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SCIENTIFIC OPINION

Evolus® and reduce arterial stiffness

Scientific substantiation of a health claim related to *Lactobacillus helveticus* fermented Evolus® low-fat milk products and reduction of arterial stiffness pursuant to Article 14 of the Regulation (EC) No 1924/2006[1]

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2008-218)

Adopted on 2 October 2008

PANEL MEMBERS

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SUMMARY

Following an application from Valio Ltd. submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Finland, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific opinion on *Lactobacillus helveticus* fermented Evolus® low-fat milk products related to reduction of arterial stiffness.

The scope of the application falls under disease risk reduction claim.

Evolus® products are fermented low-fat, low-lactose milk drinks flavoured with juice preparations made from various berries or fruits. The products contain the two tripeptides Val-Pro-Pro and Ile-Pro-Pro, which are released from milk proteins during fermentation with a *Lactobacillus helveticus* LKB-16H starter culture from the applicant´s collection. The strain has been characterised biochemically and its origin and previous food use have been described. Complete specifications, full description of the manufacturing process and stability information, and specifications on the average content of main macro- and micronutrients have been provided for each commercial version of Evolus® products. Daily doses recommended by the applicant have been calculated to correspond to about 5 mg tripeptides/daily portion.

The Panel considers that *Lactobacillus helveticus* fermented Evolus® low-fat milk food products are sufficiently characterised.

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from Valio Ltd. on the scientific substantiation of a health claim related to *Lactobacillus helveticus* fermented Evolus® low-fat milk products and reduction of arterial stiffness. *The EFSA Journal* (2008) 824, 1-12

The claimed effect is to reduce arterial stiffness in mildly hypertensive subjects, and consequently the risk of cardiovascular disease. The Panel considers that it has not been established that reducing arterial stiffness is beneficial to the health of mildly hypertensive subjects by reducing their risk of cardiovascular disease.

A total of 13 publications reporting intervention studies in humans, 9 reviews, 4 meta-analyses and three guidelines were identified by the applicant and considered as pertinent to the health claim. Eleven of the human intervention studies presented had blood pressure (BP) taken at the brachial artery as primary outcome and do not report any measurement of arterial stiffness. Four of them have been conducted with Evolus® products. The Panel considers that these studies are not directly pertinent to the health claim under evaluation.

The remaining two human interventions presented address the effects of the consumption of Evolus® products on arterial 'stiffness indices'.

In the first study, 94 (60 women) hypertensive volunteers, who were not on antihypertensive medication, were randomised to consume either 150mL of Evolus® products or 150mL of a control milk twice daily for 10 weeks with a double-blind design. Daily doses of tripeptides in the intervention group (52.5mg) were about 10 times higher than daily doses recommended by the applicant for the claimed effect. BP was taken as 24-h ambulatory BP monitoring (24-h ABPM) using an automatic BP recorder at the beginning and end of the study. Arterial stiffness was calculated as ambulatory arterial stiffness index (AASI) from 24-h ABPM measurements. Changes in BP were the primary outcome of the study. At the end of the 10-wk intervention period, AASI decreased significantly from baseline in the intervention group, but not in the placebo group. The Panel notes a number of weaknesses in this study: AASI is not a generally accepted method for the assessment of arterial stiffness, differences in changes between the intervention and the control groups were not reported, the study was not sufficiently controlled for confounders that could potentially have affected the outcome (e.g., background diet and physical activity were not reported).

In the second study, 89 (54 males) hypertensive volunteers, who were not on antihypertensive medication, were randomised to consume either 200mL of Evolus® products or 200mL of a control milk twice daily for 24 weeks with a double-blind design. Daily doses of tripeptides in the intervention group during the first 12 weeks (10mg) and during the second 12 weeks (51mg) were about 2 and 10 times higher, respectively, than daily doses recommended by the applicant for the claimed effect. BP was measured using an oscillometric technique. Aortic stiffness was assessed by pulse wave analysis as augmentation index (AIx), and as time to return of the reflected wave (Tr). The primary outcomes of the study were arterial stiffness and endothelial function. No significant differences were observed between intervention and control groups after the first 12 weeks of the intervention in any of the haemodynamic parameters measured (i.e., AIx, Tr, BP or endothelial function). At the end of the 24-week period, AIx decreased significantly in the intervention group as compared to controls. No significant differences between groups where observed in Tr, BP, or endothelial function at the end of the 24-week intervention.

