EFSA experience in reviewing human studies submitted for the scientific substantiation of health claims

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EFSA – NDA Panel

Support by the EFSA Secretariat (Nutrition Unit)

Panel on Dietetic Products, Nutrition and allergies
20 Members appointed for 3 years

Safety and suitability

Safety

Upper Level

Infant Formulae/Dietetic Foods

Dietary Reference Values

Scientific advice

Novel Foods

Food Allergy

Claims

Evaluation of scientific substantiation

on nutrition and health claims made on foods
EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel):

- Scientific criteria for substantiation of claims made on foods & EFSA role
- Review of evidence submitted: issues identified & highlights
Main criteria for health claims & EFSA’s role

Regulation (EC) No 1924/2006 - Claims substantiated by:

- “generally accepted scientific evidence” (Article 6.1)
- “totality of the available scientific data” (Recital 17)
- “weighing the evidence” (Recital 17)

- Health claims should only be authorised for use in the Community after “a scientific assessment of the highest possible standard” (Recital 23)

- In order to ensure harmonised scientific assessment of these claims, **EFSA** should carry out such assessments (Recital 23)
  - Whether the evidence for a claim meets this standard is a scientific judgement of the NDA Panel
  - EFSA NDA Panel adopts scientific opinions

**AUTHORISATION:** by Commission/Member States, with European Parliament scrutiny
EU Register of Claims (http://ec.europa.eu/nuhclaims/)
1. Is the food/constituent **defined** and **characterised**?

2. Is the claimed effect **defined**, and is it a **beneficial physiological effect**?

3. Is a **cause and effect relationship** established between consumption of the food/constituent and the claimed effect?
   - for the **target group** and under the **proposed conditions of use**
   - **Human data are central**

➢ **Scientific substantiation requires a favourable outcome to ALL three questions**
1. Selection & review of relevant human studies – hierarchy of evidence

- Individual human studies have appropriate design and quality?
- Carried out with a food/constituent complying with the food specification that is the subject of the claim
- Appropriate outcome measure(s) for the claimed effect - what is generally accepted by experts in the field?
- Conditions for human studies vs. conditions of use for the claim (e.g. quantity of food/constituent)
- Study group representative of the target group, or extrapolation to the target group possible?

2. Review of supportive studies: in vitro, animal and mechanistic studies, etc. (e.g. biological plausibility)
3. Weighing the evidence

combining the relevant human studies + other studies to conclude on substantiation
## Health claims applications

by November 2013

<table>
<thead>
<tr>
<th>Year</th>
<th>No of applications received in the year</th>
<th>Status of applications processed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug-Dec 2007</td>
<td>5</td>
<td>3 adopted / 2 withdrawn</td>
</tr>
<tr>
<td>2008</td>
<td>243</td>
<td>80 adopted / 9 in progress / 32 under validation (children c.) / 120 withdrawn</td>
</tr>
<tr>
<td>2009</td>
<td>36</td>
<td>24 adopted / 12 withdrawn</td>
</tr>
<tr>
<td>2010</td>
<td>29</td>
<td>15 adopted / 14 withdrawn</td>
</tr>
<tr>
<td>2011</td>
<td>27</td>
<td>24 adopted / 3 withdrawn</td>
</tr>
<tr>
<td>2012</td>
<td>52</td>
<td>43 adopted / 9 withdrawn</td>
</tr>
<tr>
<td>2013 (on-going)</td>
<td>27</td>
<td>10 adopted / 14 in progress / 2 under validation / 1 withdrawn</td>
</tr>
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### Claims applications - evaluation & timelines
(August 2007 - 31 August 2013)

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<th><strong>Art. 13(5) health claims</strong> (newly developed scientific evidence and/or request for protection of proprietary data):</th>
<th><strong>Art. 14 health claims</strong> (disease risk reduction, children’s development and health):</th>
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</table>
| **Legal deadline**             | **5 months**  
Applicant has 15 days to reply to EFSA request for supplementary information                                                | **5 months**                                                                         |
| **Number of applications received** | **129**                                                                                        | **283**                                                                             |
| **Number of clock stops for supplementary information** | **73**  
(1 clock stop for 63 applications; ≥ 2 clock stops for 10 applications)                                                      | **36**  
(1 clock stop for 29 applications; ≥ 2 clock stops for 7 applications)               |
| **Evaluation time** (range in months) | **1.7 to 8.2 months**                                                                            | **2.2 to 24 months**                                                                  |
| **Finalised applications**     | **91**  
(13 positive; 78 negative)                                                                                   | **100**  
(33 positive; 67 negative)                                                           |
| **In progress:**               | **11**                                                                                       | **4**                                                                                |
| **Under validation:**          | **4**                                                                                         | **41**                                                                               |
| **Withdrawn applications**     | **23**                                                                                       | **138**                                                                              |
1. During the validation period

No timeframe
Via the Applications Desk/NutritionUnit
Once the dossier is validated = start the clock

2. During the assessment period

Time constraints from the regulation
Questions from the Working Group Claims/NDA Panel
Clock stop
412 Applications received

Status of claim applications Art. 13.5 & 14
(01 August 2007 – 31 August 2013)

- Adopted 46 %:
  - Positive 24 %
  - Negative 76 %

- Negative outcome 35 %
- Positive outcome 11 %
- Withdrawn 39 %
- Under validation 11 %
- In progress 4 %
Issues arising while reviewing scientific evidence for health claims

