

**Application for the Approval of Egg Membrane as a
Novel Food**

Pursuant to

***Regulation (EC) No 258/97 of the European Parliament and of the
Council of 27th January 1997 Concerning Novel Foods and Novel
Food Ingredients***

Non-Confidential Summary

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Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 Concerning Novel Foods and Novel Food Ingredients

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Application for the Approval of Egg Membrane as a Novel Food

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 Concerning Novel Foods and Novel Food Ingredients

INTRODUCTION

Biova, LLC (Biova) proposes to market egg membrane as an ingredient in food supplements in the European Union (EU). The egg membrane ingredient is harvested from chicken egg-breaking facilities and maintains the natural ratios of collagen, elastin, glycosaminoglycans, and other constituents of eggshell membrane.

Approval is sought for the egg membrane under Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients (hereafter referred to as EC 258/97). Accordingly, this submission has been prepared pursuant to the Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients (hereafter referred to as the Commission Recommendation of 1997) (European Parliament and the Council of the European Union, 1997).

Article 1(2.) of EC 258/97 states that the regulation "...shall apply to the placing on the market within the Community of foods and food ingredients which have not hitherto been used for human consumption to a significant degree within the Community and which fall under the following categories... foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe food use" (European Parliament and the Council of the European Union, 1997). The egg membrane ingredient is thus considered a novel food ingredient within this category.

Section 4 of the Commission Recommendation of 1997 outlines recommendations made by the Scientific Committee on Food (SCF) related to the "Scientific Classification of Novel Foods for the Assessment of Wholesomeness", which facilitates the safety and nutritional evaluation of a given novel food/food ingredient (Recommendation 97/618/EC - Commission of the European Communities, 1997). Of the 6 classes identified, the egg membrane would be classified in Class 2 as a "complex NF from non-GM source", since the preparation of the ingredient is through conventional techniques, and with no use of genetic modification. Furthermore, the source of the ingredient has a history of consumption in the European Community. Accordingly, egg membrane would be further allocated under Sub-Class 2.1: "the source of the novel food has a history of food use in the Community".

SUMMARY OF THE DOSSIER

The scientific evidence presented by Biova demonstrates that the ingredient is not anticipated to pose any risk to human health under the intended conditions of use as a novel food ingredient in food supplements.

ADMINISTRATIVE DATA

Applicant Details:

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I SPECIFICATIONS FOR EGG MEMBRANE

I.A Identity and Specifications

The name, identifier, and description of the ingredient are presented in Table I.A-1 below.

| | |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Common or Usual Name | Egg membrane |
| Chemical Abstract Service Number | Not available |
| Description | The egg membrane is derived from chicken eggs intended for human consumption. It is prepared as a water-soluble off-white powder. |
| Chemical composition | The ingredient is comprised predominantly of protein, with the remainder being moisture, ash, and calcium. The natural ratios of collagen, elastin, glycosaminoglycans, and other constituents of eggshell membrane are maintained during the manufacturing process. |

Detailed analyses of the composition and characteristics of the egg membrane ingredient are presented in Table I.A-2 below.

| Parameter | Egg membrane (as is basis) | Methods |
|------------------------------------|----------------------------|------------------------------------------|
| Total protein (% w/w) (Kjeltec) | 88 | AOAC 2001.11 |
| Total protein (% w/w) (combustion) | 88 | AOAC 992.15 , AOAC 990.03, AOCS Ba 4e-93 |
| Collagen (% w/w) | 16 | Sircol™ Soluble Collagen Assay (ELISA) |
| Elastin (% w/w) | 25 | Fastin™ elastin Assay (ELISA) |
| Total glycosaminoglycans (% w/w) | ≥5 | Titration |
| Carbohydrates (% w/w) | <0.01 | Calculated |
| Total dietary fibre (% w/w) | 2.0 | AOAC 991.43 |
| Total fat as triglycerides (% w/w) | 1.79 | AOCS Ce 2-66 AOCS Ce 1-62 |
| pH | 6.7 | 10% at 25°C |