The Panel notes a number of weaknesses in this study: AIx alone is not a generally accepted method for the assessment of arterial stiffness, the clinical significance of the observed differences in AIx changes between the intervention and control groups was not reported, the study was not sufficiently controlled for confounders that could potentially have affected the outcome (e.g., background diet and physical activity were not reported).

The Panel considers that the significant weaknesses of these studies greatly limit their value as a source of data to substantiate the claimed effect. The Panel notes that Evolus® products,

which provide daily doses of 5 mg tripeptides as recommended by the applicant for the claimed effect, have not been tested with regard to their effect on arterial stiffness.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of *Lactobacillus helveticus* fermented Evolus® low-fat milk products and the reduction of arterial stiffness in mildly hypertensive subjects.

Key words: *Lactobacillus helveticus*, fermented milk, tripeptides, Val-Pro-Pro, Ile-Pro-Pro, arterial stiffness, blood pressure, cardiovascular disease.

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BACKGROUND

Regulation (EC) No 1924/2006[2] 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 that Regulation and are authorised in accordance with this Regulation and included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of that Regulation lay down provisions for the authorization and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of that Regulation, an application for authorisation 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 European Food Safety Authority (EFSA).

Steps taken by EFSA:

- The application was received on 12/03/2008.
- The scope of the application falls under disease risk reduction claim.
- During the completeness check[3] of the application, the applicant was requested to provide missing information on 02/04/2008.
- The applicant provided the missing information on 15/05/2008 and on 05/06/2008.
- The application was considered valid by EFSA and the scientific evaluation procedure started on 15/06/2008.
- During the meeting on 02/10/2008, the NDA Panel, in the light of the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to *Lactobacillus helveticus* fermented Evolus® low-fat milk products and reduction of arterial stiffness.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA is requested to issue a scientific opinion on the information provided by the applicant concerning: *Lactobacillus helveticus* fermented Evolus® low-fat milk products and reduction of arterial stiffness.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of *Lactobacillus helveticus* fermented Evolus® low-fat milk products, a positive assessment of its safety, nor a decision on whether *Lactobacillus helveticus* fermented Evolus® low-fat milk products are, or are not, classified as a foodstuff. It should be noted that such an assessment or a decision are not foreseen in the framework of Regulation (EC) No 1924/2006.

[2] European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

[3] In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

It should also be highlighted that the scope and the proposed wording of the claim as considered by the EFSA in this opinion may be subject to changes pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

ACKNOWLEDGEMENTS

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1. Information provided by the applicant

Applicant's name and address: Valio Ltd - PO Box 30 - 00039 Valio – Finland.

The application includes a request for the protection of proprietary data.

1.1. Food/constituent as stated by the applicant

Evolus® products are *Lactobacillus helveticus* fermented low-fat milk products, which may contain fruit or berry juice as an ingredient. Current commercially available Evolus® products are fermented milk products with or without added sugar, and fermented daily-dose drinks. Evolus® products contain the biologically active peptides Isoleucyl-Prolyl-Proline (Ile-Pro-Pro) and Valyl-Prolyl-Proline (Val-Pro-Pro), which are derived from milk proteins through a fermentation process.

1.2. Health relationship as claimed by the applicant

The applicant states that Evolus® products contain biologically active peptides (Ile-Pro-Pro and Val-Pro-Pro) that have been shown to reduce arterial stiffness and consequently lower blood pressure in mildly hypertensive subjects. Thus Evolus® fermented milk products have a beneficial effect on arterial stiffness and thus they consequently lower the risk of cardiovascular disease.

