Position papers

Committee Advice on the safety of cannabidiol (CBD) isolate as a novel food for use in food supplements - RP345

Reference number RP345

Advisory Committee on Novel Foods and Processes (ACNFP)

Regulated Product Dossier Assessment

Assessment finalised: 24th of April 2025

Summary

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in February 2021 from Medicanna Ltd. (“the applicant”) for the authorisation of cannabidiol (CBD) isolate as a novel food.

The novel food is a CBD isolate which is intended to be used as a food ingredient in food supplements for adults (excluding pregnant and lactating women and other specifically identified vulnerable groups such as those taking medication and the immunosuppressed).

The novel food was assessed based on the data provided. This review indicated it was appropriate for the provisional ADI for 98% or greater purity CBD to form part of the evidence for this assessment. For CBD a provisional acceptable daily intake (ADI) of 10 mg/day for a healthy 70 kg adult 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.

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 Committee concluded that the applicant had provided sufficient information to assure the novel food, which is an isolated CBD as detailed in application RP 345, 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.

1. Introduction

1. The ACNFP assessed the food safety risks of CBD isolated from hemp (*Cannabis sativa*) 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 retained technical guidance put in place by the European Food Safety Authority (EFSA) for full novel food applications is applicable and formed the basis and structure for the assessment (EFSA NDA Panel, 2016).
2. An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in February 2021 from Medicanna Ltd. (“the applicant”) for the authorisation of isolated cannabidiol (CBD) as described in RP 345, as a novel food. The novel food is a ≥98% pure, hemp-derived (*Cannabis sativa*) CBD isolate, which is intended to be used as an ingredient in food supplements for adults excluding pregnant and lactating women and other specifically identified vulnerable groups.
3. Advice was sought from the Joint Subgroup of the 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 (ACNFP and COT, 2023). 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 the 171st meeting, final recommendations were presented, allowing the Committee Advice to be concluded.
5. This document outlines the conclusions of the ACNFP on the safety of isolated cannabidiol (CBD) as detailed in application RP 345, 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 greater than 99%. 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.

Diagram 1: The molecular structure of CBD.

1. Confirmation of its identity and purity was provided by Nuclear Magnetic Resonance Spectroscopy (qNMR).

2.2 Production Process

1. The CBD isolate is manufactured using a multi-step process under controlled conditions.
2. 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 with and reviewed by the ACNFP.
3. The industrial hemp is first tested to ensure it meets all internal specifications and regulatory requirements before it is accepted. Manufacturing begins with botanical raw material in the form of stalk and stem material. It then undergoes an extraction using ethanol to produce a crude hemp-oil, which is then refined further to produce a high-CBD distillate. The distillate then goes through several distilling, refining, and crystallisation processes to produce a highly purified CBD isolate.
4. 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 that remain in the novel food, comparison was

made to residue limits for other consumed products as detailed in Table 1.

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

Solvent used	Available data on safe maximum level of consumption	Level in specification for the novel food
Ethanol	Guidance on residues in pharmaceutical products states it to be a class 3 solvent which should be limited by GMP or other quality-based requirements. A permissible daily exposure of up to 50 mg would be acceptable without justification[1]	≤ 50 mg/kg CBD (50 ppm)
Heptane	Guidance on residues in pharmaceutical products states it to be a class 3 solvent which should be limited by GMP or other quality-based requirements. A permissible daily exposure of 50 mg would be acceptable without justification[1]	≤ 50 mg/kg CBD (50 ppm)

[1] Q3C (R8) Step 5 - impurities: guideline for residual solvents (europa.eu)

5. The evidence presented (see Table 2 below) 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.
6. A 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.

2.2 Production Process

5. 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.
6. Table 2 presents data on the physiochemical properties of five independent batches of isolated CBD. The data presented in Table 2 indicates CBD

content is consistently above 99% purity with negligible amounts of starting materials detected across the five representative batches.

7. 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 CBD Subgroup and remain a source of uncertainty in the assessment.

Table 2. Physiochemical analysis of five independent representative batches of cannabidiol (CBD) isolate.