SUMMARY OF THE DOSSIER

| Table I.A-2 Composition and Characteristics of Egg Membrane Ingredient | | |
|-------------------------------------------------------------------------------|-----------------------------------|---------------------------------|
| Parameter | Egg membrane (as is basis) | Methods |
| Ash (% w/w) | 7.85 | AOAC 942.05 |
| Moisture (% w/w) | 7.4 | AOAC 925.09 |
| Water activity | 0.173 | Vapour pressure at 25°C |
| Solubility | Soluble in water | 10% solution at 25°C |
| Bulk density (g/cc) | 0.69 | USP 616 |
| Mineral profile | | |
| Calcium (% w/w) | 0.44 | ICP - AOAC 965.17 / 985.01 mod. |
| Iron (% w/w) | 0.0006 | ICP - AOAC 965.17 / 985.01 mod. |
| Potassium (% w/w) | 0.01 | ICP - AOAC 965.17 / 985.01 mod. |
| Sodium (%) | 2.36 | ICP - AOAC 965.17 / 985.01 mod. |
| Phosphorus (ppm) | 226 | AOAC 993.14 mod. |
| Manganese (ppm) | 0.271 | AOAC 993.14 mod. |
| Zinc (ppm) | 6.23 | AOAC 993.14 |

ELISA = enzyme-linked immunosorbent assay; ICP-MS = inductively coupled mass spectrometry; USP = United States Pharmacopeia.

I.B Proposed Specifications

The product specifications for Biova's egg membrane are presented in Table I.B-1. Appropriate parameters for the identity and characterisation of the ingredient, as well as appropriate limits for potential contaminants (*i.e.*, heavy metal and microbiological) have been established.

| Table I.B-1 Product Specifications for the Egg Membrane Ingredient | | |
|---------------------------------------------------------------------------|----------------------|--------------------------------------------|
| Specification Parameters | Specification | Method of Analysis |
| Chemistry | | |
| Total protein (%) | ≥88 | Combustion |
| Collagen (%) | ≥15 | Sircol™ Soluble Collagen Assay (ELISA) |
| Elastin (%) | ≥20 | Fastin™ Elastin Assay (ELISA) |
| Total glycosaminoglycans (%) | ≥5 | USP 26 (chondroitin sulphate K0032 method) |
| Calcium (%) | ≤1 | AOAC 965.17 / 985.01 mod. |
| Fluorine (mg/kg) | - | AOAC 987.08 |
| Physical | | |
| pH | 6.5 to 7.6 | 10% at 25°C |
| Ash (%) | ≤8 | AOAC 942.05 |
| Moisture (%) | ≤9 | AOAC 934.01 |
| Water activity (%) | ≤0.3 | Vapour pressure at 25°C |
| Solubility (in water) | Soluble | 10% solution at 25°C |
| Bulk density (g/cc) | ≥0.6 | USP 616 |
| Heavy metals | | |
| Arsenic (mg/kg) | ≤0.5 | ICP-MS |
| Lead (mg/kg) | ≤0.2 | ICP-MS |

SUMMARY OF THE DOSSIER

| Specification Parameters | Specification | Method of Analysis |
|--------------------------------------|---------------|----------------------------------------------|
| Cadmium (mg/kg) | ≤0.1 | ICP-MS |
| Mercury (mg/kg) | ≤0.1 | ICP-MS |
| Microbiology | | |
| Aerobic plate count (CFU/g) | ≤2,500 | CMMEF, 4 th Ed., 2001, Method 7.6 |
| <i>Escherichia coli</i> (MPN/g) | ≤5 | FDA BAM 8 th Ed., ch 4 |
| Salmonella (/25 g) | Negative | AOAC 2003.09 |
| Coliforms (MPN/g) | ≤10 | FDA BAM 8 th Ed., ch 4 |
| <i>Staphylococcus aureus</i> (CFU/g) | ≤10 | FDA BAM 8 th Ed., ch 12 |
| Mesophilic spore count (CFU/g) | ≤25 | AACC 4240 |
| Thermophilic spore count (CFU/10 g) | ≤10 | AACC 4240 |
| Yeast (CFU/g) | ≤10 | AACC 9 th Ed., 42-50 |
| Mould (CFU/g) | ≤200 | AACC 9 th Ed., 42-50 |

