Meeting

Allulose - Discussion Paper

Committee Paper for Discussion - ACNFP/169/02

Advisory Committee For Novel Foods and Processes

Application for Authorisation of Allulose as a Novel Food.

Application Number RP1130

Issue

1. An application has been received under the novel food authorisation process (assimilated Regulation (EU) 2015/2283) for allulose as a new novel food for the GB market. The Committee is asked to advise whether the available data provides an adequate basis for a risk assessment, and whether the novel food is safe and not nutritionally disadvantageous under the proposed uses.

2. A draft Committee Advice Document (CAD) has been prepared to support the review of this novel food application. Members are asked to consider the CAD and provide comments.

Background

1. On 10 June 2021, the Food Standards Agency (FSA) and the Food Standards Scotland (FSS) received the submission for allulose from Savanna Ingredients GmbH.

2. The novel food is a non-digestible monosaccharide sweetener and epimer of D-fructose with 70% the sweetness of sucrose produced into syrup and crystalline forms. Monosaccharides used for their sweetening properties do not fall under the scope of the food additives legislation (regulation 2008/1333, Chapter 1, article 3). Allulose has a reported low-calorie value of ≤0.4g Kcal/g in pure form. Allulose is a naturally occurring rare sugar in foods but in quantities too low to claim a history of use.

3. The novel food is produced via enzyme-catalysed epimerisation of fructose into its c-3 epimer utilising the enzyme *D-tagatose 3-epimerase*. Fructose and allulose molecules are separated, followed by a series of filtration and purification steps, producing a syrup form and dried crystalline form. The proposed uses are as a tabletop sweetener as an alternative to sugar and in a variety of conventional foods and beverages for substitution of added free sugars (notably “sucrose” table sugar).

4. On 3 June 2021, the FSA and FSS received the submission from the same applicant for a new food enzyme, *D-tagatose 3-epimerase,* for the GB (Great Britain) market and its novel use in the manufacture of allulose, under assimilated regulations (EU) 1331/2008 and (EU) 234/2011. At EU level, the safety of the new food enzyme was assessed by EFSA (EFSA 2023) and reached a positive opinion. An FSA-FSS opinion on the food enzyme has not yet been reached. As GB does not currently have a positive list of food enzymes, the enzyme can be used in food products. However, as part of the novel food safety assessment, the production process aspect should provide key information on the identity of substances used in the manufacturing process for a safety review and with consideration of any potential by-products, impurities or contaminants in the novel food

5. The application dossier is attached as Annex A. Information requested ahead of the review can be found in Annex B and the relevant files to the dossier are attached as Annex C. A draft CAD document has been prepared by the Secretariat and can be found in Annex D. All annexes contain confidential information.

This application

Identity

6. Allulose, is a monosaccharide ketohexose carbohydrate and C-3 epimer of D-fructose (≥98.5% and ≥85% purity for crystalline and syrup forms, respectively). The structure and identity of the novel food was confirmed using nuclear magnetic resonance (NMR) spectroscopy: 1H-NMR and 13C-NMR methodologies and further categorised by High Pressure Liquid Chromatography - Refractive Index Detector (HPLC-RID).

7. Please see Annex A; p 9 – 11 of dossier. Relevant files for this section can be found in Annex C [files A2.2.1 – A2.2.4, A2.4.36 and ‘Annex 1a_Method mono-disaccharides P&L EN_20230214’).

8. Further information on the identity all molecules in the syrup form was provided in Annex B; p 1 - 3 of response letter dated 15th December 2022 including further information on the fraction of unidentifiable other sugars and Maillard Reaction Products (MRPs) in the novel food. Further information on the NMR reference sample can be found in Annex C [files 1a.01 and 1a.02] of the response dated 15th December 2022 (Annex B; p 1). confidential. Further information on the HPLC analysis was provided in Annex B; p 1 - 3 of response letter dated 15th February 2023.

Production Process

9. The novel food is produced from fructose using an enzymatic reaction. The production method is described in Annex A; p 12 – 16 of dossier. Relevant files for this section, can be found in Annex C [files A2.23, A2.24, A2.3.01 – A2.3.15, 2.c.01, A2.4.35 and A2.3.23 - A2.3.30].

10. Further details on the method (purity calculation, enzyme reaction and fructose fraction substrate) were requested and are provided in Annex B; p 11 – 12 of response letter dated 15th December 2022. The applicant clarified that magnesium chloride is no longer used in the production process and will not be replaced by another raw material (see Annex B; p 5 of response letter dated 15th February 2023).

