Safety Assessment: Outcome of assessment of Cetylated Fatty Acids as a Novel Food

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Summary

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in February 2021 from Pharmaneutra S.p.a., Italy ("the applicant") for the authorisation of cetylated fatty acids as a novel food.

The novel food is a mixture of cetylated fatty acids, cetyl myristate and cetyl oleate, which are synthesised from cetyl alcohol with myristic acid and, cetyl alcohol with oleic acid, respectively. These two cetylated fatty acids are then blended with olive oil to give a finished product containing 70 – 80% cetylated fatty acids. The application is a new application, seeking to use cetylated fatty acids within the food category: food supplements.

To support the FSA and FSS in their evaluation of the application, the Advisory Committee on Novel Foods and Processes (ACNFP) were asked to review the safety dossier and supplementary information provided by the applicant. The Committee concluded that the applicant had provided sufficient information to assure the novel food, cetylated fatty acids, was safe under the proposed conditions of use. The anticipated intake levels and the proposed use in foods and food supplements was not considered to be nutritionally disadvantageous and does not mislead consumers.

The views of the ACNFP have been taken into account in this safety assessment which represents the opinion of the FSA and FSS on cetylated fatty acids.

1. Introduction

1. The FSA and FSS have undertaken a risk assessment for cetylated fatty acids under the novel foods legislation, Regulation (EU) 2015/2283, as retained in UK law. To support the risk assessment by FSA and FSS, the ACNFP provided advice to the FSA and FSS outlined in this opinion.

2. The evaluation by the ACNFP assessed the food safety risks of the novel food and its production, in line with Article 7 of Commission Implementing Regulation (EU) 2017/2469, as retained in UK law. The regulatory framework and the technical guidance put in place by the European Food Safety Agency (EFSA) for full novel food applications is retained as the basis and structure for the assessment (EFSA NDA Panel, 2021

3. With thanks to the members of the ACNFP during the course of the assessment who were; Dr Camilla Alexander White, Dr Anton Alldrick, Alison Austin, Dr Mark Berry, Professor Dimitris Charalampopoulos, Professor Susan Duthie, Professor Susan Fairweather-Tait, Professor Paul Frazer, Dr Hamid Ghoddusi, Professor Andy Greenfield, Professor Wendy Harwood, Professor Huw Jones, Dr Ray Kemp, Dr Elizabeth Lund, Nichola Lund, Dr Rohini Manuel, Emeritus Professor Harry McArdle, Rebecca McKenzie, Professor Clare Mills, Dr Lesley Stanley, Professor Hans Verhagen, Dr Maureen Wakefield and Professor Bruce Whitelaw.

4. Following the review by the ACNFP at their meeting in November 2021, further information was requested concerning the production process and the Absorption, Distribution, Metabolism, and Excretion (ADME) of the cetylated fatty acids, in order to address information gaps in the dossier. The final recommendations from the Committee were presented at the 155th meeting, allowing the FSA and FSS to complete the risk assessment.

5. The views of the ACNFP have been taken into account in this safety assessment which represents the opinion of the FSA and FSS on cetylated fatty acids as a novel food.

2. Assessment

2.1 Identity of novel food

6. The novel food is a mixture of 70 – 80% cetylated fatty acids produced from the following chemicals: cetyl alcohol (synonyms: hexadecan-1-ol; palmitoyl alcohol) (CAS number: 36653-82-4) and the fatty acids, myristic acid (CAS number: 544-63-8) and oleic acid (CAS number: 112-80-1).

7. Smaller amounts of other cetylated fatty acids are also present from esterification of other fatty acids (such as linoleic and palmitic acid) contained in refined olive oil (CAS number: 8001-25-0). The remainder is composed of triglycerides.

8. Information to support this characterisation was provided for five batches of the novel food. The composition of the novel food was verified by Gas Chromatography with Flame Ionisation Detector (GC-FID).

