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Summary of Health Canada's Assessment of a Health Claim about Soy Protein and Cholesterol Lowering

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Food Directorate
Health Products and Food Branch

Canada

Background

In December 2011, Health Canada's Food Directorate received an application for a therapeutic claim about protein-rich soy foods and blood cholesterol lowering. The information below is a summary of Health Canada's review based on the *Guidance Document for Preparing a Submission for Food Health Claims*.

In 2010, Health Canada reconsidered the classification of food products with disease risk reduction claims or therapeutic claims in light of clarified principles for the classification of foods at the Food-Natural Health Product interface. Health Canada's position is that when food products are marketed for a disease risk reduction or therapeutic benefit, which comes as a result of the food's normal use as part of the diet, these products may be classified and regulated as foods. In other words, the use of a disease risk reduction claim or a therapeutic claim alone is not sufficient to classify the product as a natural health product.

Scientific Evidence Supporting the Claim

The foods that are the subject of the proposed health claim are foods or food ingredients that contain proteins derived from the soybean (*Glycine max* (L.) Merr., Fabaceae). Foods and ingredients eligible for the claim include soy beverages, tofu, miso, tempeh, natto, soy cheese, soy nuts, isolated soy protein (ISP), soy protein concentrate (SPC), textured soy protein (TSP) and soy flour (SF). Soy sauce and soybean oil are excluded from the claim because they lack substantial amounts of soy protein.

The petitioner provided a literature search covering the period from 1980 to March 2010 to substantiate the proposed health claim. The literature search was updated by Health Canada's Food Directorate to encompass studies published to March 2013. A total of 49 relevant references (1-49) were identified, for a total of 79 studies since many references included more than one comparison between a soy food and a control.

All relevant studies were clinical trials conducted in normo- and hypercholesterolemic males and females ranging from 18 to 80 years of age. Studies were carried out in the Americas, Europe, Asia and Oceania, with the vast majority conducted in the United States. Twenty studies were conducted in men, including 8 in young men; 28 studies were conducted in women, including 24 in postmenopausal women; and 31 studies were conducted in both men and women. Treatment duration ranged from 1 to 12 months and the daily intake of soy protein ranged from 11.3 g to 154 g. The majority of studies used doses in the range of 25-50 g/day. The smallest study included 9 subjects and the largest study included 352 subjects. Of the 79 studies selected for inclusion, 41 were of crossover design and 38 were of parallel design. Randomization was used in 69 of the 79 studies, 40 studies were reported as double blinded, 4 as single blinded and 35 studies did not report blinding.

The main source of soy protein administered in the studies was highly refined soy products: ISP was

used in 65 studies among which 3 studies used soy beverages made from ISP; SPC was used in 2 studies. Other soy foods were administered to a lesser extent: soy beverages made from whole soy beans were used in 2 studies, TSP was used in 1 study, SF was used in 2 studies, tofu was used alone in 1 study and in combination with other soy foods in another study and soy nuts were used in 6 studies. Fifty-three studies reported the isoflavone content of the soy treatments and 8 studies reported using isoflavone-depleted soy protein (ethanol washed soy protein). Control foods consisted of casein, milk proteins, animal protein (meat), or a control diet without soy protein.

In 60 studies, soy protein was used for partial or total replacement of animal protein in the usual diet or in the context of diets designed to reduce cholesterol (e.g., the U.S. National Institutes of Health – National Heart, Lung, and Blood Institute (NIH-NHLBI) National Cholesterol Education Program (50) and the NIH-NHLBI Therapeutic Lifestyle Changes guide (51)). In 19 studies, soy protein was consumed in supplement to the usual diet. Of the 79 studies, 44 studies reported balanced caloric and macronutrients profiles between the control and the treatment groups.

The outcomes considered were changes in total cholesterol, low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG). Of the 79 studies, 77 studies reported the effect of soy protein consumption on total cholesterol, 67 studies on LDL cholesterol, 78 studies on HDL cholesterol and 72 studies on triglycerides. LDL cholesterol is the primary target for the risk of cardiovascular disease in the 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult (52).

The quality of the studies was assessed using 4 of the SIGN criteria (53) including randomization, allocation concealment, blinding and attrition to identify the main sources of potential bias. Also, studies were rated as lower quality if caloric and macronutrients profiles of the diets were not balanced between the control and the treatment groups. An overall quality judgment was reached based on how many of the quality criteria were met. Twenty-four of the 79 studies (30%) were rated as higher quality.

The direction of effect was highly consistent towards a reduction in total cholesterol (75% of studies) and LDL cholesterol (81% of studies) levels when soy protein was consumed. A low proportion of studies showed a statistically significant reduction in total cholesterol (26% of studies) and LDL cholesterol (33% of studies) levels. These conclusions were similar when only higher quality studies were taken into account.

