Soyfoods Association of North America

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Comments on 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, appreciates the opportunity to comment on Docket No. 2007N-0464 with concern to the re-evaluation of the Soy Protein and Coronary Heart Disease (CHD) Health Claim. SANA understands that "FDA intends to evaluate the scientific evidence on soy protein and the risk of heart disease to determine if the totality of the scientific evidence continues to meet the significant scientific agreement standard"[1] and welcomes this review. SANA believes that research, conducted since the original health claim was granted in 1999, continues to support FDA's finding that soy protein lowers total and low-density lipoprotein (LDL) cholesterol levels and reduces the risk of coronary heart disease. SANA is confident that a review of the totality of scientific evidence to date on soy protein and its effect on total and LDL cholesterol levels, research reviewed for the 1999 health claim, as well as, research conducted after 1999, will confirm the heart health benefit of soy protein. SANA recommends that FDA take no new regulatory action on the soy and CHD health claim.

Purpose of Health Claims

Health claims describe a relationship between consuming a food, food component, or dietary supplement ingredient, and reducing risk of a disease or health-related condition. The public accessibility of these claims is "desirable and necessary" because they "help Americans maintain a balanced and healthful diet" and "assist Americans in following

[1] Federal Register vol. 72(245):72739.

the Surgeon General's guidelines."[2] According to FDA, a "health claim" has two essential components: (1) a substance (whether a food, food component, or dietary ingredient) and (2) a disease or health-related condition.[3]

FDA notes that any research used to substantiate a health claim should focus on (1) the substance being evaluated, in this case soy protein alone, and (2) the most appropriate endpoint or endpoint surrogate to measure a disease or health-related condition, in this case, reduction in CHD or a decrease in total and LDL cholesterol levels. FDA also notes that the scientific standard for authorization of a health claim is less stringent than the requirements for approval of a new drug.[4] Research that examines the effects of other soy substances, such as isoflavones, should not be used to substantiate or to disprove a soy protein coronary heart disease health claim and should be eliminated from scientific review. Total and LDL cholesterol concentration and blood pressure are all recognized surrogate endpoints for cardiovascular disease by the National Institutes of Health and FDA's Center for Drug Evaluation and Research.[5] Thus, FDA does not need to consider the effect of soy on triglyceride levels and other endpoints as significant to a health claim for soy and CHD risk. SANA agrees with FDA that a re-evaluation of the soy protein CHD health claim should focus exclusively on soy protein's impact on total and LDL cholesterol levels. Other soy constituents and additional CHD endpoints are not valid for re-evaluating the soy protein coronary heart disease health claim.

FDA states that "health claims involve reducing the risk of a disease in people who do not have the disease that is the subject of the claim."[6] This role of FDA's health claims coincides with the National Cholesterol Education Programs' goal to reduce the percentage of Americans with high blood cholesterol levels through public education.[7] From a public health perspective, health claims educate Americans about potential ways to improve their health and prevent disease. SANA recommends that FDA continue to consider the overall public health effects of the soy protein coronary heart disease health claim. As FDA noted in the Final Rule, "the modest lowering of total and LDL-cholesterol levels generally observed in these studies can effect a significant reduction in CHD risk."[8]

SANA understands that this re-evaluation of health claims is historic for FDA. Before FDA embarks on the re-evaluation of the four identified health claims, the Agency might first finalize the July 2007 Draft Guidance for Industry, Evidence-Based Review System for the Scientific Evaluation of Health Claims and the December 22, 1999, Draft Guidance for Industry, Significant Scientific Agreement in the Review of

[2] U.S. House of Representatives, Committee on Energy and Commerce, *Nutrition Labeling and Education Act of 1990 Report*. June 13, 1990, Report 101-538, pages 9-10.
[3] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Claims for Conventional Foods and Dietary Supplements,* accessed at: http://www.cfsan.fda.gov/~dms/hclaims.html on January 11, 2008.
[4] U.S. Food and Drug Administration, Department of Health and Human Services, Food Labeling: Health Claims; Soy Protein and Coronary Heart Disease, Final Rule, Federal Register, vol 64(206):57720.
[5] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims*,December 22, 1999, accessed at: http://www.cfsan.fda.gov/~dms/hclmgui5.html on January 21, 2008.
[6] Ibid.
[7] National Institutes of Health, National Heart, Lung and Blood Institute, *National Cholesterol Education Program: PROGRAM DESCRIPTION*, accessed at: http://www.nhlbi.nih.gov/about/ncep/ncep_pd.htm on January 21, 2008.
[8] Federal Register vol. 64(206):57709.

