REGULATED PRODUCTS SAFETY ASSESSMENT

Safety Assessment on Cannabidiol (CBD) Used as a Novel Food for Use in Food supplements. (RP11)

Food Standards Agency[1], Food Standards Scotland[2]

[1] Regulated Products Risk Assessment, Food Standards Agency, UK, [2] Risk Assessment, Food Standards Scotland, UK

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FSA Research and Evidence

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in January 2021 from BSPG Laboratories Limited. ("the applicant") for the authorisation of cannabidiol (CBD) isolate as a novel food.

The novel food is a ≥98% pure form 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.

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% or greater CBD to form part of the evidence for this assessment. For CBD a provisional 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 Advisory Committee on Novel Foods and Processes (ACNFP) reviewed the 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 FSA and FSS concluded, based on the advice of the ACNFP, that the applicant had provided sufficient information to assure the novel food, CBD isolate, was safe under the proposed conditions of use. The anticipated intake levels and the proposed use in food supplements was not considered to be nutritionally disadvantageous.

This safety assessment represents the opinions of the FSA and FSS.

This is a joint FSA and FSS publication.

1. Introduction

FSA and FSS have undertaken safety assessments for CBD isolate under the novel foods legislation, assimilated Regulation (EU) 2015/2283. To support the safety assessment, the ACNFP provided the advice outlined in this opinion to the FSA and FSS.

The evaluation by the ACNFP assessed the food safety risks of the novel food and its production, in line with Article 7 of assimilated Commission Implementing Regulation (EU) 2017/2469. The regulatory framework and the technical guidance put in place by the European Food Safety Agency (EFSA) for full novel food applications is used as the basis and structure for the assessment (EFSA NDA Panel, 2016).

An application was submitted to the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in January 2021 from BSPG Laboratories Limited ("the applicant") for the authorisation of cannabidiol (CBD) isolate as a novel food. The novel food is a ≥98% pure form 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.

The final advice from the ACNFP was agreed at the 167th meeting, allowing the FSA and FSS to complete the risk assessment.

The document outlines the conclusions of the FSA and FSS on the safety of a ≥98% pure form CBD isolate (as detailed in application RP11) as a novel food.

2. Assessment

2.1. Identity of the novel food

The novel food is a cannabidiol (CBD) isolate in the form of a white to off-white crystalline powder of purity equal to or greater than 98.0%. Information to support this characterisation was provided for five batches of the novel food.

CBD is characterised by the chemical formula: $C_{21}H_{30}O_2$; 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

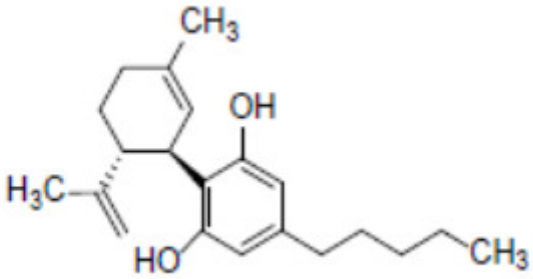

Diagram 1. The molecular structure of CBD

Confirmation of its identity and purity was provided by nuclear magnetic resonance spectroscopy (NMR), high performance liquid chromatography – ultraviolet (HPLC-UV), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier-transform infrared spectroscopy (FTIR), mass spectrometry (MS), X-ray diffraction (XRD) and energy dispersive X-ray (EDX) analysis.

2.2. Production Process

The CBD isolate is manufactured from industrial hemp using a multi-step extraction process under controlled conditions.

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.

The industrial hemp is first tested to ensure it meets all internal specifications for moisture content and THC content. It is also visually inspected for the absence of weeds, sludge, and debris. Manufacturing begins with dried hemp flowers and leaves which undergo ethanolic extraction followed by washing, filtration and crystallisation, to produce the final, highly pure, ingredient.

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
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].	NA (≤ 51 mg/kg LOD)
n-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. 50 mg per day or less (5000 ppm) would be acceptable without justification[1].	< 250 mg/kg CBD
Acetone	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 mg/ kg CBD

NA= not applicable; LOD= limit of detection

[1] ICH guideline Q3C (R8) on impurities: guideline for residual solvents

The evidence presented (see Table 7 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.

