Webinar on scientific aspects to consider when preparing a health claim application

Speakers:
Professor Sean Strain
Professor Alfonso Siani

10 March 2016

Time: 10:00-11:00am

efsa
European Food Safety Authority

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- The webinar **is in English** and questions should be submitted in English.

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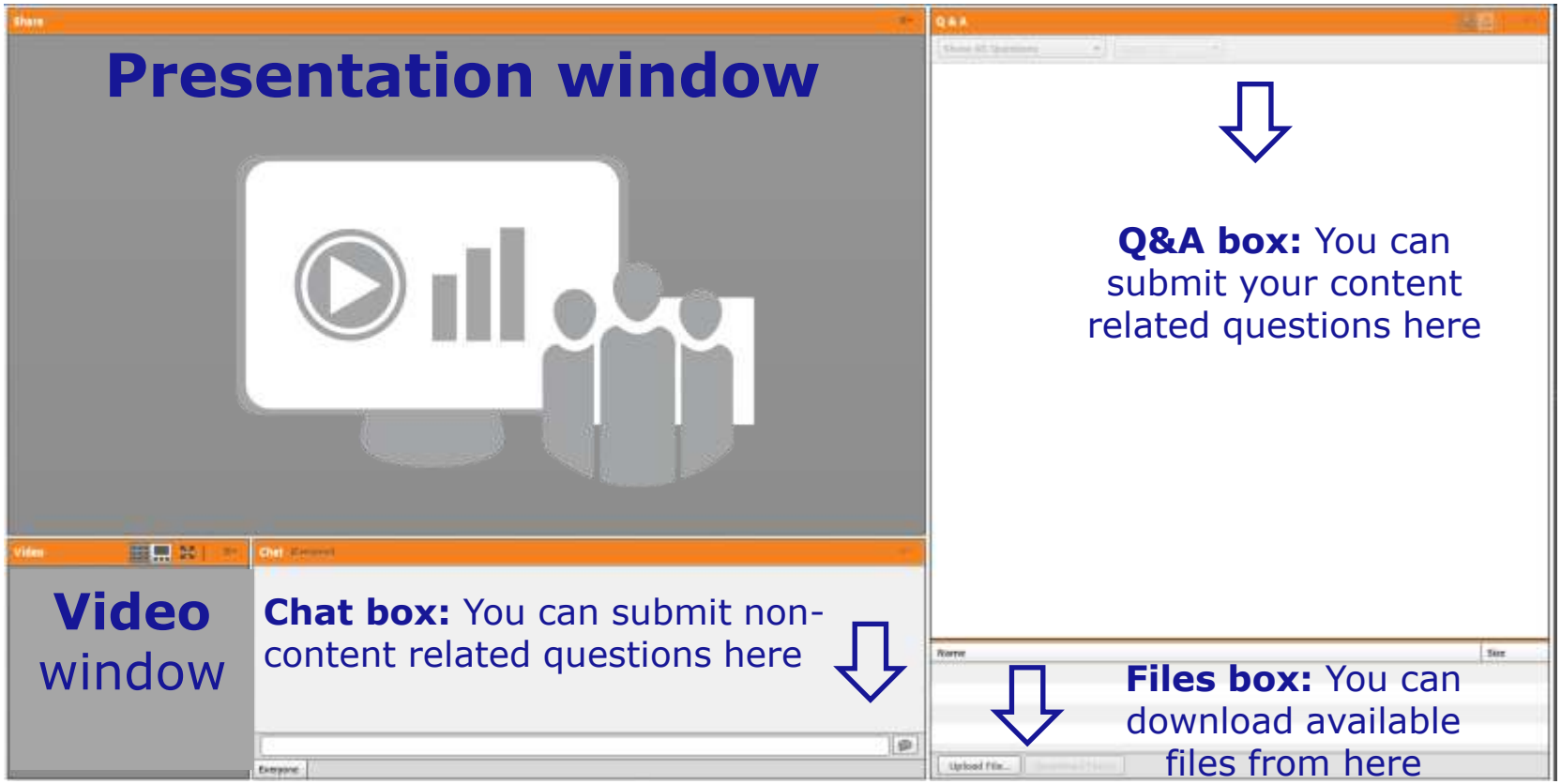
The Virtual Room