Parameter (and Method)	Specification	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
CBD Identification and Purity % w/w (qNMR - FSG787)	Complies / ≥99% CBD	0.002	99.7	99.4	99.4	99.5	99.4

Table 3. Cannabinoid analysis of five independent representative batches of cannabidiol (CBD) isolate.

Parameter and Method	Specification	Reporting Limit	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
CBD Content (% w/w)	≥99% CBD	0.002	99.7	99.4	99.4	99.5	99.4
Δ9-THC (mg/kg) LC-MS/MS - FSG788/ GC-MS/MS FSG786	200	2.5 / 0.1	12.3	7.6	7.5	12.9	7.3

Δ8-THC (mg/kg)							
LC-MS/MS - FSG788	100	2.5	2.5	2.5	2.5	2.5	2.5
THCA (mg/kg)							
LC-MS/MS - FSG788	≤ 1000	5	1	1	1	1	1
CBN (mg/kg)							
LC-MS/MS - FSG788/GC-MS/MS FSG786	100	2.5 / 0.1	2.6	2.6	2.7	2.5	2.5
THCV (mg/kg)							
LC-MS/MS - FSG788/GC-MS/MS FSG786	≤ 1000	2.5/0.1	0.025	0.025	0.025	0.025	0.025
THCVA (mg/kg)							
LC-MS/MS - FSG788	≤ 1000	2.5	1.7	1.7	1.7	1.6	1.6
CBC (mg/kg)							
LC-MS/MS - FSG788	≤ 1000	2.5	5	5	5	5	5
CBCA (mg/kg)							
LC-MS/MS - FSG788	≤ 1000	2.5	1.75	1.75	1.75	1.75	1.75

CBDA (mg/kg) LC-MS/MS - FSG788	≤ 1000	2.5	1.75	1.75	1.75	1.75	1.75
CBDVA (mg/kg) LC-MS/MS - FSG788	≤ 1000	2.5	1	1	1	1	1
CBDV (mg/kg) LC-MS/MS - FSG788	≤ 2500	2.5	1638	1436	2194	1414	1509
CBGA (mg/kg) LC-MS/MS - FSG788	≤ 1000	2.5	1.75	1.75	1.75	1.75	1.75
CBG (mg/kg) LC-MS/MS - FSG788	≤ 1000	20	20	20	20	20	20

10. Analytical data concerning the microbiological content from five independent batches of the novel food were reported (Table 4). The process in manufacturing this novel food uses extreme high and low temperatures and alcohol solvents.

Table 4. The microbiological analysis of the novel food.

Parameter and Method	Specification	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5

Escherichia coli (E. coli) *Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*	Not applicable	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g
Salmonella *Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*	Not applicable	Absent in 25g	Absent in 25g	Absent in 25g	Absent in 25g	Absent in 25g
Total coliforms *Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*	Not applicable	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g
Total Viable Count *Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*	10^4 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	40 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g
Total Mould and Yeast Count *Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*	10^3 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g	≤ 10 cfu/g

Table footnotes: a. All analyses carried out in triplicate b. A result of ≤ 10 cfu/g indicates all three replicates were the same. cfu = colony forming unit.

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

12. Results from the mycotoxin analysis for five independent representative batches of isolated CBD are presented in Table 5. The data show that the isolated CBD consistently complies with the specifications set for mycotoxins within the final product.

Table 5. Mycotoxin analysis of five independent representative batches of cannabidiol (CBD) isolate.

Parameter and Method	Specification	Reporting Limit	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Mycotoxins (B1, AFB1) (µg/kg) HPLC – FSG251	≤ 0.1	0. 2	0.1	0.1	0.1	0.1	0.1
Mycotoxins (B2, AFB2) (µg/kg) HPLC – FSG251	≤ 0.1	0. 2	0.1	0.1	0.1	0.1	0.1
Mycotoxins (G1, AFG1) (µg/kg) HPLC – FSG251	≤ 0.1	0. 2	0.1	0.1	0.1	0.1	0.1
Mycotoxins (G2, AFG2) (µg/kg) HPLC – FSG251	≤ 0.1	0.2	0.1	0.1	0.1	0.1	0.1
Total Aflatoxins (µg/kg) HPLC – FSG251	N/A	0.8	0.5	0.5	0.5	0.5	0.5

Ochratoxin A (µg/kg) HPLC – FSG251	≤ 0.1	0.2	0.2	0.2	0.2	0.2	0.2

13. Novel food products must comply with the legal requirements for heavy metal contaminants in food. Analytical data, 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 (applicable for Arsenic, Cadmium, Mercury and Lead) (Table 6).

