

## 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<sup>1</sup> following a request in accordance with Article 19 of Regulation (EC) No 1924/2006**

**EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)<sup>2,3</sup>**

European Food Safety Authority (EFSA), Parma, Italy

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#### **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.

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<sup>1</sup> On request from the Competent Authority of Belgium following an application by Barry Callebaut Belgium NV, Question No EFSA-Q-2013-00832, adopted on 10 April 2014.

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**KEY WORDS**

cocoa flavanols, extract, endothelium-dependent vasodilation, health claims

## SUMMARY

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, which was authorised by Commission Regulation No 851/2013. The authorised conditions of use of the claim are: “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 modification concerns an extension of the authorised conditions of use of the claim to a high-flavanol (HF) cocoa extract to be consumed in capsules, tablets or added to “other foods, including beverages”.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence and including a request for the protection of proprietary data.

The Panel notes that cocoa flavanols, which are the subject of the health claim, have been sufficiently characterised.

The Panel considers that maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect. The target population is the general healthy adult population.

In the partially-blinded, controlled, cross-over study, which was provided by the applicant as being pertinent to the health claim, six healthy subjects were randomised to consume cocoa flavanols from different formulations: cocoa extract in capsules, cocoa powder and dark chocolate bars. Plasma concentrations of epicatechins, which are likely to be responsible for the acute effect of cocoa flavanols on endothelium-dependent flow-mediated vasodilation, were measured at different time points after the consumption of the different formulations. The absorption of epicatechins from the HF cocoa extract in capsules when consumed with water was not lower than that observed for epicatechins in HF cocoa powder or HF dark chocolate, the food matrices for which the health claim has been authorised.

Two studies were provided by the applicant as supportive of the health claim. The Panel considers that, in the absence of a direct comparison between the food matrices investigated in these studies (milk chocolate drink and nut cream) and cocoa powder or dark chocolate, no conclusions can be drawn from these studies for the extension of the conditions of use to the food matrices investigated in the studies.

In weighing the evidence, the Panel took into account that the absorption of epicatechins from HF cocoa extract in capsules when consumed with water was not lower than that observed for epicatechins in HF cocoa powder or HF dark chocolate in a human intervention study. The Panel also took into account that, even if epicatechins are likely to be responsible for the acute effect of cocoa flavanols on endothelium-mediated vasodilation rather than for the long-term effect, it is unlikely that daily consumption of cocoa flavanols in the HF cocoa extract would have different long-term effects on endothelium-mediated vasodilation than cocoa flavanols in cocoa powder or dark chocolate. The Panel considers that the bioavailability of cocoa flavanols from HF cocoa extract in capsules and in tablets is not different from HF cocoa powder or dark chocolate.

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 (0.25-0.67 g) 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.

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## BACKGROUND

Regulation (EC) No 1924/2006<sup>4</sup> harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

The same Regulation, as referred to in Article 19, also lays down provisions for modification, suspension and revocation of authorisations. The procedures laid down in Article 15 and 18 shall apply *mutatis mutandis*.

According to Article 18 of that Regulation, an application for the modification, suspension or revocation of authorisations of health claims included in the Community list of permitted claims referred to in Art 13(3) shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

## STEPS TAKEN BY EFSA

- The application was received on 17/10/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- The scientific evaluation procedure started on 06/11/2013.
- On 22/01/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the clock was stopped on 03/02/2014 in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 14/02/2014, EFSA received the requested information and the clock was restarted.
- During its meeting on 10/04/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation.

## TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 19 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: cocoa flavanols and maintenance of normal endothelium-dependent vasodilation.

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<sup>4</sup> Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

## **EFSA DISCLAIMER**

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of cocoa flavanols, a positive assessment of its safety, nor a decision on whether cocoa flavanols is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

## **INFORMATION PROVIDED BY THE APPLICANT**

**Applicant's name and address:** Barry Callebaut Belgium NV, Aalstersestraat 122, B-9280 Lebbeke-Wieze, Belgium.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006 for one unpublished study report (ProDigest, 2012). The applicant also claimed confidentiality rights for information pertaining to the composition and the manufacturing process of the cocoa extract.

