EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to alpha-cyclodextrin and reduction of post-prandial glycaemic responses (ID 2926, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

EFSA Publication

Link to article, DOI:
10.2903/j.efsa.2012.2713

Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to alpha-cyclodextrin and reduction of post-prandial glycaemic responses (ID 2926, further assessment) pursuant to Article 13(1) 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 a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a health claim pursuant to Article 13.1 of Regulation (EC) No 1924/2006 in the framework of further assessment related to alpha-cyclodextrin and reduction of post-prandial glycaemic responses. The food constituent that is the subject of the claim, alpha-cyclodextrin, is sufficiently characterised. The claimed effect, reduction of post-prandial glycaemic responses (as long as post-prandial insulinaemic responses are not disproportionally increased), may be a beneficial physiological effect. The proposed target population is individuals who wish to reduce their post-prandial glycaemic responses. In weighing the evidence, the Panel took into account that two intervention studies showed a significant effect of alpha-cyclodextrin added to starch on post-prandial glycaemic responses without disproportionally increasing post-prandial insulinaemic responses, that one study on alpha-cyclodextrin added to sucrose did not show an effect on post-prandial glycaemic responses, and that there is some evidence in support of a plausible mechanism by which alpha-cyclodextrin could exert the claimed effect. On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of alpha-cyclodextrin with starch-containing meals and reduction of post-prandial glycaemic responses. The Panel considers that in order to obtain the claimed effect, at least 5 g of alpha-cyclodextrin per 50 g of starch should be consumed. The target population is adults who wish to reduce their post-prandial glycaemic responses.

KEY WORDS

alpha-Cyclodextrin, glycaemic response, health claims.

[1] On request from the European Commission, Question No EFSA-Q-2012-00172, adopted on 25 April 2012.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank for the preparation of this opinion: The members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen.

Suggested citation: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to alpha-cyclodextrin and reduction of post-prandial glycaemic responses (ID 2926, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2012;10(6):2713 [17 pp.]. doi:10.2903/j.efsa.2012.2713. Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. This opinion addresses the scientific substantiation of a health claim in relation to alpha-cyclodextrin and reduction of post-prandial glycaemic responses. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims, references that EFSA has received from Member States or directly from stakeholders, and the additional information provided by the competent Authority of the Netherlands for further assessment of this claim.

The food constituent that is the subject of the health claim is alpha-cyclodextrin. The Panel considers that alpha-cyclodextrin is sufficiently characterised.

The claimed effect, which is eligible for further assessment, is reduction of post-prandial glycaemic responses. The proposed target population is individuals who wish to reduce their post-prandial glycaemic responses. The Panel considers that reduction of post-prandial glycaemic responses (as long as post-prandial insulinaemic responses are not disproportionally increased) may be a beneficial physiological effect.

In its earlier opinion the Panel considered one human intervention study and an unpublished project report which only contained the description of a study but not the results. In the framework of further assessment, 11 additional studies were provided. This evaluation is based on the scientific references provided in the present and the previous submission which addressed the effects of alpha-cyclodextrin on post-prandial glycaemic responses, and the mechanisms by which alpha-cyclodextrin could exert the claimed effect in the target population.

Six human intervention studies and one systematic review addressed the effects of alpha-cyclodextrin on health outcomes other than post-prandial glycaemic responses or of constituents other than alpha-cylcodextrin. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Two human intervention studies showed an effect of alpha-cyclodextrin added to starch on reduction of post-prandial glycaemic responses without disproportionally increasing post-prandial insulinaemic responses, while one study in which alpha-cyclodextrin was added to sucrose did not observe such an effect.

With respect to the proposed mechanism, it was stated that due to the structural similarity of alpha-cyclodextrin to the helical parts of starch, alpha-cyclodextrin has an inhibitory effect on pancreatic amylase, and that alpha-cyclodextrin may also slow gastric emptying. It was also suggested that the post-prandial attenuation by alpha-cyclodextrin of the glycaemic and insulinaemic response is more pronounced if the meal contains starch rather than sucrose as the glycaemic component. The Panel notes that the proposed mechanism (inhibitory effect of alpha-cyclodextrin on pancreatic alpha-amylase) is in line with the evidence provided from the three intervention studies, i.e. two studies conducted with starch showed an effect of alpha-cyclodextrin on post-prandial glycaemic responses, whereas the study conducted with sucrose did not show such an effect.

