Position papers

Committee Advice on the safety of cannabidiol (CBD) isolate as a novel food for use in a range of food categories including food supplements - RP793

Reference number RP793

Advisory Committee on Novel Foods and Processes (ACNFP)

Regulated Product Dossier Assessment

Summary

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) March 2021 from CBD Industries LLC. (“the applicant”) for the authorisation of cannabidiol (CBD) isolate as a novel food. The novel food is an isolated >97% pure form of CBD which is intended to be used as a food supplement for adults (excluding pregnant and lactating women and other specifically identified vulnerable groups including those on medication and the immunosuppressed).

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.

The FSA and FSS concluded based on the advice of the ACNFP that the applicant had provided sufficient information to assure the novel food, a CBD isolate as outlined in application RP793, was safe when used at 10mg a day in food supplements. It was noted a higher use level of 24mg /day was sought but when considered in the context of the wider data for 98% or greater CBD safety for the higher level could not be assured. The anticipated intake levels and the proposed use of this pure form of CBD in foods and food supplements was not considered to be nutritionally disadvantageous.

The views of the ACNFP have been taken into account in the regulatory assessment which represents the opinion of the FSA and FSS.

1. Introduction

1. The ACNFP assessed the food safety risks of CBD isolate extracted from hemp (*Cannabis sativa*) and its production under the proposed uses in line with Article 7 of assimilated Commission Regulation (EU) 2017/2469. The regulatory framework and the retained technical guidance put in place by the European Food Safety Agency (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 March 2021 from CBD Industries LLC by Legal Foods (“the applicant”) for the authorisation of cannabidiol (CBD) isolate as described in RP793, as a novel food. The novel food is >97% pure form CBD isolate which is intended to be used as a food supplement 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 taken into account in reviewing the toxicological evidence for this application.

4. Following the review by the ACNFP at their 168th meeting in September 2024, final recommendations from the Committee were presented, allowing the Committee Advice to be concluded.

5. This document outlines the conclusions of the ACNFP on the safety of an isolated cannabidiol (CBD) as detailed in application RP 793, as a novel food.

2. Assessment

2.1 Identity of novel food

6. The novel food is a CBD isolate which is a purified white to off white powder of primarily CBD of 97%-100% purity together with minor cannabinoids representing 2.5% of the final novel food. 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.

8. Confirmation identity of the CBD isolate was provided by ultra-high performance liquid chromatography-diode array detection (UHPLC-DAD); identity of compounds was confirmed during method validation using DAD-UV and mass spectrometry and quadrupole-time-of-flight mass spectrometry (Q-TOFMS).

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 industrial hemp is first tested to ensure it meets all internal specifications before it is accepted. Manufacturing begins with botanical raw material which is ground. It is then extracted using alcohol before filtration, decarboxylation and distillation. The distillate then goes through several crystalisation , washingand filtering steps to produce the highly purified cannabidiol (CBD) isolate.

12. The FSA and FSS considered whether the use of solvents as processing aids resulted in residues that require highlighting to risk manager. 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. Residues of solvents included in the specification.

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. 50 mg per day or less (5000 ppm) would be acceptable without justification.[1]	5000 µg/g CBD
Ethyl ether	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. 50 mg per day or less (5000 ppm) would be acceptable without justification.[1]	5,000 µg/g CBD
n-heptane	Used as an extraction solvent, but only in accordance with good manufacturing practices, which should result in minimal residue.[2]	5000 µg/g CBD

Pentane	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. 50 mg per day or less (5000 ppm) would be acceptable without justification.[1]	5000 µg/g CBD

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

2 Scientific Opinion on the evaluation of the substances currently on the list in the annex to Commission Directive 96/3/EC as acceptable previous cargoes for edible fats and oils – Part II of III

13. 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.

14. A Hazard Analysis 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

15. Results from analysis of five independent batches of the novel food demonstrated that the CBD content is produced consistently. The data is presented in tables 2- 5 below.

16. Table 2 presents data on the physiochemical properties of five independent batches of isolated CBD.

Table 2: Compositional analysis of representative batches of cannabidiol (CBD) isolate.

