February 21, 2022

Dockets Management Branch

Food and Drug Administration

5630 Fishers Lane, Room 1061

Rockville, MD 20852

CITIZEN PETITION: CANNABIDIOL’S IMPROPER EXCLUSION FROM THE DEFINITION OF A DIETARY SUPPLEMENT UNDER THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT AND SPECIFIC ENFORCEMENT DISCRETION TO REVIEW PREMARKET NOTIFICATION OF CANNABIDIOL

Dear Sir/Madam:

The undersigned, on behalf of the Natural Products Association ("NPA")¹, submits this petition under 21 U.S.C. §321(ff) and 21 C.F.R. §10.30, among other provisions of law, to request that the Commissioner of Food and Drugs either determine: (1) that cannabidiol ("CBD") is not

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¹ Founded in 1936, the Natural Products Association ("NPA") is the nation’s largest and oldest nonprofit organization dedicated to the natural products industry. Natural products include a wide array of consumer goods that grow in popularity each year. These products include natural and organic foods, dietary supplements, pet foods, health and beauty products, “green” cleaning supplies and more. Generally, natural products are considered those formulated without artificial ingredients and that are minimally processed. NPA advocates for the right of consumers to have access to products that will maintain and improve their health, and for the right of retailers and suppliers to sell these products. NPA represents over 1,400 members, accounting for more than 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including foods, dietary supplements, and health/beauty aids. NPA unites a diverse membership, from the small health food stores to large dietary supplement manufacturers.

NPA played a key role in the passage of the Dietary Supplement Health and Education Act of 1994 ("DSHEA"), Pub. L. No. 103-417, 108 Stat. 4325. This important legislation struck a balance between the need for consumers to have access to and information about safe and effective dietary supplements while preserving the government’s interest in protecting the public from unsafe products and false and misleading claims. Currently, NPA advocates before Congress, the Food and Drug Administration ("FDA" or "Agency"), the Federal Trade Commission ("FTC"), and other federal and state agencies, legislatures, state attorneys’ general and courts.
excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3); or (2) that the Commissioner exercise enforcement discretion in a specific and selective manner to review the safety data of a CBD product consistent with 21 CFR Part 190.6. Alternately, the Agency may recommend to the Secretary of the Department of Health and Human Services ("HHS"), that the Agency promulgate a regulation, after notice and comment, establishing that CBD is lawful under the Food, Drug and Cosmetic Act (the “Act”).2

I. ACTION REQUESTED

For the following reasons, based on the facts provided herein, NPA respectfully requests that the Commissioner of Food and Drugs either: (1) determine that CBD is not excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B); or (2) that the Commissioner exercise enforcement discretion in a specific and selective manner over CBD products following a safety review of a notification on an individual dietary supplement product submitted consistent with 21 C.F.R. Part 190.6. Or, in the alternative, the Agency may recommend and support to the Secretary of HHS, that in his discretion he issue a regulation, after notice and comment, establishing that CBD is lawful under the Act.

More particularly, NPA requests that the Agency conclude and state that CBD is a lawful dietary ingredient and is not excluded from the definition of a dietary supplement under the relevant definitions of DSHEA. Should FDA conclude that CBD is not lawful and is excluded from the definition of a dietary supplement under DSHEA’s definitions, then the Agency should state that it will scientifically review, safety data related to CBD, including any safety data submitted as part of any premarket regulatory submission. To the extent that the Agency’s decisions to the foregoing are governed by overly rigorous safety data requirements—akin to those

applied to drug approvals—the Agency should alter those policies and only require safety data submissions that accord with the proper standards—i.e., a basis for concluding a reasonable expectation of safety—that is applied to safety determinations of dietary supplements and dietary ingredients.

II. STATEMENT OF GROUNDS

A. Background


Section 201(ff)(3)(B) of the Act, prohibits from the definition of a dietary supplement any article:

- that is approved under 21 U.S.C. §355 (section 505 of the Act); or
- authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public.


- verifiable, contemporaneous evidence documenting that the article or any other compound containing the article as its active moiety was marketed as a dietary supplement or as a food prior to the article’s authorization for investigation as a new drug under an Investigational New Drug (“IND”); or
- the Secretary, at the Secretary’s discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under the Act.

This section of the Act has come to be known in the industry as creating a “race to market” between those interested in investigating an article as a drug and others interested in marketing the
same article in a product labeled as a dietary supplement. This section of the Act purportedly is intended to preserve the financial and public health incentives to both bring dietary ingredients to market and to conduct research on new drugs.\(^3\)

NPA submits this Petition. As discussed further herein, cbdMD, Inc. ("cbdMD") has met with representatives from FDA to discuss portions of the issues presented herein. cbdMD, in addition to NPA, seeks answers and actions as requested in this Petition.

B. **Argument**

1. **FDA should cease its inequitable interpretation and application of 21 U.S.C. §321(ff)(3).**

In passing the Act, Congress charged the FDA to "protect the public health" by ensuring that "foods are safe, wholesome, sanitary, and properly labeled." 21 U.S.C. §393(b)(2)(A). In 1994, the Act was further amended with the Dietary Supplement Health and Education Act.\(^4\) DSHEA established dietary supplements as a new category of food products with unique standards that comprehensively cover safety, labeling, manufacturing and other related topics. DSHEA was introduced to counteract unnecessarily stringent federal intervention into the manufacturing, sale, and labeling of dietary supplements.\(^5\)

a. **The definition of “old dietary ingredients” includes ingredients like CBD that were marketed as dietary ingredients prior to passage of DSHEA.**

DSHEA established the definition of a dietary supplement under Section 201(ff) of the Act. Under this definition, a dietary supplement must contain at least one dietary ingredient, be swallowed, not be intended to replace a meal, and not contain an ingredient found to be excluded

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from the definition of a dietary supplement. DSHEA also established the definition of a "new dietary ingredient" ("NDI") under Section 413(d) of the Act to mean a dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994. The term "old dietary ingredient" has never been defined in a statute or regulation, but it is commonly defined as an ingredient that was marketed prior to DSHEA and would satisfy the definition of a dietary ingredient under DSHEA.\footnote{21 U.S.C. §321(ff); 21 U.S.C. §350b(d); and 21 U.S.C. §321(ff)(1).} There is no authoritative list of old dietary ingredients that were marketed in dietary supplements prior to October 15, 1994. Prior to DSHEA, there was no need for a responsible distributor to be concerned with the approval date of a drug, biologic, or when a new drug was authorized for investigation. For these reasons, records of dietary supplement sales and products were often not memorialized or cataloged prior to DSHEA. The Congressional Record that accompanied the passage of DSHEA provides insight. For example, the Senate Report published by the Committee on Labor and Human Resources, of which Senator Hatch was the chairman, stated:

On occasion, a substance that is properly included as a dietary ingredient in a dietary supplement (food) product may also function as an active ingredient in a drug product. There is nothing particularly surprising about this fact.

As an example, the dietary substance, L-carnitine may properly be used as an ingredient in a dietary supplement (as FDA itself has acknowledged), although it is also the active ingredient in a drug product that has been approved by FDA for a particular prescription-only usage. Similarly, the substance caffeine is a natural component of food products such as coffee and tea; it is used as an added ingredient in foods, including carbonated beverages, and it has only been approved by FDA as a drug.

It is clear from the language in the Report that both L-carnitine and caffeine were marketed as both dietary ingredients and approved drugs prior to the passage of DSHEA. It is also clear from the Report's language that Congress intended for these ingredients to continue to be marketed as
both drugs and dietary ingredients after the effective date of DSHEA, October 15, 1994. It is telling
that the report establishes Congress’s intention to allow unnecessarily hindered marketing of
dietary supplements without any analysis under, or even reference to, the “race to market”
paradigm of Section 201(ff)(3) of the Act as amended by DSHEA. This indicates that Congress
intended that articles that were marketed as both drugs and dietary ingredients prior to the effective
date of DSHEA could continue to be marked as such under Section 201(ff)(3).

b. Hemp-derived products were in the food supply prior to passage of
DSHEA and are not excluded by the Act.

FDA’s Draft Guidance *Dietary Supplements: New Dietary Ingredient Notifications and
Related Issues* published in August 2016 (herein “Draft Guidance”) and directs companies
intending to demonstrate that their ingredient was marketed prior to October 15, 1994, to provide
documentation that specifies the plant part from which the botanical dietary ingredient was
derived. For botanical extracts, the documentation should also specify the extract type. The United
States Pharmacopeia (“USP”) is an independent, nonprofit organization outside of the US
government that was founded to bring a national set of standards to the US by compiling quality
specifications used to confirm composition, identity, purity and strength of specified material for
use in medicines and food products. In 1848, Congress passed the Drug Importation Act, which
officially recognized the USP as setting standards for identity, purity and strength for the specified
material. The USP first documented the use of hemp-derived products with its entry, “*Extractum
Cannabis. Extract of Hemp*” which was listed as being an alcohol-based “extract of the dried tops
of Cannabis sativa—variety *Indica*” in 1850.7 The USP establishes the historical use of cannabis,
its extracts, and its components—including CBD. The inclusion of “*Extractum Cannabis. Extract

of Hemp” in the 1850 edition of the USP definitively meets the bar established by the Act for a company to demonstrate that an ingredient was marketed in a product prior to the passage of DSHEA because it shows that CBD was marketed as a dietary ingredient nearly 150 years before the passage of DSHEA. The evidence demonstrating CBD’s presence in the diet is widely available and irrefutable, so the Agency should easily determine that CBD is not excluded from DSHEA’s definition of dietary supplement/ingredient. Accordingly, the Agency could and should conclude that CBD is not excluded by the drug exclusion of Section 201(ff)(3) and state that CBD is a dietary ingredient as defined by DSHEA.

2. cbdMD has presented a dossier of data to the Agency demonstrating the safety of CBD and cbdMD stands ready, willing, and able to submit a full NDI submission should the Agency agree to earnestly review the data.

Although it is unnecessary for the Agency to consider CBD safety data because of CBD’s status as an old dietary ingredient, cbdMD studied CBD’s safety so that it could further demonstrate the untenability of the Agency’s historical treatment of this dietary ingredient and its corresponding safety data. cbdMD spent approximately $1,000,000.00 (USD) to prepare identity and safety data to answer all safety questions posed by the Agency, and the Agency has no proper justification to refuse review of cbdMD’s data or NDI submission under the faulty pretense that CBD is excluded from the definition of a dietary supplement under DSHEA, or by dodging the consideration of convincing safety data. Indeed, cbdMD conducted these studies with the well-known understanding that the CBD market has evolved faster than the related regulatory

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* There are ample records available demonstrating that CBD was marketed as a dietary ingredient prior to CBD’s approval as a drug or passage of DSHEA. However, as a general matter, it would be unworkable, inefficient, and unlikely to benefit consumers or public health to require companies to maintain records to demonstrate that such products were on the market prior to the passage of DSHEA. There is no basis in DSHEA or otherwise in the Act to institute such a requirement, and nothing specified herein should be construed to support such a requirement.
framework and seeks to provide safe products to an ever-growing market in a good-faith effort to promote public health. To this end, former Commissioner Hahn on March 5, 2020, stated:  

The marketplace for CBD-containing products is quickly evolving and it is critical that we work together with stakeholders and industry to develop high-quality data to close the knowledge gaps about the science, safety and quality of many of these products, as well as further evaluate any potential benefits outside of the one FDA-approved drug product to treat two rare, severe pediatric epilepsy disorders.

To address the questions and concerns we’ve already raised, we’re seeking reliable and high-quality data. This includes data on, among other things: the sedative effects of CBD; the impacts of long-term sustained or cumulative exposure to CBD; transdermal penetration and pharmacokinetics of CBD; the effect of different routes of CBD administration (e.g., oral, topical, inhaled) on its safety profile; the safety of CBD for use in pets and food-producing animals; and the processes by which “full spectrum” and “broad spectrum” hemp extracts are derived, what the content of such extracts is, and how these products may compare to CBD isolate products.

Given the importance of answering these questions, we’re exploring a number of ways to address the data gaps as quickly as possible. This includes encouraging, facilitating and initiating more research on CBD, providing venues for industry and researchers to share new data with the agency and identifying opportunities to further collaborate with our federal partners at Centers for Disease Control and Prevention, Substance Abuse and Mental Health Services Administration and National Institute on Drug Abuse on this important issue.

cbdMD has compiled a dossier of identity and safety data for submission as a novel food ingredient for the European Union, and for submission in support of a new dietary ingredient notification ("NDIN") to FDA.  

The United Kingdom has already reviewed this data and the European Union is on track to review it as well. cbdMD has presented this information to FDA as part of its preparations for the NDIN process. Yet cbdMD will be forced to submit its NDIN without the full scope of safety data it has compiled unless the Agency agrees to review the data and provide cbdMD, in the form of an NDIN response letter, with its determination of whether it

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10 Attached hereto as Exhibit A is a redacted copy of the NDI submission that cbdMD has prepared.
agrees or objects to it on its scientific merits and not on a broad policy statement on drug exclusion. After all, submitting cbdMD’s confidential data to the Agency without the guarantee that it will be reviewed and appropriately replied to does nothing other than expose cbdMD to the risk of disclosure of the data along with potential misrepresentations of the data without any benefit to cbdMD. cbdMD should not be forced to expose itself to this risk after spending approximately $1,000,000.00 (USD) to study CBD unless it will receive a substantive response from FDA. For this reason, this Petition requests that the Agency confirm that it will actually review and reply to cbdMD’s safety data in earnest before it is included with cbdMD’s NDIN. Without the pathway for the agency to review the safety data consistent with the statute the agency has effectively reversed the marketplace, providing an advantage to companies who will NEVER conduct the required safety studies, meet cGMP and meet other regulatory requirements.

cbdMD is a reputable member of industry that has taken significant steps to ensure and demonstrate that its products are safe consistent with scientific principles and the statute. cbdMD’s ingredients, including the one subject to the proposed NDIN, are produced under good manufacturing practice ("cGMP") conditions from the Cannabis sativa L. plant. That ingredient is of natural origin and entirely sourced from domestic farms. cbdMD’s CBD was fully characterized, including all chemical constituents, with the use of validated methods established by the Association of Agricultural Chemists ("AOAC") for quantification of sixteen cannabinoids. AOAC’s methods and validations are considered reliable and often used to establish standards for these types of analyses. AOAC’s methods and protocols were properly applied to cbdMD’s studied ingredient and demonstrate that cbdMD can ensure the identity of its ingredient,

\[\text{See https://www.aoac.org/about-aoac-international/}.\]
manufactures its product under the appropriate GMP's, and that cbdMD’s natural products are wholesome and safe at the marketed doses.

