

Table 16. Summary of epidemiological studies on soy intake and colorectal cancer in humans.

Reference	Soy Products Processed	OR/RR (95% CI) <sup>1</sup> (highest vs. lowest intake)	P trend
<b>Short-Term Intervention Study</b>			
Bennink (2001)	Isolated soy protein vs. casein	Significant reduction in colon mucosa cell proliferation (proliferation zone and labeling index)( $P < 0.05$ ) in soy intervention group than in casein group.	
<b>Case-Control Studies</b>			
Seow (2002)	Soy and legumes	1.3 (0.7 – 2.4)	
Le Marchand (1997)	Legumes & soy products	0.5 (0.3 – 0.9) (women) 0.8 (0.5 – 1.2) (men)	0.05 0.31
Nishi (1997)	Tofu	0.79 (0.55 – 1.13) (colon) 1.02 (0.67 – 1.53) (rectum)	
Witte (1996)	Tofu or soybeans	0.48 (0.24 – 0.95)(adenomatous polyps)	0.04
Inoue (1995)	Bean curd	Women 1.3 (0.7 – 2.4) (proximal) 0.6 (0.4 – 1.0) (distal) 0.9 (0.6 – 1.5) (rectal)  Men 0.9 (0.5 – 1.6) (proximal) 1.7 (1.0 – 7.6) (distal) 1.2 (0.8 – 1.7) (rectal)	
Hoshiyama (1993)	Soybean products	0.4 (0.2 – 0.9) (rectum) 0.6 (0.3 – 1.3) (colon)	0.03 0.08
Hu (1991)	Bean products	Rectum: 0.33 (0.17 – 0.65)(men, 1985 data) 0.27 (0.10 – 0.74)(men, 1966 data)  Not related to rectal cancer in women nor colon cancer in either sex.	$P = 0.001$ $P = 0.007$
Tajima (1985)	Bean curd	1.08 (colon) 1.63 (rectum)	
<b>Cross-National Analysis</b>			
McKeown-Eyssen (1984)	Soybeans	$r^2 = -0.08$ (not correlated)	
<b>Ecological Study</b>			
Nagata (2000)	Soy products	$r^2 = 0.36$ (men) $r^2 = 0.51$ (women)	0.05 0.01

<sup>1</sup>OR/RR (95% CI) = odds ratio/relative risk (95% confidence interval). <sup>2</sup>Correlation coefficient.

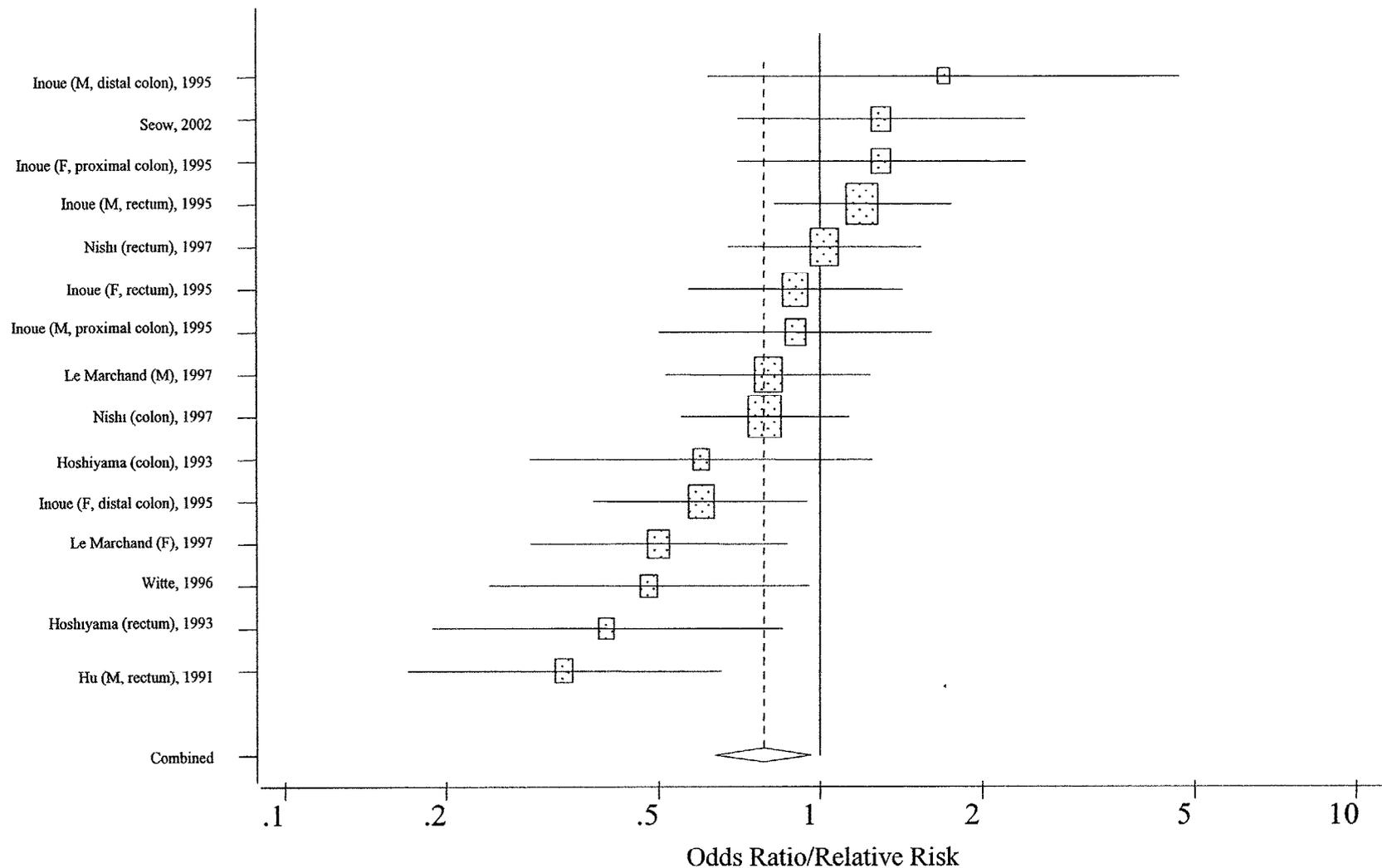


Figure 8. Meta-analysis of studies on consumption of soy protein-containing foods and colorectal cancer in humans. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio/relative risk, and left and right vertices of the diamond represent its 95% CI. The pooled estimate of odds ratio/relative risk is 0.78 (95% CI = 0.64 – 0.96;  $P = 0.02$ ), and no publication bias was detected. M = male and F = female. Results of this analysis show that consumption of soy protein-containing foods is associated with a lower risk of colorectal cancer in humans.