1.3. Wording of the health claim proposed by the applicant

Evolus® reduces arterial stiffness.

1.4. Specific conditions for use proposed by the applicant

Evolus® products are targeted at people with mildly elevated blood pressure levels or with an elevated risk of developing hypertension. The amount of bioactive peptides in a daily dose of Evolus® products should be about 5 mg (UV-HPLC method, corresponding to 4.2 - 4.6 mg by UPLC-MS method).

2. Assessment

2.1 Characterisation of the food/constituent

Evolus® products are fermented low-fat, low-lactose milk drinks flavoured with juice preparations made from various berries or fruits. The products contain the two tripeptides Val-Pro-Pro and Ile-Pro-Pro, which are released from milk proteins during fermentation with a *Lactobacillus helveticus* LKB-16H starter culture from the applicant´s collection. According to the specification, the starter culture is not genetically modified and is fit for human consumption as food ingredient. The strain has been characterised biochemically and its origin and previous food use have been described.

The manufacturing process is standardised and the batch to batch variability appears low, being affected mainly by the juice preparation. The amount of active peptides can readily be standardised by supplementation with Evolus® powder (i.e., whey peptides powder). According to the specification, average concentration of both tripeptides Ile-Pro-Pro and Val-Pro-Pro range from 11 to 21 mg/L and from to 18 to 28 mg/L respectively. The concentration of these tripeptides in the raspberry-lingonberry flavored product are almost double those in the

other flavoured products. Daily doses recommended by the applicant for the raspberry-lingonberry flavoured product (100mL) and for all other flavoured products (200mL) have been calculated to correspond to about 5 mg tripeptides/daily portion. According to quantitative analyses, the concentration of both tripeptides remains fairly stable during the "best before" storage period.

Specifications on the average content of main macro- and micronutrients have been provided for each commercial version of Evolus® products. In addition to the aforementioned tripeptides, calcium, potassium and magnesium are identified by the applicant as active compounds with a potential effect on blood pressure. Concentrations of calcium, potassium and magnesium range from 200-300mg, 330-500mg, and 15-26mg/daily dose, respectively, depending on the commercial version.

The Panel considers that *Lactobacillus helveticus* fermented Evolus® low-fat milk food products are sufficiently characterised.

2.2. Relevance of the claimed effect to human health

The claimed effect is to reduce arterial stiffness. The target population is mildly hypertensive subjects, who can be classed as adults with high normal blood pressure (SBP = 130-139 mmHg and/or DBP = 85-89 mmHg) or grade 1 hypertension (SBP = 140-159 mmHg and/or DBP = 90-99 mmHg) as defined by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (Mancia *et al.*, 2007).

The term 'arterial stiffness' lacks a precise definition, but inferences can be made about the mechanical properties of arteries by measuring a variety of 'stiffness indices'. Arterial stiffness has an independent predictive value for cardiovascular events in subjects with uncomplicated essential hypertension and in the general population, among others (Laurent et al., 2006; Hamilton et al., 2007). However, it has not been established that lowering arterial stiffness can lower the risk of cardiovascular disease (Laurent *et al.*, 2006; Graham *et al.*, 2007).

The Panel considers that it has not been established that reducing arterial stiffness is beneficial to the health of mildly hypertensive subjects by reducing their risk of cardiovascular disease.

2.3. Scientific substantiation of the claimed effect

The applicant searched PubMed for clinical trials, randomised controlled trials, meta-analysis, reviews and practice guidelines related to the effects of bioactive peptides and blood pressure using the search terms blood pressure OR hypertensi* OR ACE inhibition AND sour milk OR bioactive peptide OR fermented milk OR tripeptide* OR lactobacillus helveticus OR ile-pro-pro. Hand search was also performed. Papers belonging to another therapeutic area, addressing pharmacological treatment of hypertension, investigating peptides not identified or deviant from the Evolus® products, published in a national journal and of too general contents, or only replicating results from original articles were excluded. A total of 13 publications reporting intervention studies in humans, 9 reviews, 4 meta-analyses and three guidelines were identified by the applicant and considered as pertinent to the health claim.

