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Update on Walnut Case Study



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Overview of Presentation

- **Purpose of walnut case study**
- **Progress on 3 key scientific areas - safety, quality, causality/generalizability**
- **Progress on 15-step process to address causality/generalizability**



Purpose of Project

- **To apply Canada’s revised Guidance Document for food health claim submissions to a food/health relationship, specifically walnuts and cardiovascular health.**
- **To provide feedback and recommendations on the comprehensibility and ease of use of the Guidance Document.**



Characterization of Food/Health Relationship

- **Food/health relationship**
 - Walnuts (whole, paste, oil) and cardiovascular health
- **Benefits of walnut consumption on cardiovascular health primarily attributed to improvement of lipid profile – e.g., the replacement of saturated fatty acids (SFAs) with monounsaturated fats (MUFAs) and polyunsaturated fats (PUFAs)**



Biomarkers of Food/Health Relationship

- **Biomarkers of walnut intake**
 - Dietary intake assessment - consumption of calories, total fat, total PUFAs, total MUFAs
 - 100g of walnuts:
 - **65g total fat**
 - 6g SFAs
 - 9g MUFAs
 - **47g PUFAs** (38g linoleic acid, 9g alpha-linolenic acid)
- **Biomarkers of cardiovascular health**
 - Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides



Progress on 3 Key Scientific Areas in Guidance Document

1) Safety

- Limited requirements since walnuts are not a novel food
- Dietary intake estimates – completed

2) Quality Assurance

- Limited requirements since walnuts are not a novel food

3) Causality/Generalizability

- Majority of progress achieved here



Dietary Intake Estimations

Estimated <u>Daily Intake</u> of Walnuts in the U.S. by Population Group (2005-2006 USDA NHANES Data)						
Population Group	Age Group (Years)	% Users	All-Users Consumption			
			Mean (g)	Percentiles (g)		
				25 th	50 th	90 th
Infant	0-2	2.0	0.5*	0.2*	0.3*	1.2*
Child	3-11	8.2	1.2	0.5	0.6	1.8
Female Teenager	12-19	6.8	1.4	0.5	1.2	2.7
Male Teenager	12-19	6.6	1.6	0.5	1.0	1.8
Female Adult	20+	9.9	4.2	0.5	1.2	12.4**
Male Adult	20+	8.8	2.9	0.6	1.4	6.9
Total Population	All Ages	7.7	3.1	0.5	1.2	7.5

*Estimate may not be statistically reliable

**12.4g=~1/8th cup of walnut halves



Causality/ Generalizability

- **Health Canada's 15 step approach**
 - Step 1. Describe the search strategy for literature retrieval
 - Step 2. Implement the search strategy for literature retrieval
 - Step 3. Generate one reference list from the literature retrieved
 - Step 4. Develop inclusion and exclusion criteria to filter the literature
 - Step 5. Filter the literature
 - Step 6. Refine the reference list
 - Step 7. Summarize relevant information in a table
 - Step 8. Evaluate study quality
 - Step 9. Streamline data reporting
 - Step 10. Rate statistical agreement
 - Step 11. Discuss the relationship between the food exposure and its effect on the health effect
 - Step 12. Discuss the physiological meaningfulness of the effect of the food exposure
 - Step 13. Discuss the feasibility of consuming an effective amount of the food
 - Step 14. Infer the target population of the food/health relationship from the evidence
 - Step 15. Make conclusions



Step 1

- **Step 1: Describe search strategy for literature retrieval**

Keywords for exposure	Walnut(s), Juglan(s)
Keywords for health outcome	Cholesterol, triglycerides, hyperlipidemia, hypertriglyceridemia, dyslipidemia, hypercholesterolemia, adiposity, lipid, waist circumference, body composition, weight, body mass index, body fat, BMI, blood pressure, hypertension, glycemia, hyperglycemia, glucose, insulin, diabetes, hyperinsulinemia, metabolic syndrome, metabolic disease, ischemia, angina, arrhythmia, atherosclerosis, heart attack, myocardial infarction
Keywords for study population	Human, person (s), people, men, man, male, males, woman, women, female, females, adult (s), senior (s), elderly, subject (s), volunteer (s), patient (s), participant (s)