### **Food/constituent as stated by the applicant**

According to the applicant, the food constituent that is the subject of the health claim is cocoa flavanols.

### **Health relationship as claimed by the applicant**

The applicant indicated that a cause and effect relationship between the consumption of cocoa flavanols and endothelium-dependent vasodilation has already been established (EFSA NDA Panel, 2012; Regulation (EC) No 851/2013).

### **Wording of the health claim as proposed by the applicant**

The applicant has proposed the following wording for the health claim: "Cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow".

### **Specific conditions of use as proposed by the applicant**

According to the applicant, the target population is the general healthy adult population.

In order to obtain the claimed effect, 200 mg cocoa flavanols should be consumed daily. As an alternative to 2.5 g of high-flavanol (HF) cocoa powder or 10 g of HF dark chocolate (EFSA NDA Panel, 2012), this amount could also be provided by 0.25-0.67 g of HF cocoa extract in the form of capsules, tablets or added to food applications as such. The flavanols' content in the HF cocoa extract varies between 80% and 30% flavanols (DP1-10). The HF cocoa extract is easily dissolvable in water, and can be consumed in the context of a balanced diet. The amount of HF cocoa extracts added to food applications, including beverages, should accommodate the highest possible losses due to treatment of the food.

## **ASSESSMENT**

The Panel has already adopted an opinion on the scientific substantiation of a health claim related to cocoa flavanols and maintenance of normal endothelium-dependent vasodilation with a favourable outcome pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (EFSA NDA Panel, 2012). On 3 September 2013, the European Commission adopted Regulation No 851/2013<sup>5</sup>, which authorised a health claim related to "cocoa flavanols help maintain the elasticity of blood vessels, which contributes to normal blood flow". The authorised conditions of use of the claim are: "Information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 200 mg of

<sup>5</sup> Commission Regulation (EU) No 851/2013 of 3 September 2013 authorising certain health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health and amending Regulation (EU) No 432/2012. OJ L 235, 4.9.2013, p. 3–7.



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”.

With the present application, the applicant has requested an extension of the conditions of use to a HF cocoa extract. The amount of 200 mg of cocoa flavanols can be provided by 0.25-0.67 g of HF cocoa extract in capsules or tablets. In the HF cocoa extract, monomeric flavanols (epicatechin and catechin) account for about 23 % of total flavanols (ProDigest, 2012). Information pertaining to the manufacturing process and the nutritional composition of the HF cocoa extract has been provided. Thirty-nine months stability data of the HF cocoa extracts with different flavanols content and two months stability data of the HF cocoa extract in water-based beverages have been provided.

The applicant proposes that the HF cocoa extract providing 200 mg of cocoa flavanols could be consumed in capsules or tablets or added to “other foods, including beverages”, in order to obtain the claimed effect.

Thus, the present opinion will address whether the conditions of use for this claim could be extended to the HF cocoa extract under the proposed uses (consumed in capsules, tablets or “other foods, including beverages”).

### **1. Characterisation of the food/constituent**

The food constituent that is the subject of the health claim is cocoa flavanols.

The Panel notes that cocoa flavanols, which are the subject of the health claim, have been sufficiently characterised (EFSA NDA Panel, 2012).

### **2. Relevance of the claimed effect to human health**

The Panel considers that maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect (EFSA NDA Panel, 2012). The target population proposed by the applicant is the general healthy adult population.

### **3. Scientific substantiation of the claimed effect**

In order to apply for this extension of the conditions of use, the applicant performed a literature search in PubMed to retrieve comparative studies on the bioavailability of epicatechins, which are considered by the applicant to be responsible for the claimed effect, from different cocoa formulations. Various combinations of the following terms were used in the literature search, which was limited to “humans” and “clinical trial”: “cocoa”, “capsule”, “tablet”, “extract”, “epicatechin”, “flavanols”, “flavan-3-ols” and “pharmacokinetics”. No pertinent studies were identified by the applicant through this literature search.