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Zoom in and out

Full screen
Zoom in/out

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Sending questions - Q&A box

- Questions should be **concise** and submitted **only once.** Follow-up questions should be **self-explanatory**
- You can ask questions **only until 11:00am**
- You will see the **answer** right below the question row
- We will address them as soon as possible and **no later than 11:30am**
- If you do not receive an answer to your question, feel free to re-submit it through the **EFSA APDESK** web form:

  http://www.efsa.europa.eu/en/applicationshelpdesk/askaquestion?ScientificArea=zero

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Q&A contributors' Team

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Objectives of the webinar:

- **Present practical examples** to illustrate key scientific aspects to consider when preparing health claim applications. Examples will focus on: (1) **health claims based on the essentiality of nutrients** and (2) **other claims**
- The webinar and Q&A **will NOT** address:
  - Advice on health claims which have not yet been evaluated by the NDA Panel
  - Advice on particular scientific studies
  - Questions related to legal framework and to risk management

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Outcome of the webinar:

WE WILL PUBLISH:

- Final agenda
- Presentation
- Webinar recording

WE WILL NOT PUBLISH:

- Log of questions and answers

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Webinar outline

10:00-10:05	INTRODUCTION: OBJECTIVE AND OUTLINE OF THE WEBINAR
10:05-10:55	PRACTICAL EXAMPLES ON SCIENTIFIC ASPECTS TO CONSIDER WHEN PREPARING A HEALTH CLAIM APPLICATION
10:55-11:00	KEY MESSAGES AND CLOSE

11:00-11:30	TIME RESERVED FOR ADDRESSING PENDING QUESTIONS. NO FURTHER QUESTIONS CAN BE SUBMITTED IN THIS PERIOD.

Scientific aspects to consider when preparing a health claim application

Speakers:
Professor Sean Strain and Professor Alfonso Siani

10 March 2016

OUTLINE

1. Consider the type of claim
2. Characterisation of the food/constituent
3. Formulation of the claimed effect
4. Comprehensive review of human studies
5. Quality of individual human studies
6. Rationale on biological plausibility
7. Scientific judgement of the evidence
8. Refining the claimed effect
9. Defining wording and conditions of use (CoU)

1. TYPE OF CLAIM

1) Claims based on the essentiality of nutrients

only if the nutrient:

is required for normal human body function(s)

i.e. has an essential mechanistic role in a metabolic function and/or the ability to reverse clinical signs and symptoms of its deficiency

cannot be synthesised by the body, or not in adequate amounts to maintain normal body function(s)

must be obtained from a dietary source

1. TYPE OF CLAIM

1) Claims based on the essentiality of nutrients

Example 1:

Vitamin C and normal collagen formation

✓ Coenzyme in normal collagen formation; vitamin C deficiency (scurvy) dominated by clinical signs of abnormal collagen formation (reversed with vitamin C intake)

✓ cannot be synthesised by the body

✓ must be obtained from a dietary source

1. TYPE OF CLAIM

1) Claims based on the essentiality of nutrients

Example 2:

Vitamin D and maintenance of normal muscle function

- ✓ clinical symptoms of vitamin D deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairment
- ✓ can be synthesised by the body but not always in sufficient amounts for normal muscle function
- ✓ must be obtained from a dietary source

1. TYPE OF CLAIM

2) Other claims i.e. NOT based on the essentiality of nutrients

Examples:

- Claim on vitamin C and immune system in subjects performing intense physical activity
- Claim on vitamin D and reduction of the risk of falling in the elderly
- Claims on carotenoids
- Claims on different classes of polyphenols
- Claims on micro-organisms

1. TYPE OF CLAIM

2) Other claims

Example:

Vitamin C and function of the immune system in subjects performing intense physical activity