The direction of effect was moderately consistent towards an increase in HDL cholesterol levels but highly consistent when only higher quality studies were taken into account. Fifteen percent (15%) of studies showed a statistically significant increase in HDL cholesterol levels. The direction of effect was moderately consistent towards a reduction in triglyceride levels. Eleven percent (11%) of studies showed a statistically significant reduction in triglyceride levels. These conclusions were similar when only higher quality studies were taken into account.

The petitioner conducted a meta-analysis which was reproduced and expanded by Heath

Canada's Food Directorate to include studies not captured in the petitioner's systematic review and meta-analysis. Results of both meta-analyses were similar. The estimates from the Food Directorate meta-analysis are reported here.

The meta-analysis included a total of 68, 59, 68 and 64 studies from 42, 38, 43 and 40 references for total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels, respectively. Final values for the control and treatment groups were extracted from the studies and used in the meta-analysis. In addition to the overall analysis, subgroup analyses were undertaken to investigate the influence of the following factors on the cholesterol-lowering effect of soy protein: mean baseline total cholesterol levels (elevated total cholesterol levels > 5.2 mmol/L vs. normal total cholesterol levels < 5.2 mmol/L); source of soy protein (highly refined soy products (e.g., ISP, SPC, soy beverages made from ISP) vs. other soy foods (e.g., soy beverages made from whole soy beans, tofu, soy flour, TSP, soy nuts); isoflavones (present vs. depleted); study design (parallel vs. crossover); sex (male vs. female); type of diet (usual vs. recommended for heart health); pattern of consumption (as supplement vs. as replacement of animal protein in the diet); quality of studies (higher vs. lower) and balancing of caloric and macronutrients profiles between the control and the treatment groups (balanced vs. not balanced). The results of the subgroup analyses are reported below only for the outcome of LDL cholesterol.

Overall, the weighted mean difference was -0.15 mmol/L (95% CI, -0.21 to -0.08, $p<0.00001$) for total cholesterol levels and -0.15 mmol/L (95% CI, -0.19 to -0.11, $p<0.00001$) for LDL cholesterol levels, representing approximately 2.6% and 4% reductions, respectively.

The changes in HDL cholesterol levels (+0.03 mmol/L (95% CI, +0.01 to 0.06, $p=0.002$)) and in triglyceride levels (-0.06 mmol/L (95% CI, -0.10 to -0.02, $p=0.001$)) were statistically significant in the overall analysis.

The reduction in LDL cholesterol was similar and statistically significant in all subgroups, except when only the studies using isoflavone-depleted ISP were considered. The difference between subgroups was not statistically significant, except between the subgroup of studies with highly refined soy products and the subgroup of studies with other soy foods ($p=0.01$).

Regression analyses were conducted to confirm the results of the subgroup analyses. Only gender was found to impact the LDL cholesterol lowering effect in a multivariate analysis, that is, the LDL cholesterol lowering effect was larger in studies conducted in men than in studies with women only or with both men and women. The regression analysis showed that the absence of isoflavones did not impact the LDL cholesterol lowering effect of soy protein. However, this conclusion is limited by the small number of studies that used isoflavones-depleted soy protein.

No apparent dose-response relationship was observed for LDL cholesterol lowering. Therefore, the dose most commonly used in the studies reviewed (25 g of soy protein per day) is considered as the minimum effective daily intake.

Health Canada's Food Directorate Conclusion

The evidence consistently supports a direction of effect towards a reduction in total and LDL cholesterol levels when soy protein is consumed. A meta-analysis showed a statistically significant reduction in total and LDL cholesterol levels with soy protein consumption and no detrimental effect on HDL cholesterol and triglyceride levels.

Health Canada's Food Directorate has concluded that scientific evidence exists to support a claim about soy protein and blood cholesterol lowering. The claim is relevant and generally applicable to the Canadian population on the basis that 39% of Canadians aged 6 to 79 years had unhealthy levels of total cholesterol (>5.2 mmol/L for adults) during the time period of 2009-2011[1].

Health Claim

The following statements may be made in the labelling and advertising[2] of food products meeting the qualifying criteria.

Primary statement[3]*:*

> [*Serving size from Nutrition Facts table in metric and common household measures*] of (*brand name*) [*name of food*] supplies/provides X% of the daily amount of soy protein shown to help reduce/lower cholesterol.

For example[4]:

> 150 g of tofu supplies 70% of the daily amount of soy protein shown to help lower cholesterol.
>
> 250 mL (1 cup) of enriched soy beverage supplies 30% of the daily amount of soy protein shown to help lower cholesterol.