The Panel noted that cocoa flavanols (mostly epicatechins) may exert an acute effect on endothelium-dependent flow-mediated dilation (ED-FMD) by enhancing nitric oxide production in the endothelium each time they are consumed. The Panel also noted that the evidence provided in support of mechanisms by which repeated consumption of cocoa flavanols may induce longer-term effects on fasting ED-FMD was weak and may have been related more to the gut metabolism of procyanidins and the fraction of epicatechin which is not absorbed in the small intestine, than to the fraction of epicatechin which is absorbed up to four to six hours after consumption (EFSA NDA Panel, 2012).

The applicant provided the unpublished study report by ProDigest (2012) as being pertinent to the health claim. This is a randomised, partially-blinded, controlled, cross-over study which compared

plasma concentrations of epicatechins at different time points after consumption of cocoa flavanols from different formulations (i.e. cocoa extract in capsules vs. cocoa powder vs. dark chocolate in bars).

Six healthy subjects (three men, mean age  $26.7 \pm 10.3$  years) were randomised to consume a pre-established sequence of five cocoa formulations in a single dose with a wash-out period in between of at least five days: HF cocoa extract in capsules (449 mg of flavanols per portion), low-flavanol (LF) and HF cocoa powder (27 mg and 459 mg of flavanols per portion, respectively), and LF and HF dark chocolate (60 mg and 460 mg of flavanols per portion, respectively). For the different cocoa formulations the epicatechin and catechin content per portion was provided: 96 mg and 7 mg in the HF cocoa extract in capsules, 2 mg and 4 mg in the LF cocoa powder, 95 mg and 29 mg in the HF cocoa powder, 14 mg and 6 mg in the LF dark chocolate, and 86 mg and 11 mg in the HF dark chocolate. The Panel notes that the monomeric flavanol/total flavanol ratio in the three HF formulations (cocoa powder, dark chocolate and cocoa extract) was comparable (22-27%). Although it was possible to identify the different type of cocoa formulations given to participants (i.e. capsules, powder sachet and chocolate bars), neither investigators nor participants were able to distinguish the HF and LF study products. Upon a request by EFSA for clarification on the selection of the sample size, the applicant indicated that the sample size was based on a previous study with a similar design which had investigated the rate and extent of absorption of epicatechins from five different chocolate matrices, and in which six individuals were sufficient to detect relevant differences between the interventions (Neilson et al., 2009).

After an overnight fast (except for the consumption of water which was allowed), subjects consumed the study products with 200 mL of water at the clinical facility and after two hours they consumed a standardised meal under the researchers' supervision. Subjects were requested to refrain from consuming HF-containing products for two days prior to each study day. Blood samples for the detection of plasma epicatechins were taken at baseline ( $t = 0$ ) and then at 0.5, 1, 2, 4, and 6 hours after consumption of the study products. Maximum plasma concentrations achieved ( $C_{max}$ ), time to maximum concentrations observed ( $T_{max}$ ) and area under the curve (AUC) for plasma epicatechins were analysed using a General Linear Model. Differences between periods were determined based on the Least Significant Difference test.  $C_{max}$  and AUC values were significantly higher for HF dark chocolate and HF cocoa powder compared with their LF controls.  $C_{max}$ ,  $T_{max}$  and AUC did not differ significantly between HF cocoa extract in capsules and HF cocoa powder. However, the AUC for HF cocoa extract in capsules was significantly higher than the AUC for HF dark chocolate ( $p = 0.03$ ) and not significantly different from the AUC for HF cocoa powder.  $C_{max}$  for HF cocoa extract in capsules was not significantly different from  $C_{max}$  for HF dark chocolate and  $C_{max}$  for HF cocoa powder. The Panel notes that the amount of flavanols per portion used in this study was more than double the amount required to achieve the claimed effect, as well as the amount of epicatechins generally contained in 200 mg of cocoa flavanols. However, the Panel considers that the absorption of epicatechins from 200 mg of flavanols in the HF cocoa extract in capsules, when consumed with water, would not be lower than that observed for epicatechins from the same amount of flavanols in cocoa powder or dark chocolate, the food matrices for which the health claim has been authorised.

