Aspects réglementaires limitant l'usage des allégations avec le terme « antioxydants » - Comment valoriser un potentiel réel ?

Pascale Fança-Berthon

Avignon, 29 juin 2017 – Journée d'échange SFR TERSYS

Réglementation européenne des allégations nutritionnelles et de santé portées par des denrées alimentaires (Règlement CE n°1924/2006) – **Définition, principes et notions élémentaires**

Qu’est-ce qu’une allégation?

« **tout message ou toute représentation**, non obligatoire en vertu de la législation communautaire ou nationale, y compris une représentation sous la forme d'images, d'éléments graphiques ou de symboles, quelle qu'en soit la forme, **qui affirme, suggère ou implique qu'une denrée alimentaire possède des caractéristiques particulières**

Sur ce qu’il contient = ALLEGATIONS NUTRITIONNELLES

Sur le contenu
« contient du calcium »

Comparatives
« enrichi en calcium »

OU

Sur ce qu’il fait = ALLEGATIONS SANTE

ALLEGATIONS FONCTIONNELLES

Basées sur des données scientifiques généralement admises
« Le calcium est nécessaire à la santé des os »

Basées sur des données scientifiques nouvellement établies ou sur des données exclusives
« Le calcium présent dans le produit X est particulièrement biodisponible et favorable à la santé des os »

ALLEGATIONS DE REDUCTION DE FACTEUR DE RISQUE DE MALADIE
« Le calcium diminue le risque d’ostéoporose en favorisant une bonne densité minérale de l’os »

ALLEGATIONS CIBLANT LES ENFANTS
« Le calcium favorise la croissance de l’os »

Cas des allégations nutritionnelles

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« ne sont autorisées que si elles sont énumérées dans l'annexe et conformes aux conditions fixés dans le présent règlement »

Liste évolutive

- ✓ Faible valeur énergétique
- ✓ Valeur énergétique réduite
- ✓ Sans apport énergétique
- ✓ Faible teneur en matières grasses
- ✓ Sans matières grasses
- ✓ Faible teneur en graisses saturées
- ✓ Sans graisses saturées
- ✓ Faible teneur en sucres
- ✓ Sans sucres
- ✓ Sans sucres ajoutés
- ✓ Pauvre en sodium ou en sel
- ✓ Très pauvre en sodium ou en sel
- ✓ Sans sodium ou sans sel
- ✓ Sources de fibres
- ✓ Riche en fibres

Liste initiale

- ✓ Source de protéines
- ✓ Riche en protéines
- ✓ Source de [vitamines] et/ou [minéraux]
- ✓ Riche en [vitamines] et/ou [minéraux]
- ✓ Contient [nom du nutriment ou d'une autre substance]
- ✓ Enrichi en [nom du nutriment]
- ✓ Réduit en [nom du nutriment]
- ✓ Allégé/Light
- ✓ Naturellement/Naturel

- ✓ Source d'acide gras oméga-3
- ✓ Riche en acide gras oméga-3
- ✓ Riche en graisses monoinsaturées
- ✓ Riche en graisses polyinsaturées
- ✓ Riche en graisses insaturées

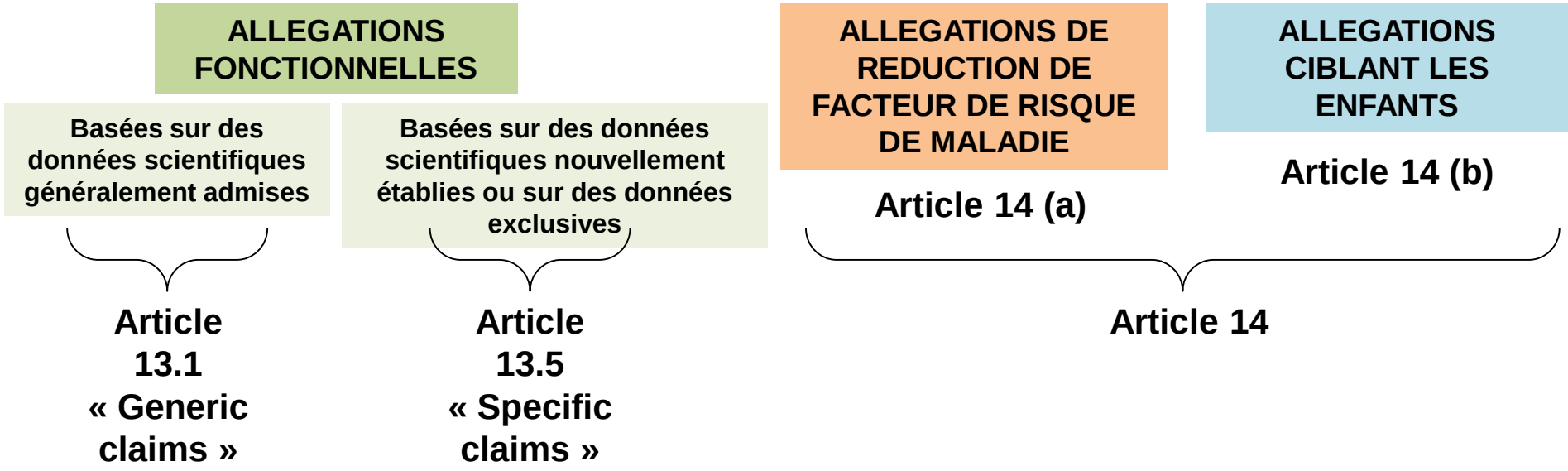
Liste actualisée le 9 février 2010

Pas de valeurs nutritionnelles de référence pour les phytonutriments (et donc les antioxydants hors Vit C et Vit E)

