Meeting

Akkermansia Muciniphila Discussion Paper

Committee Paper for Discussion - ACNFP/159/07.

Advisory Committee For Novel Foods and Processes.

Application for Akkermansia Muciniphila as a Novel Food from the Akkermansia Company SA (Previously A-Mansia Biotech SA).

Application number RP1468.

Issue

An application has been received under the novel food authorisation process (regulation 2015/2283 as repatriated) for pasteurised cells of *Akkermansia muciniphila*. The Committee is asked to advise on 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 use and use levels.

Introduction

1. An application was submitted to the Food Standards Agency in April 2021 by The Akkermansia Company SA (previously A-Mansia Biotech SA), for the authorisation of Pasteurised *Akkermansia muciniphila* (pasteurised cells of the bacterial species *Akkermansia muciniphila*) as a food supplement and as an ingredient in foods with special medical purposes (FSMPs), under the novel foods regulation (EU) 2015/2283 as repatriated.

2. This product has been authorised for use in the European Union (EU) as a food supplement and as an ingredient of foods with special medical purposes (FSMPs) under regulation (EU) 2015/2283. It has yet to be assessed for authorisation in

Great Britain.

3. Akkermansia muciniphila is a human gut commensal, non-motile, non-spore forming, elliptical bacterium. The species accounts for between 1% and 5% of healthy intestinal microbiota.

4. The applicant's intention is to market *Akkermansia muciniphila* as a freeze-dried powder containing a minimum of $2.5x10^{10}$ total cells per gram and 500 viable cells per gram (500cfu/g). This number of viable cells represent 0.000002% of total *Akkermansia muciniphila* cells in the final product. It is intended for use in food supplements at up to $5x10^{10}$ cells/day in the healthy population, excluding pregnant or lactating women.

5. The European Food Safety Authority (EFSA) has established a framework known as the Qualified Presumption of Safety (QPS) concept which provides a generic assessment system that can be applied to all requests received for the safety assessments of microorganisms deliberately introduced into the food chain. Microorganisms not considered suitable for QPS remain subject to a full safety assessment. *Akkermansia muciniphila* was evaluated in 2020 and was not recommended for the QPS list due to safety concerns surrounding the possibility of the organism contributing to the progression of neural diseases.

6. The full technical dossier submitted by the applicant is attached as Annex A, a folder of the literature referenced within the application is attached as Annex B, and Annexes C to S contain supplemental information to the full technical dossier. All annexes should be treated as confidential.

This application Identity

7. Data has been provided as evidence for the identity of the novel food seeking authorisation; pertinent to foods consisting of, isolated from, or produced from microorganisms, fungi, or algae. All data submitted can be found in section 2.a of Annex A and within Annex C.

8. The novel food product seeking authorisation, pasteurised *Akkermansia muciniphila*, is derived from a bacterium. A full taxonomic ranking has been provided, which places the source microorganism within the bacterial family *Verrucomicrobiaceae*, genus *Akkermansia*, and species *Akkermansia muciniphila*

(*A. muciniphila*). The strain has been given as *Akkermansia muciniphila* Muc^T

(ATCC BAA-835), which has been verified through 16s rRNA sequencing and PacBio and Illumina whole genome sequence analysis, referenced with the National Centre for Biotechnology Information (NCBI) sequence for *Akkermansia muciniphila*. The 16s rRNA sequence analysis revealed a 100% homology to the reference sequence; the PacBio and Illumina whole genome sequence analyses revealed a 99.6% and 99.8% homology, respectively, to the NCBI reference sequence.

9. The 16s rRNA sequencing certificate of analysis, can be found on pages 2 and 3 of Annex C. The report on the whole genome sequence analyses of the novel food product can be found on pages 135 to 144 of Annex C.

10. The origin of the source microorganism (*Akkermansia muciniphila* Muc^T (=ATCC BAA-835) is a healthy human intestinal tract. A reference article has been provided as evidence, in which the organisms origin is described. The article is attached within Annex B - (Derrien *et al.,* 2004).

11. The strain has been deposited within two officially recognised culture collections: American Type Culture Collection (ATCC); Collection de l’institut Pasteur (CIP).

The respective access numbers are ATCC BAA-835 and CIP 107961. The applicant considers this provides adequate evidence of the identity of the microbe used in production.

