



**PULSES AND HEART DISEASE / DIABETES:  
A CASE STUDY FOR HEALTH CLAIM  
SUBSTANTIATION IN CANADA, THE EUROPEAN  
UNION AND THE UNITED STATES**

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# **PULSES AND HEART DISEASE / DIABETES: A CASE STUDY FOR HEALTH CLAIM SUBSTANTIATION IN CANADA, THE EUROPEAN UNION AND THE UNITED STATES**

## **1.0 BACKGROUND**

### **1.1 Impetus for Project**

Canada's pulse industry is seeking to develop nutrition and health opportunities for pulses in the marketplace. To address this goal, Pulse Canada, an industry association that represents growers, processors and traders of pulse crops in Canada, developed a strategy and action plan for 2008 to 2011 – “Pulse Innovation: Food and Nutrition Initiative” – describing four areas of strategic focus: research leadership; business development; capacity building; and, knowledge transfer through consumer gatekeepers. The assessment of opportunities for health claims is part of the action plan to address these areas of strategic focus (Pulse Canada, 2007).

To initiate the assessment of opportunities for health claims, in early 2007, Pulse Canada conducted two critical reviews on pulses and health: pulses and cardiovascular disease (Vanstone, 2007); and pulses and diabetes (BDSK Consulting, 2007). Both critical reviews were evaluated by an independent consultant (Johnson, 2007) who made conclusions and recommendations for moving forward on health claims in the United States.

In December 2007, the Canadian Health Food Association (CHFA) provided funding to Cantox Health Sciences International (Cantox) to conduct a “case study”. The case study was the last task of a four-task project funded by CHFA and carried out by Cantox. Tasks 1 to 3 culminated into a comprehensive report that summarized the health claim management frameworks and health claim substantiation requirements in five jurisdictions – Australia/New Zealand, Canada, the European Union (EU), Japan, and the United States (US). Pulse Canada's existing body of evidence related to heart disease and diabetes was chosen as the subject of the case study. The purpose of the case study was to provide an analysis of the extent to which an existing body of evidence (Pulse Canada's) met pre-market health claim substantiation information requirements in 3 jurisdictions – Canada, the US, and the EU – and to identify and describe the information gaps in terms of the nature of the additional evidence required.

## 1.2 Pulses

Pulses are edible seeds of leguminous plants and include dry beans (*e.g.*, kidney beans, lima beans), dry peas (*e.g.*, split peas), chickpeas, and lentils (Food and Agriculture Organization, 2001). According to the Food and Agriculture Organization, the term pulses is reserved for crops solely harvested for the dry grain. As such, the following are excluded from the definition of pulses: 1. green beans and green peas since they are considered vegetable crops; 2. crops mainly grown for oil extraction such as soybeans and peanuts; and, 3. crops exclusively grown for sowing such as clovers and alfalfa (Food and Agriculture Organization, 1994).

Pulses contain many healthful components. The estimated order of their importance is soluble dietary fibre, plant protein, oligosaccharides, isoflavones, phospholipids and fatty acids, phytosterols, saponins, and others (vitamins, minerals, antioxidants, phytates, tannins) (Anderson and Major, 2002).

## 1.3 Heart Disease

Heart disease, more correctly termed coronary heart disease (CHD), is one of the categories of cardiovascular disease (CVD); other categories include cerebrovascular disease and peripheral arterial disease (Mensink *et al.*, 2003). A main factor in the etiology of CVD (and CHD) is atherosclerosis – a narrowing of the arteries (Mensink *et al.*, 2003). Tobacco use, physical inactivity and an unhealthy diet (*e.g.*, high in total fat and saturated fat, high in dietary cholesterol, low in dietary fibre) can lead to atherosclerosis (Anderson and Major, 2002).

According to the World Health Organization, CVD is the number one cause of death globally, representing 30% of all global deaths (World Health Organization, 2008). Most CVD/CHD deaths are preventable through lifestyle alteration measures such as avoidance of cigarette smoking, physical activity, and diet (Anderson and Major, 2002).

### 1.3.1 Measurable Endpoints

Risk of CHD can be assessed by evaluating clinical endpoints such as myocardial ischemia (inadequate flow of blood to the heart) (Thomas, 1997), myocardial infarction (heart attack) (Thomas, 1997), atherosclerosis (cholesterol-lipid-calcium deposits in arterial linings) (Thomas, 1997), or cardiovascular death, or by measuring surrogate endpoints as substitutes of clinical endpoints such as Total Cholesterol (TC) and/or LDL Cholesterol (LDL-C); LDL-C is considered to have greater specificity over TC as a predictor of CHD risk (Tardif *et al.*, 2008). Since lowering of HDL Cholesterol is in and of itself an independent risk factor for CHD, its assessment is also recommended (Mensink *et al.*, 2003).

## 1.4 Diabetes

In the US and Canada, the prevalence of Type 2 diabetes is estimated at 7.9% (Harris *et al.*, 1998; Mokdad *et al.*, 20003) and 5.8% (Health Canada, 1999), respectively. Type 2 diabetes is associated with microvascular complications (*e.g.*, nephropathy, retinopathy and neuropathy) (American Diabetes Association, 1999; Aiello *et al.*, 1998; Mayfield *et al.*, 1998) and macrovascular complications (*e.g.*, cardiovascular disease) (Couthinho *et al.*, 1999; Smith *et al.*, 2002). Related to the latter, individuals with Type 2 diabetes are at a four-fold greater risk of myocardial infarction, stroke and death from CVD than those without it.

