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

[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

[2] 21 U.S.C. §301, *et seq.*

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

1. Exclusion from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B).

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.

21 U.S.C. §321(ff)(3)(B). There are two exceptions to §201(ff)(3)(B):

- 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

[3] FDA Response to BioStratum Inc., Docket No. FDA-2005-P-0259 (formerly Docket No. 2005P-0305). Page 14

[4] Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §301 *et seq.* (1998). Pub. L. No. 103-417, §4, 108 Stat. 4325 (1994).

[5] *See, e.g.,* 103 CONG. REC. S17049 (daily ed. Nov. 23, 1993) (statement of Sen. Hatch).

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.[6] 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

[6] 21 U.S.C. §321(ff); 21 U.S.C. §350b(d); and 21 U.S.C. §321(ff)(1).

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*

[7] https://archive.org/details/b24907030/page/50/mode/2up?q=hemp.

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.[8] 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

[8] 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:[9]

> 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.[10] 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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[9] https://www.fda.gov/news-events/press-announcements/fda-advances-work-related-cannabidiol-products-focus-protecting-public-health-providing-market (emphasis added)

[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.[11] AOAC's methods and protocols were properly applied to cbdMD's studied ingredient and demonstrate that cbdMD can ensure the identity of its ingredient,

[11] *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 hepatoxicity 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.[12] 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."[13] are made in public forums, it implies that

[12] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf
[13] https://pubmed.ncbi.nlm.nih.gov/33175977/.

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.[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

[14] *United States v. Two Plastic Drums of Article of Food*, 791 F. Supp. 751 (C.D. Ill. 1991).

supplement product on its scientific merits consistent with statutory and regulatory authorities that mandate the review of a specific product or ingredient.[15] 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

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[15] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=190.6; https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/new-dietary-ingredients-dietary-supplements-background-industry.

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.

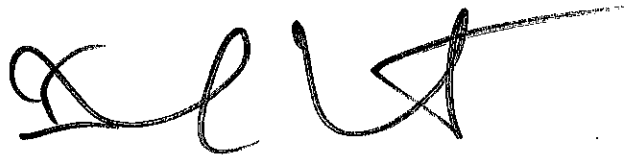
III. ENVIRONMENTAL IMPACT

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.



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Application submitted by:

[redacted]

[redacted]

[redacted]

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Summary of the dossier: Cannabidiol

[redacted]

[redacted] has constructed an application for the authorisation of [redacted] as a novel food ingredient for the European Union. This dossier for a novel food (NF) approval [redacted] 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 [redacted] and produced under GLP/GMP conditions from the 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 include 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 [redacted] 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.

[redacted] These studies are based on a tied 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.

[redacted]

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

[redacted]

1.2.2 Contact (Responsible person)

[redacted]

1.2.3 Name of Novel Food Ingredient

[redacted]

1.2.4 Date of Application

[redacted]

[1] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. OJ L 327, 11.12.2015, p. 1–22

[2] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. C/2017/8874. OJ L 351, 30.12.2017, p. 64–71

[3] European Food Safety Authority. Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal 2016;14(11):4594

[4] European Food Safety Authority. Administrative guidance on the submission of applications for authorisation of a novel food pursuant to Article 10 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.

Member State	Plant part addressed in legislation	Dose range	Comment	Regulation/Legislation
Austria	All	No dose range permissible as Cannabis extract is considered as novel.	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.	Confirmed as novel in a Decree BMASGK-75100/0020-IX/B/16a/2018.
Belgium	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.	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.	Cannabis sativa L. is included in List 1 'Dangerous plants which cannot be used as or in foodstuffs' annexed to the Royal Decree of 29 August 1997 on the manufacture of and trade in foodstuffs composed of or containing plants or plant preparations.	ARRETE ROYAL du 29 AOUT 1997 relatif à la fabrication et au commerce de denrées alimentaires composées ou contenant des plantes ou préparations de plantes (M.B. 21.XI.1997)
Denmark			Considered novel/medicinal and pre-market assessment to be undertaken for all Cannabis extracts. Narcotic classification dependent on THC content.	Executive order no. 950 of 23 June 2020 on euphoriant substances (incl. a list of euphoriant substances) DVFA Guidance on regulations for food containing cannabidiol (CBD) 19 March 2019.
Germany	Cannabis sativa whole plant	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.	THC is considered as unsafe if exceeding Afrd of 70ug or medicinal if THC> 2.5mg. In addition, CBD as an extract is considered as a Nf.	Narcotics Act (BtMG) Annex I. Safety (BfR Opinion No. 034/2018 of November 8, 2018) Novel within meaning of regulation (EU) 2015/2283
Ireland	Cannabis sativa (hemp) is legal for sale	There is approved dose of hemp but the presence of a controlled substance is prohibited.	Cannabis sativa (hemp) is legal for sale but if hemp is processed involving solvents, like supercritical CO_2 or ethanol it is viewed as novel. A dose of THC > 1µg/kg body weight is deemed unsafe.	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)

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 in food supps derived from hemp.		CBD would have been considered as a narcotic under a decree based on THC being a psychoactive substance. However, in 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 Definizione di livelli massimi di tetraidrocannabinolo (THC) negli alimenti. (20A00016) (GU Serie Generale n.11 del 15-01-2020) Under Article. 5 of Regulation (EEC) no. 315/1993 Italy is considering levels of THC that may be a safe contaminant level and now under discussion
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 EC/EFSA.	Novel	Novel within meaning of regulation (EU) 2015/2283
Netherlands	All		According to the Netherlands Food and Consumer Product Safety Authority (NVWA) hemp oil is listed in List I of the Opium Act, and under List II as 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)

* Belgium - https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/consolidated_version_rd_29_august_1997_v10-02-2017_fr.pdf

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.

Country	Plant part	Dose range	Regulation/Legislation
USA	Seed accepted in GRAS notifications as HEMP source but extracts of concentrated CBD/THC or other cannabinoids are not permitted.	<0.3% of THC (U.S.C. § 7129) in hemp no defined threshold for CBD or other cannabinoids.	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(ll) of the Federal Food, Drug, and Cosmetic Act. At state level, CBD from hemp (<0.3% THC) is permissible for recreational use but if sourced from marijuana (>0.3% THC) it is restricted or limited to medical use.
Canada	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.	Hemp-containing products that contain less than 10ppm THC.	Cannabis Act (S.C. 2018, c. 16)
Brazil	Permits the use of cannabidiol only in medical (compassionate) use cases.	<0.2% for prescription-based use but >0.2% in terminally ill. No food use is authorised.	Federal Council of Medicine – Resolution No 2,113 of October 30 2014
Colombia	Permissible for sale in foods and as medicine	Not clear any restriction in dose.	Decree 613/2017 Source: https://asocolcanna.org/normativa/
Uruguay	Permissible for sale in foods and as medicine	Extraction from all plant parts permissible but limit of 1% THC with 0.5% stated for seeds.	Law 19.172
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 [redacted] grown in the USA. The NF is proposed to be added as a food ingredient in 'food supplements' (Directive 2002/46/EC),[5] [redacted], 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.'

[redacted]

[5] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements OJ L 183 , 12/07/2002. P 51 - 57
[6] *Supra* note 2
[7] *Supra* note 3 & 4

2.2 Characterisation of the novel food

2.2.1 Taxonomic review – Cannabis sativa extract [redacted]

The novel food is herein stated as a [redacted] 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).

Rank	**Scientific and Common Name**
Kingdom	Plantae – Plants
Subkingdom	Tracheobionta – Vascular plants
Superdivision	Spermatophyta – Seed plants
Division	Magnoliophyta – Flowering plants
Class	Magnoliopsida – Dicotyledons
Subclass	Hamamelididae
Order	Urticales
Family	Cannabaceae – Hemp family
Genus	Cannabis L. – hemp
Species	Cannabis sativa L. – hemp
Subspecies	Cannabis sativa L. subsp. *Sativa* – hemp
Variety*	C. *sativa* L. subsp. *sativa* (L.) Small et Cronquist var. sativa (L.) Small et Cronquist, Taxon 25 (1976) 421. C. *sativa* L. subsp. *sativa* (L.) Small et Cronquist var. *spontanea* Vavilov, Taxon 25 (1976) 423

Table 3: Taxonomic classification of Cannabis sativa *(Source: Small E and Cronquist A. 1976. A practical and natural taxonomy for Cannabis. Taxon 25(4): 405-43, and the International Plant Name Index (IPNI), The Plant List (TPL) and the World Flora Online Consortium). *Based on classification descriptions of Quimby (1974) and Small & Cronquist (1976).*

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

Arabic	Al-Bhango; Al-Hashish; Al-Qanaap
Chinese	Xian ma; ye ma; Ma-yo; Hou-ma
Danish	Hemp
Dutch	Hennep
English	Hemp; marihuana
French	Chanvre; chanvre d'Inde; chanvre indien
German	Hanf; Haschisch; indischer Hanf
Indian	Bhang; charas; ganja
Japanese	Mashinin
Portuguese	Canhamo; maconha
Russia	Kannabis sativa
Spanish	Mariguana; marijuana

Table 4: Alternate nomenclature for Cannabis sativa. **Source:**[8] Chandra S, et al. 2017

[8] Chandra S, et al. *Canabis Sativa* L. Botany & Horticulture. Pg. 81. In: Cannabis sativa L. Botany & Biotechnology. Eds Chandra S, Lata H, ElSohly MA. Springer International Pub. 2017. Switzerland.

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.[9] 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 axils 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.[10, 11] 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.[12] 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.[13, 14, 15] 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.[16] The estimated size of the haploid genome is 818 Mb for female plants and

[9] Farag, S., Kayser, O., 2017. The cannabis plant: botanical aspects. In: Preedy, V.R. (Ed.), Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, & Treatment. Faculty of Life Sciences and Medicine, King's College, London, United Kingdom, pp. 3–12.
[10] Happyana, N., Agnolet, S., Muntendam, R., Van Dam, A., Schneider, B., Kayser, O., 2013. Analysis of cannabinoids in laser-micro dissected trichomes of medicinal Cannabis sativa using LCMS and cryogenic NMR. Phytochemistry 87, 51–59
[11] Huchelmann, A., Boutry, M., Hachez, C., 2017. Plant glandular trichomes: natural cell factories of high biotechnological interest. Plant Physiol. 175, 6–22
[12] Andre, C.M., Hausman, J.-F., Guerriero, G., 2016. Cannabis sativa: the plant of the thousand and one molecules. Front. Plant Sci. 7, 19
[13] de Meijer de EPM, Bagatta M, Carboni A, Crucitti P, Moliterni VMC, Ranalli P, Mandolino G (2003) The inheritance of chemical phenotype in Cannabis sativa L. Genetics 163:335–346
[14] Mandolino G, Bagatta M, Carboni A, Ranalli P, de Meijer EPM (2003) Qualitative and quantitative aspects of the inheritance of chemical phenotype in Cannabis. J Ind Hemp 8:51–72
[15] Pacilco D, Miselli F, Micheler M, Carboni A, Ranalli P, Mandolino G (2006) Genetics and marker-assisted selection of the chemotype in Cannabis sativa L. Mol Breed 17:257–268
[16] Ming R, Bendahmane A, Renner SS: Sex chromosomes in land plants. Ann Rev Plant Biol 2011, 62:485-514.

843 Mb for male plants, owing to the larger size of the Y chromosome.[17] 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.[18, 19] with recent identification of draft genome sequences for wild type Cannabis sativa.[20] 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).[21] 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%)[22]; and chemotype V, with amounts of all cannabinoids practically undetectable by standard gas-chromatographic analysis.[23]

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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[17] Sakamoto K, Akiyama Y, Fukui K, Kamada H, Satoh S: Characterization; genome sizes and morphology of sex chromosomes in hemp (Cannabis sativa L.). Cytologia 1998, 63:459-464

[18] NCBI database search November 12, 2020

[19] Marks MD, Tian L, Wenger JP, Omburo SN, Soto-Fuentes W, He J, Gang DR, Weiblen GD, Dixon RA: Identification of candidate genes affecting Δ9- tetrahydrocannabinol biosynthesis in Cannabis sativa. J Exp Bot 2009, 60:3715-2610.

[20] Gao S, Wang B, Xie S, Xu X, Zhang J, Pei L, Yu Y, Yang W, Zhang Y. A high-quality reference genome of wild Cannabis sativa. Hortic Res. 2020 May 2;7:73.

[21] Small E, Beckstead HD (1973) Common cannabinoid phenotypes in 350 stocks of Cannabis. Lloydia 36:144–165

[22] Fournier G, Richez-Dumanois C, Duvezin J, Mathieu J-P, Paris M (1987) Identification of a new chemotype in Cannabis sativa: cannabigerol-dominant plants, biogenetic and agronomic prospects. Planta Medica 53:277–280

[23] Mandolino G, Carboni A (2004) Potential of marker assisted selection in hemp genetic improvement. Euphytica 140:107–120

[24] Latta RP, Eaton BJ (1975) Seasonal fluctuations in cannabinoid content of Kansas marijuana. Econ Bot 29:153–163

[25] de Meijer EPM, van der Kamp HJ, van Eeuwijk FA (1992) Characterization of Cannabis accessions with regard to cannabinoid content in relation to other plant characters. Euphytica 62:187–200

[26] Fetterman PS, Keith ES, Waller CW, Guerrero O, Doorenbos NJ, Quimby MW (1971) Mississippi -grown Cannabis sativa L. Preliminary observation on chemical definition of phenotype and variations in THC content versus age, sex and plant part. J Pharm Sci 60:1246

[27] Fairbairn JW, Rowan MG (1975) Cannabinoid pattern in Cannabis sativa L. seedlings as an indication of the chemical race. J Pharm Pharmacol 27:90P (supplement)

[28] Andre CM, Hausman JF, Guerriero G. Cannabis sativa: The Plant of the Thousand and One Molecules. Front Plant Sci. 2016 Feb 4;7:19.