### Short-Term Intervention Study

Bennink (2001) investigated the effect of soy consumption on colon cancer risk in an “at risk” population in a short-term double-blind intervention study. Forty-two subjects with a history of colon polyps or colon cancer were randomly assigned to two groups. One group (n = 29) had a daily intake of 39 g soy protein isolate, and the other (n = 13) had an equal amount of casein for one year. Colon mucosa biopsies collected before and after the intervention were compared on crypt cell proliferation patterns using immunohistochemical detection of proliferative cell nuclear antigen (PCNA). There is a significant reduction in labeling index ( $P \leq 0.05$ ) and proliferation zone ( $P \leq 0.05$ ) in subjects consumed soy protein, whereas these measurements remain unchanged in those consumed casein. The presence of nuclear PCNA indicates that a cell is capable of division, and the lack of it implies that the cell has terminally differentiated. Bennink (2001) interpreted the downward shift in proliferation zone and the decrease in labeling index as a meaningful decrease in colon cancer risk, and concluded, “Overall, our results strongly suggest that eating soy flour or isolated soy protein will reduce colon cancer risk.”

### Case-Control Studies

Seow et al (2002) assessed food intake in relation to colorectal cancer in a Chinese population in Singapore (121 cases, 222 controls). The diet questionnaire included nine groups of food, and soy and legumes were categorized as one food group. Consumption of soy and legumes is not related to colorectal cancer in this study population (adjusted OR = 1.3, 95% CI = 0.74-2.4) when the highest intake ( $\geq 234$  portions/y) is compared with the lowest ( $< 78$  portions/y).

Le Marchand et al (1997) investigated the relationship between diet and colorectal cancer in a population-based case-control study in the United States (1,192 cases, 1,192 controls). Soy products and legumes were analyzed as one group of food, and tofu was further separately analyzed. Intake of soy products and legumes is related to a 50% reduction in colorectal cancer risk in women (adjusted OR = 0.5, 95% CI = 0.3-0.9) and a 20% reduction in men (adjusted OR = 0.8, 95% CI = 0.5-1.2) when the highest quartile of

intake is compared with the lowest. The test for trend is  $P = 0.05$  for women and  $P = 0.31$  for men. The trend persists in both sexes after further adjustment for non-starch polysaccharides from vegetables, but the strength of the association is attenuated somewhat. The highest and the lowest quartiles of soy and legume intake are  $>44$  g/d and  $<9$  g/d for women, and  $>46$  g/d and  $<11$  g/d for men, respectively. Intake of tofu is not related to colorectal cancer in either sex in this study population.

Nishi et al (1997) examined the relationship between eating habits and colorectal cancer risk in a community-based case-control study in Japan (330 cases, 660 controls). Tofu and deep-fried tofu were assessed in this study. Intake of tofu and deep-fried tofu is associated with a lower risk of colon cancer when the frequent users ( $\geq 3$  times/wk) are compared with the non-users. The RR is 0.79 (95% CI = 0.55-1.13) for tofu and 0.72 (95% CI = 0.48-1.07) for deep-fried tofu. Neither tofu nor deep-fried tofu is related to rectal cancer.

Adenomatous polyps are considered a pre-neoplastic stage of colon cancer, and people with adenomatous polyps are known to have a significantly increased risk of developing colon cancer. Witte et al (1996) evaluated diet in relation to the risk of adenomatous polyps in a case-control study in the United States. A total of 488 cases with histologically confirmed adenomatous polyps and an equal number of controls were recruited. Tofu was one of the food items assessed in this study. Consumption of tofu is related to a significantly lower risk of colorectal adenomatous polyps ( $P$  trend = 0.04). The adjusted OR is 0.48 (95% CI = 0.24-0.95) when the highest intake ( $\geq 1$  serving/wk) is compared with the non-users. The trend persists after further adjustment for other potential anti-carcinogenic dietary constituents, e.g., dietary fiber, folate, beta-carotene, and vitamin C, ( $P$  trend = 0.18). The adjusted OR is 0.55 (95% CI = 0.27-1.11) when the highest intake is compared with the non-users.

Inoue et al (1995) evaluated risk factors for colorectal cancer in a hospital-based case-control study in Japan. They compared 432 colorectal cases (94 proximal colon, 137 distal colon, and 201 rectum) with 31,782 cancer-free outpatients. Bean curd was one of

the food items assessed in this study. The adjusted OR for proximal, distal, and rectal cancer is 0.9 (95% CI = 0.5-1.6), 1.7 (95% CI = 1.0-2.6), and 1.2 (95% CI = 0.8-1.7) for men and 1.3 (95% CI = 0.7-2.4), 0.6 (95% CI = 0.4-1.0), and 0.9 (95% CI = 0.6-1.5) for women, respectively. The comparison is between often users ( $\geq 3$ -4 times/wk) and less often users ( $< 3$  times/wk).

Hoshiyama et al (1993) investigated colorectal cancer in relation to diet, cigarette smoking, and alcohol use in a population-based case-control study in Japan (181 cases, 653 controls). Soybean products (except miso soup) were assessed as one category of food. Consumption of soybean products is related to a lower risk of rectal and colon cancer ( $P$  trend = 0.03 for rectal cancer,  $P$  trend = 0.08 for colon cancer). The adjusted RR is 0.4 (95% CI = 0.2-0.9) for rectal cancer and 0.6 (95% CI = 0.3-1.3) for colon cancer when the high intake ( $\geq 8$  times/wk) is compared with the low intake ( $\leq 4$  times/wk).