Health Claims for Conventional Foods and Dietary Supplements. There were comment periods for each document, but FDA has not yet issued the final guidance documents that reflect the public comments. FDA has also indicated that it will reexamine its system for ranking the strength of the scientific evidence for a health claim based on consumer studies it conducts.

FDA has a number of decisions to make in the process of establishing the criteria that would guide the re-evaluation process. If the re-evaluation process for the four identified health claims begins before Guidance for Industry is finalized, SANA encourages FDA to be transparent in what data are reviewed and the weight given to each research study. Likewise, it will be important for the Agency to define clearly what is and what is not meant by significant scientific agreement regarding the relationship between a substance and a disease or health related condition.

Consumers Perceptions

In addition to the inherent benefit of soy protein on the reduction of cholesterol and CHD, an additional substance/disease relationship exists when soy protein substitutes for other protein sources higher in saturated fat and cholesterol. The goal of a health claim is to provide the public with relevant health knowledge that can assist them in choosing a healthier diet that lowers their risk of disease.

Since FDA approved the soy protein coronary heart disease health claim nine years ago, the association between soy protein and heart health has resonated with consumers. According to the United Soybean Board's *2007 Consumer Attitudes about Nutrition: Insights into Nutrition, Health & Soyfoods* on an unaided basis, 16 percent of general consumers recognize soyfoods and beverages for their heart health function and 11 percent recognize them for their cholesterol lowering properties.[9] Consumer awareness of the health benefits of soyfoods has translated into a 127% increase in sales from $1,747 million in 1998, the year prior to the issuance of the Health Claim, to $3,972 million in 2006[10], the last year for which we have market data.

Over the past twenty years, American consumers have received significant information about the role of diet and their risk of CHD from Dietary Guidance as well as health claims. Overall, a healthy diet that is low in saturated fat and cholesterol and higher in soy protein, soluble fiber, and plant sterols and stanols has helped to lower blood cholesterol and the risk of coronary heart disease. Since 1999, deaths from Heart Disease continued the decline;[11] and mean serum total cholesterol levels of U.S. adults aged 20 years and older declined from 204 mg/dL in 1999–2000 to 199 mg/dL in 2005–2006. Specifically, among men aged 40–59 years, mean serum total cholesterol declined from 214 mg/dL in 1999–2000 to 205 mg/dL in 2005–2006, a difference of 9 mg/dL. Over the same period of time, mean serum total cholesterol levels declined from 206 mg/dL to 189

[9] United Soybean Board, *Consumer Attitudes about Nutrition: Insights into Nutrition, Health & Soyfoods*, accessed at: http://www.soyconnection.com/health_nutrition/pdf/ConsumerAttitudes2007.pdf on January 16, 2008.
[10] Data Provided by Soyatech and SPINS Inc.
[11] Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2006.* Figure 27, Data from the National Vital Statistics System.

mg/dL for men aged 60 years and older, a difference of 17 mg/dL, and from 224 mg/dL to 209 mg/dL for women aged 60 years and older, a difference of 15 mg/dL. FDA's impact on transforming the American diet through the use of health claims and other dietary guidance is obvious.

FDA Review of Evidence for the 1999 Health Claim on Soy and CHD

In the original review of scientific research for the 1999 soy protein coronary heart disease health claim, FDA examined 27 studies that met the criteria: 1) reliability and accuracy of the methods used in nutrient (soy protein) intake analysis; 2) estimation of intake of saturated fat and cholesterol; 3) including available information on the soy protein test products and control foods; 4) measurement of study endpoints (i.e., blood lipid levels); and 5) general study design characteristics including randomization of subjects, appropriateness of controls, selection criteria of subjects, attrition rate, presence of recall bias, recognition and control of confounding factors (i.e. weight loss), appropriateness of statistical tests and comparisons, and statistical power of the studies.