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). [redacted]

2.3.2 Growing information

[redacted]

The cultivation and extraction processes are presented in Figure 1.

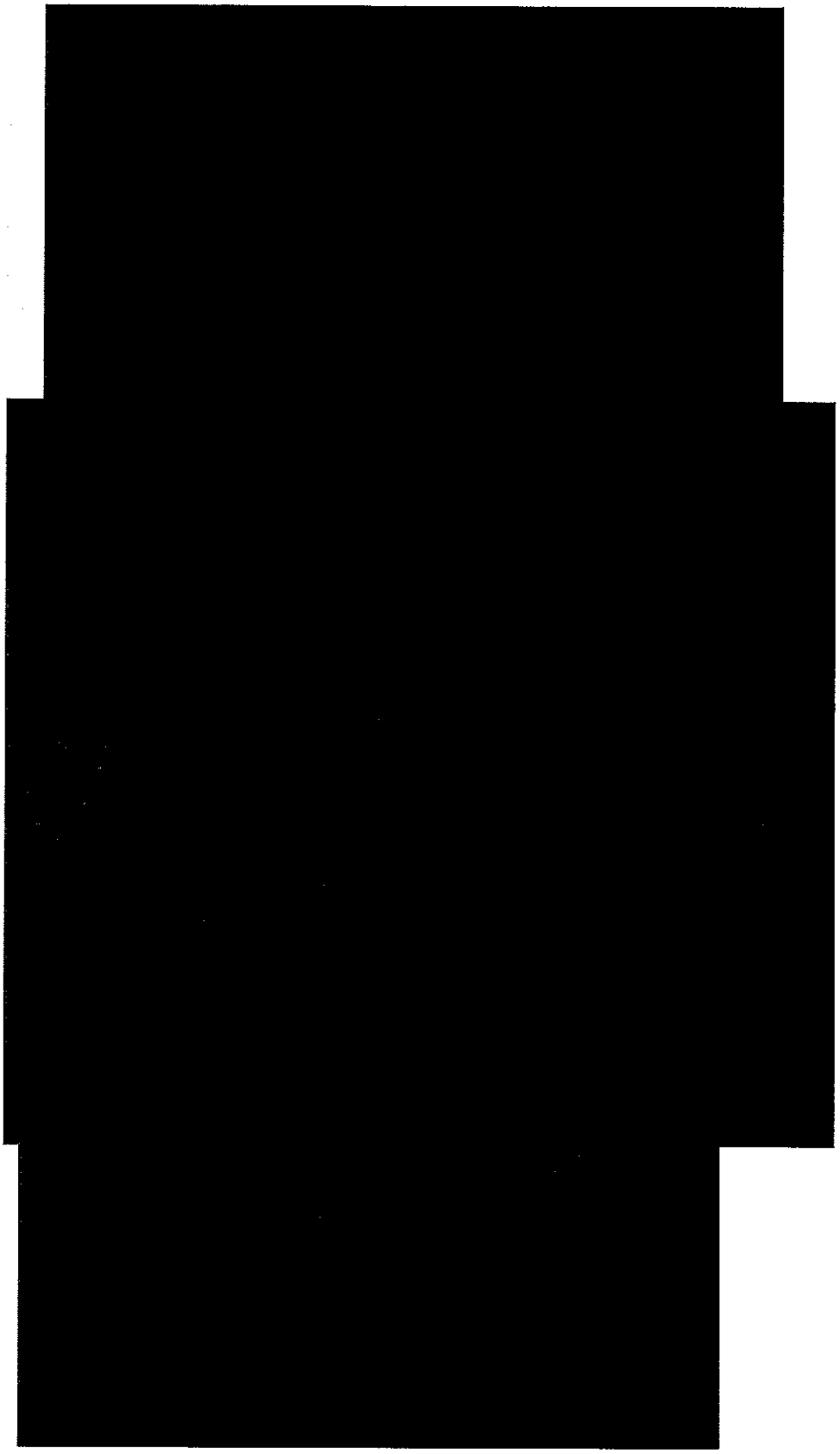

Figure 1: Cultivation & extraction process [redacted]

[redacted]

2.3.3 Extraction information

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

2.3.4 Manufacturing of consumer products & use [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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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- [redacted]

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[redacted]

Third-party testing includes:

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

2.3.5 [redacted] production process

[redacted]

[redacted]

2.4 Compositional data

[redacted]

2.4.1 Analytical methods

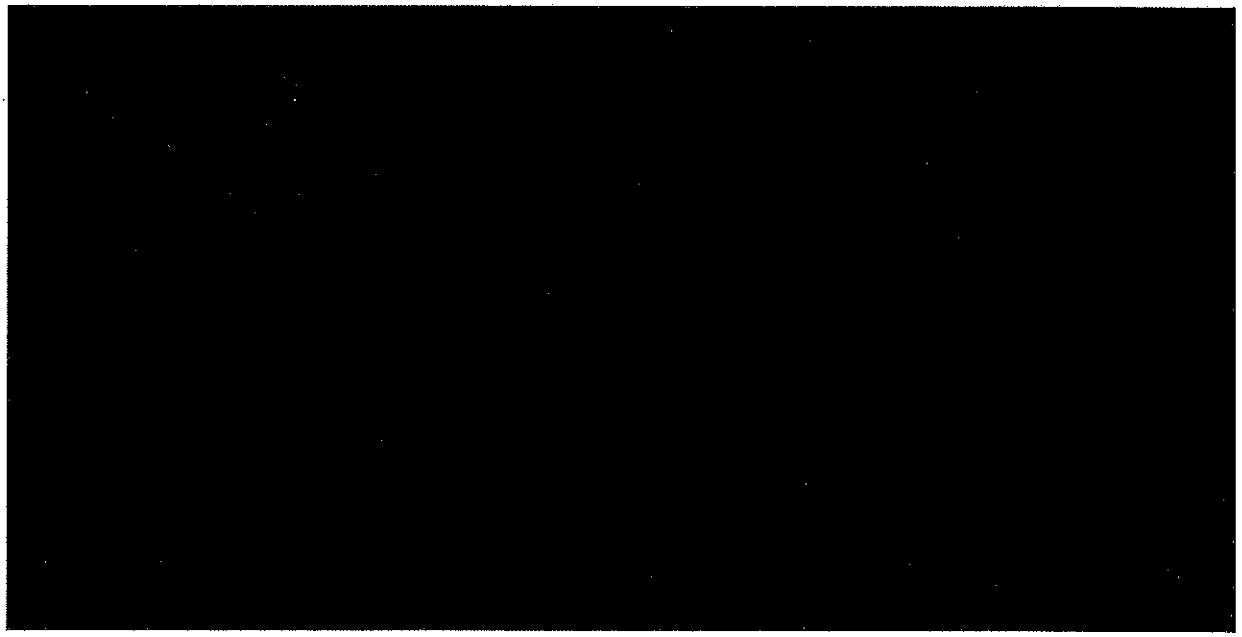
[redacted]

2.4.2 Identity

[redacted]

[30] Vaclavik, L et al. Quantitation of Cannabinoids in Cannabis Dried Plant Materials, Concentrates, and Oils Using Liquid Chromatography–Diode Array Detection Technique with Optional Mass Spectrometric Detection: Single-Laboratory Validation Study, First Action 2018.11, Journal of AOAC INTERNATIONAL, Volume 102, Issue 6, 1 November 2019, Pages 1822–1833,

a. [redacted]



b. [redacted]

Figure 2: [redacted]

[redacted]

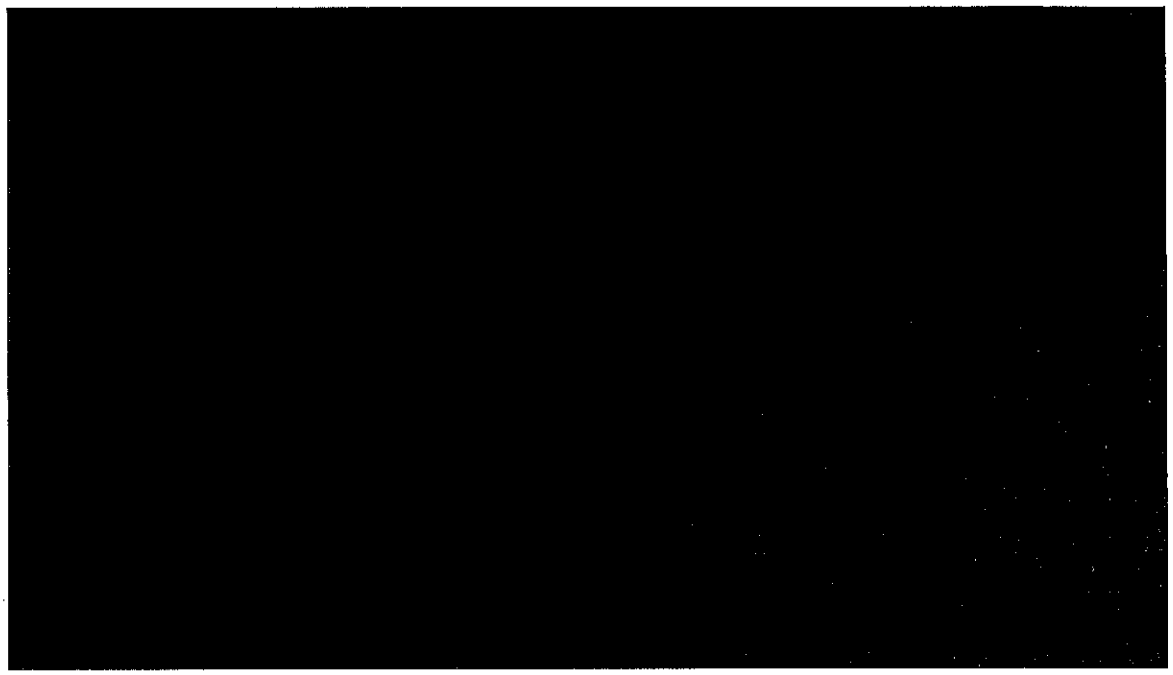


Figure 3: [redacted]

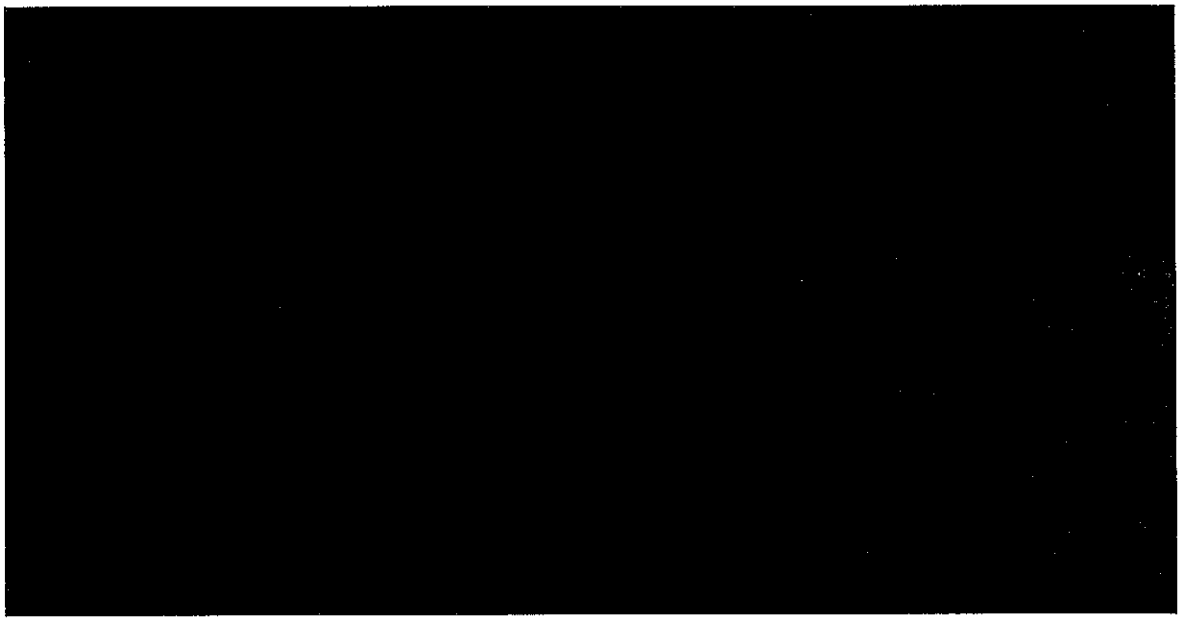


Figure 4: [redacted]

[redacted]