In weighing the evidence, the Panel took into account that two intervention studies showed a significant effect of alpha-cyclodextrin added to starch on post-prandial glycaemic responses without disproportionally increasing post-prandial insulinaemic responses, that one study on alpha-cyclodextrin added to sucrose did not show an effect on post-prandial glycaemic responses, and that there is some evidence in support of a plausible mechanism by which alpha-cyclodextrin could exert the claimed effect.

On the basis of the data provided, the Panel concludes that a cause and effect relationship has been established between the consumption of alpha-cyclodextrin with starch-containing meals and reduction of post-prandial glycaemic responses.

The Panel considers that the following wording reflects the scientific evidence: "Consumption of alpha-cyclodextrin contributes to the reduction of the blood glucose rise after starch-containing meals".

The Panel considers that in order to obtain the claimed effect, at least 5 g of alpha-cyclodextrin per 50 g of starch should be consumed. The target population is adults who wish to reduce their post-prandial glycaemic responses.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

EFSA DISCLAIMER

See Appendix B

INTRODUCTION

The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. These claims include already assessed claims related to micro-organisms which the Panel considered to be not sufficiently characterised and claims for which the NDA Panel concluded that there was insufficient evidence to establish a cause and effect relationship between the consumption of the food and the claimed effect.

Following an opinion of the NDA Panel on a health claim pursuant to Article 13 of Regulation (EC) No 1924/2006[4] in which the Panel concluded that the evidence provided was insufficient to establish a cause and effect relationship between the consumption of alpha-cyclodextrin and reduction of post-prandial glycaemic responses (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010), EFSA received additional information from the competent Authority of the Netherlands for further assessment of this claim.

ASSESSMENT

1. Characterisation of the food/constituent (ID 2926)

The food that is the subject of the health claim is alpha-cyclodextrin.

Alpha-cyclodextrin (cyclohexaamylose or cyclomaltohexaose) is a cyclic saccharide comprised of six glucose units linked by alpha-1,4 bonds. It is produced by the action of cyclodextrin glucosyltransferase on hydrolysed starch syrups. The annular structure of alpha-cyclodextrin provides a hydrophobic cavity that allows formation of inclusion complexes with a variety of non-polar organic molecules of appropriate size. The hydrophilic nature of the outer surface of the cyclic structure makes alpha-cyclodextrin water-soluble. Human salivary and pancreatic amylases cannot hydrolyse alpha-cyclodextrin to a significant extent, but alpha-cyclodextrin can be hydrolysed by alpha-amylases of bacterial origin in the human intestine. Alpha–cyclodextrin is considered a soluble dietary fibre.

The Panel considers that the food constituent, alpha-cyclodextrin, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health (ID 2926)

The claimed effect, which is eligible for further assessment, is reduction of post-prandial glycaemic responses. The proposed target population is individuals who wish to reduce their post-prandial glycaemic responses.

Postprandial glycaemia is interpreted as the elevation of blood glucose concentrations after consumption of a food and/or meal. This function is a normal physiological response which varies in magnitude and duration and may be influenced by the chemical and physical nature of the food or meal consumed, as well as by individual factors (Venn and Green, 2007). Reducing post-prandial blood glucose responses may be beneficial to subjects with impaired glucose tolerance as long as post-prandial insulinaemic responses are not disproportionally increased. Impaired glucose tolerance is common in the general population of adults.

The Panel considers that reduction of post-prandial glycaemic responses (as long as post-prandial insulinaemic responses are not disproportionally increased) may be a beneficial physiological effect.

[4] 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.

3. Scientific substantiation of the claimed effect (ID 2926)

In its earlier opinion (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010), the Panel considered one human intervention study on the effect of alpha-cyclodextrin on post-prandial glycaemic responses (Buckley et al., 2006) and an unpublished project report which only contained the description of a study but not the results (Diamantis and Bär, 2002a). Based on the information initially provided, the Panel concluded that the evidence was insufficient to establish a cause and effect relationship between the consumption of alpha-cyclodextrin and reduction of post-prandial glycaemic responses (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010).