Reasons for clock stops requesting supplementary information

(from 109 clock stop letters to applicants)
Reasons for clock stops

- Characterisation of the food constituents: 12%
- Claimed effect & target population: 13%
- Studies submitted for substantiation of claims: 75%
Questions on studies submitted for substantiation of claims

- Study participants: 8%
- Study products vs. controls: 9%
- Outcomes: 13%
- Sample size/power calculation: 5%
- Blinding: 3%
- Randomisation: 5%
- Statistics: 23%
- Result reporting: 14%
- Others: 20%
48 questions on the characterisation of the food/constituent:

- Quantitative/qualitative composition, specification of the food in relation to the claim (e.g. macro- & micronutrient composition), analytical aspects (e.g. extraction, extract used)
- Characterisation of microorganisms at strain level
- For comparative claims: specification of the food vs. the comparator
- Rationale for product specific claims
51 questions on the claimed effect/outcome measures & target population:

- **Several claims/non-specific claimed effect** (e.g. improve body’s resistance, healthy teeth).
- **Single claim** but unclear which is the appropriate outcome measure(s)
- **Confusion on the claimed effect vs. the mechanism(s) to achieve the claimed effect**
- **Disease risk reduction claims**: risk factor not defined, or rationale for an association between the risk factor and the claimed effect not given (e.g. Secretory-Immunoglobuline A and development of common cold or influenza).
- **Evidence for a health benefit of the claimed effect** not provided (e.g. decreasing number of adipocytes at the abdominal level per se)
- **Specific physiological function of the body** not identified (e.g. reduces wrinkles)
- **Target population** unclear (e.g. “sensitive adults”)

Issues identified (cont.)
237 questions on studies submitted for substantiation:

- **Participants** (23): study population/number, baseline characteristics, inclusion/exclusion criteria, background diets, medication used (*e.g.* antibiotics)

- **Products used in the study intervention** (27) vs. food/constituent for the claim (*e.g.* the strains of microorganisms used in the studies not given) vs. control products (*e.g.* unspecified or not neutral in relation to the claimed effect)

- **Study outcomes** (38): appropriateness in relation to the claimed effect, primary/secondary not specified, validity of questionnaires used for self reporting

- **Sample size** (15): power calculation, hypotheses and the primary outcome tested not specified

- **Randomisation** (16): method not reported

- **Blinding** (8): procedure not specified
237 questions on studies submitted for substantiation (cont.):

- **Statistics** (67): methods not given or inappropriate for the study design (*e.g.* cross-over), unclear rationale for using different statistical models (*e.g.* for per protocol vs. ITT analysis, multiple comparisons/outcome measures not considered in analyses (*e.g.* simple ANOVA), unclear statistical treatment of data & handling of missing data

- **Results** (43): numbers analysed unclear, reasons for dropouts not given, inconsistent (*e.g.* text vs. table vs. study report) or incomplete (*p*-values, *SD*, confidence intervals), or selective reporting; unplanned sub-group/post-hoc analyses, no between-group comparisons
61 other questions on studies submitted for substantiation:

- Full study reports/protocols for pertinent proprietary studies not provided (20)
- Rationale for extrapolation of data (15): e.g. diseased population under pharmacological treatment to general healthy population without treatment
- Plausibility of the effect/mechanisms of action (10)
- Pertinent study selection (8): inclusion/exclusion criteria, meta-analyses
- Ethic Committee approval (5)
- Conditions of use (3)
Issues arising with review by EFSA of evidence on health claims

Highlights
Mis-reporting of studies

- **Published papers** may not accurately represent what was done and what was the outcome
  - incomplete reporting, e.g. subject selection, enrolment, randomisation, retention and drop outs; statistical analyses
  - selective reporting of outcomes, subgroup analyses – mainly favourable outcomes reported

- EFSA may request additional information from the applicant, including full study report for key studies
Commonly observed sources of bias

Intervention studies

- design – insufficient size, insufficient control of confounding, inadequate protocols for measurement of outcomes
- execution - randomisation, blinding, compliance with study protocol
- statistical analysis - drop outs and treatment of missing data, treatment of multiple outcomes, unplanned sub-group/post-hoc analyses

Observational studies

- measurement of relevant exposure, confounding
The pooling of data from a number of similar studies in a meta-analysis can be a useful method of weighing the evidence from these studies.

- Meta-analysis must be carried out with great care to avoid biased conclusions.

Commonly observed sources of bias:

- **Transparency** - incomplete reporting of studies, inclusion/exclusion criteria, primary/secondary analyses, pre-planned comparisons/sensitivity analyses.

- **Study selection** – inappropriate inclusion/exclusion criteria, inappropriate (restricted) search.

For key meta-analyses with potential sources of bias, EFSA may exclude the meta-analysis or may request a re-analysis from the applicant.
However, the articles included in our analysis did not provide the information needed to evaluate any potential differences between different types of chocolate in the associations with cardiometabolic disorders.

In addition, contrary to scientific journals, pivotal papers may be critically appraised by 20-30 peer-reviewers and collectively discussed for as long as needed to reach a full agreement on the conclusion of this peer-review process.
THANK YOU FOR YOUR KIND ATTENTION