Parameter	Method of Analysis	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Mean (SD)
Colour	Visual	Complies (White to off-white)	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	-
Form	Visual	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	Complies (Solid, free flowing powder)	-
CBD (%)	AOAC 2018.11	99.6	99.1	99.7	99.6	98.9	99.0 (0.8)
Cannabigerol (CBG; %)	AOAC 2018.11	1.71	1.69	1.55	1.15	1.6	1.54 (0.23)
Cannabinol (CBN; %)	AOAC 2018.11	0.473	0.464	0.483	0.703	0.765	0.578 (0.145)
Cannanbidivarin (CBDV; %)	AOAC 2018.11	0.217	0.218	0.215	0.270	0.216	0.227 (0.024)
Delta-9 Tetrahydrocannabinol	AOAC 2018.11	0.025	0.025	0.025	0.025	0.025	
Delta-9 Tetrahydrocannabivarin (THCV)	AOAC 2018.11	0.025	0.025	0.025	0.025	0.025	

Delta-8 Tetrahydrocannabinol	AOAC 2018.11	0.05	0.05	0.05	0.05	0.05

17. CBD content is consistently above 97% purity with an average of 99% across five representative batches.

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

19. Analytical data concerning the microbiological content from five batches of the novel food was reported (Table 3).

Table 3: The microbiological analysis of the novel food.

Parameter	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**
Total aerobic microbial plate count	10 CFU/g	10 CFU/g	10 CFU/g	10 CFU/g	10 CFU/g
Total yeast and mould plate count	10 CFU/g	10 CFU/g	10 CFU/g	10 CFU/g	10 CFU/g

CFU = colony forming unit

20. The process in manufacturing this novel food uses extreme high and low temperatures, harsh pH conditions and alcohol solvents. Full microbial risk assessment as United States Pharmacopeia 61 (USP 61) and USP 62 confirm that the novel food does not raise a safety concern and consistently meets the proposed microbial specification levels.

21. 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 Maximum Residue limits (MRL) in assimilated legislation where applicable (applicable for arsenic, cadmium, mercury and lead) (Table 4).

Table 4: Elemental Impurities in the novel food for 2 batches of the novel food.

Maximum concentration measured (ppb)

Parameter (mg/kg)	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Arsenic	10	10	10	10	10
Lead	0.5	0.5	0.5	0.5	0.5
Cadmium	0.5	0.5	0.5	0.5	0.55
Mercury	0.5	0.5	0.5	0.5	0.5

22. Results from the residual solvent analysis for five independent representative batches of isolated CBD are presented in Table 5. The data show that the isolated CBD is able to consistently comply with the specifications set for residual solvents within the final product.

Table 5 Analysis of solvents residues present in the novel food.

Residues (mg/kg)	**Method of Analysis**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Mean (SD)**
Ethanol (µg/g)	USP 467	200	200	200	200	200	-
Heptane (µg/g)	USP 467	200	200	200	200	200	-
Pentane (µg/g)	USP 467	382	483	421	1760	1630	935.2 (696)
Total Class 3 5000 µg/g	USP 467	Pass	Pass	Pass	Pass	Pass	-

Triethylamine	GC (in house method)	≤500	≤500	≤500	≤500	≤500	-
Isopropanol	GC (in house method)	≤500	≤500	≤500	≤500	≤500	-
Isooctane	GC (in house method)	≤500	≤500	≤500	≤500	≤500	-

AOAC = Association of Official Agricultural Chemists ; USP = United States Pharmacopeia.

23. The data presented indicated the novel food was appropriately characterised.

THC as a potential contaminant in the novel food.

24. Contaminating cannabinoids other than CBD have been considered as part of the application. In particular, delta-9-tetrahydrocannabinol (Δ9-THC) is analysed due to the potential for toxic effects resulting from its consumption and its status as a controlled drug within the UK. 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.

25. 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).

26. Evidence from an EFSA review by the CONTAM panel suggests 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. Uncertainty factors were then applied to identify a safe upper intake level. These included an uncertainty factor of 3 to extrapolate from a LOAEL to a NOAEL (No Observed

Adverse Effect Level); which was considered appropriate considering the effects are mild to moderate in severity. A further factor of 10 was applied to account for individual 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).

27. 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 THC at very low levels. The Subgroup commented that there was no data to verify this assumption, but if setting limits the dataset is the best available.

28. The analysis for delta-9-tetrahydrocannabidiol as a potential contaminant in the novel food was declared as not detected in any of the six batches tested (Table 2), with a limit of quantification of 0.025% (w/w).

29. The levels of Δ9-THC in the novel food, once adjusted to take account the proposed uses – 10 mg of CBD being consumed a day - were below the ARfD of 1 µg /kg bw/day or 70 µg/day for a healthy adult identified by EFSA and adopted by the UK. This level does not present a concern in terms of consumer safety for the novel food where the proposed use is less than 10mg a day of CBD.

30. To ensure Δ9-THC levels remain consistently low in the production of CBD, THC should be a standard substance included in the specification as relevant to all batches produced.