Table 6. Heavy metal analysis of five independent representative batches of cannabidiol (CBD) isolate.

Parameter and Method	**Specification**	**Reporting Limit**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**
Arsenic (mg/kg) ICPMS – FSG461, FSG457	1.0	0.01	0.01	0.01	0.01	0.01	0.01
Cadmium (mg/kg) ICPMS – FSG461, FSG457	1.0	0.01	0.005	0.005	0.005	0.005	0.005
Lead (mg/kg) ICPMS – FSG461, FSG457	1.0	0.02	0.01	0.01	0.01	0.01	0.01

Mercury (mg/kg) ICPMS – FSG461, FSG457	0.1	0.01	0.01	0.01	0.01	0.01	0.01

14. Results from the residual solvent analysis for five independent representative batches of isolated CBD are presented in Table 7. The data show that the isolated CBD is able to consistently comply with the specifications set for residual solvents within the final product.

Table 7. **Residual solvent analysis of five independent representative batches of cannabidiol (CBD) isolate.**

Parameter and Method	**Specification**	**Reporting Limit**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**
Hexane (mg/kg) HS-GC-MS	≤ 3	0.6	0.6	0.6	0.6	0.6	0.6
Methanol (mg/kg) HS-GC-MS	≤ 30	6.0	9	9	9	9	9
Pentane (mg/kg) HS-GC-MS	≤ 50	6.0	7	7	7	7	7
Acetone (mg/kg) HS-GC-MS	≤ 50	6.0	7	7	7	7	7

Isopropyl alcohol (mg/kg) HS-GC-MS	≤ 50	6.0	7	7	7	7	7
Ethanol (mg/kg) HS-GC-MS	≤ 50	6.0	14	14	14	14	14
Heptane (mg/kg) HS-GC-MS	≤ 50	6.0	35.7	29.7	30.3	33.5	35.6

Table footnotes: Analyses were performed in triplicate and results represent the mean.

1. Additional analyses were presented to the Committee, covering dioxins, polychlorinated diphenyls, polyaromatic hydrocarbons, and pesticides. No concerns were raised regarding the additional analyses and the results demonstrated consistency in production of the novel food.

THC as a potential contaminant in the novel food

1. 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.
2. 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. 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 Δ9-THC as a contaminant in milk and meat (EFSA,2015).

3. Evidence from an EFSA review by the CONTAM panel suggested a point of departure from a LOAEL (lowest observed adverse effect level) of 0.036mg/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 1µg /kg bw/day for Δ9-THC consumed as a contaminant in food. This was identified an acute reference dose (ARfD) (EFSA, 2015)
4. The Subgroup agreed the Acute Reference Dose (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.
5. The analysis for Δ9-THC as a potential contaminant in the novel food was declared as being between 7.5-12.9mg/kg the five batches tested (Table 3), with a limit of quantification of 2.5mg/kg.
6. The levels of Δ9-THC, 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.
7. To ensure Δ9-THC levels remain consistently low in the production of CBD, THC and its precursor acid combined, should be a standard substance included in the specification as relevant to all batches produced.
8. The data presented did not indicate any additional hazards for inclusion in the specification.

2.4 Stability

9. The stability of the novel food was assessed in real-time under ambient conditions (21°C) in five batches for 24 months. Results showed that the novel food meets the specification criteria for CBD and other cannabinoid

content, and microbiological stability over these time periods. The Δ9-THC content was also tested and no significant changes in the levels of Δ9-THC were observed.

10. The data provided supports the stability of CBD isolate for a period of at least 18 months.

2.5 Specification

1. The applicants' 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 to 7 and indicate the novel food can be produced consistently to the specification.

Table 8. Specification of the novel food.

