October 29, 1998

Name of petitioner:
American Soybean Association
12125 Woodcrest Executive Drive
St. Louis, MO 63141-5009
[1-314-576-1770]

HEALTH CLAIM PETITION FOR SOY PROTEIN

Elizabeth Campbell
Director, Office of Food Labeling
Center for Food and Drug Administration
U.S. Food and Drug Administration
200 C Street, SW
Washington, DC 20204

Dear Ms. Campbell:

Please find enclosed a document which comprehensively reviews the available scientific data underlying the healthful relationship between the consumption of soy protein and the reduction in risk of heart disease through the reduction in serum cholesterol. This document supports a "cardioprotective" health claim applicable to food items that contain at least 6.25 gm of soy protein (RACC) from any commercially-available source.

The American Soybean Association represents principally soybean farmers but the effort underlying this submission has been a multiyear collaborative project involving the efforts and contributions of soybean farmers and their representatives, soybean processors and their representatives, producers of consumer products that contain soy protein as well as nutritionists, physicians and other health scientists from a broad array of academic and other institutions. During the preparation and internal review of this submission, in May 1998, one soybean processor and a participant in the drafting, Protein Technologies International ("PTI"), Inc., submitted an earlier but incompletely edited version as their own health claim petition. That petition also contained some minor supplemental modifications, specific to the proprietary interests of PTI, which have not been generally supported by the other members of this collaborative effort. More specifically, the PTI petition is alone in proposing an "active ingredient" of qualifying level role for undisturbed isoflavones. In the more important particulars, however, ASA supports the PTI petition's request for a health claim that specifies the effect of soy protein on cardiovascular disease.

In short, this final consensus submission represents a thorough, complete and carefully reviewed summary of the science underlying a soy protein health claim. This submission is supported by a wide array of parties interested in the healthful effects of soybeans. We have also provided a balanced discussion of the known effects of soy isoflavones. Please note as well that the earlier draft submitted by PTI contains a number of small errors that were identified in the review process for the enclosed final submission. For instance, the table entries for content of soy protein in test diets and net effect of soy protein on reduction of cholesterol levels have been corrected.

The first 55 pages of this petition represent a summary of the scientific studies which provide assurance that there is significant scientific agreement, as shown by the consistency, direction, and significance of the effect of a soy protein diet, that soy protein reduces harmful cholesterol levels generally found in the average American consumer. The following section, pages 55 through 72, address the issue of the role of isoflavones and other constituents. The next section, pages 72 through 83, address regulatory issues. The final section, pages 83 through 97, address concerns of the collaborative group with regard to fashioning model health claims that are accurate and truthful representation of the science, but also meet the equally important statutory mandate that "the public…comprehend the information provided in the claim."

This final section reviews concerns set forth by the agency in proposed rule-making on health claims that were a result of the Keystone Dialogue on Health Claims and a letter form the National Food Processors Association. 60 FR 66206 (Dec. 21, 1995). This proposed rule has not yet been made final. ASA proposes a policy on these issues that is both scientifically sound and meets the need of consumers to understand the claims. This policy would also facilitate the fundamental purpose of the NLEA – to use the label on food products healthful dietary recommendations.

We would appreciate your careful consideration of this submission in the development of a proposed regulation governing health claims for soy protein or for whatever other purpose that the agency may deem appropriate.

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[1] To that end, PTI's Table 4 corresponds to this submission's Table 7. This table reviews data on normal, healthy (not hypercholesterolemic) adults with cholesterol levels between 300 and 200 mg/dL. There are two Mercer studies within the same publication: one with 33 patients and another with a subset of 5 patients (not one with 5 patients). The amount of soy protein consumed in the van Raaij studies was 42 and 31 g, respectively, not 55 g as provided in the PTI petition. These small errors are largely inconsequential

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American Soybean Association

To the best of my knowledge, petition is a representative and balanced submission that includes unfavourable information as well as favourable information known to me to be pertinent to the evaluation of the proposed health claim.

Sincerely,

Mike Yost
President
American Soybean Association

cc. Beth Yetley
Director, Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
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Enclosures: Final Soy Protein Health Claim Petition
Appendices
Citations/References in Two Volume

Soy protein ingestion was associated with a reduction of risk of prostate cancer in a study of 7,999 men in Hawaii. Age-adjusted relative risk was reduced by 22% in men in the second tertile of tofu consumption and 65% in the third tertile with 18-21 years of follow-up.[154]

2. Potential Risks

None of the various effects associated with ingestion of large amounts of soy protein, which may include allergenicity, exposure to isoflavones, historic allegations of decreased protein quality, mineral bioavailability, and exposure to trypsin inhibitors, represent a realistic public health concern on careful review.

(a) Allergenicity

Any food protein can stimulate a food allergy. Food allergies are commonly found due to milk, egg, and nut proteins. Soy-milk substitutes are frequently prescribed for highly allergenic children who have developed cow's milk allergies or food intolerance. In this group of high-risk infants, soy protein allergy may also develop but only in a small subset. These infants are not the target of a health claim applicable to general food commodities. Finally, the presence of a labeled health claim for soy protein would likely increase the chance that such patients can identify soy-protein based products and avoid consumption.