Step 1 cont'd

Electronic databases used	Medline, AGRICOLA, Allied & Complementary Medicine, CAB Abstracts, FOODLINE®: Science, Biosis Previews®, Federal Register, ELSEVIER, BIOBASEFOODLINE®: Market, EMBASEDIOGENES®, FDA News Mar., Adis Clinical Trials Insight, BCC Market Research
Non-electronic methods used	Yes (Hand-searching reference lists)
Language limitations	English only
Date limitations	Start of database to January 2009



Step 2

- **Step 2: Implement the search strategy for literature retrieval**
- **Results: 636 publication titles retrieved (minus duplicates)**



Step 3

- **Step 3. Generate one reference list from the literature retrieved**
- **One reference list generated from retrieved literature (to be included in application)**



Step 4

- **Step 4: Develop inclusion and exclusion criteria to filter the literature**

Factor	Inclusion Criteria	Exclusion Criteria
Type of publication	<ul style="list-style-type: none"> • Original Research <ul style="list-style-type: none"> ◦ Intervention studies ◦ Observational studies (Cohort, case-control, cross-sectional, ecological) • Systematic Reviews / Meta-Analyses • Authoritative Statements 	<ul style="list-style-type: none"> ◦ A short publication ◦ Abstract ◦ Editorial ◦ Short opinion ◦ Consumer letter ◦ Case study
Language	English	All but English
Year	Start of database to date of search	N/A
Duplicate	N/A	Publication is a duplicate



Step 4 cont'd

Factor	Inclusion Criteria	Exclusion Criteria
Food	<ul style="list-style-type: none"> • Walnut exposure quantified • Walnuts administered singly (intervention studies) 	<ul style="list-style-type: none"> • Food of interest not quantified: dose of food not known (intervention studies); amount of food consumed not calculated (observational studies) • Food of interest not administered as a single intervention
Health effect	<ul style="list-style-type: none"> • Measure of Total Cholesterol, LDL-C, HDL-C, TAG 	<ul style="list-style-type: none"> • Blood lipid not measured • Reference to health benefits that are not the health effect of interest
Population	<ul style="list-style-type: none"> • Normo-, hyper-cholesterolemics 	<ul style="list-style-type: none"> • Hospitalized or sick or diseased individuals
Duration	<ul style="list-style-type: none"> • ≥ 3 weeks exposure in intervention studies • Follow-up time adequate 	<ul style="list-style-type: none"> • < 3 weeks in intervention studies • Follow-up time not adequate



Step 5

- **Step 5: Filter the literature**
- **3-stage filtering process based on title, abstract, or full-text**

Stage of Filtering	Number Excluded
Title stage	582
Abstract stage	32
Full-text stage	23
Total number of relevant publications that met inclusion criteria	25 (4% of all retrieved publications)



Step 6

- **Step 6: Refine the reference list**
- **Of the 25 relevant studies identified:**
 - 19 intervention studies
 - 1 R, DB, C
 - **15 R, C**
 - 1 R, NC
 - 2 NR, C
 - 1 observational study (cross-sectional)
 - 5 systematic reviews



Step 7

- **Step 7: Summarize relevant information in a table**
- **Tabulation of:**
 - Aim of study
 - Research design
 - Sample characteristics
 - Exposure and duration
 - Background diet & assessment tool
 - Results and statistics
 - Relevant authors' conclusions



Step 8

- **Step 8: Evaluate Study Quality**
 - To be completed



Step 9

- **Step 9: Streamline Data Reporting**
- **Tabulation of:**
 - Study design
 - Quality score (not yet completed)
 - Sample size
 - Duration
 - Dose
 - Effect size
 - Statistical significance



- **Overview of important data from Step 9 pertaining to intervention studies only reported in next few slides**



Research Design and Sample Size

- Research Design
 - Both crossover and parallel studies
 - 1 R, DB, C
 - **15 R, C**
 - 1 R, NC
 - 2 NR, C
- Sample Size
 - Range of 10 to 64 subjects



Baseline Health Status

- Normolipidemics: 5/19 studies
- **Hyperlipidemics: 11/19**
- Metabolic syndrome: 2/19
- Type II diabetes: 1/19



Dose and Duration

Matrix and Dose Range

- **Whole Walnuts: 15/19 studies; 20 to 108 g/day**
- Walnut Paste: 2/19 studies; 19.4 to 21.4 g/day
- Walnut Oil: 1/19 studies; 3,000 mg/day
- Whole walnuts and walnut oil: 1/19 studies; 37 g whole + 15 g oil/day