Hu et al (1991) assessed diet in relation to colorectal cancer in a hospital-based case-control study in China (336 cases, 336 controls). Food consumption data were collected in 1985 and 1966, and bean products were analyzed as one group of food. Consumption of bean products is related to a significantly lower risk of rectal cancer in men ( $P$  trend = 0.001 for the 1985 data,  $P$  trend = 0.007 for the 1966 data). The estimated OR is 0.33 (95% CI = 0.17-0.65) from the 1985 data and 0.27 (95% CI = 0.10-0.74) from the 1966 data when the highest intake is compared with the lowest. The highest and the lowest intakes of bean products are  $> 9$  kg/yr and  $< 2$  kg/yr from the 1985 data, and  $> 13.5$  kg/yr and  $< 1.5$  kg/yr from the 1966 data. The intake of bean products is not associated with rectal cancer in women nor colon cancer in either sex.

Tajima et al (1985) investigated dietary habits in relation to gastro-intestinal cancer in a hospital-based case-control study in Japan (93 colorectal cancer cases, 93 stomach cancer cases, 186 controls). Bean curd intake was assessed in this study. Intake of bean curd is not related to colon cancer (RR = 1.08), but is related to an increase in rectal cancer risk

(RR = 1.63) when the frequent users ( $\geq 4$  times/wk) are compared with the occasional users ( $<1$  time/wk). The 95% confidence interval was not presented in this publication.

#### Cross-National Analysis

In a cross-national analysis, McKeown-Eyssen and Bright-See (1984) correlated food availability with the mortality of colon cancer in men using data from 38 countries. Food availability data (years 1972-1974) from United Nations sources were correlated with the 1974 colon cancer mortality data. All plant foods, including soybeans, were analyzed as sources of dietary fibers. The availability of soybeans is not correlated with the death rate of colon cancer (correlation coefficient =  $-0.08$ ).

#### Ecological Study

Nagata et al (2000) assessed the relationship between soy intake and cancer mortality in Japan. Soy intake data from a National Nutritional Survey Report 1980-1985 were correlated with mortality data (colorectal, breast, prostate, stomach, and lung cancer) from the National Vital Statistics 1995. Soy consumption was standardized to soy protein intake before data were analyzed. Results of the analysis show that soy protein intake is correlated with an increase in colorectal mortality in men (correlation coefficient =  $0.36$ ,  $P < 0.05$ ) and women (correlation coefficient =  $0.51$ ,  $P < 0.01$ ). This analysis also shows that soy intake is correlated with a lower mortality of stomach cancer, and not correlated with breast, prostate, and lung cancer. (see the respective sections for details)

Table 17. Epidemiological studies on soy consumption and colorectal cancer in humans.

Intervention Study						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Bennink (2001)	One-year intervention study	Forty-two "at risk" subjects* assigned to two groups, casein (n = 13) and isolated soy protein (n = 29).	N/A	Casein: 39 g/d  Isolated soy protein: 39 g/d	N/A	Colon mucosa biopsies collected before and after the intervention were compared. There is a significant reduction in labeling index ( $P \leq 0.05$ ) and proliferation zone ( $P \leq 0.05$ ) in subjects consumed soy protein, and these variables remain unchanged in subjects consumed casein.  *Subjects with a history of colon polyps or colon cancer.
Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Seow (2002)	Population-based case-control study (1999-2000), questionnaire (in-person interview)	Cases: 121, Controls: 222, Ages (mean): 65 yrs (men), 57 yrs (women), Chinese /Singapore	Age, family history of colorectal carcinoma, gender, smoking history, years of formal education, and usual number of hours of moderate /vigorous exercise per week.	Soy and Legumes* Highest: $\geq 234$ portions/y Lowest: $< 78$ portions/y  *yong tau foo, taupok, and taukwa.	1.3 (0.7-2.4)	Intake of soy and legume is not associated with colorectal cancer in this study population.

Table 17. Epidemiological studies on soy consumption and colorectal cancer in humans (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>†</sup> (Highest vs. Lowest Intake)	Major Findings
Le Marchand (1997)	Population-based case-control study (1987-1991), food frequency questionnaire (in-person interview).	Cases: 1,192, Controls: 1,192, Multi-ethnic (Japanese, Caucasian, Filipino, Hawaiian, and Chinese)/U.S.A.	Age, family history of colorectal cancer, alcoholic drink per week, pack-years of cigarette smoking, lifetime recreational activity, Quetelet index 5 years earlier, total calories, and egg and calcium intake.	Soy products and legumes Women: Q4: > 44 g/d Q1: <9 g/d  Men: Q4: >46 g/d Q1: <11 g/d  Tofu Q4: >25 g/d Q1: none	Soy products and legumes: Women: 0.5 (0.3-0.9)  Men: 0.8 (0.5-1.2)  Tofu Women: 0.9 (0.5-1.5)  Men: 1.0 (0.6-1.6)	Consumption of soy products and legumes is associated with a lower risk of colorectal cancer in women ( <i>P</i> trend = 0.05), but not in men ( <i>P</i> trend = 0.31). The trend persists after further adjustment for non-starch polysaccharides from vegetables, but the strength of the association is attenuated ( <i>P</i> trend = 0.18, for women).  Tofu intake is not related to colorectal cancer in either sex.
Nishi (1997)	Community-based case-control study (1987-1990), questionnaire (interview)	Cases: 330, Controls: 660, Ages: not presented, Japanese/Japan	Not presented.	Tofu Frequent users (≥3 times/wk) vs. non-users.  Deep-fried tofu Frequent users (≥3 times/wk) vs. non-users.	Colon: Tofu: 0.79 (0.55-1.13) Deep-fried tofu: 0.72 (0.48-1.07)  Rectum: Tofu: 1.02 (0.67-1.53) Deep-fried tofu: 1.22 (0.79-1.89)	Intake of tofu or deep-fried tofu is associated with a lower risk of colon cancer, but not related to rectal cancer.