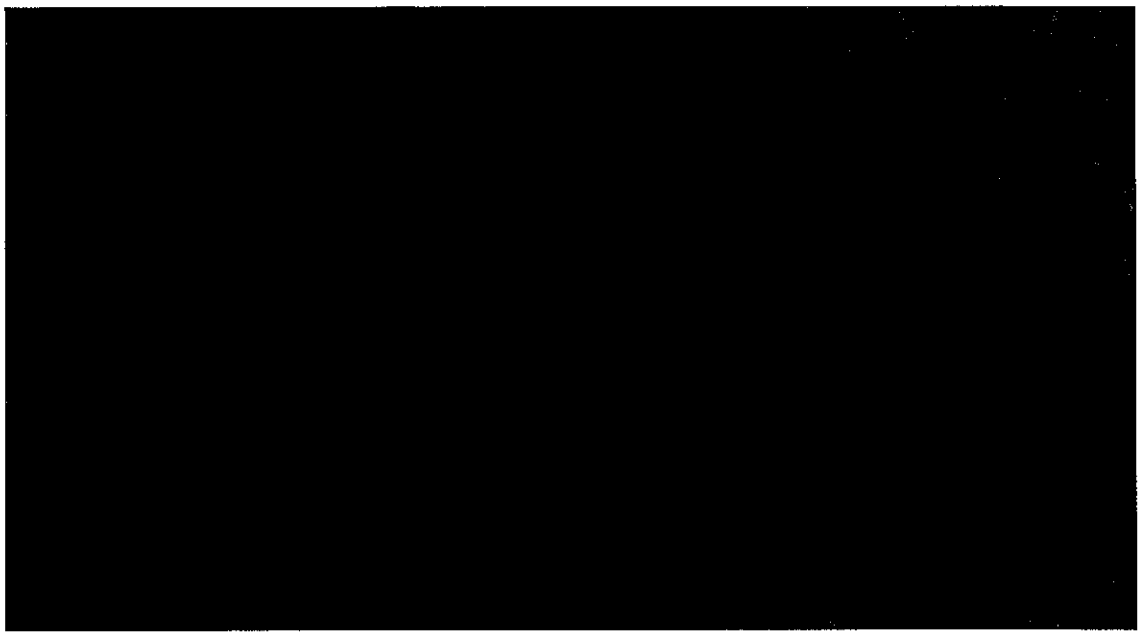


Figure 5: [redacted]

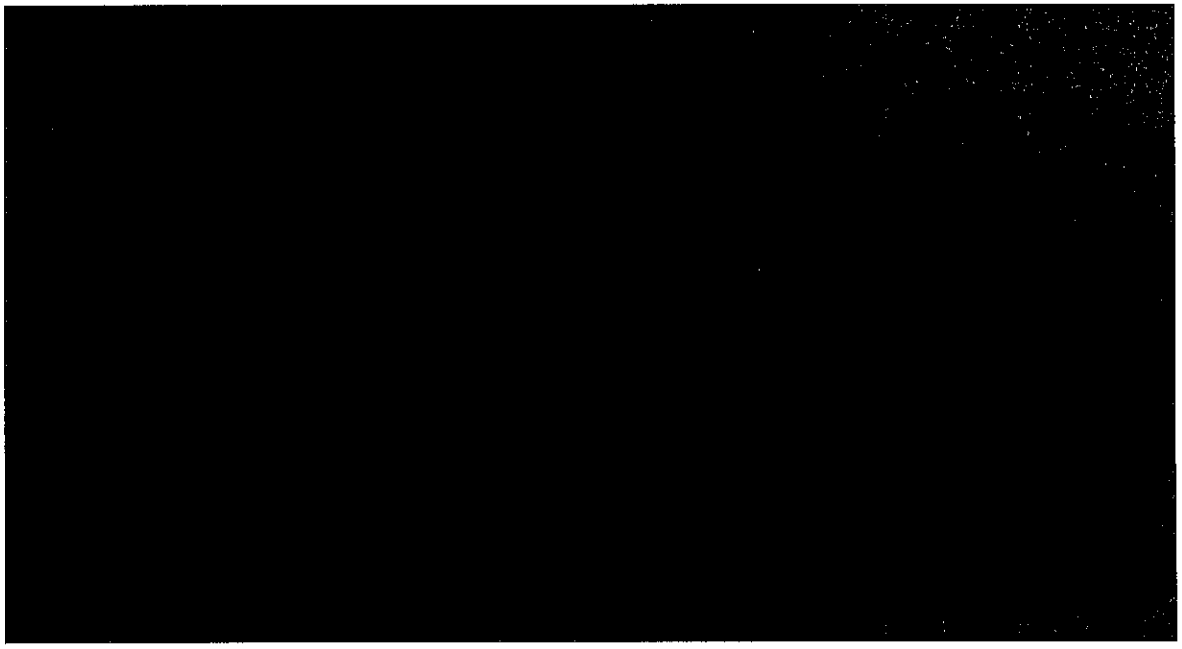


Figure 6: [redacted]

[redacted]

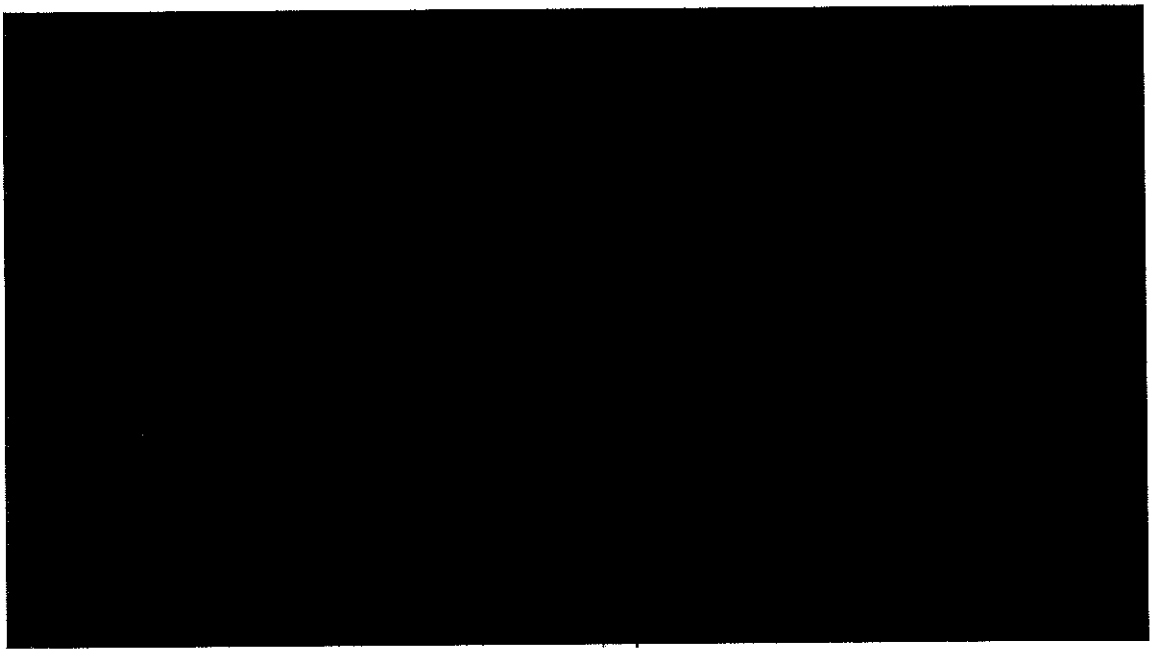


Figure 7: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.4.3 Identity - Physiochemical properties and purity

[redacted]

[redacted]

[redacted]

2.4.4 Product composition

[redacted]

[31] Nelson KM, Bisson J, Singh G, Graham JG, Chen SN, Friesen JB, Dahlin JL, Niemitz M, Walters MA, Paull GF. The Essential Medicinal Chemistry of Cannabidiol (CBD). J Med Chem. 2020 Nov 12;63(21):12137-12155.

[redacted]

[redacted]

Table 5: [redacted]

2.4.4.1 Mycotoxins

[redacted]

[redacted]

[redacted]

Table 6: Mycotoxins analysis of five batches [redacted]

2.4.5 Stability

[redacted]

2.4.5.1 Stability of the novel food under accelerated conditions (6 months)

[redacted]

[redacted]

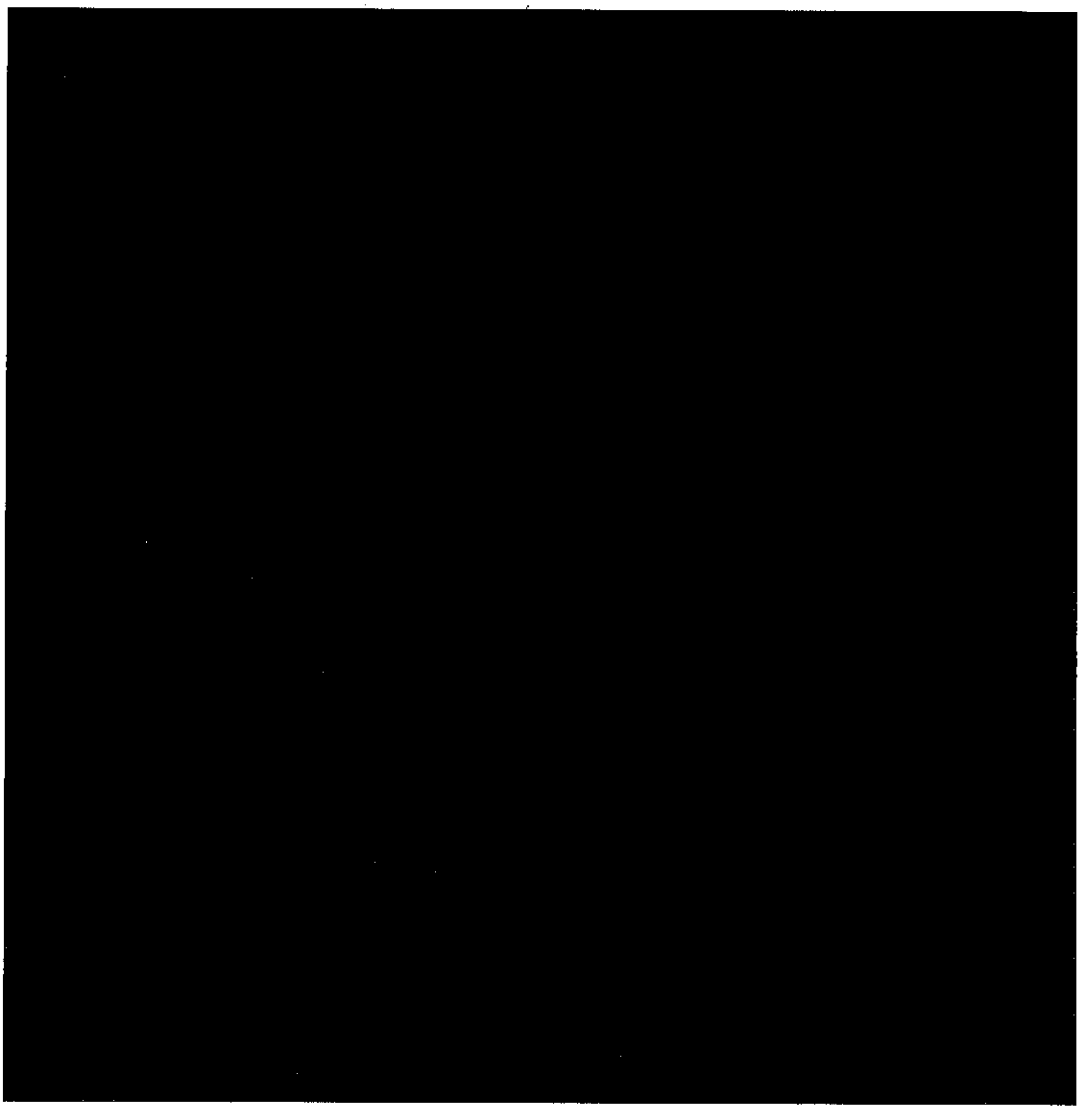


Table 7: Accelerated stability [redacted]

[redacted]

[redacted]

Table 7: Accelerated stability [redacted]

Method: Vaclavik, et al., (2019) J AOAC Int. 102(6) 1822–1833.
Lab Reference: Eurofins Food Chemistry Testing Madison, Inc. ISO/IEC 17025:2005 Certificate Number: 2918.01: Chemical Field of Testing

2.4.5.2 Stability under intended conditions of use

[redacted]

[redacted]

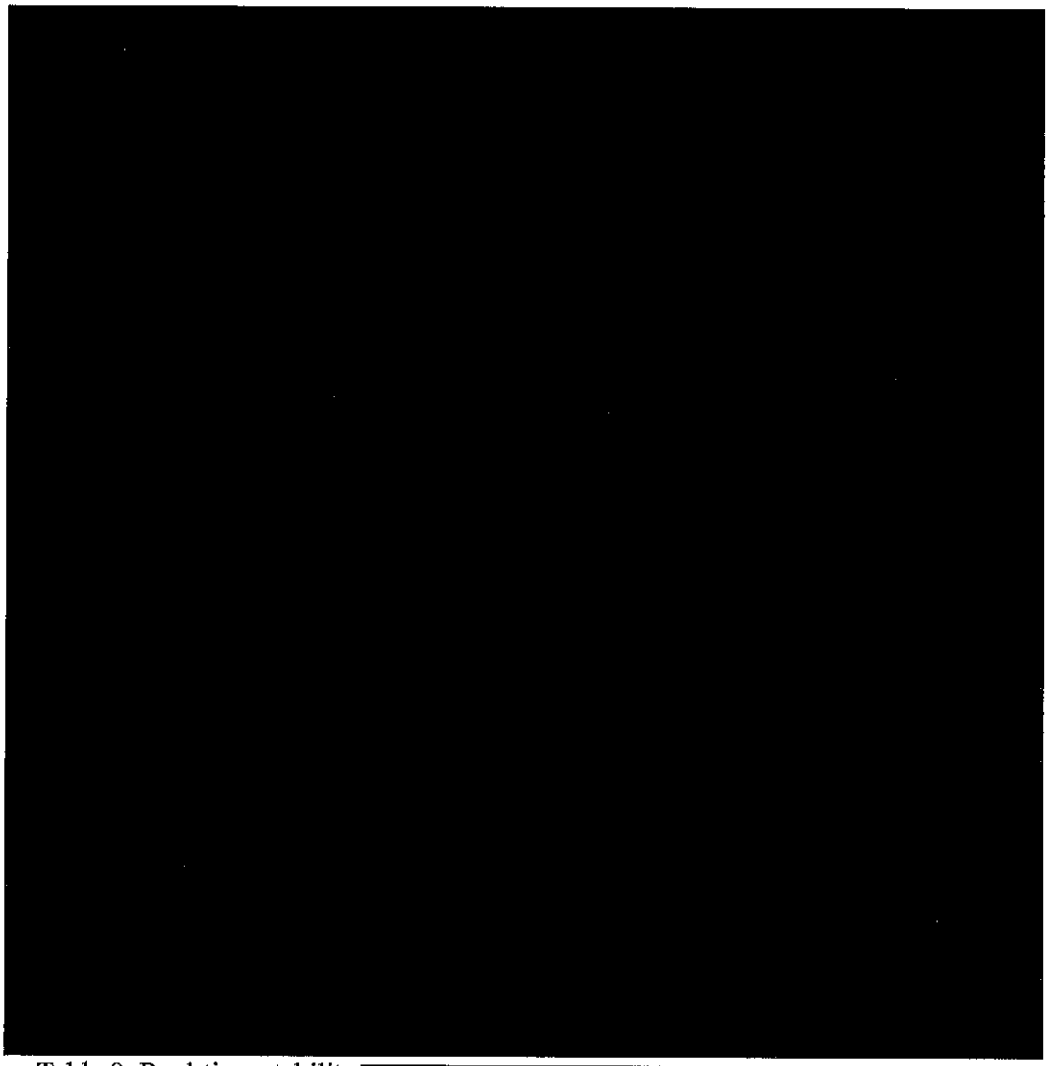


Table 8: Real-time stability [redacted]