Eleven of the human intervention studies presented had blood pressure (BP) taken at the brachial artery as primary outcome and did not report any measurement of arterial stiffness. Four of them had been conducted with Evolus® products. The Panel considers that these studies are not directly pertinent to the health claim under evaluation.

The remaining two human interventions presented address the effects of the consumption of Evolus® products on arterial 'stiffness indices' (Jauhiainen *et al.*, 2007; unpublished study).

In the first study (Jauhiainen *et al.*, 2007), 94 (60 women) hypertensive volunteers (SBP 140-180mmHg and/or DPB 90-110 mmHg) not on antihypertensive medication were randomised to consume either 150mL of Evolus® products or 150mL of a control milk twice daily for 10 weeks with a double-blind design after a 4-wk run-in period and entered data analysis. Subjects had a follow-up of 4-wk after the intervention period was completed. Daily doses of tripeptides in the intervention group (52.5mg) were about 10 times higher than daily doses recommended by the applicant for the claimed effect. Daily doses of calcium, sodium, potassium and magnesium in the test and control milk products were 690mg vs. 300mg, 123 mg vs. 108mg, 1530mg vs. 450mg, and 93mg vs. 33mg, respectively. BP was taken nine times as office measurements during the study and as 24-h ambulatory BP monitoring (24-h ABPM) using an automatic BP recorder at the beginning and end of the study (Jauhiainen *et al.*, 2005). Arterial stiffness was calculated as ambulatory arterial stiffness index (AASI) from 24-h ABPM measurements. Intervention (n = 47, office SBP = 149 ± 7 mmHg and office DBP = 94 ± 6 mmHg as means ± SD at baseline) and control (n = 47, office SBP = 150 ± 9 mmHg and office DBP = 93 ± 6 mmHg as means ± SD at baseline) groups did not differ significantly at baseline with respect to age, sex, body weight, BP values or AASI. Changes in BP were the primary outcome of the study. Sample size was calculated to detect differences of 5 mmHg in SBP between the intervention and control groups (P = 0.05, power = 90%). The Panel notes that daily doses of tripeptides and minerals with a putative effect on BP (as stated by the applicant) were several times higher than in the food of the health claim described in the application. The Panel also notes that the study population is not representative of the target population (i.e. subjects with grade 2 hypertension or higher have been included), and that the characteristics of the subjects' diet and level of physical activity were not reported.

At the end of the 10-wk intervention period, AASI decreased significantly from baseline (mean ± SD = 0.36 ± 0.15 in the intervention vs. 0.36±0.17 in the control group) in the intervention group (-0.043, 95%CI: -0.084 to -0.001, p = 0.043), but not in the placebo group (-0.019, 95%CI: -0.074 to 0.035, p = 0.47). Differences in AASI changes between the intervention and control groups were not reported.

The Panel notes a number of weaknesses in this study: AASI is not a generally accepted method for the assessment of arterial stiffness (Laurent et al., 2006), differences in AASI changes between the intervention and the control groups were not reported, the study was not sufficiently controlled for confounders that could potentially have affected the outcome (e.g., background diet and physical activity were not reported).

The Panel considers that the significant weaknesses of this study greatly limit its value as a source of data to substantiate the claimed effect.