2.2 Production Process

9. The certificates of analysis for the raw materials and the processing aids used in the manufacture of the cetylated fatty acids state that they are food grade. The ‘myristic acid’ contains 99.8% myristic acid with the remainder reported as shorter or longer fatty acids (< 1%). The ‘oleic acid’ contains > 78% oleic acid with linoleic acid (? 13%) and palmitic acid (? 6%), with the remainder reported as fatty acids with shorter or longer chains. This may include traces of polyunsaturated fatty acids, such as linolenic acid (? 0.5%). The ‘cetyl alcohol’ contains ? 98% of cetyl alcohol with the remainder reported as hydrocarbons (? 0.5%).

10. The cetylated fatty acids are manufactured in compliance with the principles of Good Manufacturing Practice (GMP) according to internationally recognised standards, and Hazard Analysis and Critical Control Points (HACCP). The manufacturing process does not use any extraction solvents but does utilise heating and filtration steps to remove any potential contaminants (see Figure 1).

Figure 1: Simplified schematic of production process for cetylated fatty acids

Diagram shows the process starting at Synthesis of cetylated fatty acids to Decolourisation to Filtration to Blend with olive oil to Deodorisation to Filtration to Transfer to storage.

11. The cetylated fatty acids, cetyl myristate and cetyl oleate, are synthesised by reacting cetyl alcohol with myristic acid and cetyl alcohol with oleic acid in separate reaction vessels respectively. Both reactions employ a zinc catalyst alongside high temperature and vacuum.

12. After cooling, the cetylated fatty acids undergo refining by a decolourisation step followed by filtration, which also removes the catalyst. These refined cetylated fatty acids are mixed with olive oil, and then placed under high temperature and vacuum. This mixture of cetylated fatty acids in olive oil undergoes a deodorisation step followed by a final filtration step.

13. A worse case scenario, that all unsaturated fatty acids in the novel food could be hydrogenated during the production process, was explored. It was suggested that this could lead to the consumption of 0.77 g of trans fats per 2.1 g of novel food. The most recent data indicates UK dietary intake levels of trans fats by adults are 1.0 g/day (SACN, 2019). Therefore, the combined intake level for trans fats in UK consumers of the novel food would not be expected to exceed 1.77 g/day. The UK dietary reference values for trans fats confirm intake levels should not exceed 5.1 – 6.2 g/day and 4.1 – 4.8 g/day for men and women, respectively (SACN, 2007; SACN, 2011).

14. The production process has characterised the potential hazards and detailed the corresponding control measures sufficiently.

2.3 Compositional Information

15. The results from five independent batches of cetylated fatty acids demonstrate that the novel food consists mainly of the cetylated fatty acids, cetyl myristate and cetyl oleate, and triglycerides (Table 1).

Table 1: Physicochemical analysis of Cetylated Fatty Acids

Parameter	Method of Analysis	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Physical status at 25oC	Visual	Solid	Solid	Solid	Solid	Solid
Colour (APHA colour)	AOCS Ea9-65	? 600	? 600	? 600	? 600	? 600
Acid value (mg KOH/g)	AOCS Cd3d-63	0.8	0.7	0.7	0.4	0.8
Iodine (g I**2**/100)	AOCS Cd1-25	30.3	30.5	32.2	30.1	30.1

Parameter	Method of Analysis	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Saponification value (mg KOH/g)	AOCS Cd3-25	134.4	138.2	138.6	141.3	136.6
Hydroxyl value (mg KOH/g)	AOCS Cd13-60	6.3	7.1	6.0	4.1	7.4
Ester content (%)	GC-FID	75.14	74.38	74.23	72.19	73.49
Cetyl oleate (%)	GC-FID	23.95	23.80	23.77	23.10	23.48
Cetyl myristate (%)	GC-FID	49.37	48.82	48.69	47.39	48.25
Triglycerides (%)	GC-FID	22.83	23.81	24.82	24.85	22.84
Aluminium (mg/kg)	ICP-MS	1.57	1.26	1.03	1.49	1.70

16. The fatty acid profile obtained for one batch of cetylated fatty acids showed that oleic acid and myristic acid were the major fatty acids present at 45.98% and 40.96% respectively. Linoleic acid (7.97%) and palmitic acid (3.24%) were also detected along with smaller quantities of other fatty acids (~ 1%).