The "daily amount" referred to in the primary statement is 25 g of soy protein. This amount is based on the evidence available concerning the amount of soy protein shown to help reduce cholesterol. In this statement, the percentage of the daily amount of soy protein provided in one serving should be rounded to the nearest multiple of 5%.

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[1] Statistics Canada. 2012. Cholesterol levels of Canadians, 2009 to 2011. [last accessed on January 21, 2015].
[2] The information in this document complements the *labelling information* published by the Canadian Food Inspection Agency. It is the responsibility of all manufacturers and importers to ensure that their products comply with all relevant Canadian legislation and regulations.
[3] [ ] = mandatory; ( ) = optional; / = acceptable alternate wording
[4] Examples are for illustration purposes only. They do not necessarily reflect acceptable health claims.

Additional statements:

The following additional statements could be placed adjacent to the primary statement, in letters up to twice the size and prominence of those in the primary statement:

- Soy protein helps reduce/lower cholesterol
- High cholesterol is a risk factor for heart disease
- Soy protein helps reduce/lower cholesterol, (which is) a risk factor for heart disease

Conditions for Foods to Carry the Claim

The following qualifying criteria apply to all food products carrying the above-mentioned health claim.

The food:

a) contains at least 6 g of soy protein
   i. per reference amount and per serving of stated size, or
   ii. per serving of stated size, if the food is a prepackaged meal, a nutritional supplement or a meal replacement;
b) contains at least 10% of the weighted recommended nutrient intake (WRNI) of a vitamin or mineral nutrient
   i. per reference amount and per serving of stated size, or
   ii. per serving of stated size, if the food is a prepackaged meal, a nutritional supplement or a meal replacement;
c) contains 100 mg or less of cholesterol per 100 g of food;
d) contains 0.5% or less alcohol;
e) contains
   i. less than 15% of the Daily Value (DV) of sodium per reference amount and per serving of stated size, and per 50 g if the reference amount is 30 g or 30 mL or less, or
   ii. less than 15% of the Daily Value (DV) of sodium per serving of stated size, if the food is a nutritional supplement or a meal replacement, or
   iii. less than 25% of the Daily Value (DV) of sodium per serving of stated size, if the food is a prepackaged meal;
f) meets the conditions for "free of saturated fatty acids" or "low in saturated fatty acids" (Items 18 and 19, respectively, in the table following section B.01.513 of the *Food and Drug Regulations*);
g) meets the requirements for fortified plant-based beverages if it is a soy beverage[5].

[5] Soy beverages can be consumed as substitutes for cow's milk which is an important source of essential nutrients such as calcium and vitamin D. Therefore, the nutritional profile of soy beverages should be similar to cow's milk for these essential nutrients. For current requirements for fortified plant-based beverages, please consult the *Interim Marketing Authorization to permit the optional addition of vitamins and mineral nutrients to plant-based beverages*.

In addition to these conditions and as per B.01.305(1) of the *Food and Drug Regulations*, a food making a representation regarding proteins must also meet the requirement of "source of protein" set out in column 2 of item 8 of the table following B.01.513. Therefore, a Reasonable Daily Intake (RDI) of the food must have a protein rating of 20 or more.

When no RDI is established in Schedule K for the food or a similar food, the reference amount can be used to calculate its protein rating. For soy beverages, it is acceptable to use the RDI of milk to calculate the protein rating based on the consideration that soy beverages are used as milk substitutes. For nutritional supplements and meal replacements, it is acceptable to use the stated serving size in calculating protein rating.

Regulatory Requirements for Food Products that are Substitutes for Other Foods

Any food, including a soy food product, represented as a substitute for another food, must meet specific requirements of the *Food and Drug Regulations* where applicable. For example, simulated meat products and simulated poultry products must meet requirements set out in B.14.085 and B.22.029, respectively, of the *Food and Drug Regulations*. Please contact the *Canadian Food Inspection Agency* for further information on these requirements.

Consultation

Health Canada's Food Directorate carried out a public consultation to receive input from the scientific community and all interested parties on a proposal to accept a health claim about soy protein and cholesterol lowering. This consultation was open from October 22, 2014 to November 21, 2014.

Health Canada received comments from 13 interested parties including academics, consultants, scientific services representatives, industry representatives and industry associations. The majority of comments received were in favour of Health Canada's proposal and supported the approach taken by Health Canada for the substantiation of the claim. Health Canada thoroughly analyzed the comments received and made adjustments to the proposal as deemed necessary.

To obtain an electronic copy of the document "*Summary of Comments on Health Canada's Proposal to Accept a Health Claim about Soy Protein and Cholesterol Lowering"*, please send an e-mail to publications@hc-sc.gc.ca with the subject heading "HPFB BNS Summary of comments on soy protein and cholesterol lowering".

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