A Hazards Analysis and Critical Control Points (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

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.

Table 2 presents data on the physiochemical properties of five independent batches of isolated CBD. The data presented in Table 3 indicates CBD content is consistently above 98% purity with negligible amounts of starting materials detected across the five representative batches.

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.

Analytical data concerning the microbiological content from nine independent batches of the novel food were reported (Table 4). The process in manufacturing this novel food uses several alcohol-based solvents, high temperature steps, and drying, which may mitigate the proliferation of microbes within the final product. The microbiological data presented confirm that the novel food does not raise a safety concern and consistently meets the proposed microbial specification levels.

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.

It is expected that novel food products comply with the legal requirements for heavy metal contaminants in food. Analytical data, presented for one replicate each from 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).

Results from the residual solvent and pesticide 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 and pesticides within the final product.

2.4. THC as a Potential Contaminant in the Novel Food

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.

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

Parameter	Method of Analysis	Specification	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Colour and Appearance	Visual	White to off- white crystalline powder free of particulates	Conforms	Conforms	Conforms	Conforms	Conforms
CBD Identification	FTIR HPLC	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corresponds to reference	Corresponds to reference

FTIR = Fourier-transform infrared spectroscopy; HPLC = High performance liquid chromatography

Table 3. Cannabinoid analysis as % weight for weight of five independent representative batches of cannabidiol (CBD) isolate

Parameter	Method of Analysis	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
CBD content (% w/w)	HPLC	98.0-102.0	98.7	98.5	99.2	98.5	99.1
Delta-9-THCA (% w/w)	LC-MS	< 0.01	ND	ND	ND	ND	ND
Delta-8-THC (% w/w)	LC-MS	< 0.01	ND	ND	ND	ND	ND
Delta-9-THC (% w/w)	LC-MS	< 0.01	ND	ND	ND	ND	ND
THCV (% w/w)	LC-MS	< 0.01	ND	ND	ND	ND	ND
CBDA (% w/w)	LC-MS	< 0.01	ND	ND	ND	ND	ND
CBN (% w/w)	LC-MS	< 0.0.1	ND	ND	ND	ND	ND
CBG (% w/w)	LC-MS	< 0.01	ND	ND	ND	ND	ND
Butyl-CBD (% w/w)	LC-MS	NA	0.057	0.05	0.053	0.054	0.054
CBDV (% w/w)	LC-MS	< 0.01	< 0.01	< 0.01	0.013	0.011	0.011
Total Impurities	----------	< 0.5	0.057	0.05	0.066	0.066	0.065

LOQ = Limit of quantification; LC-MS = liquid chromatography–mass spectrometry; ND = not detected

Table 4. The microbiological analysis of the novel food

Parameter	Specification	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9	Method of Analysis
Total aerobic microbial count (CFU/g)	≤ 10^3	≤ 10^2	≤ 10^2	≤ 10^2	≤ 10^2	≤ 10^2	≤ 10^2	≤ 10^2	≤ 10^2	≤ 10^3	Ph.Eur.5.1.4
Total combined yeasts and mould count (CFU/g)	≤ 10^2	≤ 10^1	≤ 10^1	≤ 10^1	≤ 10^1	≤ 10^1	≤ 10^1	≤ 10^1	≤ 10^1	≤ 10^1	Ph.Eur.5.1.4
Escherichia coli (*E. coli*) (/1 g)	Absent	ND	ND	ND	ND	ND	ND	ND	ND	ND	Ph.Eur.5.1.4

CFU = colony forming unit; ND = not detected; NM = not measured; Ph. Eur. = European Pharmacopeia.

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

Parameter	Method of Analysis	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Mycotoxins (B1, AFB1, µg/kg)	BA-TM-10#	≤ 0.1	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Mycotoxins (B2, AFB2, µg/kg)	BA-TM-10#	≤ 0.1	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Mycotoxins (G1, AFG1, µg/kg)	BA-TM-10#	≤ 0.1	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Mycotoxins (G2, AFG2, µg/kg)	BA-TM-10#	≤ 0.1	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Total Mycotoxins (µg/kg)	BA-TM-10#	≤ 4.0	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ

= In-house UKAS accredited method for the analysis of B1, B2, G1 and G2 are determined using immunoaffinity clean-up and high-performance liquid chromatography with fluorescence detection.