- ✓ cannot be synthesised by the body
- ✓ must be obtained from a dietary source
- ➢ **BUT** infections/common cold is not among the signs/symptoms of vitamin C deficiency
- ➢ Claim assessed as duration/severity of common cold symptoms during/after extreme physical exercise in RCTs at doses of vitamin C beyond the DRV

1. TYPE OF CLAIM

2) Other claims

Example:

Vitamin D and reduction of the risk of falling in the elderly. Falling is a risk factor for bone fractures

✓ well-established role of vitamin D on normal muscle function

✓ **BUT** substantiation of the specific claim was based on RCTs showing an effect of vitamin D supplementation on reducing the risk of falling

✓ CoU not linked to nutrition claims but specific for reducing the risk of falling

2. CHARACTERISATION OF THE FOOD/CONSTITUENT

1) Claims based on the essentiality of nutrients

Chemical forms as present in foods or added to foods

→

Regulation (EC) No 1170/2009

2. CHARACTERISATION OF THE FOOD/CONSTITUENT

2) Other claims

i. Composition/characteristics	**plant sterols/stanols**: LDL-cholesterol **resistant starch**: post-prandial blood glucose **sugar-free gum**: tooth mineralisation
ii. Manufacturing process	**water-soluble tomato concentrate**: standardised by the total of 37 constituents inhibiting platelet aggregation *in vitro*
iii. Known mechanism of action	**non-digestible carbohydrates**: post-prandial blood glucose
ii. and iii.	**aqueous extract from white kidney bean:** inhibitory activity on pancreatic α-amylase

3. FORMULATION OF THE CLAIMED EFFECT

1) Claims based on the essentiality of nutrients

consider:

- Mechanistic role on a body function
- Signs/symptoms of deficiency
- Whether or not the nutrient can be synthesised by the body, or in adequate amounts to maintain the function
- Must be obtained from a dietary source

3. FORMULATION OF THE CLAIMED EFFECT

1) Claims based on the essentiality of nutrients:

Vitamin A

Maintenance of normal vision → required for transduction of light into neural signals → necessary for vision → night blindness: a symptom of vitamin A deficiency → **establish wording + CoU** ➢**submit application**

Maintenance of bones →
Maintenance of nails →
no established mechanistic or structural role, not among signs/symptoms of deficiency

3. FORMULATION OF THE CLAIMED EFFECT

1) Claims based on the essentiality of nutrients:

Iodine

Normal thyroid function → essential component of thyroid hormones → signs/symptoms of thyroid dysfunction: apparent in iodine deficiency → **establish wording + CoU**

➢ **submit application**

Maintenance of hair

Maintenance of nails

→ **no established mechanistic or structural role, not among signs/symptoms of deficiency**

3. FORMULATION OF THE CLAIMED EFFECT

1) Claims based on the essentiality of nutrients:

DHA

Maintenance of normal brain function → major structural component of brain tissue/retina → ALA deficiency= neurological impairment + low DHA concentrations; conversion of ALA to DHA very low → **establish wording + CoU**

➢**submit application**

Blood triglycerides →

LDL-oxidation →

no established mechanistic or structural role, not among signs/symptoms of deficiency

3. FORMULATION OF THE CLAIMED EFFECT

2) Other claims

consider:

- Exploratory review of the human studies available
- Identify the health/disease outcome(s) in relation to the food/constituent and for which the available evidence may be strong
- Do outcome(s) describe a beneficial physiological effect?
- Are outcome variable(s) direct measures of the claimed effect?
- Are the assessment methods appropriate?

3. FORMULATION OF THE CLAIMED EFFECT

2) Other claims:

Cocoa flavanols - Exploratory review

Outcomes assessed in human intervention studies

- ✓ blood pressure (BP)
- ✓ endothelium-mediated vasodilation
- ✓ platelet aggregation
- ✓ insulin sensitivity
- ✓ lipid peroxidation
- ✓ cognitive function
- ✓ incidence of Alzheimer disease

Outcomes describe a beneficial physiological effect

NOT for reduction in Alzheimer disease incidence
(no identified risk factor which could be modified by dietary cocoa flavanols)

3. FORMULATION OF THE CLAIMED EFFECT

2) Other claims:

Cocoa flavanols - Exploratory review (cont.)