Prediabetes occurs when individuals have blood glucose levels that are elevated but not quite at the level that defines a diabetes diagnosis. People with these elevated levels, called impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), are at increased risk for developing diabetes and its complications over time (Canadian Diabetes Association, 2008a). Rising glucose levels in prediabetes can be reduced to normal levels, often without medication, by simple lifestyle modifications, including exercise, and a healthy, low-fat meal plan (Canadian Diabetes Association, 2008a).

### 1.4.1 Measurable Endpoints

Measurable endpoints to assess the regulation of blood glucose levels in humans (with Type 1 or Type 2 diabetes, or, at risk of developing Type 2 diabetes), include fasting and/or post-prandial blood glucose; fasting and/or post-prandial blood insulin; area under the curve for blood glucose and/or blood insulin; oral glucose tolerance test; or, more long-term indicators of blood glucose control (glycated haemoglobin – HbA1c).

Although it is believed that Type 1 diabetes is not preventable (Canadian Diabetes Association, 2008b), researchers have nevertheless shown an association between low glycemic index foods and a lower risk for developing both Type 1 and Type 2 diabetes, as compared to high glycemic index foods (Salmeron *et al.*, 1997a, b; Seewi *et al.*, 1999). Measurement of a food's glycemic index is thus an additional outcome measure, albeit a controversial one, to study the association of a food and its effect on glycemic control/risk of developing diabetes.

## 2.0 METHODS

Pulse Canada provided Cantox with 1. two critical reviews - pulses and heart disease (Vanstone, 2007), and pulses and diabetes (BDSK Consulting, 2007); 2. an independent consultant's review and opinions pertaining to the body of evidence on pulses and heart disease/diabetes with conclusions and recommendations for health claim opportunities in the United States (the consultant was given the two critical reviews as a starting point and additionally supplemented his report by retrieving more recent clinical studies) (Johnson, 2007);

and, 3. original copies of the primary literature (intervention and observational studies) on pulses and heart disease; the primary literature on pulses and diabetes was not made available.

The methodological quality of relevant studies (human studies) determines the adequacy of a body of evidence for health claim substantiation. It is thus an important element of health claim substantiation. Methodological quality can be evaluated using a tool – a study quality appraisal tool – which is essentially a checklist of factors that, if unaccounted for, could bias the research results. The factors selected for inclusion in a quality appraisal tool; the weight (*i.e.*, score) assigned to each factor in a tool; the method of scoring the totality of factors; and, the overall quality rank assigned to a study based on its overall score are subjective decisions. As such, transparency of the quality appraisal process is paramount. Upon a preliminary review of the agreement in quality appraisal between the authors of the critical reviews and the independent consultant (Johnson, 2007), differences were apparent; as such, Cantox carried out an independent evaluation of study quality on the primary literature, if it was available. The primary literature was only available for pulses and blood cholesterol/heart disease and not for pulses and diabetes. Quality appraisal was therefore not carried out for the latter; see Appendix 1 for the study quality appraisal tool used by Cantox.

Cantox's evaluation of the totality of evidence on pulses and blood cholesterol/heart disease was solely based on human intervention studies. Due to time constraints, observational studies were not assessed. Moreover, additional publications retrieved by Johnson (2007) (Pulses and heart disease: Pittaway *et al.*, 2006; Finley *et al.*, 2007; Winham *et al.*, 2007; Pulses and diabetes: Finley *et al.*, 2007; Winham *et al.*, 2007) were considered in a minor way since the original publications were not available at the time of assessment.

Health claim applications in Canada, the EU, and the US require information on safety, quality assurance and efficacy; see Table 5. Without proof of efficacy (even though safety and quality assurance are approved) a health claim application is meaningless and as such, Cantox focused its efforts on assessing the efficacy of pulses. Of the different components to evaluate for efficacy (see Table 5), statistical significance (or probability) and consistency are useful to assess initially since lack of support in these variables decreases the likelihood of a successful health claim application. Consistency assesses the degree of agreement across the body of evidence based on whether the food causes a favourable effect (*i.e.*, the direction of effect), regardless of statistical significance. Statistical significance/probability assesses whether there exists a statistically significant relationship between the food and the health effect. Cantox attempted to make inferences on these two variables as much as possible, rating the strength of agreement in one or both of these variables based on the totality of evidence on the food and health effect. Agreement was rated as high if there was 70% or more agreement among the studies; moderate if there was 51 to 69% agreement among studies; and, low, if agreement was 50% or less. Agreement could be in a favourable or unfavourable direction and as such, the agreement was qualified based on whether it was in a favourable or unfavourable direction.

Information gaps in the body of evidence on pulses and heart disease/diabetes with respect to meeting health claim substantiation requirements for efficacy, safety, and quality assurance, in Canada, the EU, and the US, were based on requirements for disease risk reduction claims *i.e.*, risk reduction claims in Canada; Article 14 claims in the EU; and unqualified, FDA-authorized health claims in the US.

## **3.0 RESULTS**

### **3.1 Pulses and Blood Cholesterol/Heart Disease**

#### **3.1.1 Literature Selection**

Pulse Canada retrieved 348 publications on pulses and blood cholesterol/heart disease using five databases (Medline, Cochrane Library, Agricola, Embase, CINAHL) and the following keywords: pulses, legumes, lentils, beans, peas, chickpeas, cholesterol, homocysteine, cardiovascular disease. No date limitation was imposed on the search and only English publications were retrieved.