Method: Vaclavik, et al., (2019) J AOAC Int. 102(6) 1822–1833.
Lab Reference: Eurofins Food Chemistry Testing Madison, Inc. ISO/IEC 17025:2005 Certificate Number: 2918.01: Chemical Field of Testing

2.5 Specifications

[redacted]

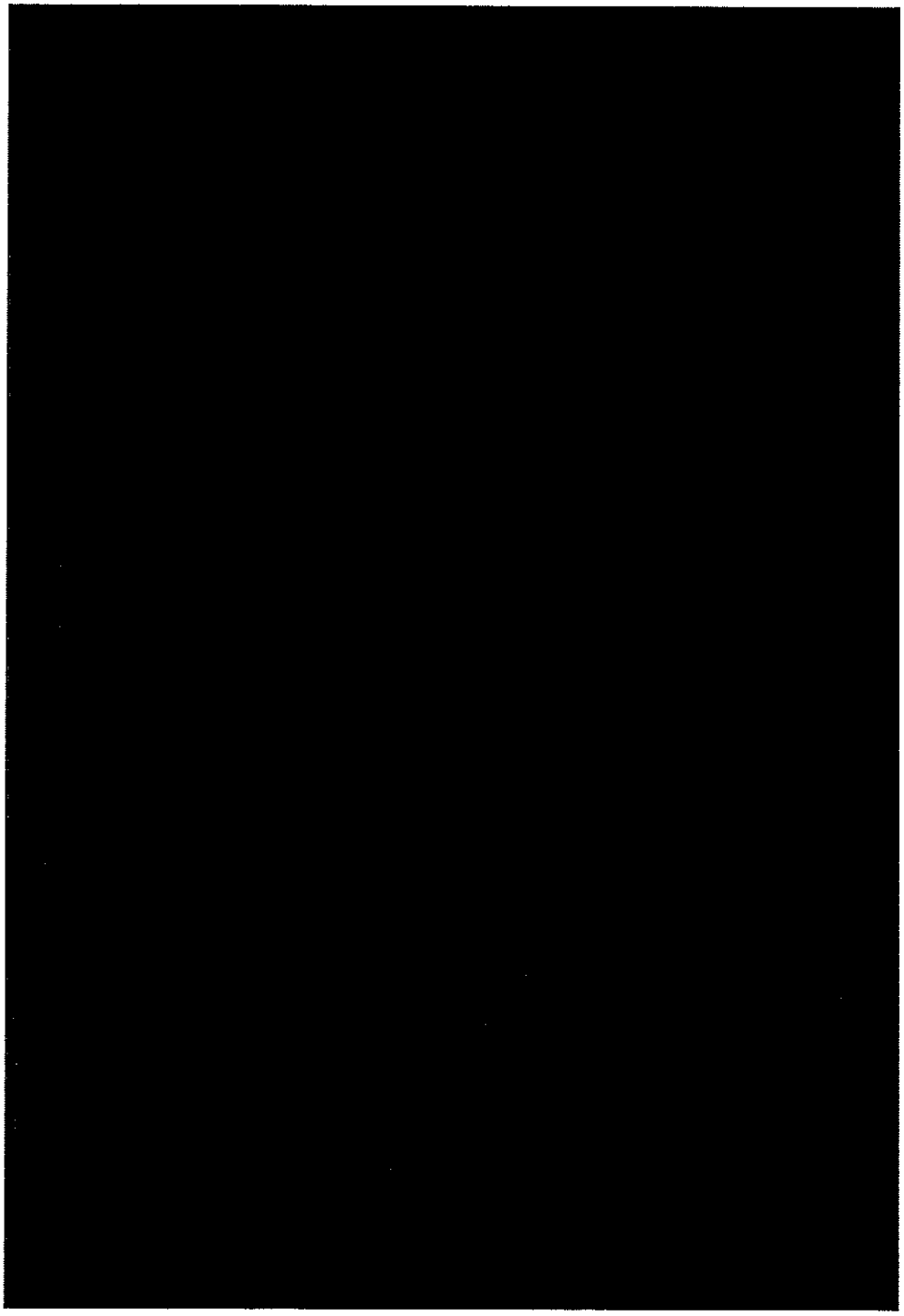


Table 9: Specifications [redacted]

[redacted]

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 tragêmata or 'snacks' consumed while drinking at a symposium (the ancient equivalent of the modern Greek mezedhes), including kannabís (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 (Semientiatka), 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)

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[32] Butrica JL. The Medical Use of Cannabis Among the Greeks and Romans. J Cannabis Thera. 2(2), 2002, pg. 51 - 70

[33] Ratsch C. The encyclopedia of psychoactive plants: Ethnopharmacology and its applications. Park Street Press, USA. 2005. Pg. 147.

[34] Dembinska's M. Konsumpcja Żywnościowa W Polsce Średniowiecznej (Food Consumption in Medieval Poland). 1963. PhD Thesis. Translated in: Hempseed porridge/soup appears to have been served in monasteries, garrisons and to the poor; it's unclear whether the hempseed oil was extracted first (Dembinska, p 113-114). In Woys Weaver W. Food and Drink in Medieval Poland: Rediscovering a Cuisine of the Past. University of Pennsylvania press. USA. 1999

[35] Brown DT. Cannabis: The Genus Cannabis. Harwood academic publishers. 1998. Pg. 14

18. *Ibid*

[36] *Ibid* note 34

[37] Sirek, J., 1955. Vyznam konopné ho semence therapii tuberkulosy (Hempseed in the treatment of tuberculosis). Acta Universitatis Palacklanae Olomucensis 6: 1–13. In Kabelik (1955) Hemp as a medicament. Acta Universitatis Palackianae Olomucensis. TOM VI.1955, p53

[38] Schultes, RE. Random thoughts and quires on the botany of cannabis. In Joyce CRB, Curry SH (eds), The Botany and Chemistry of Cannabis, JA. Churchill, London, UK, p.11-38

[39] Bradshaw THW, Coxon P, Greig JRA, Hall AR. New fossil evidence for the past cultivation and processing of hemp (Cannabis Sativa L.) in Eastern England. 1981. New Phytol. 89(3), 503-510

[40] Kalant OJ. An interim guide to the cannabis (marihuana) literature. Addiction Research Foundation, Bibliographic series 2, p. 1.

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]

[41] Le Strange R. (1977) A history of herbal plants, Arco publishing House Inc., New York, USA. p. 64-65

[42] McPartland JM. Cannabis sativa and Cannabis Indica versus "Sativa" and "Indica". Chapter 4. P 101-121 in Chandra S, et al. Canabis Sativa L. Botany & Horticulture. Pg. 81. In: Cannabis sativa L. Botany & Biotechnology. Eds Chandra S, Lata H, ElSohly MA. Springer International Pub. 2017. Switzerland.

2.7. Proposed uses and use levels and anticipated intake

[redacted]

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.[redacted]

[redacted]

[redacted]

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.

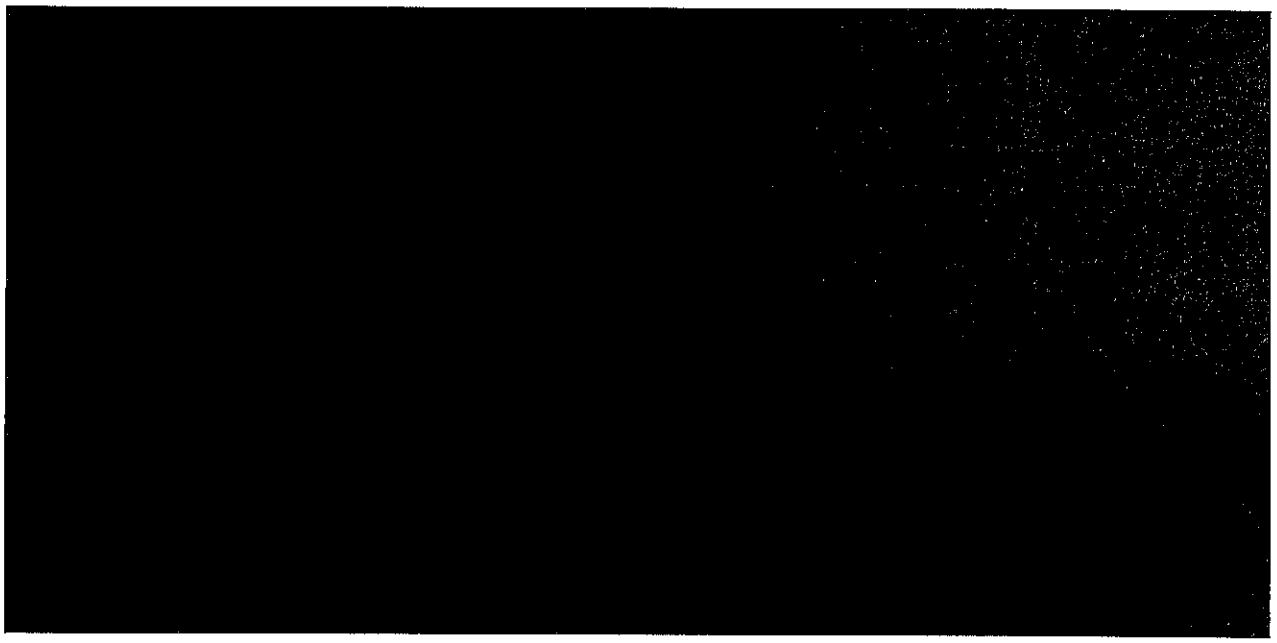
2.7.3. Anticipated intake of the novel food

[redacted]

[43] EFSA.Turck D, et al (2019). Scientific Opinion on the safety of phenylcapsaicin as a novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal. 17(6) 5718, 24 pp.
[44] EFSA. Arcella D, et al. (2020). Acute human exposure assessment to tetrahydrocannabinol (D 9-THC). EFSA Journal. 18(1):5953, 41 pp.
[45] and Astragalus membranaceus (AstraGinTM) as a novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal.18(5) 6099, 16 pp.
[46] EFSA. Turck D, et al. (2020b). Scientific Opinion on the safety of vitamin D2mushroom powder as a novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal. 18(1) 5948, 23 pp.
[47] EFSA, Turck D, et al (2021a). Scientific Opinion on the safety of a change in the conditions of use of galacto-oligosaccharides as a novel food ingredient in food supplements pursuant to Regulation (EU) 2015/2283. EFSA Journal. 19(1) 6384, 9 pp.
[48] EFSA. Turck D, et al (2021b). Scientific Opinion on the safety of water extract of Cistanchetubulosa stems as a Novel food pursuant to Regulation (EU) 2015/2283. EFSA Journal 2021;19(1):6346, 10 pp.
[49] UK Data Service. Health survey for England, 2019. Available: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2019/health-survey-for-england-2019-data-tables REME

[redacted]

[redacted]



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,[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)[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 90th 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 90th percentile.

[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

[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 P1042 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.