Parameter	Specification	Method
Identity	Complies	qNMR (FSG787)
CBD (% w/w)	≥99%	qNMR (FSG787)
THC Content (% w/w)	≤ 200 mg/kg	LC-MS/MS (FSG788)
Cannabinoids	Individual Limits	LC-MS/MS (FSG788)

Residual solvents

Parameter	Specification	Method
Hexane	≤ 3 mg/kg	HS-GC-MS: in house method
Methanol	≤ 30 mg/kg	HS-GC-MS: in house method
Pentane	≤ 50 mg/kg	HS-GC-MS: in house method

Acetone	≤ 50 mg/kg	HS-GC-MS: in house method
Isopropyl alcohol	≤ 50 mg/kg	HS-GC-MS: in house method
Ethanol	≤ 50 mg/kg	HS-GC-MS: in house method
Heptane	≤ 50 mg/kg	HS-GC-MS: in house method

Elemental Impurities

Parameter	Specification	Method
Arsenic	1.0 mg/kg	ICP-MS[3]
Cadmium	1.0 mg/kg	ICP-MS[3]
Lead	1.0 mg/kg	ICP-MS[3]
Mercury	0.1 mg/kg	ICP-MS[3]

Aflatoxins

Parameter	Specification	Method
M1	≤ 0.00005 mg/kg	FSG251 - HPLC
B1 (AFB1)	≤ 0.001 mg/kg	FSG251 - HPLC
B2 (AFB2)	≤ 0.001 mg/kg	FSG251 - HPLC
G1 (AFG1)	≤ 0.001 mg/kg	FSG251 - HPLC

G2 (AFG2) ≤ 0.001 mg/kg FSG251 - HPLC

Additional Analyses

Parameter	Specification	Method
Dioxins	0.000001 mg/kg	FSG403,404,405,406,407,408
Polychlorinated Biphenyls	0.01 mg/kg	FSG407
Polyaromatic Hydrocarbons	0.01 mg/kg	FSG410
Total Mycotoxins	0.004 mg/kg	FSG261
Pesticides	0.1 mg/kg	FSG167 – QuEChERS Method GC-MS/LC-MS
Total Bacteria Count	10^4	*Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*
Total Yeast and Mould Count	10^3	*Ph. Eur. 2.6.12* *Ph. Eur. 2.6.13*

CBD = cannabidiol; GC = gas chromatography; HPLC = high-performance liquid chromatography; IR = infrared spectroscopy; USP = United States Pharmacopeia; DAD = diode-array detection; HS-GC-MS = headspace gas chromatography-mass spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; GC-MS/MS = gas chromatography tandem mass spectrometry, [1]= LOQ and LOD values for cannabinoids found in Table 2.4.1-7 in application, [2]= Individual pesticides and associated limits found in Table 2.5.4-1 in application, [3]=AOAC

2011.19 / modified 993.14.

1. The ACNFP concluded the information provided is sufficient for the specification of CBD and appropriately characterises the novel food seeking authorisation.

2.6 History of Use

1. 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, at the time of publication, no previous applications for CBD have yet received authorisation as a novel food.
2. 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 effects on liver, thyroid and potential impacts on reproductive organs. Also reported are behavioural effects such as somnolence (sleepiness)(COT, 2020).
3. 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.
4. 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). Based on the COT assessment, therefore, the FSA concluded in February 2020 that 1 mg/kg bw/day, or 70 mg in a 70 kg adult, was a pragmatic upper level of intake above which there would be clear concerns about safety.
5. 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.

6. Within the literature, further human studies utilising chemically derived CBD provides further evidence of a history of synthetic CBD use (Izegelov *et al.,* 2010; Stereo Biotechs Ltd., 2020; Klotz *et al*., 2019; Wheless *et al.,* 2019). A review by Heuestis *et al*., 2019 of 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.
7. 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

8. The intended use is food supplements as defined The Food Supplements (England, Scotland and Wales) Regulations 2003 in a range of forms.
   The applicant initially proposed a use level of 70 mg/day CBD for the novel food in adults, excluding pregnant or lactating women. As a result of consultation with the applicant 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) as detailed in section 2.10. The proposed maximum use levels for the novel food are outlined in Table 9.

Table 9. Amended proposed uses and maximum use levels for the novel food.