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

Parameter	EU Limits[1] (µg/kg)	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Arsenic	200	ND	ND	ND	ND	ND
Cadmium	1000	0.54	0.44	0.34	0.56	0.25
Lead	3000	2.6	1.1	1.3	0.039	0.16
Mercury	100	ND	ND	ND	ND	ND

ND = not detected

[1]= Maximum levels according to Commission Regulation (EC) No. 1881/2006: for arsenic [non-parboiled milled rice (polished or white rice)], cadmium (food supplements), lead (food supplements), and mercury (food supplements)

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

Parameter	Method of Analysis	LOQ	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Residual Solvent- Ethanol (mg/kg)	HS-GC	51	< 51	< 51	< 51	< 51	< 51
Pesticides	LC-MS/MS and GC-MS/MS (EN-15662:2008)*	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

HS = Headspace; GC = Gas chromatography; MS/MS = tandem mass spectrometry

*= Procedure was developed in-house, based on EN-15662:2008 Foods of plant origin – Determination of pesticide residues using GC-MS and/or LC-MS/MS following acetonitrile extraction/ partitioning and cleanup by dispersive SPE – QuEChERS method.

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).

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

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 (EFSA, 2015). The Subgroup commented that there were no data to verify this assumption, but if setting limits the dataset is the best available.

The analysis for delta-9-tetrahydrocannabidiol as a potential contaminant in the novel food was declared as [not detected] in any of the five batches tested (Table 3), with a limit of quantification of 0.01% (w/w).

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.

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.

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

2.5. Stability

The stability of the novel food was assessed in real-time under ambient (25°C and 60% relative humidity) and intermediate (30°C and 60% relative humidity) conditions in three batches for 36 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 stability of the CBD isolate was assessed under accelerated conditions (40 ^{o}C and 75% relative humidity) in three batches for 6 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. The THC content was also tested and no significant changes in the levels of THC were observed.

The data provided supports the stability of CBD isolate for a period of at least 36 months.

2.6. Specification

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

Table 8. Specification of the novel food

Description		
Cannabidiol is a white to off-white crystalline powder free of particulates produced by a multistep extraction process		
Parameter	**Specification**	**Method**
Appearance	White to off-white crystalline powder free of particulates	Organoleptic
Identity	Positive match to reference spectrum; Retention time of 9 minutes	FTIR: Ph. Eur. 2.2.24 HPLC: Ph. Eur. 2.2.29
Specific Optical Rotation (°)	-129.5 to -135.0	Ph.Eur.2.2.27
Melting Point (°C)	65 - 69	Ph.Eur.2.2.60
Sulphated Ash (%)	< 0.1	Ph.Eur.2.4.14
Water Content (%)	< 0.5	Ph.Eur.2.5.32
Purity	----------	----------
CBD (% w/w)	98.0 to 102.0	Ph.Eur.2.2.29
THC (%)	< 0.01	Ph.Eur.2.2.29
Unknown impurities (%)	< 0.01	Ph.Eur.2.2.29
Total impurities (%)	< 0.5	Ph.Eur.2.2.29
Residual solvents	----------	----------
n-Heptane (mg/kg)	< 250	Ph.Eur.2.2.28
Acetone (mg/kg)	< 5000	Ph.Eur. 2.2.28

Description		
Dichloromethane (mg/kg)	< 600	Ph.Eur.2.2.28
Microbiological criteria	----------	----------
Total aerobic microbial count (CFU/g)	≤ 10^3	Ph.Eur.5.1.4
Total combined yeasts and mould count (CFU/g)	≤ 10^2	Ph.Eur.5.1.4
Escherichia coli (/1 g)	Absent	Ph.Eur.5.1.4

CBD = Cannabidiol; CFU = colony forming units; FTIR = Fourier transform infrared spectroscopy; HPLC = high-performance liquid chromatography; Ph. Eur. = European Pharmacopeia; THC= tetrahydrocannabinol.