11. Since the development of the initial submission, the applicant has scaled up their production. The applicant provided further information on method controls and changes made to the larger commercial scale production (Annex B; p 3 – 4 of response letter dated 15th February 2023). On request, the applicant provided information on their food safety management plan (Annex B; p 1-2 of response letter dated 4th April 2023 and Annex C [files A2.3.31 – A2.3.32]).

12. The applicant provided information to show that the production organism for the food enzyme used is absent from the enzyme preparation and no recombinant DNA remains. Absence of bacteria from the *Enterobacteriaceae* family, *Escherichia coli* and residual bacterial DNA of the genetically modified strain was also provided with regards to the enzyme preparation. Further verification is provided in the compositional analyses of the novel food.

Composition

13. The crystalline novel food is primarily allulose (≥99.2g/100g) with trace levels of fructose (≤0.66g/100g) and water (≤0.2 g/100g). The syrup novel food consists of ≥60 g/100g allulose in addition to ≤27.9 g/100g water, ≤0.66g/100g fructose and ≤11.44g/100g of unidentified products of Maillard reactions as minor components. Allulose will be produced in both crystalline and syrup forms depending on the use.

14. Information on composition can be found in Annex A; p 17 – 23 of dossier. Relevant files for this section, can be found in Annex C [files A2.4.37-A2.4.46, A.2.4.01- A.2.4.11 (Certificates of Analyses), file A2.4.52, A2.4.53, annexes 3.a.1 - 3.a.4 and annex 4.a].

15. Batch data is provided for 5 independent batches of allulose syrup and crystalline allulose at pilot scale as updated in Annex B; p 5 – 10, Tables 3 and 4 of response letter dated 15th February 2022. Further batch data for 6 independent batches of allulose syrup at commercial plant scale was provided in Annex B; p 2, Table 1 of response letter dated 15th February 2023. Parameters included physicochemical, biochemical and microbiological, including data to show absence of contamination from use of the food enzyme.

16. Following a request for information on laboratory accreditation, a response was provided by the applicant in Annex B; p 13-14 of response letter dated 15th December 2022. The applicant provided further information on manufacturing consistency in Annex A; p 35 of dossier and Annex B; p 16 of response letter dated 15th February 2023 and subsequently lowered the specification for allulose content from ≥63g/100g to ≥60g/100g.

Stability

17. The applicant has provided a range of analytical data which investigated the stability of allulose under normal and accelerated storage conditions. Information on stability can be found in Annex A; p 24 – 34 of dossier. Relevant files for this section, can be found in Annex C [files A2.4.12 – A2.4.35, A2.4.53 and A2.4.60]

18. The applicant provided further information on packaging and variation in parameters during the stability study in allulose syrup in Annex B ; p14 – 16 of response letter dated 15th December 2022 and p 5 – 9 of response letter dated 15th February 2023 . The applicant states that the colour parameter is a quality measure and to potentially mitigate generating undesirable Maillard Reaction Products. Information is also provided on allulose in a limited range of final

products.

Specifications

19. The specification parameters for the novel food in crystalline and syrup forms, were assessed using internationally recognised methods or are otherwise determined using internally developed and validated methods. The applicant stated that allulose and fructose are the parameters chosen to characterise and substantiate the purity of the crystalline and syrup products with a specification of ≥85 % and ≥98.5%, respectively. A minimum allulose content is also set at ≥60 % and the maximum at ≥98.5 %.

20. Information on specifications can be found in Annex A; p 35 of dossier. Following a request for further information (Annex B; p 17 of response letter dated 15th December 2022), updated specifications can be found in Annex C [files A2.5.1 and A2.5.2.

History of Use

21. Information on history of use can be found in Annex A; p 36 of dossier) which provides a review of foods containing allulose in trace levels. Information on authorisations in non-EU countries is also provided.

Proposed Use and Anticipate Intake

22. The applicant states that the novel food ingredient is intended to be used by the general population which excludes infants and young children (18 months).

23. Information on the proposed uses can be found in Annex A; p 37-39 of dossier and updated maximum use levels can be found in Annex B; p 2-3, Table 1 of response letter dated 31st August 2023. Further information on the target population can be found in Annex B; p 18-19 of response letter dated 15th December 2022 and p 9 – 10 of response letter dated 15th February 2022.

