Soyfoods Association of North America

1050 17th Street, NW • Suite 600 • Washington, DC 20036 • USA

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

Claudine Kavanaugh
Center for Food Safety and Applied Nutrition (HFS-830)
Food and Drug Administration
5100 Paint Branch Pkwy
College Park, MD 20740-3835

Additions to Docket No. 2007N-0464 Health Claims and Qualified Health Claims; Dietary Lipids and Cancers, Soy Protein and Coronary Heart Disease, Antioxidant Vitamins and Certain Cancers, and Selenium and Certain Cancers; Re-evaluation; Opportunity for Public Comment

Dear Ms. Kavanaugh:

The Soyfoods Association of North America (SANA), which represents the interests of small and large soyfood manufactures, soy processors, suppliers, soybean farmers, and other industry stakeholders, would like to make additions to Docket No. 2007N-0464 with concern to the re-evaluation of the Soy Protein and Coronary Heart Disease (CHD) Health Claim[1]. Since FDA released the public notice of plans to re-evaluate several health claims and SANA submitted comments to that notice, several relevant research articles on soy and heart disease have been published and the scientific evidence should become part of the FDA official record. SANA remains confident that an FDA review of the totality of scientific evidence to date on soy protein and its effect on total and low density lipoprotein cholesterol (LDL-C) levels, research reviewed for the 1999 health claim, as well as, research conducted after 1999, will confirm the heart health benefit of soy protein and discharge the need for any regulatory action on the soy and CHD health claim.

Recent Evidence Based Reviews Since the Soy and CHD Health Claim Approval

SANA believes that in the time following FDA's original approval of the soy protein and CHD health claim in 1999, newer scientific evidence substantiates the FDA finding that soy protein reduces total and LDL cholesterol levels. Although researchers have found soy protein to lower total and LDL-C at varying degrees, the consistent association

[1] 72 FR 72739 (December 21, 2007).

between soy protein and a reduction in total and LDL-C warrants the continuation of the soy protein and CHD health claim.

In FDA's initial review of the research on soy and CHD, the Agency concluded "that the totality of the available scientific evidence supports a consistent, if not universal, hypocholesterolemic effect of soy protein included in a low saturated fat and low cholesterol diet."[2] In the final rule, FDA noted some of the reasons why not all of the studies showed significant reductions of total and LDL-C levels: 1) large range of individual responses, such as the results found in the effectiveness of Step I and Step II National Cholesterol Education Program (NCEP) diets in free-living subjects, 2) different forms and amounts of soy protein tested, 3) different experimental designs and diets studied, and 4) the variability in baseline cholesterol levels of the subjects. FDA observed in the final rule that non-responders to dietary interventions can result in significant underestimation of the effectiveness of dietary intervention when only the mean response is considered.[2]

Since February 2008, when SANA submitted comments and a review of research in support of the FDA health claim for soy protein, three new meta-analyses have been conducted and several additional studies on soy protein and cholesterol lowering have been published. These are reviewed below.

New Meta-Analyses Published since 2008

Harland and Heffner[3]

Harland and Haffner conducted a meta-analysis that found when soy protein was included in the diet of adults, statistically significant reductions in total and LDL-C occurred. An average intake of 24 grams of soy protein led to reductions in LDL-C (9.7 mg/dL), total cholesterol (9.7 mg/dL), and blood triglycerides (11.5 mg/dL). The total-high density lipoprotein cholesterol (HDL-C) ratio decreased and HDL-C was marginally increased. This achievable daily-intake of soya protein, particularly when used in association with other dietary measures can make a useful contribution to blood cholesterol management.

Jenkins et al.[4]

In the meta-analyses by Jenkins *et al*., the studies from the AHA Soy Advisory review[5] and original Anderson[6] meta-analyses were reviewed. One of the objectives of this analysis was to re-evaluate the studies identified in the AHA Soy Advisory review[5] and apply a rigorous statistical analysis to determine whether the heart health claim for soy

[2] 64 FR 57709 (October 26, 1999).

[3] Harland J , Haffner T. Systematic review, meta-analysis and regression of randomised controlled trials reporting an association between an intake of circa 25g soya protein per day and blood cholesterol. *Atherosclerosis*. 2008;200:13-27.