(b) Isoflavone Exposure

Concern that exposure to soy isoflavones may affect human fertility was initially raised in the 1940s following reports of infertility among sheep grazing on subterranean clover in western Australia. [155] Clover (*Trifolium subterranean L.*) was identified as a source of various phytoestrogenic compounds. Subsequent studies in primates which assessed reproductive hormone concentrations and organ weights at necropsy did not demonstrate any adverse effects of soy phytoestrogens on reproductive systems in either males or females.[116] Primate studies have also suggested that the estrogenic effects of soy phytoestrogens are selective, affecting breast tissue, but not reproductive tissue, in surgically postmenopausal macaques.[156]

(c) Protein Quality

Since 1993, the protein digestibility-corrected amino acid score (PDCAAS) has been adopted by the FDA to replace the Protein Efficiency Ratio (PER) in evaluating protein quality for food labeling purposes. The Food and Agriculture Organization and the World Health Organization recognize the PDCAAS as a more accurate standard for this purpose than the PER. The PDCAAS takes into account protein digestibility, amino acid profile and, the ability of the amino acid profile to meet the needs of 2-5 year old children, the population group with the highest protein needs. Using the PDCAAS, the protein quality of soy flour, SPC, or ISP is found to be identical to that of casein and egg white, and higher than those of protein found in beef, kidney beans, pinto beans, lentils, peanuts, and wheat.[123]

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[154] Sverson RK, Nomura AM, Grove JS, Stemmermann GN. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res.* 49:1857-1860, 1989.
[155] Moule GR. Clinical aspects of nutritional infertility in ewes. *Australian Veterinary J.* 46(9):428-435, 1970.
[156] Cline JM, Pashold JC, Anthony MS, Obasanjo IQ, Adams MR. Effects of hormonal therapies and dietary soy phytoestrogens on vaginal cytology in surgically postmenopausal macaques. *Fertil. Steril.* 65:1031-1035, 1996.

(d) Decreased Mineral Bioavailability

Phytic acid and, to a lesser extent, dietary plant fiber, may reduce absorption. Absorption of divalent minerals (calcium, magnesium, zinc, copper, iron) is reported to be less efficient in the presence of leguminous plant intake, although this effect was not reported with concurrent Consumption of soy protein.[157] Data on the effects of soy protein on mineral balance have used animal models. Results in human studies suggest that the effects of soy ingestion on mineral balance in humans cannot be predicted from animal studies.[158] Zinc and iron ingestion may be compromised by soy products due to phytic acid content. 94 Although mineral absorption may be less efficient from soy protein sources compared with animal protein sources, overall mineral balance is not significantly affected.

(e) Pancreatic Hyperplasia

Trypsin inhibitors may stimulate pancreatic hyperplasia in many animal species. [159] The concern that pancreatic hyperplasia may lead t carcinogenesis does not appear to be borne out, however, by epdiemiological or experimental data. To that end, human pancreatic cancer is generally ductal in nature and related to alcohol and cigarette consumption, whereas animal models treated with trypsin inhibitors develop acinar cellular proliferation.[153]

F. ANALTICAL DATA

Soy-based food products eligible to bear the soy protein health claim may be classified into two general categories for analytical purposes. The first category consists of products manufactured from whole soybeans such as tofu, soynuts, soy milk, soy cheese, and soy yohurt and products whose protein compositions solely from soy protein products such soy flour, ST flour, ISP, and SPC. The amount of soy protein present in these products is represented by the total protein content. Consequently, the standard protein assay method approved by the Association of Official Analytical Chemists (AOAC) may be applied for evaluating the amount of soy protein in the RACC for these foods.

The second category of soy-based foods eligible for the claim consists of products manufactured only in part using soybean-derived protein ingredients such as soy flour, ST flour, ISP, and SPC. In these products, soy protein would represent a calculable fraction of the total protein content. The clinical evidence reviewed for this petition indicates that the cholesterol-lowering effect observed when the minimum effective daily intake of soy protein is consumed is not impaired by concurrent ingestion of other protein sources (**Holmes I & II; Carrol I & II**). ASA recommends the adoption of one or both of the following methods to assess soy protein content in mixed foods:

1. Calculated Values

Based on the known amount of protein per gram of soy derivative product (soy flour, SPC,ISP), the quantity of soy protein in a final food product can be calculated based on known ratio of added products multiplied by the measured protein content using a standard analytical assay.

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[157] Leiner IE. Factors affecting the nutritional quality of soya products. *J. Amer. Oil Chem. Soc.* 58:406-415, 1981.
[158] Erdman JW Jr, Forbes RM. Effects of soya protein on mineral availability. *J. Amer. Oil Chem. Soc.* 58:489-493, 1981.
[159] Roebuck BD. Trypsin inhibitors: Potential concern for humans? *J. Nutr.* 117:398-400, 1987.