AACC = American Association for Clinical Chemistry; CFU = colony forming units; CMMEF = Compendium of Methods for the Microbiological Examination of Foods; ELISA = enzyme-linked immunosorbent assay; FDA BAM = United States Food and Drug Administration's Bacteriological Analytical Manual; ICP-MS = inductively coupled mass spectrometry; IR = infrared; MPN = most probable number; PCB(s) = polychlorinated biphenyl(s); PCR = polymerase chain reaction; USP = United States Pharmacopeia.

I.C Analytical Data

The results of batch analyses of 3 independent lots of egg membrane are summarised in Table I.C-1 below. The results indicate that the manufacturing process yields a consistent product compliant with the established specifications.

| Specification Parameter | Specification | Egg Membrane Ingredient Lot No. | | |
|------------------------------|---------------|---------------------------------|---------|---------|
| | | P3095 | P4132 | P4252-1 |
| Chemistry | | | | |
| Total protein (%) | ≥88 | 90.79 | 89.69 | 89.47 |
| Collagen (%) | ≥15 | 20 | 22 | 25 |
| Elastin (%) | ≥20 | 26 | 26 | 22 |
| Total glycosaminoglycans (%) | ≥5 | 12.7 | 19.8 | 21 |
| Calcium (%) | ≤1 | 0.14 | 0.36 | 0.42 |
| Physical | | | | |
| pH | 6.5 to 7.6 | 6.6 | 6.9 | 6.8 |
| Ash (%) | ≤8 | 5.28 | 6.68 | 5.69 |
| Moisture (%) | ≤9 | 6.6 | 6.95 | 7.4 |
| Water activity (%) | ≤0.3 | 0.207 | 0.249 | 0.244 |
| Solubility (in water) | Soluble | Soluble | Soluble | Soluble |
| Bulk density (g/cc) | ≥0.6 | 0.66 | 0.66 | 0.63 |
| Heavy Metals | | | | |
| Arsenic (mg/kg) | ≤0.5 | 0.02 | 0.02 | 0.02 |
| Lead (mg/kg) | ≤0.2 | 0.02 | 0.03 | 0.09 |
| Cadmium (mg/kg) | ≤0.1 | 0.010 | 0.010 | 0.010 |

SUMMARY OF THE DOSSIER

| Table I.C-1 Summary of the Results of Batch Analyses for Egg Membrane | | | | |
|------------------------------------------------------------------------------|---------------|---------------------------------|----------|----------|
| Specification Parameter | Specification | Egg Membrane Ingredient Lot No. | | |
| | | P3095 | P4132 | P4252-1 |
| Mercury (mg/kg) | ≤0.1 | 0.010 | 0.010 | 0.010 |
| Microbiology | | | | |
| Aerobic plate count (CFU/g) | ≤2,500 | 150 | 60 | 90 |
| <i>Escherichia coli</i> (MPN/g) | ≤5 | <3 | <3 | <3 |
| Salmonella (/25 g) | Negative | Negative | Negative | Negative |
| Coliforms (MPN/g) | ≤10 | <3 | <3 | <3 |
| <i>Staphylococcus aureus</i> (CFU/g) | ≤10 | <10 | <10 | <10 |
| Mesophilic spore count (CFU/g) | ≤25 | 20 | 20 | 20 |
| Thermophilic spore count (CFU/10 g) | ≤10 | <10 | <10 | <10 |
| Yeast (CFU/g) | ≤10 | <10 | <10 | <10 |
| Mould (CFU/g) | ≤200 | <10 | <10 | 10 |

CFU = colony-forming units; MPN = most probable number.

