Developing a self-substantiated health claim for kiwifruit: lessons to be learnt

Carolyn Lister
Lynley Drummond (DFSA)
Talk outline

» Background
  » Why develop a health claim?
  » The process for a self-substantiated health claim
  » Claims for digestive health

» Developing the claim for kiwifruit
  » Defining the kiwifruit-health relationship
  » The review: searching, quality assessment, assessment of overall causality
  » Outcome

» Lessons learnt
  » Food characterisation
  » Searching
  » The review
  » Clinical trials
Why develop a health claim?

» Financial drivers

» There were wider motivations in developing the kiwifruit claim
  » Zespri markets kiwifruit off-shore so why a health claim in Australia and NZ?
    » Leadership role
    » Zespri acknowledges the role of health & nutrition to support growth in consumption of kiwifruit
    » Grower base is here – local exposure
    » Recognition for kiwifruit
    » Provides a platform for global initiatives

» Each jurisdiction will have it’s own regulations to comply with but there is increasing alignment of requirements
The step-up approach for claims

- FSANZ Standard 1.2.7

<table>
<thead>
<tr>
<th>Pre-approval or self-substantiation</th>
<th>Pre-market assessment and approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying criteria, nutrient profiling scoring criteria (NPSC)</td>
<td>Qualifying criteria, nutrient profiling scoring criteria (NPSC)</td>
</tr>
<tr>
<td>Nutrition content claims</td>
<td>General level health claims</td>
</tr>
</tbody>
</table>

NPSC - compositional profiling - for foods carrying health claims

What is self-substantiation?

» Substantiation is the process of evaluating the body of scientific evidence for a food-health relationship.

» The key objective of the substantiation process is to determine whether the evidence for the relationship between a food or property of food and a health effect is sufficiently certain that it “is unlikely to be reversed by an additional well conducted high quality study”.

» Viewed as a critical step for BGA:

  » “The benefits of providing for this additional way of complying with the Standard are that it improves the investment proposition for firms developing new products, by improving speed to market, and enhancing exclusive use of claims and intellectual property protection. This is important for New Zealand, as innovation in food exports to third markets, and research into the health benefits of foods that underpins this are considered to be key drivers for growth in the New Zealand economy.”

Health Claims Workshop Note 4, NZ Position.
Key considerations to achieve a claim

» Claimed effect of food (characterised) is beneficial to human health (physiological benefit)

» A cause & effect relationship is established between consumption of the food and the claimed effect in humans

» The quantity of food and pattern of consumption required to obtain the claimed effect could be reasonably achieved as part of a balanced diet

» The specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended

» There are no adverse side effects
How: systematic review process

Guidance on establishing food-health relationships for general level health claims

Food Standards Australia New Zealand

Version 1.1
September 2013


1. Describe food and food-health relationship

2. Literature search
   a. Search strategy
   b. Refine list of studies fitting criteria

3. Detailed study information

4. Quality assessment of the studies

5. Assessment of overall causality

6. Conclusion
   » Quantity required to achieve health effect
   » Safety
» Used Health Claims Canada tool (there is another tool for observational studies)

<table>
<thead>
<tr>
<th>Item</th>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inclusion/Exclusion Criteria</td>
<td>Were the inclusion and/or exclusion criteria for study participation reported (e.g., age greater than 50 years, no history of heart disease)?</td>
<td></td>
</tr>
<tr>
<td>2. Group Allocation¹</td>
<td>Was the study described as randomized?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was the randomization method reported?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was the randomization method appropriate?²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was allocation concealed?³</td>
<td></td>
</tr>
<tr>
<td>3. Blinding</td>
<td>Were the study subjects blinded to the intervention received?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Were the research personnel blinded to the intervention received by the subjects?</td>
<td></td>
</tr>
<tr>
<td>4. Attrition</td>
<td>Was attrition numerically reported?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Were the reasons for withdrawals and dropouts provided?⁴</td>
<td></td>
</tr>
<tr>
<td>5. Exposure/Intervention</td>
<td>Was the type of food described (e.g., composition, matrix)?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was the amount of food described (i.e., dose)?</td>
<td></td>
</tr>
<tr>
<td>6. Health Effect</td>
<td>Was the methodology used to measure the health effect reported?</td>
<td></td>
</tr>
<tr>
<td>7. Statistical Analysis</td>
<td>Was a between-group statistical analysis of the health effect conducted (i.e., control vs. intervention)?</td>
<td></td>
</tr>
<tr>
<td>8. Potential Confounders</td>
<td>Were potential confounders of the food/health relationship considered?⁶</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE (maximum of 15):**
- Higher quality (Score ≥ 8)
- Lower quality (Score ≤ 7)