During cbdMD’s testing, five representative batches were screened for contaminants that may be present in hemp-derived products, including microbials, mycotoxins, residual solvents, pesticides, and heavy metals. The ingredient consistently and fully complies with established specifications. Accelerated and real-time stability testing were performed on the ingredient and on final finished product formats containing the ingredient to assess composition across the suggested life of the product. The composition was stable and within specifications for the proposed shelf life. In compiling its safety dossier on the ingredient, cbdMD commissioned a series of toxicological studies, including a 14-day dose-range finding study with pharmacokinetics, a 90-day subchronic study with recovery, and a combination of genotoxicity studies and reprotoxic assessments. The data demonstrates that the ingredient is not genotoxic and is reasonably expected to be safe over subacute and subchronic exposures at the proposed level of consumption to be included in the proposed NDIN.

FDA has already received several NDINs for CBD. These earlier notifications received letters indicating that, due to FDA’s position on CBD being excluded from the definition of a dietary supplement, the notifications would not receive a substantive review of the submitted identity or safety data. Two recent notifications received response letters with comments indicating that the evidence presented as the general history of use of the ingredient was too vague and did not provide an adequate description of the cannabis preparations (e.g., composition), serving levels, or frequency and durations of use for comparison relative to the proposed ingredient use in the NDIN. One of the notifications included toxicology data from a subchronic study performed on the ingredient but, according to the agency’s response letter, did not provide data to address the
Agency’s concerns related to hepatotoxicity and reproductive toxicity. cbdMD’s safety data contains substantial data that specifically addresses those endpoints and cannot be ignored under FDA’s prior rationales. Further, cbdMD has sold millions of products to consumers in the last few years and has never received an adverse event report from a consumer. cbdMD has thus conducted the robust testing that demonstrates that its products are reasonably expected to be safe and should allay any concern for the public health, thereby warranting that the Agency fulsomely review and respond to any data submitted by cbdMD concerning its CBD ingredient.

Clearly, cbdMD has done its due diligence to establish the safety of CBD through its extensive testing. However, that safety data can only benefit the public if it is reviewed and appropriately replied to in earnest by the Agency. And that data can only be reviewed and replied to if the Agency changes course from its present practice of refusing to provide a substantive review and reply of safety data of NDINs concerning CBD—even after the Agency has specifically requested such data. Not only does this refusal deny a regulatory path to market for safe CBD products made by reputable companies, but it also incentivizes bad actors to avoid following the rules because they know that FDA currently has no intention of acknowledging CBD under an NDIN or taking action to remove otherwise unsafe products from the market. The current status of CBD regulation by FDA is antithetical to the Agency’s mission to promote public health. Thus, the Agency should state that it will scientifically review, and then substantively reply to the CBD safety data that has been submitted thus far along with the data that cbdMD will submit once the Agency has agreed to review and appropriately reply to it.

3. FDA is improperly applying drug approval requirements to CBD by requiring safety data in a manner not in accord with the Act.

A review of the previously submitted NDINs demonstrates that the safety data requirements imposed by the Agency relative to CBD differ from what has been required for other
supplements and is akin the requirement for drug approval. cbdMD presented safety data for CBD during its pre-NDI meeting to demonstrate CBD’s safety—data that was well-received by the Agency’s representatives in attendance. But an NDIN need only present threshold evidence showing that the dietary ingredient is reasonably expected to be safe under the supplement’s labeled conditions of use under 21 U.S.C. §350b(a)(2). The standard for showing that a new dietary ingredient is reasonably expected to be safe is far less rigorous than the safety standards applied to drug approval submissions. While cbdMD’s CBD safety data exceeds the criteria that should be applied to NDINs, it is not at all clear if it will satisfy the Agency’s moving-target requirements for demonstrating safety of hemp-derived products. The Agency has been improperly applying drug approval rigor to its safety reviews of CBD as a dietary ingredient, demonstrating its arbitrary and capricious application of the Act. FDA should cease to require safety data submissions that exceed what is required by the Act for articles marketed as dietary ingredients or dietary supplements.

cbdMD is a natural product company. Natural products are used safely every day as both foods and drugs. The conditions of use in cbdMD’s submission are not suggesting that a consumer should ingest a drug-level dose of CBD. In fact, the level of CBD in their dietary supplement (at 50 mg/day) is at approximately 10-30 times lower than the doses for approved CBD drugs.\footnote{https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf} Despite the striking differences in dose, there is a persistent misconception that hemp-derived CBD-containing dietary supplements should be treated like drugs. When statements that “cannabis-containing consumer products have not undergone the type of drug safety and efficacy testing that was performed with Epidiolex or Marinol.”\footnote{https://pubmed.ncbi.nlm.nih.gov/33175977/} are made in public forums, it implies that
there is a similar standard for safety and efficacy testing applied to dietary supplements and drugs. This is not the case because dietary ingredients and dietary supplements are not subjected to this same rigor as explained by the plain terms of DSHEA. However, CBD and hemp products are being subjected to a different standard than other dietary ingredients or supplements. In fact, supplements containing CBD are being subjected to the standard applied to drugs, which has no basis in the Act, Congressional intent, or formal rulemaking. Nevertheless, despite there being no requirement that cbdMD submit safety and identity data to the same level of rigor as drugs, cbdMD has gone to great lengths to provide data beyond what is required for a NDIN and approaching what is expected for the preclinical study of drug candidates.

As noted above, we are requesting that FDA review cbdMD’s safety data and respond substantively in an NDIN respond letter in earnest on its specific scientific merits. However, even if the Agency refuses to do so, it should acknowledge that FDA’s overly rigorous safety data requirements for CBD have no basis in the Act. DSHEA was introduced to counteract unnecessarily stringent federal intervention into the manufacturing, sale, and labeling of dietary supplements (i.e. treating dietary ingredients as unapproved food additives or drugs requiring premarket approval), and CBD should not be required to adhere to drug-like stringency based solely on ill-conceived preconceptions about CBD.\textsuperscript{14} Indeed, cbdMD does not solely seek a broad policy statement from the agency on CBD’s universal qualification as a lawful dietary ingredient not excluded from the definition of a dietary supplement — as the Agency has avoided a broad policy conclusion on CBD due to its stated belief that more universal safety data is needed. But, nothing precludes the Agency from reviewing cbdMD’s submission on its merits and replying with a formal decision because the Agency has NOT to date stated it could not review a single

supplement product on its scientific merits consistent with statutory and regulatory authorities that mandate the review of a specific product or ingredient. Therefore, we are asking the Agency to follow the intent of Congress as stipulated in DSHEA, and review, consider, and issue a formal decision concerning cbdMD’s safety and identify data utilizing the proper analysis applied to dietary supplements.

C. Conclusion

We ask the Agency to properly conclude that CBD is an old dietary ingredient and, as such, does not fall under the drug exclusion provision of DSHEA. In the alternative, given the awareness of the Agency’s reluctance to issue a broad policy statement, we request that the Agency agree to scientifically review, and substantively reply concerning the safety data that cbdMD has compiled in accordance with the Agency’s authorities and the regulations for dietary supplement products, suspending their desire to invoke the drug exclusion clause, to conduct an actual review of the science on a case-by-case basis. cbdMD has presented FDA with the information that they continue to say FDA lacks and are asking them to review it in earnest. Despite repeated requests from multiple stakeholders and safety data presented in a number of forums, FDA continues to point to a lack of safety data, which cbdMD has presented. Now, we ask that FDA review the available safety data one notification at a time, the way they would for any other new dietary ingredient.

As former FDA Commissioner Dr. Hahn noted, it would be a “fool’s errand” to try to remove CBD from the marketplace, and that the Agency will possibly issue a regulation to create a pathway to market for CBD and possibly other cannabinoids in dietary supplements and conventional foods in the immediate future. It would be in the best interest of all stakeholders that

FDA actively use all tools at their disposal to meet their mandate of protecting and promoting the public health in the interim, such as those provided above. If the Agency is overly concerned about an omnibus policy or regulation on CBD, there is nothing in the Act restricting the agency from reviewing the safety data of an ingredient and/or supplement on a case-by-case, product-by-product basis. In fact, which is the very structure of the Act and the Agency's mandate establishing the requirement to review an NDI or a supplement containing a new ingredient through that specific lens.

NPA respectfully requests that the Commissioner of Food and Drugs either determine, based on the facts provided herein, that CBD is not excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B) and can be submitted for review as an NDI and will NOT receive a response that it is ineligible as a dietary supplement or ingredient under the definition of a dietary supplement. In the alternative, we ask the Agency to recommend and support to the Secretary of HHS, that, in his discretion, he issues a regulation, after notice and comment, finding that CBD would be lawful under the Act.

III. ENVIRONMENTAL IMPACT

The Petitioners claim a categorical exclusion from the requirements for an Environmental Assessment under 21 CFR §25.32 in light of the fact that the FDA granting NPA's request will not affect the environment.

IV. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which is unfavorable to the petition. If I received or expect to receive payments, including cash or other forms of consideration, to file
this information or its contents, I received or expect to receive those payments from the following persons or organizations: NONE. I certify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Daniel Fabricant, Ph.D.

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Washington, D.C. 20001

(202) 223-0101
Application submitted by:
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Summary of the dossier: Cannabidiol

The applicant has constructed an application for the authorisation of Cannabidiol as a novel food ingredient for the European Union. This dossier for a novel food (NF) approval pursuant to Article 10 of Regulation (EC) No 2015/2283 on novel foods and novel foods ingredients. Its preparation was in accordance with the guidance issued by the European Food Safety Authority (EFSA) regarding an Article 10 submission.

The ingredient from Cannabis Sativa L. plant thus of natural origin. The ingredient is fully characterised including all chemical constituents with the use validated liquid chromatography–diode array detection (LC–DAD) method for quantification of 16 cannabinoids. An identity and compositional analysis of nutritional, microbials, mycotoxins and metals were also assessed from several representative batches including when included in food forms. The ingredient fully complies with established specification.

A range of accelerated and real time stability testing was carried out on including when present in final food forms such as gummies, soft gel capsules and tinctures (Food supplements). Again the composition was stable and within specification.

These studies are based on a tiered approach as proposed in guidance from EFSA and the Organisation for Economic Co-operation and Development (OECD). Propriety studies included a 14-d dose range finding study with pharmacokinetics, a 90-d subchronic trial with recovery, and a combination of genotoxicity studies and reprotoxic assessments. The result demonstrated the ingredient is not genotoxic and safe over subacute and subchronic exposures at the proposed use level in food supplements.

The applicant has applied for data protection in accordance with Article 26 of the novel foods regulation and confidentiality under Article 23 for certain data.
PART 1: ADMINISTRATIVE DATA

1.1 Confidentiality and proprietary data statement

In accordance with the Novel Foods Regulation ((EU) 2015/2283),\(^1\) its implementing legislation (2017/2469)\(^2\) and the corresponding guidance,\(^3,4\) in respect of applications made to the European Commission (EC) and European Food Safety Authority (EFSA), this dossier and the pertinent parts safety studies are understood to be made public. However, certain information related to marketing and the production process is confidential (article 23 of Regulation (EU) 2015/2283) and proprietary (Article 26 of Regulation (EU) 2015/2283) and has been removed from this version. A complete dossier has been made available to the competent body for their consideration.

1.2 Applicant

1.2.1 Company organisation

\[\text{Company Name}\]

1.2.2 Contact (Responsible person)

\[\text{Contact Name}\]

1.2.3 Name of Novel Food Ingredient

\[\text{Ingredient Name}\]

1.2.4 Date of Application

\[\text{Date}\]

---


\(^4\) European Food Safety Authority. Administrative guidance on the submission of applications for authorisation of a novel food pursuant to Article 30 of Regulation (EU) 2015/2283. EFSA Supporting publication 2018.EN-1381
1.3  Regulatory status outside and within the European Union

Most Member States, including the United Kingdom, view Cannabis sativa extracts as either novel and/or a narcotic based on the method of extraction and/or the presence of psychoactive substances such as THC. A brief overview of a selection of Member States is shown in Table 1 including their status dependent on form, part of plant and composition.

<table>
<thead>
<tr>
<th>Member State</th>
<th>Plant part addressed in legislation</th>
<th>Dose range</th>
<th>Comment</th>
<th>Regulation/Legislation</th>
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<td>Austria</td>
<td>All</td>
<td>No dose range permissible as Cannabis extract is considered as novel.</td>
<td>Clarification of the position in Austria was provided in October 2018 by the Ministry of Labour, Social Affairs, Health and Consumer Protection in a published decree.</td>
<td>Confirmed as novel in a Decree BM/ASCG-75(000020-IX/B16c/2018).</td>
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<td>Belgium</td>
<td>Not permitted as an extract, as CBD novel or THC considered a narcotic at certain dosages. Hemp powder is permitted from seed and non-controlled parts but to be assessed for levels of THC before being placed on the market.</td>
<td>Extracts not permitted but hemp can be if given a derogation (2, § 2, 2nd point of the Decree) and THC below 0.2%. However, Cannabis sativa is on List 1 prohibiting use irrespective of THC levels without a derogation.</td>
<td>Cannabis sativa L. is included in List 1 &quot;DANGEROUS PLANTS WHICH CANNOT BE USED AS OR IN FOODSTUFFS&quot; annexed to the Royal Decree of 29 August 1997 on the manufacture and trade in foodstuffs compound of or containing plants or plant preparations.</td>
<td>ARRÊTE ROYAL de 29 AOUT 1997 relatif à la fabrication et au commerce de divers aliments composés ou contenant des plantes ou préparations de plantes (M.B. 21.XI.1997).</td>
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<td>Denmark</td>
<td>Considered novel/medicinal and pre-market assessment to be undertaken for all Cannabis extracts. Narcotic classification depends on THC content.</td>
<td></td>
<td>Executive order no. 980 of 23 June 2020 on euphoriant substances (incl. a list of euphoriant substances)</td>
<td>DVARA Guidance on regulations for food containing cannabis (CBD) 19 March 2019.</td>
</tr>
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<td>Germany</td>
<td>Cannabis sativa whole plant</td>
<td>No dose permissible in food of CBD but hemp seeds, hemp seed oil, hemp seed flour, defatted hemp seeds are permissible. Extraction and levels of controlled substance can impact classification.</td>
<td>THC is considered an unsafe if exceeding 40g of 70ug or medicinal if THC &gt; 2.5mg. In addition, CBD as an extract is considered as a NF.</td>
<td>Narcotics Act (BlMG) Anzox L Safety (BHR Opinion No. 034/2018 of November 8, 2018) Novel within meaning of regulation (EU) 2015/2283</td>
</tr>
<tr>
<td>Ireland</td>
<td>Cannabis sativa (hemp) is legal for sale</td>
<td>There is approved dose of hemp but presence of a controlled substance is prohibited.</td>
<td>Cannabis sativa (hemp) is legal for sale but if hemp is processed involving solvents, like supercritical CO2 or ethanol it is viewed as novel. A dose of THC &gt; 1µg/kg body weight is deemed unsafe.</td>
<td>Misuse of Drugs Acts 1977 and Novel Foods Regulation (Implemented Food Safety Authority of Ireland Act 1998 (Amendment of First Schedule) Order 2020). Safety (S.I. No 747 of 2007).</td>
</tr>
<tr>
<td>Country</td>
<td>Status and List Details</td>
<td>Note</td>
<td>Reference</td>
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| Italy     | Seeds, oil and supplements from hemp. Approval (now repealed) was based on THC levels of 2mg/kg in flour from hemp seeds, 5mg/kg in oil, and 2mg/kg in food supplements derived from hemp.  
  CBD would have been considered as a narcotic under a decree based on THC being a psychoactive substance. However, in October 2018 the Ministry of Health issued a decree suspending the former one. Currently, THC-free extracts are not considered narcotics in Italy. | Decreto 28 ottobre 2020 (GU General Series n. 270 of 29-10-2020) repealing Decreto 4 novembre 2019  
  Difinitivo dei livelli massimi di tetraidrocanabianolo (THC) negli alimenti. (28A00016) (GU Serie Generale n. 1 del 15-01-2020)  
  Under Article 5 of Regulation (EU) no. 315/1993 Italy is considering levels of THC that may be a safe constituent level and now under discussion | Under Article 5 of Regulation (EU) no. 315/1993 Italy is considering levels of THC that may be a safe constituent level and now under discussion | [https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000004680088&dateTexte=19930524](https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000004680088&dateTexte=19930524) |
| Luxembourg| There is no plant list or other substances list in Luxembourg. The Member State uses other countries’ lists as a reference.  
  Hemp extracts are considered novel and the government of Luxembourg follows the position of ECJ/FAO. | Novel  
| Netherlands| All  
  According to the Netherlands Food and Consumer Product Safety Authority (NVWA) hemp oil is listed in List 1 of the Opium Act, and under List II at any part of the plant from which the resin has been extracted with the exception of seeds not the fibre is low in THC. Thus, such substances under the Act are narcotics. Novel foods would apply but because they view the parts above as falling within the Opium Act, it is theoretical. | Opium Act 1976 (as amended) | With EU | [https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000004680088&dateTexte=19930524](https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000004680088&dateTexte=19930524) |