Duration of studies

- 4 weeks to 6 months



Background Diets

- **Profile of Diets**
 - North American Diet: 5/19 studies
 - Mediterranean Diet: 3/19
 - Other: 11/19 (study settings: Japan; Australia/New Zealand, Spain, Iran, South Africa)
- **Walnuts added to background diet: 5/19 studies**
 - Addition of walnuts ↑ overall kcal, total fat, MUFAs, PUFAs, ALA, and LA intake, and tended to ↓ saturated fat intake.
- **Walnuts substituted components in background diet: 14/19 studies**
 - Walnuts were substituted for other fat sources/other foods in the diet, e.g., olive oil, avocados, saturated fats, MUFAs, meats.



Health Outcomes

- **Total Cholesterol: 17/19 studies**
- **LDL Cholesterol: 17/19**
- **HDL Cholesterol: 19/19**
- **Triglycerides: 18/19**



Step 10

- **Step 10: Rate statistical agreement**
 - Agreement between statistically significant and non-significant studies for a beneficial effect of exposure
 - HIGH agreement: $\geq 75\%$
 - MODERATE agreement: 60-74%
 - LOW agreement: $< 60\%$



Agreement on Beneficial Effect

Beneficial Effect	Proportion	Range of Effect
↓ Total Cholesterol (n=17)	16/17 (94%) HIGH AGREEMENT	-0.16 to -0.61 mmol/L (-2.8 to -14.2%)
↓ LDL Cholesterol (n=17)	16/17 (94%) HIGH AGREEMENT	-0.1 to -0.47 mmol/L (-2.5 to -16.3%)
↑/- HDL Cholesterol (n=19)	10/19 (52.6%) LOW AGREEMENT	+0.03 to +0.15 mmol/L (+3.1 to 14.1%)
↓ Triglycerides (n=18)	13/18 (72.2%) MODERATE AGREEMENT	-0.03 to -1.43 mmol/L (-1.3 to -22.5%)



Agreement on Beneficial Effect AND Statistical Significance ($p < 0.05$ between groups)

Beneficial Effect	Proportion	Range of Effect
↓ Total Cholesterol (n=17)	9/17 (52.9%) LOW AGREEMENT	-0.19 to -0.58 mmol/L (-3.0 to -12.4%)
↓ LDL Cholesterol (n=17)	9/17 (52.9%) LOW AGREEMENT	-0.20 to -0.46 mmol/L (-5.7% to -14.0%)
↑/- HDL Cholesterol (n=19)	0/19 (0%) LOW AGREEMENT	n/a
↓ Triglycerides (n=18)	1/18 (5.6%) LOW AGREEMENT	-0.27 mmol/L (-22.5%)



Observational Study

- **Cross-sectional study in France**
 - 857 subjects (M, F, free-living, 18-65 yrs old)
 - Dietary intake of walnuts and walnut oil were assessed using food frequency questionnaires
 - No association between walnut intake and serum LDL-C and Total Cholesterol levels.



Next Steps

- **Communicate with Health Canada to learn whether updates on Guidance Document available**
- **Remaining steps from approach shared at GFTC to be implemented in case study on walnuts:**
 - Step 8. Evaluate study quality
 - Step 10. Rate statistical agreement (accounting for quality appraisal)
 - Step 11. Discuss the relationship between the food exposure and its effect on the health effect
 - Step 12. Discuss the physiological meaningfulness of the effect of the food exposure
 - Step 13. Discuss the feasibility of consuming an effective amount of the food
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Conclusions

- **Guidance document clearly communicates expectations of deliverables and is straightforward in implementation**
- **It is systematic, encourages transparency and comprehensiveness, and a focus on original research in humans**



Conclusions cont'd

- **The majority of intervention studies on walnuts and cardiovascular health:**
 - Are randomized and controlled
 - Administered whole walnuts (20 to 108 g/day)
 - Studied the effect of walnut substitution (for other foods)
 - Used hyperlipidemics
- **Agreement for a beneficial effect of walnuts is HIGH for Total Cholesterol, HIGH for LDL Cholesterol, MODERATE for Triglycerides and LOW for HDL Cholesterol**
 - These agreement ratings all changed to LOW when statistical significance considered



- **Thank you!**
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