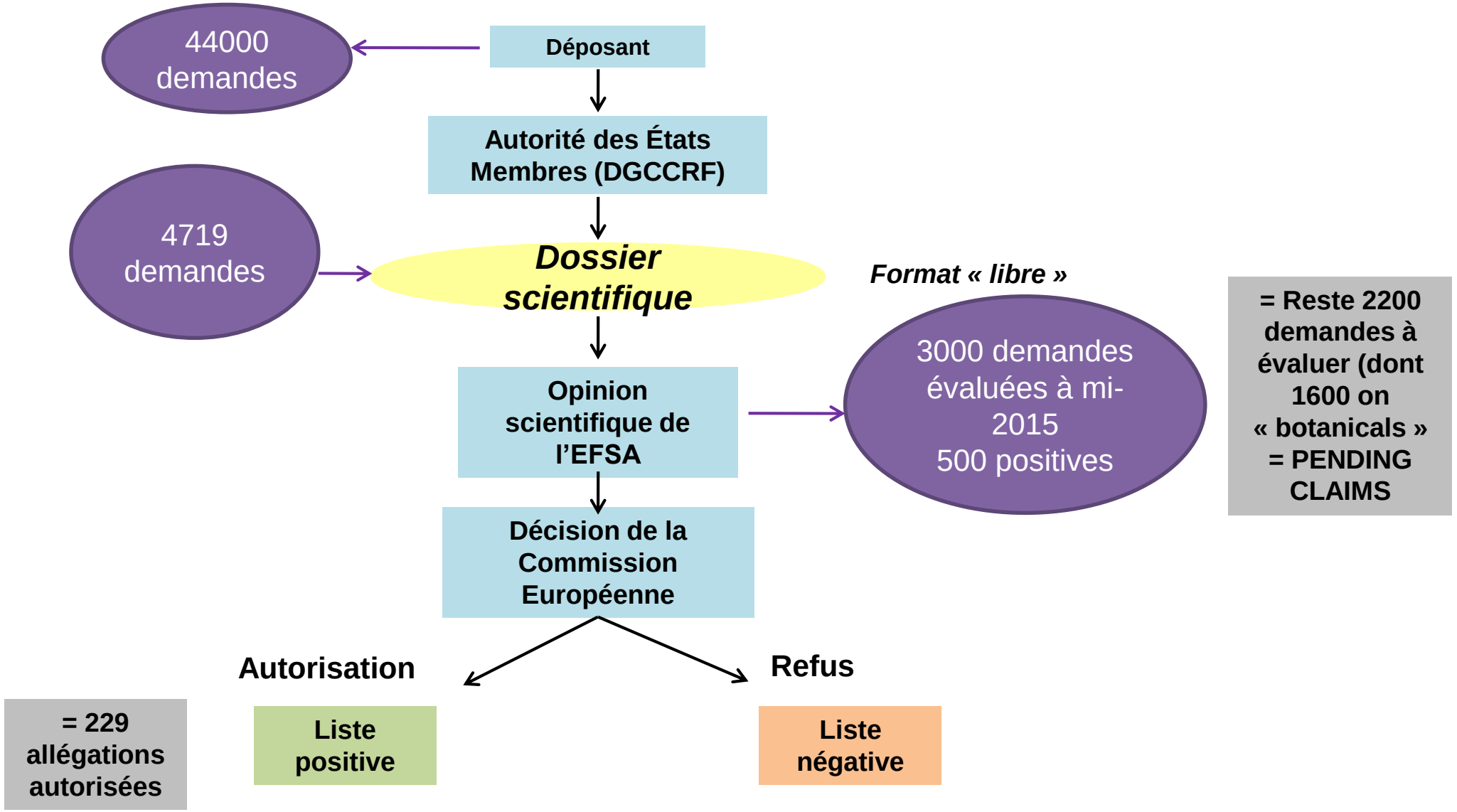
Cas des allégations de santé

✓ Quelles soient fonctionnelles, de réduction de facteur de risque de maladie ou destinées aux enfants, les allégations de santé **nécessitent une autorisation a priori**

✓ MAIS il existe une **procédure d'autorisation différente selon l'article du règlement dont relève l'allégation:**



Allégations de l'article 13.1



Allégations de l'article 13.1 (suite)

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Environ 500 opinions + (en 6 batches) sur
- ✓ **Vitamines, minéraux (300)**
- ✓ **Protéines, sucres**
- ✓ **Acides gras**
- ✓ **Fibres (24)**
- ✓ **Autres substances: phytostérols/stanols, chewing gum, substitut de repas, polyols…**

« Ils participent au bon fonctionnement cardiovasculaire et à l'équilibre en acides gras essentiels »

« pour des os plus solides »

« vous aide à perdre du poids et à stabiliser votre poids après un régime»

« l'avoine contribue à réguler le cholestérol»

Allégations de l'article 13.1 (suite)

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Et beaucoup d'abus sur la qualité des dossiers!

Pour le « Panax ginseng et la performance cognitive »:
Ezekiel 27.17. The Old Testament In: The **Holly Bible**.

Wikipedia, Tribulus,
http.//en.wikipedia.org/wiki/Tribulus

Caffeine. 2000. In: The American Heritage **Dictionary** of the English Language

Beck,L. The complete **idiot's guide** to total nutrition for Canadians (équivalent de la gamme « …pour les nuls »)

Allégations de l'article 13.1 « pending »

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Les allégations en attente d'évaluation sont autorisées tant qu'elles n'ont pas été évaluées (certainement rien de prévu avant 2019!)