Virulence and Antibiotic Resistance of the Source Microorganism

12. Data has been provided on the virulence and antibiotic resistance of the source organism, *Akkermansia muciniphila* (ATCC BAA-835). A bioinformatic approach has been used to determine the presence of virulence determinants, toxigenicity, and for the analysis of the *A. muciniphila* genome for antimicrobial resistance genes. Antimicrobial resistance has also been evaluated through minimal inhibitory concentration (MIC) assay using a wide range of antimicrobials of human and veterinary importance. The applicant concluded that *A. muciniphila* is unlikely to pose any safety concerns related to virulence factors and antibiotic resistance potential. Further details, including methods of analysis, can be found in section 2.i.7, pages 45 to 53 of Annex A.

Antimicrobial Resistance

13. An antimicrobial resistance study has been provided, which assesses the susceptibility of pasteurised Akkermansia muciniphila (ATCC BAA-835), along with 5 other *Akkermansia muciniphila* strains and 1 strain of *Akkermansia glycaniphila* Pyt^{t}, to a range of antimicrobial compounds. The study was performed in accordance with the EFSA *guidance on the assessment of bacterial susceptibility to antimicrobials of human and veterinary importance*.

14. The results of the study do indicate resistance to some of the compounds tested. However, the applicant concludes that any antimicrobial resistance observed is intrinsic and therefore confers a low risk of horizontal spread to environmental species and does not pose any strain specific risk based on the antimicrobial resistance pattern. The evidence for this can be found on pages 45 to 47 of Annex A; the full study report and results can be found attached within Annex D.

15. The applicant proves a bioinformatic assessment of the whole genome sequence of pasteurised *Akkermansia muciniphila* with reference to known antimicrobial resistance genes. The whole genome sequence was first annotated using tools hosted by Pathosystems Resource Integration Centre (PATRIC), with subsequent searches for sequence homologies within the Comprehensive Antibiotic Resistance Database (CARD) and the National Database of Antibiotic Resistant Organisms (NDARO); using the Basic Local Alignment Search Tool (BLAST) to align the sequences and identify any antimicrobial resistance genes that may be present.

16. The applicant concludes that the results do not suggest that the pasteurised *Akkermansia muciniphila* genome contains any antimicrobial resistance genes which may be subject to horizontal gene transfer, nor any other genetic material which may also be subject to horizontal gene transfer. The applicant also provides a consideration of publicly available literature on the *Akkermansia muciniphila* genome, which includes a bioinformatic assessment of antibiotic resistance genes. The literature reveals the presence of putative antibiotic resistance genes, although an argument is provided for why this is of no risk, using both literature evidence and results from the antimicrobial resistance study. The full details of the bioinformatic assessment and the literature review can be found on pages 47 to 50 of Annex A.

Virulence Determinants

17. Both a literature review and a bioinformatic assessment using the whole genome sequence of pasteurised *Akkermansia muciniphila* have been used to assess and identify possible virulence determinants (also called virulence factors) associated with the novel food product. Full information can be found in **section** 2.i.7.4 on page 50 of Annex A, articles refenced here can be found attached within Annex B.

18. Within the literature, there were some reports of sequence homology between proteins present in the *A. muciniphila* proteome and putative virulence factors in a number of online databases. However, there are no reported cases, or reports which indicate that *A. muciniphila* exhibits pathogenic behaviour. The justification provided for this is that virulence factors present in one organism, do not necessarily perform as virulence factors in another, regardless of sequence homology.

19. Further to the literature review, a bioinformatic assessment of the whole genome sequence of pasteurised *Akkermansia muciniphila* has been provided to highlight possible virulence determinants. The online tool VirulenceFinder 2.0 was used to search for potential virulence factors relating to *Escherichia coli* and its verocytotoxin subtypes (VTECs), and the online tool PathogenFinder 1.1 was used to predict the pathogenicity potential of *A. muciniphila* to a human host. The presence of genetic elements encoding virulence factors was determined using BLAST to align pasteurised *A. muciniphila* amino acid sequences against putative virulence factors from PATRIC_VF, VFDB, and Victors online databases.

20. The assessment highlighted putative virulence factors which shared significant sequence homology with many proteins present in the pasteurised *A. muciniphila* proteome. However, the justification provided by the applicant as to why there is little risk from this is that there are no reported cases of *A. muciniphila* causing disease or pathogenicity in humans.