Fourteen of the studies included subjects that were representative of the general US population and avoided design problems. Of these fourteen studies, baseline cholesterols were below 300 mg/dl and two had baseline cholesterols below 150 mg/dl. For most of these studies, LDL cholesterols were reduced from 1 to 11 percent. The four studies reporting no significant change in LDL cholesterol levels had very low initial baseline cholesterol, a very high attrition rate (32 percent), a very low cholesterol and saturated fat baseline diet, or a typical western baseline diet. Three additional studies were examined but the subjects were either obese or strict vegetarians. Two of these studies showed no significant change. FDA reviewed ten other studies that had been conducted using subjects with Type II or Familial Hypercholesterolemia with baseline cholesterol levels above 300 mg/dl. All but one of these studies found significant (10-30%) reductions of LDL cholesterol levels for subjects following restricted saturated fat and cholesterol diets. The one exception studied children with extremely high baseline cholesterol levels. Clearly, those studies that included hypercholesterolemic subjects should be expected to see a greater change in total and LDL cholesterol levels than in studies that include subjects with normal or moderately elevated cholesterol levels. The type of baseline diet the subjects consumed in studies appeared to effect blood cholesterol endpoints. FDA concluded that the effectiveness of soy was strong when it was added to a low saturated fat, low cholesterol diet.

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 coronary heart disease 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 cholesterol at varying degrees, the consistent association between soy protein and a reduction in total and LDL cholesterol warrants the continuation of the soy protein coronary heart disease 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."[12] In the final rule, FDA noted some of the reasons why not all of the studies showed significant reductions of total and LDL cholesterol levels: 1) large range of individual responses, such as was found in the effectiveness of Step I and Step II NCEP diets in free-living subjects[13], 2) different forms and amounts of soy protein tested, 3) different experimental designs and diets studied, and 4) the variability in initial 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.

Several groups have compiled evidence-based reviews of the role of soy in coronary heart disease using various soy substances and CHD endpoints and have documented various ranges of responses.

The Agency for Healthcare Research and Quality (AHRQ) report evaluated only randomized trials with at least 10 subjects who consumed a soy product that included isoflavone supplements alone, soy protein, soymilk and other soyfoods.[14] AHRQ considered as markers of cardiac function (e.g. triglycerides, endothelial function, oxidized LDL) that are not recognized by the FDA for heart disease risk as validated surrogate endpoints.[15] Studies of low-calorie diets designed to promote weight loss were excluded from the AHRQ review and none of the remaining studies reported substantial weight loss by study subjects. It is not clear what type of diet subjects in these studies followed during the soy intervention, a factor that may affect the degree of reduction. As mentioned previously, FDA noted that the effectiveness of soy protein was strong when added to a low saturated fat, low cholesterol diet.

There were 55 studies, dating from 1982 to 2004, that analyzed LDL cholesterol as an outcome. Only three of these studies found no effect. Section 3.2.3 of this AHRQ report describes the following results for low density lipoprotein from the 52 studies that showed an effect, 4 were rated good quality (A), 28 were rated fair quality (B), and 20 were rated poor quality (C). In this evidence-based review, supplements referred to soymilk, isolated soy protein, as well as the isoflavone supplement alone. Because soy isoflavones have not been found to reduce LDL cholesterol, combining studies of isoflavone supplements along with soy protein and soymilk studies when analyzing the LDL impact distorts the results and minimizes the true cholesterol reduction of soy protein studies alone. In a separate analysis, AHRQ combined studies using textured soy protein, tofu, soybeans, soy flour, or other soyfoods. The report notes that the meta-analysis conducted by AHRQ showed dietary soy products alone yielded a summary net

[12] Federal Register vol.64(206):57709.
[13] Yu-Poth S, G Zhao, T Etherton, et al. Effects of the National Cholesterol Education Program's Step I and Step II Dietary Intervention Programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr.* 1999 Jun;69:632-646.
[14] U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality (AHRQ), *Effects of Soy on Health Outcome*. Evidence Report/ Technology Assessment Number 126, August 2005, pages 42-55.
[15] Federal Register vol. 64(206):72739.

change in LDL of -7 (95%CI-9,-4) mg/dL, which is somewhat greater than the net change among the soy supplements studies, -4 (95% CI-7,-1) mg/dl[16]. Regardless of how the interventions were categorized, the analysis shows that soy protein reduces LDL cholesterol.

As the substance of the health claim relates only to soy protein, research that studies soy isoflavones alone or any other soy constituent should not be considered among the body of research to support the health claim. Therefore, the findings of the AHRQ study should be considered cautiously, and the studies with isoflavones alone should be excluded from the FDA's re-evaluation of the soy protein coronary heart disease health claim.

