Position papers

ACNFP Advice on the safety of synthetic cannabidiol (CBD) as a novel food for use in food supplements.

Reference Number RP07

Regulated Product Dossier Assessment

Assessment finalised: 29th of April 2024

Summary

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in January 2021 from Chanelle McCoy CBD Ltd. (“the applicant”) for the authorisation of synthetic cannabidiol (CBD) as a novel food. The novel food is a synthetic >98% pure form of CBD which is intended to be used as a food supplement for adults.

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.

To support the FSA and FSS in their evaluations 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 not putting consumers at a nutritional disadvantage.

The Committee concluded that the applicant had provided sufficient information to assure the novel food, a synthetic CBD as outlined in application RP07, was safe under the proposed conditions of use. 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.

1. Introduction

1. The ACNFP assessed the food safety risks of synthetic CBD 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 EFSA for full novel food applications is applicable and formed the basis and structure for the assessment (EFSA NDA Panel, 2021).

2. An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in January 2021 from Chanelle McCoy CBD Ltd. (“the applicant”) for the authorisation of synthetic cannabidiol (CBD) as a novel food. The novel food is a synthetic >98% pure form of CBD which is intended to be used as a food supplement for adults.

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 statement on a provisional ADI that can be applied to CBD ingredients containing 98% or more CBD. This, and wider evidence available in the public domain, was taken into account in reviewing the toxicological evidence for this application.

4. The final advice from the Committee was agreed at the 164th meeting, allowing the FSA and FSS to complete the risk assessment.

5. This document outlines the conclusions of the ACNFP on the safety of a synthetic >98% pure form CBD (as detailed in application RP07) as a novel food.

2. Assessment

2.1 Identity of novel food

6. The novel food is a synthetic >98% pure form of CBD which is a white to slightly beige crystalline powder of experimentally derived 100%± 2% purity. CBD is found in natural form in hemp as the (-)- trans isomer. As this CBD was synthesised chemically, chirality analysis of the compound by a commercially validated chiral HPLC method demonstrated a chiral purity of no less than 99.5% (-) - *trans* cannabidiol. Information to support stereoselective synthesis, and characterisation, was provided for six batches of the novel food.

7. CBD in this application is characterised by the chemical formula: C21H30O2; molecular mass: 314.46 g/mol; CAS number: 13956-29-1; isomer: (-)-*trans*-cannabidiol; 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 of its identity was provided by Infrared (IR) spectroscopy, ^{1}H Nuclear Magnetic Resonance (NMR) spectroscopy, mass spectrometry, and Ultraviolet visualisation (UV-Vis).

2.2 Production Process

9. The synthetic >98% pure form of CBD is manufactured using a stereoselective multi-step process under controlled conditions.

10. Certificates of analysis for raw starting materials used in the chemical synthesis were provided to demonstrate the effectiveness of the controls at this point in the process.

11. This process begins with olivetol and menthadienol as the primary starting materials, which undergo mixing, filtration, and distillation steps with catalysts present, resulting in the formation of the desired synthetic >98% pure CBD form.

12. For optional purification steps for commercial purposes, the crude final CBD ingredient is washed and separated several times using various processing aids.

13. The ACNFP considered whether the use of solvents as processing aids left any residues that needed to be flagged to risk managers. Comparison was made to residue limits for other consumed products as detailed in Table 1. Residues of solvents have been 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
Dichloromethane	Guidance on residues in Pharmaceutical products sets a Permissible Daily Exposure of 6.0 mg/day or at a concentration of 600 ppm[1] Permitted extraction solvent residue on coffee at 2mg/kg and 5 mg/kg in tea[2]	600 mg/kg CBD
Methanol	Guidance on residues in pharmaceutical products sets Permissible Daily Exposure of 30.0 mg/day or a concentration of 3000 ppm.[3] Extraction solvent residue maximum level of 10mg/kg product for all food uses[2].	3000 mg/kg CBD
Isopropanol	Extraction solvent residue maximum level of 10 mg/kg[2] ADI of 2.4 mg/kg bw as acceptable previous cargoes for edible fats and oils.[4]	5000 mg/kg CBD
n- heptane	Used as an extraction solvent, but only in accordance with good manufacturing practices, which should result in minimal residue[4]	5000mg/kg CBD