Food category	**Maximum use level per day (mg CBD/day)**
Food Supplements (for adults) as defined in the Food Supplements (England) Regulations 2003 and other equivalent legislation in the other nations of the UK as capsules, chewable forms, liquid or drops in dose form intended for those 18 years of age or over. Excluding pregnant and lactating women and other specifically identified vulnerable groups.	10

9. 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 10mg of CBD per day from all sources (as concluded in section 2.10 of this assessment).
10. 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.
11. 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 10mg per day for a healthy adult.
12. 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).
13. 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.
14. 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.

15. 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 or for use during pregnancy or breastfeeding. As well as information on its suitability if the consumer is taking medication or has existing health conditions.

2.8 Absorption, Distribution, Metabolism and Excretion (ADME)

9. The Absorption, Distribution, Metabolism and Excretion (ADME) of CBD are known to be complicated by the food matrix and are currently still being defined by professional bodies.
10. 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 in humans (Miller *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, up to 5-fold if eaten with a high fat meal. As such the potential for matrix effects that impact bioavailability cannot be ruled out.
11. Following oral absorption, 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 cannabidiol; however, several other hepatic cytochrome P450 isoforms (CYP1A1, CYP1A2, CYP2C9, CYP2D6, and CYP3A5) have also demonstrated a capability of metabolising cannabidiol (Jiang *et al*., 2011; Zendulka *et al*., 2016).
12. The metabolism of CBD is thought to follow two separate pathways. One is P450-mediated, in which cannabidiol is metabolised into its major metabolite 7-COOH-CBD. 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).

13. 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 been reported in dosing studies over 5–9 days (Millar *et al.,* 2018; Sellers *et al.,* 2013; Stott *et al*., 2013).
14. The pharmacokinetics of CBD have also 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. With 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, with a half-life between 1 to 3 hours. Given the intended use of this CBD, with an approximate half-life of one to three hours, with a total clearance of 6 hours, there are no significant concerns of accumulation. (Millar *et al.,* 2018).
15. 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 the matrix. It was noted that the potential for CBD to accumulate in the body has not been examined based on the data supplied. This also suggests the food context for CBD could impact whether the CBD present in the ingredient is more, or less, bioavailable. This has been taken into account when considering the additional uncertainty factors used for setting the provisional ADI.

2.9 Nutritional information

23. 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 some minerals), tannins (which can inhibit the absorption of iron), trypsin inhibitors (which can affect protein digestion), and saponins (which can cause gastric irritation and increase the permeability of the intestine).
24. 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.

25. 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

23. 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. How data on systemic toxicity was managed and interpreted in the context of the provisional ADI is explained in the sub chronic toxicology section 2.10.2, below.

2.10.1 Genotoxicity

1. *In vitro* genotoxicity testing of CBD was conducted under Good Laboratory Practice (GLP) conditions and utilised the following OECD guidelines: *in vitro* bacterial reverse mutation test (OECD TG 471) and *in vitro* mammalian cell micronucleus test (OECD TG 487). The approach using these two genotoxicity tests *in vitro* 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.
2. The *in vitro* bacterial reverse mutation test demonstrates that this CBD ingredient is non-mutagenic, in the absence or presence of metabolic activation.
3. In addition, an *in vitro* mammalian cell micronucleus assay was initially provided as part of the application, which is noted to be unsuitable for demonstrating the genotoxicity of the novel food. Further information was requested, and a new study was provided. Following review of the new study by expert members of the ACNFP and COT, it is noted that it is appropriate for risk assessment and the results do not raise any concerns around genotoxicity. The *in vitro* mammalian cell micronucleus test demonstrates that CBD is non-clastogenic and non-aneugenic in the absence and presence of metabolic activation.
4. The results from these *in vitro* studies support the conclusion that the novel food (≥99% pure CBD) 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 toxicology study

1. 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 examination of data submitted to support individual novel food applications.
2. This applicant provided a Repeated Dose 90-Day Oral Toxicity Study in Rodents, 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 rats which were dosed with 0 (control – coconut-based MCT oil), 25, 75 or 225 mg/kg bw/day CBD once per day by oral gavage at a dose volume of 0.8 mL/kg bw/day. Satellite groups of 5 female and 5 male rats were treated with MCT oil or CBD (225 mg/kg bw/day) in the same way as test animals during the treatment phase of the study and allowed 28 days' untreated recovery after dosing was completed. The applicant concluded a NOAEL of 225 mg/kg bw/day based on effects seen in organ weight, liver and adrenal endpoints.
3. The Subgroup reviewed the data and concluded the effects seen at 75 mg/kg bw/day were minimal but not adverse, however the effects seen at 225 mg/kg bw/day are potentially adverse. As such the Subgroup considered that the NOAEL for the study be 75mg/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.
4. 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.
5. 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.