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

2.4 Stability

32. The stability of the novel food was assessed under real-time conditions (25^{o}C and 60% relative humidity) for 6 months for 3 batches of CBD isolate, and accelerated conditions (40 ^{o}C and 75% relative humidity) for 6 months for 5 batches of CBD isolate. Results showed that the novel food meets the specification criteria for CBD content, and no changes in cannabinoid profile were observed. No changes in aerobic plate count or yeast and mould count are seen over these time periods. The Δ-9 THC content was also tested using liquid chromatography-diode array detection (LC-DAD) with optional mass spectrometric detection and remained consistently below 0.025% w/w across the time period

which is consistent with the specification.

33. Using a representative batch of each, the stability of the novel food under intended conditions of use (gummies, soft gel capsules and tincture food form) was assessed for 6 months under real time conditions (25^{o}C and 60% relative humidity) and accelerated conditions (40^{o}C and 75% relative humidity). Results showed that the final products meet the specification criteria for CBD content, and no significant changes in cannabinoid profile. The THC content was also tested using UHPLC-DAD and remained consistently below 0.025% w/w across the time period which is consistent with the specification.

34. The THC content was also tested in both studies and no significant changes in the levels of THC were observed.

35. The data provided supports the stability of CBD isolate for a period of at least 12 months based on extrapolation from the data submitted.

2.5 Specification

36. The specification parameters reported in Table 6-12 were assessed using internationally recognised methods or determined using internally developed and validated methods. The results of the analysis are detailed in Table 2-5 and indicate the novel food can be produced consistently to the specification.

Table 6: Specification of the novel food.

Physical properties.

Parameter	Specification	Method
Colour	White to off-white	Visual
Form	Solid, free-flowing powder	Visual

Chemical properties (%)

Parameter	Specification	Method
Cannabidiol (CBD)	97-100	AOAC 2018.11 / QSP-1157

Cannabigerol (CBG)	0-2	AOAC 2018.11 / QSP-1157
Cannabinol (CBN)	0-0.85	AOAC 2018.11 / QSP-1157
Cannabidivarin (CBDV)	0-0.25	AOAC 2018.11 / QSP-1157
Delta-9- Tetrahydrocannabinol	0.025	AOAC 2018.11 / QSP-1157
Delta-9-Tetrahydrocannabivarin (THCV)	0.025	AOAC 2018.11 / QSP-1157
Delta-8-Tetrahydrocannabinol	0.05	AOAC 2018.11 / QSP-1157

Table 7. Microbial specification of the novel food.

Microbial Content.		
Aerobic Plate Count	1000 CFU/g	USPC_61/QSP-6794
Yeast and Mold Count	100 CFU/g	USPM_61/QSP-6794
Escherichia coli		USPE_62/QSP-1221
Salmonella (USP)		USPS_62/QSP-1221

Table 8. Pesticides specification of the novel food.

Pesticides (ppm)		
Piperonylbutoxide	0.1	QSP-1212; QSP-1213/AOAC 2007.01
Spinosad	0.1	QSP-1212; QSP-1213/AOAC 2007.01
Chlorpyrifos	0.1	QSP-1212; QSP-1213/AOAC 2007.01

66 pesticides on BCC list	0.1	QSP-1212; QSP-1213/AOAC 2007.01

Table 9. Mycotoxins specification of the novel food.

Mycotoxins (µg/kg)		
Aflatoxin B1	2.0	QSP-1212 (HPLC-MS)
Aflatoxin B2	1.8	QSP-1212 (HPLC-MS)
Aflatoxin G1	1.0	QSP-1212 (HPLC-MS)
Aflatoxin G2	1.2	QSP-1212 (HPLC-MS)
Ochratoxin	6.3	QSP-1212 (HPLC-MS)

Table 10. Heavy metals specification of the novel food.

Heavy Metals (µg/g)		
Arsenic	0.02	2011.19, 993.14; QSP-1160 (ICP-MS)
Lead	0.04	2011.19, 993.14; QSP-1160 (ICP-MS)
Cadmium	0.02	2011.19, 993.14; QSP-1160 (ICP-MS)
Mercury	0.002	2011.19, 993.14; QSP-1160 (ICP-MS)

Table 11. Residual solvents specification of the novel food.

Residual solvents (µg/g)		
Ethanol	5000	QSP-1204 (GC-MS)

Ethyl ether	5000	QSP-1204 (GC-MS)
Heptane	5000	QSP-1204 (GC-MS)
Pentane	5000	QSP-1204 (GC-MS)

Table 12. Other properties specification of the novel food.

Other properties.