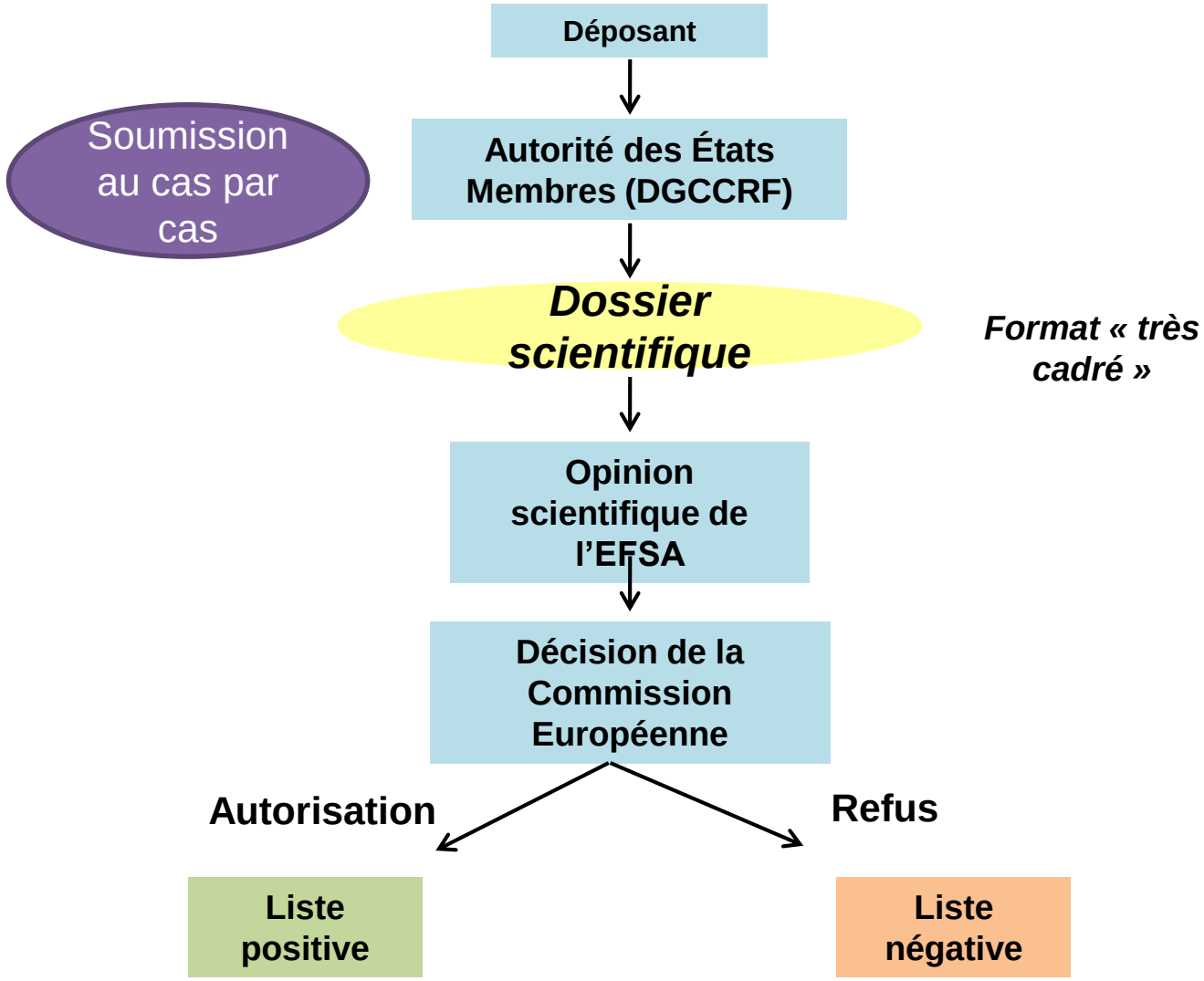
"French maritime pine bark helps to maintain good health by protecting cells & tissues through its antioxidant property."

"Blueberry, Olive leaf, Gingko… contains antioxidants that can protect from free radicals and helps in case of foods intake deficiency or increased amount of nutrients."

"Artichoke Contains naturally occurring antioxidants/antioxidants help protect you from radicals which cause cell damage/antioxidants help protect your cells and tissues from oxidative damage/antioxidants contribute to the total antioxidant capacity of the body "

"Milk Thistle contains antioxidants that protect against the free radicals action due to stress, alcoholics, UV exposure or polluted ambiance conditions"

Allégations des articles 13.5 et 14



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Structure et exigences du dossier de demandes d'autorisation d'allégations des articles 13.5 ou 14 (Règlement CE n°1169/2009):

1- Caractérisation du produit
Analytique, stabilité, biodisponibilité, procédé de fabrication

2- Revue bibliographique des données existantes
- ✓ Recherche systématique, exhaustive et transparente des données obtenues **chez l'homme**
- ✓ Littérature scientifique produite par le déposant
- ✓ Présentation de chaque étude jugée pertinente

3- Conclusion permettant d'établir
- ✓ Que **l'effet allégué est bénéfique** pour la santé
- ✓ Une **relation de cause à effet** entre la consommation de la denrée et l'effet allégué selon certaines conditions (dose, population cible, durée)

Allégations des articles 13.5 et 14

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Pour l'instant: peu de succès = 1 opinion + sur 4 !

Type d'allégation	Opinion positive	Opinion négative	Taux de succès
Art 13.5 Données nouvelles/propriétaires	**15**	103	**13%**
Art 14 (a) Réduction facteur de risque de maladie	15	25	37%
Art 14 (b) Enfants	29	46	38%
TOTAL	59	174	**25%**

données actualisées à mi- 2015

Allégations des articles 13.5 et 14

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Pourquoi tant de refus?

- Caractérisation insuffisante

"The food/constituent that is the subject of the claim is Regulat®, a liquid concentrate derived from a stepwise fermentation of 17 vegetable and fruit species by five different fermentation steps involving five different strains of *Lactobacillus, which are inactivated by heat and removed after the fermentation process.* ***The bacterial cultures used are not clearly identified and characterised****. The types of bacteria may have an impact on the fermentation outcome and the metabolites present in the final product.* ***The Panel considers that Regulat® has not been sufficiently characterised****. "*

- Effet allégué non bénéfique pour la santé

"The Panel considers the evidence provided does not establish that firmer and fuller breasts per se is a measure of breast function or beneficial to human health": **Avoir des seins plus gros et plus fermes n'ai pas représentatif de la fonction mammaire et ne constitue pas un bénéfice pour la santé en soi!**

- Effet allégué non mesurable

" While a well functioning immune system is important for maintaining physiological integrity and thus health and growth, the claimed effect (support/modulate/improve the immune system in children) **is not sufficiently defined**"

Allégations des articles 13.5 et 14

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- Relation de cause à effet non établie

✓**Qualité des études: taille de l'échantillon, durée de l'étude, puissance statistique…**
✓**Ampleur de l'effet: significatif statistiquement ≠ significatif cliniquement**

"*The **short duration and lack of statistical power** of this study considerably limit its value.*"

- Résultats obtenus dans des conditions différentes de celles de l'utilisation du produit

✓**Quantité de produit à consommer**
✓**Population de l'étude non représentative de la population cible (âge, pathologies…)**
✓**Conditions de test particulières**

"The Panel considers that in the absence of evidence for substantiation of the claim from studies on the food for which the claim is made, **the studies on the effects of individual constituents cannot be used for substantiation of the claim for the product itself**."

"The Panel notes that the study investigated the effect of IBD on the severity and duration of symptoms in individuals already suffering from common cold. However the evidence provided **does not establish that results obtained in studies on subjects with common cold infections** relating to the treatment of symptoms of common cold **can be extrapolated** to the claimed effect of strengthening body's defences by supporting the immune system and reducing susceptibility to pathogens **in healthy people** (without common cold infections)."