Table 1: Regulatory status of CBD within the European Union

In contrast to those products controlled within the EU, globally hemp (Cannabis sativa) and its extracts can be viewed in a different manner. Some of these third countries are considered in Table 2, in regards to the legislative controls in place.
<table>
<thead>
<tr>
<th>Country</th>
<th>Plant part</th>
<th>Dose range</th>
<th>Regulation/Legislation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Seed accepted in GRAS notifications as HEMP source but extracts of concentrated CBD/THC or other cannabinoids are not permitted.</td>
<td>&lt;0.3% of THC (U.S.C. § 7129) in hemp no defined threshold for CBD or other cannabinoids.</td>
<td>In the USA hemp is authorised for use in foods with contaminant levels of THC/CBD. However, CBD as an extract is prohibited at federal level by legislation under Section 301(l) of the Federal Food, Drug, and Cosmetic Act. At state level, CBD from hemp (&lt;0.3% THC) is permissible for recreational use but if sourced from marijuana (&gt;0.3% THC) it is restricted or limited to medical use.</td>
</tr>
<tr>
<td>Canada</td>
<td>Non-viable seeds, hemp seed derivatives that are compliant with the Industrial Hemp Regulations, mature stalks that do not include any leaves, flowers, seeds or branches and fibre from such stalks are also excluded from the Cannabis Act.</td>
<td>Hemp-containing products that contain less than 10ppm THC.</td>
<td>Cannabis Act (S.C. 2018, c. 16)</td>
</tr>
<tr>
<td>Brazil</td>
<td>Permits the use of cannabidiol only in medical (compassionate) use cases.</td>
<td>&lt;0.2% for prescription-based use but &gt;0.2% in terminally ill. No food use is authorised.</td>
<td>Federal Council of Medicine – Resolution No 2,113 of October 30 2014</td>
</tr>
<tr>
<td>Colombia</td>
<td>Permissible for sale in foods and as medicine</td>
<td>Not clear any restriction in dose.</td>
<td>Decree 613/2017 Source: <a href="https://asococanna.org/normativa/">https://asococanna.org/normativa/</a></td>
</tr>
<tr>
<td>Uruguay</td>
<td>Permissible for sale in foods and as medicine</td>
<td>Extraction from all plant parts permissible but limit of 1% THC with 0.5% stated for seeds.</td>
<td>Law 19.172</td>
</tr>
</tbody>
</table>

**Note:** A number of countries permit the sale of hemp but as a narcotic or medicine, and confusion over the classification of extracts that are high in a specific cannabinoid such as CBD has resulted. In general, Europe considers food use of extracts as novel or narcotic depending on the part used. Similarly, in Asia and Australasia, CBD as an extract other than for medicinal purposes is prohibited. A full regulatory review is accessible in Taylor M. Cannabis Law and Regulation. Bloomsbury Professional Law Insight. Bloomsbury Publishing Plc.

Table 2: Regulatory status of CBD outside of the European Union
PART 2: CHARACTERISATION OF THE NOVEL FOOD TECHNICAL AND SCIENTIFIC DATA

2.1 Introduction

The novel food (NF) which is subject to the application is produced from the Cannabis sativa, subsp. Sativa, plant grown in the USA. The NF is proposed to be added as a food ingredient in ‘food supplements’ (Directive 2002/46/EC),\(^5\) in the general adult population excluding pregnant and lactating women, children and those on prescription medications. The applicant indicates that, as defined by Regulation (EU) 2015/2283, Article 3 (iv), the NF falls under the category:

‘food consisting of, isolated from or produced from plants or their parts, except when the food has a history of safe food use within the Union and is consisting of, isolated from or produced from a plant or a variety of the same species obtained by:

— traditional propagating practices which have been used for food production within the Union before 15 May 1997; or

— non-traditional propagating practices which have not been used for food production within the Union before 15 May 1997, where those practices do not give rise to significant changes in the composition or structure of the food affecting its nutritional value, metabolism or level of undesirable substances.’

---


\(^6\) Supra note 2

\(^7\) Supra note 3 & 4
2.2 Characterisation of the novel food

2.2.1 Taxonomic review – Cannabis sativa extract

The novel food is herein stated as a _C. sativa_ and is an extract from the dried annual dioecious plant Cannabis sativa Linnaeus (L.) (whole plant extract) as summarised in the taxonomic table below (Table 3).

<table>
<thead>
<tr>
<th>Rank</th>
<th>Scientific and Common Name</th>
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<tr>
<td>Kingdom</td>
<td>Plantae – Plants</td>
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<tr>
<td>Subkingdom</td>
<td>Tracheobionta – Vascular plants</td>
</tr>
<tr>
<td>Superdivision</td>
<td>Spermatophyta – Seed plants</td>
</tr>
<tr>
<td>Division</td>
<td>Magnoliophyta – Flowering plants</td>
</tr>
<tr>
<td>Class</td>
<td>Magnoliopsida – Dicotyledons</td>
</tr>
<tr>
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<td>Urticales</td>
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<tr>
<td>Family</td>
<td>Cannabaceae – Hemp family</td>
</tr>
<tr>
<td>Genus</td>
<td>Cannabis L. – hemp</td>
</tr>
<tr>
<td>Species</td>
<td>Cannabis sativa L. – hemp</td>
</tr>
<tr>
<td>Subspecies</td>
<td>Cannabis sativa L. subsp. Sativa – hemp</td>
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<table>
<thead>
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</thead>
<tbody>
<tr>
<td>C. sativa L. subsp. sativa (L.) Small et Cronquist var. sativa (L.) Small et Cronquist, Taxon 25 (1976) 421.</td>
<td></td>
</tr>
<tr>
<td>C. sativa L. subsp. sativa (L.) Small et Cronquist var. spontanea Vavilov, Taxon 25 (1976) 423</td>
<td></td>
</tr>
</tbody>
</table>


In addition to its taxonomic classification, it is known by many common names in different languages, including:

<table>
<thead>
<tr>
<th>Arabic</th>
<th>Al-Bhang; Al-Hashish; Al-Qanaap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>Xian ma; ye ma; Ma-ye; Hon-ma</td>
</tr>
<tr>
<td>Danish</td>
<td>Hemp</td>
</tr>
<tr>
<td>Dutch</td>
<td>Hemep</td>
</tr>
<tr>
<td>English</td>
<td>Hemp; marihuana</td>
</tr>
<tr>
<td>French</td>
<td>Chanvre; chanvre d’Inde; chanvre indien</td>
</tr>
<tr>
<td>German</td>
<td>Hanf; Haschisch; indischer Hanf</td>
</tr>
<tr>
<td>Indian</td>
<td>Bhang; charas; ganja</td>
</tr>
<tr>
<td>Japanese</td>
<td>Mashinin</td>
</tr>
<tr>
<td>Portuguese</td>
<td>Canhano; maconha</td>
</tr>
<tr>
<td>Russia</td>
<td>Cannabis sativa</td>
</tr>
<tr>
<td>Spanish</td>
<td>Marihuana; marijuana</td>
</tr>
</tbody>
</table>

Table 4: Alternate nomenclature for Cannabis sativa. Source: Chandra S, et al. 2017

2.2.2 Plant morphology

The C. sativa species. C. sativa is a dioecious, rarely monoecious, annual plant of the family Cannabinaceae, having erect stems, which, depending on the environmental conditions and the genetic variety, can reach up to 5 m. The palmate leaves, usually composed of five to seven leaflets, are linear-lanceolate, tapering at both ends and the margins sharply serrate. The male flowers do not present petals, axillary or terminal panicles, have five yellowish tepals and five anthers. The female flowers germinate in the axil and terminally with one single-ovulate closely adherent perianth. A single, small, smooth, light brownish-green fruit is produced per flower and propagated, thanks to bird predation. Moreover, C. sativa is rich in trichomes, epidermal glandular protuberances covering the leaves, bracts and stems of the plant. These glandular trichomes enclose secondary metabolites as phytocannabinoids, responsible for the defence and interaction with herbivores and pests, and terpenoids, which generate the typical smell of the C. sativa. The form of the plant varies according to the climate and variety.

2.2.3 Genetic identification

Recent genetic analyses demonstrated that the cannabinoid type (i.e., the chemotype) with which a Cannabis plant is endowed is determined by the allelic status at a single locus, B; as a consequence of this simple determinism, the chemotype can be easily introgressed and segregates into any genetic background. However, full genomic analysis is rare and in relation to assessment of food safety is of limited value.

To date Cannabis has a diploid genome (2n = 20) with a karyotype composed of nine autosomes and a pair of sex chromosomes (X and Y). Female plants are homogametic (XX) and males heterogametic (XY) with sex determination controlled by an X-to-autosome balance system. The estimated size of the haploid genome is 818 Mb for female plants and

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843 Mb for male plants, owing to the larger size of the Y chromosome. The genomic resources available for Cannabis are mainly confined to transcriptome information: NCBI contains 12907 ESTs and 23 unassembled RNA-Seq datasets of Illumina reads, with recent identification of draft genome sequences for wild type Cannabis sativa. Although these are the beginnings of genetic identification of Cannabis species, the primary method of characterisation is based on their chemotype (chemovar) by principal component analysis.

2.2.4 Chemotypes

The chemical phenotype (chemotype) of C. sativa variants with different phenotypes characterised by specific cannabinoid ratios and quantities, have been described in the literature (chemotypes). Chemotype I is typical of a ‘drug’ type, with a THC amount over 0.30% of inflorescence dry weight, and a CBD content lower than 0.50% (i.e., with low CBD/THC ratio). Chemotype II, the intermediate type, has both CBD and THC, in a ratio around the unity (typically 0.5–2.0); chemotype III, the ‘fibre’ type, has mainly CBD, and a level of THC lower than 0.30% (down to undetectability). Later, two other chemotypes were defined: chemotype IV has a prevalence of CBG (>0.30%), but also CBD (<0.50%), and chemotype V, with amounts of all cannabinoids practically undetectable by standard gas-chromatographic analysis.

However, the chemical fingerprint will be influenced by several factors such as temperature,24, 25 plant sex, and phase of development at time of harvest.26, 27 There is also the consideration as to whether it is part of the plant or the whole plant that is used in the final product due to the concentration of different phytochemicals in the seed, mature stalk, leaf or flower.28

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28 NCBI database search November 12, 2020
31 Small E, Beckstead HD (1973) Common cannabinoid phenotypes in 350 stocks of Cannabis, Llloydia 36:144-165
34 LaFer RA, Eaton BJ (1975) Seasonal variations in cannabinoid content of Kansas marijuana, Econ Bot 29:153-163
2.3 PRODUCTION PROCESS

2.3.1 Growing and harvesting
The NF is produced according to Good Manufacturing Practice (GMP) and Hazard Analysis Critical Control Points (HACCP) principles (see Annex 2).

2.3.2 Growing information

The cultivation and extraction processes are presented in Figure 1.
Figure 1: Cultivation & extraction process
2.3.3 Extraction information
2.3.4 Manufacturing of consumer products & use
Third-party tests include:

- Cannabinoid Concentration Profile
- Any other active ingredient concentration assays
- Terpene screening
- Residuals (pesticides, solvents, mycotoxins)
- Microbial (aerobic plate count, coliforms, E. coli, listeria, S. aureus, salmonella, yeast and mould)
- Heavy metals
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- Residuals (pesticides, solvents, mycotoxins)
- Microbial (aerobic plate count, E. coli, listeria, salmonella, yeast and mould)
- Heavy metals.