In the framework of further assessment, 11 additional studies (Comerford et al., 2011; Diamantis and Bär, 2002b; Gentilcore et al., 2011; Grunberger et al., 2007; Koukiekolo et al., 2001; Li et al., 2009; Ochiai et al., 2008; Oudjeriouat et al., 2003; Shimazu et al., 2009; Weyer et al., 2001; Yun et al., 2009) were provided. Two human intervention studies (Comerford et al., 2011; Grunberger et al., 2007) investigated the effects of alpha-cyclodextrin on health outcomes (e.g. blood lipids, weight loss, and body weight) other than post-prandial glycaemic responses; two human intervention studies (Ochiai et al., 2008; Shimazu et al., 2009) addressed the effects of an anti-diabetic medication (i.e. acarbose) on adiponectin levels; two papers (Weyer et al., 2001; Yun et al., 2009) described the relationship between plasma adiponectin concentrations and insulin sensitivity and insulinaemia in obesity and/or type 2 diabetes; and one systematic review (Li et al., 2009) examined the association between plasma adiponectin levels and incidence of type 2 diabetes. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

This evaluation is based on the scientific references provided in the present and the previous submission which addressed the effects of alpha-cyclodextrin on post-prandial glycaemic responses, and the mechanisms by which alpha-cyclodextrin could exert the claimed effect in the target population.

In the study by Buckley et al. (2006), the effects of boiled white rice with 50 g of digestible carbohydrates, to which 0, 2, 5 or 10 g of alpha-cyclodextrin were added, on post-prandial glycaemic and insulinaemic responses were investigated in 10 healthy subjects (five females), using a double-blind, randomised cross-over design. All subjects received the four test meals on a single occasion, after an overnight fast, with a wash-out period of two days. Blood glucose and insulin concentrations were measured at baseline and over a 2 h period after the ingestion of each meal. Repeated measures analysis of variance (RM-ANOVA) followed by pair-wise comparison of the means by using a test of least significant differences was used to determine the effects of the treatment. The incremental area under the curve (iAUC) for the glucose response was significantly lower for the boiled white rice to which 5 g (mean±SEM -20.4±15.4%; p=0.03) or 10 g (mean±SEM -49.6±9.9%; p=0.001) alpha-cyclodextrin was added compared to the control rice (without alpha-cyclodextrin). No effect on post-prandial serum insulin concentrations was observed for either dose of alpha-cyclodextrin. The Panel notes that this study shows a dose-dependent effect of alpha-cyclodextrin on reduction of post-prandial glycaemic responses without disproportionally increasing post-prandial insulinaemic responses.

The unpublished study by Diamantis and Bär (2002b) was a single-blind, cross-over study in 12 healthy males (age 23-24 years and mean weight of 73.3 kg) to determine the effect of alpha-cyclodextrin on the glycaemic and insulinaemic response to starch. Subjects consumed either 100 g white bread (providing 50 g starch) together with 0 or 10 g alpha-cyclodextrin or 25 g alpha-cyclodextrin alone (alpha-cyclodextrin was dissolved in 250 ml water) in fasting conditions, with a wash-out period of at least two days. Blood glucose and serum insulin concentrations were measured before and up to 180 min after the consumption of the meal. The glycaemic response of alpha-cyclodextrin and of white bread with alpha-cyclodextrin was 4.3 % and 43 % relative to that of the bread alone (100 %), respectively. The insulinaemic response of white bread with alpha-cyclodextrin was 45 % relative to that of the bread alone (100 %). The iAUC for blood glucose concentrations was significantly lower after consumption of the starch together with 10 g alpha-cyclodextrin compared to

the control (starch without alpha-cyclodextrin) (-58.63%; mean±SEM: 1543.5±469.6 *vs.* 3731.2±581.9 mg/dl/min; $p<0.01$), as was the iAUC for insulin (-56.48%, mean±SEM: 2559.9±255.2 µU/ml/min *vs.* 5883.5±479.0 µU/ml/min; $p<0.001$). Data were also analysed using a linear mixed model. A significant difference between consumption of the starch to which 10 g alpha-cyclodextrin was added and consumption of the control starch was found for T15-T90 min for glucose concentrations and for T30-T45 min for insulin concentrations. The Panel notes that this study shows an effect of alpha-cyclodextrin on reduction of post-prandial glycaemic responses without disproportionally increasing post-prandial insulinaemic responses.

