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

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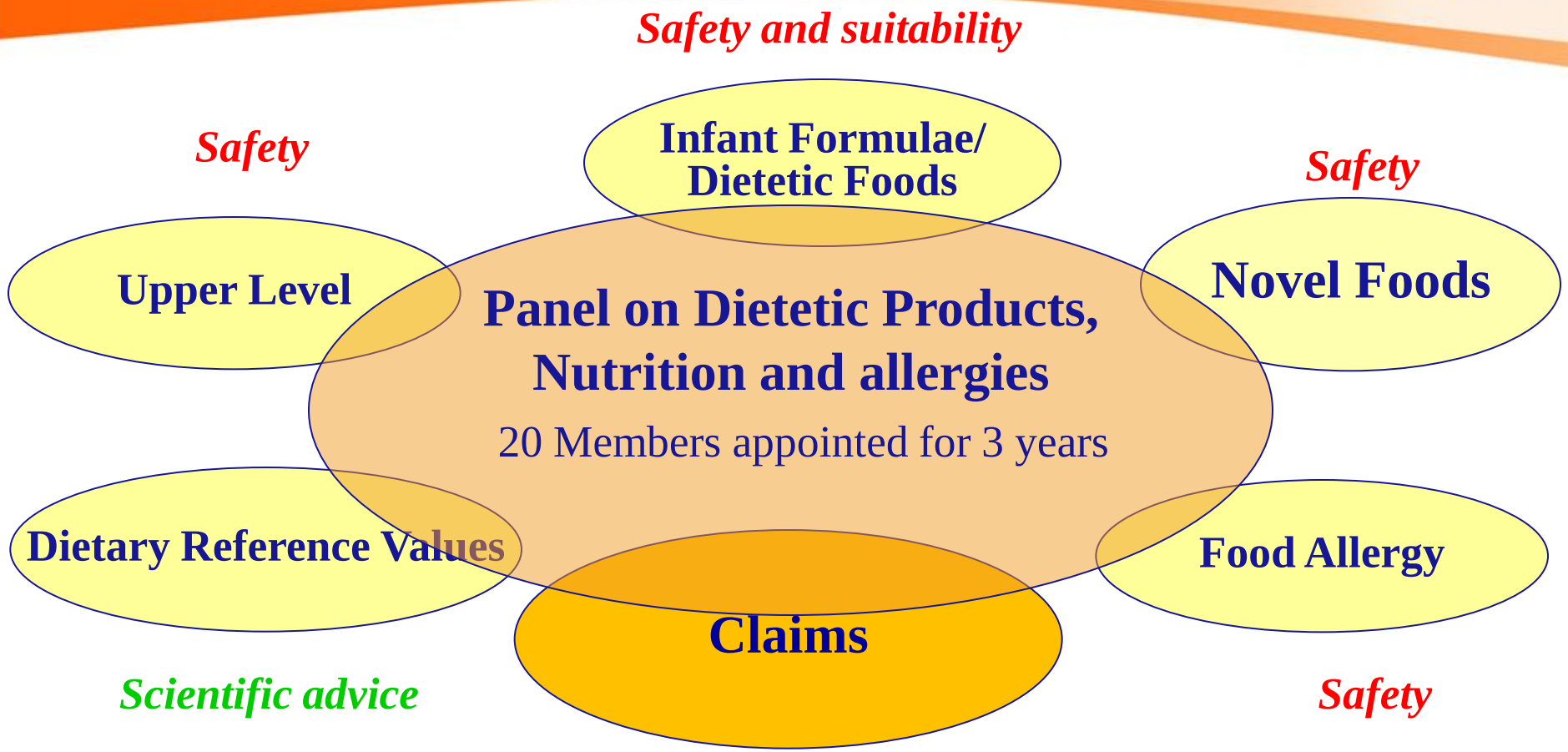
EFSA – NDA Panel



Supported by the EFSA Secretariat (Nutrition Unit)

Regulation (EC) No 1924/2006 of the European Parliament and of the Council

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of 20 December 2006

on nutrition and health claims made on foods

This presentation

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/)

Main issues addressed by NDA Panel

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Defining the claim

1. Is the food/constituent **defined** and **characterised** ?
2. Is the claimed effect **defined**, and is it a **beneficial physiological effect** ?

Substantiation

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**

EFSA evidence assessment-steps

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)**

EFSA evidence assessment-steps (cont.)