Table 17. Epidemiological studies on soy consumption and colorectal cancer in humans (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Witte (1996)	Case-control study (1991-1993), food frequency questionnaire (in-person interview).	Cases (adenomatous polyps): 488, Controls: 488, Ages: 50-74 yrs, Southern Californians /USA	Race, body mass index, physical activity, smoking, calories, and saturated fat.	Tofu ≥1 servings/wk vs. none	0.48 (0.24-0.95)	Consumption of tofu is associated with a significantly lower risk of colorectal adenomatous polyps* ( <i>P</i> trend = 0.04). The trend persists after further adjustments for other potential anti-cancer constituents, e.g., dietary fiber, folate, beta-carotene, and vitamin C ( <i>P</i> trend = 0.17).  *Adenomatous polyps are a pre-neoplastic stage of colorectal cancer.
Inoue (1995)	Hospital-based case-control study (1988-1992), self-administered questionnaire	Cases: 432 Controls: 31,783 Ages: >18 yrs Japanese/Japan	Age.	Bean curd (Intake level not reported) ≥3-4 times/wk vs. less	Men: P: 0.9 (0.5-1.6) D: 1.7 (1.0-2.6) R: 1.2 (0.8-1.7)  Women: P: 1.3 (0.7-2.4) D: 0.6 (0.4-1.0) R: 0.9 (0.6-1.5)	Bean curd intake is not related to proximal and rectal cancer, but related to distal cancer risk in men. Bean curd intake is not related to proximal and rectal cancer, but related to a lower risk of distal cancer in women.  *P = proximal cancer, D = distal cancer, and R = rectal cancer.
Hoshiyama (1993)	Population-based case-control study (1984-1990), Questionnaire (in-person interview)	Cases: 181, Controls: 653, Ages: 40-69 yrs, Japanese/Japan	Sex and age.	Soybean products (except miso soup) high: ≥8 times/wk Low: ≤4 times/wk	Rectum: 0.4 (0.2-0.9)  Colon: 0.6 (0.3-1.3)	Consumption of soybean products is related to a lower risk of rectal cancer ( <i>P</i> trend = 0.03) and colon cancer ( <i>P</i> trend = 0.08).

Table 17. Epidemiological studies on soy consumption and colorectal cancer in humans (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Hu (1991)	Hospital-based case-control study (1985-1988), questionnaire (in-person interview)	Cases: 336, Controls: 336, Ages: 29-74 yrs, Chinese/China	Not reported.	Bean products* 1985 data highest: >9 kg/y lowest: <2 kg/y 1966 data highest: >13.5 kg/y lowest: <1.5 kg/y  *Bean curd, bean curd derived products, and bean sprouts.	Rectum: 1985 data 0.33 (0.17-0.65)**  1966 data 0.27 (0.10-0.74)**  **Estimated RR from data presented.	Two sets of food intake data collected in 1985 and 1966 were analyzed. Consumption of bean products is associated with a lower risk of rectal cancer in men ( $P = 0.001$ for 1985 data; $P = 0.007$ for 1966 data).  Intake of bean products is not related to the risk of rectal cancer in women nor colon cancer in either sex.
Tajima (1985)	Hospital-based case-control study (1981-1984), questionnaire (interview)	Cases: 186, Controls: 186, Ages: 40-70 yrs, Japanese/Japan	Age and sex.	Bean curd Frequent users ( $\geq 4$ times/wk) vs. occasional users (<1 time/wk)	Colon: 1.08  Rectum: 1.63	Intake of bean curd is not related to colon cancer, but is related to the risk of rectal cancer.
Cross-Sectional Analysis						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
McKeown-Eyssen (1984)	Cross-national analysis using data from 38 countries from United Nations sources	Correlation on food availability (1972-1974 data) with colon cancer mortality in men (1974 data). Analysis conducted in Canada .	N/A	Soybeans*  *Analyzed as sources of dietary fiber.	$r^{*} = -0.08$  *correlation coefficient	The availability of soybeans is not correlated to the mortality of colon cancer in men.

Table 17. Epidemiological studies on soy consumption and colorectal cancer in humans (continued).

Ecological Study						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Nagata (2000)	Ecological study	Correlation analysis using data from National Nutritional Survey Report 1980-1985 and National Vital Statistics 1995, Japanese/Japan	Mean age, proportion of current smokers, and intake of alcoholic and animal fat.	Soy protein* 6.5 ± 0.8 g/d (mean ± SD)  *Standardized from soyfoods (miso, tofu, fried tofu, soybeans, soy milk, and yuba).	Men: $r^{**} = 0.36$  Women: $r^{**} = 0.51$  **Correlation coefficient	Consumption of soyfoods is correlated to the risk of colorectal cancer in men ( $P < 0.05$ ) and women ( $P < 0.01$ ).

<sup>1</sup>OR/RR (95% CI) = odds ratio/relative risk (95% confidence interval).

### B.3.3 (3). Animal Studies

#### Summary

This section reviews studies that related soy protein to experimentally induced gastro-intestinal tumorigenesis in animals. It evaluates studies that used soy protein as a component of a diet and examined the preventive effect of such a diet on gastro-intestinal tumorigenesis (the experimental diet was given to animals prior to carcinogen treatment). Twelve studies are available to date (Table 18). Results of these studies support the epidemiological findings that consumption of soy protein-containing foods is related to a lower risk of gastro-intestinal cancer. Isolated soy protein (ISP), soybean high-molecular weight fraction (HMF), soybean curd refuse, soybean flakes, flour, and soybean meal were assessed in these studies. Soybean HMF was a fraction of protease-treated ISP after removal of water-soluble peptides. It had an amino acid composition similar to ISP. Soybean curd refuse was a byproduct from the process of bean curd, and it contained approximately 20% protein. In these studies ISP or a soy protein-containing preparation was supplemented to the diet at the expense of casein (a protein source of standard research diets), and ISP was compared with casein as the sole source of dietary protein (e.g., 20% soy protein vs. 20% casein) in most studies. The dietary levels of soy protein and casein in each of these studies are summarized in Table 18. Results of seven of these studies show that dietary supplementation with soy protein inhibits experimentally induced colon tumorigenesis. Three studies show that soy has no inhibitory effect (Davies et al., 1999; McIntosh et al., 1995; Sorensen et al., 1998) (two were done using a high-fat diet as the basal diet (Davies et al., 1999; Sorensen et al., 1998)). Two studies show that soy protein enhances 1,2-dimethylhydrazine (DMH)-induced colon tumorigenesis in rats (Gee et al., 2000; Reddy et al., 1976) (one was a comparison between a high-fat, high-soy protein diet and a low-fat, low-soy protein diet (Reddy et al., 1976)).