The study by Gentilcore et al. (2011) was a double-blind, randomised cross-over study to investigate the effect of alpha-cyclodextrin on the gastric emptying of, and the glycaemic response to, an oral sucrose load. Thirteen subjects (median age 70 years, BMI 26.9 kg/m^2) consumed a drink comprising 100 g sucrose dissolved in water, or 10 g of alpha-cyclodextrin added to 100 g sucrose before being dissolved in water (total volume of the drink 300 ml), with a wash-out period of at least seven days. Three subjects did not complete the study. Blood glucose and serum insulin concentrations were measured before and up to 300 min after consumption of the drink. Absolute values for blood glucose and serum insulin concentrations were analysed using repeated-measures two-way ANOVA followed by *post hoc* analyses of differences between treatments at each time point, corrected for multiple comparisons. No statistically significant difference in the iAUC for the glucose and insulin response between the control and the alpha-cyclodextrin group was shown. Peak blood glucose ($p=0.88$) and serum insulin ($p=0.22$) concentrations were not statistically significantly different between the control and alpha-cyclodextrin group. A significant treatment x time interaction ($p<0.001$) for blood glucose concentrations was observed. At t=60 min blood glucose was slightly greater ($p<0.05$) and at t=180 and 210 min slightly less ($p<0.005$) after the control drink when compared to alpha-cyclodextrin. The Panel notes that this study does not show an effect of alpha-cyclodextrin added to sucrose on reduction of post-prandial glycaemic responses.

With respect to the proposed mechanism, it was stated that due to the structural similarity of alpha-cyclodextrin to the helical parts of starch, alpha-cyclodextrin has an inhibitory effect on pancreatic amylase, and that alpha-cyclodextrin may also slow gastric emptying. It was also suggested that the post-prandial attenuation by alpha-cyclodextrin of the glycaemic and insulinaemic response is more pronounced if the meal contains starch rather than sucrose as the glycaemic component.

One human study (Gentilcore et al., 2011) which investigated the effects of alpha-cyclodextrin on gastric emptying, and two *in vitro* studies (Koukiekolo et al., 2001; Oudjeriouat et al., 2003) on the inhibitory effect of alpha-cyclodextrin on pancreatic alpha-amylase and barley amylase were provided in support of the proposed mechanisms.

The human intervention study by Gentilcore et al. (2011), as described above, also measured the amounts of the drink remaining in the total, proximal and distal stomach for up to 300 min after consumption of the drink, and the 50 % gastric emptying time (T_{50}) was calculated. Gastric emptying time, expressed as AUC and T_{50}, was not statistically significantly different between the control and the alpha-cyclodextrin group analysed using repeated-measures two-way ANOVA.

Kinetic studies have been carried out to determine the inhibitory effect of alpha-cyclodextrin on porcine pancreatic alpha-amylase using as amylose as the substrate (Koukiekolo et al., 2001). The inhibition of amylose hydrolysis by alpha-cyclodextrin was of competitive type with an inhibition constant of 7.0 mM. Kinetic studies have also been carried out to determine the inhibitory effect of alpha-cyclodextrin on barley alpha-amylase isozymes using DP-4900 amylose as the substrate (Oudjeriouat et al., 2003). alpha-Cyclodextrin was shown to be a weak inhibitor of barley alpha-amylase isozymes, compared to acarbose, a strong inhibitor of pancreatic alpha-amylase. Similar results were reported by Rejzek et al. (2011), where alpha-cyclodextrin was shown to have a weak inhibitor activity on barley β-amylase when soluble starch was used as the substrate.