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

2.7. History of Use

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.

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 and thyroid, and potential impacts on reproductive organs. Also reported are behavioural effects such as somnolence (sleepiness) (COT, 2020).

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.

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, of CBD represented a pragmatic upper level of intake above which there would be clear concerns about safety, until further data are available.

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.

Within the literature, further human studies utilising chemically derived CBD provides further evidence of a history of synthetic CBD use (Izgelov et al., 2020; Klotz et al., 2019; Stero Biotechs Ltd., 2020; 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.

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.

2.8. Proposed Use and Anticipated Intake

The intended use is food supplements as defined by GB legal requirements (The Food Supplements (England, Scotland and Wales) Regulations 2003) in a range of forms and a range of food and beverages.

The applicant initially proposed a use level of 35 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). 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 intake level from product use
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, 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 mg per day

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 below a maximum of 10 mg of CBD per day from all sources.

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 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.

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.

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).

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.

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.

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 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 or during pregnancy or breastfeeding. Information on its suitability for consumers taking medication or who have existing health conditions should also be included.

2.9. Absorption, Distribution, Metabolism and Excretion (ADME)

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.

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 & McArdle, 2004). The low systemic availability was demonstrated by Martin-Santos et al., 2012 and further supported by a literature search which identified the pharmacokinetics of CBD (Millar et al., 2018). The COT statement on CBD of 2020 noted that although CBD has low fasting bioavailability (<10%), consumption with food could increase CBD uptake by, for example, 5-fold if eaten with a high fat meal. As such the potential for matrix effects that impact bioavailability cannot be ruled out.

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).

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).

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).

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 (C_{max}) of 0.9 and 2.5 ng/ml. The time to maximum concentration (T_{max}) was approximately 1 hour, 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).

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 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 has not been examined based on the data supplied. This has been taken into account in considering the assessment factors to account for uncertainty in setting the provisional ADI.

2.10. Nutritional Information

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).

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.

The data on nutritional composition confirm 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.

2.11. Toxicological Information

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.

2.11.1. Genotoxicity

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 assimilated Regulation (EU) 2015/2283.

The *in vitro* bacterial reverse mutation test [(Grindey, 2020)] demonstrated that this CBD ingredient was non-mutagenic, in the absence or presence of metabolic activation. In addition, the *in vitro* mammalian cell micronucleus test demonstrated that CBD was non-clastogenic and non-aneugenic in the absence and presence of metabolic activation.

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 as a substance from evidence available in the public domain (Committee on Mutagenicity, 2020).

2.11.2. Sub-chronic toxicology study

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. This included data submitted to support individual novel food applications.

This applicant provided a 14-Day Oral Dose Range Finding Study in Rodents [(Hackford, 2021)] and a Repeated Dose 90-Day Oral Toxicity Study in Rodents [(Tilley, 2021)]. In the 14-day study, male and female rats in groups of 5 were dosed with 0 (vehicle-corn oil), 50, 75 and 100 mg/kg/day CBD by oral gavage at a dose volume of 4 mL/kg bw. It was found that CBD was well tolerated at all dose levels and these conclusions were used to select dose levels for the 90-day study.

The 90-day study was conducted under GLP conditions and to OECD Test Guideline 408. In this 90-day study, male and female rats were dosed once a day with 0 (corn oil), 15, 25, or 50 mg/kg bw/day CBD by oral gavage at a dose volume of 4 mL/kg bw. The control group (0 mg/kg bw/day) and high-dose group (50 mg/kg bw/day) both contained 15 male and female rats, and dose groups 15 and 25 mg/kg bw/day both contained 10 male and female rats. Of the control group and high-dose group, 5 males and females were allocated to the recovery period and retained not dosed for 28 days.

The applicant concluded a NOAEL of 50 mg/kg bw/day, the subgroup reviewed the data and concluded the effects seen at 25 mg/kg bw/day were minimal but not adverse, however the effects seen at 50 mg/kg body weight/day are potentially adverse. Therefore, a Point of Departure (POD) of 25 mg/kg was determined. Review of the study by the Subgroup supported the conclusion that it was of sufficient quality to support the safety of the novel food.