Tool for assessment of overall causality

- Used Health Claims Canada tool (there is another tool for observational studies)

Digestive (gastro-intestinal) health

» EFSA have identified the fundamental parameters required to substantiate health claims related to gastro-intestinal function.

» Central to the rationale is the concept of “physiological benefit and/or defined clinical outcome”

» 6 areas where claims legitimate
  1. Bowel function
  2. Gastro-intestinal discomfort
  3. Function claims related to defence against pathogens
  4. Reduction of a risk factor for infection
  5. Function claims on gastro-intestinal microbiota
  6. Function claims on digestion/absorption of nutrients
Measures of bowel function

» Accepted measures of normal bowel function:
  » Frequency / transit time
  » Ease of evacuation
  » Stool characteristics

» Outcomes should be measured by generally accepted methods (e.g. Bristol stool scale) including validated questionnaire-based assessments.

» Patients with functional constipation & IBS patients are generally considered an appropriate study group to support claims intended for the general population.
Why bowel function for kiwifruit?

» Bowel habit is an accepted biomarker of gut function

» Constipation is the most common functional bowel disorder
  » Known to affect up to 15% of adult population in western countries

» Well documented biomarkers for bowel function

» Kiwifruit known to improve bowel function

» Zespri Health & Nutrition strategy (2012/13)
  » “Digestive health”
  » Focus and future plan
The consumption of kiwifruit helps to maintain / promote normal bowel function/habit
The review: literature search

- Defining the search terms for both food & health outcome

<table>
<thead>
<tr>
<th>Link to food</th>
<th>Link to health effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>kiwifruit</td>
<td>bowel</td>
</tr>
<tr>
<td>kiwi</td>
<td>comfort</td>
</tr>
<tr>
<td>Actinidia</td>
<td>laxati* (to encompass laxation and laxative)</td>
</tr>
<tr>
<td>actinidin</td>
<td>constipat* (to encompass constipation and constipated)</td>
</tr>
<tr>
<td>Chinese gooseberry</td>
<td>regular* (to encompass regular and regularity)</td>
</tr>
<tr>
<td></td>
<td>gut</td>
</tr>
<tr>
<td></td>
<td>stool</td>
</tr>
<tr>
<td></td>
<td>health</td>
</tr>
<tr>
<td></td>
<td>intestin* (to encompass intestine and intestinal)</td>
</tr>
<tr>
<td></td>
<td>digest* (to encompass digestion and digestive)</td>
</tr>
</tbody>
</table>
The review: literature search

» Search strategy
  » Databases
  » Internal reports, etc
  » Patents
  » Clinical trials registers

» Inclusion & exclusion criteria

Key evidence

Mechanistic evidence

Supporting evidence

- Studies identified in full literature search \( (n = 11,899) \)
- Duplicates removed from list \( (n = 4,395) \)
- Excluded (title and abstract revealed not appropriate) \( (n = 7,017) \)
- Excluded using refined criteria \( (n = 419) \)
- Studies of direct relevance to health target, including animal and in vitro studies \( (n = 68) \)
- Human clinical studies with kiwifruit. Digestion / laxation not necessarily primary target \( (n = 16) \)
- Human clinical studies using fresh kiwifruit as food intervention and digestive health targets \( (n = 7) \)
- Excluded \( (n = 9) \) because:
  • Not fresh kiwifruit

