

# Real Life Examples of a Successful Claim Based on Good Clinical Science

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# Cocoa flavanols and vascular elasticity

## Timeline:

Application submitted: 14 December 2011

Start scientific evaluation: 20 January 2012

2 clock-stops

Opinion adopted: 27 June 2012

COMMISSION REGULATION (EU) No 851/2013 of 3 September 2013

# Health claim particulars

Applicant:	Barry Callebaut nv, Belgium
Food Constituent:	Cocoa flavanols
Health relationship:	regular consumption of at least 200 mg of cocoa flavanols leads to a sustained and physiologically relevant increase in endothelium-dependent vasodilation.
Proposed Claim wording:	‘cocoa flavanols help maintain endothelium-dependent vasodilation which contributes to healthy blood flow’
Specific conditions:	daily consumption of at least 200 mg cocoa flavanols

# Scientific substantiation

Literature search in Pubmed:

- 25 potentially pertinent studies

Application of self-defined exclusion criteria:

- 18 studies excluded
- Further exclusion of 2 studies because of lack of control group, lack of PC and/or high drop-out rate on measurement primary endpoint

Result search and selection process:

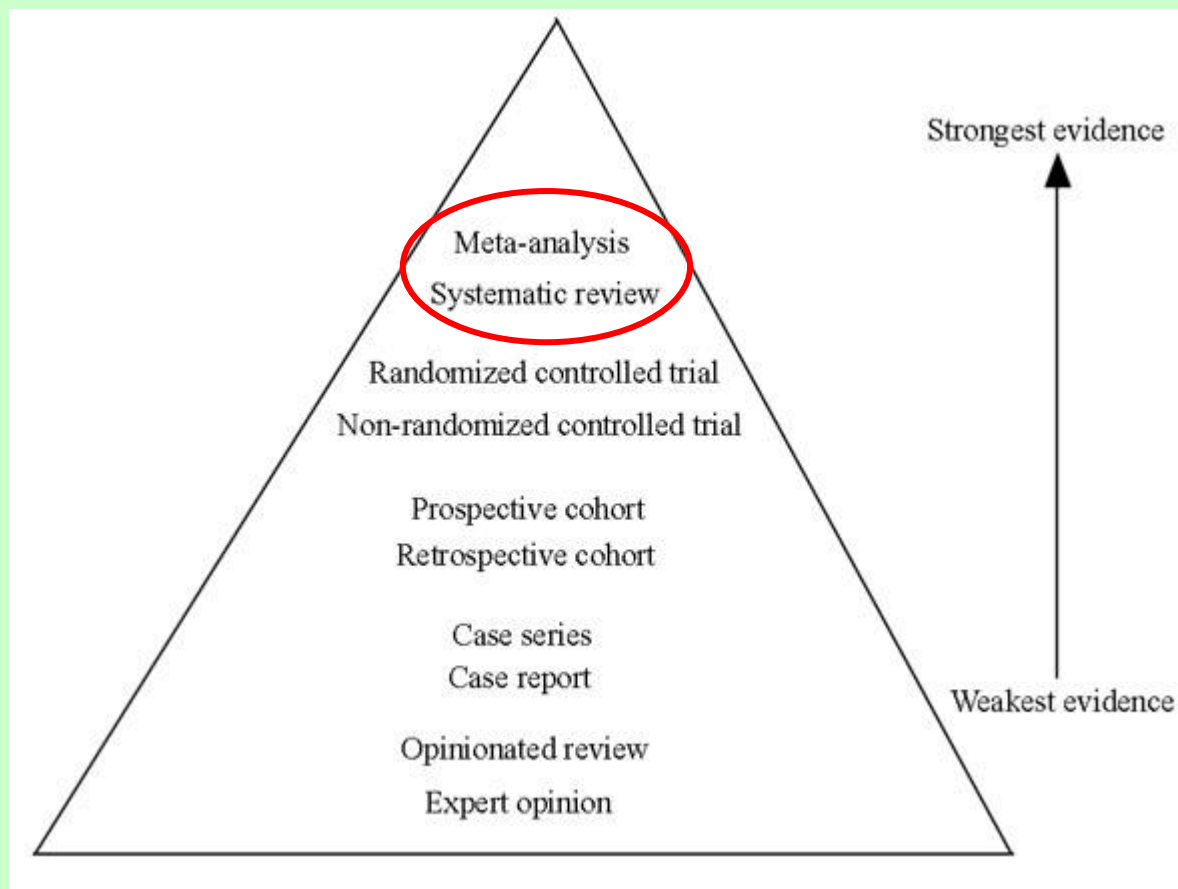
- 5 studies considered pertinent
- 1 unpublished proprietary study