The number of publications determined as relevant after a title-filtering and abstract/full-text filtering was 130, 40 of which were primary human studies (23 intervention studies and 17 observational studies); the remaining relevant publications were animal studies (n=40); *in vitro* studies (n=3); and meta-analyses or reviews (n=47). Included in the inclusion criteria during filtering was the administration of pulses (as a single type or as a combination of pulses) and the measurement of a relevant health outcome – blood lipids for intervention studies (TC, LDL-C, HDL-C, Triglycerides or TAG), and clinical endpoints for observational studies (death from CHD, myocardial infarction, *etc.*). For further details on the search and filtering criteria, see Pulse Canada's critical review (Vanstone, 2007).

Due to time limitations and the higher weight given to intervention studies over observational studies in health claim substantiation across the 3 jurisdictions (Canada, EU, US), only the intervention studies were evaluated by Cantox in a detailed manner. Of the 23 intervention studies selected as relevant by Pulse Canada, 8 were excluded for evaluation and quality appraisal by Cantox due to: inadequate study duration (*i.e.*,  $\leq 3$  weeks) (Dubois *et al.*, 1993); co-administration of pulses with other foods/food components that could affect blood cholesterol (Jarvi *et al.*, 1999; Simpson *et al.*, 1981; McAuley *et al.*, 2002; Jang *et al.*, 2001; Gardner *et al.*, 2005; Appel *et al.*, 2005); and, lack of administration of pulses to subjects (subjects given green beans) (Tjokroprawiro *et al.*, 1983).

#### **3.1.2 Study Quality Appraisal and Inter-Rater Agreement**

Fifteen of 23 studies remained for quality appraisal. Of the 15 studies appraised for study quality using the tool in Appendix 1, 9 studies received an inadequate quality appraisal score

(five or less) while 6 received an adequate study quality appraisal score (6 or more). Therefore, six of the original 23 studies qualified for the evaluation of efficacy; see studies that received a score of 6 or more in Table 1 using Cantox's quality appraisal system.

Assuming that studies receiving a 6 or greater quality score (Cantox system), or a (+) or (∅) score (Pulse Canada and consultant), would be included for evaluation of efficacy, the inter-rater agreements were 9/15 (60%) between Cantox and Pulse Canada (Vanstone) (*i.e.*, of 15 studies, the two parties agreed on inclusion or exclusion for 9 studies, or 60% of the time); 9/11 (82%) between Cantox and the consultant (Johnson); and, 6/11 (55%) between Pulse Canada and the consultant (Johnson); see Table 1.

<b>Table 1 Results of Quality Appraisal of 15 Intervention Studies on Pulses and Blood Cholesterol</b>			
Reference	Cantox's Quality Appraisal Score (0 to 10)	Pulse Canada's Quality Appraisal Rank (+,∅,-) <sup>1</sup>	Consultant's (Johnson) Quality Appraisal Rank (+,∅,-) <sup>1</sup>
Anderson <i>et al.</i> , 1984	8	-	+
Anderson <i>et al.</i> , 1990	6	∅	∅
Cobiac <i>et al.</i> , 1990	7	-	∅
Fruhbeck <i>et al.</i> , 1997	6	-	+
Mackay and Ball, 1992	8	∅	∅
Oosthuizen <i>et al.</i> , 2000	7	-	∅
Anderson, 1987	2	∅	+
Birketvedt <i>et al.</i> , 2002	0	∅	NE <sup>2</sup>
Contaldo <i>et al.</i> , 1983	0	-	NE
Duane, 1997	3	-	∅
Jenkins <i>et al.</i> , 1983	3	-	-
Karlstrom <i>et al.</i> , 1987	3	-	NE
Mathur <i>et al.</i> , 1968	0	-	-
Nervi <i>et al.</i> , 1989	4	-	NE
Shutler <i>et al.</i> , 1989	3	-	-

<sup>1</sup>(+) indicates that issues of scientific quality have been adequately addressed; (∅) indicates that some uncertainty exists as to whether issues of scientific quality have been adequately addressed; (-) indicates that issues of scientific quality have not been adequately addressed.

<sup>2</sup>NE: not evaluated

### 3.1.3 Synopses of Individual Studies and Evaluation of Totality of Evidence

Six studies of adequate quality (according to Cantox's study quality appraisal system) were summarized individually and as a group; see Tables 2 and 3.

Small sample sizes were used across all studies varying from 10 to 28 subjects. Most study populations were hypercholesterolemic (five of six studies) with one study (Fruhbeck *et al.*, 1997) using borderline hypercholesterolemic subjects. Studies were of short duration ranging

from 3 to 6 weeks. The majority of studies (four of six) had subjects maintain their usual diets while two studies (Mackay and Ball, 1992; Fruhbeck *et al.*, 1997) used low-fat diets. The type of pulses administered were beans in various forms: two of six studies administered canned beans (120g/day, 162g/day or 440g/day); two of six studies administered beans that were cooked from dry form (non-canned) (80g/day or 101g/day); and, two of six studies included a bean extract into common foods (90g/day processed field bean flour or 110g/day extruded dry beans).