Most studies on **endothelium-dependent vasodilation and blood pressure**

→ Few studies on other outcomes with mixed results

→ Candidates for claims

→ ✓ **Maintenance of normal endothelium-dependent vasodilation**

→ ✓ **Maintenance of normal BP**

→ ✓ **Disease risk reduction claims on diseases for which high BP is a risk factor**

FOR OTHER CLAIMS

NOT based on the essentiality of nutrients

4. Comprehensive review of human studies
5. Quality of individual human studies
6. Rationale on the biological plausibility
7. Scientific judgement of the evidence
8. Refine the claimed effect
9. Define wording and conditions of use (CoU)

4. COMPREHENSIVE REVIEW OF HUMAN STUDIES

Search and check for:

- Published/unpublished studies
- Compliance of the food/constituent with the specification
- Suitability of the study group

→

- Only studies with a DIFFERENT food/constituent → Consider changing/refining characterisation of the food/constituent
- Only studies in UNSUITABLE study groups → Consider changing the target population, or conducting additional studies
- At least ONE study in a SUITABLE study group → Proceed with the application

4. COMPREHENSIVE REVIEW OF HUMAN STUDIES

Example 1

Fixed combination of two microorganisms

and

defence against pathogens in the GI tract

→

Most studies conducted with one of the microorganisms

No studies with the fixed combination

→

Consider reformulation of the food/constituent to the single strain

4. COMPREHENSIVE REVIEW OF HUMAN STUDIES

Example 2

A microorganism

and

defence against pathogens in the GI tract for the general population

Only studies in infants

= extrapolation of results to adults NOT POSSIBLE

Consider changing the target population and the scope of the application

from Art.13(5) to Art.14

4. COMPREHENSIVE REVIEW OF HUMAN STUDIES

Example 3

Glucosamine and joint function

Only studies in subjects with osteoarthritis

= extrapolation of results to the target population **NOT POSSIBLE**

Consider conducting studies in healthy study groups

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

- Different tools available to appraise the design/quality of human studies with respect to the risk of bias
- Common core concepts for assessing study quality
- In principle, human intervention studies to be assessed first
- Randomised controlled trials (RCTs) at top of the hierarchy of evidence

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

Main aspects to consider for appraisal of RCTs

- **Study design**
- **Characteristics of participants**
- **Settings**
- **Interventions**
- **Outcomes**
- **Sample size calculation** and **primary outcome(s)**
- **Randomisation**
- **Blinding**

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

Main aspects to consider for appraisal of RCTs (cont.)

- **Main data analysis**
- **Additional data analyses**
- **Results and conclusions**

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

Study evaluation with respect to risk of bias:

Study at LOW risk of bias	**Conclusions can be drawn** about the effect of the food/constituent on the outcome(s)
Study at MODERATE risk of bias	**Conclusions can be drawn despite some methodological limitations**
Study at HIGH risk of bias	**NO conclusions can be drawn**

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

Examples:

Test and control foods differ in characteristics other than the food/constituent
which could affect the claimed effect

Dark vs. white chocolate
for a claim on cocoa flavanols and BP
(Test and control foods also ≠ in their content of caffeine and theobromine, which could affect BP)

Study design NOT appropriate for the claim

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

Examples:

Subjects NOT blinded to the intervention

+ self-reported outcome
(GI discomfort)

Randomisation prior to eligibility check

Subjects excluded post-randomisation as non-eligible

Loss of randomisation

High dropout rate in the intervention group vs. placebo, or vice versa

HIGH risk of bias

5. EVALUATE QUALITY OF INDIVIDUAL HUMAN STUDIES

Examples:

Intervention vs. control groups ≠ at baseline for the outcome of interest

UTI incidence in past year for a claim on defence against pathogens in lower urinary tract