#### Isolated Soy Protein

Hakkak et al (2001) conducted a multi-generation feeding study in which male offspring from dams on a soy protein diet were mated and maintained on the same diet for two generations before receiving a treatment of azoxymethane. Azoxymethane is a

commonly used carcinogen for experimental colon tumorigenesis in animals. Dietary supplementation with 20% ISP significantly reduces the incidence of colon tumor in offspring compared with the controls maintained on a casein-based diet ( $P < 0.001$ ). Consumption of ISP diet significantly decreases the incidence of invasive carcinoma ( $P < 0.05$ ) and benign tumors ( $P < 0.05$ ) compared with the controls when data are analyzed on the basis of tumor types.

Wang and Higuchi (2000) studied the effect of ISP on changes in intestinal polyamine level in rats. Polyamines are a marker of colorectal proliferation, and their cellular level increases when cells are stimulated to proliferate. Elevated cellular polyamine levels have been found in neoplastic cells and colorectal mucosa of individuals at increased risk of neoplasia. Dietary supplementation with 20% ISP significantly reduces polyamine levels in small and large intestines compared with the controls maintained on a casein diet ( $P < 0.05$ ).

Three studies investigated the effect of soybean high-molecular-weight fraction (HMF) in azoxymethane-induced and deoxycholate-promoted colonic tumorigenesis in animals (Azuma et al., 1999a; Azuma et al., 1999b; Azuma et al., 2000). Deoxycholate is a carcinogen promoter. Treatment of animals with deoxycholate results in a hyperproliferative effect in colon and increases in tumor incidence and multiplicity. Azuma et al (1999a) reported that dietary supplementation with 26% soybean HMF significantly reduces the tumor promoting effect of deoxycholate by reversing the deoxycholate-induced decrease in colonic aberrant crypt foci compared with the casein-fed controls ( $P < 0.05$ ). Dietary supplementation with soybean HMF at a lower level (13.5%) results in a  $\geq 50\%$  reduction in the incidence of colon tumor, but the difference between the soybean HMF group and the controls is not statistically significant (Azuma et al., 1999b; Azuma et al., 2000).

Two studies compared ISP with low-isoflavone ISP (Davies et al., 1999; Sorensen et al., 1998). The basal diet used in these studies was a high-fat diet (14.7% lard, 6% corn oil), and the low-isoflavone ISP was the protein source of the control diet. No protein from

other sources was compared in this study. Davies et al (1999) reported that there are no differences in the numbers of azoxymethane-induced colon tumor and aberrant crypt foci between the ISP and the control groups. Sorensen et al (1998) compared these two types of ISP using a Min mouse spontaneous intestinal tumor model. There are no differences in the incidence, multiplicity, size, and distribution of intestinal tumors between the groups.

Results of two studies show that soy protein enhances 1,2-dimethylhydrazine-induced colon tumorigenesis in rats. Gee et al (2000) reported that feeding rats a soya protein diet before, but not after, the carcinogen treatment results in a 2-fold increase in the number of aberrant crypt foci in distal colon compared with the controls ( $P < 0.05$ ). Reddy et al (1976) reported that consumption of a high-fat, high-soy protein diet (25% corn oil, 40% soy protein) significantly increases the multiplicity (tumors/rat) of colon tumor compared with rats maintained on a low-fat, low-soy protein diet (5% corn oil, 20% soy protein). No comparison was made on soy protein using a diet containing an equal amount of dietary fat in this study, and the type of soy protein assessed was not presented.

#### Soybean Curd Refuse

Azuma et al (1999b) reported that feeding rats a diet containing 50% soybean curd refuse significantly reduces tumor incidence compared with the casein-fed controls ( $P < 0.05$ ). Soybean curd refuse is a byproduct containing 20% protein from the process of bean curd.

#### Soy Flakes, Soy Flour, and Soybean Meal

Three studies investigated effects of soy flakes, soy flour, or soybean meal on chemically induced colon tumorigenesis or epithelial damage in animals.

Thiagarajan et al (1998) reported that providing rats a diet containing 46% full-fat soy flakes ( $P \leq 0.05$ ) or 36% defatted soy flour ( $P \leq 0.05$ ) results in a significant reduction in the number of azoxymethane-induced aberrant crypt foci in rats compared the controls. Logvinova et al (1999) investigated the effect of soy flour and other soy preparations on

methotrexate-induced gastrointestinal damage in rats. Methotrexate, similar to other chemopreventive agents and radiation treatment, increases the incidence of apoptosis in the areas of rapidly dividing cells, including gastrointestinal tract mucosa. Dietary supplementation with 10% unheated, defatted soy flour markedly reduces methotrexate-induced apoptosis in villi epithelium and necrotic damage in the crypts compared with the controls maintained on a casein-based diet (a histological comparison). Dietary supplementation with 1.64% soy-derived anti-apoptotic fraction or 1.64% Lexirin has similar inhibitory effects. Soy-derived anti-proliferative fraction was an alcohol extract of defatted soy flour, and Lexirin was a water extract of heat-treated soy protein isolate.

McIntosh et al (1995) reported that there is no statistically significant difference in 1,2-dimethylhydrazine-induced tumorigenesis (tumor incidence, tumor burden (tumors/group), and tumor mass index) between the groups fed a soybean meal diet and a casein-based control diet.