Overall, there was low agreement for a statistically significant effect of pulses on LDL-C and TC reduction with 1 of 6 studies (17%) (Anderson *et al.*, 1984) and 3 of 6 studies (50%) (Anderson *et al.*, 1990; Fruhbeck *et al.*, 1997; Anderson *et al.*, 1984) showing a statistically significant favourable effect on these blood parameters, respectively. Consideration of 3 additional studies (Pittaway *et al.*, 2006; Finley *et al.*, 2007; Winham *et al.*, 2007) retrieved by Johnson (2007) did not change the statistical agreement for LDL-C but increased the statistical agreement for TC from low to moderate. For HDL-C, there was low agreement, in an unfavourable direction (*i.e.*, decrease in HDL-C), for a statistically significant effect of pulses. Inclusion of 1 of 3 studies (Finley *et al.*, 2007) retrieved by Johnson (2007), which showed a statistically significant reduction in HDL-C, did not change the level of agreement; see Appendix 2 and Tables 3 and 4.

For consistency (*i.e.*, direction of effect regardless of statistical significance), there was moderate agreement among studies in LDL-C reduction (favourable); high agreement for TC reduction (favourable); and moderate agreement for HDL-C reduction (unfavourable). Consideration of the additional studies retrieved by Johnson (2007) changed the level of agreement in LDL-C from moderate to high. There was no change in the level of agreement in TC, and the change for HDL-C could not be evaluated; see Appendix 2 and Tables 3 and 4.

Reference	Subjects	Design/Duration	Intervention	Statistically significant effect of pulses vs control (direction of effect)	Non-statistically significant effect of pulses vs control (direction of effect)	Comments
Mackay and Ball, 1992* *Not all group comparisons reported	Hyperchol (n=28)	R, C (run-in), Crossover (with oats) 6 wks	<u>80g/d cooked beans</u> in low-fat diet vs Low-fat run-in diet (4 wks)	HDL-C (10.4%↑)	TC (0.8%↓) LDL-C (0%) TAG (0.7%↓)	Total fiber sig diff: 29g (bean diet) vs 24g (run-in)
Anderson <i>et al</i> , 1990	Hyperchol (n=28)	R, C (run-in), Parallel 3 wks	<u>120g or 162g beans/d</u> (from canned pork and beans); single or divided doses in usual diet vs Usual diet run-in(1 week)	TC (10.4%↓) (all grps) TAG (14.5%↓) (162g/d, divided dose)	HDL-C (2 to 11.7% ↓) (all grps) LDL-C (7.3 to 10% ↓) (all grps)	Sig weight change not properly accounted for Total fiber sig diff: 21-23g (bean diet) vs. 13g (run-in)
Fruhbeck <i>et al</i> , 1997*  * Not all group comparisons reported	Borderline High Chol (n=20)	NR, C, Parallel 1 month	<u>90g/d processed field bean flour</u> ; divided doses in common foods; low-fat diet vs 90g/d control flour; divided doses in common foods; low-fat diet	TC (1.3%↓) HDL-C (16.7%↑) TAG (16.6%↓)	LDL-C (2.2%↓)	No sig diff in diet (including fiber)
Anderson <i>et al</i> , 1984* *not all grp comparisons reported	Hyperchol (n=10)	R, C (run-in), Parallel (with oats) 3 weeks	<u>115g/d dried beans</u> , cooked or in soup; usual diet vs. Usual diet run-in (7 days)	TC (18.6%↓) LDL-C (24.5%↓) HDL-C (12.7% ↓)	TAG (3.0%↓)	Sig weight change and diet differences (e.g., calories) not properly accounted for Total fiber sig diff: 44g (bean diet) vs 19g (control diet)

Study	Population	Design	Intervention	Comparison	Outcomes	Notes
Cobiac <i>et al</i> , 1990	Hyperchol (n=20)	R, C, Crossover Two 4-week treatments	440g can baked beans/d; usual diet vs 440g can spaghetti/d; usual diet	none	TC (0.5%↓) LDL (0.4%↓) HDL (3.2%↓) TAG (0.8%↑)	Total fiber sig diff: 22.5g (bean diet) vs 11g (control)
Oosthuizen <i>et al</i> , 2000	Hyperchol (n=22)	R, C, Crossover Two 4-week treatments	110g/d extruded dry beans; in baked products; usual diet vs Carbohydrate exchange in usual diet	Within grp (for both grps): HDL-C (7.3%↓ for control; 13.4%↓ for beans)	Within grp (for both grps): TC (0.5%↓ for C; 1.3%↑ for beans) LDL-C (0.2%↑ for C; 8.1%↑ for beans) TAG (9.2%↓ for C; 6.7%↑ for beans)	Sig diff in diet (plant protein, fat, cholesterol, carbohydrate) between grps not accounted for Total fiber sig diff: 24.6g (bean diet) vs 19.5g (control)
<b>TOTAL</b>	n/a	n/a	n/a	<b>TC↓: 3 studies</b> <b>LDL-C↓: 1 study</b> <b>HDL-C↓: 2 studies</b> <b>HDL-C↑: 2 studies</b>	<b>TC↓: 2 studies</b> <b>LDL-C↓: 3 studies</b> <b>HDL-C↓: 2 studies</b> <b>HDL-C↑: 0 studies</b>	n/a