21. The pathogenicity of pasteurised *A. muciniphila* was further investigated using PathogenFinder 1.1, which is used to predict the pathogenicity of an organism by comparing protein families from the novel bacterium to a database of protein families associated with both pathogenic and non-pathogenic organisms. The assessment did not highlight any matches with pathogenic families of proteins and pasteurised *A. muciniphila* was predicted to be non-pathogenic in humans. Further information on the bioinformatic assessment of virulence factors and pathogenic potential of *A. muciniphila* can be found on pages 50 to 52 of Annex A.

Toxigenicity

22. An bioinformatic assessment of the toxigenic potential of *A. muciniphila* was conducted by comparing amino acid sequences from pasteurised *A. muciniphila* against a database of animal venom proteins and toxins using BLAST. The search identified a single protein present in the proteome of *A. muciniphila* which shares significant sequence homology with four animal venom proteins. The animal venom proteins which share this homology with *A. muciniphila* amino acid sequences can be found in table 6.5.2.2-1 on page 53 of Annex A.

23. Two of the identified venom proteins have targets in non-vertebrates and are therefore not a concern for humans. The other two venom proteins which share sequence homology with the *A. muciniphila* amino acid sequence do have vertebrate targets, however, further BLAST analysis revealed the sequence codes for *A. muciniphila* ankyrin proteins and is highly conserved across strains of the same species. This suggests that the amino acid sequence and resulting protein does not function as a toxin and is therefore not of toxicological concern. Specific details on the toxigenicity of *A. muciniphila* can be found on pages 52 and 53 of Annex A.

Production Process

24. The novel food, pasteurised *Akkermansia muciniphila*, is produced through a number of steps which create a powdered final product. Initially, a bacterial cell culture is produced via resuscitation from a master cell bank, propagation via anaerobic fermentation, and subsequent heat-inactivation through pasteurisation at 67°C to 73°C, for between 25 and 35 minutes. The pasteurised cells are then concentrated and mixed with cryoprotectants prior to freeze-drying and mixing with a food grade excipient such as corn starch or maltodextrin. The final cell concentration is stated to be at least $2.5x10^{10}$ bacterial cells per gram of powdered final product. The final product in powder form is stored in bulk in heat-sealed, three-layer, waterproof and airproof pouches at -18°C.

25. Full details of the production process, including operational parameters, can be found within section 2.b of Annex A. Process-flow steps and a process flow diagram can be found on pages 12 and 13, respectively. The process steps are then described in detail on pages 13 to 15. Details regarding the raw materials and processing aids used throughout the production process have been provided, along with descriptions and explanations of their use and function (table 2.b.1.11, page 11 of Annex A). Certificates of analysis for all raw materials have also been

provided and can be found within Annex E.

26. Management of the production process is demonstrated through a range of inprocess analyses, which have been detailed throughout the production process. Both culture based analyses (microscopy and colony morphology) and genetic analyses (16s rRNA and whole genome sequencing) are used initially to confirm the identity of the starting inoculum. Culture purity and viability are assessed following anaerobic fermentation through plating. Viability is checked once again after pasteurisation to validate effectiveness of the heat-treatment. Total cell counts are performed throughout the production process using hemocytometry or flow cytometry.

27. A hazard analysis and critical control points (HACCP) declaration has been provided along with a schematic diagram of the critical control points (CCPs) identified. The in-process testing at CCPs are detailed throughout the production process; the HACCP declaration and diagram can be found attached in Annex F.

Compositional Data

28. A range of analyses have been provided in relation to the composition, characterisation, and identity of the novel food. This information can be found in full on pages 16 to 20 of Annex A. Certificates of analysis for each of the five independent batches have been provided and can be found attached as Annex G.

29. The final consumer product intended for market is an off-white to beige homogenous powder with a minimum purity of $2.5x10^{10}$ *A. muciniphila* cells per gram. Analyses of both total *A. muciniphila* cell counts and viable *A. muciniphila* cell counts have been performed on five independent batches using flow cytometry and plating methods, respectively. Species identification using 16s rRNA gene sequencing has also been performed to confirm the identity of each of the five independent batches, all of which conform to the specification. The results of the analyses can be seen summarised in table 2.c.1.1-1 on page 16 of Annex A. The certificates of analysis can be found attached in Annex G.

30. Particle size distribution analysis of the final product has been provided, which shows the final product is free from nanosized structures. The particle size distribution analysis report can be found attached as Annex H.

31. A proximate analysis of the final product has been provided which accounts for one-hundred percent of the mass of the final product. The applicant states this shows full characterisation of the product in terms of the composition. A summary

table of the proximate analysis of five independent batches can be seen in table 2.c.1.2-1 on page 17 of Annex A. The certificates of analysis are provided in Annex G. The results show that the novel food is mostly comprised of carbohydrate and protein, with small amounts of lipid present.