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

[2] Directive 2009/32/EC of the European Parliament and of the Council of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients

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

4 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

14. The evidence presented (see Table 2 below) on composition shows the residues of solvents in the product were consistently below the level set in the specification. 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 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 six independent batches of the novel food demonstrated that the CBD content was being produced consistently (Table 2).

Table 2: Compositional analysis of representative batches of CBD

Parameter	**Method of Analysis**	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch**
Identity and Composition						
Appearance	Visual	White crystalline powder	White crystalline powder	Almost white crystalline powder	White to slightly beige crystalline powder	White slightl beige crysta powde
Identification by IR	USP 197	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corres to refe

Identification by HPLC	In house method	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corres to refe
Water content (%)	USP 921	≤0.05	≤0.05	≤0.05	0.0	0.2
Residue on ignition (%)	USP 281	≤0.05	≤0.05	≤0.05	0.1	0.1
Specific optical rotation (degrees)	USP 781	-128	-130	-132	-129	-129
CBD (%)	HPLC (in house method)	99.4	99.8	99.9	100.5	100.7
Olivetol content (%)	HPLC (in house method)	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
4-monobromo-cannabidiol (%)	HPLC (in house method)	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
Delta-9-tetrahydrocannabidiol (%)	HPLC (in house method)	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02
Individual unspecified impurities (%)	HPLC (in house method)	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
Total impurities (%)	HPLC (in house method)	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05

Residues (mg/kg of CBD)						
Methanol	GC (in house method)	≤300	≤300	≤300	NM	NM
n-heptane	GC (in house method)	≤500	≤500	≤500	≤500	≤500
Dichloromethane	GC (in house method)	≤60	≤60	≤60	≤60	≤60
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

GC = Gas chromatography; HPLC = high-performance liquid chromatography; IR = infrared spectroscopy; NM = not measured; USP = United States Pharmacopeia .

17. CBD content is consistently above 98% pure with negligible amounts of starting materials detected across the six 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. As a result, the robustness, accuracy and precision of the methods have been considered in interpreting the data on THC and were considered appropriate in this case.

19. Delta-9-tetrahydrocannabidiol (THC), as a potential contaminant in the novel food, was detected at levels at or below 0.02 mg/kg CBD in all six batches tested.

20. 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 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 THC as a contaminant in milk and meat (EFSA,2015). The point of departure was a LOAEL (Lowest Observed Effect Level) of 0.036mg/kg/bw/day from the most sensitive individuals and the lowest dose tested in the human clinical studies reviewed.

21. Uncertainty factors, including a factor of 3 to extrapolate from LOAEL to a NOAEL (No Observed Adverse Effect Level) were applied to the LOAEL identified. This 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 a total uncertainty factor of 30. The factor of 30 applied to the 0.036mg/kg/bw/day LOAEL results in a level of 1µg /kg bw/day that would be represent a safe upper intake for consumed THC as a contaminant in food. This was identified an acute reference dose (ARfD) (EFSA, 2015)

22. 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 have 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 not data to verify this assumption, but if setting limits the dataset is the best available.

23. The levels of THC in the novel food once adjusted to take into account of the proposed uses - 10mg of CBD being consumed a day, were below the ARfD identified by EFSA of 1µg /kg bw/day or 70µg/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.

24. To ensure 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.

25. Analytical data, presented as the mean of three independent batches of the novel food, demonstrated that heavy metals where detected were present in very low levels and were below established UK regulatory limits where applicable (arsenic, cadmium, mercury and lead) (Table 3).