17. Analytical data from three independent batches of cetylated fatty acids shows very low concentrations of heavy metals (Table 2). These values did not give cause for concern.

Table 2: The heavy metal analysis of Cetylated Fatty Acids by ICP-MS

Parameter	Batch 1	Batch 2	Batch 3
Arsenic (mg/kg)	< 0.005	not tested	< 0.02
Cadmium (mg/kg)	< 0.005	0.008	< 0.02
Mercury (mg/kg)	< 0.005	< 0.005	< 0.02
Lead (mg/kg)	0.008	< 0.005	< 0.02
Nickel (mg/kg)	0.020	not tested	not tested

18. Analytical data from five independent batches of cetylated fatty acids concerning the 3-monochloropropanediol (3-MCPD) and glycidyl ester content shows the levels are below the maximum levels permitted for fats and oils in Commission Regulation (EC) 1881/2006, as retained in UK law.

19. Similarly, analytical data from one batch of cetylated fatty acids concerning the content of polychlorinated biphenyls (PCB's) and dioxins, polycyclic aromatic hydrocarbons (PAH's) and erucic acid confirmed that the levels present were not a cause for concern.

20. Analytical data from five independent batches of cetylated fatty acids concerning the microbiological content of the novel food were reported following analysis by accredited laboratories (Table 3).

Table 3: The microbiological analysis of Cetylated Fatty Acids

Parameter	Method of Analysis	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Total aerobic microbial count (CFU /g)	ISO 4833	< 1,000	< 100	< 1,000	1,000	1,000
E. coli (negative/g)	ISO 16649-2	Not detected	Not detected	Not detected	Not detected	Not detected
Salmonella (negative /25g)	ISO 21528-1/2	Not detected	Not detected	Not detected	Not detected	Not detected

Parameter	Method of Analysis	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Staphylococcus aureus (negative/g)	ISO 6888-1	Not detected	Not detected	Not detected	Not detected	Not detected
Yeasts and moulds (CFU/g)	ISO 21527-1/2	< 100	< 100	< 10	< 100	< 100
Enterobacteriaceae (CFU/g)	ISO 6579	< 100	< 100	< 100	< 100	< 100

21. The data presented indicate the novel food can be consistently produced within the proposed specification.

2.4 Stability

22. The stability of the novel food was assessed with the same five independent batches of cetylated fatty acids that were utilised in the compositional analysis. Analytical data concerning physicochemical properties, biochemical properties and microbiological properties were reported.

23. The parameters from the real-time stability study (25 +/- 2oC) over a period of 18 months, and the accelerated stability study (40 +/- 2oC) for a period of at least 9 months, met the specification limits except for small changes in the saponification and hydroxyl value. These changes were not a cause for concern.

24. The data provided supports the stability of the novel food in bulk for a time period of 18 months.

2.5 Specification

25. The specification parameters reported in Table 4 were assessed using internationally recognised methods or are otherwise determined using internally developed and validated methods.

Table 4: Specifications of Cetylated Fatty Acids

Parameter	Specification
Physical status at 25oC	Solid
APHA Colour	? 600
Acid value (mg KOH/g)	? 5
Iodine (I_2 g/100g)	30 – 50
Saponification value (mg KOH/g)	130 – 150
Hydroxyl value (mg KOH/g)	? 20
Ester content (%)	70 – 80
Cetyl oleate (%)	22 – 30
Cetyl myristate (%)	41 – 56
Total aerobic microbial count (CFU/g)	**? 1,000**
Yeasts and moulds (CFU/g)	? 100

26. The information provided is sufficient for the specification of the cetylated fatty acids and appropriately characterises the novel food seeking authorisation.

2.6 History of Use

27. The cetylated fatty acids, cetyl myristate and cetyl oleate, have no history of use as a food ingredient.

28. Myristic acid and oleic acid, which are raw materials in the manufacture of the novel food, are reported to be naturally occurring fatty acids with a long history of use in the UK and the European Union. Oleic acid is found in high concentrations in olive (80%), pecan (60%) and peanut (85%) oils (CIR, 1987). Esterified oleic acid is reportedly found in many vegetable oils and animal fats, usually at greater than 50% of the total fatty acid concentration. Myristic acid is sourced from coconut oil, nutmeg butter, palm seed oil and milk fats (CIR, 1987). The evidence provided from the literature supported the suggestion that the use of these fatty acids was safe, and no specific risks were identified that required further evaluation.