Table 18. Animal studies on dietary soy protein and experimentally induced colon tumorigenesis.

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Hakkak (2001)	Rats/Sprague-Dawley, male	Azoxymethane	Casein (20%)  ISP <sup>1</sup> (20%)	Dietary supplementation with ISP for two generations significantly decreases the incidence of colon tumor, invasive adenocarcinoma, and benign tumor in offspring compared with the controls. The incidence of colon tumor is 12% for the ISP group and 50% for the controls ( $P<0.001$ ), that of invasive adenocarcinoma is 10% and 31% ( $P<0.05$ ), and that of benign tumors is 5% and 19% ( $P<0.05$ ), respectively.
Wang (2000)	Rats/Wistar, male	N/A	Casein (20%)  ISP (20%)	Dietary supplementation with ISP significantly reduces polyamine levels in small and large intestines compared to the controls ( $P<0.05$ ). Polyamine is a marker of colorectal proliferation.
Azuma (1999a)	Rats/F344, male	Azoxymethane and deoxycholate	Casein (20%)  Soybean high-molecular-weight fraction (HMF)* (26%)	Dietary supplementation with soybean HMF significantly reduces the tumor promoting effect of deoxycholate by reversing deoxycholate-induced decrease in colonic aberrant crypt foci compared with the controls ( $P<0.05$ ).  *A fraction after removal of water-soluble peptides from protease-treated ISP, and having an amino acid composition similar to ISP.
Azuma (2000)	Rats/F344, male	Azoxymethane and deoxycholate	Casein (10%)  Soybean HMF (13.5%)	Dietary supplementation with soybean HMF results in a $\geq 50\%$ reduction in incidence of colonic tumor compared with the controls fed a casein-based diet.
Azuma (1999b)	Rats/F344, male	Azoxymethane and deoxycholate	Casein (10%)  Soybean HMF (13.5%)  Soybean curd refuse* (50%)	Dietary supplementation with soybean HMF results in a $\geq 50\%$ reduction in the incidence of colonic tumors compared to the controls. Feeding rats a soybean curd refuse-supplemented diet results in a significant reduction in the incidence of colonic tumor compared with the controls ( $P<0.05$ ).  *A byproduct (containing 20% protein) from process of bean curd.

Table 18. Animal studies on dietary soy protein and experimentally induced colon tumorigenesis (continued).

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Findings
Davies (1999)	Rats/F344, male	Azoxymethane	High-fat (14.7% lard, 6% corn oil), low-isoflavone ISP* (23%) diet  High-fat (14.7% lard, 6% corn oil) ISP** (23%) diet	There are no differences in the number of colonic tumors (1.36 vs. 1.38 tumors/rat) and aberrant crypt foci (5.0 vs. 2.81 foci/rat) between the low-isoflavone ISP and the ISP groups.  *Containing 0.09 mg isoflavones/g protein. **Containing 2.46 mg isoflavones/g protein.
Sorensen (1998)	Mice/Apc <sup>Min</sup> , male and female	Spontaneous intestinal tumor development	High-fat (14.7% lard, 6% corn oil), low-isoflavone ISP* (23%) diet  High-fat (14.7% lard, 6% corn oil) ISP** (23%) diet	There are no significant differences in incidence, multiplicity, size, and distribution of intestinal tumors between the low-isoflavone ISP and the ISP groups.  *Containing 16 mg isoflavones/kg diet. **Containing 476 mg isoflavones/kg diet.
Gee (2000)	Rats/Wistar, male	1,2-dimethyl hydrazine	Casein (20%)  Soya protein isolate (20.8%)	Feeding rats a soya protein diet before, but not after, the carcinogen treatment results in a 2-fold increase in the number of aberrant crypt foci in distal colon compared with the controls ( $P<0.05$ ).
Reddy (1976)	Rats/F344, female	1,2-dimethyl hydrazine	Low-fat, low -soy protein* diet (5% corn oil, 20% soy protein)  High-fat, high-soy protein* diet (25% fat, 40% soy protein)	Consumption of a high-fat, high-soy protein diet significantly increases the number of colon tumors compared with rats maintained on a low-fat, low-soy protein diet ( $P<0.05$ ).  *The type of soy protein assessed in this study was not presented.

Table 18. Animal studies on dietary soy protein and experimentally induced colon tumorigenesis (continued).

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Thiagarajan (1998)	Rats/F344, male	Azoxymethane	Soy protein concentrate* (28.5%)  Full-fat soy flakes (46%)  Defatted soy flour (36%)	Dietary supplementation with full-fat soy flakes ( $P \leq 0.05$ ) or defatted soy flour ( $P \leq 0.05$ ) significantly reduces the number of colonic aberrant crypt foci compared with the controls.  *Protein source of the control diet containing isoflavone aglycones at 40 mg/kg diet.
Logvinova (1999)	Rats/Sprague-Dawley, male	Methotrexate	Casein (20%)  Unheated, defatted soy flour (10%)	Dietary supplementation with soy flour markedly reduces methotrexate-induced apoptosis in villi epithelium and necrotic damage in the crypts compared with the controls (a histological comparison).
McIntosh (1995)	Rats/Sprague-Dawley, male	1,2-dimethyl hydrazine	Casein (20%)  Soybean meal (33%)	There are no significant differences in tumor incidence, tumor burden (tumors/group), and tumor mass index between the soybean meal group and the control group.

\*ISP = isolated soy protein.

#### ***B.4. There is Significant Scientific Agreement that Soy Protein May Reduce the Risk of Some Types of Cancer***

From data provided in the detailed review of the scientific literature (Section B. Scientific Evidence: B.3. Details of the Scientific Review) we conclude there is significant scientific agreement among scientists qualified to review these data that soy protein may reduce the risk of some types of cancer.

To further support our view, a scientific advisory panel was commissioned to review the data in this section. This panel also concluded that there was significant scientific agreement that soy protein may reduce the risk of certain types of cancer. Appendix VII contains information about the scientific panel members and a summary letter of their conclusions regarding the scientific support for the health claim of this petition.