Crystallographic analysis showed that three alpha-cyclodextrin molecules bind to the alpha-amylase enzyme, two of these in the active site cleft of the amylase and a third quite far from the active site, not associated with the substrate-binding cleft (Larson et al., 1994). alpha-Cyclodextrin is considered chemically identical to amylose and its cyclic structure resembles the six glycosyl-residue turn in the amylose helix. It is quite plausible that the association of alpha-amylose with cyclodextrins reflects the binding of helical turns of natural substrate (e.g. amylose). Using crystallographic analyses of porcine pancreatic alpha-amylase with alpha-cyclodextrin, a model for the binding of polysaccharides with a similar helical character as in natural substrates (i.e. starch and glucagon) was proposed (Larson et al., 2010).

The Panel notes that the proposed mechanism (inhibitory effect of alpha-cyclodextrin on pancreatic alpha-amylase) is in line with the evidence provided from the three intervention studies, i.e. two studies conducted with starch showed an effect of alpha-cyclodextrin on post-prandial glycaemic responses, whereas the study conducted with sucrose did not show such an effect.

In weighing the evidence, the Panel took into account that two intervention studies showed a significant effect of alpha-cyclodextrin added to starch on post-prandial glycaemic responses without disproportionally increasing post-prandial insulinaemic responses, that one study on alpha-cyclodextrin added to sucrose did not show an effect on post-prandial glycaemic responses, and that there is some evidence in support of a plausible mechanism by which alpha-cyclodextrin could exert the claimed effect.

The Panel concludes that a cause and effect relationship has been established between the consumption of alpha-cyclodextrin with starch-containing meals and reduction of post-prandial glycaemic responses.

4. Panel's comments on the proposed wording (ID 2926)

The Panel considers that the following wording reflects the scientific evidence: "Consumption of alpha-cyclodextrin contributes to the reduction of the blood glucose rise after starch-containing meals".

5. Conditions and possible restrictions of use (ID 2926)

The Panel considers that in order to obtain the claimed effect, at least 5 g of alpha-cyclodextrin per 50 g of starch should be consumed. The target population is adults who wish to reduce their post-prandial glycaemic responses.

CONCLUSIONS

On the basis of the data presented (initially and for further assessment), the Panel concludes that:

- The food constituent, alpha-cyclodextrin, that is the subject of the health claim, is sufficiently characterised.
- The claimed effect, which is eligible for further assessment, is reduction of post-prandial glycaemic responses. The proposed target population is individuals who wish to reduce their post-prandial glycaemic responses. Reduction of post-prandial glycaemic responses (as long as post-prandial insulinaemic responses are not disproportionally increased) may be a beneficial physiological effect.
- A cause and effect relationship has been established between the consumption of alpha-cyclodextrin with starch-containing meals and reduction of post-prandial glycaemic responses.
- The following wording reflects the scientific evidence: "Consumption of alpha-cyclodextrin contributes to the reduction of the blood glucose rise after starch-containing meals".

- In order to bear the claim, at least 5 g of alpha-cyclodextrin per 50 g of starch should be consumed. The target population is adults who wish to reduce their post-prandial glycaemic responses.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 for further assessment (No: EFSA-Q-2012-00172). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims, references that EFSA has received from Member States or directly from stakeholders and the additional information provided by the competent Authority of the Netherlands for further assessment of this claim (available on: http://www.efsa.europa.eu/en/topics/topic/article13.htm).

REFERENCES

Buckley JD, Thorp AA, Murphy KJ and Howe PR, 2006. Dose-dependent inhibition of the post-prandial glycaemic response to a standard carbohydrate meal following incorporation of alpha-cyclodextrin. Annals of Nutrition and Metabolism, 50, 108-114.

Comerford KB, Artiss JD, Jen KL and Karakas SE, 2011. The beneficial effects of alpha-cyclodextrin on blood lipids and weight loss in healthy humans. Obesity (Silver Spring), 19, 1200-1204.

Diamantis I and Bär A, 2002a. Effect of alpha-cyclodextrin on the glycemic index (GI) and insulinemic index (II) of starch in human volunteers. Unpublished study protocol.