[4] Jenkins DJ, Mirrahimi A, Srichaikul K, Berryman CE, Wang L, Carleton A, et al. Soy protein reduces serum cholesterol by both intrinsic and food displacement mechanisms. *J Nutr* 2010;140:2302S-2311S.

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

[6] Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995;333:276-282.

continues to be justified. In addition, the data presented in their analyses permitted an estimation of "the intrinsic effect of soy protein" on LDL-C (that relates to the soy protein per se) and the extrinsic (displacement) potential of soy as it replaces saturated fat and other components in the diet that can lead to elevated blood lipids. Eleven random controlled trials (RCTs) where macronutrient profiles of both soy protein and protein control diets were carefully balanced were included in one meta-analysis to demonstrate the intrinsic effect of soy to lower plasma cholesterol. The results from this meta-analysis showed a mean LDL-C reduction of 0.17 mmol/L ($n = 22$; $P < 0.0001$) or 4.3% for soy protein which could be attributable to the protein itself since there were no other confounding dietary factors in these carefully selected studies. Using NHANES III intake data to estimate animal protein intakes in the typical American diets, Jenkins et al[4] then estimated the displacement value of soy by modeling the isocaloric displacement of a range of 13–58 g/d soy protein for animal protein foods. Using standard predictive equations for LDL-C[7] the "extrinsic" effect of soy protein in displacing foods higher in saturated fat and cholesterol was calculated. The proposed "extrinsic" effect of soy was an estimated 3.6–6.0% reduction in LDL-C, due to displacement of saturated fats and cholesterol from animal foods by soy protein. In conclusion, the total LDL-C reduction attributable to the combined intrinsic and extrinsic effects of soy protein foods, therefore, ranged from 7.9 to 10.3%. The data from this robust and careful meta-analyses support the maintenance of the soy protein and heart health claim.

Anderson and Bush[8]

Anderson and Bush conducted a meta-analysis and quality assessment of RCTs published 1996 through 2008 that tested the effects of soy protein on serum lipoprotein risk factors for CHD. The analysis included 20 parallel-design studies and 23 crossover studies. The results of the parallel studies showed soy protein intake was associated with a 5.5% reduction in serum LDL-C. Results were not as prominent in crossover studies. Parallel studies that scored significantly higher in study quality were significantly associated with greater improvements in LDL-C. Parallel studies also showed that soy produced net serum HDL-C values 3.2% lower and fasting serum triacylglycerol values 10.7% lower than a control. The median intake associated with a significant improvement in lipoprotein risk factors for CHD was 30 g. The results of this quality assessment and meta-analysis show that routine consumption of 15-30 g of soy protein per day (2-4 servings) has a significant effect on the reduction of serum lipoprotein risk factors for CHD.

Studies Assessing Cholesterol Lowering Efficacy of Soy Protein Alone

Hodis et al.[9]

Hodis and colleagues of the University of Southern California, Keck School of Medicine, studied 350 postmenopausal women aged 45-92 years without diagnosed diabetes or

[7] Katan MB, Tilburg TV, Luger M. Katan Calculator: predicted effect of diet on blood lipids and lipoproteins. Available from: http://www.katancalculator.nl/

[8] Anderson JW and Bush HM. Soy protein effects on serum lipoproteins: A quality assessment and meta-analysis of randomized, controlled studies. *Jour Amer Col Nutr.* 2011;30:79–91.

[9] Hodis HN, Mack WJ, Kono N, Azen SP, Shoupe D, Hwang-Levine J, Petitti D, Whitfield-Maxwell L, Yan M, Franke A, Selzer RH. Isoflavone soy protein supplementation and atherosclerosis progression in healthy postmenopausal women. *Stroke.* 2011;42:3168-3175.

heart disease in a double-blind, placebo-controlled parallel-design study. The women were randomly divided into two groups who consumed 25 g doses of soy protein (containing 91 mg aglycon isoflavone) or total milk protein (placebo) daily for 2.7 years. Carotid artery intima-media thickness progression rate was measured to evaluate soy's potential cardio-protective effects. There were no changes in total or LDL-C between groups, however there was a significant increase in HDL-C in those who consumed soy protein. It should be noted that cholesterol and lipid measures were secondary endpoints, baseline values for serum total and LDL-C were not reported, and diet was not controlled in this study.

