European perspective on the use of biomarkers for substantiation of health claims on foods

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Outline

• EFSA review of the evidence for scientific substantiation of health claims

• Biomarkers for substantiation of
  – claims for reduction of disease risk
  – function claims

• Conclusions
EFSA review of the evidence submitted for scientific substantiation of health claims

- EU Regulation 1924/2006 on Nutrition and Health Claims made on foods
Features of the EU Regulation (vs USA)

- Health claims include:
  - reduction of disease risk claims
  - function claims
  - claims on development and health of children

- Applies equally to foods and food supplements

- All claims must be authorized (by Eur. Commision) and all must be assessed by EFSA before authorization

- A single standard of evidence for substantiation of all health claims

- No provision for qualified health claims
EU evidence standard for health claims

• All claims must be substantiated by generally accepted scientific evidence, taking into account the totality of available scientific data, and by weighing the evidence = generally accepted by scientific experts

• Standard similar to FDA Significant Scientific Agreement

• Whether the evidence for a claim meets this standard is a scientific judgement of EFSA’s NDA Panel
Main issues addressed by NDA Panel

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 the consumption of the food/constituent and the claimed effect?
   - For the target group
   - Under the proposed conditions of use
Evidence review - steps

1. Selection and review of **relevant human studies** (central studies for substantiation)

2. Review of studies on biological plausibility - mechanisms, bioavailability

3. Weighing the evidence to conclude on substantiation
   - transparent scientific judgement of the NDA Panel
   - published scientific opinion in EFSA journal:
Relevant human studies

• studies carried out with the food/constituent for claim

• **appropriate outcome measure(s)** for the claimed effect

• conditions for studies comparable to conditions of use for claim (e.g. quantity of food/constituent)

• study groups representative of the target group or extrapolation to the target population possible
EFSA consideration of biomarkers as appropriate outcomes for human studies

Q. What is generally accepted by scientific experts?

1. Assessment of applications for health claims
   – dialogue with applicant
   – outcome published in scientific opinions

2. Guidance for applicants for health claims
   – public consultation - submissions from stakeholders
   – outcome published in guidance documents & technical reports
EFSA guidance on scientific requirements for specific types of claims (2010-12)

- which relationships are eligible for health claims?
- what types of studies, outcome measures (incl. biomarkers) and study groups are appropriate?
  - Gut, immune
  - Bone, joints, skin, oral
  - Appetite, body weight, blood glucose
  - Antioxidants, cardiovascular
  - Physical performance
  - Neurological, psychological

Biomarkers for Substantiation of Claims for Reduction of Disease Risk
Reduction of disease risk claims: EU definition

- must be based on reduction of a risk factor for development of a disease
- not reduction of disease risk
- Substantiation requires human studies with a risk factor as outcome
Risk factors for disease

- physiological factors (or biomarkers) which are predictors of disease risk
- Interventions that change the risk factor also change the risk of disease
- only few biomarkers considered appropriate for general use as risk factors for disease
Authorized claim:

Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.

EFSA: - claim substantiated

- **Key studies**: intervention studies in adults showing sterols/stanols reduced serum LDL-cholesterol (risk factor for CHD)
- No studies needed on sterols/stanols and CHD risk
Criteria for risk factors

Serum LDL-cholesterol for coronary heart disease (CHD):

• can be reliably and accurately measured

• strong evidence of association with CHD risk, including interventions that reduce both LDL-C and CHD risk

• evidence for the role of elevated LDL-C in development of atherosclerosis
Vitamin D and osteoporotic fracture

Claim (pending authorization):

Vitamin D may reduce the risk of falling. Falling is a risk factor for bone fracture.

EFSA: - Claim substantiated

- Key studies: intervention studies with vitamin D showing reduced risk of falling (risk factor for osteoporotic fracture) in older adults
- Evidence that falling is a risk factor for bone fracture in older adults
Some biomarkers are considered appropriate as risk factors for specific foods/nutrients based on

- effect of the food/nutrient on both biomarker and clinical outcome (disease onset) in intervention studies

- biological plausibility for a role for the putative risk factor in the observed reduction of disease risk
Xylitol chewing gum and dental caries

Authorized claim:

Chewing gum sweetened with 100% xylitol has been shown to reduce dental plaque. High level of dental plaque is a risk factor in the development of caries in children.

EFSA: claim substantiated

- Key studies: intervention studies showing xylitol chewing gum reduces dental plaque (and risk of caries) in children
- Biological plausibility for role for reducing dental plaque in reducing development of caries
Calcium and osteoporotic fracture

Claim (pending authorization):

Calcium may reduce the loss of bone mineral in postmenopausal women. Low bone mineral density is a risk factor in development of osteoporotic bone fractures.