<b>Table 3 Summary of Totality of Evidence on Pulses and Blood Cholesterol</b>	
<b>ITEM</b>	<b>RESULTS (n=6)</b>
Sample Sizes	10 to 28 subjects
Study Population	5/6 studies: hypercholesterolemic 1/6 studies: borderline hypercholesterolemic
Study Duration	3 to 6 weeks
Background Diet	4/6 studies: usual diet 2/6 studies: low-fat diet
Interventions	6/6 studies used beans: 2/6 canned (120 to 440g/d); 2/6 cooked (80 to 101g/d); 2/6 extracts into common foods
Agreement on Statistical Significance	<p>↓ LDL-C in 1/6 studies (dried beans) (17%): <u>Low agreement</u> for a favourable statistical effect</p> <p>↓ TC in 3/6 studies (50%): <u>Low agreement</u> for a favourable statistical effect</p> <p>↓ HDL-C in 2/6 studies (33%): <u>Low agreement</u> for an unfavourable statistical effect</p>
Agreement on Consistency (Direction of Effect) <sup>1</sup>	<p>↓ LDL-C in 4/6 studies (67%): <u>Moderate agreement</u> for a favourable direction of effect</p> <p>↓ TC in 5/6 studies (83%): <u>High agreement</u> for a favourable direction of effect</p> <p>↓ HDL-C in 4/6 studies (67%): <u>Moderate agreement</u> for an unfavourable direction of effect</p>

<sup>1</sup>Includes studies that showed statistical significance and statistical non-significance

## 3.2 Pulses and Glycemia/Diabetes

### 3.2.1 Literature Selection

Pulse Canada retrieved 163 publications from five databases (Pubmed, EMBASE, HealthSTAR, Cochrane library, CINAHL) using the following keywords: (pulses or beans or legumes or peas or lentils or chickpeas) and (glucose or insulin or diabetes or HbA1c or glycemia). No date limitation was imposed on the search and only English publications were retrieved. An inclusion criteria was applied to titles and the abstract/full-text. Among the inclusion criteria were healthy humans or humans with impaired fasting glucose, impaired glucose tolerance or diabetes (Type 1 or Type 2); acute (e.g., test meal) or non-acute pulse consumption; and, measure of relevant endpoints (blood/plasma/serum glucose or insulin or HbA1c); see BDSK Consulting, 2007.

Of the 163 publications originally retrieved, 82 were deemed relevant: 24 non-acute studies (endpoints: fasting glucose; fasting insulin; HbA1c- most relevant); 40 acute post-prandial

studies (endpoints: post-prandial peak levels of insulin or glucose; area under curve for glucose or insulin); and 18 glycemic index studies (endpoints: glycemic index). For further details on the search and filtering process, see BDSK Consulting, 2007.

### **3.2.2 Study Quality Appraisal**

#### *3.2.2.1 Non-acute studies*

Since the original publications were not available, Cantox did not independently evaluate the methodological quality of non-acute studies and relied on the quality appraisal scores assigned by the author of the critical review; see BDSK Consulting, 2007. Three of the 24 non-acute studies received a (-) score and were excluded from the evaluation, leaving 21 studies of (∅) or (+) quality.

#### *3.2.2.2 Acute studies (Postprandial and glycemic index)*

Since the original publications were not available, Cantox did not independently evaluate the methodological quality of acute studies and relied on the quality appraisal scores assigned by the author of the critical review; see BDSK Consulting, 2007. Since the author did not appraise the quality of acute studies, all studies used by the author were considered by Cantox.

### **3.2.3 Evaluation of Totality of Evidence**

#### *3.2.3.1 Non-Acute studies\**

\*See BDSK Consulting, 2007 for reference citations

Of 21 adequate quality studies, 11 studies reported the most reliable index of more long-term glycemic control – HbA1c (Anderson *et al.*, 1991; Chandalia *et al.*, 2000; Cho *et al.*, 2005; Giacco *et al.*, 2000; Jarvi *et al.*, 1999; Jenkins *et al.*, 1987a; Jenkins *et al.*, 1988; Karlstrom *et al.*, 1987; Kinmonth *et al.*, 1982; O’Dea *et al.*, 1989; Simpson *et al.*, 1981). Seven of these studies did not report a statistically significant change in HbA1c (Anderson *et al.*, 1991; Chandalia *et al.*, 2000; Cho *et al.*, 2005; Kinmonth *et al.*, 1982; Simpson *et al.*, 1981; Karlstrom *et al.*, 1987; O’Dea *et al.*, 1989); and, four reported statistically significant changes in HbA1c with pulse intake (in a favorable direction) for a within-group analysis rather than as a between-group comparison (pulses versus control) (Jarvi *et al.*, 1999; Jenkins *et al.*, 1987b; Jenkins *et al.*, 1988; Giacco *et al.*, 2000). Therefore, 4 of 11 studies (36%) showed a statistically significant effect, in a favorable direction, of pulse intake on HbA1c – a low agreement. Agreement on consistency was not ranked since data on the direction of change in HbA1c in the studies that did not report statistical significance was not available in the critical review nor were the original publications available; see Table 4.

### 3.2.3.2 *Acute studies – Postprandial studies\**

\*See BDSK Consulting, 2007 for reference citations

Fourty post-prandial studies were retrieved, four of which included data on two studies, therefore 44 studies were reviewed. Thirty-five of these 44 studies compared pulses to a control (e.g., a carbohydrate such as bread, pasta, potatoes, cereal, isolated beet fiber, isolated Brussel sprouts fiber). Of these 35 studies, all measured postprandial glucose, and 29 of 35 studies (83%) reported statistically significant reductions in post-prandial peak glucose or AUC compared to control – a high agreement, in a favorable direction. Of the 35 studies, 23 measured insulin, 17 (74%) of which reported a statistically significant reduction in post-prandial peak insulin or AUC compared to control – a high agreement, in a favorable direction. Agreement on consistency was not evaluated since statistical significance, a more difficult parameter to achieve, received a high level of agreement; see Table 4.