2.3.5 Production process
2.4 Compositional data

2.4.1 Analytical methods

2.4.2 Identity

Figure 2:
2.4.3 Identity - Physiochemical properties and purity

2.4.4 Product composition

2.4.4.1 Mycotoxins

Table 6: Mycotoxins analysis of five batches
2.4.5 Stability
2.4.5.1 Stability of the novel food under accelerated conditions (6 months)

Table 7: Accelerated stability
Table 7: Accelerated stability


2.4.5.2 Stability under intended conditions of use
Table 8: Real-time stability

2.5 Specifications

Table 9: Specifications

<table>
<thead>
<tr>
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<th>Value</th>
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<tr>
<td>Specification 1</td>
<td>Value 1</td>
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<tr>
<td>Specification 2</td>
<td>Value 2</td>
</tr>
<tr>
<td>Specification 3</td>
<td>Value 3</td>
</tr>
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</table>
2.6 History of source (about Cannabis sativa history)

Cannabis sativa (hemp) has a significant history of use in foods within the EU. Perhaps the earliest entry in the literature was in the middle of the 4th century BCE when the comic poet Ephippus constituted a list of τραγάνατα or ‘snacks’ consumed while drinking at a symposium (the ancient equivalent of the modern Greek mezedhes), including cannabis (seed cake).32 One of the earliest entries was by Democritus (460–371 BCE) who described the plant as being drunk in wine, while in Italy, Galen (ca. 13–199 BCE) wrote about it being served as small cakes as a dessert.33 Similarly, the seeds were used by the Romans and Greeks as a dessert.34 In Poland, the hemp dance was performed on Shrove Tuesday. Sometimes the seeds were eaten on special occasions. In Lithuania, Cannabis seed soup has traditionally been prepared on Christmas eve (Semientia), and in Latvia the seed is eaten on Three Kings’ Day.35 Hemp seed oil has also been used in a variety of dishes when religious restrictions prohibit use of animal-based oils as a cooking medium. Indeed, its use in Poland and the Czech Republic in porridge and soup is well known.36, 37

2.6.1 History of use of extracts outside of the EU including the United Kingdom

Historic use

Cannabis seeds and leaves have been discovered in the UK dating back to between 500BC and 300AD,38 although the presence of these parts of the Cannabis plants at excavation sites was not defined. The processing of hemp during medieval times has also been suggested based on fossil and pollen evidence.39 Its use historically outside of the EU was predominantly for medicinal, narcotic and ceremonial purposes, originating as a euphoriant from India and the Middle East and then in North Africa.40 Much of the information on early Cannabis and its extracts related to the Indica species (higher in THC than its sativa cousin)

32 Butrica JL. The Medical Use of Cannabis Among the Greeks and Romans. J Cannabis Therap. 2(2), 2002. pg. 51 - 70
34 Dembińska M. Konsumpcja Żywiołowa W Polsce Średniowiecznej (Food Consumption in Medieval Poland). 1963. PhD Thesis. Translated in: Hempseed porridge/soup appears to have been served in monasteries, gardens and to the poor; it’s unclear whether the hempseed oil was extracted first (Dembińska, p.113-114). In Wysy W. Food and Drink in Medieval Poland: Rediscovering a Cuisine of the Past. University of Pennsylvania press, USA, 1999
36 Ibid
37 Ibid note 64

35
with medicinal properties of the Indian variety of Cannabis being recognised by O'Shaughnessy, a British physician working in Calcutta, who is believed to have introduced the herb to Western medicine. This Indica species (referring to an Indian provenance) was the main form in most medicines,⁴¹ but this distinction between species has, due to cross-breeding, in essence rendered such terminology almost irrelevant, with most plants identified now, on the basis of their chemical fingerprint (Cultivar to Chemovar approach), as sativa-dominant (low THC; high CBD) to Indica dominant (high THC; low CBD). For detailed discussion on botanical taxonomy, we recommend a recent review by McPartland et al.⁴²

2.7. Proposed uses and use levels and anticipated intake

2.7.1. Target population
The intended target population are adults (aged 18 and over), excluding pregnant and lactating women.

Infants, children, pregnant and lactating women are excluded from the intended uses. Also excluded are adults consuming food or food supplements containing CBD or *C. sativa* extracts, and adults using medicines, cosmetic products, vaping or smoking products containing CBD or *C. sativa* extracts.

2.7.2. Proposed uses and use levels
The NF is proposed to be used as another substance in food supplements. The applicant proposes to market food supplements containing the NF in a single- or multi-serving format, corresponding to the same daily use level.
Proposed average and maximum daily intakes for different age groups are indicated in the following section. Given the instructions of use, no difference in intake by gender is expected, with the exception of pregnant and lactating women, who are not expected to consume the NF.

2.7.3. Anticipated intake of the novel food

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The methodological aspects of the intake assessment are as follows:

- the sources of data used: instructions for use of the products, including portions of the product recommended for daily consumption, and use levels in the different products, in line with EFSA's standard practice for food supplements;
- the assumptions made and their rationale: in line with EFSA's standard practice, it is assumed that consumers use food supplements according to instructions of use.

Uncertainties

While there is limited uncertainty in reference to consumption for food supplements when instructions for use are taken into account and compliance by consumers is expected, uncertainty persists in the analytical determination of CBD amounts in individual products, including variable selectivity, extraction efficiency and conversion. Moreover, some batch-to-batch variability can occur within specification limits. No extrapolation of food consumption data was required between populations or assumptions concerning frequency of consumption.
2.7.4. Combined intake from the novel food and other sources

Potential sources of intake of the NF have been taken into account (such as natural occurrence in food) in assessing the NF. CBD, in very low amounts, has been reported to occur in very small amounts in hemp seed, hemp seed oil, hemp seed flour and hemp seed protein. Such products are not considered novel,\textsuperscript{50} and are thus legally available in the UK and in the European Union. In this NF application its only use will be in food supplements pursuant to the labelling requirements in Directive 2002/46.

Occurrence of CBD in foods in Australia and New Zealand (FSANZ, 2017)\textsuperscript{51} has been reported in hemp seed on average at 0.44 mg/kg, with a maximum amount of 4.9 mg/kg, in hemp seed oil on average at 7.9 mg/kg, with a maximum amount of 23 mg/kg, in hemp seed flour on average at 0.36 mg/kg, with a maximum amount of 2.0 mg/kg, in hemp seed protein powder 0.87 mg/kg, with a maximum amount of 6.3 mg/kg.

As for hemp seeds, EFSA (2020) reported data on 54 hemp seeds samples (6% left censored); the median content was 0.094 and 0.107 mg/kg (LB–UB) and a mean of 23.804 and 123.807 mg/kg (LB–UB), demonstrating a positively skewed distribution. The median content is lower than the FSANZ average content used for the anticipated intake assessment (see below). As for hemp flour, EFSA (2020) provided analytical results for CBD for 20 samples (5% left censored) with a median of 2.61 (LB = UB) mg/kg. This is higher than reported by FSANZ (2017), on average.

Only 17 results of CBD were reported by EFSA (2020) for hemp oil (6% left-censored); the median CBD content was 5.9 (LB = UB) mg/kg and a maximum of 75 mg/kg. In this case, the median amount is lower than FSANZ's estimate.

Under a conservative scenario, mean exposure, in Australia, has been estimated for the population 15 years and above at 0.0037 mg kg bw/day, and at 0.0077 mg kg bw/day at the 90\textsuperscript{th} percentile (FSANZ, 2017). In the case of New Zealand, resulting mean anticipated intake of CBD, in Australia, has been estimated for the population 15 years and above at 0.0028 mg/kg bw/day, and at 0.0059 mg/kg bw/day at the 90\textsuperscript{th} percentile.

\textsuperscript{50}Cannabidiol (CBD) guidance. Business guidance on cannabidiol (CBD) as a novel food. Available at: https://www.food.gov.uk/business/guidance/cannabidiol-cbd. Last access: March, 3 2021
\textsuperscript{51}FSANZ. Supporting document 1. Updated estimates of dietary exposure to 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) from foods containing low THC hemp seed (at Approval) – Proposal PD042 low THC Hemp Seeds as Food. 23 March 2017 [08–17]
The FSANZ report concluded that the amount of the hemp seed food listed above that would need to be consumed to be of concern for CBD would be many orders of magnitude higher than is realistically possible.

Anticipated intake from natural occurrence in food would constitute less than 2.7% of the combined CBD intake from the NF and from natural occurrence, under the most conservative scenario developed by FSANZ (Australia, 90th percentile).

Although dietary patterns differ in the UK and in the European Union from those of Australia and New Zealand, such differences are very unlikely to result in dietary exposure to CBD from hemp seed foods of a magnitude that would significantly modify the anticipated exposure from the NF itself. No other significant sources of CBD have been found to occur in the diet from natural occurrence.

EFSA (2020) reported occurrence data for 28 Food Categories (other than hemp) with the highest mean values reported for ‘Dietary supplements’, ‘Tea (Infusion)’, ‘Tea and herbs for infusions (Solid)’, ‘Animal fat’ and ‘Fine bakery wares’. Few details are provided on the samples. In the case of food supplements, the information appears to refer to CBD-containing products, given an average content of 10.58 mg/g. EFSA (2020) further explained that nine samples were reported as ‘dietary supplements’ with no further specification of the classification, with indication of hemp content because of THC content. Two samples were reported as ‘Vitamin Supplements’, and also were likely to have some hemp content; eight samples were described as ‘Protein and amino acids supplements’ also with THC, with seven identified as ‘Plant extract formula’ with THC.

The same is likely to apply to ‘Tea (Infusion)’, ‘Tea and herbs for infusions (Solid)’. The average CBD content was 805 and 481 mg/kg. As for animal fat, only one sample was found to contain CBD. As for fine bakery wares, EFSA (2020) reported data on 22 samples (6% left censored); the median content was 0.216 mg/kg and a mean of 35.5 mg/kg, demonstrating a positively skewed distribution. Fine bakery wares were also found to contain THC, indicating that hemp derivatives had been used for manufacturing such products. Overall, there is no indication of occurrence in foods other than hemp seed products.
CBD is currently used in a variety of foods and food supplements in the European Union. There is considerable uncertainty as to the regulatory status of CBD-Containing products, and it is difficult to anticipate intake from such sources. As a consequence, precautions of use have been introduced to prevent concurring intake from food fortification or from food supplements. As a consequence, no daily intake from food fortification or supplements other than uses in this application is expected given the precautions for use.

Other potential non-dietary sources (e.g. from consumer products such as cosmetics, and from pharmaceuticals) have also been considered. CBD is used in cosmetic products, in medicines, in vaping and in smoking. Given the extensive uncertainty in exposure to CBD from such products in a rapidly evolving marketplace, and the potential dermal absorption of CBD through topical use, the applicant has chosen to include appropriate precautions of use to exclude exposure from those products and to restrict use to food supplements.

2.7.5. Estimate of exposure to undesirable substances
Exposure estimates are also provided for relevant undesirable substances identified in the compositional analysis and for potential secondary plant metabolites.

No other relevant residues, contaminants or degradation products have been identified which might be present in the novel food due to its source or the manufacturing process, or due to its use and storage. Specifically, with the proposed conditions of use and specifications, the applicant considers that the exposure to undesirable substances does not raise safety concerns.
2.7.6. Precautions and restrictions of use

Proposed precautions (including directions for its preparation and/or use) and restrictions of use are based on all available information on safety.

Children (under 18), pregnant and lactating women should not consume the NF. The applicant has not examined the available dataset to completely assess the safety for such population at the time of the application. Thus, the restrictions are in place as a precaution, and as part of labelling restrictions imposed by Directive 2002/46 as no such concerns were demonstrated in the toxicological analysis of the NF.

Moreover, the product should bear labelling indicating it is not to be used on the same day as any other food supplements or food containing CBD, *Cannabis sativa* extracts. The label should also indicate that it is not to be used on the same day as using CBD-containing medicines, vapes or smoking *Cannabis sativa* extracts.

All other mandatory warning pursuant to Directive 2002/46 will also be implemented.
2.8 Absorption, distribution, metabolism & excretion (ADME)

2.8.1 Systematic review of the literature on ADME
This systematic review was carried out based on PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-analyses) guidelines. A review of PubMed was conducted to retrieve all articles reporting pharmacokinetic data for the primary cannabinoids in the test substance (See Table 14).

The results of the search are as shown in Figure 9 and the eligibility criteria are in Table 14.

![Flow chart identifying study retrieval and selection of relevant ADME studies and related pharmacokinetic data](chart.png)

Figure 9: Flow chart identifying study retrieval and selection of relevant ADME studies and related pharmacokinetic data

Table 14: Protocol and exclusion criteria applied to ADME search
SE: Search element  SH: Number of search hits  BO: Boolean operator
2.8.2 Search strategy

Search terms included [REDACTED] with no restrictions applied to the start date of the search, publication type or year at the time of the search. The searches were carried out by two independent researchers by 01/01/2021 and thus this should be considered the end of the search period.

2.8.3 Eligibility criteria

In the manual assessment of the papers meeting the search criteria and study question, search terms such as C\textsubscript{max}, plasma concentration, half-life, peak concentration, absorption, bioavailability, AUC; T\textsubscript{max}, C\textsubscript{min} and volume of distribution were used to identify relevant studies. Any papers containing at least one of these search criteria were included in the final data analysis and generation of subsequent qualitative data extraction (Tables 15a-c).

2.8.4 Data acquisition

[REDACTED]

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Table 15a: Summary of data from systematic review of peer reviewed studies
In SH4/SH5 manual assessments where the composition of the extract (and delivery vehicle if appropriate) was not clear, we contacted the authors of the papers for further details. Spindle et al. as an example confirmed that the CBD was synthetic and not plant based. As this form may have a different enantiomeric structure than plant-derived CBD\textsuperscript{66,67} and because of this may act on different receptors,\textsuperscript{68,69} and thus have a different toxicological threshold, it was as per the exclusion criteria omitted for inclusion in the qualitative analysis.

In addition, we contacted the authors of other papers such as Patrician et al.,\textsuperscript{70} who utilised a generic CBD described as a ‘multi-spectrum hemp oil’. The authors confirmed other cannabinoids were present but could not disclose further details and thus the paper was excluded. Finally, in the Williams et al. paper, we requested additional information on a CBD tincture (30 mg CBD Isolate) and CBD (30 mg) as powder that were consumed with 227 ml of water. No additional detail could be provided according to the authors of the study as to the amount of MCT or distilled water present in the base formulation that would have impacted the concentration of the CBD. No additional information was available from the study authors, who referred us to the ingredient supplier, who again did not provide detail as such; although the study data has been included, these issues should be considered a limitation.

### 2.8.5 Definitions of PK parameters

- **$T_{\text{max}}$**: Time to the maximum measured plasma concentration.
- **$C_{\text{max}}$**: Maximum measured plasma concentration over the time span specified.
- **$t_{0.5}$**: Final time taken for the plasma concentration to be reduced by half.
- **$\text{AUC}_{0-t}$**: The area under the plasma concentration vs. time curve, from time zero to 't' ($t = \text{last time point measurement}$).
- **$\text{AUC}_{0-\infty}$**: The area under the plasma concentration vs time curve from zero to $t$ calculated as $\text{AUC}_{0-t}$ plus the extrapolated amount from time $t$ to infinity.

\textsuperscript{65} Hanus L0, Tchililiba S, Ponde D, Breuer A, Frode E, Mechoulam R. Enantiomeric cannabidiol derivatives: synthesis and binding to cannabionoid receptors. Org Biomol Chem. 2005 Mar 21; 3(6):1116-23

\textsuperscript{66} Merakos, P, Reggio, PH, Jagerovic, N. An overview on medicinal chemistry of synthetic and natural derivatives of cannabidiol. Front Pharmacol 2017; 8: 422


AUClast: area under the plasma/serum concentration vs time curve from time zero to the last quantifiable concentration.

Kd: The first-order final elimination rate constant.