Storage/Shelf life	The product should be stored in a cool, dry place away from direct heat, sunlight and moisture. The product specifications are stable and should not exceed 12 months from date of manufacture.

AOAC = Association of Official Agricultural Chemists; GC-MS = gas chromatography-mass spectometry; HPLC = high-performance liquid chromatography; ICP-MS = inductively couples plasma-mass spectrometry; IR = infrared spectroscopy; QSP = XXXXX ; USP = United States Pharmacopeia.

37. The FSA and FSS concluded the information provided is sufficient for the specification of CBD and appropriately characterises the novel food seeking authorisation.

2.6 History of Use

38. 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.

39. 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).

40. 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.

41. 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. 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.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 sole requirement instead being that the products are safe. This means that outcomes that are considered to be an adverse event for food might be weighed differently in the context of the clinical benefits in a medicinal study.

42. 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.

43. 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

44. The intended use is food supplements as defined by GB legal requirements (The Food Supplements (England)) Regulations 2003 and equivalent legislation in the other nations of GB) in the form of tinctures, gummies and soft gel capsules. The applicant proposed a use level of 24 mg/day CBD for the novel food in adults, excluding pregnant or lactating women. (Table 13).

Table 13. 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 as capsules, liquids or drops intended for those over 18 years of age or over.	24mg/day

2.7.1 Anticipated intake of the novel food

45. The applicant's proposed use would lead to exposure by the target population of 24 mg of CBD per day. The safe level identified in the toxicological assessment (section 2.10) is 10 mg per day of CBD.

2.7.2 Considerations in assessing the proposed use

46. 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 at a maximum consumption of 10 mg of CBD per day from all sources (as concluded in section 2.10 of this assessment).

47. 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.

48. 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

detailed in section 2.10.

49. 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).

50. The FSA and FSS 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.

51. 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.

52. The food supplement products are to be labelled in accordance with the labelling requirements of Food Supplements (England, Scotland and Wales) Regulations 2003. The FSA and FSS recommended that this applicant’s 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)

53. 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.

54. 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, 5-fold if eaten with a high fat meal. As such the potential for matrix effects that impact bioavailability cannot be ruled out.

55. Following oral consumption, cannabidiol 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).

56. The metabolism of cannabidiol 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 cannabidiol 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).

57. 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 5–9 days (Millar et al., 2018; Sellers et al., 2013; Stott et al., 2013).

58. 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 h, with 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 1 to 3 hours, with a total clearance of six hours, there are no significant concerns of accumulation (Millar et al., 2018).

59. 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 CBD could impact on CBD bioavailability. It was noted that the potential for CBD to accumulate in the body was partially examined based on the data supplied. This also suggested 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 additional ADI.

2.9 Nutritional information

60. 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).

61. The product is highly purified as indicated in the information on the composition. There are no substances present that would be expected to impact the digestion or absorption of nutrients from the diet.

62. 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

63. 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 subchronic

toxicology section below.

2.10.1 Genotoxicity

64. *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). This approach is recommended by the UK Committee on Mutagenicity and is also the basis of guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283.

65. The *in vitro* bacterial reverse mutation test [(Rao, 2021 (unpublished)] demonstrated that this CBD ingredient was non-mutagenic in the absence and presence of metabolic activation. In addition, the in vitro mammalian cell micronucleus test [(Swartz, 2021 (unpublished)] demonstrated that cannabidiol was non-clastogenic and non-aneugenic in the absence and presence of metabolic activation

66. The results from these *in vitro* studies support the conclusion that the novel food (>97% 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 Acute Toxicology

67. 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 reviewing data submitted to support individual novel food applications.

68. This applicant provided a Repeated Dose 90-Day Oral Toxicity Study in rodents (Blum, 2021 unpublished), conducted under GLP conditions and following OECD TG 408. In this 90-day feeding study, two groups comprised of 20 female and 20 male rats and three groups comprised of 15 female and 15 male rats, were dosed with 0 (control – medium chain triglyceride oil), 91.05, 349.41, 698.79 or 1397.57 mg/kg bw/day test item once per day by oral gavage, corresponding to 30, 115.13, 230.25 and 460 mg/kg bw/day of the active ingredient CBD.

69. The applicant concluded a NOAEL of 50 mg/kg bw/day. The Subgroup reviewed the data and concluded the effects seen at 91.05 mg/kg bw/day were

minimal but not adverse, however the hepatic centrilobular hypertrophy and histological changes seen on the liver in males at 349.41 mg/kg bw/day were potentially adverse. Therefore, a NOAEL of 91.05 mg/kg bw/day was determined, corresponding to a NOAEL of 30 mg/kg bw/day for the active CBD ingredient once corrected for the CBD content of the test material.