For both the post-prandial glucose and post-prandial insulin studies, less processed pulses (e.g., home-cooked pulses versus canned pulses, or whole pulses versus ground pulses) showed more favorable glycemic and/or insulinemic responses (*i.e.*, lower responses).

### 3.2.3.3 *Acute studies – Glycemic Index studies\**

\* See BDSK Consulting for reference citations

Eighteen glycemic index studies were retrieved, all of which were controlled. All 18 (100%) showed that pulses had a significantly lower glycemic index compared to the control (white bread, wholemeal bread, glucose, glucose and bread combined) – a high agreement, in a favorable direction. Agreement on consistency was not evaluated since statistical significance, a more difficult parameter to achieve, received a high level of agreement; see Table 4.

<b>Table 4 Summary of Level of Agreements for Totality of Evidence on Pulses and Blood Cholesterol/Glycemia</b>			
Type of study	Endpoint	Statistical Agreement (in a favorable direction) <sup>1</sup>	Consistency (Agreement on direction of effect - in a favorable direction) <sup>1</sup>
<i>Blood Cholesterol/Heart Disease<sup>2</sup></i>			
Intervention studies	LDL-C	Low	High
Intervention studies	TC	Moderate	High
<i>Glycemia/Diabetes</i>			
Non-Acute Intervention Studies	HbA1c	Low	n/a
Acute Intervention Studies	Post-prandial glucose or AUC	High	n/a
Acute Intervention Studies	Post-prandial insulin or AUC	High	n/a
Acute Intervention Studies	Glycemic index	High	n/a

<sup>1</sup>Agreement was rated as high if there was 70% or more agreement among the studies; moderate if there was 51 to 69% agreement among studies; and, low, if agreement was 50% or less.

<sup>2</sup>Agreement includes studies retrieved by Johnson (2007)

## 4.0 HEALTH CLAIM SUBSTANTIATION REQUIREMENTS

As Table 5 indicates, all three jurisdictions require information pertaining to safety, quality assurance, and efficacy, in a health claim application on a diet-disease relationship. Information on safety and quality assurance to be included in an application are largely dependent on the degree of processing to the food and/or the novelty of the bioactive included in the food (if it is the subject of the health claim). For efficacy, the breadth of topics to be addressed for each jurisdiction are listed in the table; these topics do not change with the subject of the health claim – they must all be addressed regardless of the degree of processing to the food/bioactive or its novelty.

<b>Table 5 Requirements for Health Claim Substantiation in Canada, the EU, and the US</b>			
CRITERION	CA	EU	US
Safety <sup>1</sup>	X	X	X
Quality Assurance <sup>2</sup>	X	X	X
Efficacy			
Effective intake/dose-response	X	X	X
Statistical significance of outcome	X	X	X

<b>Table 5 Requirements for Health Claim Substantiation in Canada, the EU, and the US</b>			
<b>CRITERION</b>	<b>CA</b>	<b>EU</b>	<b>US</b>
Specificity of effect	n/a	X	n/a
Alternative explanations/independence of association	n/a	X	X
Physiological relevance of magnitude of outcome	X	X	n/a
Consistency of findings across studies	X	X	X
Sustainability of effect	X	X	n/a
Biological plausibility	n/a	X	n/a
Whether effective intake can reasonably be achieved under conventional use	X	X	X
Relevance of studies' findings to population/dietary patterns/target group	X	X	X

<sup>1</sup>Information pertains to the toxicological safety (data from animal tests; data from adverse effects in clinical studies) and nutritional/dietary safety of the food (data from dietary intake modeling; information on interactions of food with diet, nutrients, drugs). Each jurisdiction requires information on safety, however, the scope of information provided in a health claim applications varies depending on 1. the degree of modification to the food/bioactive (*i.e.*, its novelty); and 2. whether a safety evaluation has or will be conducted on the food (*e.g.*, food additive application; novel food approval; generally recognized as safe- GRAS)

<sup>2</sup>All jurisdictions require information to justify a proxy measure (and its analytical method) of food exposure. Other requirements to be included in a health claim application vary between jurisdictions and depend on 1. the degree of modification to the food/bioactive (*i.e.*, its novelty) and 2. whether a safety evaluation has or will be conducted on the food (*e.g.*, food additive application; novel food approval; generally recognized as safe-GRAS).

## **5.0 CONCLUSIONS AND RECOMMENDATIONS**

Statistical significance depends on statistical power and statistical power is often limited in food/nutrition interventions due to small sample sizes and a low to moderate magnitude of effect of the food/nutrient. The majority of intervention studies on pulses and blood cholesterol/heart disease used small sizes. Moreover, the magnitude of effect of pulses on LDL-C appears to be low; the effect on TC is higher than on LDL-C. Small sample sizes and a low magnitude of effect are plausible explanations for the low and moderate agreements on statistical significance for LDL-C and TC, respectively. The level of agreement related to the direction of effect of pulses on LDL-C and TC – high agreements in a favourable direction – appear promising; however, the low magnitude of effect of pulses on LDL-C, the most specific biomarker for risk of

CHD, limit the strength of support for an effect of pulses. Before a sound judgement on the potential for a health claim to be substantiated on pulses and blood cholesterol/heart disease can be made, the observational studies retrieved by Vanstone (2007) need to be reviewed. Although observational studies are assigned a lower weight as compared to human intervention studies in the evaluation of health claims, they typically have large sample sizes and, if analyzed well, can control for many confounding variables. Evaluation of relevant observational studies is therefore recommended as a next step. If there is interest to expand the evidence base on pulses and blood cholesterol with additional clinical trials, research elements recommended for consideration are included in Appendix 3.