2.8.6 Analysis of ADME based on published data

2.8.7 Bioavailability (general)

CBD has a low water solubility and high lipophilicity as expressed by its high logP of >5, leaving it likely to be highly permeable to lipid membranes. This is demonstrated in its low bioavailability (F) of circa 13–19% in dogs (Samara et al. 1988),71 and 8.63% in mice (Xu et al. 2019).72 Its lipophilicity has been demonstrated when comparing the impact of fasting vs fed and high-fat (>58%) feedings (Taylor et al. 2018).73 In Taylor et al., a 912 kcal/60% high-fat meal increased Cmax and AUC (AUC1 and AUC0→) 4.85 and 4.2-fold respectively. The likely effect is from the increase in bile salt secretion, which solubilises the CBD and enhances absorption via transport through hydrophobic barriers.74 However, it has been suggested that after lipolysis, over 30% of CBD molecules are distributed into micellar fractions, suggesting at least a third of the orally administered dose would be available for absorption due to lymphatic transport.75

There is little to no data on CBD-only interventions and elimination rate examination, though it could be argued that where CBD is delivered concomitantly with a lipid/fat-based food, the diversion of CBD from portal to lymphatic circulation may be a result.76 Therefore,
chylomicron-associated molecules (CBD + lipid) secreted from the enterocyte into the lymphatic circulation may avoid significant hepatic first-pass metabolism. The consequence is minimised pre-systemic elimination and enhanced bioavailability.

In support of this view, Crockett et al. demonstrated that CBD taken with a high-fat/high-calorie meal (circa 60% fat/918 kcsals) vs fasted increased AUC_{0-\infty} 3.8-fold, and 5.2-fold for C_{max}. A low-fat/low-calorie meal also increased AUC_{0-\infty} and C_{max} (2.7-fold 3.8-fold, respectively). Similarly, when dosed with whole milk, CBD exposure increased by 2.4-fold for AUC_{0-\infty} and 3.1-fold for C_{max}.

These feeding studies however did not examine if the improved bioavailability was the amount of fat or calories. Data from Williams et al. (2021) demonstrated that when CBD was delivered in a low-calorie but lipid base (MCT's) vs a water base, it was 33% higher, suggesting lipid-based delivery vehicles, either as high or low calorie, result in significantly greater bioavailability.

The following provides a detailed assessment of the PK results from the systematic review of the published literature followed by the results of the PK study on our client’s test substance used in the toxicological studies described in this novel foods dossier.

2.8.8 Absorption

Although the increase in C_{max} seems to be dose-dependent, the C_{max} between higher doses does not differ greatly, suggesting a saturation effect (e.g. Taylor et al. 2018\textsuperscript{78} demonstrate an 83% increase from 1500 mg to 3000 mg but only an 8% increase from 4500 mg to 6000 mg). The influence of a meal concomitantly with CBD results in a greater increase in C_{max} in the fed vs fasted state (3-fold (Taylor et al. 2018)\textsuperscript{79} 7–10-fold (Crockett et al. 2020)).\textsuperscript{80} Figure 10 shows an average C_{max} of 457 ± 481 ng/ml (Range 0.65–1050 ng/ml) for a mean single dose of 19.4 ± 25 mg.

\textsuperscript{78} Gershovitch P. Lipophilic activated ester produg approach for drug delivery to the intestinal lymphatic system. J Control Release. 2018 Sep 28;286:10-19.
\textsuperscript{79} Brocks DR, Davies NM. Lymphatic Drug Absorption via the Enterooycte: Pharmacokinetic Simulation, Modelling, and Considerations for Optimal Drug Development. J Pharm Pharm Sci. 2018;21(1s):254S-270S.
\textsuperscript{80} Supra 6.2
However, the extent by which orally administered CBD reaches the systemic circulation is reflected by the AUC and not by $C_{\text{max}}$, which is more a reflection of the rate of absorption.  

Thus, AUC is a more robust PK measure as it typically includes numerous PK metrics in comparison to only $C_{\text{max}}$ which is in effect a measure dependent on the frequency/timing of blood sampling. As such, in the food effect studies mentioned above, the AUC increase is about 4-fold when taken as a high-fat meal, whereas the $C_{\text{max}}$ ranges between 4.8 and 14 times higher compared to fasting conditions. In the systematic review the data gave the following values:

\[
AUC (0-\infty) = 2759.6 \pm 2395 \text{ ng.h/ml (Intake Range - 22.6 mg.kg to 26.2 mg/kg)}
\]
\[
AUC (0-t) = 2232 \pm 2322 \text{ ng.h/ml (Intake Range - 19.4 mg.kg to 25.4 mg/kg)}
\]

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Figure 11. demonstrates a relationship between increasing dose and AUC. Assuming an oral bioavailability of 6–8% after fasting, co-administration with a high-fat meal would be expected to result in a bioavailability of about 25%, demonstrating the importance of considering the vehicle used in toxicological and ADME-based studies.

![Graph showing the relationship between dose and AUC](image)

Figure 11. The effect of a single dose of CBD on plasma AUC across a systematic review of published human data

The mean $T_{max}$ occurs between 0.9 and 5hrs and, based on the limited data from the systematic review, does not seem to be dose-dependent, despite the suggestion in Figure 12 that this is the trend. Average $T_{max}$ in selected studies = 3.5 ± 1.3hr (Range 0.9–5hr) for an average dose of 19.4 ± 25 mg. Taylor et al. (2018), in an ascending dose study, found that between 22.8 and 85.7mg/kg, no significant difference was shown in $T_{max}$ values at 5 ± 2hr, in line with the totality of the data from the review.

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*Sura 62*
The mean half-life (T½) of CBD was 20.8 ± 14.1 (Intake bolus range = 22.6 mg.kg to 26.2 mg/kg). In fasted state and 17 ± 12.6h and 28.4 ± 16.3h in fed state suggests a longer half-life, yet we are given very little data on elimination rate constant (Kₑ) or the absorption rate constant (Kₐ), making insight difficult. In fasted vs fed state with the same single dose bolus, there was no significant effect on half-life. It is to be noted, however, that in the Taylor et al. (2018) study, t₅₀ₑff was used in place of T½ and takes into consideration the entire concentration-time profile of a drug. This was to take into account slower oral absorption and wide distribution of CBD taken with a meal and thus is a better descriptor of the rate of drug accumulation and of systemic removal across the entire dosing interval.

The volume distribution (Vₐ) from the review was 368.1 ± 256.2 L·h⁻¹ kg⁻¹ (range 53.9–612 L·h⁻¹ kg⁻¹) (Dose Range = 22.6 mg.kg to 26.2 mg/kg). There is limited data in the literature related to oral intake and distribution. However, post-mortem cases support uptake of cannabinoids including CBD preferentially into organs with high lipid content such as
adipose. However, these human and indeed similar animal studies are related to cannabinoid intake from smoking or ip. The data suggests that biliary excretion is an important route of elimination for cannabinoids, and their enterohepatic recirculation is a significant factor to consider when analysing prolonged blood elimination profiles.

In the review clearance ($CL/F$) was $754.7 \pm 5921$/hr (range 154–1,909/hr) (Dose Range – 2.24 mg/kg to 85.7 mg/kg). Of note to the kinetics involved in these studies is better assessed by considering the effect of feeding and fasted states. The clearance ($CL/F$) of 630–1,900 l/hr in fasted (intake 10.4–85.7 mg/kg) and 154–422 l/hr (2.24–21.4 mg/kg) in the fed state equates to $7–21 \times$ (Fasted) and 1.7–4.7 $\times$ (fed) hepatic blood flow. In Crockett et al. CBD resulted in a 4-fold greater clearance in the fasted vs fed (high-fat/high-caloric) state at an equivalent CBD dose. Similarly, Taylor et al. (2018) saw a 4-fold difference between fasted and fed for the same CBD dose, with an increasing dose over the 21.4–85.7 mg/kg range being associated with a parallel increase in volume distribution.

In all studies oral clearance estimates are higher than liver blood flow. This is explained by the fact that these estimates reflect $CL/F$ values: e.g. calculated by assuming complete oral bioavailability. In fact, as discussed above, the actual bioavailability is circa 8%. Then these values would be 50–152 l/hr (fasted) and 12–34 l/hr (fed), which is much closer to the values from an IV injection of 20 mg deuterium-labelled CBD in five health subjects.

2.8.9 Metabolism

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86 Leighton EG, Metabolism and distribution of cannabinoids in rats after different methods of administration. Biochem Pharmacol. 1973 Jul 1;22(13):1613-21
2.8.10 Excretion

The overall plasma clearance of CBD varies depending on the fed vs fasted state.
Mean elimination rate (Ka) does not change significantly between the fed and fasted state.
We have considered studies conducted on Epidiolex® but have reservations over the
applicability of that data to a health population at a food level of intake. In addition, many of
the patients in the Epidiolex trials used anti-epileptic medication including valproic acid
know to result in hepatotoxicity.94

Thus, there is limited data on excretion in healthy subjects at a nutritionally comparable
intake level to food use. However, data from studies using deuterium-labelled CBD have
provided insight. In a study assessing IV administration of 20 mg [3H]CBD, 16% of total
reactivity was excreted in urine and 33% in faeces within 72 hours,95 suggesting at least 50%
of the CBD making it into systemic circulation is excreted.

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96 Ibid.
97 Spero note 89
2.8.11 Proprietary toxicokinetic study – during OECD 407 trial

Figure 13: Pharmacokinetic analysis (Non-compartmental model)
Figure 14: Pharmacokinetic analysis (compartamental model)
2.9.2 Nutritional equivalence in human diet

As discussed in Section 2.6, Cannabis sativa has been consumed as a food source for thousands of years. Human physiology has been exposed to cannabinoids, even as hemp (low THC), in modern-day foods such as hemp proteins and cold-pressed hemp seed oils. In recent studies, data demonstrates that hemp-derived feed for cattle has resulted in cannabinoids being present in commodity food goods such as milk (and milk-based foods), eggs and meat. It has been shown that the main cannabinoids in the NF must not only be present in the normal dietary experience due to hemp-based animal feeds but also as part of modern-day consumption of hemp-based oils and protein.

Of course, this NF is more concentrated than that experienced from inadvertent intake or even that from typical hemp food (protein) and oil, and the compounds are selective. To that extent there is no equivalence to the use of this NF as a replacement for a similar food in the modern diet. The total dietary intake in respect to specific population groups and appropriate labelling as an adult-only food, not for use by pregnant or lactating women nor those on medication.

2.9.3 Nutritional benefits

Phytocannabinoids are compounds with potentially many molecular targets that when effectuated result in health benefits of which the most widely publicised is the treatment of disease-related symptoms of epilepsy and related neurocognitive conditions. However, there is emerging evidence of a number of wellness benefits of phytocannabinoids as a food substance akin to those achieved from everyday foodstuffs.

The primary molecular targets for the delivery of a health benefit are likely the cannabinoid receptors (Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2)), which are G protein-coupled protein
receptors. CB1 receptors are located throughout the central nervous system, as well as within cardiac, lung, small intestine, kidney and liver tissues, and on immune cells. In contrast, CB2 receptors are located on immune cells, in the gastrointestinal tract, and at lower densities within the central nervous system.

Recent review evidence points to CBD effects on CB1 receptors due to indirect effects (i.e., no direct interaction with the orthosteric CB1 receptor-binding site). Other targets will likely include transient receptor potential vanilloid (TRPV) channels and serotonin (5-HT1A) receptors. Whatever the underlying mechanism, the benefits proposed and demonstrated with oral CBD intake include reduction in social anxiety, and stress, improved memory, anti-inflammatory benefits, less exercise-related muscle damage.

2.9.4 Nutritional benefits of minor cannabinoids

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121 Castaño MG, Grausen IA, Steverssen IA, Rees RA, Pertwee RG. Evidence that the plant cannabinoid cannabidiol is a highly potent alpha-adenoreceptor antagonist and moderately potent SHT1A receptor antagonist. Br J Pharmacol. 2010 Jan;159(2):129-41.
2.9.4.2 Anti-nutritional factors

An important consideration of any NF is the potential of its actives to deliver an anti-nutrition effect. With reference to the source botanical, hemp has been considered to contain some anti-nutritional substances such as phytic acid, trypsin inhibitors, condensed tannins,

cyanogenic glycosides and saponins.\textsuperscript{126} However, these factors may be trait dependent,\textsuperscript{127} and also may be impacted by processing such as heat treatment and pH.

However, in order for such anti-nutritional factors to have a significant effect, they need to be >1 mg.\textsuperscript{128} In the context of this NF, although its source material is Cannabis sativa, which has anti-nutritional compounds, the NF is an extract delivered in final form in the 10s of mg range and not tens of grams as with hemp protein or oil. Thus, given the measured content or primary cannabinoids in the final NF extract, the presence of any anti-nutritional factors would not be of concern and are likely present at μg concentrations per daily intake.


2.10 Toxicological information

2.10.1 General considerations

The applicant conducted their own proprietary toxicological evaluation of the Cannabis extract [REDACTED], which is the material specific to this application. In the absence of any published studies on this specific extract, including significant data gaps in relevant toxicologically relevant end points related to oral consumption, a selection of rodent and in vitro studies in line with EFSA guidance have been conducted (see Table 17).

<table>
<thead>
<tr>
<th>Study Design</th>
<th>OECD No</th>
<th>Year</th>
<th>Batch No</th>
<th>CRO</th>
<th>GLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutagenicity – Reverse mutation (AMES Assay)</td>
<td>471</td>
<td>2021</td>
<td></td>
<td></td>
<td>Yes (ISO 4238.01)</td>
</tr>
<tr>
<td>In vitro micronucleus Test</td>
<td>487</td>
<td>2021</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>14d oral range finding</td>
<td>407</td>
<td>2020</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>14-day pre-natal oral tolerability/toxicity range-finding study</td>
<td>414</td>
<td>2020</td>
<td></td>
<td>Non-GLP</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic analysis – CBD</td>
<td>N/A</td>
<td>2020</td>
<td></td>
<td>N/A</td>
<td>(REDACTED)</td>
</tr>
<tr>
<td>90-day oral toxicity study with reproductive functionality and 28-day recovery</td>
<td>408</td>
<td>2020/2021</td>
<td></td>
<td>Yes (ISO 4238.01)</td>
<td></td>
</tr>
</tbody>
</table>

Table 17: Proprietary toxicity studies with Cannabis extract [REDACTED] conducted on behalf of applicant, for which the full study reports are available (Annex 6).

The studies listed in Table 17. are original trials funded by the applicant and considered confidential (Article 23 of Regulation (EU) 2015/2283) and proprietary (Article 26 of Regulation (EU) 2015/2283). The study reports are included in full in Annex 6.
2.10.1.1 Systematic review of published human studies

2.10.1.2 Identification – The systematic review was performed using these databases: PubMed, SCOPUS, EMBASE, MedLine. The search terms used and the dates of searches are provided below:

- 

These initial searches were independently verified, and records kept.

The CBD search from SCOPUS resulted in a large number of records (n = 8287). Therefore, further filters were applied as detailed below:

- SCOPUS – From initial search of CBD literature, filters (e.g., language to English, document type – article) were applied (n = 4503). Limits (keyword) were then applied from the options available – article or human or controlled study or male or humans or female or adult, or cannabidiol or major clinical study or dose response or dose response relationship, drug or randomised control trial or double-blind procedure or clinical trial or normal human. These resulted in 3523 records.
2.10.1.3 Screening

Records from the identification stage were imported to Legacy REFWORKS into individually named folders. Exact duplicates were removed followed by close duplicates (Appendix 1–3).