- Human clinical studies with kiwifruit but not human clinical \( (n = 42) \)
Key studies with fresh kiwifruit


Review: tabulation of study data

- Schedule 6 – Required elements of a systematic review: table with key information from each included study. This must include information on:
  (a) the study reference
  (b) the study design
  (c) the objectives
  (d) the sample size in the study groups and loss to follow-up or non-response
  (e) the participant characteristics
  (f) the method used to measure the food or property of food including amount consumed
  (g) confounders measured
  (h) the method used to measure the health effect
  (i) the study results, including effect size and statistical significance
  (j) any adverse effects.
### Review: summarising the studies

**Table 8. Summaries of human intervention studies with fresh whole green kiwifruit (Actinidia deliciosa 'Hayward'), used for this systematic review.**

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study design</th>
<th>Study objectives</th>
<th>Sample size &amp; loss to follow up</th>
<th>Characteristics of participants</th>
<th>Exposure, duration &amp; background diet</th>
<th>Assessment tool methods &amp; confounders measured</th>
<th>Results &amp; statistics</th>
<th>Adverse effects noted</th>
<th>Relevant conclusions</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. (2007)</td>
<td>Single centre, age and sex-matched, case control.</td>
<td>To determine if increased dietary fibre, in the form of kiwifruit, was effective in constipated patients.</td>
<td>Recruited: N=35 treatment, N=20 control. Final sample: N=33 treatment, N=20 control.</td>
<td>Country: China. Health status: Constipated patients (duration &gt;6 months &amp; &lt;3 complete spontaneous bowel movements (CSBM)/week) versus 'normal' control Setting: free living Age range: ≥18: averages 49.9±12 treatment, 50.8±14 control Gender (M:F): 1: 2.67 treatment: 1:4 control.</td>
<td>2 Ze斯匹® Green Kiwifruit ('Hayward') per day – 1 in am after breakfast, 1 in pm after dinner 2 week baseline &amp; 4 week treatment Normal diet pattern and activity</td>
<td>Diary of constipation symptoms: • CSBM/week • straining score (0-2) • Bristol stool scale (1-7) • satisfaction score (0-4) • bother score of constipation (0-4) • Laxative use Bowel transit time by X-ray and colonic motility studies Anorectal manometry Statistical analysis: SPSS - Student's t-test (continuous variables) or χ² (categorical data.) Paired t-test used for bowel habit and anorectal physiology before &amp; after treatment within same group.</td>
<td>Constipated group: • Responder rate 54.5% • CSBM increased after treatment (2.2±2.6 v. 4.4±4.6. P=0.013) • Improvement in bother score (2.6±0.9 v. 2.0±1.1, P=0.02) • Increased satisfaction of bowel habit (2.7±0.9 v. 1.6±1. P=0.001) • Reduction in laxative use (2.2±2.5 v. 0.8±1.5. P=0.003). • Improvement in transit time (54.5±29 v. 39.6±22, P=0.003)</td>
<td>No patients or controls reported bloating or gas, or intolerance No other side effects reported in either treatment group or control, no reported diarrhoea.</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
The review: quality assessment

» Used the “quality appraisal tool” from Health Canada
  » Scoring system for ranking
    » Maximum score 15
    » ≥8 is higher quality
    » 4/6 trials appraised were “higher quality”

» Ranking was completed independently by both reviewers
  » Also discussed with peer review team

» A key challenge for natural whole foods is blinding

» Most studies were before & after interventions
  » Often no opportunity for randomisation
### Human clinical trials with fresh kiwifruit

