dietetic Products was asked to deliver an opinion on the scientific substantiation of a health claim related to isolated soy protein (ISP) and reduction of blood LDL-cholesterol concentrations. The Panel considered four randomized controlled trials (RCTs) which reported an effect, 14 RCTs which did not report an effect, and another RCT showed no consistent effects. **The opinion of the panel is that a cause and effect relationship has not been established between the consumption of ISP (as defined by the applicant) and a reduction in blood LDL-cholesterol concentrations.**"

2012 Haines CD et al. Estrogenic compounds are not always cardioprotective and can be lethal in males with genetic heart disease. *Endocrinology*. 2012 Sep;153(9):4470-9.

"Hypertrophic cardiomyopathy (HCM) is more severe in male than female mice eating a soy-based diet. . .**Estrogen was not protective in male or female mice with HCM and, in fact, was lethal in phytoestrogen-fed male mice with HCM**. . . Phytoestrogens led to distinct programs of gene expression in hearts from males vs. females with HCM (Hypertrophic cardiomyopathy) suggesting mechanisms by which males are more sensitive to the detrimental effects of phytoestrogens and females are protected. These results implicate the phytoestrogen genistein in mediating cardiac pathology in males with HCM and, importantly, establish that estrogen is not protective in the setting of HCM."

2012 EFSA European Food Safety Authority. (2012a). Scientific opinion on the substantiation of a health claim related to isolated soy protein and reduction of blood LDL-cholesterol concentrations pursuant to article 14 of Regulation (EC) No 1924/2006. *EFSA Journal*, 10(2), 2555.

"Following an application from the European Natural Soyfood Manufacturers Association (ENSA), and others submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, asked the Panel on Dietetic Products to deliver an opinion on the scientific substantiation of a health claim related to isolated soy protein (ISP) and reduction of blood LDL-cholesterol concentrations, referring to disease risk reduction. In weighing the evidence, the Panel four randomised controlled trials (RCTs) reported an effect of ISP on blood LDL/non-HDL cholesterol concentrations, whereas 14 RCTs did not report such an effect, and another RCT showed no consistent effects. The Panel also took into account that most of these RCTs were at high risk of bias, that differences in the results obtained between trials appear unrelated to the dose of ISP used, to sample size or to study duration, and that the evidence provided in support of a possible mechanism was not convincing. **A cause and effect relationship has not been established between the consumption of ISP (as defined by the applicant) and a reduction in blood LDL-cholesterol concentrations**.

2012 EFSA European Food Safety Authority. (2012b). Response to comments on the scientific opinion on the substantiation of a health claim related to isolated soy protein and reduction of blood LDL-cholesterol concentrations pursuant to article 14 of Regulation (EC) No 1924/2006. Supporting publications 2012:305. (7 pp.). Available online. www.efsa.europa.eu.

"Following a request from the European Commission, EFSA was asked to review the scientific comments received on the Scientific Opinion of the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) on the scientific substantiation of health claims related to isolated soy protein and reduction of blood LDL-cholesterol concentrations pursuant to Article 14 of Regulation (EC) No 1924/2006. originating from the applicant (ENSA/EUVEPRO/SPA), from the ENSA Scientific Advisory Committee, from Dr. Penny M. Kris-Etherton (Professor of Nutrition, Pennsylvania State University), and from David J.A. Jenkins, Arash Mirrahimi, Kristie Srichaikul, Laura Chiavaroli, Livia S.A. Augustin, John L. Sievenpiper, Russell J. de Souza and Cyril W.C. Kendall (joint response). In its opinion adopted on 18 January 2012, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) concluded that **a cause and effect relationship had not been established between the consumption of isolated soy protein and reduction of blood LDL-cholesterol concentrations. The comments received do not change the conclusions of the Panel.**"

2012 Liu ZM et al. The effects of isoflavones combined with soy protein on lipid profiles, C-reactive protein and cardiovascular risk among postmenopausal Chinese women. *Nutr Metab Cardiovasc Dis*. 2012 Sep;22(9):712-9

"Soy protein with isoflavones, or isoflavones alone at the provided dosage showed no significantly beneficial effects on measured cardiovascular risk factors in postmenopausal Chinese women with early hyperglycaemia."

2010 Campbell SC. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. *Menopause*. May 2010; 17(3): 587-593.

"Our data indicate that 1-year soy protein supplementation did not confer cardiovascular benefits, in terms of favorable alterations in the lipid profile, in this cohort of postmenopausal women. These findings, as well as those from other studies, lend credence to the decision of the Food and Drug Administration to reevaluate the soy protein health claim issued a decade ago."