# RCTs in healthy subjects

Pertinent studies were aimed at assessing:

- Effects of cocoa flavanols on ED-FMD
- In fasting conditions
- During regular consumption (1-12 weeks)
- Non-diseased populations

# Hierarchy of strength of evidence from peer-reviewed studies



# Meta-analysis

## Cocoa flavanols & ED FMD

(Hooper et al., 2012)

Selection criteria applied to determine low risk of bias:

- adequate allocation concealment
- Blinding of participants, providers, and outcome assessors
- Absence of industry funding
- study arms were similar in respect to saturated fat intake

All other trials were considered at moderate or high risk of bias.

*Note: no thorough consideration of criteria that are key to EFSA*

# Effect of cocoa, chocolate, or both on FMD

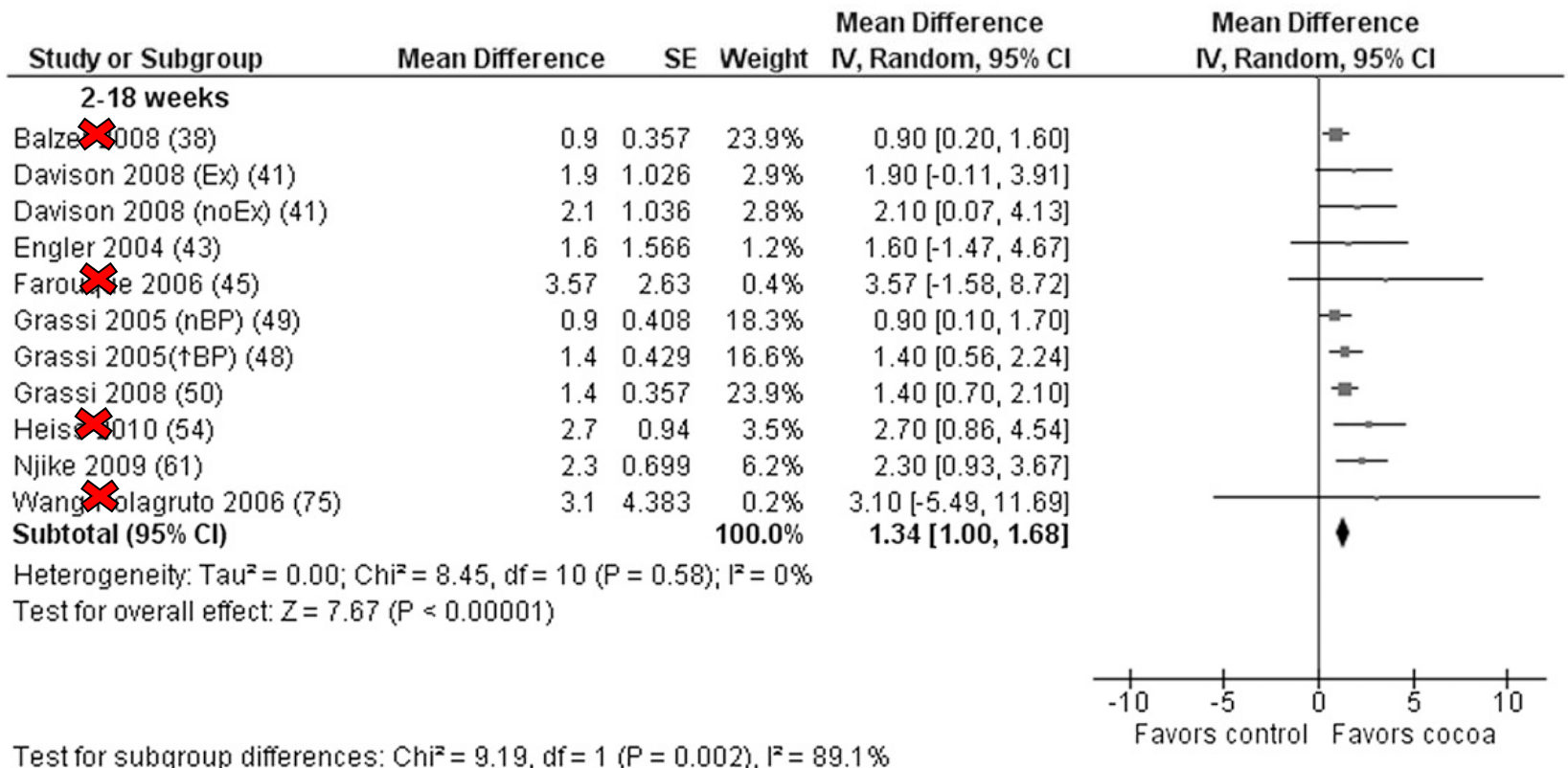
(Hooper et al., 2012)