32. Analyses for mycotoxins and polycyclic aromatic hydrocarbons (PAHs) in the final novel food product have not been provided within this application. However, the justification for omission is all raw materials used within the production process have undergone mycotoxin and PAH testing prior to use and have been shown to be free of such contaminants. The certificates of analysis for the raw materials can be found attached in Annex E. The applicant states that the production process does not introduce any mycotoxins or PAHs, thus analysis for these compounds is not relevant to the novel food. Consideration of microbiological and chemical contaminants can be found in full on page 17 of Annex A.

33. A heavy metals analysis of five independent batches has been provided. The results show that the levels of heavy metals (arsenic, cadmium, mercury, lead) consistently remain below the specified EU limits. A summary of the five batch analysis can be found in table 2.c.1.3.1-1 on page 18 of Annex A.

34. Microbiological analyses of five independent batches has been provided and the results are summarised in table 2.c.1.3.2-1 on page 19 of Annex A. Certificates of analysis can be found attached in Annex G. The tested batches all conform with the specification and the applicant states this is in part due to the way the product is produced not allowing the growth or survival of other microbes.

35. A single, representative batch of final product was screened for pesticides, in which none of the compounds tested for appeared above the limit of quantification or limit of detection. This information can be found attached on page 19 of Annex A. The applicant states this demonstrates the absence of pesticides in the final product. Furthermore, evidence is provided in Annex E for the absence of pesticides within the raw materials.

Specifications

36. A specification summary table has been provided and can be found attached as table 2.d-1, on page 23 of Annex A. This provides details of all parameters which are being managed by the applicant and includes specifications for: physical characterisation and identity, proximate analysis, microbiological

contaminants, and heavy metals. The methods used are stated in the table and further details regarding the methods can be found attached as Annex I.

37. The European Food Safety Authority (EFSA) have advised in their scientific opinion the number of viable *Akkermansia muciniphila* cells per gram should be less than 10 colony forming units (10cfu/g). The specification for this novel food diverges from this advice, where it has been set at less than 500 colony forming units per gram (500cfu/g). The justification for this divergence from the EFSA advice is based around the organism being a non-pathogenic, commensal bacterium that is naturally abundant in the human gut. Further justification is given that the specification limits for *Bacillus cereus* in dried infant formular is 500cfu/g; the organism is not only pathogenic, but the food is intended for consumption by infants (a vulnerable population group), whereas the pasteurised *Akkermansia muciniphila* is only intended for consumption by adults. There have also been no recorded adverse effects arising from consumption of the novel food product. The full justification provided by the applicant can be found attached on page 24 of Annex A.

Stability

38. A range of analytical data which characterises and describes the stability of pasteurised *Akkermansia muciniphila* over a 12 month period has been provided. Summary tables and further information can be found attached on pages 20 to 22 of Annex A. The full, technical stability reports can be found attached as Annex J.

39. The data provided includes real-time monitoring of the novel food at 25°C and 60% relative humidity for 12 months, and monitoring under accelerated conditions at 40°C and 75% relative humidity for 12 months. Data for three batches are presented, although analysis of a further two batches is currently ongoing and can be provided upon completion of the studies.

40. The parameters measured in the stability studies include physiochemical and biochemical parameters (total *A. muciniphila* and viable *A. muciniphila* cell counts), and microbiological contaminants pertinent to the novel food. All results currently available demonstrate the long term stability of the novel food over a 12 month period, under both real-time and accelerated conditions.

History of Use and History of the Source

41. The history of use section provided covers both history of the source organism and a history of use of the novel food. The history of use as described by the applicant can be found on page 25 of Annex A. A range of literature has been provided and details of the literature search can be found attached as Annex K.

42. Evidence of consumption of the source organism is provided. The applicant states *Akkermansia muciniphila* cells have been detected in human breast milk, which is evidence of consumption of the source organism from birth. Evidence is also brought forward which confirms the presence of *Akkermansia muciniphila* in the human gastrointestinal tract during infancy, from as young as one month old. The abundance of *A. muciniphila* in the human gastrointestinal tract is stated to increase with age up to adulthood. A study is brought forward by the applicant which describes the prevalence of *A. muciniphila* in samples taken from various human populations. A total of 96% of samples taken from adults and the elderly had detectable *A. muciniphila* cells, it was also detected in 16% of samples taken form 1 month old infants.