Table 3: The content of heavy metals, minerals and trace elements in the novel food

Parameter (mg/kg)	Maximum concentration measured (mg/kg)
Arsenic	≤0.1
Cadmium	≤0.1
Mercury	≤0.1
Lead	≤0.1
Cobalt	≤0.1
Nickel	0.2
Vanadium	≤0.1
Silver	≤0.1
Gold	≤0.2
Iridium	≤0.1
Osmium	≤0.7
Palladium	≤0.1

Platinum	≤0.1
Rhodium	≤0.1
Ruthenium	≤0.1
Selenium	≤0.1
Thallium	≤0.1
Barium	≤1
Chromium (3)	0.1
Copper	0.1
Lithium	≤0.1
Molybdenum	≤0.4
Antimony	≤0.1
Tin	≤0.1

26. Analytical data concerning the microbiological content from three independent batches of the novel food were reported (Table 4). The process in manufacturing this novel food uses extreme high and low temperatures, harsh pH conditions and alcohol solvents. Full microbial risk assessment as per USP 61 and USP 62 confirm that the novel food does not raise a safety concern and consistently meets the proposed microbial specification levels.

Table 4: The microbiological analysis of the novel food

Parameter	Batch 1	Batch 2	Batch 3
Total aerobic microbial plate count	100 CFU/g	100 CFU/g	100 CFU/g
Total yeast and mould plate count	100 CFU/g	100 CFU/g	100 CFU/g

27. Additionally, water activity as measured in aw values, of three representative samples of the novel food was measured as per USP 1112. The results further demonstrate that microbial growth in the CBD novel food is unlikely at the low aw values (below 0.6) for the final ingredient (Table 5). Therefore, microbial analysis is not a required parameter for inclusion in the specification.

Table 5: Water activity analysis

Batch	Result aw
1	0.40
2	0.40
3	0.27
Average	**0.36**

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

2.4 Stability

29. The stability of the synthetic CBD was assessed under real-time conditions (25oC and 60% relative humidity) and under refrigerated conditions (5oC) in 3 batches for 3 months, in a further 3 batches for 6 months and another 3 batches for 9 months. Results showed that the novel food meets the specification criteria for CBD content, and no changes in appearance, water content and impurity levels are seen over these time periods. The THC content was also tested using

HPLC and remained consistently below 0.05% w/w across the time period which is below the 0.10%w/w in the specification.

30. The stability of the synthetic CBD was assessed under accelerated conditions (40oC and 75% relative humidity) in six batches over a maximum period of 9 months. Results confirmed that the novel food meets the specification criteria for CBD content and no changes in appearance, water content and impurity levels are seen over these time periods over this time period.

31. The data provided supports the stability of the novel food for a period of at least 9 months.

2.5 Specification

32. The specification parameters reported in Table 6 were assessed using internationally recognised methods or determined using internally developed and validated methods. The data in Table 2 demonstrates the novel food can be produced consistently to the proposed specification.

Table 6: Specification of the novel food

Description		
Cannabidiol is a white to slightly beige powder produced by chemical synthesis		
Parameter	**Specification**	**Method**
Appearance	White to slightly beige crystalline powder	Visual inspection
Identity	Complies	IR: USP 197 HPLC: in-house method
Water content (%)	≤0.5	USP 921

Residue on ignition (%)	≤0.2	USP 281
Specific optical rotation (degrees)	-140 to -122	USP 781
CBD (%)	97 to 102	HPLC: in house method
Olivetol content (%)	≤0.15	HPLC: in house method
4-monobromo-cannabidiol (%)	≤0.15	HPLC: in house method
Delta-9-tetrahydrocannabidiol (THC) (%)	≤0.10	HPLC: in house method
Individual unspecified impurities (%)	≤0.15	HPLC: in house method
Total impurities (%)	≤1.0	HPLC: in house method
Residual solvents (mg/kg CBD)		
Methanol	≤3000	GC: in house method
n-Heptane	≤5000	GC: in house method