EFSA: - claim substantiated (also for Ca + Vit. D)

- Key studies: intervention studies showing calcium reduces loss of BMD (and risk of osteoporotic fracture) in postmenopausal women

- biological plausibility for a role for reducing loss of BMD and reduced risk of fractures
Biomarkers for Substantiation of Function Claims
Function claims: EU scope

Health claims describing or referring to:

• the role of a nutrient or other substance in growth, development and the functions of the body

• psychological and behavioural functions

• slimming or weight control, or a reduction in the sense of hunger, or an increase in the sense of satiety, or the reduction of the available energy from the diet
Defining function claims

- a **beneficial physiological effect** related to a function
- can be accurately and reliably measured
- rationale - why effect is beneficial in a specific context
  - evidence for physiological consequences of the effect
  - target population group (e.g. age, gender, physiological status)
  - conditions in which the benefit may be derived (e.g. acute/chronic, post-prandial, physical activity)
Study outcomes for substantiation of function claims

- Selection of appropriate outcomes (including biomarkers) of human studies for substantiation of function claims
  - case-by-case consideration
  - how claim is defined and how it relates to a function
  - the context of the claim, e.g. target population group, conditions for the claim
  - the study design, e.g. study group, duration, outcome measurement
Study outcomes for substantiation of cardiovascular function claims

- There are several claims related to cardiovascular function for which substantiation may be based on outcomes (biomarkers) that can be reliably measured in intervention studies of relatively short duration.
Claims related to cardiovascular function

- Maintain/improve elasticity of blood vessels (endothelium-dependent vasodilation)
- Maintain normal platelet aggregation
- Contribute to the protection of blood lipids from oxidative stress (protection of LDL particles from oxidative damage)
- Maintain normal blood LDL-cholesterol, or HDL-cholesterol, or triglycerides
- Maintain normal blood pressure
- Contribute to a reduction of the blood glucose rise after a meal
Claims on endothelial function

Endothelium-dependent vasodilation:

• Can be reliably and accurately measured – e.g. flow mediated vasodilation (FMD)

• Rationale - strong evidence for role of impaired endothelium-dependent vasodilation in development of vascular damage (e.g. atherosclerosis) in adults
Walnuts and elasticity of blood vessels

**Authorized claim:**
Walnuts contribute to the improvement of the elasticity of blood vessels

**EFSA:**
- claim substantiated
- **Key studies:** intervention studies showing walnut consumption led to a sustained improvement in endothelium-dependent vasodilation in healthy adults and type II diabetics
Cocoa flavanols and endothelial function

Claim (authorization pending):

Cocoa flavanols help maintain endothelium-dependent vasodilation which contributes to a healthy blood flow.

EFSA:

- claim substantiated

- Key studies: intervention studies showing cocoa flavanols consumption led to a sustained improvement in endothelium-dependent vasodilation in healthy adults and subjects with coronary artery disease.
Claims for platelet function

Platelet aggregation:

• Can be reliably and accurately measured ex vivo

• Rationale - strong evidence for role of elevated platelet aggregation in the development of atherosclerosis and its complications in adults
Water soluble tomato concentrate (WSTC) and platelet function

Authorized claim:

Water-Soluble Tomato Concentrate helps maintain normal platelet aggregation, which contributes to healthy blood flow

EFSA:

- claim substantiated

- Key studies: intervention studies showing WSTC consumption reduces platelet aggregation in healthy subjects
Olive oil polyphenols and oxidative stress

Authorized claim:
Olive oil polyphenols contribute to the protection of blood lipids from oxidative stress

EFSA: - claim substantiated

- **Key studies**: intervention studies showing olive oil polyphenols consumption led to a dose-dependent reduction in plasma oxLDL in healthy adults

- Changes in serum LDL conjugated dienes and *ex vivo* resistance of LDL to oxidation considered supportive
Claims related to immune function

- For immune function it is difficult to define claims that do not require clinical outcomes for substantiation
Study outcomes for substantiation of claims related to immune function

- (immune) defence against pathogens
  - clinical outcome – infection (+ immune markers)
  - clinically relevant reduction of the presence of specific pathogens, their toxins, or other virulence factors (+ immune markers)
  - stimulation of protective antibody titres in response to vaccination
Conclusions

Appropriate biomarkers for health claim substantiation:

• case by case scientific judgement by EFSA’s NDA Panel
  – what is generally accepted by scientific experts?

• reduction of disease risk claims - few biomarkers
  – level of evidence needed is demanding

• function claims - biomarkers for many (e.g. cardiovascular), more limited for others (e.g. immune)

• challenges:
  – defining acceptable function claims
  – defining relationship of putative biomarkers to functions