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Pulses and Heart Disease/Diabetes: Gap Analysis for Health Claim Substantiation



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Overview of Presentation

- **Background**
- **Definition of pulses**
- **Pulses and blood cholesterol/heart disease**
- **Pulses and diabetes**
- **Gap analysis**
- **Recommendations**

Background

- **Included in Nutri-Net’s original proposal for Cantox to conduct an international comparison of health claim management was a “case study”**
- **Pulse Canada’s “Pulse Innovation Project” includes an assessment of opportunities for health claims**
- **Pulse Canada’s two critical reviews on pulses and cardiovascular disease and diabetes (2007) were chosen as the “case study” to assess information gaps for health claim substantiation**

Health Claim Categories of Relevance

- **Assessment of Pulse Canada's evidence was based on the information requirements for:**
 - CA: Health Canada-authorized claims that require a regulatory amendment for use on foods (e.g., reduction of disease risk)
 - EU: EFSA-authorized Article 14 claims related to reduction of disease risk
 - US: FDA-authorized health claims related to reduction of disease risk

Definition of Pulses

- **Edible seeds of leguminous plants: dry beans (e.g., kidney, lima), dry peas (e.g., split pea), chickpeas, lentils**



Definition of Pulses cont'd

- The term “pulses”, as used by the FAO (Food and Agriculture Organization), is reserved for crops harvested solely for the dry grain
 - Green beans and green peas (considered vegetable crops) excluded
 - Crops mainly grown for oil extraction (oilseeds like soybeans and peanuts) excluded
 - Crops used exclusively for sowing (clovers, alfalfa) excluded

Pulses' Healthful Components

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

Pulses' Mechanism of Action

- **Blood Cholesterol/CHD**
 - Decreased re-absorption of bile acids
 - Fermentation of soluble fibers in the colon with production of short chain fatty acids contributing to decreased hepatic cholesterol synthesis
- **Blood Cholesterol/CHD and Diabetes**
 - Variations in hormone concentrations: insulin, glucagons, glucocorticoids, thyroid hormones

Coronary Heart Disease

- **Coronary heart disease (CHD) is one of the categories of cardiovascular disease (CVD); other categories include cerebrovascular disease and peripheral arterial disease**
- **Tobacco use, physical inactivity, and an unhealthy diet can lead to atherosclerosis (narrowing of arteries), which can lead to cardiovascular disease such as CHD**

Public Health Importance of CVD/CHD

- **According to the World Health Organization, CVD is the number one cause of death globally representing 30% of all global deaths**
- **CHD is the leading cause of death in Canada and the United States**

Measurable Endpoints for Risk of CHD

- **Disease endpoints**
 - Incidence of coronary events (myocardial infarction, ischemia), cardiovascular death, coronary artery disease, atherosclerosis
- **Surrogate endpoints**
 - Total Cholesterol (TC) and LDL Cholesterol (LDL)
 - LDL cholesterol is considered to have greater specificity over TC

Pulse Canada's Literature Retrieval and Selection

- **Five databases searched for literature on pulses and blood cholesterol/CHD**
- **348 publications retrieved by Pulse Canada**
 - 130 publications deemed relevant
 - 40 primary human studies
 - 17 observational studies
 - 23 intervention studies
 - Measured endpoints: Total Cholesterol (TC), LDL, HDL, TAG
 - 6 intervention studies of acceptable quality (by Cantox)

Evidence on Pulses and Heart Health

	Subjects	Design/Duration	Intervention	Stat sig effect of pulses vs control	Non-stat sig effect of pulses vs control	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 (10.4%) ↓ LDL/HDL ratio (6.6%)	TC <u>LDL</u> TAG	Total fiber sig diff: 29g (bean diet) vs 24g (run-in)
Anderson et al, 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 (2 to 11.7% ↓) (all grps) <u>LDL</u> (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 et al, 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 (16.7%) ↓TAG (16.6%)	<u>LDL</u> (2.2% ↓)	No sig diff in diet (including fiber)