70. 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.

71. A weight of evidence approach has 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.

72. It was considered whether the wider data and therefore the provisional ADI for CBD of 98% or greater purity 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 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 (Blum, 2021 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.

73. It was noted that the applicant proposed use of a higher body weight for a UK adult on the basis of average adult weight recorded from UK data. This was

considered, however for consistency across novel food assessments 70 kg for average body weight for an adult was used in the assessment. This was to allow consistency with other novel foods where a standard value for adult weight is used no matter the subpopulations that are targeted or excluded that could alter the average body weight applied. This approach is consistent with other assessors internationally and the advice of the Committee on Toxicity.

2.11 Allergenicity

74. This CBD isolate comprises >97% 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.

75. Given CBD as a substance is not considered allergenic, the allergenicity assessment considered whether the other 3% of the novel foods 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. Suggesting the potential to elicit reactions in those sensitive to those foods is unlikely.

76. The novel food is unlikely to trigger allergic reactions in the target population under the proposed conditions of use.

3. Discussion

77. The novel food is a CBD isolate ingredient containing >97% CBD, produced using a multi-step manufacturing process.

78. This CBD isolate is intended to be used as food ingredient in food supplements for adults, excluding pregnant and lactating women and other specifically identified vulnerable groups, as tinctures, soft gel capsules or as gummies at a dose of 24 mg a day; it is not intended to replace any other food.

79. 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) for a 70kg adult. 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.

80. 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 novel food discussed in this assessment is of high purity containing 97% or above CBD, and demonstrates a similar toxicological profile as novel foods containing >98% CBD content. The evidence presented is consistent with evidence presented to support the development of the 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.

81. 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.

82. 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.

4. Conclusions

83. The FSA and FSS have undertaken a review of this CBD isolate and concluded that the novel food is safe when used at 10 mg a day in food supplements. It was noted a higher use level of 24 mg /day was sought by the applicant but, when considered in the context of the wider data for 98% or greater CBD, safety for the higher level proposed could not be assured. The NOAEL from applicant’s sub-chronic toxicology study was within the NOAELs identified from studies in the provisional ADI statement and the same uncertainty factors were also relevant. Therefore the body of evidence reviewed by FSA and FSS on substances with a similar composition and demonstrating similar effects is relevant to this assessment.

84. 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:

Systematic review of published human studies; annexes to the dossier which relate to the production process and associated certificates of analysis, and toxicology;

- *in vitro* bacterial reverse mutation test (Rao, 2021 (unpublished);
- *in vitro* mammalian cell micronucleus test (Swartz, 2021 (unpublished) and 90-day repeat dose feeding study (Blum, 2021 (unpublished).

The members of the ACNFP during the course of the assessment who were; Dr Camilla Alexander White, Dr Anton Alldrick, Dr Kimon Andreas Karatzas, Alison Austin, Professor George Bassel, Dr Mark Berry, Dr Christine Bosch, Professor Dimitris Charalampopoulos, Dr Meena Cush, Dr Catharina Edwards, Professor Susan Fairweather-Tait, Dr Sophie Foley, Professor Paul Frazer, Dr Hamid Ghoddusi, Professor Andy Greenfield, Professor Wendy Harwood, Professor Huw D. Jones, Dr Ray Kemp, Dr Elizabeth Lund, Professor Harry J. McArdle, Mrs Rebecca McKenzie, Dr Lynn McIntyre, Professor Clare Mills, Dr Antonio Peña-Fernández, Dr Isabel Skypala, Professor Lesley Stanley, Professor Hans Verhagen, Dr Maureen Wakefield, and Professor Bruce Whitelaw.

85. 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
ACMD	Advisory Council on the Misuse of Drugs

ACNFP	Advisory Committee on Novel Foods and Processes
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
AOAC	Association of Official Agricultural Chemists
bw	body weight
CAS	Chemical Abstracts Service
CBD	Cannabidiol
Cmax	Peak serum concentration
COT	Committee on Toxicity
CFU	Colony Forming Unit
DAD	Diode array detection
EC	European Commission
EFSA	European Food Safety Agency
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
ICP	Inductively couples plasma
IR	Infra-red
LOAEL	Lowest Observable Adverse Effect Level
LOD	Limit of Detection
LOQ	Limit of Quantification
NOAEL	No Observable Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
Q-TOFMS	Quadupole time-of-flight mass spectrometry
THC	Tetrahydrocannabinol
Tmax	Time to maximum concentration

UHPLC	Ultra high-performance liquid chromatography
USP	United States Pharmacopeia
UV	Ultra-violet