<table>
<thead>
<tr>
<th>Reference and daily intervention</th>
<th>Country</th>
<th>Population group</th>
<th>Study Quality</th>
<th>Frequency</th>
<th>Stool form</th>
<th>Ease/comfort</th>
<th>Transit time</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. (2007): two Zespri® Green Kiwifruit</td>
<td>China</td>
<td>Functional constipation</td>
<td>High</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Chang et al. (2010): two Zespri Green Kiwifruit</td>
<td>Taiwan</td>
<td>IBS-C</td>
<td>Low</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Hiele (2010): three Zespri Green Kiwifruit</td>
<td>Belgium</td>
<td>Functional constipation</td>
<td>High</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Marzo &amp; Cunillera (2013): three green kiwifruit (‘Hayward’)</td>
<td>Spain</td>
<td>Functional constipation</td>
<td>High</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Ohsawa et al. (2010): two Zespri Green Kiwifruit</td>
<td>Japan</td>
<td>Prone to constipation</td>
<td>High</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Rush et al. (2002): pre trial, one Zespri Green Kiwifruit per 30 kg bodyweight</td>
<td>New Zealand</td>
<td>Healthy</td>
<td>Low</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Rush et al. (2002): main trial, one Zespri Green Kiwifruit per 30 kg bodyweight</td>
<td>New Zealand</td>
<td>Healthy elderly</td>
<td>Low</td>
<td>↑, SS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
</tbody>
</table>

SS = statistically significant (P < 0.05); NSS = not statistically significant
## Human clinical trials with kiwifruit products

<table>
<thead>
<tr>
<th>Reference and daily intervention</th>
<th>Country</th>
<th>Population group</th>
<th>Study Quality</th>
<th>Frequency</th>
<th>Stool form</th>
<th>Ease/comfort</th>
<th>Transit time</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hill (2002): Kiwi Crush™ (made from New Zealand green kiwifruit, <em>A. deliciosa</em>)</td>
<td>New Zealand</td>
<td>Elderly Parkinson’s patients</td>
<td>High</td>
<td>↑, SS</td>
<td>↑, SS</td>
<td>↑, SS</td>
<td>↓, SS</td>
<td>none</td>
</tr>
<tr>
<td>Udani &amp; Bloom (2013): Kivia™ powder (made from New Zealand green kiwifruit, <em>A. deliciosa</em>)</td>
<td>USA</td>
<td>Occasional constipation</td>
<td>Low</td>
<td>↑, NSS</td>
<td>↑, NSS</td>
<td>↑, NSS</td>
<td>↑, SS</td>
<td>none</td>
</tr>
<tr>
<td>Uebaba et al. (2009): freeze-dried kiwifruit juice</td>
<td>Japan</td>
<td>Elderly</td>
<td>Not able to assess</td>
<td>No change</td>
<td>No change</td>
<td>Not measured</td>
<td>?</td>
<td>none</td>
</tr>
<tr>
<td>Weir (2010) - Trial 1: kiwifruit compositions (made from New Zealand green kiwifruit, <em>Actinidia deliciosa</em>)</td>
<td>China</td>
<td>Constipated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weir (2010) - Trial 2: kiwifruit compositions (made from New Zealand green kiwifruit, <em>Actinidia deliciosa</em>)</td>
<td>China</td>
<td>Constipated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SS = statistically significant ($P < 0.05$); NSS = not statistically significant
Review: assessment of causality

» Based on 3 key parameters related to normal bowel function

» Assesses consistency of direction of effect & strength of the association
  » Accounts for study quality

» Significant improvement in each biomarker
  » Consistently strong evidence for normalisation of bowel habit
  » Several studies also showed improvement in transit time

<table>
<thead>
<tr>
<th>Health Effect</th>
<th>Direction of favourable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Frequency of defecation</td>
<td>85.7%</td>
</tr>
<tr>
<td>Ease of defecation</td>
<td>83.3%</td>
</tr>
<tr>
<td>Stool form / consistency</td>
<td>83.3%</td>
</tr>
</tbody>
</table>
Review: effective “dose” and safety

- Target population is the “general population”
  - Studies completed on adults
    - Healthy
    - Constipated
    - Prone to constipation

- No specific “dose-response” studies

- **2 green kiwifruit per day** have a meaningful effect on the health response

- No adverse effects in healthy (non-constipated) individuals
Key considerations to achieve a claim met

