Position papers

Committee Advice Document: Safety of Cannabidiol (CBD) as a novel food for use in food and food supplements - RP521

Reference number RP521

Food Standards Agency (FSA) and Food Standards Scotland (FSS)

Regulated Product Dossier Assessment

Assessment finalised: 10th of January 2025

Summary

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in March 2021 from TTS-Pharma Limited, UK ("the applicant") for the authorisation of cannabidiol (CBD) isolate as a novel food.

The novel food is produced by solvent extraction of dried *Cannabis sativa* leaves, followed by a series of processing steps, before recrystallisation to yield the cannabidiol isolate (≥ 99.5% purity) as a white to off-white crystalline powder.

This new application is seeking to use the novel food as an ingredient in beverages, chewing gum, gummies, preserves, sports gels and powders, and food supplements for adults (excluding pregnant and lactating women and other specifically identified vulnerable groups including those taking medication and the immunocompromised).

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 did not consider any potential health benefits or claims arising from consuming the food, as the focus of the novel food assessment is to ensure the

food is safe and does not put consumers at a nutritional disadvantage.

The novel food was assessed based on the data provided. This review indicated it was appropriate for the provisional Acceptable Daily Intake (ADI) for 98% purity or greater CBD to form part of the evidence for this assessment.

For CBD, a provisional acceptable daily intake (ADI) of 10 mg/day has been published by the FSA and was considered in assessing this novel food. The provisional ADI (section 2.7) was recommended, subject to the existing advice to consumers that pregnant and breastfeeding women and people taking any prescription medication should avoid the consumption of CBD. Consumers on regular medications should seek advice from a medical professional before using any type of CBD food product. In addition, children and prospective parents trying for a baby are advised against consumption of CBD, as are those who are immunosuppressed, due to remaining data gaps and residual uncertainties concerning the safety of CBD for these groups of consumers. These contraindications would also apply to this novel food.

The Committee concluded that the applicant had provided sufficient information to assure the novel food was safe under the proposed conditions of use. The anticipated intake levels and the proposed use in food and food supplements was not considered to be nutritionally disadvantageous.

1. Introduction

1. The ACNFP assessed the food safety risks of the novel food and its production under the proposed uses, in line with Article 7 of assimilated Commission Implementing Regulation (EU) 2017/2469. 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, 2016).

2. In March 2021, TTS-Pharma Ltd, UK (“the applicant”) submitted a full novel food application for the authorisation of cannabidiol (CBD). The novel food is a white to off-white crystalline powder consisting primarily of CBD with a purity ≥ 99.5%. The novel food is manufactured by solvent extraction of dried *C. sativa* leaves with further processing to yield the CBD isolate and is intended to be used as an ingredient in beverages, chewing gum, gummies, preserves, sports gels and powders, and food supplements.

3. Advice was sought from the joint Subgroup of the Advisory Committee for Novel Foods and Processes (ACNFP) and the Committee on Toxicity (COT) on CBD and hemp derived products on the quality of the toxicological evidence submitted to support the application. The ACNFP and COT have issued a joint statement on the safe upper intake of ingredients containing 98% or more CBD. This and wider evidence available in the public domain, was considered in reviewing the toxicological evidence for this application.

4. Following the review by the ACNFP at their meeting in November 2024, final recommendations from the Committee were presented, allowing the Committee Advice to be concluded.

5. The Committee Advice Document (CAD) outlines the conclusions of the ACNFP on the safety of a ≥ 98% pure form CBD isolate (as detailed in application RP521) as a novel food.

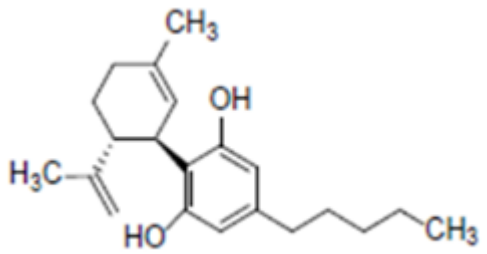
2. Assessment

2.1 Identity of novel food

6. The novel food is a cannabidiol (CBD) isolate in the form of a white to off white crystalline powder of purity equal to or greater than 98%. Information to support this characterisation was provided for five batches of the novel food.

7. CBD is characterised by the chemical formula: C21H30O2; molecular mass: 314.46 g/mol; CAS number: 13956-29-1; IUPAC name: 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol.

Figure 1: The molecular structure of CBD.



8. Confirmation of its identity and purity was provided by nuclear magnetic resonance (NMR) and comparing the spectra with an internal standard.

2.2 Production Process

9. The CBD isolate is manufactured using a multi-step process under controlled conditions.

10. Certificates of analysis for raw starting materials used in the extraction process were provided to demonstrate the effectiveness of the controls at this point in the process. The details of the commercially sensitive extraction process were shared and reviewed by the ACNFP.

11. The dried *C. sativa* leaves are extracted using 2-propanol. The resulting alcoholic extract is separated from the biomass and the solvent is removed by rotary evaporation. The dried extract is dissolved in the ethanol and undergoes winterisation to remove the waxes. The ethanol is then removed to yield a dried extract which is decarboxylated. The decarboxylated extract undergoes distillation to remove unwanted impurities, e.g. terpenes, before repeated recrystallisation in a hydrocarbon solvent. Distillation removes the solvent residues to yield the highly purified CBD (purity ≥ 99.5%).

12. The ACNFP considered whether the use of solvents as processing aids resulted in residues that require highlighting to risk managers. To assess the safety of the solvent residues in the novel food, a comparison was made to residue limits for other consumed products (Table 1). Solvent residues are included in the specification for the novel food (Table 8).

Table 1. Comparison of information on permitted residue levels for solvents used in the novel foods production process compared to the proposed specification.