Dichloromethane	≤600	GC: in house method
Triethylamine	≤5000	GC: in house method
Isopropanol	≤5000	GC: in house method
Isooctane	≤5000	GC: in house method

CBD = cannabidiol; GC = gas chromatography; HPLC = high-performance liquid chromatography; IR = infrared spectroscopy; USP = United States Pharmacopeia

33. Following discussion with the applicant it was agreed that information on microbiological and heavy metal limits did not need to be included in the specification to appropriately characterise the novel food. No specific recommendations were made to amend the specification. The ACNFP concluded the information provided is sufficient to meet the specification of CBD and appropriately characterises the novel food seeking authorisation.

2.6 History of Use

34. 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.

35. 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).

36. 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.

37. 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 in humans has not been determined.

38. It is noted that the doses of CBD 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 to be an adverse event for food might be weighed differently in the context of the clinical benefits in a medicinal study.

39. 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.

40. 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

41. The proposed use for the novel food is as a food supplement in the form of an oil sold as capsules and drops at the dose of 10mg per day of CBD. The intended use is food supplements as defined by UK legal requirements (The Food Supplements (England) Regulations 2003) as capsules, liquid or drops in dose form. A provisional acceptable daily intake (ADI) for the use of >98% pure form CBD has been established at 10 mg per day (October 2023) and discussed in the Toxicological information section.

Food Category	Maximum intake level of CBD from product use
Food Supplements (for adults) as defined in the Food Supplements (England) Regulations 2003 as capsules, liquids or drops intended for those 18 years of age or over.	10mg per day

42. It is noted that there are already many products available containing CBD. As such, the assessment has been made on the basis of identification of a maximum level of CBD that can be consumed per day per product. As such proposed uses will only be considered safe for all consumers within the assessment when below an intake maximum of 10mg of CBD per day.

43. 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 a provisional acceptable daily intake of 10mg per day for a healthy adult.

44. 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. 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.”

45. The food supplement products are to be labelled in accordance with the labelling requirements of Food Supplements (England) Regulations 2003as follows: Does not exceed the safe limit of 10 mg/day for a 70kg healthy adult. The novel food authorisation should also include the following: Not suitable for use under the age of 18. Not suitable for use during pregnancy or breastfeeding. If you are taking medication or have existing health conditions, please consult your doctor before using this product.

46. The ACNFP explored the potential for foreseeable misuse of the novel food. 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.

2.8 Absorption, Distribution, Metabolism and Excretion (ADME)

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

48. 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 and concluded with dose dependent peak plasma concentrations of CBD and area under the curve results indicating minimal accumulation (Miller et al., 2018).

49. 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).

50. 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. 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).

51. Accumulation of CBD in plasma of up to 2-fold has been reported when steady state levels are compared with a single dose (such as in Taylor et al., 2018). Additionally, 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).

52. The pharmacokinetics of CBD (24 studies) have also been systematically reviewed by Millar et al., 2018., 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 synthetic 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 h, with a half-life between 1 and 3 hours. Given the intended use of this synthetic 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.

53. Based on the information on ADME it is noted that, the bioavailability of CBD when consumed orally is typically low, but can be affected by food matrix. It was noted that the potential for CBD to accumulate in the body has not been examined based on the data supplied. This provides context for interpreting the toxicological data. This also suggests the food context for the novel ingredient could impact whether the CBD present in the ingredient is more or less bioavailable. This has been taken into account in considering the assessment factors to account for uncertainty in setting the provisional ADI.

2.9 Nutritional information

54. The ACNFP sought clarification of the potential for the presence of antinutritional factors from the preparation. As the product is chemically derived from a well-defined synthetic process and characterisation indicated high CBD purity, no antinutritional factors were expected to be present. Information on the composition has confirmed that there is no presence of other components that would impact the digestion or absorption of nutrients from the diet.

55. 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

56. 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 below.

2.10.1 Genotoxicity

57. 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.