The egg membrane ingredient also has undergone a comprehensive pesticide screen (using the United States Food and Drug Administration Pesticide Analytical Manual methods) as well as an antibiotic screen (in accordance with AOAC 995.09 methods). Furthermore, the egg membrane has undergone testing for the presence of dioxins. The results indicate the absence of such contaminants in the ingredient. It is further noted that Biova's products contain less than 1% fat and are exempt from dioxin testing under Commission Regulation (EC) No 1881/2006 (Commission of the European Communities, 2006); however, it is noted that baseline testing on Biova products confirm that dioxin and dioxin-like PCB content was below the limit of detection.

I.D Stability

Egg membrane has a low water activity level, which hinders the growth of microorganisms; however, the intended shelf life is specified as a period 48 months in a cool, dry environment, with a retest period at 48 months to confirm compliance with the product specifications. The results of real-time stability testing on the egg membrane ingredient conducted over a period of 48 months at warehouse room temperature (relative humidity not specified) are collated and support the stability of the ingredient over its intended shelf life.

SUMMARY OF THE DOSSIER

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO THE INGREDIENT

The egg membrane ingredient is produced according to Good Manufacturing Practice (GMP) under Hazard Analysis Critical Control Points (HACCP) principles. The manufacture of egg membrane occurs in a registered third country establishment, as listed on the European Commission website (European Commission, 2016).

Eggshells from USDA-inspected egg-breaking facilities in the United States undergo hydro-mechanical separation to obtain the egg membranes. Once obtained, the membranes are processed using a patented solubilisation method in which the pH and temperature are raised for specific amounts of time. Following the solubilisation process, the solution is spray-dried and packaged.

During the manufacturing process, the ratios of collagen, elastin, glycosaminoglycans, and other constituents are not altered from their natural occurrences in egg membrane.

The manufacture of egg membrane follows traditional mechanical separation and spray drying techniques typical of the food industry; therefore, it is not anticipated that any toxicological, nutritional, or microbiological hazards will arise from the production process. This is supported by the results of analyses for heavy metal, microbiological, pesticide, and antibiotics, which demonstrate that the ingredient is free from contamination.

III HISTORY OF THE SOURCE ORGANISM (EGGS)

Biova's egg membrane is derived from farmed chicken eggs produced for human consumption. To this end, the egg membranes may be considered a by-product of the food industry.

Chicken eggs have a well-established history of wide consumption, with eggs of the chicken hen *Gallus domesticus* consumed in the human diet for 4,000 to 5,000 years, and the domestication of fowl in Asia documented approximately 3,000 years ago (McGee, 2004; Guerrero-Legarreta, 2010).

In the past decade, the estimated national egg consumption in the United Kingdom alone has increased from 10.3 billion eggs in 2004 to 11.7 billion eggs in 2014 (data from the British Egg Industry Council, 2016). The average consumption of fresh eggs (in g/day), as reported in the European Food Safety Authority (EFSA) Comprehensive Food Consumption Database (EFSA, 2015), is summarised in Table III-1.

SUMMARY OF THE DOSSIER

| Table III-1 Mean Egg Consumption in European Adults (EFSA Comprehensive Food Consumption Data, 2015) | | | | |
|-------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------|
| Country | Survey Name | Mean Egg Consumption¹ (Total Population) in g/day | Percentage of Consumers (%) | Mean Egg Consumption¹ (Consumers only) in g/day |
| Belgium | Diet_National_2004 | 9.5 | 39.1 | 25.0 |
| Czech Republic | SISP04 | 19.5 | 86.1 | 22.6 |
| Germany | National_Nutrition_Survey_II | 7.1 | 98.9 | 16.3 |
| Denmark | Danish_Dietary_Survey | 16.2 | 80.4 | 20.0 |
| Spain | AESAN | 24.4 | 86.2 | 17.5 |
| Spain | AESAN_FIAB | 28.5 | 24.0 | 30.3 |
| Finland | FINDIET_2007 | 16.1 | 97.2 | 27.1 |
| France | INCA2 | 15.3 | 84.1 | 14.2 |
| United Kingdom | NDNS | 17.1 | 74.3 | 28.7 |
| Hungary | National_Repr_Surv | 26.4 | 18.6 | 46.6 |
| Ireland | NSIFCS | 11.9 | 22.8 | 21.8 |
| Italy | INRAN_SCAI_2005_06 | 21.3 | 74.1 | 32.9 |
| Latvia | EFSA_TEST | 8.7 | 89.2 | 32.0 |
| Netherlands | DNFCS_2003 | 5.0 | 61.4 | 20.0 |
| Sweden | Riksmaten_1997_98 | 12.3 | 86.0 | 19.8 |

EFSA = European Food Safety Authority.