29. The history of use data supplied does not indicate any further areas for evaluation.

2.7 Proposed Use and Anticipated Intake

30. Adults in the general population are identified as the target population of the novel food. The cetylated fatty acids are not intended for consumption by infants or young children.

31. The novel food is intended for use in food supplements, at 2.1 g/day (equivalent to 30 mg/kg body weight/day for a 70kg adult), and is not intended to replace any other food in the diet.

32. EFSA (2017) report that the highest intake of saturated fatty acids (91 g/day) comes from the regular diet. This compared favourably with the anticipated intake level of 2.1 g/day for the cetylated fatty acids, which consists of saturated and unsaturated fatty acids.

33. Whilst there are other sources of saturated fatty acids in the diet, the proposed intake level for the novel food was considered to be safe when compared to the No Observed Adverse Effect Level (NOAEL) of 3,000 mg/kg identified in the 90-day feeding study (Piras, 2020 [unpublished]).

34. The information provided is sufficient and does not raise any further areas for evaluation.

2.8 Absorption, Distribution, Metabolism and Excretion (ADME)

35. The ADME of the fatty acids, myristic acid and oleic acid, involves absorption from the gastrointestinal tract and catabolism (either immediately or after incorporation into chylomicrons) via the ß-oxidation pathway and the tricarboxylic acid cycle. This yields carbon dioxide which is excreted in expired air (EFSA, 2017; Gyamfi et al., 2019).

36. The ADME of cetyl alcohol reportedly follows a similar pathway as the fatty acids. Initially, the alcohol is oxidised to hexadecanal, which is rapidly oxidised to palmitic acid and subsequently metabolised via the fatty acid and tricarboxylic acid pathways (Williams, 1959; JECFA, 1999). Animal studies indicate that ~15% of the cetyl alcohol remains unchanged and is primarily eliminated in the faeces (Blomstrand and Rumpf, 1954; Baxter et al., 1967).

37. The ADME pathways of the fatty acids and cetyl alcohol are well understood as evidenced by the published literature.

2.9 Nutritional information

38. The fatty acids present in the novel food are also found in vegetable oils which are part of the regular UK diet.

39. The consumption of fatty acids as a food additive, E570, may contribute around 1% of the dietary exposure to saturated fatty acids from all fat sources (EFSA, 2017). This includes the use of myristic acid and oleic acid, either separately or in combination. Based on this information, the

novel food would not be nutritionally disadvantageous as the proposed intake level is comparable to the consumer exposure to saturated fatty acids from E570.

40. Cetylated fatty acids are not intended to replace fatty acids from other food sources. At the proposed maximum intake level of 2.1 g/day, the novel food is not expected to be nutritionally disadvantageous for consumers.

2.10 Toxicological information

41. Toxicological studies were performed with cetylated fatty acids to support the safety assessment of the novel food. The respective study reports are unpublished and claimed as proprietary data. They were considered essential in the assessment the safety of the novel food and were reviewed by the ACNFP.

42. In vitro genotoxicity testing of cetylated fatty acids was conducted under Good Laboratory Practice (GLP) conditions and utilised the followed OECD guidelines: in vitro bacterial reverse mutation test (OECD TG 471) and in vitro mammalian cell micronucleus test (OECD TG 487). This approach is recommended by the UK Committee on Mutagenicity , and is also the basis of guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283, as retained in UK law.

43. The in vitro bacterial reverse mutation test (Thompson, 2017 [unpublished]) demonstrated that cetylated fatty acids are non-mutagenic, in the absence or presence of metabolic activation.

44. The in vitro mammalian cell micronucleus test (Morris, 2017 [unpublished]) demonstrated that cetylated fatty acids are non-clastogenic and non-aneugenic in the absence and presence of metabolic activation.