Réglementation européenne des allégations nutritionnelles et de santé portées par des denrées alimentaires (Règlement CE n°1924/2006) – **Comment alléguer avec les antioxydants?**

First option: follow the related Guidelines !

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European Food Safety Authority

EFSA Journal 2011;9(12):2474

SCIENTIFIC OPINION

Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

KEEP CALM & FOLLOW THE RULES

What EFSA doesn't accept

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- Les allégations sur les capacités antioxydantes des aliments/ingrédients mesurées *in vitro*
- Les allégations sur les défenses antioxydantes par la mesure du potentiel antioxydant du sang (plasma) issu d'étude clinique via les différentes méthodes:
  - Total reactive antioxidant potential (**TRAP**)
  - Trolox-equivalent antioxidant capacity (**TEAC**)
  - Ferric reducing antioxidant potential (**FRAP**)
  - Oxygen radical absorbance capacity (**ORAC**)
  - Ferrous oxidation-xylenol orange (**FOX**)
- La **mesure seule de l'induction d'enzymes** de défenses contre le stress oxydant: superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px) et haemoxigenase

What EFSA recommends

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Les allégations sur la protection des cellules et des molécules (ADN, protéines ou lipides) vis-à-vis des dommages de l'oxydation, incluant les dommages de la photo-oxydation (induite par les UV)

Définition des marqueurs « gold standard » à utiliser selon la cible moléculaire visée

"Oxidative damage to proteins"	"Oxidative damage to lipids"	"Oxidative damage to DNA"
Mesure des changement induit par l'oxydation des acides aminés par HPLC-MS	**F2α-isoprostanes** dans l'urine (échantillon de 24h) en chromatographie gazeuse (détection par spectrométrie de masse de préférence) **Ou LDLox** + autres marqueurs d'oxydation lipidique (MDA, lipid peroxides) as supportive only	**Comet assay modifié** (utilisation d'endonucléase III pour détecter les bases pyrimidines oxydées) dans les lymphocytes circulant + 8-hydroxy-2-deoxy-guanosin (8-OHdG) as supportive only

Second option: find a health benefit behind !

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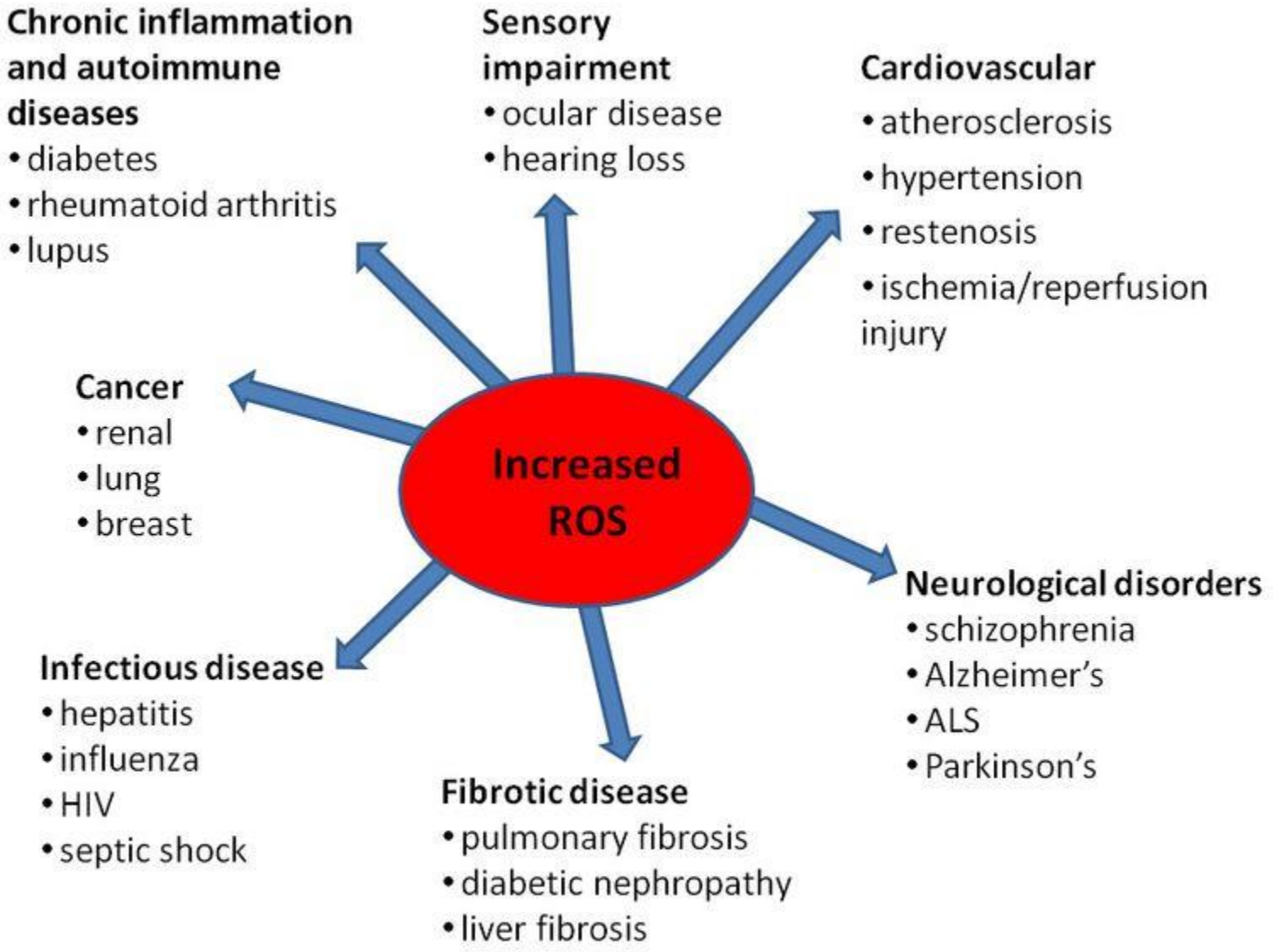