The Nutrition Committee for the American Heart Association (AHA) published a science advisory on soy protein, isoflavones, and cardiovascular health.[17] Only one of the cited studies used subjects with baseline total cholesterol levels over 300 mg/dL. It is not clear what type of diet the subjects in these studies followed during the soy intervention, a factor that may affect the degree of reduction. AHA reviewed 22 randomized human research trials and found in the majority of the studies isolated soy protein with isoflavones as compared with milk or other proteins, decreased LDL cholesterol concentrations; the average effect was about 3%. Furthermore, this paper concludes that of the 19 studies of soy isoflavones alone, the average effect on LDL cholesterol was nil. When AHA looked at studies on soy protein with isoflavones, they found between a 1 - 8% decrease in total cholesterol and a 1 – 10% reduction in LDL cholesterol levels. Overall, the range of total and LDL cholesterol reduction observed by AHA supports the FDA's original findings.

Cesare Sitori from Italy

A review[18] by well-known cardiologist Cesare Sirtori, M.D., Ph.D., University of Milano, Italy, published in the May issue of *British Journal of Nutrition,* examined 33 studies from 25 manuscripts published since publication of Dr. James Anderson's 1995 meta-analysis[19] that found a 9.3% drop in total cholesterol and a 12.3% drop in LDL cholesterol when soy was substituted for animal protein. Sirtori and his colleagues provided quartile data from the original meta-analysis, as well as, the 33 studies conducted after 1995, according to baseline levels of cholesterol. The authors separately calculated the cholesterol-lowering effect of soy protein consumption for each of the 4 groups. Sirtori et al. found that the cholesterol lowering impacts of soy protein in recent studies were accurately predicted by a nomogram developed from Anderson's original results and based on baseline cholesterol level.

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[16] U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality (AHRQ), *Effects of Soy on Health Outcome*. Evidence Report/ Technology Assessment Number 126, August 2005, page 45.

[17] Sacks et al. Soy Protein, Isoflavones, and Cardiovascular Health: An American Heart Association Science Advisory for Professionals from the Nutrition Committee. *Circulation.* 2006 Feb;113:1034-1044. Page 5, Table 2.

[18] Sirtori CR, Eberini I and Arnoldi A, Hypocholesterolaemic effects of soya proteins: results of recent studies are predictable from the Anderson meta-analysis data. *Br J Nutr.* 2007 May;97(5):00, 1–8.

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

Sirtori and his colleagues consider the impact of soy protein on cholesterol levels to be one of an intrinsic nature rather than a substitution effect. In the recent studies that they examined, soy was only partially substituted for animal protein or added to a regular diet. This demonstrates that soy protein's cholesterol-lowering effect is not merely observed when it replaces foods high in cholesterol and saturated fat.

Harland and Haffner from UK

Harland and Haffner[20] recently conducted a meta-analysis and presented results at the HEART UK 21st Annual Medical and Scientific Meeting in June 2007. Their analysis found when soya[21] protein was included in the diet of adults, statistically significant reductions in total and LDL cholesterol occurred. Average intake of soya protein of 24.3g/day led to reductions in LDL, total cholesterol and blood triglycerides of 9.7 mg/dL; $P<0.0001$, 9.7 mg/dL; $P<0.0001$ and 11.5 mg/dL; $P=0.003$, respectively. Total HDL ratio was significantly lower and HDL cholesterol was marginally increased. All data was tested for heterogeneity and none was identified. 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.

No Evidence of Adverse Effects of Soy Protein Consumption

In making the conclusion that soy protein is "safe and lawful" at the levels suggested by the health claim, the Agency noted it "did not find documented evidence of adverse effects in humans and did not receive information about actual levels of potentially harmful components or about threshold levels for adverse effects in humans."[22] FDA reviewed information submitted about potential risks of consuming soy products, related to allergenicity, exposure to trypsin inhibitors, reduced bioavailability of minerals such as zinc, and potential hormonal disturbances due to soy isoflavones.

In *Guidance for Industry on Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements,* FDA indicates that the primary type of research considered in the review of health claims is human randomized controlled clinical trials.[23] SANA suggests that FDA continue to place emphasis on human randomized controlled clinical trials, as with health claim evidence review, when assessing any potential adverse effects on human health.