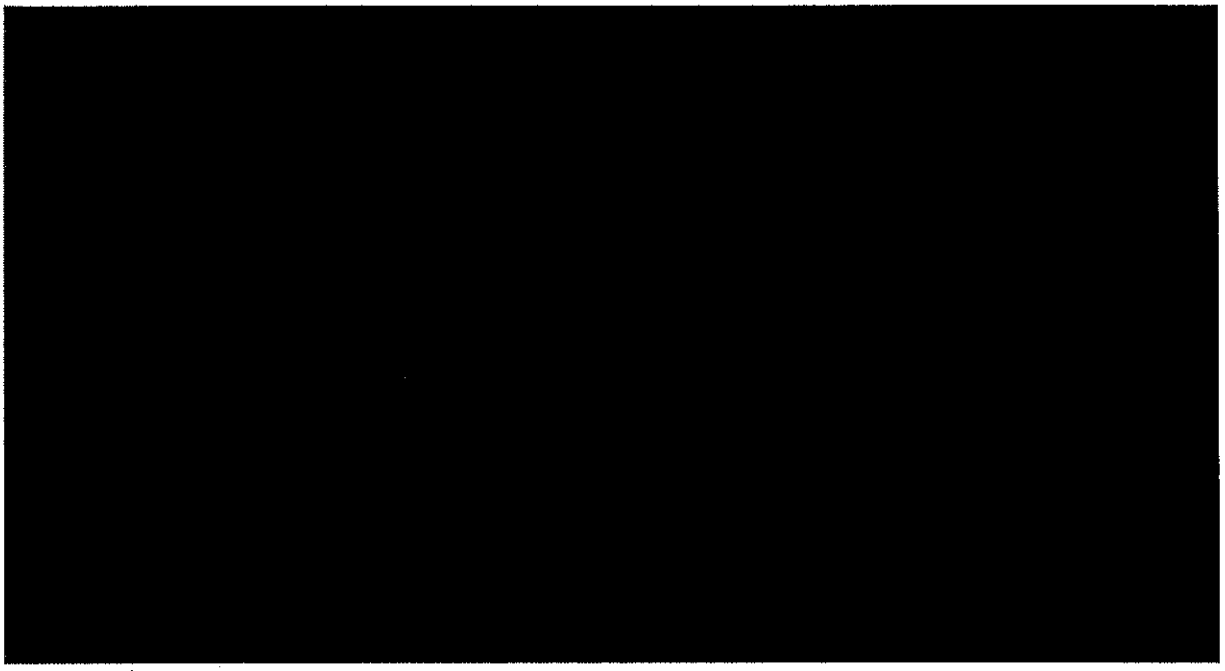
Other potential non-dietary sources (e.g. from consumer products such as cosmetics, and from pharmaceuticals) have also been considered. CBD is used in cosmetic products, in medicines, in vaping and in smoking. Given the extensive uncertainty in exposure to CBD from such products in a rapidly evolving 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 [redacted]

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.

[redacted]



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.[52] A review of PubMed was conducted to retrieve all articles reporting pharmacokinetic data for the primary cannabinoids in the test substance [redacted] (See Table 14).

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

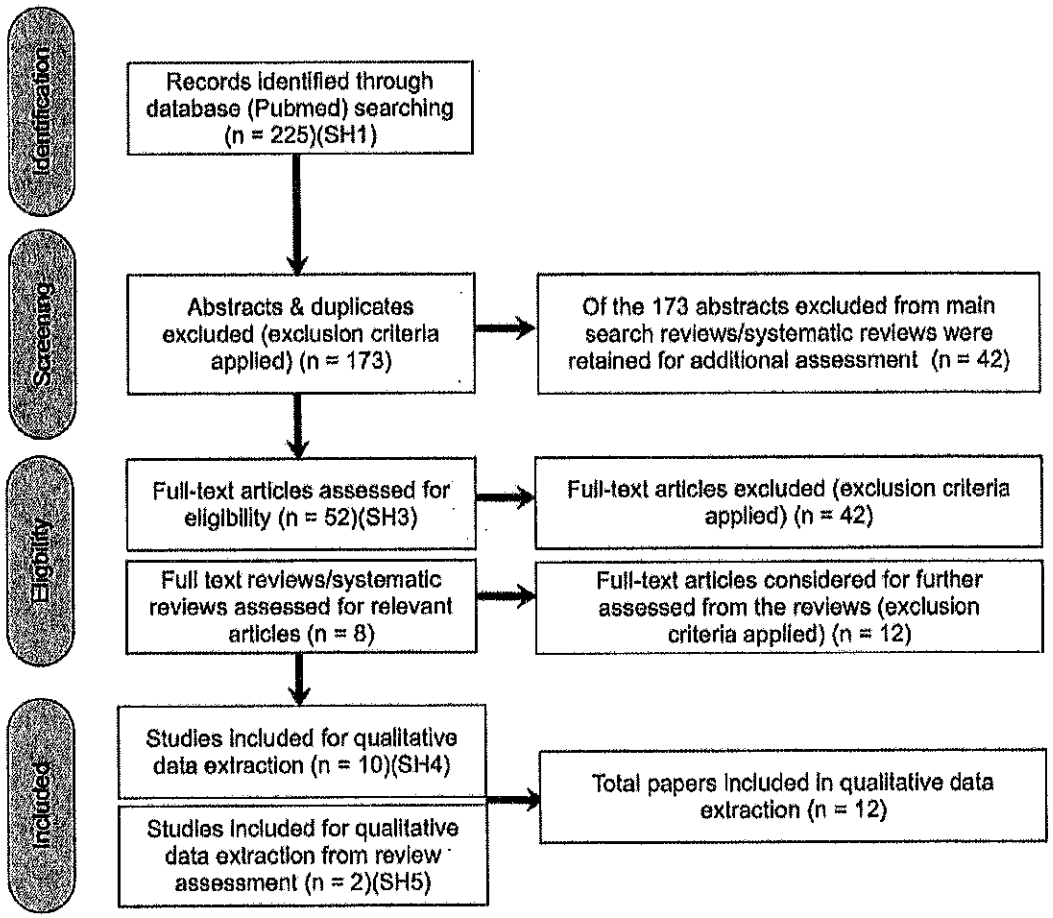


Figure 9: Flow chart identifying study retrieval and selection of relevant ADME studies and related pharmacokinetic data

[52] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097

[redacted]

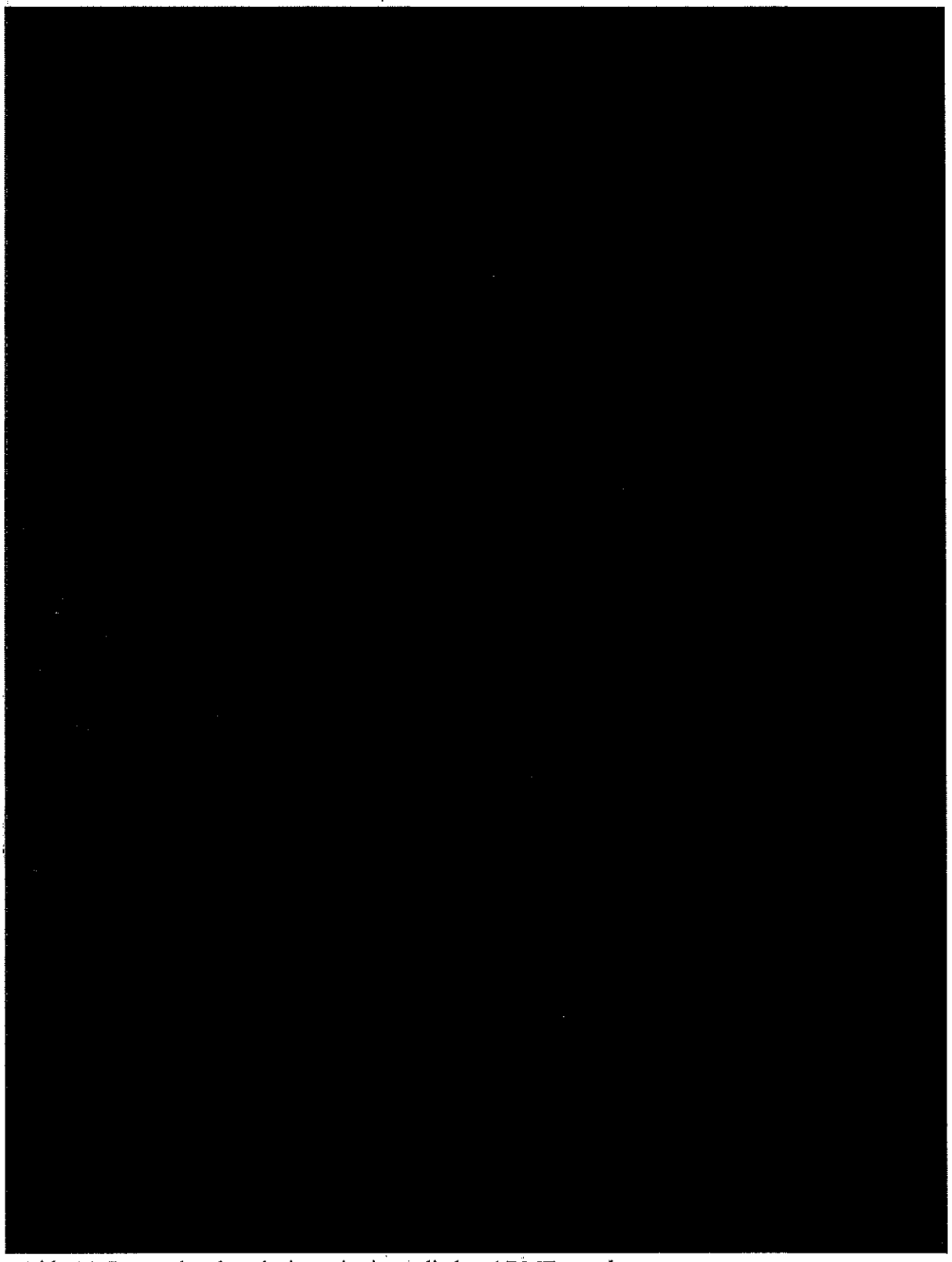


Table 14: Protocol and exclusion criteria applied to ADME search
SE: Search element SH: Number of search hits BO: Boolean operator

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.

[redacted]

2.8.3 Eligibility criteria

In the manual assessment of the papers meeting the search criteria and study question, search terms such as C_{max}, plasma concentration, half-life, peak concentration, absorption, bioavailability, AUC, T_{max}, C_{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]

[53] Ellis GM Jr, Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin Pharmacol Ther. 1985 Nov;38(5):572-8.

[54] Ogungbenro, K., Aarons, L., and Graham, G. (2006). Sample size calculations based on generalized estimating equations for population pharmacokinetic experiments. J. Biopharm. Stat. 16, 135–150.

[redacted]

Table 15a: Summary of data from systematic review of peer reviewed studies [redacted]