45. The results from these in vitro studies support the conclusion that the novel food is not genotoxic.

46. A Repeated Dose 90-Day Oral Toxicity Study in Rodents (Piras, 2020 [unpublished]) was conducted under Good GLP conditions and followed OECD TG 408 guidelines as recommended by the Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283, as retained in UK law. The aim of the study was to identify any adverse effects following the consumption of cetylated fatty acids.

47. In this 90-day feeding study, each group consisted of 10 female and 10 male rats which were fed 0 (control – corn oil), 1,500, 3,000 or 4,500 mg/kg cetylated fatty acids twice per day by oral gavage. A reference control group consisting of the same number animals were fed 4,500 mg/kg of myristic acid and oleic acid in olive oil. Additionally, a group consisting of 5 female rats and 5 male rats for the control group, high dose group and the reference control group were used as recovery groups.

48. No deaths, test item-related clinical abnormalities, ocular changes, or differences in food consumption and bodyweight between test groups were observed. In addition, there were no statistically significant dose dependant changes in haematology, serum hormone levels, or organ weights.

49. Statistically significant differences between the high dose female rats and control group in the following parameters were noted – urea levels decreased by 26%, sodium levels increased by 6.1% and, plasma potassium levels increased by 43%. The levels of urea were also reported to be higher in the low and mid-dose male rat groups, but not in the high dose male rat group. In the recovery groups, the potassium values were statistically significantly higher in both the female and male high dose groups, and the reference control group compared to the control group. The sodium levels in the control reference group were also statistically significantly higher in both the

female and male rats compared to the control group.

50. No dose dependent related abnormalities were observed during the necropsy or histopathological evaluation. Several non-test item related observations were reported, but these observations were not considered to be toxicologically relevant.

51. The no observable adverse effect level (NOAEL) for the novel food was the mid-dose of 3,000 mg/kg. This value was considered appropriate because of the reported physiological disturbances in the electrolyte levels observed at the highest dose level of 4,500 mg/kg.

2.11 Allergenicity

52. The cetylated fatty acids are not proteinaceous, and under the proposed conditions of use, the novel food is very unlikely to cause allergic reactions in consumers?

3. Discussion

53. The novel food is a mixture of 70 – 80% cetylated fatty acids which are produced from the reaction of cetyl alcohol with myristic acid and oleic acid. Other smaller amounts of the cetylated fatty acids are formed by the esterification of the fatty acids (such as linoleic and palmitic acid) contained in refined olive oil.

54. The history of use for olive oil, oleic acid and myristic acid in the diet is well established, but there is no such data available for the consumption of cetylated fatty acids. To support the safe use of the novel food, a Repeated Dose 90-Day Oral Toxicity Study in Rodents was conducted. The NOAEL was identified as 3,000 mg/kg rather than the highest dose tested (4,500 mg/kg).

55. To derive a daily intake value for the cetylated fatty acids using this NOAEL, an uncertainty factor of 100 and 70kg as the default adult body weight were used. The uncertainty factor is derived from two factors: the inter-species variability when extrapolating from experimental animals to humans (factor of 10), and the intra-species variability between humans (factor of 10). The combination of these two factors (10 x 10) gives the value of 100 for the uncertainty factor (EFSA, 2012). The value of 70kg for the adult body weight is the recommended default value when empirical data is not available and a substitute figure is required to complete the risk assessment (EFSA, 2012).

56. By applying these default values for the uncertainty factor and the adult body weight, the intake for cetylated fatty acids is 2.1 g/day.

4. Conclusions

57. The FSA and FSS have undertaken the assessment of cetylated fatty acids and concluded that the composition of the novel food is safe under the proposed conditions of use and does not pose a safety risk to human health.

58. These conclusions were based on the information in the novel food dossier submitted by the applicant plus the supplementary information and could not have been reached without the following data claimed as proprietary by the applicant:

- annexes to the dossier which relate to the production process, composition and stability of the novel food.
- bacterial reverse mutation test (Thompson, 2017 [unpublished]), in vitro micronucleus test (Morris, 2017 [unpublished]) and 90-day repeat dose feeding study with the novel food (Piras, 2020 [unpublished]) including the summary table of the statistically significant

observations in the 90-day study (Appendix B.3).

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