Solvent used	Available data on safe maximum level of consumption	Level in specification for the novel food (mg/kg)
Ethanol *	Guidance on residues in pharmaceutical products sets a Permissible Daily Exposure of 50 mg/day or at a concentration of 5,000 ppm *	≤ 5,000

Hexane *	Guidance on residues in pharmaceutical products sets a Permissible Daily Exposure of 2.9 mg/day or at a concentration of 290 ppm *	< 1
Pentane	Guidance on residues in pharmaceutical products sets a Permissible Daily Exposure of 50 mg/day or at a concentration of 5,000 ppm *	No level defined as solvent is no longer used in the production process
2-propanol *	Guidance on residues in pharmaceutical products sets a Permissible Daily Exposure of 50 mg/day or at a concentration of 5,000 ppm *	≤ 10

* ICH Impurities: Guideline for residual solvents Q3C (R9) (pharmaceuticals)

13. The use of pentane as a solvent has been discontinued and replaced with hexane (see Specification – Table 8).

14. The evidence presented (see Table 2) on composition indicates compliance with the specification for residues of solvents. When considered at the level of consumption the evidence suggests the levels of solvent residues in the novel food are below those which would represent a safety concern.

15. A Hazard Analysis and Critical Control Point (HACCP) statement was provided along with further details of the process and how it operates. The production process has characterised the potential hazards and detailed the corresponding control measures sufficiently.

2.3 Compositional Information

16. Results from analysis of five independent batches of the novel food demonstrated that the CBD content is produced consistently. The data is presented within Tables 2 to 7 below.

17. The data presented in Table 2 indicates CBD content is consistently above 98% purity with negligible amounts of starting materials detected across the five representative batches.

Table 2. Cannabinoid analysis (% w/w) of five independent batches of cannabidiol (CBD) isolate.

Cannabinoid *	Specification	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
CBD (%)	≥ 99.5		99.5 – 100.4	99.6 – 100.6	98.9 – 99.9	99.5 – 100.4	99.3 – 100.4
CBC (mg/kg)		< 60	< 60	< 60	< 60	< 60	< 60
CBC-A (mg/kg)		< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5
CBD-A (mg/kg)		< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5
CBDV (mg/kg)		< 2.5	1134 – 1270	1022 – 1285	1079 – 1303	1074 – 1521	1041 – 1318
CBDV-A (mg/kg)		< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5
CBG (mg/kg)		< 15	< 15	< 15	< 15	< 15	< 15
CBG-A (mg/kg)		< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5
CBN (mg/kg)		< 1	0.43 – 0.44	0.45 – 0.49	0.48 – 0.51	0.48 – 0.51	0.45 – 0.49
Δ8-THC (mg/kg)		< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5

Δ9-THC (mg/kg)	< 1	3.8 – 5.4	3.9 – 4.6	3.7 – 5.5	3.7 – 5.1	3.9 – 5.1
THC-A (mg/kg)	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5
THCV (mg/kg)	< 1	< 1	< 1	< 1	< 1	< 1
THCV-A (mg/kg)	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5	< 2.5

* All batches of the novel food were analysed in triplicate and the results reported in the table are the mean of the three values. CBD determined by quantitative NMR; other cannabinoids by LC-MS/MS; cannabinol, delta-9-tetrahydrocannabinol and tetrahydrocannabivarin were determined by GC-MS/MS.

CBD = Cannabidiol; CBC = Cannabichromene; CBC-A = Cannabichromenic acid; CBD-A = Cannabidiolic acid; CBDV = Cannabidivarin; CBDV-A = Cannabidivarinic acid; CBG = Cannabigerol; CBG-A = Cannabigerolic acid; CBN = Cannabinol; Δ8-THC = Delta-8-Tetrahydrocannabinol; Δ9-THC = Delta-9-Tetrahydrocannabinol; THC-A = Tetrahydrocannabinolic acid; THCV = Tetrahydrocannabivarin; THCV-A = Tetrahydrocannabivarinic acid; LOQ = limit of quantification

18. It is recognised that the detection and characterisation of cannabinoids in a range of food matrices is an evolving area and there are yet to be internationally recognised methods. The limitations of analytical methodology available have been subject to discussion in the Joint ACNFP and COT Subgroup and remain a source of uncertainty in the assessment.

19. Analytical data concerning the microbiological content from five batch of the novel food was reported (Table 3). The process in manufacturing this novel food uses extreme high and low temperatures and alcohol solvents. Total aerobic colony count, total coliforms, *E. coli*, total yeasts and total moulds were all below the limit of enumeration. *Salmonella* was not detected in any batches.

20. The microbiological data presented confirm that the novel food does not raise a safety concern and consistently meets the proposed microbial specification levels.

Table 3. Microbiological quality of five independent batches of novel food.

Parameter	Specification	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Total aerobic colony count (CFU/g)		< 10	< 10	< 10	< 10	< 10
Total coliforms (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10
E. coli (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10
Yeasts (CFU/g)	< 200	< 10	< 10	< 10	< 10	< 10
Moulds (CFU/g)	< 200	< 10	< 10	< 10	< 10	< 10
Salmonella (absent in 25g)	Absent in 25g	Absent	Absent	Absent	Absent	Absent

BS = British Standard; CFU = colony forming units; ELISA = enzyme linked immunosorbent assay; EN = English; ISO = International Organisation for Standardisation

Total aerobic colony count – BS EN ISO 4833-1:2013; total coliforms, presumptive – VRB Agar layer plate at 37°C; *E. coli* – BS ISO 16649-2:2001; Yeasts and Moulds – BCA spread plate at 22 – 25°C; *Salmonella* – Solus Scientific ELISA kit with confirmation using Biomerieux API20E and serology

21. Results from the mycotoxin analysis for five independent representative batches of CBD isolate are presented in Table 4. The data show that the novel food consistently complies with the specifications set for mycotoxins within the final product.

Table 4. Mycotoxin analysis of five independent batches of cannabidiol (CBD) isolate.