Evidence on Pulses and Heart Health

	Subjects	Design/ Duration	Intervention	Stat sig effect of pulses vs control	Non-stat sig effect of pulses vs control	Comments
Anderson et al, 1984* *not all grp comparisons reported	Hyperchol (n=10)	R, C (run-in), Parallel (with oats) 3 weeks	<u>101g/d dried beans</u> , cooked or in soup; usual diet vs Usual diet run-in (7 days)	↓ TC (21.7%) ↓ <u>LDL</u> (24.5%)	HDL (↓) TAG (↓)	Sig weight change and diet differences (e.g., calories) not properly accounted for Total fiber sig diff: 44g (bean diet) vs 19g (control diet)
Cobiac et al, 1990	Hyperchol (n=20)	R, C, Crossover Two 4-week treatments	<u>440g can baked beans/d</u> ; usual diet vs 440g can spaghetti/d; usual diet	none	TC <u>LDL</u> HDL TAG	Total fiber sig diff: 22.5g (bean diet) vs 11g (control)
Oosthuizen et al, 2000	Hyperchol (n=22)	R, C, Crossover Two 4- week treatments	<u>110g/d extruded dry beans</u> ; in baked products; usual diet vs Carbohydrate exchange in usual diet	Within grp (for both grps): ↓HDL	Within grp (for both grps): TC <u>LDL</u> TAG	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)

Evidence on Pulses and Heart Health

ITEM	RESULTS (n=6)
Sample Sizes	10 to 28 subjects
Study Population	5/6 hyperchol 1/6 borderline high chol
Study Duration	3 to 6 weeks
Background diet	4/6 usual diet 2/6 low-fat diet
Interventions	6/6 beans: 2/6 canned (120 to 440g/d); 2/6 cooked (80 to 101g/d); 2/6 extracts into common foods
Statistical Significance	↓ LDL in 1/6 (dried beans); non- significant favorable trend seen in 2/6 (canned beans; bean flour) ↓ TC in 3/6; 1/3 did not decrease HDL (bean flour)
Consistency	Low

Diabetes: Public Health Importance

- In the U.S. and Canada, the prevalence of type 2 diabetes is estimated at 7.9% and 5.8%, respectively
- Type 2 diabetes is associated with microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (cardiovascular disease) complications
- Recent analyses show that after adjustment for other cardiovascular disease (CVD) risk factors, there is a significant positive association between plasma glucose and CVD risk; relationship is strongest for 2-hour post-prandial plasma glucose
- Individuals with type 2 diabetes are at a 4-fold greater risk of myocardial infarction (heart attack), stroke and death from CVD than those without it

Pulse Canada's Literature Retrieval and Selection

- **Five databases searched for literature on pulses and risk of type 1 or type 2 diabetes (assessed by glycemia, insulinemia, and HbA1c – glycated hemoglobin)**
- **163 publications retrieved**
 - 82 publications (all in humans) deemed relevant
 - 24 non-acute intervention studies
 - Endpoints: fasting glucose; fasting insulin; glycated hemoglobin (HbA1c)
 - 40 acute (i.e., post-prandial) studies
 - Endpoints: Post-prandial peak levels of insulin and glucose; area under curve (AUC) for glucose and insulin
 - 18 glycemic index studies
 - Endpoints: glycemic index; insulin index

Evidence on Pulses and Diabetes

- **24 non-acute clinical studies**
 - 3/24 of adequate quality
 - Chickpeas in non-diabetics (Nestel *et al.*, 2004)
 - Beans in non-diabetics (Fruhbeck *et al.*, 1997)
 - Beans and peas in diabetics (Karlstrom *et al.*, 1987)
 - FDA states that studies in “diseased individuals” are acceptable if: mechanism of effect for mitigation/treatment in diseased populations is the same as mechanism of risk reduction in non-diseased populations; and the “substance” affects these mechanisms in the same way
 - Only Fruhbeck *et al.* (1997) measured HbA1c (gold standard measure for long-term glycemic control) and no significant between-group differences observed
 - Significant between-group effects seen on fasting glucose and insulin (Fruhbeck *et al.*, 1997) and post-prandial glucose (Karlstrom *et al.*, 1987)