In the second study (unpublished study), 89 (54 males) hypertensive volunteers (SBP 140-155mmHg and/or DPB 85-99 mmHg), who were not on antihypertensive medication, were randomised to consume either 200mL of Evolus® products or 200mL of a control milk twice daily for 24 weeks with a double-blind design after a 4-wk run-in period and entered data analysis. Subjects had a follow-up of 4-wk after the intervention period was completed. Daily doses of tripeptides in the intervention group during the first 12 weeks (10mg) and during the second 12 weeks (51mg) were about 2 and 10 times higher, respectively, than daily doses recommended by the applicant to obtain the claimed effect. Daily doses of calcium, sodium, potassium and magnesium in the test and control milk products during the last 12 weeks were 600mg vs. 400mg, 128 mg vs. 144mg, 960mg vs. 640mg, and 50mg vs. 44mg, respectively, assuming that the composition of the control sour milk was equivalent to that used in Jauhiainen *et al.* (2005), as stated by the applicant. BP was measured using an oscillometric technique. Aortic stiffness was assessed by pulse wave analysis as AIx, and as time to return of the reflected wave (Tr). Intervention (n = 45, SBP = 151 ± 15 mmHg and DBP = 95

± 125 mmHg as means ± SD at baseline) and control (n = 44, SBP = 155 ± 14 mmHg and DBP = 94 ± 9 mmHg as means ± SD at baseline) groups did not differ significantly at baseline regarding age, sex, body weight, BP or "stiffness indices". The primary outcomes of the study were arterial stiffness and endothelial function. Characteristics of the subjects' diet and level of physical activity were not reported. The Panel notes that, in the last 12 weeks of the intervention, daily doses of tripeptides and minerals with a putative effect on BP (as stated by the applicant) were several times higher than in the food of the health claim described in the application.

No significant differences were observed between intervention and control groups after the first 12 weeks of the intervention in any of the haemodynamic parameters measured (i.e., AIx, Tr, BP or endothelial function). At the end of the 24-week period, AIx decreased significantly from baseline (mean ± SD = 20.0 ± 8.4% in the intervention vs. 24.3 ± 8.4% in the control group) in the intervention group as compared to controls (-2.30%, 95%CI = -4.3 to -0.28 vs. 1.74%, 95%CI = 0.44 to 3.04, p =0.004). Changes in AIx values correlated significantly with baseline SBP and DBP. No significant differences between groups where observed in Tr, SBP, DBP or endothelial function at the end of the 24-week intervention.

The Panel notes a number of weaknesses in this study: AIx alone is not a generally accepted method for the assessment of arterial stiffness (Laurent *et al.*, 2006), the clinical significance of the observed differences in AIx changes between the intervention and control groups was not reported, the study was not sufficiently controlled for confounders that could potentially have affected the outcome (e.g., background diet and physical activity were not reported).

The Panel considers that the significant weaknesses of this study greatly limit its value as a source of data to substantiate the claimed effect.

The Panel notes that Evolus® products which provide the daily doses of tripeptides recommended by the applicant for the claimed effect (5mg) have not been tested with regards to their effect on arterial stiffness.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *Lactobacillus helveticus* fermented Evolus® low-fat milk products and the reduction of arterial stiffness in mildly hypertensive subjects.

CONCLUSIONS

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

- The food for which the claim is made, i.e. *Lactobacillus helveticus* fermented Evolus® low-fat milk products, has been sufficiently characterised.
- The claimed effect is to reduce arterial stiffness in mildly hypertensive subjects, and consequently the risk of cardiovascular disease. It has not been established that reducing arterial stiffness is beneficial to the health of mildly hypertensive subjects by reducing their risk of cardiovascular disease.
- A cause and effect relationship has not been established between the consumption of *Lactobacillus helveticus* fermented Evolus® low-fat milk products and the reduction of aortic stiffness in mildly hypertensive subjects.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on *Lactobacillus helveticus* fermented Evolus® low-fat milk products and reduce arterial stiffness pursuant to Article 14 of the Regulation (EC) No 1924/2006 (Claim serial No: 0136-FI). June 2008. Submitted by Valio Ltd.

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Unpublished study. Long-term intervention with *Lactobacillus helveticus* fermented milk improves arterial stiffness in hypertensive subjects.

GLOSSARY / ABBREVIATIONS

AASI	Ambulatory arterial stiffness index
AIx	Augmentation index
BP	Blood pressure
DBP	Diastolic blood pressure
SBP	Systolic blood pressure