EFSA update on gut and immune related health claims

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EFSA NDA Panel
IATA-CSIC, Valencia, Spain
Reg. (EC) No 1924/2006

- Authorization of health claims in the EU is based on a scientific assessment following the highest possible standards.
- Consumer protection, fair competitiveness and innovation

EFSA assessment

- “Characterization of the food/constituent”
- “Claimed effect defined and beneficial”
- “Substantiation: human data are central”

Scientific substantiation requires a favourable outcome in ALL
<table>
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<th>Regulation (EC) 1924/2006</th>
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<tr>
<td><strong>Art.13.1</strong></td>
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<tr>
<td>Generally accepted scientific evidence</td>
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<td>List Claims</td>
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FAVORABLE HEALTH CLAIMS (ART 13.1)

Out of 421 IDs related to this area: **42 with favourable outcomes**

- **14** related to immune function (essential nutrients i.e.: copper, folate, iron, selenium, vit D, A, B12, B6, C, and zinc)
- **15** related to GI function
  - **10** bowel function (e.g. dried prune, lactulose, wheat bran fibre, rye fibre, oat and barley grain fibre)
  - **4** GI discomfort caused by lactose intake in lactose intolerant (e.g. foods with reduced lactose content)
  - **1** reduction of intestinal gas accumulation (e.g. Activated charcoal)
- **13** related to absorption/digestion
  - **7** Absorption of micronutrients (e.g. Vit C, D, meat or fish, fats)
  - **2** Digestion (e.g. Ca, chloride)
  - **4** lactose digestion:
    - (i.e. lactase, live yoghurt cultures)
### Regulation (EC) 1924/2006

<table>
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<th>Art.13.1</th>
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<th>Art.14</th>
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<tr>
<td>Generally accepted scientific evidence</td>
<td>Newly developed scientific data / proprietary data</td>
<td>Reduction of disease Risk</td>
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<td>Children’s development &amp; health</td>
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**List Claims**

**Applications**
FAVORABLE HEALTH CLAIMS (ART 13.5, 14)

Of **155 applications** related to this area (07/2015):

- 7 applications under evaluation or validation
- 90 applications withdrawn during the evaluation
- **58** applications with opinions adopted/published
  - 1 with the food not characterised
  - 5 with insufficient evidence
  - 45 with cause and effect relationship not established
- **7 with favourable outcomes:**
  - 3 Immune system (e.g. Vitamin D, Zinc)
  - 3 bowel function (i.e. sugar beet fibre)
    - chicory inulin, hydroxyanthracene deriv.
  - 1 Absorption of micronutrient (e.g. Vitamin C)

Adapted from Altin Cekodhima 2013
Lessons from experience with first batch of claims

FIRST GUIDANCE ON GUT-IMMUNE CLAIMS (2011)

Lack of characterization a major reason for unfavourable opinions (Art 13.1)

Not just a recommendation as in the past


- Non-characterised microorganisms (80%)
- Others related to microorganisms (20%)
FIRST GUIDANCE ON GUT-IMMUNE CLAIMS (2011)

The claim effect: specific, measurable and beneficial

Question

Gut health

Bowel habits

Non-beneficial per se

Specific + Measurable =

By Harun Yahya

Specific

Beneficial

No measurable in vivo

Inhibition of adhesion to uro-epithelial cells
Lessons from experience with first batch of claims

FIRST GUIDANCE ON GUT-IMMUNE CLAIMS (2011)


Clinical utility of probiotics in inflammatory bowel disease.
Cain AM, Karpa KD.
York Hospital, Pennsylvania, USA.

Studies oriented to the treatment of diseases


Probiotics and prebiotics: clinical effects in allergic disease.
Tang ML, Lahtinen SJ, Boyle RJ.
Department of Allergy and Immunology, Royal Child.

Studies on reducing incidence of a disease failed to identify risk factors


The effectiveness of probiotics in reducing acute rotavirus diarrhoea. A randomized, double-blind,
Grandy G, Medina M, Soria R, Terán CG, Araya M.
Paediatric Centre Albina Patiño, Department of Gastroenterology and Nutrition, Cochabamba, Bolivia. ggrandy@inta.cl
PROBIOTICS IN (SOME) PROFESSIONAL GUIDELINES

General recommendations vs health claims approval

WGO Practice Guideline - Probiotics and Prebiotics

- Treatment of acute diarrhea:
- Hepatic encephalopathy

- Allergy  Treatment of atopic eczema
- Inflammatory bowel disease (IBD)

- Necrotizing enterocolitis
- Radiation-induced diarrhea:

- Pouchitis:
- Ulcerative colitis:

October 2011
PROPOSALS TO CIRCUMVENT THE PROBLEM FROM (SOME) STAKEHOLDERS

- **Clustering probiotic strains** for claims, while it was generally accepted that probiotic effects were strain-specific unless the opposite is demonstrated.