From Reactive oxygen species: from health to disease, Brieger et al, 2012

Allégation 13.5: opinion positive de l'EFSA – le cas des **flavanols de cacao**

THE 13.5 CLAIM ON COCOA FLAVANOLS

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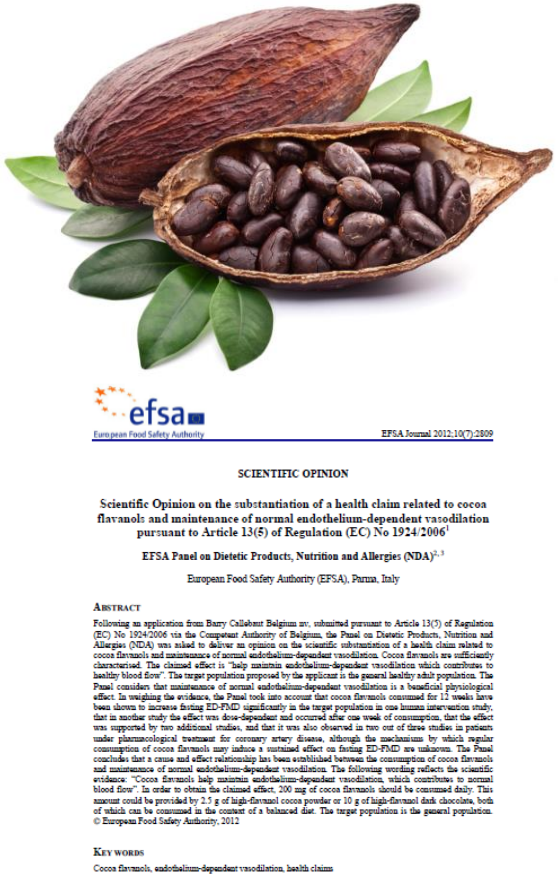
“Cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow”



efsa
European Food Safety Authority
EFSA Journal 2012;10(7):2809

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Barry Callebaut Belgium nv, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation. Cocoa flavanols are sufficiently characterised. The claimed effect is "help maintain endothelium-dependent vasodilation which contributes to healthy blood flow". The target population proposed by the applicant is the general healthy adult population. The Panel considers that maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect. In weighing the evidence, the Panel took into account that cocoa flavanols consumed for 12 weeks have been shown to increase fasting ED-FMD significantly in the target population in one human intervention study, that in another study the effect was dose-dependent and occurred after one week of consumption, that the effect was supported by two additional studies, and that it was also observed in two out of three studies in patients under pharmacological treatment for coronary artery disease, although the mechanism by which regular consumption of cocoa flavanols may induce a sustained effect on fasting ED-FMD are unknown. The Panel concludes that a cause and effect relationship has been established between the consumption of cocoa flavanols and maintenance of normal endothelium-dependent vasodilation. The following wording reflects the scientific evidence: "Cocoa flavanols help maintain endothelium-dependent vasodilation, which contributes to normal blood flow". In order to obtain the claimed effect, 200 mg of cocoa flavanols should be consumed daily. This amount could be provided by 2.5 g of high-flavanol cocoa powder or 10 g of high-flavanol dark chocolate, both of which can be consumed in the context of a balanced diet. The target population is the general population.

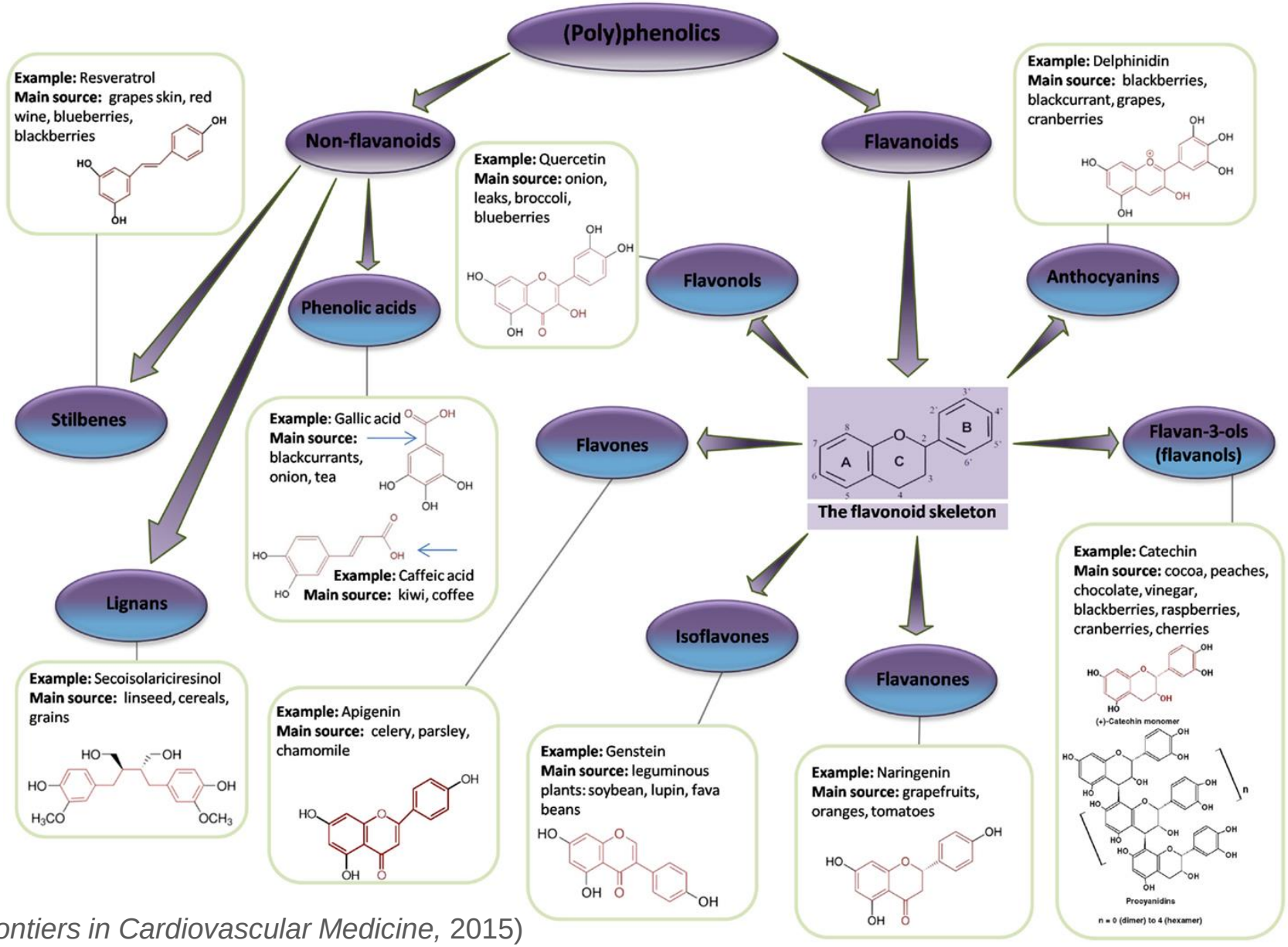
KEY WORDS

Cocoa flavanols, endothelium-dependent vasodilation, health claims

- ✓ 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

Commission Regulation (EU) No 2015/539

What are cocoa flavanols?



