COMMITTEE PAPER FOR DISCUSSION **ACNFP/108/6**

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

NATTOKINASE

ISSUE

The Belgian Competent Authority (CA) has prepared an initial opinion on an application for the authorisation of nattokinase, as a novel food ingredient under the Novel Food Regulation (EC) No. 258/97. The Committee is asked whether it agrees with the conclusions of the Belgian CA or whether it has any further comments or objections to make on the application. The Committee's advice will form the basis for the UK's formal response.

Background

1. On 15 October 2012, the European Commission forwarded the Belgian CA's initial opinion on an application made by Nutraveris, on behalf of Japan Bioscience Laboratory under Article 4(1) of Regulation (EC) 258/97, for the authorisation of nattokinase (the 'novel ingredient') as a novel food ingredient for use in food supplements. The Belgian CA was not content with the data provided by the applicant and concluded that the information supplied was insufficient to demonstrate the safety of the novel ingredient, and also expressed concern that it is uses may be regarded to be medicinal. (Belgian opinion attached at **Appendix 1**).

2. Nattokinase is regarded to be novel as it a purified extract of natto, a traditional Japanese food, also marketed in the EU, which is obtained by the fermentation of soya beans using the bacterium *Bacillus subtilis var natto*. Despite its name nattokinase is not a kinase enzyme, but is regarded to have fibrinolytic qualities.

3. The Belgian CA assessment of the novel ingredient has concluded that there are potential safety concerns related to side effects that could occur in subgroups of the targeted population (individuals at risk of cardiovascular disease), and also notes that the ingredient may be a medicinal product rather than a food.

4. Following receipt of an initial opinion from another CA, EU Member States have 60 days to comment on, or provide reasonable objections to, the marketing of the food in question. Given their concerns, the Belgian assessment is restricted to the potential side effects and they have not commented on the other sets of information which are submitted in support of novel food applications (see para 6

below). Therefore this paper provides a detailed overview of the areas highlighted by Belgium as a course for concern and only gives a a brief overview of each of the other areas. Additional information on these aspects can be found in the dossier (attached at **Appendix 2**[1])

5. In regard to the potential medicinal function the Secretariat is discussing this product with the MHRA and will provide an update at the meeting.

6. Although the applicant refers to a history of use of the source material in the dossier it is incorrectly classified as Class 2.2 'a complex novel food from a non-GM source' in the dossier where the source of the novel ingredient has a history of food use in the Community. The requirements for a submission of either class are relatively unchanged and are as follows:

I	**Specification of the NF**	**X**
II	**Effect of the production process applied to the NF**	**X**
III	History of the organism used as the source of the NF	
IV	*Effect of the genetic modification on the properties of the host organism*	**-**
V	*Genetic stability of the GMO*	**-**
VI	*Specificity of expression of novel genetic material*	**-**
VII	*Transfer of genetic material from GM microorganisms*	**-**

VIII	*Ability to survive in and colonise the human gut*	**-**
IX	**Anticipated intake/extent of use of the NF**	**X**
X	**Information from previous human exposure to the NF or its source**	**X**
XI	**Nutritional information on the NF**	**X**
XII	**Microbiological information on the NF**	**-**
XIII	**Toxicological information on the NF**	**X**

The information presented in the dossier is structured accordingly and is considered below under these schemes.

I. Specification of the novel food

Appendix 2, p5-10

7. The applicant has provided detailed analyses in support of the specification of the novel ingredient including the starting materials and the bacterium used in the fermentation process. The specification of the novel ingredient is detailed in full on page 8 of Appendix 2 and this indicates nattokinase present at a level of at least 20000 FU[2]/g. Levels of heavy metals (<20ppm), Lead (<5ppm) and Arsenic

[1] Annexes to Appendix 2 are available from the Secretariat upon request.

[2] One Fibrinolytic Unit (FU))is defined as the amount of enzyme that increases the absorbance of the sample by 0.1 per min (at 275nm)

(<3ppm) are also detailed. Confirmatory analyses are provided on p9 of Appendix 2. Compositional analyses (Appendix 2 p17) indicate that the novel ingredient comprises around 91% carbohydrates and 6% protein. The applicant does not detail the proportion of protein that is the active enzyme.

II. Effect of the production process applied to the novel food

Appendix 2, p 10-13 (PROTECT – COMMERCIAL)

8. The applicant has provided details of the fermentation and extraction process that is used to produce this novel ingredient. Details of the process are commercially confidential and can be found in Appendix 2. The process, which involves production of natto by fermentation of soybeans using a patented strain of *B. subtilis var natto*[3] followed by an extraction and purification process which removes the majority of vitamin K2 present. Vitamin K2, present in relatively high levels in natto, is removed as it is regarded to function as a blood coagulant and, as such, conflicts with the perceived antithrombotic function of the novel ingredient.