» Claimed effect of food (characterised) is beneficial to human health (physiological benefit)

» A cause & effect relationship is established between consumption of the food and the claimed effect in humans

» The quantity of food and pattern of consumption required to obtain the claimed effect could be reasonably achieved as part of a balanced diet

» The specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended

» There are no adverse side effects
Review: outcome

- Systematic review supports the claim:
  
  “Zespri® Green Kiwifruit can contribute to normal bowel function”

- Claim lodged with FSANZ:
  - [http://www.foodstandards.govt.nz/industry/labelling/Pages/Notified-food-health-relationships.aspx](http://www.foodstandards.govt.nz/industry/labelling/Pages/Notified-food-health-relationships.aspx)

<table>
<thead>
<tr>
<th>29 April 2014</th>
<th>Zespri International Ltd</th>
<th>400 Maunganui Rd, Mount Maunganui 3118 NEW ZEALAND</th>
<th>Zespri green kiwifruit (Actinidia deliciosa cv. ‘Hayward’)</th>
<th>Can contribute to normal bowel function</th>
</tr>
</thead>
</table>

- First NZ lodged claim under the new regulations
- First for natural whole fresh fruit

- Reviewed by MPI
Lessons: the food

» Characterisation of the food is particularly important
  » This may be defined by variety or composition

» With current evidence we could not have applied the current claim to all kiwifruit
  » It is specific to green kiwifruit and in particular the Hayward variety because this was what clinical trials were conducted with
  » If the active components were conclusively identified then may be a slightly different claim (e.g. if a kiwifruit contained a set level of fibre and actinidin shown to be efficacious then could make a claim on this basis and may apply to other kiwifruit)

» There are cases with other foods where it is critical to link the claim to levels of a particular nutrient(s) or phytonutrient(s)
  » For example an EFSA claim for olive oil and protection of blood lipids from oxidative damage requires a specific level of particular polyphenols to be present
Lessons: searching

» Important that clearly define parameters at the start

» Search as far and wide as possible

» Keep good records for future reference:
  » We conducted a lot of searching online and discarded at that point
  » However, important to keep record of excluded references not just numbers
Lessons: the review

» Health Canada tools particularly relevant for food

» There is value in involvement of an expert panel (span from food knowledge through to the health outcome area)

» Include MPI in discussions

» Importance of including only those studies/results that use appropriate biomarkers
  » Digestion area relatively simple but other health areas may present challenges, e.g. antioxidant claims
  » Biomarkers database will be useful in this regard

» ESFA publications are particularly useful
Lessons: physiological effects & biomarkers

» EFSA has developed guidance documents on the scientific requirements for health claims:
  » Post-prandial blood glucose responses/blood glucose control
  » Weight management, energy intake and satiety
  » Protection against oxidative damage
  » Cardiovascular health
  » Bone, joints, and oral health
  » Neurological and psychological functions
  » Physical performance

» Include information on the claimed effects are considered to be beneficial physiological effects and studies / outcome measures / biomarkers that are appropriate for the substantiation of function claims and disease risk reduction claims.

» Individual application outcomes also useful
The lessons: clinical trials

» Discipline of systematic review highlighted “weaknesses” in clinical trials from design to reporting:

  » Design
    » Inability to blind / lack of control
    » Choice of study participants / randomisation
    » Duration / intervention period / washout

  » Analysis
    » Statistics & stratification

  » Reporting

» Benefit of review is has enabled these points to be carefully considered as move into future studies

» Consider all aspects of likely claim before planning a clinical trial (Health Canada guidance document)
Conclusions

» Remember the need for the following key elements:
  » Claimed effect of food (characterised) is beneficial to human health (physiological benefit)
  » A cause & effect relationship is established between consumption of the food and the claimed effect in humans
  » The quantity of food and pattern of consumption required to obtain the claimed effect could be reasonably achieved as part of a balanced diet
  » The specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended
  » There are no adverse side effects
Thank you for your attention

www.plantandfood.co.nz

carolyn.lister@plantandfood.co.nz