Monomeric flavanols (DP1)

Polymeric flavanols (DP2 to DP10)

(Goszcz et al, *Frontiers in Cardiovascular Medicine,* 2015)

The Health claim dossier

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- 25 potentially pertinent publications – 4 published studies were used and discussed in the health claim application

EFSA concluded that:

- 1 study showed an effect on fasting ED-FMD after 12 weeks consumption of cocoa flavanols (Davison 2008)
- 1 study showed a dose dependent effect on fasting ED-FMD after one week of consumption (Grassi 2015)
- 2 additional studies (without proper control) were considered as supporting data (Grassi 2005 and 2008)

EFSA considered that the following studies provided supportive evidence:

- Patients with coronary artery disease (Balzer 2008 and Heiss 2010)
- Acute studies (Heiss 2007, Balzer 2008, Heiss 2003, Heiss 2005, Heiss 2007)
- Acute study/obese participants (Berry 2010)
- Acute healthy older adults (Monahan 2011)

Davison, *International Journal of Obesity* 2008

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Design: Randomized, double blind, placebo controlled, parallel.

Population: 49 Overweight and Obese adults

Site: Nutritional Physiology Research Centre at the University of South Australia

Dose: 902 mg flavanols + exercise, 902 mg flavanols w/o exercise, 36 mg flavanols + exercise, 36 mg flavanols w/o exercise

Duration: 12 weeks

Results: Compared to LF, HF increased FMD acutely (2 h post-dose) by 2.4% (P<0.01) and chronically (over 12 weeks; P<0.01) by 1.6%

Element	Remarks
EFSA Opinion	Key Study
Improvements in FMD	**Acute and Chronic, Significant and Clinically Relevant**
Improvements in Blood Pressure	Significant ($p < 0.05$)

International Journal of Obesity (2008) 32, 1289–1296

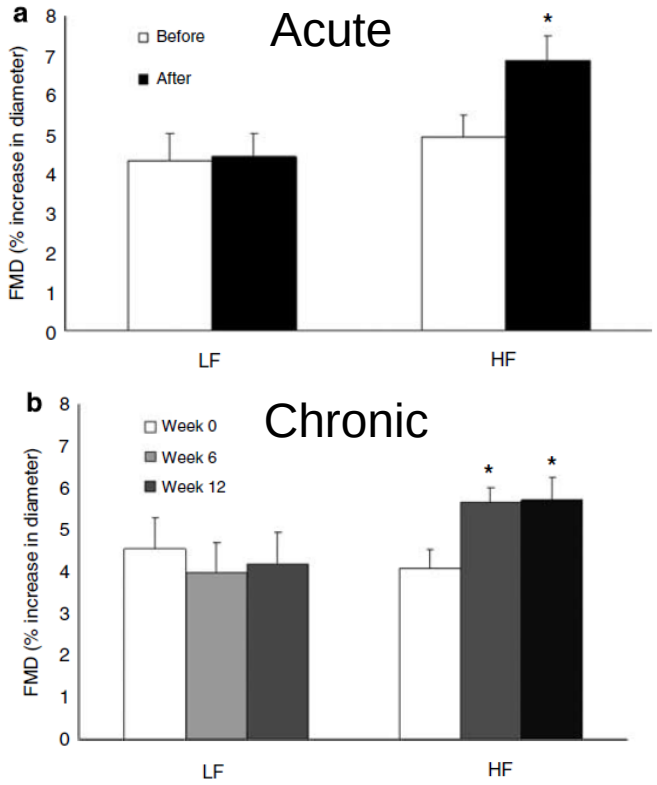
0307-0565/08 $30.00
www.nature.com/ijo

ORIGINAL ARTICLE

Effect of cocoa flavanols and exercise on cardiometabolic risk factors in overweight and obese subjects

K Davison[1,2,3], AM Coates[2,3], JD Buckley[2,3] and PRC Howe[2,3]

[1]*School of Molecular and Biomedical Sciences, University of Adelaide, Adelaide, South Australia, Australia;* [2]*Nutritional Physiology Research Centre, School of Health Sciences, University of South Australia, Adelaide, South Australia, Australia and* [3]*ATN Centre for Metabolic Fitness, School of Health Sciences, University of South Australia, Adelaide, South Australia, Australia*



Grassi, *Journal of Hypertension* 2015

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Design: Randomized, double blind, controlled, cross-over.

Population: 20 healthy volunteers

Dose: 0, 80, 200, 500 and 800mg cocoa flavanols/day in five periods lasting 1 week each

Duration: 1 week (treatment)

Results: Cocoa dose-dependently increased FMD from 6.2% (control) to 7.3, 7.6, 8.1 and 8.2% after the different flavanols doses, respectively (P<0.0001).