Failure of randomisation

Cross-over design

Analysed as a parallel study by pooling results from the intervention and control periods

Inappropriate analysis for the study design

One out of 20 relevant outcomes positive (p< 0.05)

No *a priori* definition of the primary outcome

No statistical adjustment for multiple testing

High risk of chance finding

6. RATIONALE ON BIOLOGICAL PLAUSIBILITY

- **knowledge of enzymes or biological compounds regulating the claimed effect**
  - HMG-CoA reductase in modulating blood cholesterol concentrations
  - ACE in modulating BP
  - eNOS and RXNO species in modulating endothelium-dependent vasodilation
- **knowledge of mechanisms of action for compounds with similar structure**
  - Lovastatin effects on blood cholesterol: same chemical structure as Monacolin K in red yeast rice preparations

6. RATIONALE ON THE BIOLOGICAL PLAUSIBILITY

Biological activity *in vitro*:

- **how it may work**
  - red yeast rice preparation: inhibitory effect on HMG-CoA reductase activity
  - milk tripeptides: inhibitory effect on ACE activity
  - water-soluble tomato concentrate: inhibitory effect on platelet aggregation

6. RATIONALE ON THE BIOLOGICAL PLAUSIBILITY

Bioavailability/mechanistic studies in humans:

- **food constituent (its active form) reaches target site for the effect**
  - plasma concentrations of cocoa flavanols significantly ↑after administration
- **the effect time course consistent with pharmacodynamics**
  - maximum effect on endothelium-dependent vasodilation = 2h, when plasma concentrations of cocoa flavanols are at peak, effect disappears at ~ 4h
- **plausible mechanism of action**
  - plasma RXNO increase along with flavanols and vasodilation. Vasodilation does not occur following administration of eNOS inhibitors.

6. RATIONALE ON THE BIOLOGICAL PLAUSIBILITY

Efficacy, bioavailability and mechanistic studies in animals/*in vitro*:

Example: Water-soluble tomato concentrate (WSTC)

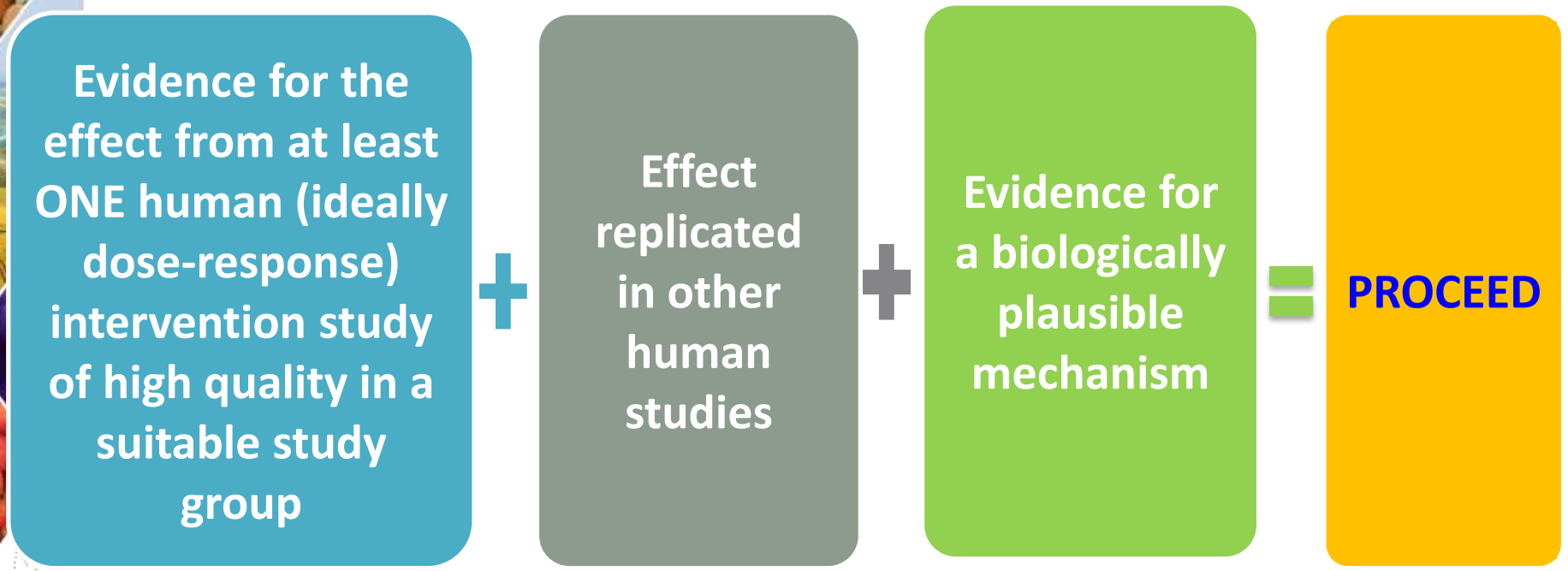
- **Mechanistic studies *in vitro*:** 37 compounds in WSTC showed different degrees of inhibition of platelet aggregation *in vitro*
- **Efficacy studies in animals:** WSTC characterised by the manufacturing process and HPLC profile for the compounds identified in the *in vitro* studies showed dose-dependent inhibition on markers of platelet aggregation in animals