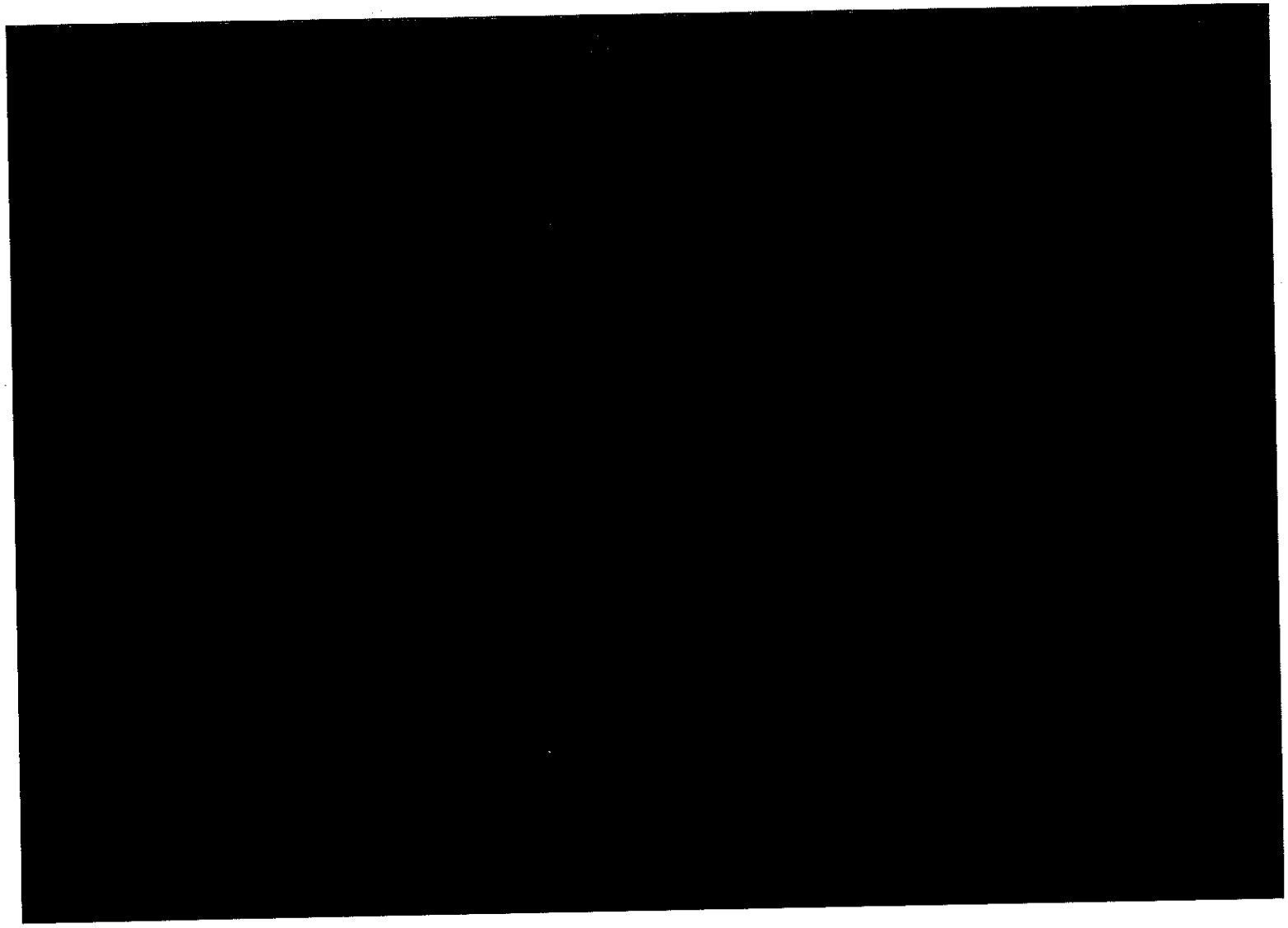


Table 15b: Summary of data from systematic review of peer reviewed studies

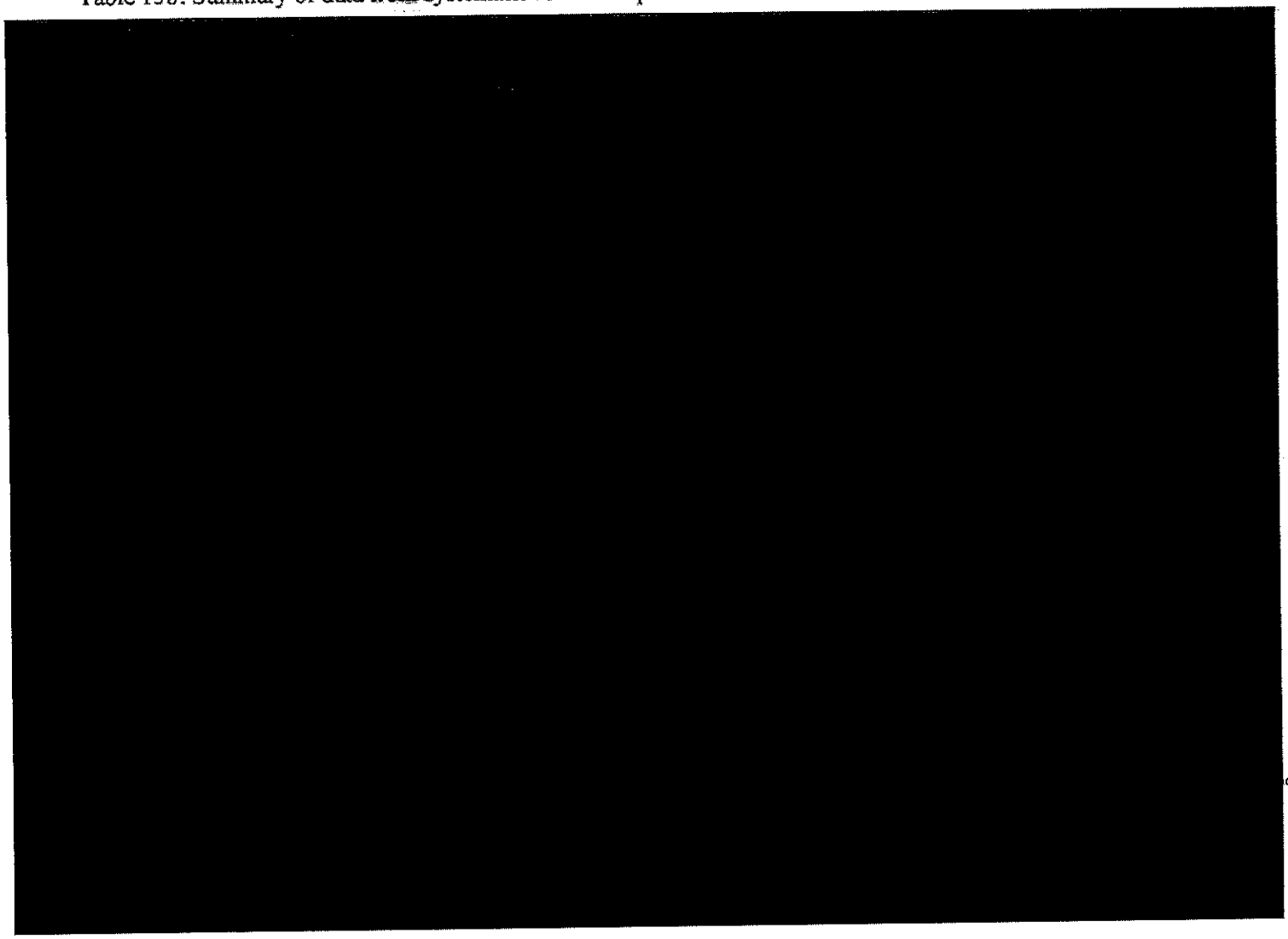
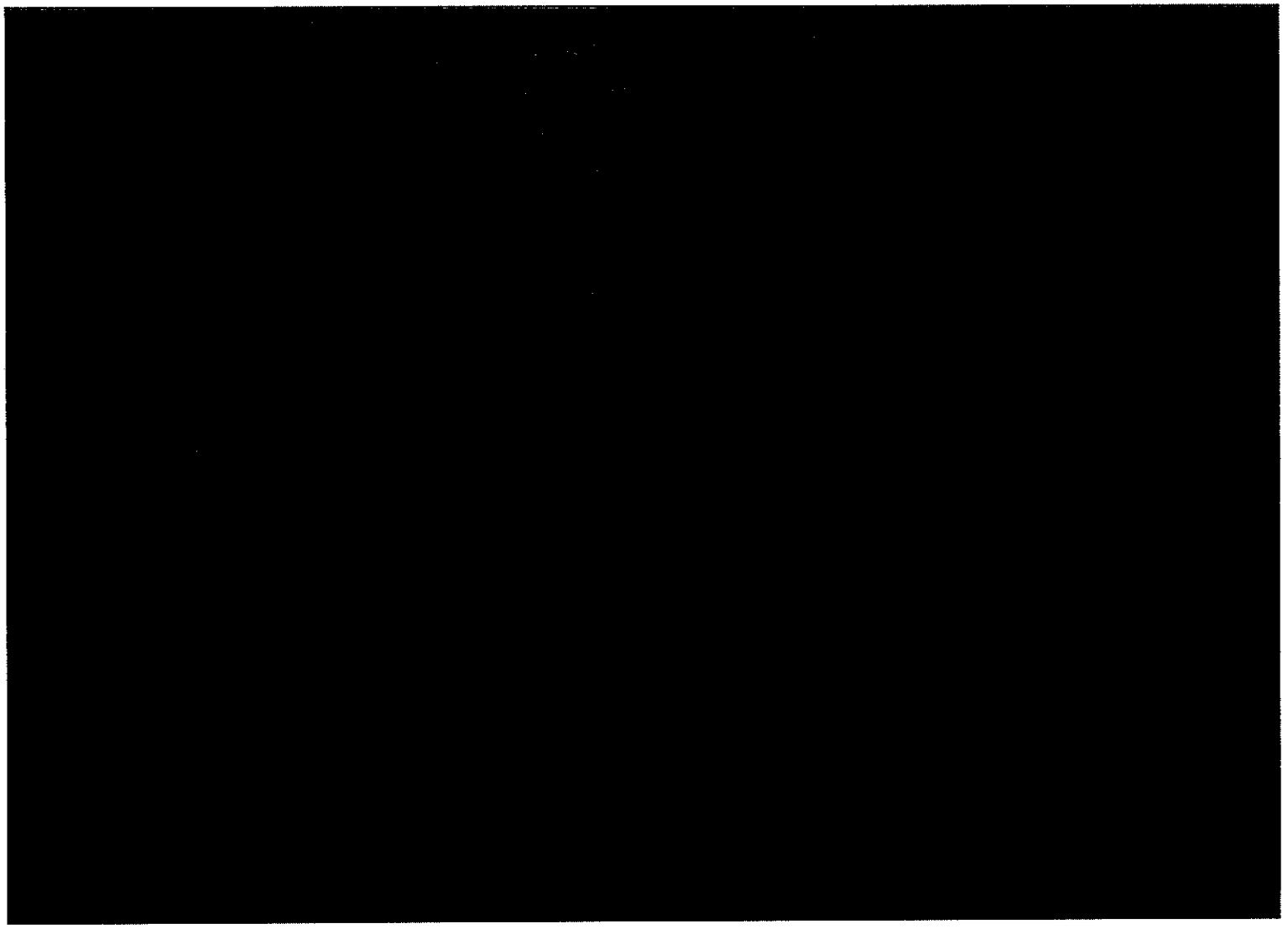


Table 15c: Summary of data from systematic review of peer reviewed studies [redacted]



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[66,67] and because of this may act on different receptors,[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.,[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_{max}: Time to the maximum measured plasma concentration.

C_{max}: Maximum measured plasma concentration over the time span specified.

$t_{1/2}$: Final time taken for the plasma concentration to be reduced by half.

AUC_{0-t}: The area under the plasma concentration vs. time curve, from time zero to 't.' (t = last time point measurement).

$AUC_{0-\infty}$: The area under the plasma concentration vs time curve from zero to t calculated as AUC0–t plus the extrapolated amount from time t to infinity.

[66] Hanus LO, Tchilibon S, Ponde DE, Breuer A, Fride E, Mechoulam R. Enantiomeric cannabidiol derivatives: synthesis and binding to cannabinoid receptors. Org Biomol Chem. 2005 Mar 21;3(6):1116-23

[67] Morales, P, Reggio, PH, Jagerovic, N. An overview on medicinal chemistry of synthetic and natural derivatives of cannabidiol. Front Pharmacol 2017; 8: 422

[68] Bisogno, T, Hanuš, L, De Petrocellis, L, et al Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001; 134: 845–852

[69] Fride, E, Ponde, D, Breuer, A, et al Peripheral, but not central effects of cannabidiol derivatives: mediation by CB1 and unidentified receptors. Neuropharmacology 2005; 48: 1117–1129.

[70] Patrician A, Versic-Bratincevic M, Mijacika T, Banic I, Marendic M, Sutlović D, Dujić Ž, Ainslie PN. Examination of a New Delivery Approach for Oral Cannabidiol in Healthy Subjects: A Randomized, Double-Blinded, Placebo-Controlled Pharmacokinetics Study. Adv Ther. 2019 Nov;36(11):3196-3210

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

K_{el}: 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 C_{max} and AUC (AUC_t and AUC_∞) 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,

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[71] *Supra* note 60

[72] *Supra* note 65

[73] *Supra* note 62

[74] Moghimipour E, Ameri A, Handali S. Absorption-enhancing effects of bile salts. Molecules. 2015;20(8):14451–73.

[75] Zgair A, Wong JC, Lee JB, Mistry J, Sivak O, Wasan KM, Hennig IM, Barrett DA, Constantinescu CS, Fischer PM, Gershkovich P. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. Am J Transl Res. 2016 Aug 15;8(8):3448-59.

[76] Lee JB, Zgair A, Malec J, Kim TH, Kim MG, Ali J, Qin C, Feng W, Chiang M, Gao X, Voronin G, Garces AE, Lau CL, Chan TH, Hume A, McIntosh TM, Soukarieh F, Al-Hayali M, Cipolla E, Collins HM, Heery DM, Shin BS, Yoo SD, Kagan L, Stocks MJ, Bradshaw TD, Fischer PM,

chylomicron-associated molecules (CBD + lipid) secreted from the enterocyte into the lymphatic circulation may avoid significant hepatic first-pass metabolism.[77] 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 kcals) 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 (MCTs) 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[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)[79] 7–10-fold (Crockett et al. 2020)).[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 ± 25mg.

Gershkovich P. Lipophilic activated ester prodrug approach for drug delivery to the intestinal lymphatic system. J Control Release. 2018 Sep 28;286:10-19.

[77] Brocks DR, Davies NM. Lymphatic Drug Absorption via the Enterocytes: Pharmacokinetic Simulation, Modeling, and Considerations for Optimal Drug Development. J Pharm Pharm Sci. 2018;21(1s):254s-270s.

[78] *Supra* 62

[79] *Supra* 62

[80] *Supra* 57

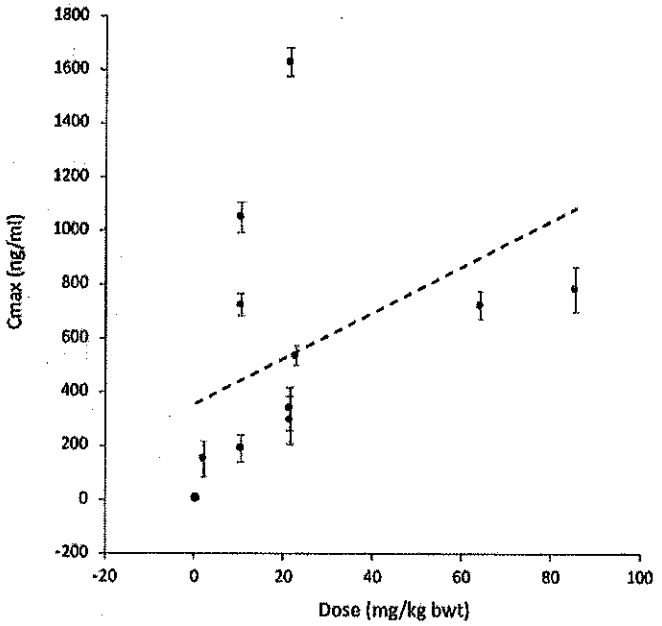

Figure 10: The effect of a single dose of CBD on plasma C_{max} across a systematic review of published human data

However, the extent by which orally administered CBD reaches the systemic circulation is reflected by the AUC and not by C_{max}, which is more a reflection of the rate of absorption.[81] Thus, AUC is a more robust PK measure as it typically includes numerous PK metrics in comparison to only C_{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_{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-∞) = 2759.6 ± 2395 ng.h/ml (Intake Range – 22.6 mg.kg to 26.2 mg/kg)
AUC (0-t) = 2232 ± 2322 ng.h/ml (Intake Range – 19.4 mg.kg to 25.4 mg/kg)

[81] Blaier, M., Arcavi, L., Sussan, S., Volosov, A., Yacobi, A., Moros, D. (1998). Existing and new criteria for bioequivalence evaluation of new controlled release (CR) products of carbamazepine. Epilepsy Research, 32(3), 371–378.

[redacted]

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.