A review of the non-acute studies on pulses and diabetes do not provide support for the effect of pulses on the reduction of the most reliable marker of long-term glycemic control (HbA1c). Agreement on statistical significance (*i.e.*, for pulses to have a statistically significant effect on the reduction of HbA1c levels) was ranked as low - an unfavourable finding. However, consistency in the direction of effect and the magnitude of effects were not evaluated. These are recommended as next steps to confirm the strength of association (or lack thereof) between pulses and HbA1c.

A review of the acute post-prandial and glycemic studies on pulses provides support for a positive effect of pulses. Agreements on statistical significance for pulses to have a statistically significant effect on the reduction of blood glucose, blood insulin, or glycemic index were ranked as high – favourable findings; consistency in the direction of effect was not evaluated since agreement on statistical significance was high. There is therefore sufficient evidence to consider a health claim application on pulses and the management of glucose/insulin levels whether or not mention of reduction in diabetes risk is additionally included in the claim wording. If the latter is considered (*i.e.*, a disease risk- reduction claim), the literature would have to exclude studies which included Type 1 diabetics in the study population (*e.g.*, Jenkins *et al.*, 1980; Torsdottir *et al.*, 1986) since it is not unequivocally believed that Type 1 diabetes is preventable. The relevance of glycemic index as a reliable biomarker for a health outcome related to glycemic control or diabetes risk needs to be investigated before a decision is made on the usefulness of glycemic index studies.

In addition to disease risk reduction claims, Canada, the EU, and the US have categories of claims (not all of which are classified as health claims) that do not make mention of disease but rather are intended to support/promote body structures or functions – *i.e.*, structure/function claims in Canada, Article 13 health claims in the EU, and structure/function health claims in the US; see Appendix 4. These claim categories can additionally be considered for pulses.

Structure/function claims in the US do not require approval by the US Food and Drug Administration (FDA) and depending on the degree of change in body function/structure, structure/function claims may also not require approval from Health Canada. Article 13 claims do require approval by the European Food Safety Authority (EFSA). A recent European

Commission Regulation (European Parliament, 2008) requires Article 13 claims to follow the scientific and technical guidance developed by EFSA for Article 14 claims (European Food Safety Authority, 2007). Whether or not approval is required for structure/function claims, the claims must be truthful and non-misleading, and thus a substantiation dossier that evaluates the totality of evidence, favourable and unfavourable, on the food-health relationship, is recommended for any or all claim categories.

Qualified health claims, based on a lower scientific certainty than unqualified health claims, are also an option in the U.S.; however, Dr. Steven Sundlof, the new Director of the FDA Center for Food Safety and Applied Nutrition, recently stated that the Center was told directly, during budget approvals, that they were to spend no effort or manpower on qualified health claims this year (Cantox, 2008).

Health claim applications in Canada, the EU, and the US require information on safety, quality assurance and efficacy. Information pertaining to safety and quality assurance to be included in a health claim application is largely dependent on the degree of processing applied to the food/bioactive and thus the novelty of the food/bioactive, and whether the regulatory agency has conducted a review of the food's/bioactive's safety in another application (e.g., food additive application; novel food application; generally recognized as safe application). It is thus difficult to outline specific requirements on efficacy and quality assurance without knowledge of the subject of the health claim – *i.e.*, whole or processed pulses.

Efficacy requirements are not dependent on the degree of processing to the food/bioactive. As such, a health claim application on pulses would require addressing the following components related to efficacy: effective intake/dose-response; statistical significance; specificity of effect; alternative explanations/independence of association; physiological relevance of magnitude of outcome; consistency of findings across studies; sustainability of effect; biological plausibility; whether the effective intake can reasonably be achieved under conventional use of the food; relevance of studies' findings to the population.

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**APPENDIX 1**

**QUALITY APPRAISAL TOOL FOR INTERVENTION AND OBSERVATIONAL STUDIES**

ITEM	QUESTION	YES	NO
		Circle the Score	Circle the Score
Inclusion/Exclusion Criteria	Were inclusion and/or exclusion criteria for study participation reported?	1	0
Randomization <sup>a</sup>  Comparison Group <sup>b</sup>	Were the subjects randomly allocated to a group?  Was at least one comparison group included in the statistical analysis of the effect of food exposure on the health outcome(s)?	2	0
Sample Size	Was the sample size justified (e.g. a power calculation)?	1	0
Exposure	Was the method used to analyze the food** (intervention studies) or to calculate food** intake (observational studies) reported?	1	0
Health Outcome	Was the method used to measure the health outcome/biomarker reported?	1	0
Background Diet	Was the background diet stated?	2	0
Statistical Analysis	If a comparison/control group existed, was a between-group statistical analysis of the health outcome conducted?	2	0
	Were key confounders accounted for in the statistical analysis?  Key confounders considered: Baseline blood lipid levels Weight loss Background diet Washout period (crossover study)	0	-1 (one key confounder not accounted for)  -2 (two key confounders not accounted for)  -3 (three or more key confounders not accounted for)
Adequate (Score of 6 or more): <input type="checkbox"/>  Inadequate (Score of 5 or less): <input type="checkbox"/>		TOTAL SCORE (maximum of 10):	

<sup>a</sup>For intervention/experimental studies only.