Diamantis I and Bär A, 2002b. Effect of alpha-cyclodextrin on the glycaemic index (GI) and insulinaemic index (II) of starch in healthy human volunteers. Unpublished study report.

EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010. Scientific Opinion on the substantiation of health claims related to alpha cyclodextrin and reduction of post prandial glycaemic responses (ID 856, 2926), maintenance or achievement of a normal body weight (ID 2925) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal, 8(2):1479, 13 pp.

Gentilcore D, Vanis L, Teng JC, Wishart JM, Buckley JD, Rayner CK, Horowitz M and Jones KL, 2011. The oligosaccharide alpha-cyclodextrin has modest effects to slow gastric emptying and modify the glycaemic response to sucrose in healthy older adults. British Journal of Nutrition, 106, 583-587.

Grunberger G, Jen KL and Artiss JD, 2007. The benefits of early intervention in obese diabetic patients with FBCx: a new dietary fibre. Diabetes/Metabolism Research and Reviews, 23, 56-62.

Koukiekolo R, Desseaux V, Moreau Y, Marchis-Mouren G and Santimone M, 2001. Mechanism of porcine pancreatic alpha-amylase. Inhibition of amylose and maltopentaose hydrolysis by alpha-, beta- and gamma-cyclodextrins. European Journal of Biochemistry, 268, 841-848.

Larson SB, Greenwood A, Cascio D, Day J and McPherson A, 1994. Refined molecular structure of pig pancreatic alpha-amylase at 2.1 A resolution. Journal of Molecular Biology, 235, 1560-1584.

Larson SB, Day JS and McPherson A, 2010. X-ray crystallographic analyses of pig pancreatic alpha-amylase with limit dextrin, oligosaccharide, and alpha-cyclodextrin. Biochemistry, 49, 3101-3115.

Li S, Shin HJ, Ding EL and van Dam RM, 2009. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA, 302, 179-188.

Ochiai H, Ooka H, Shida C, Ishikawa T, Inoue D and Okazaki R, 2008. Acarbose treatment increases serum total adiponectin levels in patients with type 2 diabetes. Endocrine Journal, 55, 549-556.

Oudjeriouat N, Moreau Y, Santimone M, Svensson B, Marchis-Mouren G and Desseaux V, 2003. On the mechanism of alpha-amylase. European Journal of Biochemistry, 270, 3871-3879.

Rejzek M, Stevenson CE, Southard AM, Stanley D, Denyer K, Smith AM, Naldrett MJ, Lawson DM and Field RA, 2011. Chemical genetics and cereal starch metabolism: structural basis of the non-covalent and covalent inhibition of barley beta-amylase. Molecular Biosystems, 7, 718-730.

Shimazu T, Inami N, Satoh D, Kajiura T, Yamada K, Iwasaka T and Nomura S, 2009. Effect of acarbose on platelet-derived microparticles, soluble selectins, and adiponectin in diabetic patients. Journal of Thrombosis and Thrombolysis, 28, 429-435.

Venn BJ and Green TJ, 2007. Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. European Journal of Clinical Nutrition, 61 Suppl 1, S122-131.

Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE and Tataranni PA, 2001. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. Journal of Clinical Endocrinology and Metabolism, 86, 1930-1935.

Yun JE, Sull JW, Lee HY, Park E, Kim S, Jo J, Lee SJ, Kim SY, Choi YJ, Jee SH and Huh KB, 2009. Serum adiponectin as a useful marker for metabolic syndrome in type 2 diabetic patients. Diabetes/Metabolism Research and Reviews, 25, 259-265.

APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation (EC) No 1924/2006 on nutrition and health claims made on foods[5] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[6]

Foods are commonly involved in many different functions[7] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

[5] OJ L12, 18/01/2007

[6] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.

[7] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.
- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.
- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.
- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. 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 wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

GLOSSARY AND ABBREVIATIONS

ANOVA	Analysis of variance
BMI	Body mass index
DP	Degree of polymerisation
iAUC	Incremental area under the curve
RM-ANOVA	Repeated measures ANOVA