2010 EFSA e European Food Safety Authority. (2010). 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. *EFSA Journal,* 8(7), 1688.

". . . HarlandHall Ltd. on behalf of the Soya Protein Association (SPA), the European Vegetable Protein Federation (EUVEPRO), and the European Natural Soyfood Manufacturers Association (ENSA) asked the Panel on Dietetic Products, for a scientific opinion on soy protein and reduction of blood cholesterol concentrations, a health claim referring to reduction of a disease risk for soy protein, i.e. the protein component of the soybean Glycine max.

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 considered that 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."

2008 Pan A et al. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. *J Nutr*, 138 (2008), pp. 2413–2421

"**Soy protein intake was positively significantly associated with hyperglycemia in men**, whereas it was inversely associated with elevated blood pressure and not associated with any component in women. Habitual soy protein intake may have sex-dependent effects on risk of metabolic syndrome (MetS) in middle-aged and elderly Chinese.

2008 Taku K et al. Effects of extracted soy isoflavones alone on blood total and LDL cholesterol: Meta-analysis of randomized controlled trials . *Ther Clin Risk Mgt* 2008; 4(5): 1097-1103.

"**Soy isoflavones/day (27-132 mg, as the aglycone form) alone had a nonsignificant effect on total and LDL cholesterol in menopausal women,** respectively. It is concluded that ingestion of about 70 mg extracted soy isoflavones/day alone for 1-3 months does not improve total and LDL cholesterol levels in normocholesterolemic menopausal women."

2008 Greany KA et al. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *European J Clin Nutr* 2008; 62 (12): 1419-1425.

"Results did not differ by equol production status or by baseline lipid concentration. Adjustment for intake of folate and methionine did not alter the homocysteine (Hcy) results. Conclusions: **These data suggest that decreasing vascular inflammation and Hcy concentration are not likely mechanisms by which soy consumption reduces coronary heart disease risk.**"

2008 Thorp AA et al. Soy food consumption does not lower LDL cholesterol in either equol or nonequol producers. *Am J Clin Nutr.* 3008; 88(2): 298-304.

"On the basis of urinary soy isoflavones (ISO), 30 subjects were equol producers. Lipids were not affected significantly by equol production. **Regular consumption of foods providing 24 grams of soy protein per day from ISOs had no significant effect on plasma LDL cholesterol** in mildly hypercholesterolemic subjects, regardless of equol-producing status. "

2008 Chao Wu Xiao. Health effects of soy protein and isoflavones in humans. *J Nutr* 2008; 138(6)1244S-1249S.

"The Nutrition Committee of the American Heart Association has assessed 22 randomized trials conducted since 1999 and found that isolated soy protein with isoflavones (ISF) slightly decreased LDL cholesterol but had no effect on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure… Some studies have documented potential safety concerns on increased consumption of soy products. Impacts of soy products on thyroid and reproductive functions as well as on certain types of carcinogenesis require further study in this context. **Overall, existing data are inconsistent or inadequate in supporting most of the suggested health benefits of consuming soy protein or ISF.** "

2006 Sacks et al. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee Circulation. 2006 Feb 21;113(7):1034-44. Epub 2006 Jan 17.

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"**Soy protein and its associated isoflavone components,** even though generally beneficial to overall wellbeing, **do not appear to have significant effects on cardio-health that is superior to those of other food proteins.**"

SOY AND THYROID FUNCTION

2015 Sara JD et al. Hypothyroidism Is Associated With Coronary Endothelial Dysfunction in Women. *J Am Heart Assoc.* 2015 Jul 29;4(8)

"**Hypothyroidism is associated with an increased risk of coronary artery disease, beyond that which can be explained by its association with conventional cardiovascular risk factors.** . . .Hypothyroidism in women is associated with microvascular endothelial dysfunction, even after adjusting for confounders, and may explain some of the increased risk of cardiovascular disease in these patients."

2015 Ning N et. al. Prognostic Role of Hypothyroidism in Heart Failure: A Meta-Analysis. *Medicine* (Baltimore). 2015 Jul;94(30)

"**Hypothyroidism is a risk factor of heart failure (HF) in the general population**. . . ..We found hypothyroidism associated with increased all-cause mortality as well as cardiac death and/or hospitalization in patients with HF. Further diagnostic and therapeutic procedures for hypothyroidism may be needed for patients with HF."