3. Weighing the evidence

combining the relevant human studies + other studies **to conclude on substantiation**

Health claims applications

by November 2013

Year	No of applications received in the year	Status of applications processed
Aug-Dec 2007	5	3 adopted / 2 withdrawn
2008	243	80 adopted / 9 in progress / 32 under validation (children c.) / 120 withdrawn
2009	36	24 adopted / 12 withdrawn
2010	29	15 adopted / 14 withdrawn
2011	27	24 adopted / 3 withdrawn
2012	52 (47 Art 13.5 + 5 Art 14)	43 adopted / 9 withdrawn
2013 (on-going)	27 (23 Art 13.5 + 3 Art 14 + 1 Art 19)	10 adopted / 14 in progress / 2 under validation / 1 withdrawn

Claims applications - evaluation & timelines
(August 2007 - 31 August 2013)

	Art. 13(5) health claims (newly developed scientific evidence and/or request for protection of proprietary data):	**Art. 14 health claims** (disease risk reduction, children's development and health):
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: **Under validation:**	**11** **4**	**4** **41**
Withdrawn applications	**23**	**138**

EFSA contact with applicants

1. **During the validation period**

No timeframe

Via the Applications Desk/NutritionUnit

Once the dossier is validated = start the clock

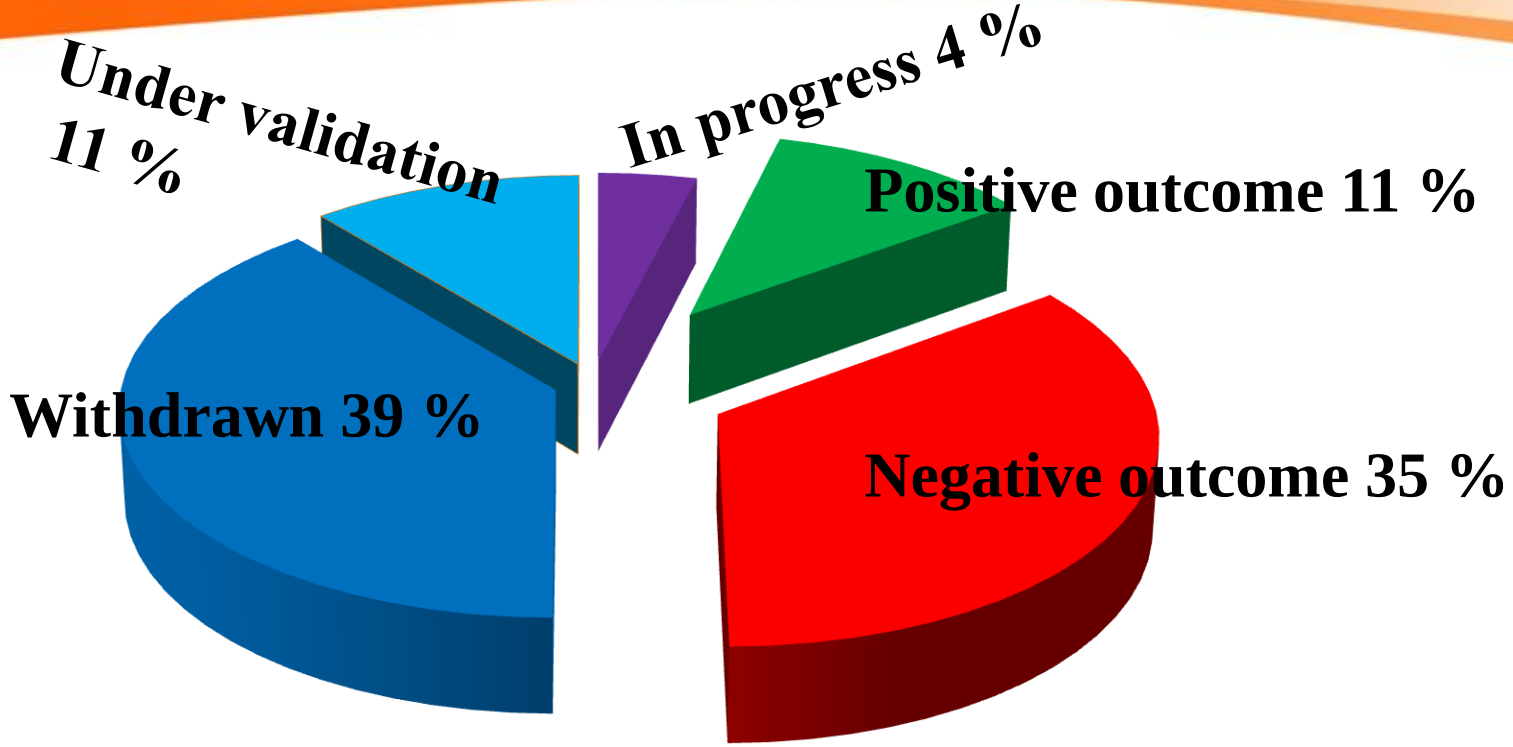
2. **During the assessment period**

Time constraints from the regulation

Questions from the Working Group Claims/NDA Panel

Clock stop

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



412 Applications received

Adopted 46 %:

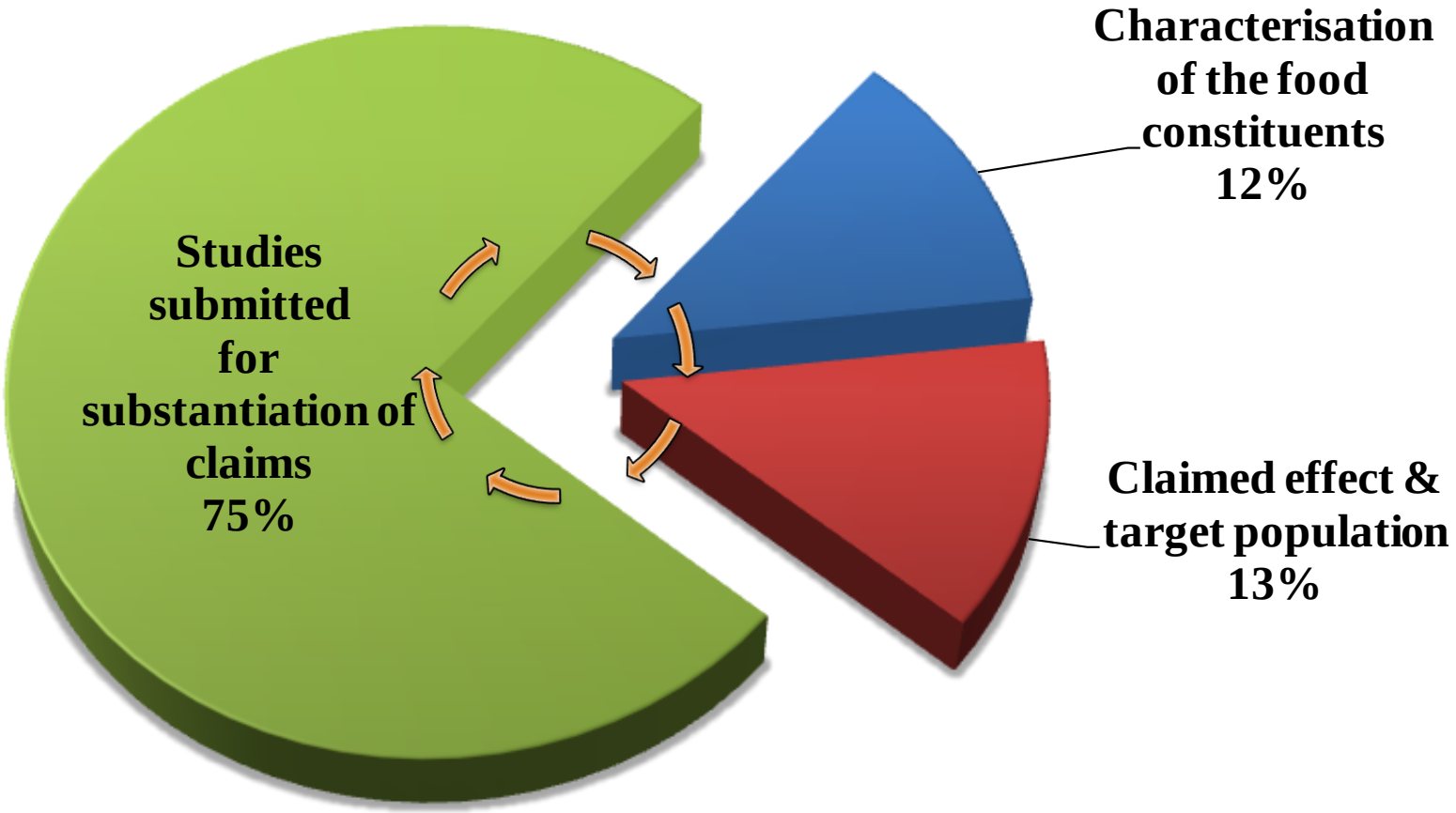
- ***Positive*** **24 %**
- ***Negative*** **76 %**