43. The applicant states that although this information evidences some form of consumption of *A. muciniphila* in the UK, the novel food seeking authorisation (pasteurised *Akkermansia muciniphila*) does not have a recorded history of consumption within the UK.

44. The authorisation of pasteurised *A. muciniphila* within the EU is brought forward here as evidence of history of consumption. Although this does demonstrate that the novel food may now be consumed within the EU, the authorisation took place in 2021, which does not demonstrate a long history of consumption within the UK. The EFSA panel opinions have been included here and are attached within Annex L.

Proposed Uses, Use Levels, and Anticipated Intake

45. Details provided by the applicant on proposed uses, use levels, and anticipated intake can be found on page 26 of Annex A. Pasteurised *Akkermansia muciniphila* is intended for use in food supplements at up to $5x10^{10}$ cells per day, and in foods with special medical purposes (FSMPs) at a use level which is to be determined on an individual basis. This novel food is not intended to replace any other food within the diet.

46. The target population for pasteurised *Akkermansia muciniphila* is adults (defined as 12 years old and above by the applicant), excluding sensitive populations (infants, young children, and pregnant or lactating women). The applicant states that products containing the novel food will be labelled accordingly to reflect these restrictions. The intended use level as an ingredient in food supplements is stated to be up to a maximum of $5x10^{10}$ cells per day. The equivalent anticipated intake for a 70kg adult at this level is up to $7.14x10^{8}$ cells/kg/day. It is also intended for use in foods with special medical purposes (FSMPs) at use levels determined on an individual basis.

47. There is not expected to be any other intake of pasteurised *Akkermansia muciniphil*a from elsewhere in the diet as there are no other known, similar products on the market in the UK. The applicant also states that consumption of both food supplements and FSMPs containing the novel food is not expected. No exposure to undesirable substances is to be expected, as evidenced within the specification and compositional data section in sections 2.c and 2.d of Annex A.

Nutritional Information

48. A summary of the proximate analysis of the novel food can be found in table 2.c.1.2-1 on page 17 of Annex A. The certificates of analysis for the proximate analysis can be found in Annex G. Further information pertaining to the nutritional information can be found on page 29 of Annex A. While not expected to provide a significant contribution to the nutritional quality of the diet, consumption of pasteurised *Akkermansia muciniphila* is not nutritionally disadvantageous under the proposed conditions of use. It does not contain any antinutritional factors or have an effect on nutrient intake.

49. The applicant states that consumption of *A. muciniphila* has been shown to have beneficial effects in humans, such as gut barrier function and counteracting obesity and metabolic syndrome. Consumption of *A. muciniphila* has also been shown to have no effect on the microbiota and abundance of other bacteria in the gut of rats. A number of literature articles have been provided in support of these claims and can be found attached as Annex M.

Absorption, Distribution, Metabolism and Excretion (ADME)

50. A consideration of the absorption, distribution, metabolism and excretion (ADME) of *Akkermansia muciniphila* has been provided, although no proprietary ADME study data is provided. Information on ADME can be found in section 2.g on page 28 of Annex A. It is suggested by the applicant that the novel food product

(and the source organism) are not absorbed systemically and are excreted in the faeces. Evidence supporting this claim has been provided; the referenced articles can be found attached in Annex N. The justification is based largely around the detection of *A. muciniphila* in faecal samples isolated from a range of human populations after oral consumption.

51. Further evidence is presented from a clinical study involving pasteurised *A. muciniphila*, which showed that the novel food did not induce changes to the human gut microbiome and was detected in faeces after oral consumption. Further details of the clinical study can be found attached in Annex O.

Toxicological Information

52. A range of proprietary toxicological studies and literature data, covering both animal and human data, have been provided in support of the safety of pasteurised *Akkermansia muciniphila*. The applicant states that all proprietary studies carried out are GLP-compliant and follow OECD guidelines. The test substance used in the proprietary studies is pasteurised *Akkermansia muciniphila* (strain ATCC BAA835), manufactured by the applicant.

53. A tiered approach to toxicity testing has been used to address the safety of the novel food. As pasteurised *Akkermansia muciniphila* is not absorbed systemically, and due to the data and results provided, a 2nd tier of toxicity testing was not triggered. A summary of the toxicity testing performed can be found in table 2.i.11 on page 30 of Annex A. The full toxicology section can be found on pages 30 to 53 of Annex A. Details pertaining to the literature search can be found attached in Annex K.