¹ Values represent the chronic consumption of “Eggs, fresh” as classified by FoodEx L2.

Egg membranes are assumed to be consumed incidentally with boiled eggs. The consumption of the maximum intended dose of Biova’s egg membrane is equivalent to the consumption of the membranes of 8 to 10 eggs. Additional information on the consumption of the ingredient is presented in Section X (*Information from previous human exposure to the novel food or its source*).

IV-VIII NOT APPLICABLE

The egg membrane ingredient is not derived from genetically modified organisms.

IX INTAKE/EXTENT OF USE OF EGG MEMBRANE INGREDIENT

Biova’s egg membrane ingredient is intended for use in food supplements providing doses not exceeding 450 mg egg membrane/day.

The marketing of food supplements containing the egg membrane will not be restricted geographically and the ingredient is not intended to replace other foods currently on the market.

SUMMARY OF THE DOSSIER

X INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO THE NOVEL FOOD OR ITS SOURCE

Egg membrane is a 100 µm thick layer attached to the eggshell and is assumed to be consumed in the regular human diet incidentally with boiled eggs. The consumption of the maximum intended dose of the ingredient is equivalent to the consumption of the egg membranes of 8 to 10 eggs. The major constituents of egg membrane (*i.e.*, collagen, elastin, and glycosaminoglycans) also have a history of human exposure as part of mammalian connective tissue. Furthermore, hydrolysed collagen has a history of consumption as gelatine.

Although the level of consumption of egg membrane from boiled eggs has not been described in published studies, it is noted that Biova has a history of marketing its egg membrane ingredient in the United States as a dietary supplement under the trade name BiovaFlex. The egg membrane ingredient was successfully notified as a New Dietary Ingredient (NDI) in the United States in 2009, and the BiovaFlex product containing this ingredient was determined by Biova to be Generally Recognized as Safe (GRAS) for use in food and food supplements. Since its release in 2009, approximately 17,034 kilograms of BiovaFlex have been sold world-wide, with no reports of adverse events to date. Furthermore, no reactions to egg membrane products on the United States market have been reported under the United States Food and Drug Administration's MedWatch adverse event reporting programme.

XI NUTRITIONAL INFORMATION

The egg membrane ingredient is not nutritionally identical to other food ingredients and is not intended to replace other foods currently on the market. However, it is noted that the ingredient's caloric value as protein is approximately 4 kcal/g dry weight.

A comprehensive analysis of the nutritional components of the egg membrane ingredient has been conducted by Biova. The results are summarised in Table XI-1 and are reported as an "as-is" and dry basis.

| Parameter | "As is" | Dry basis | Method |
|-----------------------------------|---------|-----------|----------------------------------------|
| Protein, Kjeltex (% w/w) | 87.98 | 95.02 | AOAC 2001.11 |
| Protein, Combustion (% w/w) | 87.93 | 94.97 | AOAC 992.15, AOAC 990.03, AOCS Ba3c-93 |
| Ash (% w/w) | 7.85 | 8.48 | AOAC 942.05 |
| Calories, calculated (kcal/100 g) | 368 | 397 | CFR – Atwater calculation |
| Carbohydrates, calculated (% w/w) | <0.01 | <0.01 | CFR 21 – calc |
| Moisture (% w/w) | 7.4 | NA | Vacuum oven, AOAC 925.09 |
| Calcium (% w/w) | 0.44 | 0.47 | AOAC 965.17 / 985.01 mod |
| Iron (% w/w) | 0.0006 | 0.0006 | AOAC 965.17 / 985.01 mod |