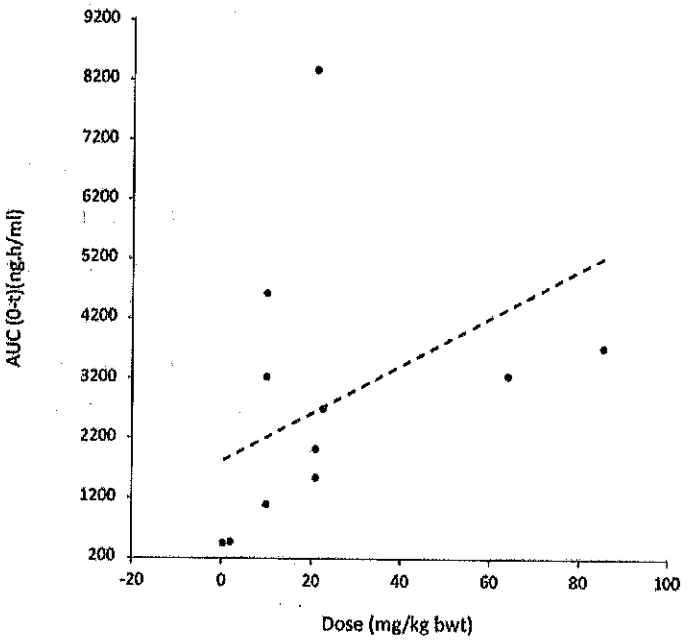

Figure 11. The effect of a single dose of CBD on plasma AUC across a systematic review of published human data

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),[82] 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.

[82] *Supra* 62

[redacted]

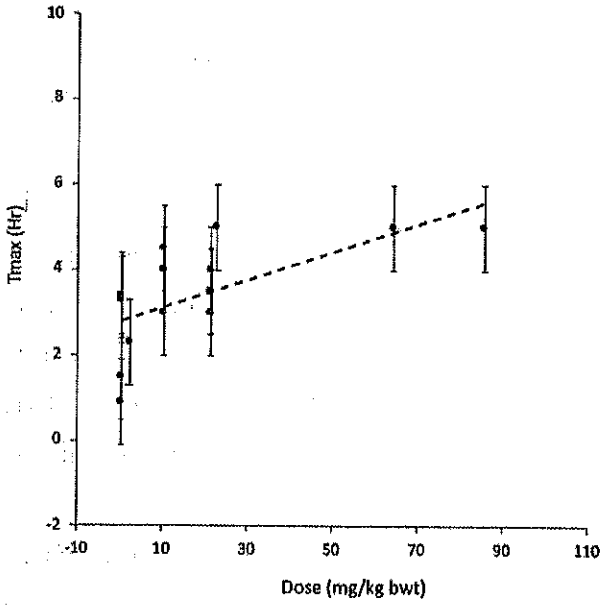

Figure 12: The effect of a single dose of CBD on plasma T_{max} across a systematic review of published human data

The mean half-life ($T_{1/2}$) 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 (K_e) or the absorption rate constant (K_a), 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, $t_{½,eff}$ was used in place of $T_{1/2}$ 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 (V_d) from the review was 368.1 ± 256.2 $L \cdot h^{-1}$ kg^{-1} (range 53.9–612 $L \cdot h^{-1}$ 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.[83, 84] However, these human and indeed similar animal studies[85, 86] 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.[87]

In the review clearance (CL/F) was 754.7 ± 592l/hr (range 154–1,909l/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 154–422l/hr (2.24–21.4 mg/kg) in the fed state equates to 7–21 × (Fasted) and 1.7–4.7 × (fed) hepatic blood flow. In Crockett et al. CBD resulted in a 4-fold greater clearance in the fasted vs fed (high-fat/high-calorie) 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 50–152l/hr (fasted) and 12–34l/hr (fed), which is much closer to the values from an IV injection of 20 mg deuterium-labelled CBD in five health subjects.[88]

2.8.9 Metabolism

[redacted]

[83] Johansson E, Norén K, Sjövall J, Halldin MM. Determination of delta 1-tetrahydrocannabinol in human fat biopsies from marihuana users by gas chromatography-mass spectrometry. Biomed Chromatogr. 1989 Jan;3(1):35-8.
[84] Gronewold A, Skopp G. A preliminary investigation on the distribution of cannabinoids in man. Forensic Sci Int. 2011 Jul 15;210(1-3):e7-e11.
[85] Brunet B, Hauet T, Hébrard W, Papet Y, Mauco G, Mura P. Postmortem redistribution of THC in the pig. Int J Legal Med. 2010 Nov;124(6):543-9.
[86] Leighty EG. Metabolism and distribution of cannabinoids in rats after different methods of administration. Biochem Pharmacol. 1973 Jul 1;22(13):1613-21
[87] Fabritius M, Staub C, Mangin P, Giroud C. Distribution of free and conjugated cannabinoids in human bile samples. Forensic Sci Int. 2012 Nov 30;223(1-3):114-8.
[88] Ohlsson A, Lindgren JE, Andersson S, Agurell S, Gillespie H, Hollister LE. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. Biomed Environ Mass Spectrom. 1986 Feb;13(2):77-83.
[89] Jiang, R., Yamaori, S., Takeda, S., Yamamoto, I., & Watanabe, K. (2011). *Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. Life Sciences, 89(5-6), 165–170.*

[redacted]

2.8.10 Excretion

The overall plasma clearance of CBD varies depending on the fed vs fasted state. Mean elimination rate (K_{el}) 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 [^{3}H]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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[90] Harvey DJ, Mechoulam R. Metabolites of cannabidiol identified in human urine. Xenobiotica 1990;20:303–20.
[91] Zendulka, O., Dovrtělová, G., Nosková, K., Turjap, M., Šulcová, A., Hanuš, L., & Juřica, J. (2016). Cannabinoids and Cytochrome P450 Interactions. Current Drug Metabolism, 17(3), 206–226.
[92] Ibid
[93] *Supra* note 89
[94] Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. Clin Biochem. 2013 Oct;46(15):1323-38.
[95] Wall ME, Brine DR, Perez-Reyes M. Metabolism of cannabinoids in man. In: *The Pharmacology of Marihuana* (Braude MC, Szara S, eds.). Raven Press: New York, 1976, pp. 93–113

2.8.11 Proprietary toxicokinetic study – during OECD 407 trial

[redacted]

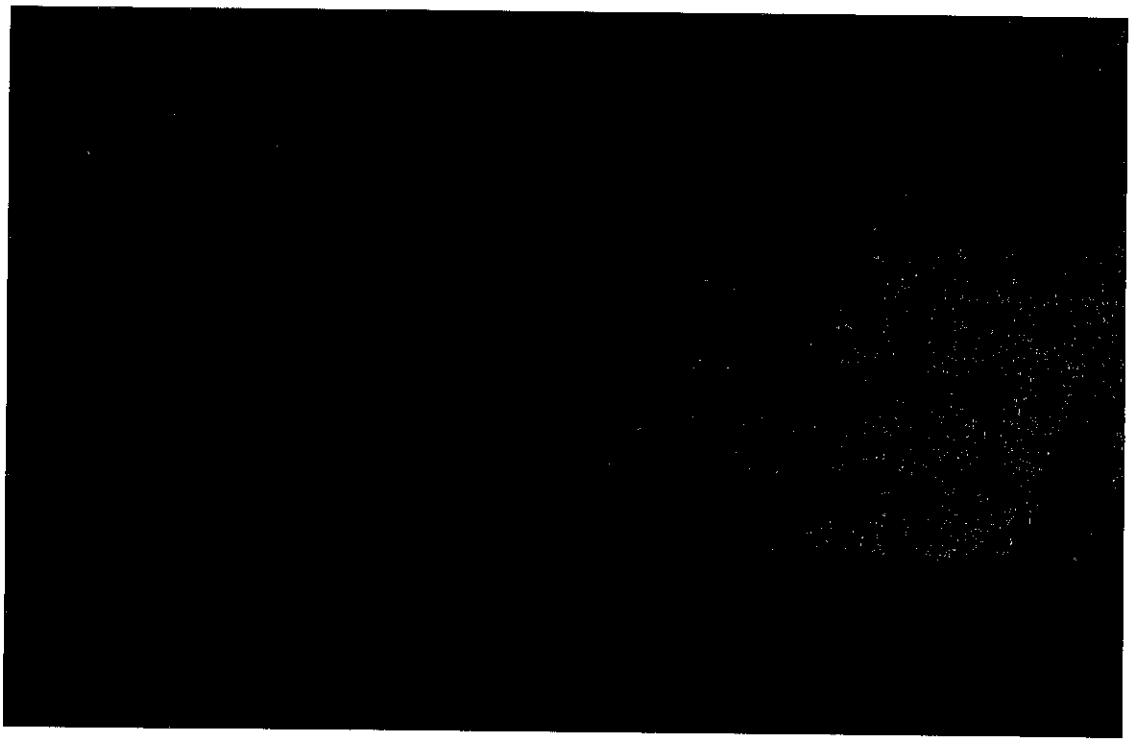


Figure 13: Pharmacokinetic analysis (Non-compartmental model) [redacted]

[redacted]

[redacted]

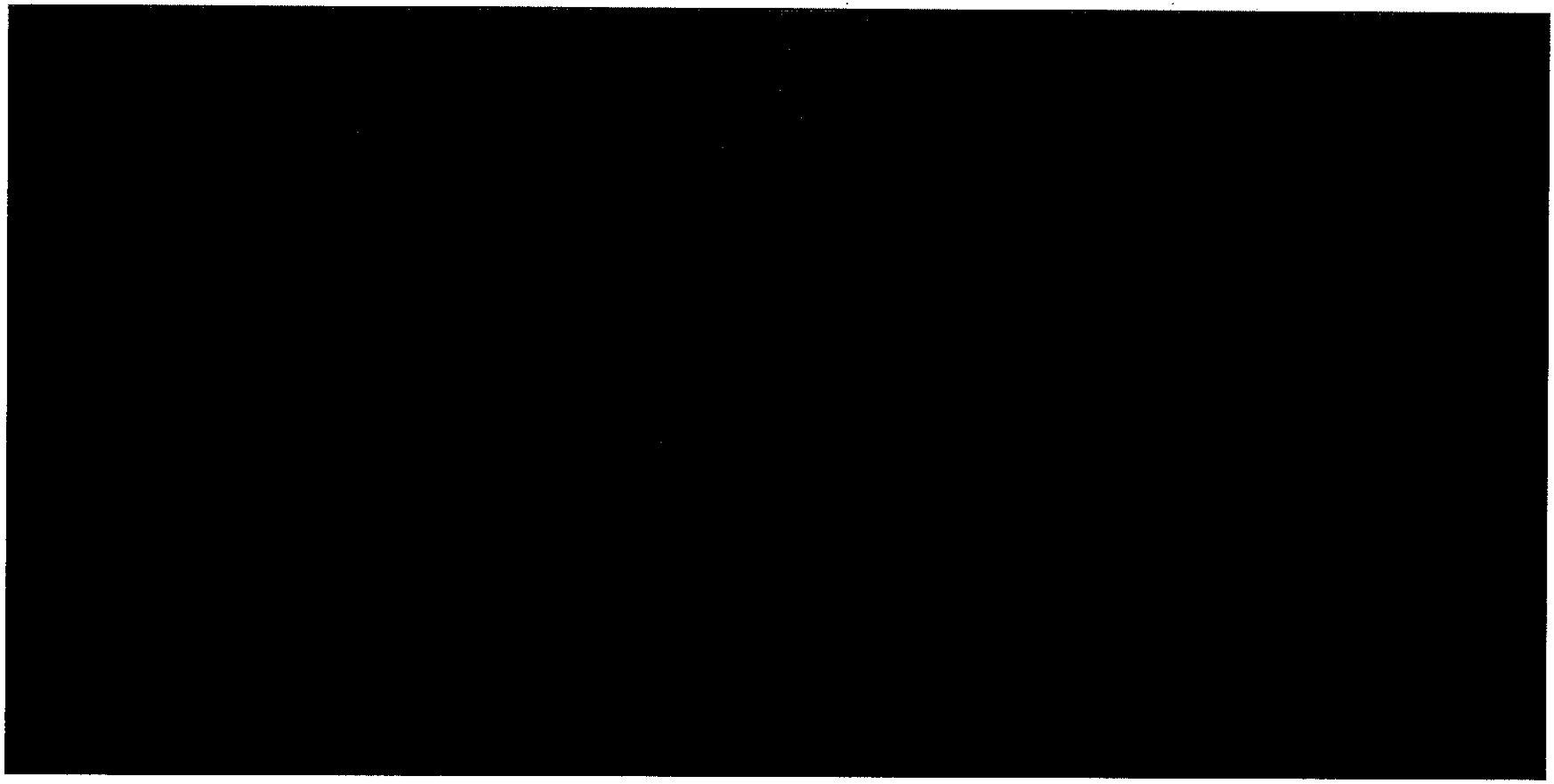
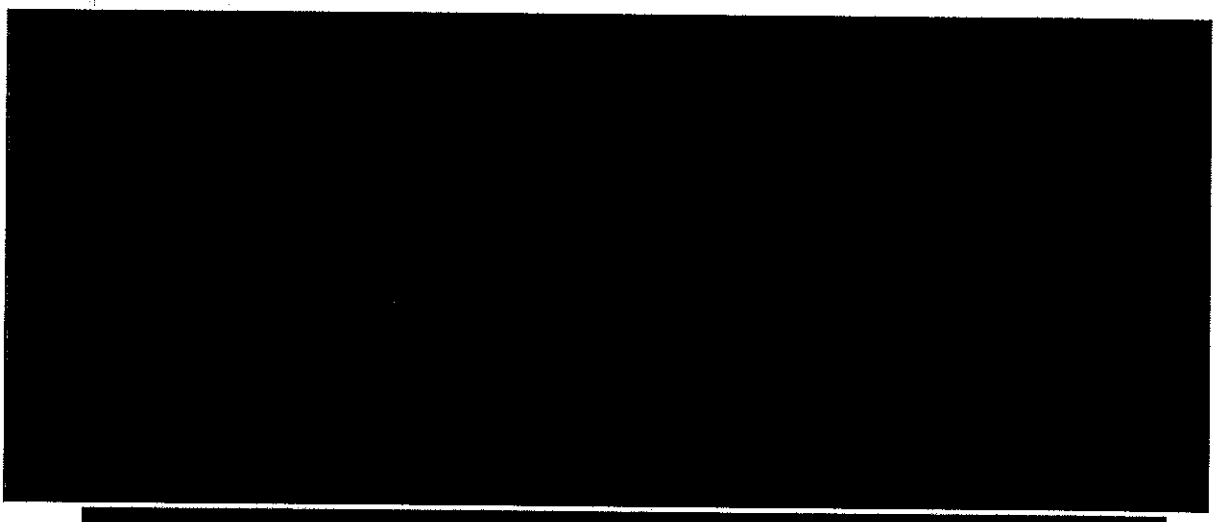