2013 Tran L. et al. Soy extracts suppressed iodine uptake and stimulated the production of autoimmunogen in rat thyrocytes. *Exp Biol Med* (Maywood). 2013 Jun;238(6):623-30.
PMID: 23918874

"**Soy isoflavones (ISF), particularly genistein, induced the production of P40, which might be responsible for the higher incidence of ATD reported in soy infant formula-fed children**. Novasoy (1, 10, and 50 μg/mL) and genistein (1 and 10 μM) markedly increased the protein content of a 40 kDa Tg fragment (P40, a known autoimmunogen)."

2011 Sathyapalan T. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study. *J Clin Endocrinol Metab*. 2011 May;96(5):1442-9.

"**There is a 3-fold increased risk of developing overt hypothyroidism with dietary supplementation of 16 mg soy phytoestrogens with subclinical hypothyroidism**."

2007 Roman GC. Autism: transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *J Neurol Sci.* 2007 Nov 15;262(1-2):15-26.

"The current surge of autism could be related to transient maternal hypothyroxinemia resulting from dietary and/or environmental exposure to antithyroid agents. Transient intrauterine deficits of thyroid hormones (as brief as 3 days) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in brains of patients with autism. Early maternal hypothyroxinemia resulting in low T3 in the fetal brain during the period of neuronal cell migration (weeks 8-12 of pregnancy) may produce morphological brain changes leading to autism. Insufficient dietary iodine intake and a number of environmental antithyroid and goitrogenic agents can affect maternal thyroid function during pregnancy. The most common causes could include inhibition of deiodinases D2 or D3 from maternal ingestion of dietary flavonoids or from antithyroid environmental contaminants. Some plant isoflavonoids have profound effects on thyroid hormones and on the hypothalamus-pituitary axis. **Genistein and daidzein from soy (Glycine max) inhibit thyroperoxidase that catalyzes iodination and thyroid hormone biosynthesis."**

European Food Safety Authority

EFSA Journal 2010; 8(7):1688

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. © European Food Safety Authority, 2010

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.

TABLE OF CONTENTS

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 ≥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

ATTACHMENT III

"Building healthier lives, free of cardiovascular diseases and stroke."

Heart Disease and Stroke. You're the Cure.

American Heart Association. | American Stroke Association.
Learn and Live.

February 19, 2008

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2007N-0464

Dear Sir/Madam:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million AHA and ASA volunteers and supporters, we appreciate the opportunity to submit our comments in response to the Food and Drug Administration's (FDA) notice on the Reevaluation of Health Claims and Qualified Health Claims.

Since 1924, the American Heart Association has dedicated itself to reducing disability and death from cardiovascular disease and stroke – the #1 and #3 leading causes of death in the United States – through research, education, community based programs, and advocacy. As part of this effort, the Association produces evidence-based clinical guidelines and scientific statements designed to raise awareness of and advise physicians and other providers regarding the prevention, treatment and management of cardiovascular diseases and stroke. Since 1999 when AHA and ASA committed to achieving a 25% reduction in cardiovascular disease, stroke, and associated risk by 2010, the Association's efforts have contributed to a 25.8% reduction in deaths from coronary heart disease – an early achievement of our goal – and a 24.4% reduction from stroke. However, we continue to work toward needed reductions in the major risk factors for these leading causes of death, as well as eliminating disparities in care for women and minority populations.

One important strategy for reducing the incidence and risk of cardiovascular disease and stroke is raising the public's awareness of the benefits of a healthy diet and active lifestyle. Promoting healthy eating patterns, a healthy body weight, and increased physical activity is a top priority of AHA. The Association

American Heart Association . Advocacy Department
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firmly believes that better food habits can significantly reduce high blood cholesterol – one of the major risk factors for cardiovascular disease – as well as support proper weight management, which is essential to cardiovascular health.

As the public learns more about the relationships between diet and disease, many consumers are striving to adopt a healthier lifestyle and make better food choices. Sixty-six percent of consumers report having made dietary changes to improve health, a nine percent increase from the previous year. Additionally, an increasing number of consumers cite healthfulness as an influential factor in food purchasing decisions.[1] AHA supports the dissemination of clear, scientifically valid information to the public to help consumers evaluate and select more nutritious foods. Health claims may serve as a way to achieve this aim.