The applicant also provided a reproductive and developmental toxicity study (Blunt, 2021). This was performed on four groups of 10 male and 10 female rats, dosed by gavage at 0 (vehicle-corn oil), 15, 25 or 50 mg/kg bw/day CBD, using a dose volume of 4 mL/kg bw. It was noted that while this provides additional evidence to support the safety of the novel food it has not fully addressed the data gaps identified in the provisional ADI statement (ACNFP and COT, 2023).

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.

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.

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 suggesting a significant impact on the toxicology. The point of departure in the form of a NOAEL from the study submitted to support safety of this novel food once corrected for CBD content is consistent with the range of the points of departure used to develop the provisional ADI (ACNFP and COT, 2023). The NOAEL was also based on the same effect – impacts on the liver. It was, therefore, considered scientifically appropriate to apply the provisional ADI of 0.15 mg/kg bw/day or 10mg/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.

2.12. Allergenicity

This CBD isolate comprises >98% 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.

Given that CBD as a substance is not considered allergenic, the allergenicity assessment considered whether the other 2% 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. This suggests that the potential to elicit reactions in those sensitive to those foods is unlikely.

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

3. Discussion

The novel food is a CBD isolate ingredient from industrial hemp containing >98% CBD, produced using a multi-step manufacturing process.

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. A safety concern was raised regarding the multiple exposures to the novel food as an ingredient and the potential to exceed the provisional ADI identified for ≥98% CBD. The assessment in this application has been of food supplements.

In October 2023, the Joint ACNFP and COT subgroup identified a provisional acceptable daily intake (ADI) of 10 mg per day (0.15 mg/kg bw/day) for CBD products containing 98% CBD or above, such as the novel

food discussed in this assessment. A weight of evidence approach was used to arrive at a provisional ADI of 10 mg/day (0.15 mg/kg bw/day). The most sensitive human health effects, that this provisional ADI protects against, are seen consistently in the liver and thyroid in a number of studies using >98% pure CBD. This value also takes account of the lack of human-based long-term evidence and evidence regarding potentially vulnerable groups, which is applied here for this CBD isolate (ACNFP and COT, 2023).

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

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.

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

The FSA and FSS have undertaken the assessment of CBD isolate and both concluded that the novel food is safe under the proposed conditions of use and does not pose a safety risk to human health. The anticipated intake levels and the proposed use was not considered to be nutritionally disadvantageous.

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:

- 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 (Grindey, 2020), *in vitro* mammalian cell micronucleus test (Clare, 2021), 14-day dose range-finding study (Hackford, 2021), 90-day repeat dose feeding study (Tilley, 2021) and a reproduction/ developmental toxicity screening test in the rat (Blunt, 2021).

Abbreviations

Abbreviation	Definition
ACNFP	Advisory Committee on Novel Foods and Processes
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
AOAC	Association of Official Analytical Chemists
ARfD	Acute Reference Dose
a_w	Water activity
bw	Body weight
CAS	Chemical Abstracts Service
CBD	Cannabidiol
Cmax	Peak serum concentration
COT	Committee on Toxicity
CFU	Colony Forming Unit
DSC	Differential scanning calorimetry
EC	European Commission
EDA	Energy dispersive X-ray
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
FTIR	Fourier-Transform Infrared Spectroscopy
GC	Gas Chromatography
GLP	Good Laboratory Practice
HACCP	Hazards Analysis and Critical Control Points
HPLC	High Performance Liquid Chromatography
HS	Headspace
ICP-MS	Inductively coupled plasma mass spectrometry
LC-MS	Liquid chromatography-mass spectrometry
LOAEL	Lowest Observable Adverse Effect Level
LOD	Limit of Detection
LOQ	Limit of quantification

Abbreviation	Definition
MS	Mass Spectrometry
ND	Not Determined
NOEL	No Observed Effect Level
NM	Not measured
OECD	Organisation for Economic Co-operation and Development
Ph.Eur	European Pharmacopeia
TGA	Thermogravimetric analysis
Tmax	Time to maximum concentration
USP	United States Pharmacopeia
UV	Ultra-violet
XRD	X-ray diffraction

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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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