Wofford et al.[10]

These researchers from Tulane University recruited 352 U.S. healthy adults with an average age of 47.7 to participate in their randomized, double-blind three phase crossover placebo controlled trial called the Protein and Blood Pressure Study. The primary endpoint of the study was blood pressure and those results are published separately[11] but the study was designed to look at plasma lipids as a secondary endpoint. Participants were assigned to receive 40 g/day supplementation of soy protein, milk protein or complex carbohydrate for eight weeks in a random order with a three week washout between each intervention. Results showed that, compared with carbohydrates, the soy protein was associated with a significant 3.97 mg/dL reduction in total cholesterol levels, and a 0.12 reduction in the ratio of total:HDL-C . In addition, compared to milk protein, the soy protein was associated with a 1.54 mg/dL increase in HDL-C levels and a 0.14 decrease in the ratio of total:HDL-C. On the other hand, milk protein supplementation was significantly associated with a 1.13 mg/dL decrease in HDL levels, compared to carbohydrate supplements.

Noroozi et al.[12]

Drs. Noroozi, Zavoshy, and Jahanihashemi from Qazvin University of Medical Studies in Qazvin, Iran, conducted a study on 52 patients of both genders and between 25-65 years to determine the effect of soy protein combined with a low-calorie diet on lipid profiles in patients with hyperlipidemia. All subjects received a low-calorie diet with 1400 kilocalories, 18% protein, 24% fat, 58% carbohydrates for four weeks and the treatment group received 30 g of soy protein per day. After four weeks on a low-calorie diet, body weight, body mass index (BMI), waist and hip circumference were significantly reduced in both groups. There were no significant differences in plasma lipid concentrations at baseline between the two groups and both groups experienced significant reductions in total cholesterol and triglyceride levels, but no significant changes in HDL-C levels. Soy protein treatment resulted in a significant 7.3% reduction in LDL-C from baseline values, whereas there was no significant reduction in the LDL-C levels of the control group. A reduction in LDL-C levels is favorable in the reduction of cardiovascular disease risk in

[10] Wofford MR, Rebholz CM, Reynolds K, Chen J, Chen C-S, Myers L, Xu J, Jones DW, Whelton PK, He J. Effect of soy and milk protine supplementation on serum lipid levels: a randomized controlled trial. *Eur J Clin Nutr*. 2011: doi: 10.1038/ejcn.2011.168

[11] He J, Wofford MR, Reynolds K, Chen J, Chen C-S, Myers L, Minor DL, Elmer PJ, Jones DW, Whelton PK. Effect of dietary protein supplementation on blood pressure: A randomized controlled trial. *Circulation* 2011; 124: 589-595.

[12] Noroozi M, Zavoshy R, Jahanihashemi H. The effects of low calorie diet with soy protein on cardiovascular risk factors in hyperlipidemic patients. *Pak J Biol Sci*. 2011;14:282-287.

people with hyperlipidemia. The authors concluded that this effect may allow potential drug therapy to be postponed in those with hyperlipidemia.

Maki et al.[13]

This randomized, controlled, parallel arm trial evaluated the effects of an insoluble fraction of soy protein, compared to total milk proteins with high calcium content, on the fasting lipid profile. It also assessed the potential contributions of increased excretion of bile acids and neutral sterols to their lipid-altering effects. Subjects for this study included men and women 18 to 79 years of age with moderately elevated cholesterol and receiving no lipid altering therapy. Participants were asked to follow a Therapeutic Lifestyle Changes diet throughout the study. Subjects were then screened for their ability to lower their cholesterol in response to a bile acid binding drug, colesevelam. A majority of subjects responded and were then randomized to the test protein groups which were a relatively insoluble fraction of soy protein and total milk protein. Both soy protein and total milk protein reduced atherogenic lipoproteins, as indicated by changes in total cholesterol (-7.4% and -3.6%), LDL-C (-10.9% and -5.9%), non-high-density lipoprotein cholesterol (-10.8% and -3.9%) and apolipoprotein B (-9.7% and -2.4%), respectively versus baseline with soy showing significantly more lowering for between group differences except LDL-C. Median HDL-C levels were increased in the soy protein group and decreased in the total milk protein group (4.0% vs. -3.3%). No significant increases were observed in either group for fecal bile acids or neutral sterols indicating that increased bile acid excretion is not an important contributor to the hypocholesterolemic effects of either protein source. However, these results do confirm that soy protein consumption in the context of a low fat diet exerts a hypocholesterolemic effect and total milk protein elicits a less pronounced response. The data continue to support a cholesterol reduction heart health claim for soy protein.