Evidence on Pulses and Diabetes

- **44 acute post-prandial studies (4 of 40 studies included data on two studies each); 29/44 studies in healthy populations**
 - 35/44 compared pulses to a carbohydrate control (e.g., bread, pasta, potatoes, cereal, isolated fiber)
 - All 35 studies measured glucose
 - 29/35 studies (83%) found statistically significant reductions in post-prandial peak glucose or AUC compared to control
 - 23 of 35 measured insulin
 - 17/23 studies (74%) found significant reductions in post-prandial peak insulin or AUC compared to control

Evidence on Pulses and Diabetes

- **18 glycemic index studies**
- **All 18 studies controlled; 8/18 studies in healthy subjects**
 - 18/18 studies (100%) showed pulses significantly lowered glycemic index compared to control (e.g., white bead, glucose, dextrose)

Results: CHD and Diabetes

- **CHD**
 - Intervention studies on blood cholesterol (n=6) showed low consistency across studies on the effect of pulses on blood cholesterol (TC, LDL)
 - 1/6 studies showed a statistically significant effect of dried beans on LDL reduction
 - 1/6 showed a statistically significant effect of bean flour on TC reduction without decreasing HDL; total fiber intakes not statistically different between groups
- **Diabetes**
 - Non-acute studies on glycemia (n=3) did not show significant effects on the most reliable marker of long-term glycemic control – *i.e.*, HbA1c
 - Positive results seen with acute and glycemic index studies; however, the usefulness of acute studies for health claim substantiation is not known

Conclusions: CHD and Diabetes

- **There is a paucity of good quality intervention studies on pulses and blood cholesterol or glycemic control for health claim substantiation**
- **Of the intervention studies evaluated for CHD and diabetes, there is low consistency across studies to support the effect of pulses for disease risk reduction claims**

Claims with a lower burden of proof/less regulatory oversight

- **US: Structure/function claims; qualified health claims**
- **Canada: Structure/function claims; function claims**
- **EU: Article 13 claims**

Authorized *Versus* Qualified Claims in the US

	Authorized	Qualified		
Study Design	R, C; cohort	R, C; NR; cohort; case control	NR; case control	NR; case control
Study Quality	High	High or moderate	Moderate or low	Moderate or low
Consistency Across Studies	High	Moderate	Low; uncertainties exist	Very low; uncertainties exist

Recommendations

- **CVD**
 - Additional well-designed randomized and controlled clinical trials that solely investigate the effect of pulses on validated biomarkers (e.g., LDL) of longer duration and with larger sample sizes
- **Diabetes**
 - Clarification of biomarkers for risk of diabetes
 - Clarification of the appropriate study population (*i.e.*, inclusion of diabetics)
 - Clarification of the usefulness of acute studies for health claim substantiation
 - Additional well-designed non-acute randomized and controlled trials that solely investigate the effect of pulses on biologically relevant indices

Recommendations

- **Science → health claims**
 - Based on current research, little potential for disease-risk reduction claims
 - Variability in matrices used (extracts vs whole beans) can limit applicability of existing research to end product intended for market
- **Health claim of interest → Science to get there**
 - A lot of potential here
 - Formulation for success: understanding and communicating scientific requirements for health claim substantiation (efficacy) + capabilities for product innovation + consumer interests/likes

Meeting Efficacy Requirements

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

Recommendations for Clinical Trials

RECOMMENDATION	EXAMPLES / ADDITIONAL COMMENTS
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	<p>Blood cholesterol studies: LDL, TC, HDL, TAG</p> <p>Diabetes: HbA1c, fasting glucose, fasting insulin</p>
Develop an appropriate inclusion/exclusion criteria for subject selection prior to study recruitment	<p>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</p>

Recommendations for Clinical Trials

RECOMMENDATION	EXAMPLES / ADDITIONAL COMMENTS
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

Health Claim Application Requirements

ASPECT OF HEALTH CLAIM APPLICATION	CANADA	EU	US
Details of health claim	☉	☉	☉
International status of health claim	☉	☉	n/a
Safety data (assuming a non-modified food)	☉	☉	☉
Quality assurance data	☉	☉	☉
Efficacy data	☉	☉	☉
Tabulation/ synopsis of data	☉	☉	☉
Items for transparency	☉	☉	☉
☉ Information requirement			