2.10.1.4 Eligibility

The records were then exported to a Microsoft Excel spreadsheet for preliminary screening based on the titles and abstracts (as required). Animal studies and studies that are not related to the compounds of our interests were excluded at this stage. Anything that was potentially relevant at this stage was further investigated on the basis of abstract, inclusion and exclusion criteria (Table 18).

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised and non-randomised trials, meta-analyses</td>
<td>Prospective cohort study, case studies (including retrospective case studies) and cross-sectional studies</td>
</tr>
<tr>
<td>Peer-reviewed research papers only</td>
<td>Paper not in English language</td>
</tr>
<tr>
<td>Studies where &gt;90% cannabidiol administered</td>
<td>Studies using cannabidiol mixed with other compounds (drugs, therapeutic agents etc.) administered or studies with cannabidiol that has THC present</td>
</tr>
<tr>
<td>Healthy subjects, male and female, &gt;18 years of age</td>
<td>Studies with &lt;18 years age, pregnant or lactating women, subjects on medication or with diseases which impact cannabidiol metabolism</td>
</tr>
<tr>
<td>Studies with orally administered cannabidiol only (gavage/feeding studies)</td>
<td>Studies lacking appropriate control or placebo groups</td>
</tr>
<tr>
<td>No date limit</td>
<td></td>
</tr>
</tbody>
</table>

Table 18: Systematic review inclusion and exclusion criteria
2.10.1.5 Inclusion

The final list of articles was downloaded and read to establish definite inclusion and exclusion. Reasoning is provided for anything that is excluded at this stage. Only articles that met our inclusion criteria (Table 18) have been included in Appendix B.4. Each of these stages has been depicted in PRISMA diagrams provided in the Figure 16.

Figure 16: Prisma design employed as part of systematic review of human toxicological analysis
Figure 17: Prisma design employed as part of systematic review of human toxicological analysis.

Figure 18: Prisma design employed as part of systematic review of human toxicological analysis.
Table 19 shows an overview of the human studies identified from the systematic review. All publications are references in Table 19 are accessible in Annex 7. Studies with the highest level of scientific evidence are presented first and we provide the following additional comments:

**Terms:** MedDra (Medical Dictionary for Regulatory Activities): Aes (adverse events); ECG (electrocardiogram)

**NB:** Taylor 2018\(^{12}\) – Food Effect study not included as no placebo

**NB:** Patrician 2019\(^{13}\) – TurboCBD not included as prepared in mixture with other compounds

**NB:** Taylor 2019\(^{14}\) – participants with mild, moderate or severe hepatic impairment were not included; not placebo-controlled

**NB:** Hundal 2018\(^{15}\) – participants exposed to virtual reality paradigm were not included. Adverse events after VR so not used

### 2.10.1.6 Results and discussion

The results from this systematic review show that there were no major safety-related concerns observed when highly purified cannabidiol was orally administered to healthy participants. Participants reported headache and diarrhoea (dose 1500 mg+). With multiple doses of cannabidiol, diarrhoea, nausea, headache, dizziness and presyncope were reported (Taylor et al. 2018).\(^{16}\) No significant effect of cannabidiol at any dose (100 mg, 600 mg and 1200 mg) vs placebo on any of the safety parameters (blood pressure, heart rate, respiratory rate, specific airway conductance and self-reported intoxication level) were reported.\(^{17}\)

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\(^{12}\) Sgro 62


\(^{14}\) Sgro 61


\(^{16}\) Sgro 62

All safety studies were reviewed, including, but not limited to, safety, tolerability, toxicology, behavioural effects, change in clinical chemistry and other biomarkers and inflammatory/allergic responses.

<table>
<thead>
<tr>
<th>Reference (author, year, title of study)</th>
<th>Study report provided in the application dossier (name of file)</th>
<th>Study design</th>
<th>Study population</th>
<th>Duration of the study</th>
<th>Tested material</th>
<th>Dosage</th>
<th>Power calculations performed</th>
<th>Safety-related parameters investigated</th>
<th>Summarized results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, L., Winwood, B., Baker, G., J.</td>
<td>Randomized, double blind, placebo-controlled, single scoping dose, multiple dose, and food effect trial.</td>
<td>Study group: 30-year-old male and female (16).</td>
<td>Single dose: 0.25 to 24 hours. Multiple dose: 7 days.</td>
<td>CBD from Cannabis sativa plant. Pharmacological formulation in oral solution (50mg/mL). Source: B receives [USC] and [UCP]. Phenomenology (USC) Delivered safely using spray.</td>
<td>Single Dose: 500, 1000, 2000 mg. Multiple Dose: 750 mg or 1250 mg (twice daily for 4 days, once on day 7).</td>
<td>No</td>
<td>Electrocardiogram (ECG)</td>
<td>Physical examination</td>
<td>No clinically significant change in ECG or physical examination. No consistent effect on sleep. No evidence of drug withdrawal. No severe or serious AEs. MM and moderate AEs were noted. Study group: CBD (2000 mg) caused greater proportion of subjects to experience diarrhea (50.59 mg: 3.14%, 1500 mg: 25%, 1000 mg: 0%, 500 mg: 0% versus placebo: 21%). No impact on other GI disturbances (nausea, abdominal discomfort), CBD (2000 mg) caused greater proportion of subjects to experience headache (1505 mg: 3.7%, 1000 mg: 6.7%, 500 mg: 0%, 200 mg: 2.2% versus placebo: 2%). No evidence of GI distress or nausea. CBD (2000 mg) caused greater proportion of subjects to experience headache, dizziness, and insomnia. At 1000 mg, CBD, 25% of subjects noted a rash compared to 0% in placebo and 7.5 mg dose groups.</td>
</tr>
<tr>
<td>Gong Jr., H., Tashkin, D.P., Brummett, M.H., Celano, C.</td>
<td>Randomized double blind placebo controlled.</td>
<td>Study group: 33-65 year all age male and female (15).</td>
<td>Single dose: 0.25 to 6 hours. Multiple dose: 14 weeks.</td>
<td>CBD</td>
<td>Study group: CBD, 1000, 500 or 0 mg. Doses: 0 mg (CBD for a single dose) and 1200 mg (CBD).</td>
<td>No</td>
<td>Complete blood count.</td>
<td>No significant effect of CBD or CBD, versus placebo, at any dose on any of the safety-related parameters. Non-significant change in the drug response (as evident by self-reported outcomes) in healthy volunteers.</td>
<td>No significant effect of CBD or CBD, versus placebo, at any dose on any of the safety-related parameters. Non-significant change in the drug response (as evident by self-reported outcomes) in healthy volunteers.</td>
</tr>
</tbody>
</table>

Table 19: Results of systematic review.
<table>
<thead>
<tr>
<th>Reference (author, year, title of study)</th>
<th>Study design</th>
<th>Study population</th>
<th>Duration of the study</th>
<th>Tested material</th>
<th>Dosage</th>
<th>Power calculations performed</th>
<th>Safety related parameters investigated</th>
<th>Summarised results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, L., Chokkattu, J., Jope, R., &amp; Morrison, G. (2019). A phase I, open-label, parallel group, single-center trial of the pharmacokinetics and safety of cannabidiol (CBD) in subjects with mild to severe hepatic impairment.</td>
<td>Open Label Parallel Group</td>
<td>48-66 year Male (8) and Female (6)</td>
<td>48 hours</td>
<td>CBD from Cannabos,s sterile plant Pharmaceutical formulation in oral solution (100mg/mL)</td>
<td>200 mg</td>
<td>No</td>
<td>Electrocardiogram (ECG), physical examination, MedDRA terms (adverse events [AE]), No clinically significant change in ECG physical examination and blood tests, ALT, AST, GGT, and bilirubin.</td>
<td></td>
</tr>
<tr>
<td>Diagman, A. L, Stilwell R., Stroobant M., Enghoff A., Murphy T., M.D. (2018). The effects of cannabidiol on perception of identity and anxiety in a high maze group.</td>
<td>Randomized Double Blind Placebo Controlled</td>
<td>18-55 year Male (8) and Female (18)</td>
<td>130, 600, 1500</td>
<td>Synthetic CBD from Canapa and placebo, CBD in liquid form</td>
<td>650 mg</td>
<td>Yes – for whole study (32 participants) – data recorded twice from baseline group only</td>
<td>Perceptivity of identity and psychotic-like experiences: Affect, Cognition, Heart rate, Blood pressure</td>
<td>No significant effect of CBD, versus placebo.</td>
</tr>
<tr>
<td></td>
<td>Randomized Double Blind Placebo Controlled</td>
<td>18-22 year Male (12)</td>
<td>0.25-hour</td>
<td>Synthetic CBD from organic multi- strain hemp oil</td>
<td>65 mg CBD (from 150 mg hemp oil), 80 mg CBD (from 300 mg hemp oil)</td>
<td>No</td>
<td>Heart rate, Blood pressure, Respiratory rate, Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), Metabolic markers (insulin, glucose)</td>
<td>No significant effect of CBD at 45 or 90 mg, versus placebo, on cardiovascular, respiratory, and metabolic markers.</td>
</tr>
<tr>
<td>Wolfe M.M., Vanacore N.D., Frederic R., Macleod T.V., Freedman C.E., et al (2020). Evaluation of pharmacokinetics and anti-inflammatory potential of two oral cannabidiol preparations in healthy adults.</td>
<td>Randomized Double Blind Parallel arm</td>
<td>23-51 year Male (6) and Female (8)</td>
<td>0.5-hour</td>
<td>CBD from Canapa, sterile filter, 3-day CBD-containing substrate prior to study</td>
<td>30 mg</td>
<td>No</td>
<td>Blood pressure, Inflammatory markers (TNF-alpha and IL-10 in peripheral blood mononuclear cells)</td>
<td>No significant effect of other water-soluble CBD, compared to baseline levels, on blood pressure, heart rate, pulse pressure or TNF-alpha and IL-10 in peripheral blood mononuclear cells (bil and IV data not available).</td>
</tr>
<tr>
<td>Reference (author, year, title of study)</td>
<td>Study report provided in the application dossier (name of site)</td>
<td>Study design</td>
<td>Study population</td>
<td>Duration of the study</td>
<td>Tested material</td>
<td>Dosage</td>
<td>Power calculations performed</td>
<td>Safety related parameters investigated</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------------------------------------------------------</td>
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<td>----------------------</td>
<td>----------------</td>
<td>--------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Garcia, P., Carlos, E. A., Swiercz, A. P., &amp; Lastra, L. A. (1999). Interaction of cannabinoids and alcohol in humans.</td>
<td>560006, 1999</td>
<td>Randomised Double Blind Placebo Controlled</td>
<td>25-35 year Male (6) and Female (4)</td>
<td>0.5-6 hour</td>
<td>99% pure crystalline cannabidiol (CBD) capsule - Source - chemex (8) Sativass, Israel</td>
<td>200 mg</td>
<td>No</td>
<td>Attention and concentration (cancellation task; differential aptitude test)</td>
</tr>
<tr>
<td>Arndt, O. L., &amp; Lie, I. I. (2017). Cannabidiol does not dampen responses to emotional stimuli in healthy subjects.</td>
<td>CCQ2017</td>
<td>Double blind Randomised Placebo controlled</td>
<td>18-35 year Male (25) and Female (18)</td>
<td>24 CBD (10 mg)</td>
<td>CBD (200 mg/ml solution)</td>
<td>300, 500, 900 mg CBD or placebo single oral dose</td>
<td>No</td>
<td>Heart rate, blood pressure, profile of mood, behavioural tasks</td>
</tr>
<tr>
<td>Belgrade, S. E., 8nd K. D., Chabner, G. R., James, D. M., Kjellin, K. E., &amp; Barlow, G. A., et al. (1999). The effect of cannabidiol, alone and in combination with ethanol, on human performance.</td>
<td>Belgrade 1979</td>
<td>Randomised Double blind Placebo controlled</td>
<td>18-24 year Male (11) and Female (6)</td>
<td>4 after light breakfast</td>
<td>CBD dissolved in sesame oil and sealed into capsules consisting 2.5, 5.0 and 10.0 mg each capsule - 4 capsules (adjusted 200 mg/100)</td>
<td>CBD</td>
<td>No</td>
<td>Standing steadiness test (eyes open and closed), visual reaction time, auditory reaction time and complex reaction time, the 2-Phase Determination to measure coordination and attention tasks, and Briggs word construction test. Subjective assessment of intoxication and pulse rate.</td>
</tr>
</tbody>
</table>

Table 19. Results of systematic review
<table>
<thead>
<tr>
<th>Reference (author, year, title of study)</th>
<th>Study report provided in the application dossier (name of file)</th>
<th>Study design</th>
<th>Study population</th>
<th>Duration of the study</th>
<th>Tested material</th>
<th>Dosage</th>
<th>Power calculations performed</th>
<th>Safety related parameters investigated</th>
<th>Summarised results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shatnawiyya, S., (2009)</td>
<td>Double-blind, randomized, placebo-controlled, repeated measures, within-subject design</td>
<td>15 people, mean age 28.7 years, no gender details</td>
<td>7 times before session light breakfast</td>
<td>A mixture capsule containing 600 mg CBD, 99.5% pure</td>
<td>600 mg CBD</td>
<td>No</td>
<td>Visual Analog Mood scale, State-Trait Anxiety Inventory by Spielberger, Analog Information Scale, and Positive and Negative Syndrome Scale (PANSS) heart rate and blood pressure</td>
<td>No significant effect was noted on either drug on heart rate, blood pressure, or performance in the verbal paired associate learning task as measured by recall score.</td>
<td></td>
</tr>
<tr>
<td>Shatnawiyya, S., Morton, P. O., Quesenberry, P., Martin-Santana, R., Trougakos, S., Winson Brown, T., et al. (2009)</td>
<td>Placebo controlled, double blind, repeated measures, within-subject design</td>
<td>Male (10) and female (5)</td>
<td>2 times before session light breakfast</td>
<td>source: THC Pharamaceutical</td>
<td>600 mg CBD (capsule)</td>
<td>No</td>
<td>Visual Analog Mood scale, State-Trait Anxiety Inventory by Spielberger, Analog Information Scale, and Positive and Negative Syndrome Scale (PANSS) heart rate and blood pressure</td>
<td>There was no change in psychiatric symptoms, and a trend for a reduction in subjective anxiety was found. No significant effects on behavioral performance of the verbal memory, viewing Scary faces or the response inhibition.</td>
<td></td>
</tr>
<tr>
<td>Bird, K. D., Bedeyou, P., Cusack, G. R., Jackson, O. M., Summer, G. A., &amp; Tay, R. C. (2009)</td>
<td>Double blind, placebo controlled</td>
<td>18-36 years old (32) and females (20)</td>
<td>6 sessions weeks ends (9-17 days)</td>
<td>100 mg after cannabidiol administration and then at hourly intervals, 2, 3 and 4 hours</td>
<td>Source - Not identified</td>
<td>CBD, CBG were dissolved in sesame oil and sealed into caps containing 2.5, 5, 10 or 15 mg. Each subject was given six capsules with the dosage of CBD and CBG adjusted to deliver approx. 320 mg/100g</td>
<td>Standing motor task (sees open and closed), visual, auditory and complex reaction times, the Wessex Depression Assessment Instrumental (VDA), the pursuit – error (error and time off target)</td>
<td>No significant effects of systematic effects including CBD or CBG.</td>
<td></td>
</tr>
</tbody>
</table>