Santo et al.[14]

Santo and colleagues examined thirty 18-30 year old sedentary males to determine if the postprandial states would be more sensitive to any favorable changes associated with consuming soy protein with or without isoflavones, compared with the fasting state lipid profile. For 28 days, participants consumed their usual diet and were randomly supplemented with 25 g/day of milk protein, isoflavone-poor soy, or isoflavone-rich soy. Serum samples were collected pre- and post-supplementation in a fasted state and postprandially at 30, 60, 120, 240, and 360 minutes following consumption of a high-fat, 1,000 kcal shake. No differences were found in the fasting lipid profiles after supplementation regardless of protein source. The area under-the-curve for postprandial triacylglycerol and triacylglycerol increased after soy intake. These results support the postprandial state as a more sensitive marker of the effects of the consumption of soy on cardiovascular disease (CVD) risk factors compared to the fasting lipid profile.

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[13] Maki KC, Butteiger DN, Rains TM, Lawless A, Reeves MS, Schasteen C, et al. Effects of soy protein on lipoprotein lipids and fecal bile acid excretion in men and women with moderate hypercholesterolemia. *Journal of Clinical Lipidology* 2010;4:531-42.

[14] Santo AS, Santo AM, Browne RW, Burton H, Leddy JJ, Horvath SM, Horvath PJ. Postprandial lipemia detects the effect of **soy** protein on cardiovascular disease risk compared with the fasting lipid profile.
Lipids. 2010;45:1127-1138.

Postprandial state is a viable and more sensitive indicator of CVD risk compared with the traditional lipid profile with respect to potential salubrious effect of consuming soy protein for 28 days in sedentary, normocholesterolemic males. The absence of isoflavones in soy protein may have deleterious consequences on purported cardio-protective effects. Removing soy isoflavones may prevent any cardio-protective effect and may even have a deleterious consequence if ingested chronically.

Pipe et al.[15]

Dr. Pipe and her colleagues studied the effect of soy protein isolate consumption compared to milk protein isolate on serum lipids in twenty-nine adults with diet-controlled type 2-diabetes. There was a 28-day washout period in this double-blind, randomized, crossover, placebo-controlled intervention study design. Compared to milk protein isolate, soy protein isolate consumption reduced serum LDL-C, LDL-C:HDL-C ratio, and apolipoprotein B:apolipoprotein A-I ratio. Soy protein isolate did not affect serum total cholesterol, HDL-C, triacylglycerol, apolipoprotein B, or apolipoprotein A-I.

Campbell et al.[16]

The primary aim of Dr. Campbell's study was to examine the effects of soy protein on bone health benefits in postmenopausal women and those results were published in a separate article.[17] This second publication reports on the serum lipid changes in that same cohort of moderately hypercholesterolemic women. Subjects were randomly assigned to consume daily for 1 year 25 g of protein from soy products or casein-based food products as the control. The test foods were in the form of snack bar, drink mix and cereal. The soy products were soy protein based and contained 60 mg of isoflavones per day. The subjects in this study were free-living and there were infrequent follow up visits for diet counseling and food records were collected only at the beginning and end of the study. There was a 29% dropout rate in this study. Since they were not the primary endpoint of the study, plasma lipids were determined only three times in a year at single visits. The results showed total cholesterol and HDL-C levels increased after 1 year of soy protein supplementation; no changes in LDL-C were observed.

Borodin et al.[18]

Dr. Borodin and others tested the effect of the type of protein, either 30 g protein daily from soybean protein isolate or skimmed curd protein in Russian style cookies, in 28 Russians over 50 years of age with hyperlipidemia. Subjects were randomly assigned to two groups and were given either cookie for 2 months separated by a month-long washout interval in a cross-over design. With the consumption of soy protein isolate for two months, concentrations of total-cholesterol dropped 17 mg/dL or 6.5%, HDL-C

[15] Pipe EA, Gobert CP, Capes SE, Darlington GA, Lampe JW, Duncan Soy protein reduces serum LDL cholesterol and the LDL cholesterol:HDL cholesterol and apolipoprotein B:apolipoprotein A-I ratios in adults with type 2 diabetes. AM. *J Nutr*. 2009;139:1700-1706.

[16] Campbell SC, Khalil DA, Payton ME, Arjmandi BH. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. *Menopause*. 2010;17:587-593.