Parameter	Specification	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Aflatoxin B1 (µg/kg)	≤ 0.5	0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
Aflatoxin B2 (µg/kg)		0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
Aflatoxin G1 (µg/kg)		0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
Aflatoxin G2 (µg/kg)		0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
Sum of aflatoxins (µg/kg)	≤ 2.0		< 0.8	< 0.8	< 0.8	< 0.8	< 0.8
Ochratoxin A (µg/kg)		0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2

Batches 1 to 5 analysed by HPLC with fluorescence detection (internal method)

22. It is expected that novel food products comply with the legal requirements for heavy metal contaminants in food. Analytical data (Table 5), presented for five independent batches of the novel food, demonstrated that heavy metals were present in low quantities and below established EU limits where applicable (cadmium, lead and mercury in food supplements).

Table 5. Heavy metal analysis of five independent batches of cannabidiol (CBD) isolate.

Parameter	Specification	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Maximum level of contaminants in foodstuffs *

Arsenic (mg/kg)	≤ 0.025	0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	
Cadmium (mg/kg)	≤ 0.025	0.005	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005	1 (FS)
Lead (mg/kg)	≤ 0.1	0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	3 (FS)
Mercury (mg/kg)	≤ 0.025	0.02	< 0.02	< 0.02	< 0.02	< 0.02	< 0.02	0.1 (FS)

FS = food supplement

Batches 1 to 5 analysed by ICP-MS (internal method)

* Assimilated Commission Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs.

Table 6, Residual solvent analysis of five independent batches of cannabidiol (CBD) isolate.

Parameter	**Specification**	**LOQ**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**	**Batch 7**	**Batch 8**
Ethanol (mg/kg)	≤ 5,000 mg/kg	6/20 *	< 6	< 6	< 6	< 6	< 6	< 20	< 20	< 20
Hexane (mg/kg)	≤ 1 mg/kg	1	-----	-----	-----	-----	-----	< 1	< 1	< 1
Pentane (mg/kg)		6	11.0 – 12.6	11.0 – 11.5	9.4 – 10.7	7.9 – 10.5	8.7 – 10.1	-----	-----	-----

2-propanol (mg/kg)	≤ 10 mg/kg	6/10 *	< 6	< 6	< 6	< 6	< 6	< 10	< 10	<10

----- = not analysed

* Batches 1 to 5 and batches 6 to 8 analysed by different contract laboratories (internal method GC-MS)

23. Results from the residual solvent analysis for five independent batches of isolated CBD are presented in Table 6. The data show that the CBD isolate consistently complies with the specifications set for residual solvents within the final product.

24. Pesticide residues were below the limit of quantification in the novel food (LC-MS/MS < 0.05 mg/kg; GC-MS/MS < 0.02 mg/kg).

25. The presence of polyaromatic hydrocarbons (PAHs) and dioxins in the novel food was assessed in five independent batches of the novel food in triplicate (Table 7).

26. Certification was provided to demonstrate that the contract laboratories were accredited to perform these analytical studies. Where in-house analysis was utilised, full methodology and supporting validation documentation was provided.

27. The data presented indicate the novel food and any hazards present were appropriately characterised.

THC as a potential contaminant in the novel food

28. The extraction process may result in other cannabinoids remaining as contaminants. In particular, delta-9-tetrahydrocannabinol (Δ9-THC), and its precursor acid, delta-9-tetrahydrocannabinolic acid (Δ9-THCA), were analysed due to the potential for toxic effects resulting from their consumption and the status of Δ9-THC as a controlled drug within the UK (Table 2). Along with Δ9-THC, other minor cannabinoids which occur at contaminant levels have the potential to play a role in the toxicity of CBD novel food products; as such, they require due consideration and monitoring to ensure the novel foods remain safe. As a result, the robustness, accuracy, and precision of the methods have been considered in interpreting the data on Δ9-THC and were considered appropriate in this case.

Table 7. Analysis of five independent batches of the novel food for certain contaminants in foodstuffs defined under assimilated Commission Regulation (EC) No 1881/2006.

Contaminant	Specification	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Maximum level of contaminants in foodstuffs *
Benzo(a)pyrene (ug/kg)	< 2	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	10 (FS)
Sum of PAHs (ug/kg)	< 10	1.13	0.94	0.51	0.52	0.51	50 (FS)
PCDD/F WHO-TEQ (ng/kg)		0.13	0.13	0.11	0.08	0.07	
PCDD/F-PCB WHO-TEQ (ng/kg)		0.16	0.16	0.14	0.10	0.09	
ICES-6 (ng/kg)		0.32	0.47	0.32	0.32	0.31	

FS = food supplement; PAH = polyaromatic hydrocarbons; PCB = polychlorinated biphenyls; PCDD = polychlorinated dibenzo-para-dioxins; PCDF = polychlorinated dibenzofurans; TEQ = toxic equivalents; WHO = World Health Organisation

* Assimilated Commission Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs.

All batches of the novel food were analysed in triplicate and the results reported in the table are the mean of the three values. PAH (internal method GC-MS); PCDDs, PCDFs and PCBs (internal method GC-HRMS); ortho-PCBs (internal method GC-MS).

Sum of PAHs = benzo(a)pyrene + benzo(a)anthracene + benzo(b)fluoranthene + chrysene; WHO-PCDD/F-TEQ = sum of dioxins; WHO-PCDD/F-PCB-TEQ = sum of dioxins and dioxin-like furans; ICES-6: sum of PCB28, PCB52, PCB101, PCB138, PCB153 and PCB180

LOQ for benzo[a]pyrene (analysed in triplicate): batch 1 – 0.37, 0.37 and 0.39 µg/kg; batch 2 – 0.38. 0.37 and 0.29 µg/kg; batch 3 – 0.27, 0.26 and 0.29 µg/kg; batch 4 – 0.29, 0.27 and 0.27 µg/kg; batch 5 – 0.27, 0.26 and 0.30 µg/kg

29. A literature review was undertaken as part of the assessment of CBD as a novel food, to understand the impact on the safety of foods with trace levels of contamination with Δ9-THC and its precursor, Δ9-THCA. The joint ACNFP and COT subgroup reviewed the information from literature and identified a point of departure from the European Food Safety Authority (EFSA) opinion on THC (Δ9-THC) as a contaminant in milk and meat (EFSA, 2015).