6. It was considered whether the wider data and therefore the provisional ADI for 98% or greater CBD was relevant to the review of the novel food. It was considered appropriate, on the basis that the test substance used in the study to support the novel food was ≥99% 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 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 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

1. This CBD isolate comprises ≥99% CBD and the production process for CBD does not introduce any risk of allergenic potential. As a chemical entity the potential for IgE mediated food allergy is unlikely.
2. Given CBD as a substance is not considered allergenic, the allergenicity assessment considered whether the other 1% of the novel food's composition was likely to be allergenic or elicit food allergic reactions. It was noted that 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 assimilated Regulation (EU) No 1169/2011 on the provision of food information to consumers. This suggests the potential to elicit reactions in those sensitive to those foods is unlikely.
3. The novel food is unlikely to trigger allergic reactions in the target population under the proposed conditions of use.

3.Discussion

4. The novel food is a CBD isolate ingredient from industrial hemp containing ≥99% CBD produced using a multi-step manufacturing process.

5. This CBD isolate is intended to be used as a food ingredient in food supplements for adults excluding pregnant and lactating women and other specifically identified vulnerable groups at a defined intake for each product type of up to 10 mg CBD per day; it is not intended to replace any food.
6. 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, which 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 or evidence regarding potentially vulnerable groups.
7. 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 provision ADI of 10 mg/day for CBD of 98% purity or above. As such the provisional ADI should be applied to this novel food.
8. 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.
9. 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

1. The ACNFP has undertaken a review of this CBD isolate and concluded that the novel food is safe under the proposed conditions of use and does not

pose a safety risk to human health. The proposed uses are not considered nutritionally disadvantageous.

2. These conclusions were supported by 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:

- *in vitro* bacterial reverse mutation test.
- *in vitro* mammalian cell micronucleus test.
- 90-day repeat dose gavage study.

3. The members of the ACNFP during the course of the assessment who were; Dr Camilla Alexander White, Dr Anton Alldrick, Alison Austin, Professor George Bassel, Dr Mark Berry, Professor Dimitris Charalampopoulos, Dr Meera Cush, Dr Catharina Edwards, Professor Susan Fairweather-Tait, Dr Sophie Foley, Paul Frazer, Professor Andy Greenfield, Professor Wendy Harwood, Professor Huw D. Jones, Dr Ray Kemp, Dr Elizabeth Lund, Professor Harry J. McArdle, Dr Lynne McIntyre, Professor Clare Mills, Dr Isabel Skypala, Professor Lesley Stanley, Professor Hans Verhagen, Dr Maureen Wakefield, and Professor Bruce Whitelaw.
4. Additional advice was provided by Dr Carol Beevers during the course of the assessment of the novel food.
5. 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 novel food Committee 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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Abbreviations

1H NMR	1H (proton) nuclear magnetic resonance
ACNFP	Advisory Committee on Novel Foods and Processes

ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
aw	Water activity
bw	body weight
CAS	Chemical Abstracts Service
CBD	Cannabidiol
Cmax	Peak serum concentration
COT	Committee on Toxicity
CFU	Colony Forming Unit
EC	European Commission
EFSA	European Food Safety Authority
EMA	Environmental Medicines Agency
EU	European Union
FDA	Food and Drug Administration (USA)
FSA	Food Standards Agency
FSS	Food Standards Scotland

GC	Gas chromatography
GLP	Good Laboratory Practice
HACCP	Hazards Analysis and Critical Control Points
HPLC	High-performance liquid chromatography
IR	Infra-red
NOAEL	No Observable Adverse Effect Level
NM	Not measured
OECD	Organisation for Economic Co-operation and Development
Tmax	Time to maximum concentration
USP	United States Pharmacopeia
UV	ultra-violet