Element	Remarks
EFSA Opinion	Key Study - proprietary
Improvements in FMD	**Significant and Clinically Relevant with Clear Dose Response**
Improvements in Blood Pressure	Significant ($p < 0.05$), with Clear Dose Response
Arterial stiffness	Dose response
Endothelin-1 (vascoconstrictor)	Dose response

Cocoa consumption dose-dependently improves flow-mediated dilation and arterial stiffness decreasing blood pressure in healthy individuals

Davide Grassi[a], Giovambattista Desideri[a], Stefano Necozione[a], Paolo di Giosia[a], Remo Barnabei[a], Leen Allegaert[b], Herwig Bernaert[b], and Claudio Ferri[a]

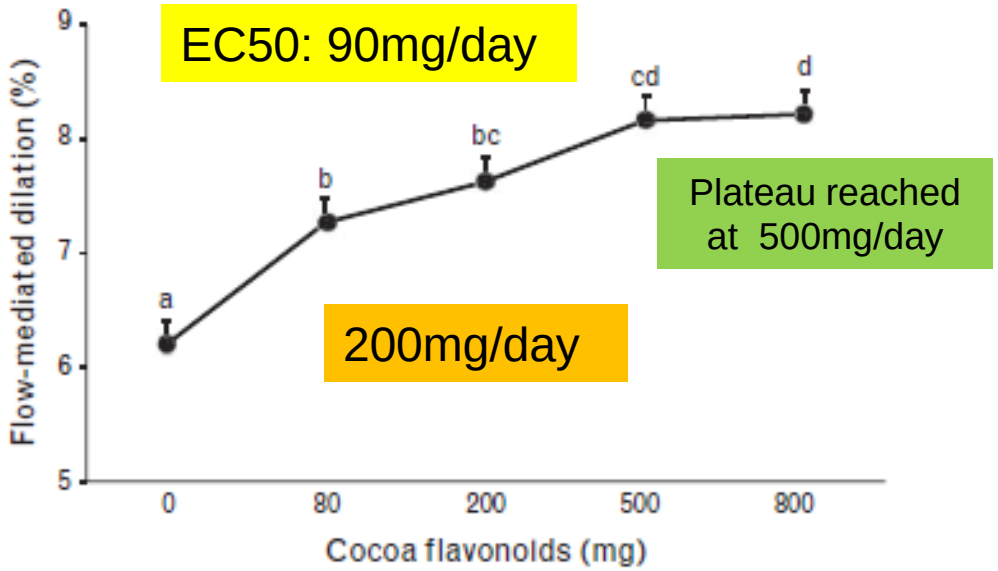

FIGURE 2 Effects of cocoa on endothelium-dependent flow-mediated dilation in 20 healthy volunteers. Data are expressed as least square means with standard error of the mean. Data points with different superscripts are significantly different. Differences are considered significant when *P* value is less than 0.05.

HIGH-FLAVANOL COCOA EXTRACT: EXTENSION OF THE 13.5 CLAIM

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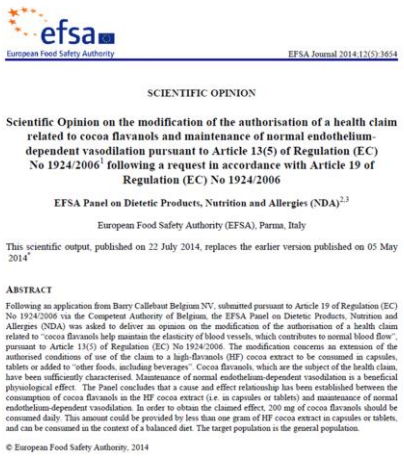
“Cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow”



efsa
European Food Safety Authority
EFSA Journal 2014;12(5):3654

SCIENTIFIC OPINION

Scientific Opinion on the modification of the authorisation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1] following a request in accordance with Article 19 of Regulation (EC) No 1924/2006

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

This scientific output, published on 22 July 2014, replaces the earlier version published on 05 May 2014*

ABSTRACT

Following an application from Barry Callebaut Belgium NV, submitted pursuant to Article 19 of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the modification of the authorisation of a health claim related to “cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow”, pursuant to Article 13(5) of Regulation (EC) No 1924/2006. The modification concerns an extension of the authorised conditions of use of the claim to a high-flavanols (HF) cocoa extract to be consumed in capsules, tablets or added to “other foods, including beverages”. Cocoa flavanols, which are the subject of the health claim, have been sufficiently characterised. Maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect. The Panel concludes that a cause and effect relationship has been established between the consumption of cocoa flavanols in the HF cocoa extract (i.e. in capsules or tablets) and maintenance of normal endothelium-dependent vasodilation. In order to obtain the claimed effect, 200 mg of cocoa flavanols should be consumed daily. This amount could be provided by less than one gram of HF cocoa extract in capsules or tablets, and can be consumed in the context of a balanced diet. The target population is the general population.

© European Food Safety Authority, 2014

- ✓ 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.
- ✓ The claim can be used only for capsules or tablets containing **high-flavanol cocoa extract which provide at least a daily intake of 200 mg of cocoa flavanols** with a degree of polymerisation 1-10.

Commission Regulation (EU) No 2015/539

ADME of flavanols

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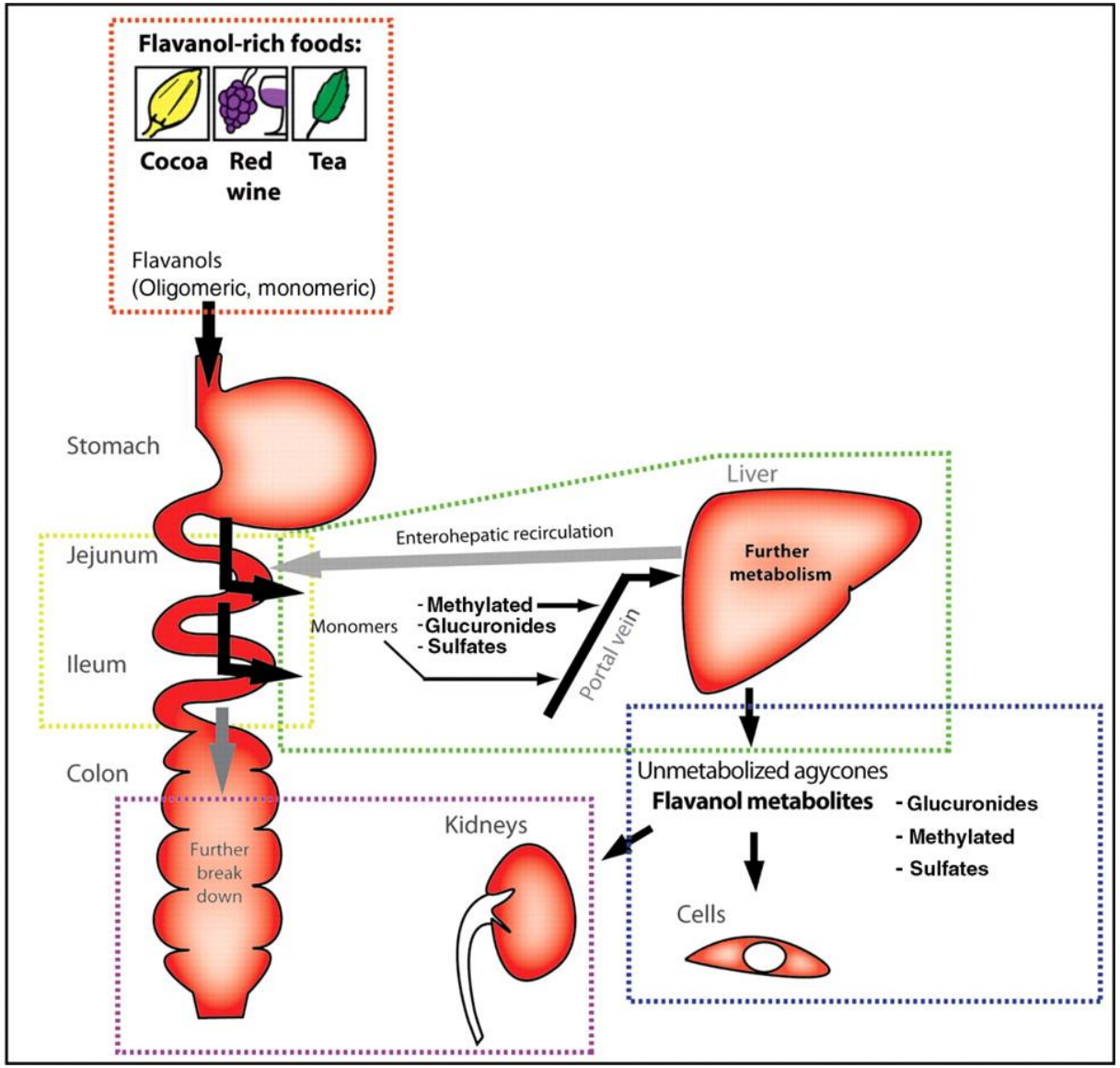
Composition