<sup>b</sup>For observational studies only.

\*\* "food" refers to a food group; a food; a component of a food.

**APPENDIX 2**

**CHANGES TO STATISTICAL AGREEMENT AND CONSISTENCY WITH THE INCLUSION  
OF ADDITIONAL STUDIES RETRIEVED BY JOHNSON (2007)**

	<b>Decrease in LDL-C</b>	<b>Decrease in TC</b>	<b>Decrease in HDL-C</b>
<b>Statistical Significance</b>			
Number of studies	1/6 studies (in critical review) + 2/3 studies (retrieved by Johnson) = 3/9 studies (33%)	3/6 studies (in critical review) + 3/3 (retrieved by Johnson) = 6/9 studies (67%)	2/6 studies (in critical review) + 1/3 (retrieved by Johnson) = 3/9 studies (33%)
Agreement on Statistical Significance	<u>Low agreement</u> for a statistically significant reduction in LDL-C	<u>Moderate agreement</u> for a statistically significant reduction in TC	<u>Low agreement</u> for a statistically significant reduction in HDL-C
<b>Consistency (Direction of Effect)</b>			
Number of studies	4/6 studies (in critical review) + 3/3 studies (retrieved by Johnson) = 7/9 studies (78%)	5/6 studies (in critical review) + 3/3 studies (retrieved by Johnson) = 8/9 studies (89%)	n/a <sup>1</sup>
Agreement on Consistency	<u>High agreement</u> for a statistically significant reduction in LDL-C	<u>High agreement</u> for a statistically significant reduction in TC	n/a <sup>1</sup>

<sup>1</sup>Johnson (2007) did not report direction of changes to HDL-C in two studies thus evaluation of the change in this variable was not feasible

**APPENDIX 3**

**RECOMMENDATIONS FOR CLINICAL TRIALS ON PULSES**

Recommendation	Examples / Additional Comments
Use a minimally biased study design	R, C, Parallel or Crossover
Ensure study population is relevant to the general population or target group of the claim	Blood cholesterol studies: Healthy normocholesterolemic or Hypercholesterolemic for studies on blood cholesterol; hospitalized subjects not relevant, for example
Carry out a sample size calculation to ensure study is appropriately powered to detect statistical significance	Blood cholesterol studies: Consider estimation based on an effect of 5% lowering in LDL above control
Investigate independent effect of pulses	Ensure the effect of pulses are solely investigated and therefore pulse intake should be the main difference between treatment and control diets
Consider whether intake studied could be reasonably achieved under conventional use	1 serving cooked beans is 175ml or 130g
Ensure an adequate study duration	Studies of at least 3-week duration are the minimum
Measure endpoints that are biologically valid with a methodologically valid analytical procedure	Blood cholesterol studies: LDL, TC, HDL, TAG Diabetes: HbA1c, fasting glucose, fasting insulin
Develop an appropriate inclusion/exclusion criteria for subject selection prior to study recruitment	Blood cholesterol studies: Include cut-off values for TC, LDL, TAG, blood pressure; lipid-lowering medications; condition that affects glucose or lipid metabolism; myocardial infarction, smokers, alcohol abusers, etc
Use a usual or low-fat diet; consider a lead-in period if low-fat diet used	Ensure between-group comparability in calorie and macronutrient profiles; total fiber and soluble fiber is expected to differ
Assess background diets using validated tools	Food frequency questionnaires are more reliable than diet records or 24-hour food recalls
Consider effect of confounders in study design/statistical analysis	Blood cholesterol studies: Confounders include inclusion of a washout (crossover studies) period; weight change; baseline lipid levels ; dietary intakes; attrition
Monitor compliance	Have subjects return unused product

**APPENDIX 4**

**SPECIFIC CLAIM DEFINITIONS FOR CANADA, THE EU, AND THE US**

	Canada: Structure/Function Claims <sup>1</sup>	EU: Article 13 Claims <sup>2</sup>	US: Structure/Function Claims <sup>3</sup>
Classified as a Health Claim	Yes	Yes	No
Definition	Relate to modifying, restoring, or correcting an organic function or body structure <u>beyond</u> normal growth and development or maintenance of good health.	Describe the role of a nutrient or other substance in growth, development and the functions of the body; or psychological and behavioural functions; or slimming or weight control; or reduction in the sense of hunger; or an increase in the sense of satiety; or to the reduction of the available energy from the diet.	Describe the role of a nutrient or dietary ingredient intended to affect normal structure or function in humans. In addition, they may characterize the means by which a nutrient or dietary ingredient acts to maintain such structure or function. Structure/function claims may also describe a benefit related to a nutrient deficiency disease (like vitamin C and scurvy), as long as the statement also tells how widespread such a disease is in the United States.
Approval by regulatory body required	Yes or No – If the change in body structure/function is within normal physiological parameters, no approval is required, since the claim is not considered a drug claim; however, if the change is beyond what is considered “normal”, the claim is a drug claim and requires approval from Health Canada.	Yes - A formal substantiation dossier is required for submission and approval by the European Food Safety Authority; see European Food Safety Authority, 2007 for guidance on preparing the submission.	No - The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims; they are not pre-approved by the FDA but must be truthful and not misleading

<sup>1</sup> See Health Canada, 2002; <sup>2</sup> See European Parliament, 2006; <sup>3</sup> See U.S. FDA, 2002