Meta-analyses suggested:

- **acute** improvement in FMD 2 h after ingestion of chocolate/cocoa
- Improvement of FMD after **chronic** intake

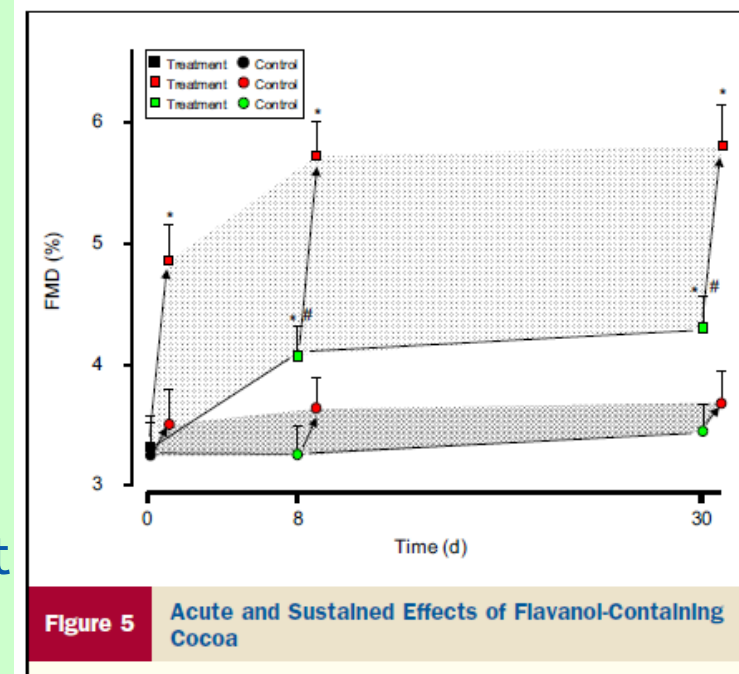


# Forest plot



# More studies got lost on the way!

- the study design did not allow an assessment of the effects of cocoa flavanols on ED-FMD either 2 h after consumption of cocoa nor in fasting conditions after regular administration of cocoa for two weeks because the measurement conditions at baseline and at the end of the study were not comparable with respect to the time at which cocoa flavanols were administered.



# More studies got lost on the way

- study appeared **not to be a standalone study**, but rather the continuation of a previous study on the acute effects of dark chocolate on ED-FMD
- Mix-up of baseline values
- unclear how acute and chronic effects could be calculated from the raw data collected.
- The applicant subsequently requested that this particular study should not be considered as pertinent to the claim. The Panel agrees that no conclusions can be drawn from this study for the scientific substantiation of the claim.