Soy Protein and Coronary Heart Disease

AHA strongly believes that health claims should be based on strong, sound evidence that indicates an unambiguous relationship between the substance and the health benefit indicated in the health claim. As the science supporting health claims is often evolutionary, AHA applauds the FDA's initiative to reevaluate the soy protein and coronary heart disease (CHD) health claim as new data has become available. In 2000, just one year after the FDA first approved the health claim, an AHA Nutrition Committee Scientific Advisory concluded that "it is prudent to recommend including soy protein foods in a diet low in saturated fat and cholesterol."[2] However, given the volume of well-controlled studies on soy protein and soy-derived isoflavones that have been released since that time, the AHA Nutrition Committee recently undertook a reevaluation of the evidence on soy protein and cardiovascular disease (CVD) to update its scientific advisory. AHA reviewed the literature and considered the effects of soy protein and isoflavones on several other CVD risk factors: HDL cholesterol, triglycerides, lipoproteins, and blood pressure. In 2006, the Association published an updated Scientific Statement titled "Soy Protein, Isoflavones, and Cardiovascular Health."[3] We reaffirmed our position in the Association's "Diet and Lifestyle Recommendations Revision 2006."[4]

In both statements, AHA acknowledges that earlier research indicated that soy protein, as compared with other proteins, potentially had clinically important favorable effects on LDL cholesterol and other CVD risk factors. However, this research has not been confirmed by many studies reported during the past 10 years. The majority of research suggests that a very large amount of soy protein, more than half the daily protein intake, may lower LDL cholesterol by a few percentage points when it replaces dairy protein or a mixture of animal proteins. However,

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[1] International Food and Information Council Foundation 2007 Food and Health Survey: Consumer Attitudes toward Food, Nutrition and Health.

[2] Erdman JW Jr. AHA Science Advisory: Soy protein and cardiovascular disease: a statement for healthcare professionals from the Nutrition Committee of the AHA. *Circulation.* 2000; 102:2555-2559.

[3] Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation.* 2006; 113:1034-1044.

[4] Lichtenstein A, Appel LJ, et al; American Heart Association Nutrition Committee. Diet and Lifestyle Recommendations Revision 2006: A Scientific Statement From the American Heart Association Nutrition Committee. *Circulation.* 2006; 114; 82-96.

this reduction is very small relative to the large amount of soy protein tested in these studies and the data are mainly from hypercholesterolemic individuals. Furthermore, there are no evident benefits of soy protein consumption on HDL cholesterol, triglycerides, lipoprotein(a), or blood pressure. Thus, the direct cardiovascular health benefit of soy protein or isoflavone supplements is minimal at best.

AHA recognizes that there is research claiming to identify a cholesterol-lowering mechanism of soy protein,[5] and there may be cardiovascular health benefits in using soy proteins to replace foods high in animal protein that contain saturated fat and cholesterol.[6] However, at this time the totality of evidence linking soy protein consumption with reduced risk of coronary heart disease is not sufficient to meet the standards of significant scientific agreement (SSA). Thus, AHA strongly recommends that FDA revoke the soy protein and CHD health claim.

We understand that if the FDA decides to revoke this SSA health claim, the Agency could consider allowing its use as a qualified health claim. We urge FDA not to do so. Consumer research conducted by AHA, FDA, and others has repeatedly shown that despite the presence of qualifying language, consumers do not understand qualified health claims and do not understand that they are based on limited and varying degrees of evidence. Therefore, AHA does not support the use of qualified health claims; only health claims meeting the SSA standard should be permitted.

In conclusion, AHA reiterates our appreciation of the Agency's decision to reevaluate the soy protein and CHD health claim. While the science originally appeared to support a strong link between soy protein and a reduced risk for CHD, recent data are less conclusive and no longer support a SSA level health claim. AHA strongly recommends that FDA revoke the soy protein and CHD health claim. In the meantime, this remains a dynamic area for research. AHA will continue to monitor the science regarding soy and CVD.

If you have any questions or need additional information, please do not hesitate to contact Susan K. Bishop, MA, Regulatory Relations Manager, at 202-785-7908 or via email at susan.k.bishop@heart.org.

Sincerely,

Daniel W. Jones

Daniel W. Jones, MD
President, AHA

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[5] Cho SJ, Juillerat MA, Lee CH. Cholesterol-Lowering Mechanism of Soybean Protein Hydrolysate. *Journal of Agricultural and Food Chemistry.* 2007; 55; 10599-10604.

[6] Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M; American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: an American Heart Association science advisory for professionals from the Nutrition Committee. *Circulation.* 2006; 113:1034-1044.