30. Evidence from an EFSA review by the Contaminants in the Food Chain (CONTAM) panel suggested a point of departure from a LOAEL (lowest observed adverse effect level) of 0.036 mg/kg BW/day, which is drawn from the most sensitive individuals and at the lowest dose tested in the clinical studies that were reviewed (EFSA, 2015). Uncertainty factors were then applied to identify a safe upper intake level. These included a factor of 3 to extrapolate from a LOAEL to a NOAEL (no observed adverse effect level), which was considered appropriate as the effects are mild to moderate in severity. A further factor of 10 was applied for person-to-person variation, resulting in total to an applied uncertainty factor of 30. This resulted in a safe upper intake level of 1 µg/kg BW/day for Δ9-THC consumed as a contaminant in food. This was identified an acute reference dose (ARfD) (EFSA, 2015)

31. The Subgroup agreed the ARfD to be sufficiently protective to apply to the UK population. It was noted that in applying the acute reference dose, EFSA has assumed that the effects seen would be the same if humans were exposed to multiple doses of Δ9-THC at very low levels (EFSA, 2015). The Subgroup commented that there was no data to verify this assumption, but if setting limits the dataset is the best available.

32. The analysis for delta-9-tetrahydrocannabinol as a potential contaminant in the novel food was declared as 3.7 – 5.5 mg/kg in the five batches tested (Table 2), with a limit of quantification of 2.5 mg/kg.

33. The combines levels of Δ9-THC and Δ9-THCA, where detected in the novel food, once adjusted to reflect the proposed use of 10 mg of CBD being consumed a day, were below the ARfD identified by EFSA of 1 µg /kg BW/day or 70 µg/day for a healthy adult. This level does not present a concern in terms of consumer safety for the novel food under the proposed conditions of use.

34. To ensure Δ9-THC levels remain consistently low in the production of CBD, Δ9-THC and Δ9-THCA should be standard substances included in the specification as relevant to all batches produced.

35. The data presented did not indicate any additional hazards for inclusion in the specification.

2.4 Stability

36. A 20-month real-time stability study (25 ± 2°C; 60 ± 5% relative humidity) was conducted for a single batch of CBD isolate (purity ≥ 99.5%). Data for the CBD content only was provided. No significant changes were observed.

37. The results from an interim stability study for three additional batches of CBD isolate (purity ≥ 99.5%) under ambient conditions (25°C and 60% relative humidity) and accelerated conditions (40°C and 75% relative humidity) were provided. Analytical data for sixteen cannabinoids were reported. No significant changes in the CBD content were observed under ambient conditions for up to nine months or under accelerated conditions for up to six months. The Δ9-THC content was also tested and no significant changes in the levels of Δ9-THC were observed. All other cannabinoids remained within specification.

38. On this basis, the data provided supports the stability of the CBD isolate for up to 24 months.

39. An on-going stability study for three batches of 20% CBD in oil with terpenes and three batches of the same formulation without terpenes under ambient conditions (25°C and 60% relative humidity) and accelerated conditions (40°C and 75% relative humidity) was provided. Analytical data for sixteen cannabinoids were reported. No significant changes in the CBD content were observed under ambient conditions for up to nine months or under accelerated conditions for up to six months. The Δ9-THC content was also tested and no significant changes in the levels of Δ9-THC were observed. All other cannabinoids remained within specification.

40. Stability data for three batches of > 80 mg/mL CBD oil emulsion with terpenes and three batches of the same formulation without terpenes under ambient conditions (25°C and 60% relative humidity) and accelerated conditions (40°C and 75% relative humidity) was provided. Analytical data for sixteen cannabinoids were reported. No significant changes in the CBD content were observed under ambient conditions for up to six months or under accelerated conditions for up to three months. All other cannabinoids remained within specification.

41. A real-time stability study (25 ± 2°C; 60 ± 5% relative humidity) was conducted for three CBD in oil products: 20% CBD in medium chain triglycerides (MCT) oil with terpenes for 14 months; 6% CBD in oil and 12% CBD in oil for 20 months. Data for the CBD content and microbiological quality were provided. No significant changes in the CBD content were observed. Total aerobic microbial count, total yeast and mould count, and bile tolerant gram-negative bacteria were not detected in any batches of novel food. *E. coli* and *Salmonella* were absent in 1g and 25g for each batch of novel food, respectively.

42. The results from on-going stability studies on a number of finished products were reported. Results from nine batches of Endopure 6000mg CBD in MCT oil in different formats (droppers, pipettes and sprays) and three batches of the same formulation with terpenes under ambient conditions (25°C and 60% relative humidity) and accelerated conditions (40°C and 75% relative humidity) were provided. Analysis data for sixteen cannabinoids were reported. No significant changes in the CBD content were observed under ambient conditions for up to nine months or under accelerated conditions for up to six months. The Δ9-THC content was also tested and no significant changes in the levels of Δ9-THC were observed. All other cannabinoids remained within specification.

43. On this basis, the data provided supports the stability of the CBD isolate in finished for at least 12 months.

2.5 Specification

44. The specification parameters reported in Table 8 were assessed using internationally recognised methods or determined using internally developed and validated methods. The results of the analysis are detailed in Tables 2 – 7 and indicate the novel food can be produced consistently to the specification.

Table 8. Specification for the novel food.