### **C. ANALYTICAL DATA**

Soybeans contain approximately 40% protein on a dry weight basis and have been consumed as a dietary protein staple by populations for centuries (Messina et al., 1994a). Dry soybeans are the starting material for the soy protein-containing foods—soy flour, soy protein concentrate, isolated soy protein, soybean curd, and soymilk. All of these products will also contain naturally occurring constituents such as fibers, isoflavones, and saponins. Protein content of a variety of commercially available food products in United States is presented in Appendix I.

### **D. MODEL HEALTH CLAIM**

#### ***D.1. Proposed Claims***

The following statement is proposed for foods that meet the qualifying criteria for the soy protein and reduced risk of certain cancers health claim:

**Soy protein may reduce the risk of certain cancers. Scientific evidence suggests that consumption of soy protein may reduce the risk of certain forms of cancer. However, this evidence is not conclusive.**

**Soy protein may produce anticarcinogenic effect in the body. Scientific evidence suggests that consumption of soy protein may produce anticarcinogenic effects in the body. However, this evidence is not conclusive.**

These claims are consistent with the model claims of other authorized cancer related health claims (Dietary Fat and Cancer - § 101.73; Fiber-Containing Grain Products - § 101.76; and Fruits and Vegetables and Cancer - § 101.78).

### ***D.2. Qualifying Levels of Soy Protein per RACC in Foods***

The approach the Agency has used in the past with epidemiological based health claims in setting the qualifying level of intake has been to encourage consumption of more servings of the selected food or food component. This is consistent with recommendations the Agency has provided in the previous authorized health claims for Fiber-Containing Grain Products (§ 101.76) and Fruits and Vegetables and Cancer (§ 101.78). In the two claims recommending increased intake of certain foods or food components, the agency stipulates that foods bearing the claim are required to contain a “good source”. Thus, food bearing the soy protein and reduced risk of certain cancers health claim would also need to provide a “good source” of protein from soy, or 5.0 g/RACC.

With this qualifying amount of soy protein, foods would meet the criteria if they contained a good source of protein from soy (at least 10% of the Daily Value (DV) for protein, or 5 g), thus satisfying 21 CFR 101.14(e)(6), which requires “the food to contain 10 percent or more of the Reference Daily Intake or the Daily Reference Value for vitamin A, vitamin C, iron, calcium, protein or fiber per reference amount customarily consumed prior to any nutrient addition” to be eligible to make a health claim on the label or in labeling. Foods qualifying to bear the claim must also not exceed 20% or more of

the DV for the disqualifying nutrients of total fat, saturated fat, cholesterol, and sodium in accordance with 21 CFR 101.14(a)(5). Foods qualifying to bear the health claim shall meet the nutrient content requirement for a low fat food (21 CFR 101.62), unless the food consists of or is derived from whole soybeans and contains no additional fat other than that present in whole soybeans. This is consistent with the previously authorized Soy Protein and Coronary Heart Disease Health Claim (21 CFR § 101.82).

To verify that increasing consumption of foods containing a good source of soy protein (e.g., 5.0 g/RACC) may be associated with a reduced risk of certain cancers, we estimated soy protein intake from the studies available. Food intake data was extracted from the published reports and used the highest level of intake in each study to base our recommended daily intake level (5.0 g/RACC). For reference purposes we also extracted the lowest level of intake as well.

Most of the studies reported the frequency of soy food intake on times per week/month/year basis. We used these values as the starting point for our calculations. If the frequency was provided on a “greater than or equal” basis we added an additional 10% to the value. If the frequency was provided on a “less than or equal” basis we subtracted 10% of the value. We used FDA serving amounts (e.g., 85 g for tofu and 8 oz. for soymilk) to define serving amount. With this approach we could estimate the soy protein intake for both controls and cancer cases in case-control studies and for the lowest/highest consumption groups in other studies. For some studies soy protein intake was not possible to determine (e.g., urinary isoflavone studies, appropriate data not provided, etc.).

After estimating soy protein intake for each study, we initially combined the estimates of soy protein intake within cancer type (e.g., breast cancer, prostate cancer, etc.). Within each cancer type, we calculated soy protein intake based on three approaches: 1) for all studies incorporated into the aforementioned meta-analysis; 2) for only studies used in the aforementioned meta-analysis that were statistically significant; and 3) all studies

regardless of incorporation into the meta-analysis. Finally, we then combined the estimated soy protein intakes across cancer types.

Tables 1-5 (Appendix VIII) provide estimates of soy protein intake for studies evaluating the various types of cancer. The estimates of mean soy protein intake for the studies on breast cancer for the three approaches mentioned above were 4.4, 1.4, and 4.4 g/day, respectively. Comparable data for prostate cancer were 4.0, 4.5, and 4.9 g/day, respectively; for stomach/esophageal cancer were 5.3, 5.4 and 5.3 g/day, respectively; and for colorectal cancer were 4.4, 4.7, and 4.7, respectively. There was remarkable similarity in the estimated intake of soy protein across cancer types.

When we combined the soy protein intake estimates across cancer types for studies in the meta-analysis (33 studies) or for all studies (43 studies), we obtained estimates of the average daily intake of 4.6 and 4.8 g/day, respectively (Table 5). From these data we recommend the qualifying amount of soy protein per RACC be set at 5.0 g/day or a good source of protein from soy. This level is similar to the amount we quantified from the studies used as the basis of this petition (rounding 4.6 or 4.8 to the nearest whole gram amount).

We also examined the average frequency of consumption of soy products in the studies mentioned above. We only used data from studies that provided clear information regarding frequency of consumption in times per week. Again we summarized the data by each cancer type (Tables 1-4) and then combined the data across cancer types (Table 5). The average frequency of consumption was 4.0, 6.0, 3.7, and 3.9 times per week for studies concerning cancer of breast, prostate, stomach/esophagus, and colon/rectum, respectively. The combined frequency of consumption across cancer types was 3.8 times per week whether we included only studies used in the meta-analysis (19 studies) or included all studies providing frequency data in times per week (23 studies). These data suggest consumers can obtain the benefits of cancer risk reduction with reasonable frequency of consumption of soy containing foods.