*Note: The table contains information on studies that evaluated the effects of cannabidiol (CBD) on various parameters such as mood, anxiety, and behavioral performance.*
<table>
<thead>
<tr>
<th>Reference (author, year, title of study)</th>
<th>Study report provided in the application dossier (name of file)</th>
<th>Study design</th>
<th>Study population</th>
<th>Duration of the study</th>
<th>Tested material</th>
<th>Dosage</th>
<th>Power calculations performed</th>
<th>Safety related parameters investigated</th>
<th>Summarised results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waskiewicz, F., Church, R., L. J. A. Commerford, Y. (2010). Capsaicin and Abnormal Liver Enzymes in Healthy Adults: Results of a Phase I Clinical Trial</td>
<td>capsaicin (2010).</td>
<td>A phase I, open-label, fixed-dose, single-blind, placebo-controlled study</td>
<td>18–60 years, male (5) and female (10)</td>
<td>23 days</td>
<td>CBD from Cannabis sativa L. plant, Pharmaceutical formulation in oral solution (100mg/ml)</td>
<td>The following regime was followed over the 23-day period for all:</td>
<td>2.5 mg, 5 mg, 10 mg, 25 mg, and 50 mg per day</td>
<td>Treatment-emergent adverse effects (AEs) and liver enzyme alanine aminotransferase (ALT) analysis</td>
<td>Treatment-emergent adverse effects (AEs) in 50% of trials; 31% were mild and 50% were moderate in severity. The most common AEs were GI disorders such as diarrhea (50%) and abdominal discomfort (31%). 31% of patients displayed elevated liver test (ALT &gt; 2 x upper limit of normal) 31% of patients displayed elevated liver test consistent with drug-induced liver injury (ALT &gt; 2 x upper limit of normal).</td>
</tr>
<tr>
<td>Bloomfield, M. A. P., Green, S. E., M. Andal, I. C., P. Cowde, I. L., Jones, A. P. M., et al. (2010). The effects of oral cannabidiol on cerebral blood flow and its relationship to memory: An arterial spin labeling magnetic resonance imaging study.</td>
<td>cannabidiol (2010).</td>
<td>Randomised, crossover, double-blind design</td>
<td>15–25 year male (0) female (9)</td>
<td>3 hr</td>
<td>Synthetic CBD (99.9% purity) obtained from St Thomas Laboratories (Bromwell, UK) and manufactured by Novo Larvandry (Leicester, UK). 600 mg CBD, 50 mg capsule, 60 mg CBD and 60 mg</td>
<td>A sensitivity power analysis conducted using 0.80 power to detect a large effect size (Cohen's d = 0.83) at an alpha of 0.05.</td>
<td>Regional cerebral blood flow and memory assessment</td>
<td>CBD increased CSI in the hippocampus. There were no differences in memory task performance, but there was significant correlation whereby greater CBD-induced increases in cerebral blood flow were associated with reduced reaction time on the 2-back working memory task.</td>
<td></td>
</tr>
<tr>
<td>Reference (author, year, title of study)</td>
<td>Study report provided in the application dossier (name of file)</td>
<td>Study design</td>
<td>Study population</td>
<td>Duration of the study</td>
<td>Tested material</td>
<td>Dosage</td>
<td>Power calculations performed</td>
<td>Safety-related parameters investigated</td>
<td>Summarised results</td>
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<tr>
<td>Stephens, S. L., Allen, P., Bhattacheraya, S., Tocchetti, P., Innes, I. A., Seed, M. I., et al. (2008). Neurological aspects of delta-9-tetrahydrocannabinol and cannabinoid effects during acute intoxication.</td>
<td>Stephens, 2008</td>
<td>Double-blind, placebo-controlled, parallel-randomised, withing-subject study</td>
<td>20-42 years, male (13)</td>
<td>1 hour, 3 hours</td>
<td>Source - not specified</td>
<td>600 mg CBD</td>
<td>No</td>
<td>Blood pressure, Visual Analogue Mood Scale (VAMS), Spielberg State Trait Anxiety Inventory (STAI) and a visual analogue intoxication scale (AIS) and positive and negative symptoms scale (PANSS)</td>
<td>Relative to placebo, CBD deactivated the left insula and the left superior and transverse temporal gyri. CBD was not associated with any significant increase in regional activation relative to placebo.</td>
</tr>
<tr>
<td>Grimm, O., Stoffel, M., Siercke, K., Hartmann, A., Bollinger, C., Loffler, M., et al. (2011). Probing the endocannabinoid system in healthy volunteers. Cannabinol alters cerebral resting-state connectivity.</td>
<td>Grimm, 2012</td>
<td>Double-blind, placebo-controlled, randomised, three-period crossover study</td>
<td>Male (16)</td>
<td>75 min</td>
<td>Source - not stated</td>
<td>600 mg CBD</td>
<td>No</td>
<td>State anxiety, positive and negative affect, subjective valence and arousal ratings, and insodative symptoms</td>
<td>Compared state anxiety, positive and negative affect, subjective valence and arousal ratings as well as insodative symptoms. No significant effect on these scales was found for CBD with placebo.</td>
</tr>
<tr>
<td>Reference (author, year, title of study)</td>
<td>Study report provided in the application dossier (name of file)</td>
<td>Study design</td>
<td>Study population</td>
<td>Duration of the study</td>
<td>Tested material</td>
<td>Dosage</td>
<td>Power calculations performed</td>
<td>Safety related parameters investigated</td>
<td>Summarised results</td>
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<tr>
<td>Garcia et al., 2019</td>
<td>31-36 years, Male (40)</td>
<td>6 days</td>
<td>45, 95 and 180 min after ingestion and again 55, 95, 155 and 160 min</td>
<td>CBD</td>
<td>15, 30 or 60 mg CBD</td>
<td>Time production tasks psychological effects of drug action were graded from 0 to 4</td>
<td>No significant change in pulse rate at 90 or 70 min after drug consumption.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawn, W. H. R.,</td>
<td>double-blind, placebo-controlled, repeated-measures design</td>
<td>19-58 year Male (11) and female (11)</td>
<td>2, 7 hr experiments</td>
<td>Pure synthetic CBD</td>
<td>50 mg capsules, participants swallowed 12 capsules to give 300 mg.</td>
<td>A power calculation was conducted using 0 Power version 3.1.9.2.</td>
<td>Whole brain analysis 1fMRI data analysis, behavioral results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawn et al., 2019</td>
<td>double-blind randomised design</td>
<td>57 males; 19-27 year</td>
<td>1.5 hour</td>
<td>CBD (150, 300 or 600 mg)</td>
<td>Powder form (95.9% purity)</td>
<td>150 and 300 and 600 mg.</td>
<td>No</td>
<td>Psychological measurements Visual analogue mood scale (VAMS)</td>
<td></td>
</tr>
<tr>
<td>Unnes et al., 2019</td>
<td></td>
<td></td>
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<td></td>
<td>1000 mg CBD showed lower anxiety than placebo. No significant group, group, or group by interaction effects were found for the VAMS factors sedation, cognitive impairment, or distress. Neither the top nor the drug affected any other VAMS dimensions.</td>
<td></td>
</tr>
<tr>
<td>Reference (author, year, title of study)</td>
<td>Study design</td>
<td>Study population</td>
<td>Duration of the study</td>
<td>Tested material</td>
<td>Dosage</td>
<td>Power calculations performed</td>
<td>Safety-related parameters investigated</td>
<td>Summarised results</td>
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<tr>
<td>Linaras, 2018, K. M., Guimaraes, A. S., Saba, A., Crippa, A. C. S., Zuardi, A. W., Souza, L. D., et al. (2018). No invite effects of cannabidiol on the sleep-wake cycle of healthy subjects: A randomized, double-blind, placebo-controlled, crossover study</td>
<td>Randomized, double-blind, and crossover study</td>
<td>20-35 year</td>
<td>Male (12); female (14)</td>
<td>0.5 – 8 g (oral)</td>
<td>CBD 300 mg (79.9% purity)</td>
<td>No</td>
<td>Polysomnographic recordings</td>
<td>No significant effect of CBD, versus placebo, on total sleep time, REM (rapid eye movement) onset, slow wave sleep, and sleep latency. No significant changes in the subjective and cognitive measures collected during the two nights of polysomnographic exams.</td>
<td></td>
</tr>
<tr>
<td>Linaras, 2018,</td>
<td></td>
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<tr>
<td>McCartney, 2020, D., Benson, M. J., Sapochnik, A. E., Irwin, C., &amp; Adell, T. R., Summala, R. R., et al. (2020). The effect of cannabidiol on simulated car driving performance: A randomized, double-blind, placebo-controlled, crossover, dose-escalating clinical trial protocol</td>
<td>Randomized, double-blind, placebo-controlled, crossover study</td>
<td>18-65 years</td>
<td>Male (10); female (14)</td>
<td>45 mm and 180 min duration</td>
<td>Oral formulations containing 300 mg/ml CBD in gel, vitamin E, and glycerol. Source: Canorex CBD Pharma Pty Ltd</td>
<td>15, 300, 600 mg CBD</td>
<td>Power calculated using Cohen’s formula</td>
<td>No significant effect of CBD, versus placebo, on cognitive function or psychomotor vigilance or cognitive and psychomotor impairment</td>
<td></td>
</tr>
<tr>
<td>Perkins, O., Butler L., Greg K., Nijayan T., Carl B., Francis B., et al. (2020). A placebo-controlled, dose-escalating study to investigate the safety, tolerability, and pharmacokinetics of cannabidiol in fast healthy volunteers</td>
<td>Randomized, double-blind, placebo-controlled, single-dose, escalation study</td>
<td>18-65 years</td>
<td>Male (14); female (4)</td>
<td>1 hour to 15 days duration</td>
<td>Cannabidiol (200g/L) plus placebo oil, 650 mg/kg</td>
<td>Single dose of CBD 5 or 10 or 200 mg/kg</td>
<td>No</td>
<td>Safety and tolerability, Treatment emergent adverse effects (TEAEs)</td>
<td>Oral vaporized formulation of cannabidiol is generally safe and well tolerated at all doses studied. No severe or serious AEs were observed and there were no safety concerns. Subjects taking CBD dosages displayed adverse events: dry skin (3/14), dizziness (1/14). No further effects were observed.</td>
</tr>
<tr>
<td>Sultan, S. A., O'Doherty, S. M., &amp; Englund, T. L. (2020). The effects of acute and sustained cannabidiol dose on the sleep-wakefulness in healthy men: A randomized, placebo-controlled trial</td>
<td>A randomized, placebo-controlled, double-blind, parallel group trial</td>
<td>25 healthy men</td>
<td>Cannabis extracts for at least 2 months prior</td>
<td>2 hours to 7 days</td>
<td>400 mg CBD</td>
<td>No</td>
<td>Mood pressure and arterial stiffness</td>
<td>There was no significant difference in arterial pressure or arterial stiffness from CBD treatment compared to placebo, but there was a significant lowering of mean arterial pressure. CBD dosing for 7 days significantly reduced arterial stiffness and improved carotid artery diameter but had no effect on mean arterial pressure.</td>
<td></td>
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<tr>
<td>Sultan 2020</td>
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<table>
<thead>
<tr>
<th>Reference (author, year, title of study)</th>
<th>Study design</th>
<th>Study population</th>
<th>Duration of Study</th>
<th>Tested matrixial</th>
<th>Dosage</th>
<th>Power calculations performed</th>
<th>Safety related parameters investigated</th>
<th>Summarized results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, S., Crocher, L., Lynch, B., Chadha, S., B. Summerville, K. (2020).</td>
<td>Randomized, double-blind trial, with a single-blind baseline assessment, with matched placebo</td>
<td>18-45 years, male (24) and female (13)</td>
<td>16-28 days</td>
<td>Highly purified CBD derived from Cannabis sativa L. plant Oral solution (10 mg/ml)</td>
<td>750 mg CBD for 28 days, twice daily for 2 weeks and 4 weeks</td>
<td>No</td>
<td>Adverse effects using MedDRA terms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taylor, 2020</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>There were differences in adverse effects between CBD and placebo mild (10 in CBD 28 days, 6 in CBD 14 days, 9 in placebo) moderate (6 in CBD 28 days) versus 0 in CBD 14 days and 0 in placebo severe (4 in CBD 28 days, 0 in CBD 14 days and 0 in placebo) discontinued volunteers due to adverse events (6 in CBD 28 days, versus 0 in CBD 14 days and 1 in placebo)</td>
</tr>
<tr>
<td>Wardi, T., Bahanger, C., Mueller, J.K., Lange, B., Reznik, Y., et al. (2020).</td>
<td>Randomized, double-blind trial, with parallel groups and placebo control</td>
<td>19-35 years, male (90)</td>
<td>295 days</td>
<td>400 mg CBD capsule Source: STH-Pharm</td>
<td>4 x 300 mg CBD or placebo</td>
<td>Yes – 20% power, 2 sided type 1 error 5%, two-sample Wilcoxon rank sum test, no multiplicity correction</td>
<td>Six emotional categories including performance-related activity, general well-being and emotional reactivity CBD treatment (CBD/PLA) had no significant effect on any of the six emotional categories 1. Performance-related activity 2. General Inactivation 3. Attention 4. General well-being 5. Emotional Reactivity 6. Depressiveness</td>
<td></td>
</tr>
<tr>
<td>Williams, N., Sevi, T., Alia, S., Alia, F., Wardi, T., et al. (2022).</td>
<td>A randomized, double-blind, repeated measures crossta study design</td>
<td>21-49 years, male (36) and female (68)</td>
<td>1 hour to 4 hours</td>
<td>CBD In 5 different preparations: CBD mixture based, CBD powder in waxes, 5% CBD concentrated liquid, 10% CBD concentrated liquid, and 5% CBD concentrated powder Source: STH-Pharm</td>
<td>One preparation at 30 mg CBD standardisation dose in 227 ml water or placebo</td>
<td>No</td>
<td>Heart rate, variability, and Blood pressure CBD treatment, in any preparation, has no significant effect on heart rate variability or blood pressure</td>
<td></td>
</tr>
</tbody>
</table>

Table 19. Results of systematic review
Please note that we have excluded three studies in the final stage – Wilson, et al,(2019), Davies et al. (2020) and Bhattacharyya et al. (2018). The reasons for our exclusion are that antipsychotic medication-naïve clinical high-risk (CHR) participants were used in the study. It is not clear from these papers whether or not cannabidiol was given to the healthy participants. In addition, the authors reported that cannabidiol may partially normalise alterations in parahippocampal, striatal, and midbrain function associated with the CHR state (Bhattacharyya, et al. 2018). This assumes CHR as a clinical condition and described by Fusar-Poli P et al. (2013, 70(1):107, JAMA Psychiatry).