Through the literature search, the applicant identified two studies as supportive of the health claim. The studies investigated plasma concentrations of epicatechins or epicatechins plus catechins after consumption of a milk-containing or a milk-free chocolate drink (Keogh et al., 2007) or a nut cream (Vitaglione et al., 2013) containing HF cocoa extracts. Considering that the availability of cocoa flavanols in either cocoa powder or dark chocolate has not been investigated in these studies, the applicant was requested to provide a rationale on how these studies could provide evidence for an extension of the conditions of use of cocoa flavanols consumed as cocoa extract. The applicant acknowledged that neither study directly compared the availability of epicatechins from the tested food matrices (i.e. chocolate drinks and nut cream) against the authorised food matrices (i.e. cocoa powder and dark chocolate), and therefore did not consider that these studies were directly pertinent to the health claim but rather were only supportive. The Panel considers that, in the absence of a

direct comparison between the food matrices investigated and the authorised food matrices, no conclusions can be drawn from these two studies for the extension of the conditions of use to the food matrices investigated in the studies.

In weighing the evidence, the Panel took into account that the absorption of epicatechins from HF cocoa extract in capsules when consumed with water was not lower than that observed for epicatechins in HF cocoa powder or HF dark chocolate in a human intervention study. The Panel also took into account that, even if epicatechins are likely to be responsible for the acute effect of cocoa flavanols on endothelium-mediated vasodilation rather than for the long-term effect, it is unlikely that daily consumption of cocoa flavanols in the HF cocoa extract would have different long-term effects on endothelium-mediated vasodilation than cocoa flavanols in cocoa powder or dark chocolate. The Panel considers that the bioavailability of cocoa flavanols from HF cocoa extract in capsules and in tablets is not different from HF cocoa powder or dark chocolate.

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.

The Panel could not have reached its conclusions without the human intervention study claimed as proprietary by the applicant (ProDigest, 2012, unpublished).

#### **4. Panel's comments on the proposed wording**

See previous assessment of the EFSA NDA Panel (2012) and Commission Regulation<sup>6</sup> dated 3 September 2013.

#### **5. Conditions and restrictions of use**

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 (0.25-0.67 g) of HF cocoa extract in capsules or tablets. This amount of HF cocoa extract can be consumed in the context of a balanced diet. The target population is the general population.

### **CONCLUSIONS**

On the basis of the data presented, the Panel concludes that:

- The food constituent, cocoa flavanols, which is the subject of the claim, is sufficiently characterised.
- Maintenance of normal endothelium-dependent vasodilation is a beneficial physiological effect.
- 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 (0.25-0.67 g) of HF cocoa extract in

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<sup>6</sup> Commission Regulation (EU) No 851/2013 of 3 September 2013 authorising certain health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health and amending Regulation (EU) No 432/2012. OJ L 235, 4.9.2013, p. 3–7.

capsules or tablets. This amount of HF cocoa extract can be consumed in the context of a balanced diet. The target population is the general population.

## DOCUMENTATION PROVIDED TO EFSA

Health claim application on cocoa flavanols and maintenance of normal endothelium-dependent vasodilation pursuant to Article 13(5) of Regulation (EC) No 1924/2006 following a request in accordance with Article 19 of the afore-mentioned Regulation (Claim serial No: 00398\_BE). October 2013. Submitted by Barry Callebaut Belgium NV.

## REFERENCES

- EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2012. 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. *EFSA Journal* 2012;10(7):2809, 21pp. doi:10.2903/j.efsa.2012.2809
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## ABBREVIATIONS

AUC	area under the curve
$C_{\max}$	maximum plasma concentration
ED-FMD	endothelium-dependent flow-mediated dilation
HF	high-flavanol
LF	low-flavanol
$T_{\max}$	time to maximum concentrations observed