In brief, FDA concluded the following about potential adverse effects and additional research supports the initial conclusions for authorizing the 1999 health claim.

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[20] Harland JI and Haffner TA. Does 25g soya protein reduce blood cholesterol: a systematic review and meta analysis H·E·A·R·T UK 21st Annual Medical & Scientific Meeting 2007, 2007 June:27-29. Heriot-Watt University, Edinburgh, UK.
[21] "Soya" used in English British lexicon that is equivalent to the US term "soy."
[22] Federal Register vol. 64(206):57703.
[23] U.S. Food and Druge Administration, Center for Food Safety and Applied Nutrtion, Office of Special Nutritionals, *Guidance for Industry on Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*, accessed at: http://www.cfsan.fda.gov/~dms/ssaguide.html on January 11, 2008.

Goitrogenic Effects - For research on the potential effect of soy isoflavones on the thyroid, SANA points to a recent review[24] of 14 human trials (thyroid function was not the primary health outcome in every trial) in which the effects of soy foods or isoflavones on at least one measure of thyroid function was assessed in presumably healthy subjects. Collectively the findings provide little evidence that in euthyroid, iodine-replete individuals, soyfoods or isoflavones adversely affect thyroid function. In the US, where iodized salt provides much of the iodine consumed symptoms of iodine deficiency are rare.[25]

Allergenicity – Of the approximately 5 million children with food allergies, less than 1 percent has allergic reactions to soy, and these adverse reactions are generally a transient allergy of infancy and childhood. Allergic reactions to ingested soyfoods are infrequent and rarely severe and life threatening.[26] The ingredient list on the package must now list and identify by the common name any of the eight major allergens the food contains.[27]

Trypsin inhibitors – SANA supports the FDA 1999 finding[28] that there is no evidence of a deleterious effect of dietary intakes of trypsin inhibitors from soy in humans. More importantly, scientists know that most of soy's trypsin inhibitory activity is removed by cooking and other heat processes to which all soyfoods are subjected.[29] Interestingly, scientists have begun to study possible anti-cancer actions of these trypsin inhibitors in preliminary research.[30]

Reduced bioavailability of minerals such as zinc - SANA has not found evidence that soyfoods that contain phytic acid significantly compromise iron and zinc status. Phytic acid, a component of all plants, may affect mineral bioavailability, but the absorption of these minerals can be affected by the nutritional status of the individual, the adequacy of zinc, iron, and calcium content in the daily diet, the amount consumed in a meal and the presence of other components in the meal that can enhance or inhibit absorption.

Hormonal disturbances due to soy isoflavones – SANA supports the FDA 1999 conclusion that there is insufficient data to document any deleterious effects of dietary intake of soy isoflavones in humans, and submits additional research that affirms the initial conclusion.

a. Proliferation of breast cells - Women who eat more soyfoods have a lower risk of developing breast cancer, compared to those who eat less soyfoods. Eating soyfoods at

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[24] Messina M and Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. *THYROID*. 2006 Nov;16(3): 249-258.

[25] Panel of Micronutrients, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academy Press. 2001, pg 284.

[26] Sicherer SH, Sampson HA. Peanut and soy allergy: a clinical and therapeutic dilemma. *Allergy*. 2000 Jun;55:515-521.

[27] As required by the Food Allergen Labeling and Consumer Protection Act of 2004 (P.L. 108-282).

[28] Federal Register vol. 64(206):57704.

[29] *J Nutr Sci Vitaminol (Tokyo)* 1997;43:575–80.

30 Huang MT, Jian-Guo Xie JG, Lin CB. Inhibitory effect of topical applications of nondenatured soymilk on the formation and growth of UVB-induced skin tumors. *Oncol Res*. 2004;14:387–97.

any age as part of a healthy diet appears to protect against developing breast cancer,[31,32] especially when soy is consumed during childhood and adolescence.[33,34,35,36,37]