2.10.1.7 Conclusion
While the number of studies is limited, the evidence from well-controlled human experimental research indicates that cannabidiol is not associated with abuse potential. This systematic review provides a thorough assessment of the academic/clinical landscape of literature on whether or not a cannabidiol extract is safe for human consumption.

2.10.1.8 Potential next steps
The key insights and findings from this systematic review can be used to develop follow-up studies in the subject area. We provide below some of the areas upon which the future studies can build.

- Possible systematic review publication on human studies review once EFSA approval process is completed
- Possible systematic review publication from animal-based studies
- Systematic review of other compounds of interest.

2.10.1.9 Limitations
Four databases were searched as agreed. Only peer-reviewed research papers that met our inclusion criteria as specified in Table 18 were included. It is noted that using other databases such as unpublished clinical trials might have provided more information.

We did not set a time or date limit in our search. One of the drawbacks of this was that the cannabidiol search, using the SCOPUS database, identified 8287 records. Therefore, filters had to be applied before exporting the list to the REFWORKS and this is detailed in the method section. While applying filters could be considered one of the limitations, not applying any
time limit is one of the strengths of our systematic review. For example, this has resulted in inclusion of the important paper by Gong Jr et al.\textsuperscript{135} (Appendix B.4).

Our inclusion criteria included the 'healthy adult' population. We noticed a large number of patients were included in the published studies as opposed to healthy participants. Widening this search to clinical risk or diagnosed individuals would have increased a number of studies and/or number of participants per study to review but this could have also resulted in confounding factors and variables. Overall, we are satisfied with our methodological approach and the outputs that our search was able to produce.
2.10.2 Genotoxicity (overview)

In accordance with EFSA guidance on genotoxic testing strategies from its Scientific Committee\textsuperscript{136} two in vitro tests have been carried out, including:

- a bacterial reverse mutation test (OECD TG 471), and
- an in vitro mammalian cell micronucleus test (OECD TG 487).

2.10.2.1 Mutagenicity -- bacterial reverse phase mutagenicity test

The bacterial reverse phase mutagenicity test (AMES) in accordance with OECD 471 guidelines was conducted\textsuperscript{136} in 2021 using test material with batch number 103501b. The aim of the study was to assess gene mutations.

\textsuperscript{136} EFSA Scientific Committee. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379
2.10.2.2  Genotoxicity – in vivo mammalian cell micronucleus test
An in vitro mammalian cell micronucleus test was conducted in accordance with OECD TG 487 guidelines (Test material: batch number 103501b). The aim of the test was to assess both structural and numerical chromosome aberrations (clastogenic and aneugenic effects).
Table 21: Summary table of results from the micronucleus study (MN)
2.10.3 Subacute and Subchronic toxicity studies

2.10.3.1 14-day subacute DRF trial
A subacute 14-day oral dose (gavage) range-finding GLP study was conducted under OECD 407 guidelines to assess suitable dose range based on subchronic toxicity for the 90-day OECD 408 trial to follow.
2.10.3.2  90-day subchronic toxicity

In accordance with OECD 408 guidelines and under GLP conditions a proprietary toxicity study was conducted as informed by the 14-day range-finding study described in Section 2.10.3.1.

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309 Suppo note 3, Section 2.10.3
312 Suppo Note 62
2.10.3.2.1 Results

Table 25: Summary of selected bodyweight, organ weight and observational findings
Table 27: Summary of selected bodyweights and organ weights.
2.10.4 Recovery and additional histopathology
2.10.5 Reproductive and development toxicity – Prenatal DRF trial

In a recent publication from the Committee on Toxicology (COT)\textsuperscript{146,147} it was highlighted that reproductive toxicology was a concern in vulnerable populations. Although the product will be excluded for use by pregnant or lactating women through labelling, we believe that the potential for inadvertent pregnancies is a possibility so a risk analysis should be considered. In consideration of a 3Rs approach to testing,\textsuperscript{148} we considered that a DRF study would provide a proportionate insight into any potential toxicity without implementing a larger-scale Developmental and Reproductive Toxicity (DART) trial. A full study report is accessible in Annex 6.


\textsuperscript{147} Committee on Toxicity of Chemicals in food, consumer products and the environment: Scoping paper on the potential adverse effects of CBD products. TOX/2013/32 Accessed online at: https://cot.food.gov.uk/sites/default/files/tox/2013/32.pdf

2.10.5.1 Reproductive and endocrinological analysis form 408 study

As discussed in Section 2.10.6 below we understand that data from the Epidiolex®
abbreviated study data suggested an increased incidence of the dioestrus/metoestrus phases of
cycle. Similarly, studies by Carvalho et al. (2018)\textsuperscript{149} and Reich et al. (1982)\textsuperscript{150} suggest a
suppressive effect on testosterone and sperm function. Thus, in consideration of these
concerns we assessed these issues during the 90-day study and the results are as follows.

\textsuperscript{149} Carvalho RK, Santos MI, Souza MB, Rocha TI, Guimarães FS, Anselmo-Franci JA, Mazaro-Costa R. Chronic exposure to cannabidiol
induces reproductive toxicity in male Swiss mice. J Appl Toxicol. 2018 Sep;38(9):1215-1223.
\textsuperscript{150} Reich R, Laufer N, Lewy BJ, Cordova-T, Ayali A, Tsahali A. In vitro effects of cannabinoids on follicular function in the rat. Bkvi
2.10.6 Human studies

Please see Section 2.10.1.1 on the systematic review of published human studies. All relevant human studies are assessed in tabular format as prescribed in EFSA administrative guidance (e.g. Appendix B.4 format).\textsuperscript{151}

There is a significant volume of data related to the medicine Epidiolex\textsuperscript{®} and we provide a full review of such data carried out in the UK by the Committee on Toxicity of Chemicals in food, consumer products and the environment (COT). The primary reviews took place in 2019 (TOX/2019/32)\textsuperscript{152} and 2020 (TOX/2020/02).\textsuperscript{153} These studies have a number of limitations as they were carried out on a clinical population that is in many cases polypharmic and known to use anti-epileptic medication (see Section 2.8.10). The studies were conducted with a view to medicinal application where liver function and other potential harms could be monitored. This is not the case for foods, where a risk–benefit approach is not appropriate. The Epidiolex\textsuperscript{®} data is also not readily accessible so we do not know what other impurities or residues are present in Epidiolex\textsuperscript{®} without full characterisation of the medicine, again limitations are present in the use of such data.

We do note the assessment report from the EMA,\textsuperscript{154} but as will a peer review paper we cannot review that actual study in detail or request the study data as we have in this dossier. This was raised by COT as a significant limitation in drawing any conclusions from the GW data in its 2020 opinion.\textsuperscript{155}

\textsuperscript{151} Supra note 4
\textsuperscript{152} Supra note 147
\textsuperscript{153} Supra note 146
\textsuperscript{155} Supra note 145, para 159 and 162.
Additional data is accessible as submitted to the FDA, but again data is limited. However, where a healthy population was used in the studies but on Epidiolex (e.g. Taylor et al. 2018, 2019) we considered these in Section 2.10.1.1.

2.11 Allergenicity

In addition to a literature-based review and assessment of allergenicity, we have given consideration to searches within allergenonline.org and allergenmatch.org and comparedatabase.org. The current data on Cannabis sativa L. as a source of allergens is still in its early phase of clinical investigation (Table 39 summarises possible allergens). Much of the data is difficult to separate the effects of inhalation of Cannabis and respiratory reactions to the burning of materials vs a true sensitisation and/or allergic response, the presence of mould-contaminated Cannabis materials or cross-reactivity with other flavouring fruits in vapes.

<table>
<thead>
<tr>
<th>Molecular weight</th>
<th>Genbank nucleotide</th>
<th>Genbank protein</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 kDa</td>
<td>HE922341.1</td>
<td>CKC33472.1</td>
<td>Lipid transfer protein precursor, partial (chloroplast)</td>
</tr>
<tr>
<td>10 kDa</td>
<td>HE922341.1</td>
<td>P66836.1</td>
<td>Non-specific lipid transfer protein</td>
</tr>
<tr>
<td>30 kDa</td>
<td>XM_0304365673.1</td>
<td>XP_030492533.1</td>
<td>Thaumatin-like protein 1b</td>
</tr>
<tr>
<td>53 kDa</td>
<td>JQ454288.1</td>
<td>YP_009123081.1</td>
<td>Ribulose 1,5-bisphosphate carboxylase/oxygenase large subunit (chloroplast)</td>
</tr>
<tr>
<td>54 kDa</td>
<td>JQ462165.1</td>
<td>YP_009123080.1</td>
<td>ATP synthase F1 beta subunit (chloroplast)</td>
</tr>
<tr>
<td>29 kDa</td>
<td>JQ475070.1</td>
<td>XP_030482568.1</td>
<td>Oxygen-evolving enhancer protein 2, chloroplastic</td>
</tr>
<tr>
<td>49 kDa</td>
<td>JQ450098.1</td>
<td>XP_030492156.1</td>
<td>Ribulose bisphosphate carboxylase/oxygenase activase, chloroplastic isoform X2</td>
</tr>
<tr>
<td>52 kDa</td>
<td>JQ510453.1</td>
<td>XP_030504809.1</td>
<td>Ribulose bisphosphate carboxylase/oxygenase activase 2, chloroplastic-like</td>
</tr>
<tr>
<td>48 kDa</td>
<td>JQ450165.1</td>
<td>XP_030507192.1</td>
<td>Glutamine synthetase leaf isozyme, chloroplastic</td>
</tr>
<tr>
<td>51 kDa</td>
<td>JQ450175.1</td>
<td>PON32724.1</td>
<td>Phosphoglycerate kinase (Trema orientale)</td>
</tr>
<tr>
<td>47 kDa</td>
<td>JQ473002.1</td>
<td>XP_030489218.1</td>
<td>Fluoride export protein 2-like isoform X1</td>
</tr>
<tr>
<td>48 kDa</td>
<td>JQ52228.1</td>
<td>PON00495.1</td>
<td>Glyceraldehyde-3-phosphate dehydrogenase, type I (Trema orientale)</td>
</tr>
</tbody>
</table>

Table 39. Possible allergens in Cannabis sativa. Source: Jackson et al. 2020

However, CS is an anemophilous plant that produces a large quantity of pollen (trizonporate) produced by inflorescence. In Europe we have incidence of rhinitis and asthma symptoms attributed to environmental exposure. However, environment allergens are of limited concern due to controlled and limited cultivation in the EU. The main consideration for allergen exposure in hemp-based foods are from protein-based allergens, and the only allergen recognised by the International Union of Immunological Society (IUIS) is that of the non-specific lipid transfer protein (nslTP) known as ‘Can s3’. These are suggested to be sensitisers in fruits, but the presence in Cannabis extracts and the effects of processing are unknown. A thaumatin-like protein (TLP), ribulose-1,5-bisphosphate carboxylase oxygenase (RuBisCO), and oxygen evolving enhancer protein 2 have also been recognised as potential sensitising allergens in Cannabis.

Despite the possible presence of such allergens/sensitisers in hemp-derived foods, the impact of processing on isolates, and/or the impact of digestion, would likely result in any surviving peptides being immunologically inactive. This seems to be supported by the almost complete absence of reported allergy reports from consumers following consumption of CBD isolates in food form.

The NF subject to this authorisation is an extract and contains none of the 14 mandatory allergens for the purposes of labelling under Annex Regulation 1169/2011.
2.12 Conclusions

The cannabinoids present in the product are naturally occurring substances that may have health-promoting actions as a food substances when provided at a safe dose. The applicant is of the opinion that the use of this plant extract is safe for use as an ingredient in food supplements by adults in the general population; it is not intended for consumption by infants, young children or pregnant or lactating women or those on medication. It will be available in the following dose forms:

- Tinctures
- Soft gel capsules
- Gummies.

Consumption of CBD would not be nutritionally disadvantageous for consumers under the proposed conditions of use in food supplements.

The data supports a possible NOAEL at 90 mg/d based on reversibility in the recovery arm of the study.
The published literature had a different composition, now access to raw data, where not conducted to GLP or OECD equivalent guidelines, used subjects exposed to toxic pharmaceuticals, and had related limitations, so is not expected to provide an accurate comparator.

The submission was generated with proprietary toxicity studies commissioned in accordance with the tiered approach to the safety assessment of food additives (described in the EFSA guidance for submission for food additive evaluations), which is also the default approach for safety assessment of novel foods. These studies were conducted using Organisation for Economic Co-operation and Development (OECD) guidelines and according to the principles of GLP, using the novel food as it is intended to be marketed (i.e. the test material was manufactured according to the described production process and met the compositional characteristics and proposed specifications). The results for the combination of genotoxic, mutagenic, DART and 90-day study demonstrate at the proposed dose was well tolerated after repeat dose subchronic exposure.

Thus, based on the available data and similar consideration of other fat-soluble substances (e.g. vitamins), we see no concern over the chronic use for the proposed dose level.

The weight of the evidence provided in this dossier on the supports the safe use under the proposed conditions of use.
3.0 ANNEXES TO THE DOSSIER

3.1 Glossary and abbreviations

Glossary
ADME  Absorption, distribution, metabolism, and excretion
AE    Adverse Events
AOAC  Association of Official Agricultural Chemists
AUC   Area under the curve
AUC_{last}  Area under the curve last
BO    Boolean Operator
BW    Body weight
BWT   Body weight
CBD   Cannabidiol
CBDV  Cannabidivarin
CBG   Cannabigerol
CBN   Cannabinol
CCP   Critical control points
EC    European Commission
EU    European Union
EFSA  European Food Safety Authority
FSA   Food Safety Authority
FSANZ  Food Standards Australia New Zealand
GLP   Good Laboratory Practice
GMP   Good Manufacturing Practice
HACCP Hazard analysis and critical control points
HPLC  High Performance Liquid Chromatography
ISO   International Organization for Standardization
LB    Lower Bound
MS    Mass Spectrometry
NF    Novel Food
NOAEL No-observed-adverse-effect level
PK    Pharmacokinetics
RH    Relative Humidity
SEM   Standard Error of the Mean
SD    Standard Deviation
SH    Search Hit
SR    Systematic Review
THC   Tetrahydrocannabinol
THCV  Tetrahydrocannabinvarin
TK    Toxicokinetics
UB    Upper Bound
UF    Uncertainty Factor
UHPLC  Ultra-high performance liquid chromatography