SUMMARY OF THE DOSSIER

| Table XI-1 Nutritional Properties of Egg Membrane | | | |
|----------------------------------------------------------|----------------|------------------|---------------------------|
| Parameter | “As is” | Dry basis | Method |
| Potassium (% w/w) | 0.01 | 0.02 | AOAC 965.17 / 985.01 mod |
| Sodium (% w/w) | 2.36 | 2.55 | AOAC 965.17 / 985.01 mod |
| Fibre, total dietary (% w/w) | 2.0 | 2.2 | AOAC 991.43 |
| Sugars, total (% w/w) | <0.35 | <0.38 | AOAC 982.14 mod |
| Fructose (% w/w) | <0.15 | <0.17 | AOAC 982.14 mod |
| Glucose (% w/w) | <0.15 | <0.17 | AOAC 982.14 mod |
| Sucrose (% w/w) | <0.15 | <0.17 | AOAC 982.14 mod |
| Maltose (% w/w) | <0.15 | <0.17 | AOAC 982.14 mod |
| Lactose (% w/w) | <0.15 | <0.17 | AOAC 982.14 mod |
| Vitamin A, total (IU/100 g) | 47.8 | 51.6 | AOAC 974.29 mod |
| Beta-carotene (IU/100 g) | <30.0 | <32.5 | AOAC 974.29 mod |
| Retinol (IU/100 g) | 47.8 | 51.6 | AOAC 974.29 mod |
| Vitamin C (mg/100 g) | <0.440 | <0.476 | AOAC 967.22 mod |
| Cholesterol (mg/100 g) | 50.3 | 54.3 | AOAC 994.10 mod |
| Total fat as triglycerides, calculated (% w/w) | 1.79 | 1.93 | AOCS Ce 2-66 AOCS Ce 1-62 |
| Total fatty acids, calculated (% w/w) | 1.75 | 1.89 | AOCS Ce 2-66 AOCS Ce 1-62 |
| Total saturated fatty acids (% w/w) | 0.37 | 0.40 | AOAC 996.06 mod |
| Cis, cis-Polyunsaturated fatty acids (% w/w) | 0.69 | 0.75 | AOAC 996.06 mod |
| Cis-Monounsaturated fatty acids (% w/w) | 0.64 | 0.69 | AOAC 996.06 mod |
| Total trans fatty acid isomers (% w/w) | 0.02 | 0.02 | AOAC 996.06 mod |

CFR = United States Code of Federal Regulations; IU = international units; NA = not applicable.

The data summarised above indicate that consumption of the egg membrane ingredient is unlikely to adversely affect the nutritional profile of the food supplements to which it is added. Furthermore, the consumption of the egg membrane is unlikely to significantly impact the intake of macronutrients in the diet. Although egg membrane is comprised mostly of protein (approximately 90% on a dry matter basis), the maximum consumption of 450 mg egg membrane per day would result in an intakes of 405 mg protein per day, which would be negligible when compared to the population reference intake (PRI) for protein established by EFSA of 0.83 g protein/kg body weight/day (equivalent to 58.1 g/day in a 70 kg individual) (EFSA, 2012).

XII MICROBIOLOGICAL INFORMATION ON EGG MEMBRANE INGREDIENT

Microbiological specifications have been established for egg membrane and batch analyses indicate that the ingredient is free from microbial contamination (see Section I). Furthermore, there is no evidence of deleterious levels of microbials even following 48 months of storage.

In conclusion, there is no anticipated presence of any microorganisms or metabolites in the novel food or as a consequence of the manufacturing process.

SUMMARY OF THE DOSSIER

XIII TOXICOLOGICAL INFORMATION ON EGG MEMBRANE INGREDIENT

Biova's egg membrane ingredient is sourced from eggs harvested for human consumption and thus has a history of safe consumption. However, to further support the safety of this ingredient, Biova's egg membrane ingredient has been evaluated in a number of product-specific toxicological studies. Based on the results of an acute oral toxicity study in rats, the oral median lethal dose is greater than 5,000 mg/kg body weight, indicating the ingredient is of low acute oral toxicity (unpublished data). The results of a bacterial reverse mutation assay and an *in vitro* micronucleus assay indicate that the ingredient is not genotoxic either in the presence and absence of metabolic activation.