Parameter	Specification	Method
Cannabidiol	≥ 99.5 %	Internal method (qNMR)
Arsenic	≤ 0.025 mg/kg	Internal method (ICP-MS)
Cadmium	≤ 0.025 mg/kg	Internal method (ICP-MS)
Lead	≤ 0.1 mg/kg	Internal method (ICP-MS)
Mercury	≤ 0.025 mg/kg	Internal method (ICP-MS)
Ethanol	≤ 5,000 mg/kg	Internal method (GC-MS)
Hexane	≤ 1 mg/kg	Internal method (GC-MS)
2-propanol	≤ 10 mg/kg	Internal method (GC-MS)
Pesticide residues	< 0.01 mg/kg	Internal method (GC-MS and LC-MS/MS)
Aflatoxin B1	≤ 0.5 µg/kg	Internal method (HPLC)
Total aflatoxins	≤ 2.0 µg/kg	Internal method (HPLC)
Total coliforms	< 10 CFU/g	Internal method (TP/007)
Yeast	< 200 CFU/g	Internal method (TP/008)
Mould	< 200 CFU/g	Internal method (TP/008)

Parameter	Specification	Method
E. coli	< 10 CFU/g	Internal method (TP/016)
Salmonella	Absent in 25g	Internal method (TP/025)

CFU = colony forming units; GC-MS = gas chromatography – mass spectrometry; HPLC = high-performance liquid chromatography; ICP-MS = inductively coupled plasma – mass spectrometry; LC-MS/MS = liquid chromatography – tandem mass spectrometry; qNMR = quantitative nuclear magnetic resonance; TP = test procedure

45. The information provided is sufficient for the specification of the novel food and appropriately characterises the novel food seeking authorisation.

2.6 History of Use

46. Hemp has been widely consumed in the UK and EU as a seed oil, in tea and as an alternative to hops in beer. Extracts of hemp including CBD and synthetic CBD have not been widely consumed and are considered novel foods. While CBD products are widely available on the UK high street, indicating some consumption of CBD as a food, no applications for CBD have yet received authorisation as a novel food. Any products which are currently on the UK market therefore remain non-compliant with the novel food regulations.

47. As detailed in the COT review of the literature, there has been use of both hemp derived and synthetic forms of CBD for medicinal purposes. These provide an indication of the toxicological effects that should be explored in the testing regime – primarily, the effects on the liver, thyroid and potential impacts on reproductive organs. Also reported are behavioural effects such as somnolence (sleepiness).

48. As reported in the COT review of the publicly available data on CBD and summary data on a medicinal product, signs of adverse effects on the liver were observed at doses of CBD as low as 5 mg/kg BW/day in patients and healthy human volunteers; this dose is equivalent to 350 mg in a 70 kg adult. The data in the literature also suggested that humans might be more sensitive to the adverse effects of CBD in the liver than laboratory animals.

49. Somnolence effects were noted at doses ≤ 10 mg/kg BW/day in human studies. Inhibitory drug-drug interactions have also been observed with some medications when CBD is co-administered at doses of 1 mg/kg BW/day (equivalent to 70 mg in a 70 kg adult); the likelihood of effects at lower doses has not been determined (COT, 2020).

50. It is noted that the doses used for medicinal purposes are higher than those proposed for food use. The purpose of an assessment for medicines authorisation is different to that for food and this is reflected in the data requirements. Unlike medicines, there is no risk-benefit context in foods with the requirement instead being that the products are safe. This means that outcomes that are considered an adverse event for food might not be considered as such in a medicinal study.

51. Within the literature, further human studies utilising chemically derived CBD provides further evidence of a history of synthetic CBD use (Izegelov *et al.*, 2010; Stero Biotechs Ltd., 2020; Klotz *et al.*, 2019; Wheless *et al.*, 2019). A review by Huestis *et al.*, (2019) on the Cannabidiol Adverse effects and Toxicity notes that, while CBD is not risk-free, severe adverse events occur at doses higher than those recommended for human pharmacotherapies which are prescribed to treat forms of epilepsy.

52. The data on previous consumption of CBD suggest areas for careful consideration in the toxicological review to understand potential effects at the lower doses used in foods.

2.7 Proposed Use and Anticipated Intake

53. The novel food is intended to be used in food supplements, as defined by the GB legal requirements (The Food Supplements (England, Scotland and Wales) Regulations 2003), in a range of forms for adults, excluding pregnant and lactating women and other specifically identified vulnerable groups. The novel food is also intended to be used as a food ingredient in beverages, chewing gum, gummies, preserves, sports gels and powders.

54. The applicant initially proposed a use level of 30 mg/day CBD for adults, excluding pregnant and breastfeeding women, for chewing gum, gummies, soft gel capsules, vegan protein powder, and whey protein; up to 25 mg/day for carbonated drinks, still drinks, and flavoured tea drinks; and up to 15 mg/day for mousse. The proposed uses have been updated to reflect the provisional acceptable daily intake (ADI) for the use of ≥ 98% pure form CBD established at 10 mg per day (ACNFP and COT, 2023). The proposed maximum use levels for

the novel food are outlined in Table 9.

55. It is noted that consumers may be exposed to CBD from a range of food categories. The standard methodology for calculating exposure for a novel food would explore intake from a range of sources and ensure that exposure via the proposed uses would not exceed any safety level identified when consumption of the food category was analysed. It is noted that for CBD that there are already many products available. The assessment has been made on the basis of identification of a maximum level of CBD that can be consumed per day. As such proposed uses will only be considered safe within the assessment when at a maximum consumption of 10 mg of CBD per day from all sources (as concluded in section 2.10 of this assessment).