### *D.3. Other Qualifying Criteria*

The beneficial relationship between soy protein consumption and reduction in risk of certain cancers is not true for all soy containing foods. Soybean paste or miso is a fermented, salted product that is low in protein and used primarily as a condiment. There have been epidemiological investigations on this product yielding either no association or a positive association with certain cancers (e.g., stomach and esophageal), which is related to the fermentation and the high level of salt (Hirohata & Kono, 1997; Kim et al., 2000; Wu et al., 2000). There have been no epidemiological studies to our knowledge investigating the relationship between oil portion of the soybean and cancer. Furthermore, there are no human data demonstrating that concentrated isoflavone preparations are associated with a reduced risk of any type of cancer. Therefore, soybean paste or miso, soybean oil, and isoflavone extracts should not be permitted to bear this claim.

Regarding the measurement of soy protein we propose to use the same approach authorized by FDA for the soy protein coronary heart disease health claim. Namely:

**“FDA will measure total protein content by the appropriate method of analysis given in the ``Official Methods of Analysis of the AOAC International,” as described at Sec. 101.9(c)(7). For products that contain no sources of protein other than soy, FDA will consider the amount of soy protein as equivalent to the total protein content. For products that contain a source or sources of protein in addition to soy, FDA will, using the measurement of total protein content, calculate the soy protein content based on the ratio of soy protein ingredients to total protein ingredients in the product. FDA will base its calculation on information identified and supplied by manufacturers, such as nutrient data bases or analyses, recipes or formulations, purchase orders for ingredients, or any other information that reasonably substantiates the ratio of soy protein to total protein. Manufacturers must maintain records sufficient to substantiate the claim for**

**as long as the products are marketed and provide these records, on written request, to appropriate regulatory officials.” (21 CFR 101.82(c)(2)(ii)(B))**

#### ***D.4. The Proposed Claim Is Consistent with Other Dietary***

##### ***Recommendations***

Consumption of a low fat diet containing plant foods is consistently recommended for reducing the risk of chronic diseases including cancer and coronary heart disease.

*Healthy People 2010: Understanding and Improving Health* promotes public health goals, including the general promotion of good health and associating diet with reduction in chronic diseases including certain cancers (U.S. Department of Health and Human Services, 2000). It reemphasizes dietary guidelines recommended by the U.S. Department of Agriculture (USDA) and the Department of Health and Human Services (HHS), which recommend a daily intake of 6-11 servings of grain foods, 2-4 servings of fruits, and 3-5 servings of vegetables for Americans (U.S. Department of Agriculture & Services, 1995). In the recent rendition of the Food Guide Pyramid, USDA is proposing to incorporate more legumes into the desired dietary pattern for Americans. Again, soy protein containing foods are consistent with this approach.

Increasing the consumption of a low fat diet containing plant foods is also recommended in the NRC's *Recommended Dietary Allowances* (National Research Council, 1989b) and their *Diet and Health* report (National Research Council, 1989a). The *Surgeon General's Report on Nutrition and Health* (U.S. Department of Health and Human Services, 1988) and the National Cancer Institute's dietary guidelines (Butrum et al., 1988) also recommend consumption of a low fat diet containing plant foods. In addition, the Food and Agriculture Organization of the United Nations (Food and Agriculture Organization of the United Nations, 1998), the American Cancer Society (American Cancer Society, 1996), and the American Dietetic Association (American Dietetic Association, 1994) all recommend increasing the intake of plant foods in order to reduce the risk of cancer.

The data presented in the current petition provides compelling evidence that soy protein may reduce the risk of certain cancers. Soy protein differs from other plant proteins in

quality, the particular composition of amino acids it provides, and the amounts and types of other naturally occurring constituents it contains. Health professionals believe a dietary pattern that contains a large number of fruits and vegetables, including legumes, may reduce the risk of several chronic diseases, including some types of cancer. For example, the American Cancer Society states in its guidelines on nutrition and physical activity for cancer prevention that:

**“Eat a variety of healthful foods, with an emphasis on plant sources**

- **Eat five or more servings of vegetables and fruit each day**
- **Choose whole grains in preference to processed (refined) grains and sugar**
- **Limit consumption of red meats, especially high-fat and processed meats**
- **Choose foods that help maintain a healthful weight” (Byers et al., 2002)**

Soy protein containing foods is consistent with these recommendations, especially as a plant source of dietary protein.

#### ***D.5. The Dietary Changes of the Proposed Claim is Feasible and Healthy for Americans***

Increased consumption of soy protein is associated with a reduced risk of certain cancers. In order for foods to bear this claim, at least 5 g soy protein must be present per RACC.

Vegetarian populations within the United States have been consuming soy protein in excess of this level of intake for almost 40 years (Messina et al., 1994b). A number and variety of products are currently available on the market, which provide qualifying amounts of soy protein, without disqualifying levels of total fat, saturated fat, cholesterol, and sodium, making the incorporation of soy protein at this level of intake readily achievable. In addition, approval of a health claim for soy protein should stimulate industry interest in making more products with qualifying amounts of this substance available to consumers. Technology is available across the industry to meet this specification.

D. Model Health Claim: This petition contains the recommended text for possible model health claims.

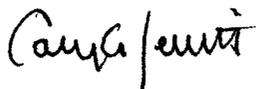
E. Environmental Impact: Solae claims a categorical exclusion from the environmental assessment (EA) and environmental impact statements (EIS).

To the best of the knowledge of the undersigned, this petition is a representative and balanced submission that also includes unfavorable information for evaluating of the proposed health claim.

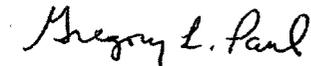
Any questions regarding this petition should be directed to Lin Yan, Ph.D. or Susan M. Potter, Ph.D., Solae, LLC at 314-982-3031.

Yours very truly,

Solae, LLC



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Gary Kussner, Esquire  
Tony L. Arnold, CEO and President



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