Absorption
Distribution
Metabolism

Excretion



The acute effects of cocoa flavanols are mainly driven by monomers (epicatechin and catechin) and their metabolites

(Heiss et al, *European Heart Journal,* 2010)

High-Flavanol cocoa extract pharmacokinetic study

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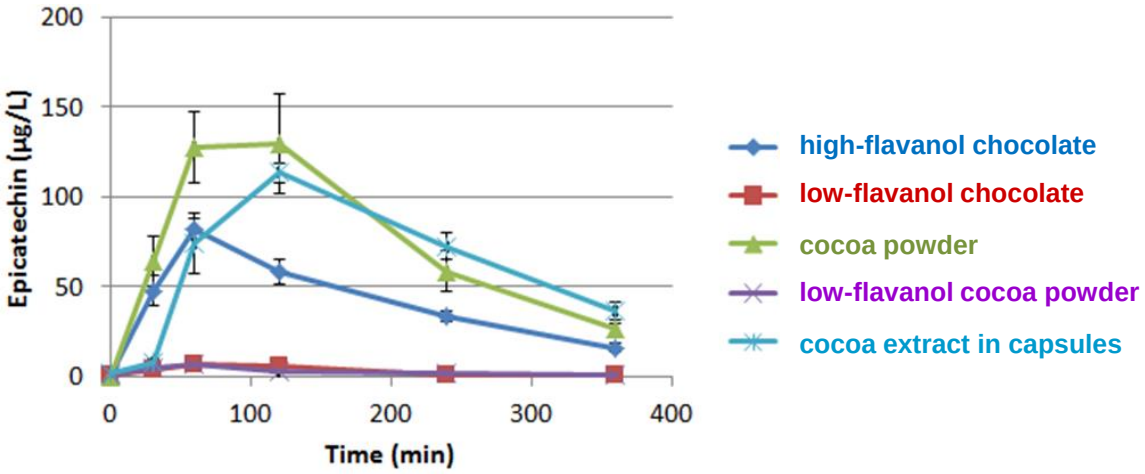
Design: Randomized, partially blinded cross-over (5-day washout period)

Population: 6 healthy participants (3 men / 3 women)

Matrix & Dose: High-flavanol chocolate (460 mg flavanols), low-flavanol chocolate (60 mg flavanols), cocoa powder (459 mg flavanols), low-flavanol cocoa powder (27 mg flavanols), cocoa extract in capsules (449 mg flavanols)

Duration: one dose acute test + blood sampling before and during 6h after consumption (30, 60, 120, 240 and 360 min)

Endpoints: PK parameters on monomeric flavanols (epicatechin) – Cmax, Tmax, AUC



Formulation	C_{MAX} (µg.L^{-1})	T_{MAX} (min)	AUC (µg.L^{-1}.h)
High-flavanol chocolate	**81.9 ± 5.7^{a}**	**60.0 ± 0.0**	**15317.2 ± 1200.1^{a}**
low-flavanol chocolate	7.7 ± 2.0^{b}	108.0 ± 35.0	1186.5 ± 303.3^{b}
cocoa powder	**151.1 ± 25.8^{c}**	**110.0 ± 28.6**	**27946.0 ± 4120.4^{c}**
low-flavanol cocoa powder	7.4 ± 1.2^{b}	50.0 ± 6.3	959.6 ± 180.6^{b}
cocoa extract (caps)	**119.6 ± 4.8^{ac}**	**100.0 ± 12.6**	**24614.1 ± 851.1^{c}**

Cocoa flavanols consumed as a high-flavanol cocoa extract in capsules are as bioavailable as those contained in other matrices (dark chocolate and cocoa powder)

Conclusion

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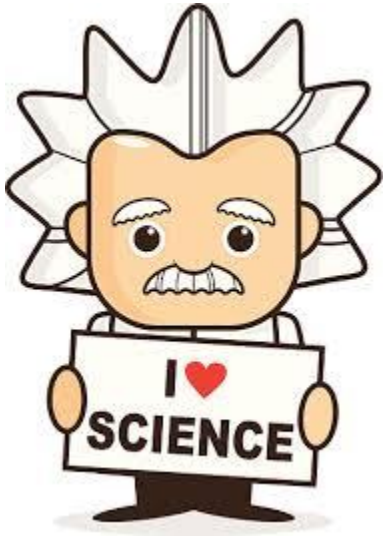
Let's make some science!



But keep in mind consumer understanding !

Thank you for your attention!

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