24. The applicant initially conducted an exposure assessment following standard methodology set out in the assimilated EFSA technical guidance. This included an assessment based on selected food categories and chronic and acute consumption data from the EFSA Comprehensive Food consumption Database (food consumption data and proposed uses combined) as a ‘Tier 1’ approach. It was noted that for sugars, a conservative estimation of exposure can be

expected. However, the estimated anticipated intake levels were in large exceedance of the safe tolerable level and the applicant had further reported that these levels were not an accurate presentation of the likely exposure. As such, the applicant was advised to make use of UK National Diet and Nutrition Survey (NDNS) individual consumption data ('tier 2 assessment') and apply a scenario-based refinement. Scenarios were applied using data on free-sugars and using NDNS categories. This included a non-standard approach using expected market-share data for allulose to calculate more realistic estimates. Information on anticipated intake levels and the results of the tier 1 exposure assessment can be found in Annex A; p 40-47 of dossier. Information on anticipated intakes from the results of the tier 2 exposure assessment with scenario-based refinements and market share data can be found in Annex B; p 1-22 of response letter dated 31st August 2023. All relevant files can be found in Annex C [files A2.7.01 – A2.7.14 and annexes 1-5)

25. The levels of exposure for the assessments were compared to the tolerable levels identified in the human tolerance study conducted by the applicant (Annex A; p 39, Table 12 and p 69 – 70 of dossier). As reported under the toxicological information section, relevant files including the study report and summary are in Annex C [files A2.10.3.1.1 - A2.10.3.1.5].

Absorption, Distribution, Metabolism, Excretion (ADME)

26. The applicant did not conduct any ADME studies and have provided a literature review (Annex A; p 48 – 51 of dossier).

Nutritional Information

27. Information on nutrition can be found in Annex A; p 52-53 of dossier. The novel food is reported by the applicant to be a low-calorie sweetener of ≤0.4g Kcal/g and 0.29 Kcal/g in the proposed crystalline and syrup forms, respectively. This nutritional information was supported by the values for allulose reported in the literature.

28. Information investigating gut microbiome interactions, prebiotic effects glycaemic effects or effects on insulin can be found in (Annex A; p 71 – 89 of dossier). Relevant files can be found in Annex C [Annex 5.a.01] and further information was provided by the applicant in Annex B; p 21-22 of response letter

dated 15th December 2022 and p11-13 of response letter dated 15th February 2023.

29. Further information on Maillard Reaction Products and levels in the novel food compared to other foods can be found Annex B; p 5 -9 of response letter dated 15 th February 2023.

Toxicological Information

30. Toxicological information from a literature review can be found in Annex A; p 54 – 60 of dossier.

31. The applicant conducted a bacterial reverse mutation assay (OECD 471) (Annex A; p 62 - 63 of dossier), an in vitro mammalian cell micronucleus test (OECD 487) (Annex A; p 63 - 64 of dossier) and a 90-day oral toxicity study in rats (OECD 408) (Annex A; p 65 - 66 of dossier). The full study reports are available in Annex C [files A2.10.2.1, A2.10.2.2 and A2.10.2.3.2].

32. A summary of statistically significant observations of the genotoxicity studies carried out can be found in Annex C [Annex 8a.01].

33. A human tolerance single centre, double-blinded, placebo-controlled, randomised, balanced, one-period, multiple dose parallel-group human tolerance study over 7 days was conducted by the applicant (Annex A; p 39, Table 12 and p 69 – 70 of dossier). Relevant files, the study report and summary are in Annex C [files A2.10.3.1.1 - A2.10.3.1.5]. A literature review of the available human studies on allulose is provided in Annex A; p 71 – 80 of dossier. This data forms the basis for the identification of the safe level to be consumed.

Allergenicity

34. Information on allergenicity can be found in Annex A; p 81-82 of dossier. The dossier focuses on the low level of protein present. Further information on protein levels in the novel food (Kjeldahl analysis and a modified Bradford assay) is provided in Annex B; p 24 of response letter dated 15th December 2022 – confidential). The respective method for the Bradford assay can be found in Annex C [Annex 9a.01 and 9a.02].

Committee Action Required

The Committee is asked whether the available data provide a satisfactory basis for evaluating the safety of this novel food ingredient.

• If so, the Committee is asked whether it is content to recommend approval for allulose as a novel food ingredient to be added to the range of foods specified.

• If not, the Committee is asked to indicate what additional data would be required.

Secretariat

October 2024

Annexes

Annex A – Dossier [Confidential].

Annex B – Requests for information with applicant’s responses [Confidential].

Annex C – Supporting documents with annexes, references and appendices [Confidential].

Annex D – Draft Committee Advice document.