9. Studies on the stability of the novel ingredient indicate stability for at least 12 months (Appendix 2 p25). This does not apply under all conditions, however, as the applicant acknowledges that the novel ingredient not suitable for use in beverages and advises special labelling of products where the ingredient is in a gel formulation. It is not clear whether these stability problems relate simply to a reduction in enzyme activity or if other changes taken place.

IX. Anticipated intake/extent of use of the novel food

Appendix 2, p13-14

10. The applicant intends that the novel ingredient will be in food supplement form, aimed at older men and women 'who want to maintain healthy blood viscosity'. The applicant advises consumption of at least 100mg/day (2000 FU/day), in line with advice from the Japanese Nattokinase Association and the Japanese Health Food and Nutrition Association relating to its purported efficacy.

11. The applicant also provides details of a number of clinical studies which indicate that nattokinase can reduce elevated blood pressure, improve circulation and normalise levels of C-reactive protein, and has fibrinolytic activity.

[3] Information in this regard may be available at http://www.freepatentsonline.com/y2007/0254347.html

X. Information from previous human exposure to the novel food or its source
XI. Nutritional information on the novel food
Appendix 2, p15-17

12. The applicant refers to the widespread consumption of natto in Japan (150 million tonnes in 2010) and provides additional compositional analyses of the ingredient which demonstrates compliance with the product specification.

XII. Microbiological information on the novel food
Appendix 2, p20,22

13. The applicant provides data demonstrating the absence of a range of microorganisms (coliforms, yeasts and moulds etc) from the novel ingredient.

14. The applicant has also assessed the safety of the production strain of *B. subtilis* concluding that it did not give rise to any infectious disease over a 14 day period following the oral administration of 7.55×10^8 CFU to mice.

XIII. Toxicological information on the novel food
Appendix 2, p 20-25

15. The applicant details a relatively comprehensive toxicological assessment of the novel ingredient noting that it is non-mutagenic, and shows no acute toxicity in rats at a dose of 2000 mg. A number of the studies appear to have been carried out on nattokinase *per se* rather than the novel ingredient (referred to as NK, rather than NSKII in the dossier.

16. Given the perceived purpose of the novel ingredient the applicant has also considered potential drug interactions. Twelve patients who were in hospital following an ischaemic stroke and were being treated with aspirin, heparin and an ant-platelet drug were also given 6000 FU/day of nattokinase for 7 days and were monitored for 3 months. Administration of nattokinase resulted in a temporary significant increase in bleeding (and clotting) time, together with a decrease in prothromibin time, thromboplastin time and D-dimer levels. Three adverse reactions were regarded to be temporary and the authors concluded that nattokinase could be administered safely to stroke patients as an adjunct to standard medical treatments. In a separate study 30 adults who were taking warfarin were given the nattokinase (1700 FU/day) for 26 weeks and, as no adverse reactions were reported, the authors concluded that that the parallel administration of nattokinase and warfarin may be possible.

17. The Belgian CA also noted that consumption of the novel ingredient may, due to its fibrinolytic activity, have a negative effect in individuals who take aspirin to prevent platelet aggregation. The Belgians also suggest that individuals who are taking hypertensive and anticoagulant medication may also be affected if they

consume the novel ingredient and this should be monitored by their physician. As the Belgian risk assessors advised that nattokinase may be medicinal the Belgian CA is checking this aspect with their national medicines authorities and, in the meantime, has issued a negative opinion noting that as the novel ingredient is likely to consumed over a long period and this may have detrimental health effects.

18. **Allergy**. The applicant advises that, due to the presence of soya based excipients, the final product will be labelled as containing soya. The Secretariat notes that, unless applicant obtains an exemption from the allergen labelling requirements set out in Directive 2001/13/EC (as amended), it would be a mandatory requirement for the novel ingredient to be labelled as containing soya.

COMMITTEE ACTION REQUIRED

19. The Committee is asked whether it agrees with the negative initial assessment report from the Belgian CA and whether they have any additional comments on the application.

20. The Committee's advice, together with the view from the MHRA will form the basis of the UK's formal response to the European Commission.

Secretariat
November 2012

Appendices attached:

Appendix 1 **PROTECT–REGULATORY**
Application for the approval of Nattokinase (Appendices available from the Secretariat on request)

Appendix 2 Belgian CA Initial Opinion