Genotoxicity

54. An *in vitro* reverse mutation assay and *in vitro* mammalian cell micronucleus test were performed on pasteurised *Akkermansia muciniphila*, following OECD 471 and OECD487 guidelines respectively. Both studies indicate that the novel food has no mutagenic, clastogenic or aneugenic effects and therefore the novel food is concluded to be non-genotoxic. Detailed descriptions of the genotoxicity analyses can be found in section 2.i.2 on pages 32 and 33 of Annex A. The study reports can be found attached in Annex P.

Sub-chronic Toxicity

55. A preliminary 14-day dose rage-finding study in rats and a 90-day repeat dose toxicity study have been provided in support of the safety of the novel food. An additional review of 4 to 5 week short-term toxicity studies has also been provided as supplemental information. Detailed descriptions of all sub-chronic studies can be found on pages 34 to 40 of Annex A.

56. The preliminary 14-day dose rage-finding study in Crl:wI(Han) rats was performed to evaluate potential short-term toxicity of the novel food and to select dose levels for use in the 90-day study. No clinical effects relating to the test item and no deaths were observed during the study. The full study report can be found attached as Annex Q.

57. A 90-day repeat dose toxicity study was conducted to evaluate the sub-chronic toxicity of the novel food. Pasteurised *Akkermansia muciniphila* was administered to Crl:WI(Han) rats via oral gavage once daily for 90 days. The study was conducted according to OECD TG 408 and the principles of GLP. No test-item related changes, effects, or deaths were observed during the study. The NOAEL drawn from the data can be found on page 37 of Annex A. The study and results are described in detail on page 36 of Annex A, the full study report can be found attached as Annex R.

58. Additionally, literature data assessing the safety of both pasteurised and viable *Akkermansia muciniphila* (not produced by A-Mansia Biotech SA.) are also presented and summarised here. This includes a number of short-term oral toxicity studies in mice. No adverse effects were seen in any of the literature articles which have been included in the review. The summaries of the data, including information on the test items used and parameters monitored, can be found in table 2.i.3.2.11 on pages 38 to 40. The literature articles can be found attached as Annex S.

Human Data

59. A randomised, double-blind, placebo-controlled clinical trial has been conducted using the pasteurised *Akkermansia muciniphila* concerned in this application. Both live and pasteurised *A. muciniphila* was administered separately to 32 clinically overweight or obese subjects once daily for 12 weeks, at a dose level of $1x10^8$ cells/day. A range of parameters were measured in the study; the results can be found summarised in table 2.i.6.1.1-1 in Annex A. The applicant concludes that there were no adverse effects observed across all measured parameters within the 12-week study. Full details of the study can be found

attached in Annex O.

Allergenicity

60. A consideration of the allergenic potential of pasteurised *Akkermansia muciniphila* has been provided. The applicant concludes that the novel food is not expected to have any allergenic potential, despite comprising of 30% protein.

61. There have been no reports of allergic reactions associated with pasteurised *A. muciniphila* and there were no reports during the 12-week human safety trial. The European Food Safety Authority concluded that as the living organism, *Akkermansia muciniphila*, is found endogenously within the human gut microbiome, the risk of allergic reactions occurring from consumption is low. The technical dossier section on allergenicity can be found on pages 53 and 54 of Annex A.

Committee Action Required

- The Committee is asked whether the available data provide a satisfactory basis for evaluating the safety of this novel food.
- If so, The Committee is asked whether it is content to recommend approval of *Akkermansia muciniphila* for the proposed uses at the proposed use levels.
- If not, The Committee is asked to indicate what additional data would be required.

Secretariat April 2023

Annexes:

Annex A – Full Technical Dossier

Annex B – All References

Annex C - Identity

Annex D – AMR Profiles (Guiemond)

Annex E – CoAs Raw Materials and Processing Aids

Annex F – Production Process CCPs (HACCP)

Annex G – CoAs and Batch Data

Annex H – Particle Size Distribution Analysis

Annex I – Analytical Methods

Annex J – Stability Reports

Annex K – Toxicology Literature Search Methodology and Results

Annex L – EFSA Opinions

Annex M – Nutritional Information References

Annex N – ADME References

Annex O – Clinical Study

Annex P – Genotoxicity Study Reports

Annex Q – Preliminary 14 day study (Bracken 2019a)

Annex R – 90-Day Repeat Dose Toxicity Study

Annex S – Short Term Oral Toxicity References