In a recent comparable human study, in which breast cancer survivors received 100 mg daily of isoflavones, which is higher than what is consumed even in a traditional Asian diet, there were no differences in breast tissue after one year compared to those who received a placebo.[38] Several other studies on soy's bioactive compounds using healthy women have found no changes associated with breast cancer such as thickening breast tissue,[39,40,41] increased breast density appearing in mammograms,[42] or increased estrogen circulating in the blood.[43,44]

b. Fertility and Hormone Levels - A review of seven intervention studies on the hormonal effects of soyfoods containing isoflavones in premenopausal women concluded that "soy and isoflavone consumption does not seem to affect the endometrium in premenopausal women."[45] Since this review was published, several additional studies have examined the possible hormonal effects of soy protein and isoflavones (70 to 120 mg per day) and have shown no adverse effects on uterine lining thickness.[46,47,48]

c. Developmental Effects

A review of the hormonal effects of soy isoflavones do not support concerns about effects of soy on reproductive hormones and semen quality of men. Three intervention studies

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[31] Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Nat Cancer Inst.* 2006;98:459 – 71.
[32] Yan L, Spitznagel E. A meta-analysis of soy foods and risk of breast cancer in women. *Int J Cancer Prevention* 2005;1:281-293.
[33] Korde L FT, Wu A, et al. Adolescent and childhood soy intake and breast cancer risk in Asian-American women. *Breast Cancer Res Treat* 2005;88:S149.
[34] Wu AH, Wan P, Hankin J, Tseng CC, Yu MC, Pike MC. Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis.* 2002;23:1491-1496.
[35] Shu XO, Jin F, Dai Q, Wen W, Potter JD, Kushi LH, Ruan , Gao YT, Zheng W. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiol Biomarkers Prev.* 2001 May;10(5):483-488.
[36] Op cit. Korde 2005.
[37] American Cancer Society. Soy and breast cancer, effects of soy and cancer still unkown, accessed at http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Soy_and_Breast_Cancer.asp on January 3, 2008.
[38] Palomares MR, Hopper L, Goldstein L, Lehman CD, Lampe JW, Storer BE and Gralow JR. Effect of soy isoflavones on breast proliferation in postmenopausal breast cancer survivors. *Breast Cancer Research and Treatment* 2004;88:S149.
[39] Maskarinec G, Takata Y, Franke AA, Williams AE, Murphy SP. A. 2-year soy intervention in premenopausal women does not change mammograhpic densities. *J Nutr* 2004;134:3089-94.
[40] Maskarinec G, Williams AE, Inouye JS, Stanczyk FZ, Frankie AA. A randomized isoflavone intervention among premenopausal women. *Cancer Epidemiol Biomarkers Prev* 2002;11:195-201.
[41] Maskarinec G, Williams AE, Carlin L. Mammorgraphic densities in a one-year isoflavone intervention. *Eur J Cancer Prev* 2003;12:165-9.
[42] Nagata C, et al. Associations of mammographic density with dietary factors in Japanese women.*Cancer Epidemiol Biomarkers Prev* 2005;14:2877–80.
[43] Kurzer MS. Hormonal effects of soy in premenopausal women and men. *J Nutr* 2002;132:570S-573S.
[44] Cheng G, Wilczek B, Warner M; Gustafsson J, Landgren, B. Isoflavone treatment for acute menopausal symptoms. *Menopause*. 2007;14(3):468-473.
[45] Kurzner MS. Hormonal effects of soy in premenopausal women and men. *J Nutr.* 2002; 132(3)570S-573S.
[46] Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P. Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril*. 2003 May;79(5):1112-7.
[47] Murray MJ, Meyer WR, Lessey BA, Oi RH, DeWire RE, Fritz MA. Soy protein isolate with isoflavones does not prevent estradiol-induced endometrial hyperplasia in postmenopausal women: a pilot trial. *Menopause.* 2003 Sep-Oct;10(5):456-64.
[48] Nikander et al, Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women. *Fertil Steril.* 2005 Jan;83(1):137-42.

found that men consuming 40-70mg/day of soy isoflavones from soyfoods or soy supplements showed few effects on plasma hormones or semen quality or motility.[49]

Conclusion

After review of the initial purpose of health claims, FDA's analysis of research findings on soy and CHD reduction, and numerous analyses of research conducted since 1999, it appears that the totality of the evidence from the 1980's to the present supports a total and LDL cholesterol lowering effect of soy protein intake. This effect benefits the heart health of all Americans both from an individual and a public health perspective. The totality of the evidence is sufficient for FDA to conclude that no regulatory action is needed regarding the current health claim for soy protein and coronary heart disease. The Soyfoods Association of North America (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, R.D., M.P.H.
Executive Director

[49] Kurzner MS. Hormonal effects of soy in premenopausal women and men. *J Nutr*. 2002;132(3):570S-573S.