The safety of the consumption of egg membrane for human consumption is further demonstrated by the results of an open-label human study in which healthy subjects were provided 450 mg/day of egg membrane (trade name BiovaFlex) at doses of 450 mg/day for 6 weeks (unpublished data). Overall health evaluations were made at 2, 4, and 6 weeks and adverse events and subject compliance was recorded in self-reported diaries and subject interviews. Blood samples were obtained at baseline and at the end of the 6-week treatment period and assessed for standard haematological and blood biological parameters. IgE antibodies to egg allergens also were determined at baseline and at the end of the treatment period. No adverse events were observed in subjects receiving the egg membrane ingredient during the study. Compared to baseline, a slight overall rise in blood chloride and urea nitrogen were noted in the laboratory analyses conducted at the end of treatment; however, the values were noted to be maintained within the reference normal ranges. No other statistically significant change from baseline values were observed in blood parameters. Additionally, no significant increases in IgE antibodies to egg allergens were observed in any subject. The study investigators concluded that the results of the study demonstrated that the consumption of BiovaFlex was considered safe, with no reported adverse effects.

As eggs are a common food allergy in man, the allergenic potential of the egg membrane ingredient was evaluated in an egg radioallergosorbent test (RAST) inhibition assay and a quantitative egg allergen test (unpublished data). No evidence of allergenicity was noted in these studies. Furthermore, the egg membrane ingredient also is not a skin sensitiser based on the results of a Buehler guinea pig sensitisation assay (unpublished data).

Although there is no additional risk of allergenicity compared to eggs, products containing the egg membrane ingredient will be conspicuously labelled in accordance with the *Food Information to Consumers Regulation* (EC) No 1169/2011, which requires information on the potential presence of substances with an allergenic or intolerance effect be given to consumers (Eggs and products thereof are listed as item 3 in *Annex II: Substances or Products Causing Allergies or Intolerances*) (European Parliament and the Council of the European Union, 2011).

SUMMARY OF THE DOSSIER

Although the chronic, developmental, and reproductive effects of egg membrane have not been evaluated in traditional toxicological studies, the safety of this ingredient is supported by the existing pre-clinical and clinical data, and the long history of safe consumption of eggs in the EU.

OVERALL CONCLUSION

Biova intends to market their egg membrane as a novel food ingredient in the EU. The egg membrane ingredient is harvested from chicken eggs intended for consumption. The ingredient is comprised predominantly of protein, with the remainder being moisture, ash, fibre, sodium, and calcium. Additionally, the ingredient is free of microbial, heavy metal, pesticide, and antibiotic contamination. Appropriate product specifications for identity and potential contaminants have been established for the ingredient. The results of batch analyses indicate that the manufacturing process yields a consistent product compliant with the established specifications. The egg membrane ingredient is produced according to GMP under HACCP principles.

Biova's egg membrane is intended for use in food supplements providing doses not exceeding 450 mg egg membrane/day. The maximum intended dose of this ingredient is equivalent to the consumption of the egg membranes of 8 to 10 eggs. Biova has a history of marketing its egg membrane ingredient in the United States since 2009, with no reports of adverse events to date.

The safety of the ingredient for its intended use in food supplements is supported by the results of pre-clinical studies demonstrating that the egg membrane ingredient is of low acute oral toxicity and is not genotoxic *in vitro*. Furthermore, the results of a human study in which the ingredient was consumed for 6 weeks indicated that no adverse health effects are anticipated with the consumption of egg membrane ingredient at up to 450 mg/day. No evidence of allergenicity was noted in a RAST inhibition assay and a quantitative egg allergen test. The egg membrane ingredient also is not a skin sensitiser. Products containing egg membrane ingredient will be labelled as being derived from eggs in accordance with Regulation (EC) No 1169/2011.

Collectively, the scientific evidence presented herein demonstrates that Biova's egg membrane ingredient is not anticipated to pose any adverse effects on human health under the proposed conditions of use as a novel food ingredient in food supplements.

SUMMARY OF THE DOSSIER

REFERENCES

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