- Use of the nutritional claim "contains probiotics", which will not allow the differentiation of products/effects.

- **Ignore claims** (just lines on a label) and use marketing strategies.
META-ANALYSIS FOR ASSESSING PROBIOTIC EFFECTS?

Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea
A Systematic Review and Meta-analysis

Susanne Hempel, PhD
Sydne J. Newberry, PhD
Alicia R. Maher, MD

Context: Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

The main limitations to this result are residual unexplained heterogeneity, poor documentation of the probiotic strains, and lack of assessment of probiotic-specific adverse events.

Conclusions: The pooled evidence suggests a reduction in AAD. More research is needed to identify the greatest efficacy and safety of probiotics.


General public health recommendations ≠
Commercial promotion of a brand/proprietary strain through claims

By Ambroise Marin
Clustered probiotic strains for claims, while it was generally accepted that probiotic-effects were strain-specific unless the opposite is demonstrated.

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NEW GUIDANCE ON GUT-IMMUNE-PATHOGEN CLAIMS

- **Improve dialogue** via several public consultations:
  - Discussion paper (Jun-Sept 2014)
  - Guidance Draft (Feb-March 2015)

- Claims with favorable opinions are used to provide **scientific advise**, while those with unfavorable opinions illustrate shortcomings.

- **Update** EFSA principles:
  - General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367
  - Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms. EFSA Journal 2016;14(1):4369
WHAT IS NEW IN THE GUIDANCE UPDATE?

Characterization

- Move to the general guidance on claims
- New molecular tools added according to the state-of-art (multilocus sequence typing, optical mapping, whole-genome sequencing, etc.). Open list to others.
- Indigenous human bacteria (called “next generation probiotics”) can be considered novel foods (Regulation EU 2015/2283). Section 9 of EFSA guidance relates to taxonomic and safety evaluation (under revision).
WHAT IS NEW IN THE GUIDANCE UPDATE?

1. Outcome variables
2. Validation of questionnaires
3. Duration of interventions
4. Biological plausibility-mechanism
4. Appropriate study population
5. Risk factors
Claims on maintenance of normal defecation

- **Outcomes variables:**
  Several outcome variables provide information about the function and the underlying mechanism of action (e.g. stool frequency, stool consistency, sensation of complete/incomplete evacuation, faecal bulk, transit time)

- **Duration.** Exclude adaptation and chance findings owing to fluctuation of outcome measures (e.g. 4–8 weeks).

- **Consistency of effects + mechanism of action**
WHAT IS NEW? CLAIMS OF GI FUNCTION

Claims on maintenance of normal defecation

- Human studies on transit time
- Known mechanism
- Lactulose

- Human studies on fecal bulk
- Known mechanism
- Dietary fibre wheat-bran, oats, barley.
WHAT IS NEW? PATHOGENS – REDUCTION OF RISK

(Immune) Defences against pathogens

- **Study population**: subjects without an infection at baseline
- **Outcome variables**:
  - Clinical outcomes alone are sufficient
  - Immune markers may explain the mechanism

Reduction of a risk factor for infection

- **Risk factors well-established**
  - Outcome: risk factor (e.g. toxigenic *Clostridium difficile*/toxins)
- **Less-well established risk factors**
  - IgA↓ and risk of respiratory tract infections
  - Outcome: clinical + risk factor
REASONS FOR CLOCK STOP = MAIN WEAKNESSES

- Characterisation of the food constituents: 12%
- Studies submitted for substantiation of claims: 75%
- Claimed effect & target population: 13%
QUESTIONS ON STUDIES SUBMITTED FOR SUBSTANTIATION

In summary

- EFSA guidance documents and scientific opinions on previous evaluations provide scientific advise and illustrate shortcomings.

- Each claim is unique. Impossible to anticipate all possibilities (claim effects, outcomes, methods) and unfair to introduce constraints.

- More important understanding the rational of the principles applied than seeking for magic recipes.
Thank you!