# More studies got lost on the way

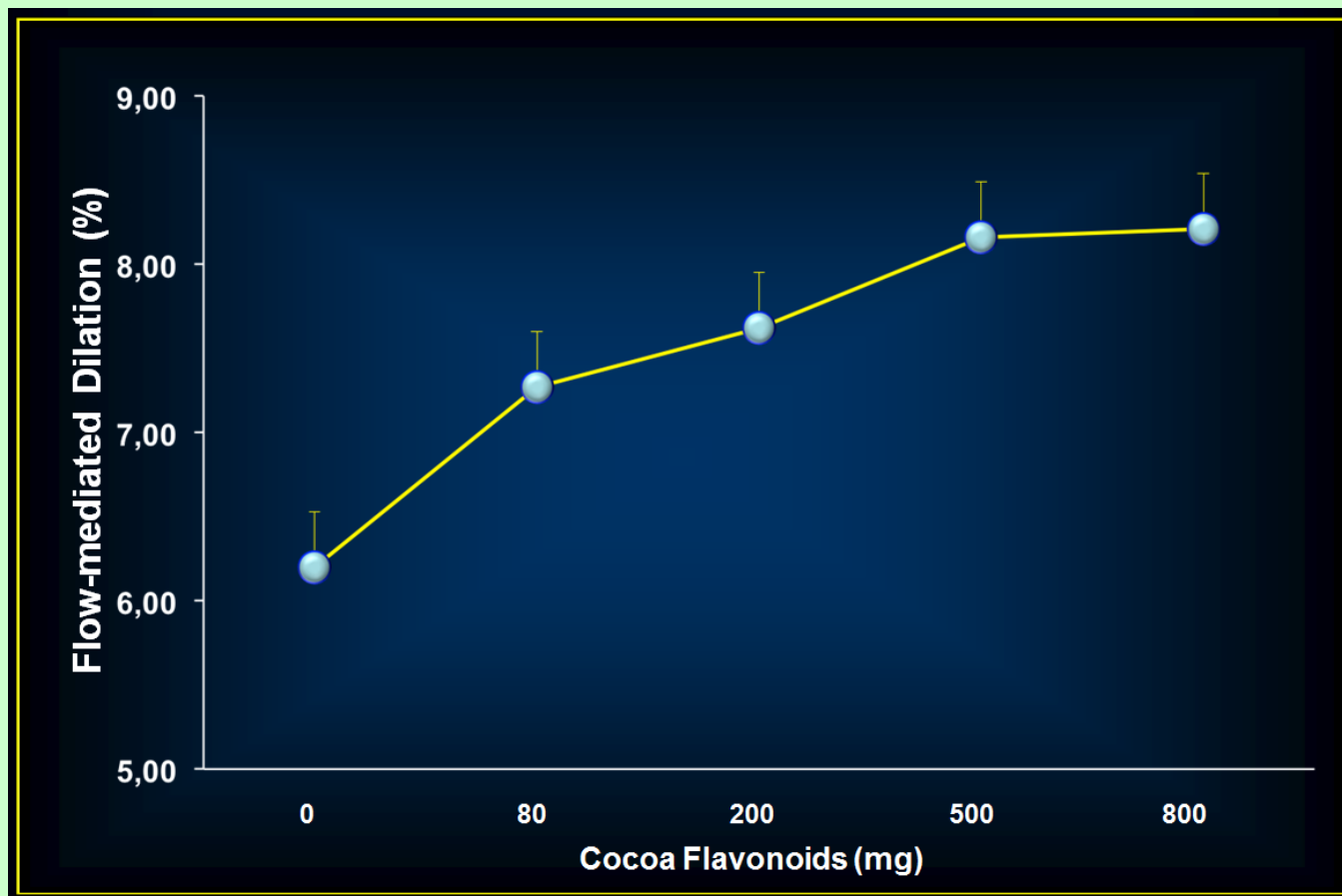
- For two studies, EFSA noted that **an effect of other food constituents** in cocoa (e.g. caffeine, theobromine) on ED-FMD could be excluded.
- White chocolate controlled
- Nevertheless, supportive

# Left-over from Hooper

1 clinical study considered pertinent!

# Dose-dependent effect

## Proprietary study



# Dose-dependent effect

## Proprietary study

- Formal assessment of dose-response effects:
  - statistically significant when using both linear and e-power regression analyses.
- The optimum curve fit was found by using a pseudo-Hill equation, which showed a plateau.
- curve started to flatten off at approximately 200 mg cocoa flavanols per day → **conditions of use!**

# In the End

The Panel noted that in healthy subjects:

- one intervention study showed an effect of cocoa flavanols consumed for 12 weeks on fasting ED-FMD
- one intervention study showed a dose-dependent effect of cocoa flavanols on fasting ED-FMD after one week of consumption, that the effect is observed under the conditions of use proposed by the applicant
- two additional intervention studies which may have not been adequately controlled for other food constituents in cocoa also supported an effect of cocoa flavanols on ED-FMD



# Cause and Effect

The Panel concluded that **a cause and effect relationship has been established** between the consumption of cocoa flavanols and maintenance of normal endothelium-dependent vasodilation.

# Proprietary Clinical Trial indispensable

The Panel could not have reached its conclusions  
without the human intervention study claimed as proprietary by  
the applicant

# Authorization

## Regulation 851/2013

Nutrient, substance, food or food category	Claim	Conditions of use of the claim	Conditions and/or restrictions of use of the food and/or additional statement or warning
Cocoa flavanols	Cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow (***)	Information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 200 mg of cocoa flavanols. The claim can be used only for cocoa beverages (with cocoa powder) or for dark chocolate which provide at least a daily intake of 200 mg of cocoa flavanols with a degree of polymerisation 1-10	-
(***) Authorised on 24.9.2013 restricted to the use of Barry Callebaut Belgium NV for a period of five years.			







*Thank you!*

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