Table 9: Amended intended food uses and maximum use levels for CBD isolate

Food category	CBD dose per serving (mg)	Maximum use level (mg/day)
Chewing gum (12 pieces)	5 or 10 mg	10
Carbonated drink (330 mL can)	5 or 10 mg	10
Still drink (330 mL can)	5 or 10 mg	10
Non-alcoholic spirt (120 mg CBD/200 cL or 420 mg/CBD in 700 cL)	≤ 16 mL	10
Gummies (10, 30, 60 or 120 pieces)	5 or 10 mg	10
Sports gel (70 g sachet)	1 – 10 mg	10
Workout gel (45 g sachet)	5 or 10 mg	10

Whey protein (1kg container – 250 mg CBD)	7.5 mg/30g scoop	10
Vegan protein powder (1kg container – 250 mg CBD)	8 mg/32g scoop	10
BCAA powder (198 g container)	0.15 – 0.9mg/6g scoop	10
Mousse (150 mL sachet)	5 or 10 mg	10
Jam (230 g jar – 90 mg CBD)	Up to 10 mg	10
Marmalade (240 g jar – 80 mg CBD)	Up to 10 mg	10
Peanut butter (220 g jar – 75 or 80 mg CBD)	Up to 10 mg	10
Chutney (220 g jar – 80 mg CBD)	Up to 10 mg	10
Barista shot (100-, 250-, 500- and 1,000mL bottle)	5 mg/shot	10
Soft gel capsules (10, 30, 60 or 120 capsules)	5 or 10 mg	10
CBD drops (10- or 30 mL bottle)	Up to 10 mg	10
CBD pipette (10- or 30 mL bottle)	Up to 10 mg	10

CBD spray (10- or 30 mL bottle)	Up to 10 mg	10

BCAA = branched chain amino acid

56. Concerns were raised by the Committee regarding the potential for foreseeable misuse of CBD if consumed in multiple formats on a single day. This is because of the increased risk of consuming CBD above the provisional acceptable daily intake (ADI). The scope of the assessment is restricted to the uses proposed and any further uses or additional food categories would be subject to the change in conditions of use process.

57. Risk managers must consider whether consumers would benefit from information on the CBD content of foods in order to ensure their consumption does not exceed the maximum intake of 10 mg per day for a healthy adult

58. As recommended in the ACNFP and COT statement on CBD of 98% purity, “The provisional ADI is recommended, subject to the existing advice to consumers that pregnant and breastfeeding women and people taking any prescription medication should avoid the consumption of CBD if possible. Consumers on regular medications should seek advice from a medical professional before using any type of CBD food product. In addition, children and prospective parents trying for a baby are advised against consumption of CBD, as are those who are immunosuppressed, due to remaining data gaps and residual uncertainties concerning the safety of CBD for these groups of consumers.” (ACNFP and COT, 2023).

59. The ACNFP explored the potential for foreseeable misuse of the novel food. It was noted that the availability of multiple formats of the novel food could create conditions where exposure estimates are exceeded. It is highlighted to risk managers that they may wish to consider whether risk management measures are needed beyond those in the food supplements regulation to ensure consumers are aware of the provisional ADI of 10 mg CBD/day for the product, a dose at which it is considered that no adverse effects would be expected.

60. It is also strongly recommended that risk managers consider how consumers can be supported to manage their intake appropriately within the safe limits identified and appreciate the nature of the potential risks at higher doses, for uses that are not in dosed forms.

61. The food supplement products are to be labelled in accordance with the labelling requirements of Food Supplements (England) Regulations 2003 and the equivalent legislation in the nations of GB. The ACNFP recommended that the applicants proposed warning labelling be updated to include information on not exceeding the safe limit of 10 mg/day for a 70 kg healthy adult and that the product is not suitable for use under the age of 18. Not suitable for use during pregnancy or breastfeeding. As well as information on its suitability if you are taking medication or have existing health conditions.

2.8 Absorption, Distribution, Metabolism and Excretion (ADME)

62. The Absorption, Distribution, Metabolism and Excretion (ADME) of cannabidiol are known to be complicated by the food matrix in which the CBD is delivered and are currently still being defined by professional bodies.

63. The oral bioavailability of CBD is low, indicating that it is not absorbed to any notable extent following ingestion (Mechoulam *et al.*, 2002). Published works report the bioavailability of CBD to be between 13 and 19% (Grotenhermen, 2003) or 6% (Hawksworth and McArdle, 2004). The low systemic availability was demonstrated by Martin-Santos *et al.*, (2012) and further supported by a literature search which identified the pharmacokinetics of CBD (Millar *et al.*, 2018). The COT statement on CBD of 2020 noted that although CBD has low fasting bioavailability (< 10%), consumption with food could increase CBD uptake, by for example, 5-fold if eaten with a high fat meal. As such the potential for matrix effects that impact bioavailability cannot be ruled out.

64. Following oral consumption, CBD is extensively metabolised in the liver. This rapid first pass metabolism contributes to the low oral bioavailability reported in the literature (Taylor *et al.*, 2018; WHO, 2018). In vitro studies indicate that CYP3A4 and CYP2C19 are the primary hepatic enzymes responsible for first-pass metabolism of CBD; however, several other hepatic cytochrome P450 isoforms (CYP1A1, CYP1A2, CYP2C9, CYP2D6, and CYP3A5) have also demonstrated a capability of metabolising CBD (Jiang *et al.*, 2011; Zendulka *et al.*, 2016).

65. The metabolism of CBD is thought to follow two separate pathways. One is P450-mediated, in which CBD is metabolised into its major metabolite 7-COOH-CBD (which is a chemically inactive compound). This is followed by further metabolic reactions which yield the minor metabolites of CBD, including 6-OH-CBD (Devinsky *et al.*, 2018; Taylor *et al.*, 2018). The other involves decarboxylation (Kraemer *et al.*, 2019). The resultant metabolites are

predominantly excreted in faeces and urine (Hawksworth and McArdle, 2004; WHO, 2018).