7. SCIENTIFIC JUDGEMENT OF THE EVIDENCE

- **On efficacy**
  - Main evidence
    - human intervention studies in suitable study groups
    - human observational studies (if available)
  - Supportive evidence
    - human intervention studies in other study groups (if available)
    - animal efficacy studies
- **On the biological plausibility of the effect**

7. SCIENTIFIC JUDGEMENT OF THE EVIDENCE

Overall evidence: Example 1



Arabinoxylan and post-prandial blood glucose reduction:

- **1 high-quality dose-response human intervention study**
- 1 human study on a surrogate marker for the effect
- well-established mechanism for the effect

7. SCIENTIFIC JUDGEMENT OF THE EVIDENCE

Overall evidence: Example 2

Effect consistently shown in several human intervention studies, in different population groups and under different testing conditions

+

Even if NO evidence for a plausible mechanism of action

=

PROCEED/ CONSIDER CONDUCTING MECHANISTIC STUDIES

Limicol® and LDL-cholesterol reduction:

- No evidence of LDL-cholesterol lowering effect for any single ingredient at proposed doses, or on how ingredients (individually or in combination) could contribute to the effect
- Lack of a dose-response relationship in 1 human study
- **3 human intervention studies conducted by two independent research groups showed an effect**

7. SCIENTIFIC JUDGEMENT OF THE EVIDENCE

Overall evidence: Example 3

Evidence for inconsistent effect across human studies

BUT inconsistency explained by heterogeneity of studies

+

Evidence for a biologically plausible mechanism

=

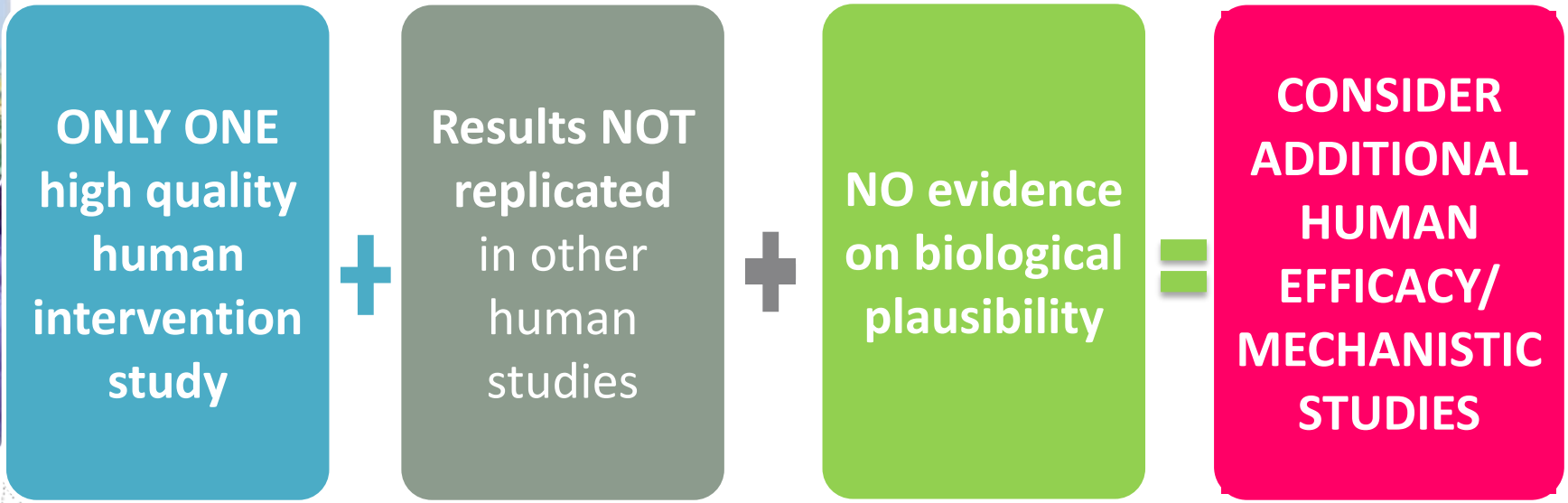
PROCEED

Creatine supplementation in combination with resistance training and increase in muscle strength:

- **3 studies showed an effect**
- 2 showed inconsistent effect
- 5 showed no effect (1 short duration, in 4 creatine was given on training days only-3 times/week)
- Plausible mechanism of action for daily creatine administration

7. SCIENTIFIC JUDGEMENT OF THE EVIDENCE

Overall evidence: Example 4



Coffee C21 and reduction of DNA damage:

- **1 high-quality human intervention study showing an effect**
- No other studies
- No evidence of biological plausibility

7. SCIENTIFIC JUDGEMENT OF THE EVIDENCE