58. The in vitro bacterial reverse mutation test [(Gijsbrechts, 2020 (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 [(de Jong, 2020 (unpublished)] demonstrated that cannabidiol was non-clastogenic and non-aneugenic in the absence and presence of metabolic activation.

59. The results from these in vitro studies support the conclusion that the novel food (>98% pure CBD) is not genotoxic. This is consistent with the view of the Committee on Mutagenicity in reviewing CBD generically from evidence available in the public domain (Committee on Mutagenicity; MUT/MIN/2020/1, 2020).

2.10.2 Sub-chronic toxicological study

60. The 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.

61. A weight of evidence approach has allowed the Subgroup to identify a provisional ADI for CBD ingredients, of >98% purity, of 0.15mg/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.

2.10.3 Sub-chronic data supplied for this application

62. This applicant provided a Repeated Dose 90-Day Oral Toxicity Study in Rodents ([McGeoghie, 2020 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 rats which were dosed with 0 (control – corn oil), 15, 36 or 72 mg/kg bw/day CBD once per day by oral gavage at a dose volume of 4mL/ kg / body weight .

63. Review of the study supported the conclusion that it was of sufficient quality to support the safety of the novel food. The findings of the study were consistent with those considered in the development of the provisional ADI . It was, therefore, considered scientifically appropriate to apply the provisional ADI of 0.15mg/kg bw/day or 10mg/day as identified in the joint statement of the ACNFP and COT on >98% pure forms of CBD.

2.11 Allergenicity

64. This synthetic CBD comprises >98% pure CBD and the production process for CBD does not introduce any risk of allergenic potential. CBD as a chemical entity, suggests the potential for IgE mediated food allergy is unlikely.

65. The assessment considered whether the remaining 2% of the novel food 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 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. Suggesting the potential to elicit reactions in those sensitive to those foods is unlikely.

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

3. Discussion

67. The novel food is a synthetic CBD containing 100% ± 2% CBD (a Group A CBD of >98% purity), chemically produced using a multi-step manufacturing process.

68. This synthetic CBD is intended to be used a food supplement for adults as an oil or as an oil in capsules at a dose of 10mg a day; it is not intended to replace any food.

69. 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 novel foods containing 98% CBD or above, such as the novel food discussed in this assessment.

70. 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 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, which is applied here for this CBD isolateACNFP & COT on establishing provisional ADI for pure form CBD in foods | Advisory Committee on Novel Foods and Processes

" href="#">(footnote).

71. 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 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.

72. 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.

73. The maximum safe exposure for healthy adults of 70kg as identified in the provisional ADI is 10mg per day. If the inclusion level of this CBD isolate leads to an intake per individual serving of each product type of 10 mg/day, only one product type per day should be consumed to ensure the provisional ADI is not exceeded. Multiple intakes of products containing CBD on the same day should be avoided to support minimising exposure to below the provisional ADI.

4. Conclusions

74. The ACNFP have undertaken a review of this synthetic CBD 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.

75. These conclusions were based on the information in the novel food dossier submitted by the applicant plus the supplementary information from a wider

review of CBD and cannabinoids and could not have been reached without the following data claimed as proprietary by the applicant:

- annexes to the dossier which relate to the identity of the novel food, the production process, stability, methods of analysis, particle size analysis and toxicology.
- *in vitro* bacterial reverse mutation test [(Gijsbrechts, 2020 (unpublished)], *in vitro* mammalian cell micronucleus test [(de Jong, 2020 (unpublished)] and 90-day repeat dose feeding study ([McGeoghie, 2020 (unpublished)].

76. 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 Catharina Edwards, Professor Susan Fairweather-Tait, 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, Professor Clare Mills, Dr Antonio Peña-Fernández, Dr Lesley Stanley, Professor Hans Verhagen, Dr Maureen Wakefield, and Professor Bruce Whitelaw.

77. 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 Committee 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
ARfD	Acute Reference Dose
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 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
IR	Infra-red
LOAEL	Lowest Observable Adverse Effect Level
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

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