66. Multiple dosing with CBD is associated with a steady state concentration up to 2-fold accumulation of CBD in plasma when compared with a single dose (Taylor *et al.*, 2018). Minimal evidence of plasma accumulation has also been reported in dosing studies over 5 to 9 days (Millar *et al.*, 2018; Sellers *et al.*, 2013; Stott *et al.*, 2013).

67. The pharmacokinetics of CBD have been systematically reviewed by Millar *et al.*, (2018) in 24 studies, most of which assessed the administration of CBD at doses of 5–20 mg/day. This correlates to a low dose application similar to this CBD novel food application. Following oral administration, single doses of 5.4 and 10 mg CBD achieved peak serum concentrations (Cmax) of 0.9 and 2.5 ng/mL, the time to maximum concentration (Tmax) was approximately 1 hour, and a half-life between 1 and 3 hours. Given the intended use of this CBD as a food supplement, with an approximate half-life of one to three hours, with a total clearance of six hours, there are no significant concerns of accumulation.

68. The ADME data provides context for interpreting the toxicological data. It is noted that the bioavailability of CBD is typically low but can be affected by food matrix. The food context for the novel ingredient could impact on CBD bioavailability. It was noted that the potential for CBD to accumulate in the body has not been examined based on the data supplied. This has been taken into account in considering the assessment factors to account for uncertainty in setting the provisional ADI.

2.9 Nutritional information

69. The ACNFP sought clarification of the potential for the presence of antinutritional factors from the preparation. It was noted that hemp can contain a range of substances that could impact the digestion and absorption of nutrients from the diet. These include phytic acid (which can negatively affect the bioavailability of dietary and endogenous minerals and proteins), tannins (which can interrupt the absorption of iron), trypsin Inhibitors (which can affect protein digestion), and saponins (which at larger quantities cause gastric irritation and increase the permeability of the intestine).

70. The product is highly purified as indicated in the information on the composition. There is no presence of other components that would impact the digestion or absorption of nutrients from the diet.

71. The data on nutritional composition confirms that CBD has no caloric or nutritional value. The application is not intending that CBD replace another food in the diet. Consumption of the novel food at the proposed use levels is not expected to be nutritionally disadvantageous for consumers.

2.10 Toxicological information

72. Toxicological studies on CBD were performed by the applicant to support the safety assessment of the novel food. The respective study reports are unpublished and claimed as confidential and proprietary data. They were considered essential in the assessment of the safety of the novel food and were reviewed by the ACNFP. The management and interpretation of systemic toxicity data by the Committee in the context of the provisional ADI is explained in the sub-chronic toxicology section below (Section 2.10.2).

2.10.1 Genotoxicity

73. *In vitro* genotoxicity testing of the CBD isolate was conducted under Good Laboratory Practice (GLP) conditions and according to the 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 assimilated Regulation (EU) 2015/2283.

74. The *in vitro* bacterial reverse mutation test (Hoffmans, 2022 unpublished) demonstrated that CBD (≥ 99.5% purity) is non-mutagenic at concentrations up to 5,000 µg CBD/plate, in the absence or presence of metabolic activation.

75. The *in vitro* micronucleus test (Damen, 2023 unpublished) demonstrated that CBD (≥ 99.5% purity) is non-clastogenic and non-aneugenic in the absence or presence of metabolic activation up to the highest concentration of 2,000 µg CBD /mL.

76. The results from these *in vitro* studies support the conclusion that the novel food (CBD > 99.5% purity) is not genotoxic. This is consistent with the view of the Committee on Mutagenicity in reviewing CBD generically as a substance from evidence available in the public domain (Committee on Mutagenicity; MUT/MIN/2020/1, 2020).

2.10.2 Sub-chronic Toxicity

77. A joint subgroup of the ACNFP and COT was formed to address a series of questions in relation to the safety of CBD, cannabinoids and hemp-derived ingredients. This included data submitted to support individual novel food applications.

78. This applicant provided a Repeated Dose 90-Day Oral gavage Toxicity Study in Rodents (Lourens, 2023 unpublished) which was conducted under GLP conditions and to OECD Technical Guideline 408. In this 90-day study, each group comprised 10 female and 10 male Wistar Han rats which were dosed with 0 (control – MCT oil [60/40]), 50, 150 or 400 mg/kg BW/day of CBD. The highest dose was increased from 400 to 600 mg/kg BW/day from day 40 onwards.

79. The subgroup reviewed the data and concluded effects were seen at 50 mg/kg BW/day in females and 150 mg/kg BW/day in males. Effects in both sexes were on the liver and in female there were effects seen in the female reproductive organs. As such the subgroup considered that the NOAEL for the study be 50 mg/kg BW/day. Review of the study by the subgroup supported the conclusion that it was of sufficient quality to support the safety of the novel food.

80. In addition to the data submitted by the applicant there is a body of evidence on the effect of 98% or greater CBD. In order to take account of all pertinent data and to put the individual assessment in the context of the totality of relevant evidence for the active substance. The data from this application was compared to the wider body of evidence.

81. A weight of evidence approach allowed the Subgroup to identify a provisional ADI for CBD ingredients of > 98% purity of 0.15 mg/kg BW/day or 10 mg per day for a 70 kg healthy adult (Joint position paper from the ACNFP and COT; FSA consumer advice published in October 2023). This value was identified to be protective of the most sensitive known effects in the liver and thyroid parameters and included consideration of data gaps and uncertainties. The dataset includes several studies where highly purified CBD has been tested. Given the low level of contaminants, it is reasonable to consider that these represent the effect of CBD as a substance and are therefore relevant to other novel foods with similar compositions.