[17] Arjmandi BH, Lucas EA, Khalil DA, Devareddy L, Smith BJ, McDonald J, Arquitt AB, Payton ME, Mason C. One year soy protein supplementation has positive effects on bone formation markers but not bone density in postmenopausal women. *Nutr J* 2005;4:8.

[18] Borodin EA, Menshikova IG, Dorovskikh VA, Feoktistova NA, Shtarberg MA, Yamamoto T, Takamatsu K, Mori H, Yamamoto S. Effects of two-month consumption of 30 g a day of soy protein isolate or skimmed curd protein on blood lipid concentration in Russian adults with hyperlipidemia. *J Nutr Sci Vitaminol* (Tokyo). 2009;55:492-497.

increased 5 mg/dL or 9%, non-HDL-C dropped 22 mg/dL or 11%, and triglycerides fell 31 mg/dL or 18%. There were no significant changes with skimmed curd protein. Administration of 30 g soy protein isolate a day for two months confirmed its favorable effects on serum lipids in Russians with hyperlipidemia.

Thorp et al.[19]

This study was a randomized, crossover controlled trial conducted on 91 adult men and women with mildly elevated cholesterol and who were non-soy consumers. Subjects were provided with 3 servings/day of food which delivered 24 g/day dairy protein, 24 g/day soy protein or a 50:50 combination of soy and dairy protein; each intervention was for 6 weeks with no washout period. Total-cholesterol was 3% lower with the soy protein diet versus the control dairy-based diet. There were no significant effects on LDL-C or HDL-C, although LDL-C was 0.10 mmol/L lower in the soy group. Total:HDL-C ratio for the dairy, soy/dairy and soy diets were 5.05, 5.01, and 4.76, respectively. Despite a trend for the ratio of Total:HDL-C to be lower with the soy protein treatment than with the dairy/soy or dairy treatments, this difference was not statistically significant. Plasma triglycerides were 4% lower with both the soy and soy/dairy diets.

Radhakrishnan et al.[20]

This study was a randomized, double-blind placebo controlled, parallel design study of postmenopausal women conducted at the University College of Medical Sciences and Guru Teg Bahadur Hospitla, Delhi, India. A total of 85 women completed the 6 month intervention study. The women were randomized into two groups: one group consumed 25 g of soy protein isolate (containing 75 mg isoflavones) or 25 g of total milk protein per day. The clinical powdered products were consumed after dissolving individual packets into water, milk or juice and subjects were instructed to consume the 25 g of protein in 2-3 divided doses per day. Primary endpoints of the study were plasma lipid and bone density changes. Plasma lipid concentrations were assessed at baseline, 3 months and 6 months. This is a relatively long term study that demonstrates that 25g soy protein leads to a 7.7% decrease in total cholesterol and a 14% decrease in LDL-C (significantly different from both baseline and control group). The effect was seen after three months and improved further at six months. No effect was seen on HDL-C or plasma triglycerides, blood pressure, sex hormones, vaginal cytology, uterine endometrium and bone densitometry. Soy supplementation was significantly superior to the placebo in reducing the Kupperman Menopausal Index (KMI).

Conclusion

The totality of the evidence reviewed in this letter is consistent and supportive of the research prior to 2008 and continues to support the effectiveness of soy protein intake and the lowering of total and LDL-C. This effect benefits the heart health of all Americans both from an individual and a public health perspective. We feel that the weight of the

[19] Thorp AA, Howe PR, Mori TA, Coates AM, Buckley JD, Hodgson J, Mansour J, Meyer BJ. Soy food consumption does not lower LDL cholesterol in either equol or non-equol producers. *Am J Clin Nutr* 2008; 88: 298-304.

[20] Radhakrishnan G, Rashmi, Agarwal A, Vaid NB. Evaluation of isoflavone rich soy protein supplementation for postmenopausal therapy. *Pak J Nutr* 2009; 8: 1009-1017.

positive evidence on soy protein should aid the FDA in their decision as to whether any regulatory action is needed regarding the current health claim for soy protein and CHD. SANA is glad to supply any of the referenced materials to FDA during this re-evaluation process. SANA is happy to assist FDA in any manner and encourages FDA to contact our office with any requests, questions, or concerns.

Sincerely,

Nancy Chapman, M.P.H., R.D.
Executive Director