Requirements for Efficacy

CRITERION	CA	EU	US
Effective intake/dose-response	☺	☺	☺
Statistical significance of outcome	☺	☺	☺
Specificity of effect	n/a	☺	n/a
Alternative explanations/independence of association	n/a	☺	☺
Physiological relevance of magnitude of outcome	☺	☺	n/a
☺ Information requirement			

Requirements for Efficacy

CRITERION	CA	EU	US
Consistency of findings across studies	☺	☺	☺
Sustainability of effect	☺	☺	n/a
Biological plausibility	n/a	☺	n/a
Whether effective intake can reasonably be achieved under conventional use	☺	☺	☺
Relevance of studies' findings to population/dietary patterns/target group	☺	☺	☺
☺ Information requirement			

Requirements for Safety and Quality Assurance

- **Vary depending on the degree of food alteration/modification**
- **Not all requirements for CA, US, and EU included in a health claim application; other routes exist – e.g., novel foods, food additives, generally recognized as safe**

Requirements for Safety

- **For unaltered foods:**
 - Current and expected dietary intakes of food (also for food and all similar sources) for the target group and groups at risk, and a comparison with dietary recommendations
 - Upper limit of intake
 - Potential replacement of existing foods
 - Adverse effects from human studies

Requirements for Quality Assurance

- **For and unaltered food:**
 - Justification of a proxy measure – *i.e.*, a quantifiable relationship between the proxy indicator in a food and its claimed effect
 - Measurement of levels of a nutrient or a food component in a food that achieves the claimed effect
 - Details of an analytical method as well as a sampling plan and variability of data
 - Documentation of consistency in the quantity of a nutrient/food component

Capitalizing on Commonalities

- **CA, EU, and US all require the implementation of a systematic approach to retrieve and evaluate the totality of evidence (in favour and not in favour) on a food-health relationship**
- **Basic components and principles of a systematic approach are similar across jurisdictions**

Common Components of a Systematic Approach

- Preliminary decisions on food-health relationship
- Literature retrieval
- Literature filtering
- Tabulation and synopsis of literature
- Study quality appraisal
- Evaluation of totality of evidence for causality and generalizability

Common Principles of a Systematic Approach

- **Comprehensiveness**
 - All relevant literature is captured (published and unpublished, favourable and unfavourable)
- **Transparency**
 - Communication of search strategy, inclusion/exclusion criteria for filtering, basis for conclusions
- **Organization**
 - Use of tables and plots to compare findings across studies
- **Focus on highest quality original research**
 - Focus is on human studies (intervention studies, observational studies) with acceptable methodological quality

Key Application Differences Among Jurisdictions

- **Format specified for data organization**
- **Process/tools used for study quality appraisal**
- **Scope of requirements on efficacy, safety and quality assurance**

The Reality

- **“One size fits all” approach – *i.e.*, one health claim application used for submission to CA, EU, US is, unfortunately, not a reality**
 - *e.g.*, EU application has 9 appendices for completion and an electronic template for the application
- **Adherence to a format specified by a jurisdiction will facilitate the evaluation process**

The Reality

- **Management of health claims reflects a country's level of interest in various factors including health promotion, trade, consumer choice, consumer protection**
- **Interpretation of science is not unequivocal**
- **Health claim approval is not universal**

Conclusions

- **Pulses have healthful components. It is not known which component(s) are responsible for their health effects**
- **Additional well-designed clinical trials are needed on pulses and blood cholesterol/diabetes for disease risk-reduction health claim substantiation**
- **Jurisdictions' commonalities for health claim applications can be capitalized on to increase the efficiency of information gathering and substantiation**
- **It is an exciting time for the pulse industry to play an important role in guiding high quality research studies**
- **Understanding and communicating (to researchers) scientific requirements for health claim substantiation + capabilities for product innovation + consumer interests/likes = a scientific-, regulatory-, and consumer-friendly product**

- **Thank you!**