82. It was considered whether the wider data and therefore the provisional ADI for CBD with a purity of 98% or greater was relevant to the review of this novel food. It was considered appropriate, on the basis that the test substance used in the study to support the novel food was 98% pure and the compositional data was consistent with a highly purified CBD. The contaminants present were not

suggestive of a significant impact on the toxicology. The point of departure in the form of a NOAEL from the study submitted to support the safety of this novel food once corrected for CBD content, is consistent with the range of the points of departure used to develop the provisional ADI (ACNFP and COT, 2023). The NOAEL was also based on the same effect - impacts on the liver. The uncertainty factors identified in the provisional ADI would also apply to the applicant's submitted study (Lourens, 2023 unpublished) for the same reasons as identified in the provisional ADI statement. It was, therefore, considered scientifically appropriate to apply the provisional ADI of 0.15 mg/kg BW/day or 10 mg/day as identified in the joint statement of the ACNFP and COT on ≥ 98% pure forms of CBD to the novel food in this application.

2.11 Allergenicity

83. The CBD isolate has a purity ≥ 99.5%. As a highly purified chemical substance, the potential for immunoglobulin E (IgE)-mediated food allergy is considered to be low.

84. The safety assessment considered whether the remaining ≤ 0.5% of the novel food composition was likely to be allergenic. None of the raw materials or processing aids used in the production process are derived from or contain any of the allergenic food ingredients specified under Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers. This suggests that the potential to elicit reactions in those sensitive to those foods is unlikely.

85. The novel food is not expected to trigger allergic reactions in the target population under the proposed conditions of use.

3. Discussion

86. The novel food is a CBD isolate ingredient from industrial hemp containing > 99.5% CBD, produced using a multi-step manufacturing process.

87. This CBD isolate is intended to be used as a food ingredient in a range of foods including food supplements for adults excluding pregnant and lactating women and other specifically identified vulnerable groups and as a food ingredient in beverages, chewing gum, gummies, preserves, sports gels and powders. A defined intake for each product type of up to 10 mg CBD per day has been identified. it is not intended to replace any food.

88. In October 2023, the Joint ACNFP and COT subgroup identified a provisional acceptable daily intake (ADI) of 10 mg per day (0.15 mg/kg BW/day) for CBD products containing 98% CBD or above, such as the novel food discussed in this assessment. A weight of evidence approach was used to arrive at a provisional ADI of 10 mg/day (0.15 mg/kg BW/day). The most sensitive human health effects, that this provisional ADI protects against, are seen consistently in the liver and thyroid in a number of studies using ≥ 98% pure CBD. This value also takes account of the lack of human-based long-term evidence and evidence regarding potentially vulnerable groups.

89. Based upon the dossier of evidence provided by the applicant, the safety of the novel food was reviewed and evidence to reach a conclusion on safety provided. The evidence presented by the applicant was then compared to the wider data set on CBD and is consistent with evidence presented to support the development of a provisional ADI of 10 mg/day for CBD of 98% purity or above. As such it is appropriate to apply the provisional ADI to this novel food.

90. This is subject to the existing advice to consumers that pregnant and breastfeeding women and people taking any prescription medication should avoid the consumption of CBD. Consumers on regular medications should seek advice from a medical professional before using any type of CBD food product. In addition, children and prospective parents trying for a baby are advised against consumption of CBD, as are those who are immunosuppressed, due to remaining data gaps and residual uncertainties concerning the safety of CBD for these groups of consumers. These contraindications would also apply to this novel food.

91. The maximum safe exposure for healthy adults of 70 kg as identified in the provisional ADI is 10 mg per day from all food sources. If the inclusion level of this CBD isolate leads to an intake per individual serving of each product type of 10 mg/day, multiple intakes of food products containing CBD on the same day should be avoided to support minimising exposure to below the provisional ADI.

4. Conclusions

92. The ACNFP have undertaken the assessment of the novel food, which is composed mainly of CBD isolate (≥ 99.5% purity) to be included in a range of food product types. It was concluded that the novel food is safe under the proposed conditions of use for each individual product type and consuming each product type with CBD at no more than 10 mg CBD/day does not pose a safety risk to human health. The anticipated intake level and the proposed use in food

and food supplements was not considered to be nutritionally disadvantageous.

93. However, with multiple daily intakes of CBD in the different marketed products possible from the range proposed, risk managers must consider whether consumers would benefit from information on the CBD content of foods in order to ensure their consumption does not exceed the maximum intake of 10 mg per day for a healthy adult. Labelling of the product types in this application against use by vulnerable groups, especially children consuming these products could also be considered as a risk management measure.

94. The advice was 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, compositional information, and stability.
- *in vitro* bacterial reverse mutation test (Hoffmans, 2022 unpublished);
- *in vitro* micronucleus test (Damen, 2023 unpublished);
- 90-day repeat dose oral gavage study with the novel food (Lourens, 2023 unpublished).

The members of the ACNFP during the course of the assessment who were;

Dr Camilla Alexander White, Dr Anton Alldrick, Ms Alison Austin, Professor George Bassel, Dr Mark Berry, Professor Dimitris Charalampopoulos, Dr Meera Cush, Dr Catharina Edwards, Professor Susan Fairweather-Tait, Dr Sophie Foley, Professor Paul Frazer, Professor Andy Greenfield, Professor Wendy Harwood, Professor Huw D. Jones, Dr Ray Kemp, Dr Elizabeth Lund, Professor Harry J. McArdle, Dr Lynn McIntyre, Professor Clare Mills, Dr Isabel Skypala, Professor Hans Verhagen, Dr Maureen Wakefield, and Professor Bruce Whitelaw.

To note, interests were received from members of the ACNFP, Dr Alldrick declared a potential interest relating to his previous employment and this was considered a potential conflict and as a result he was not present for discussions of CBD by the Committee. Emeritus Prof Harry McArdle declared an interest from his work with EFSA's Nutritional Novel Food and Food Allergens Panel in considering data requirements for CBD. While not seen as a conflict, to avoid Prof McArdle being subject to information that would influence his EFSA work, it was agreed that he would not be present in discussions for CBD by the ACNFP but could supply comments for consideration by the Committee upon review of the minutes.

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