Consider carefully how/to what extent human intervention studies showing no effect of the food/constituent affect the overall weight of the evidence

8. REFINE THE CLAIMED EFFECT

Example 1: Cocoa flavanols

Initial claim

Cardiovascular health

Exploratory review

Blood pressure OR endothelium-dependent vasodilation

Comprehensive review + scientific judgement

Endothelium-dependent vasodilation:

✓studies at low risk of bias

✓dose-response studies

✓mechanism of action for acute effect investigated

✓limited evidence for long-term effects in the CV system

Candidate claim for application

Maintenance of normal endothelium-dependent vasodilation

8. REFINE THE CLAIMED EFFECT

Example 2: Eye qTM (EPA+DHA+GLA)

Initial claim	**Cognitive function (children)**
Exploratory review	Most studies assessed several outcomes related to cognitive function in children with a disease
Comprehensive review + scientific judgement	✓1 study in healthy children showing an effect on **one aspect of working memory** ✓No biologically plausible mechanism
Candidate claim for application	**Working memory:** consider additional studies in healthy children targeting working memory as primary endpoint

9. DEFINE THE WORDING AND CONDITIONS OF USE

1. Claims based on the essentiality of nutrients

- **Wording:** the function for which the nutrient is essential
- **CoU:** nutrition claims in Regulation when possible

2. Other claims

- **Wording:** the function assessed in human studies (+ mechanism, if desired) e.g. helps maintain/contributes to the maintenance of normal defecation by decreasing stool consistency
- **CoU:** lower effective dose/pattern of consumption (e.g. once daily before/after meals), food matrix and/or preparation for use (e.g. plant sterols/stanols in dairy [not cereals], live microorganisms in yogurt [not in orange juice])

TAKE HOME MESSAGES

- **Each claim is unique**
- **Scientific requirements have to be considered in the context of a specific claim**
  - The food, target population, proposed CoU
- **Examples of past evaluations are a source of information**
  - insights on the number, type/quality of studies that may be needed for substantiation of a claim
  - highlights on shortcomings that can prevent the substantiation of certain claims

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