Issues arising while reviewing scientific evidence for health claims

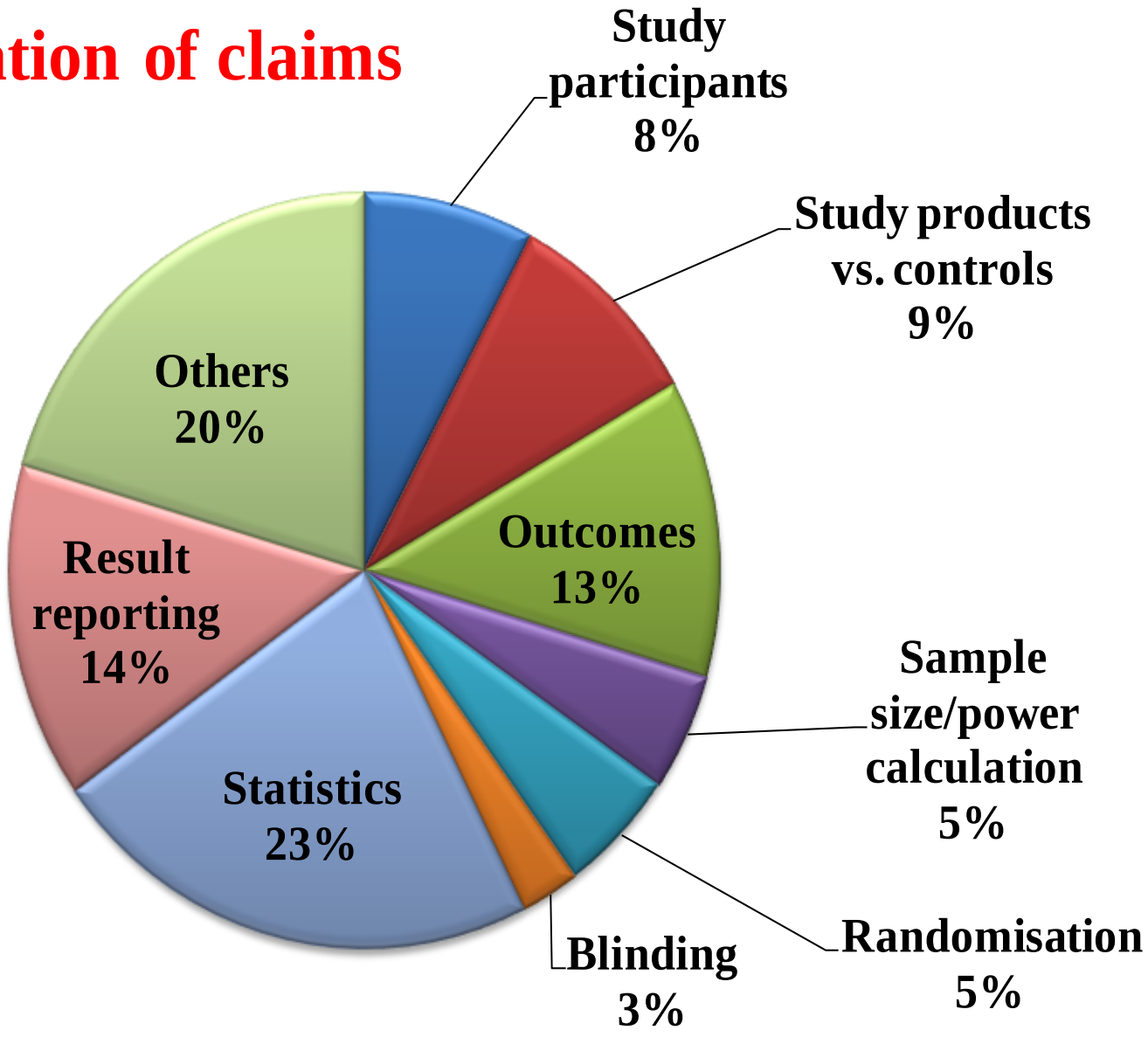
Reasons for clock stops requesting supplementary information

(from 109 clock stop letters to applicants)

Reasons for clock stops



Questions on studies submitted for substantiation of claims



Issues identified

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**

Issues identified (cont.)

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-Immunoglubuline 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

Issues identified (cont.)

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

Issues identified (cont.)

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

Quality of human studies reported

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

Systematic reviews and meta-analyses

- 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.

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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

A … , Laura
J … ersity lecturer
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…nsid… e, any conclusions should be cautious

THANK YOU FOR YOUR KIND ATTENTION