Table 16: Pharmacokinetic [redacted]



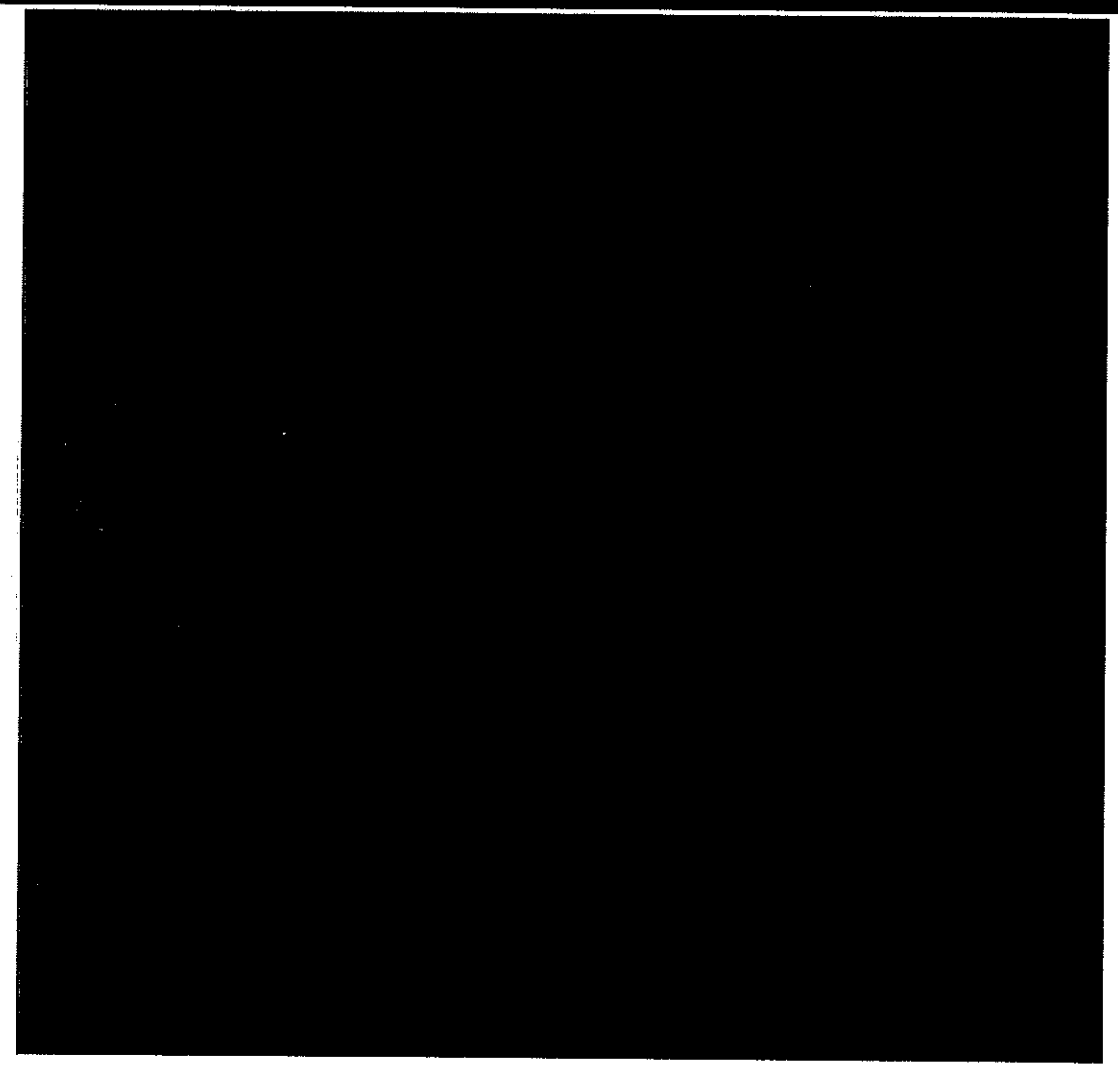


Figure 14: Pharmacokinetic analysis (compartmental model)

[redacted]

[redacted]

[redacted]

Results

[redacted]

[redacted]

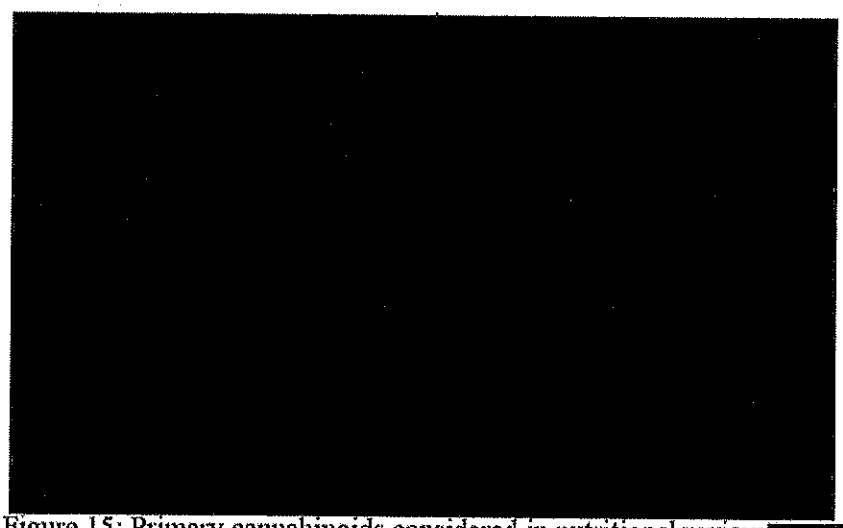


Figure 15: Primary cannabinoids considered in nutritional review [redacted]

[redacted]

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.[104, 105] 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 [redacted] 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 [redacted] 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 [redacted]

Phytocannabinoids are compounds with potentially many molecular targets that when effected result in health benefits of which the most widely publicised is the treatment of disease-related symptoms of epilepsy[107] 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 $G_{i/o}$-coupled protein

[104] CONTAM. Scientific Opinion on the risks for human health related to the presence of tetrahydrocannabinol (THC) in milk and other food of animal origin. 13(6); 2015

[105] Acrella et al. Acute human exposure assessment to tetrahydrocannabinol (Δ9-THC). European Food Safety Authority (EFSA). 18(1); 2020

[106] Kleinhenz, M.D., Magnin, G., Lin, Z. et al. Plasma concentrations of eleven cannabinoids in cattle following oral administration of industrial hemp (Cannabis sativa). Sci Rep 10, 12753 (2020).

[107] Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, Greenwood SM, Roberts C, Checketts D, VanLandingham KE, Zuberi SM; GWPCARE3 Study Group. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018 May 17;378(20):1888-1897.

receptors. CB1 receptors are located throughout the central nervous system[108], as well as within cardiac, lung, small intestine, kidney and liver tissues,[109] and on immune cells.[110] In contrast, CB2 receptors are located on immune cells,[111] in the gastrointestinal tract,[112] and at lower densities within the central nervous system.[113]

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).[114] Other targets will likely include transient receptor potential vanilloid(TRPV) channels and serotonin (5-HT1A) receptors.[115] Whatever the underlying mechanism, the benefits proposed and demonstrated with oral CBD intake include reduction in social anxiety[116, 117] and stress,[118] improved memory, anti-inflammatory benefits,[119] less exercise-related muscle damage.[120]

2.9.4 Nutritional benefits of minor cannabinoids [redacted]

[redacted]

[106] Herkenham M, Lynn AB, de Costa BR, Richfield EK. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. Brain Res. 1991 May 3;547(2):267-74.
[109] Buchholz HG, Uebbing K, Maus S, Pektor S, Afahaene N, Weyer-Elberich V, Lutz B, Schreckenberger M, Miederer I. Whole-body biodistribution of the cannabinoid type 1 receptor ligand [^{18}F]MK-9470 in the rat. Nucl Med Biol. 2017 Sep;52:63-69
[110] Galiègue S, Mary S, Marchand J, Dussossoy D, Carrière D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem. 1995 Aug 15;232(1):54-61.
[111] Núñez E, Benito C, Pazos MR, Barbachano A, Fajardo O, González S, Tolón RM, Romero J. Cannabinoid CB2 receptors are expressed by perivascular microglial cells in the human brain: an immunohistochemical study. Synapse. 2004 Sep 15;53(4):208-13.
[112] Gallazzo G, Giancola F, Stanzani A, Fracassi F, Bernardini C, Forni M, Pietra M, Chiocchetti R. Localization of cannabinoid receptors CB1, CB2, GPR55, and PPARα in the canine gastrointestinal tract. Histochem Cell Biol. 2018 Aug;150(2):187-205
[113] Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005;310:329–332
[114] McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 2015;172(3):737-753.
[115] Ibeas Bih C, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ. Molecular Targets of Cannabidiol in Neurological Disorders. Neurotherapeutics. 2015 Oct;12(4):699-730.
[116] Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schröder N, Nardi AE, Martín-Santos R, Hallak JE, Zuardi AW, Crippa JA. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. Neuropsychopharmacology. 2011 May;36(6):1219-26.
[117] Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE, McGuire PK, Filho Busatto G. Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology. 2004 Feb;29(2):417-26.
[118] Appiah-Kusi E, Petros N, Wilson R, Colizzi M, Bossong MG, Valmaggia L, Mondelli V, McGuire P, Bhattacharyya S. Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis. Psychopharmacology (Berl). 2020 Apr;237(4):1121-1130.
[119] Hobbs JM, Vazquez AR, Remijan ND, Trotter RE, McMillan TV, Freedman KE, Wei Y, Woelfel KA, Arnold OR, Wolfe LM, Johnson SA, Weir TL. Evaluation of pharmacokinetics and acute anti-inflammatory potential of two oral cannabidiol preparations in healthy adults. Phytother Res. 2020 Jul;34(7):1696-1703.
[120] Isenmann E, Veit S, Diel P. Effects Of Cannabidiol Supplementation On The Skeletal Muscle Regeneration After Intensive Resistance Training. Med Sci Sport Ex. 2020; 52(7S):766-766
[121] Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. Br J Pharmacol. 2010 Jan;159(1):129-41.
[122] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008 Jan;153(2):199-215.

[redacted]

[redacted]

[redacted]

[redacted]

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,

[123] Hill AJ, Jones NA, Smith I, Hill CL, Williams CM, Stephens GJ, Whalley BJ. Voltage-gated sodium (NaV) channel blockade by plant cannabinoids does not confer anticonvulsant effects per se. Neurosci Lett. 2014 Apr 30;566:269-74.
[124] Nachnani R, Raup-Konsavage WM, Vrana KE. The Pharmacological Case for Cannabigerol. J Pharmacol Exp Ther. 2021 Feb;376(2):204-212.
[125] Brierley DI, Samuels J, Duncan M, Whalley BJ, Williams CM. Cannabigerol is a novel, well-tolerated appetite stimulant in pre-satiated rats. Psychopharmacology (Berl). 2016 Oct;233(19-20):3603-13.

[redacted]

cyanogenic glycosides and saponins.[126] However, these factors may be trait dependent,[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.[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.

[126] Farinon B, Molinari R, Costantini L, Merendino N. The seed of industrial hemp (Cannabis sativa L.): Nutritional Quality and Potential Functionality for Human Health and Nutrition. Nutrients. 2020 Jun 29;12(7):1935.
[127] Galasso I, Russo R, Mapelli S, Ponzoni E, Brambilla IM, Battelli G, Reggiani R. Variability in Seed Traits in a Collection of Cannabis sativa L. Genotypes. Front Plant Sci. 2016 May 20;7:688
[128] Hurrell RF, Juillerat MA, Reddy MB, Lynch SR, Dassenko SA, Cook JD. Soy protein, phytate, and iron absorption in humans. Am J Clin Nutr. 1992 Sep;56(3):573-8.

[redacted]

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).

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

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

[redacted]

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.

[redacted]

2.10.1.1 Systematic review of published human studies

[redacted]

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:

- [redacted]

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 [redacted]

- 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.**

- MEDLINE – Source types – academic journals used (i.e., guidelines removed)
- PUBMED – reviews removed (included everything else – books and documents, journal article, meta-analysis, RCT and systematic review)

[redacted]

2.10.1.3 Screening

Records from the identification stage were imported to Legacy REFWORKS into individually named folders [redacted] 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).

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

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.

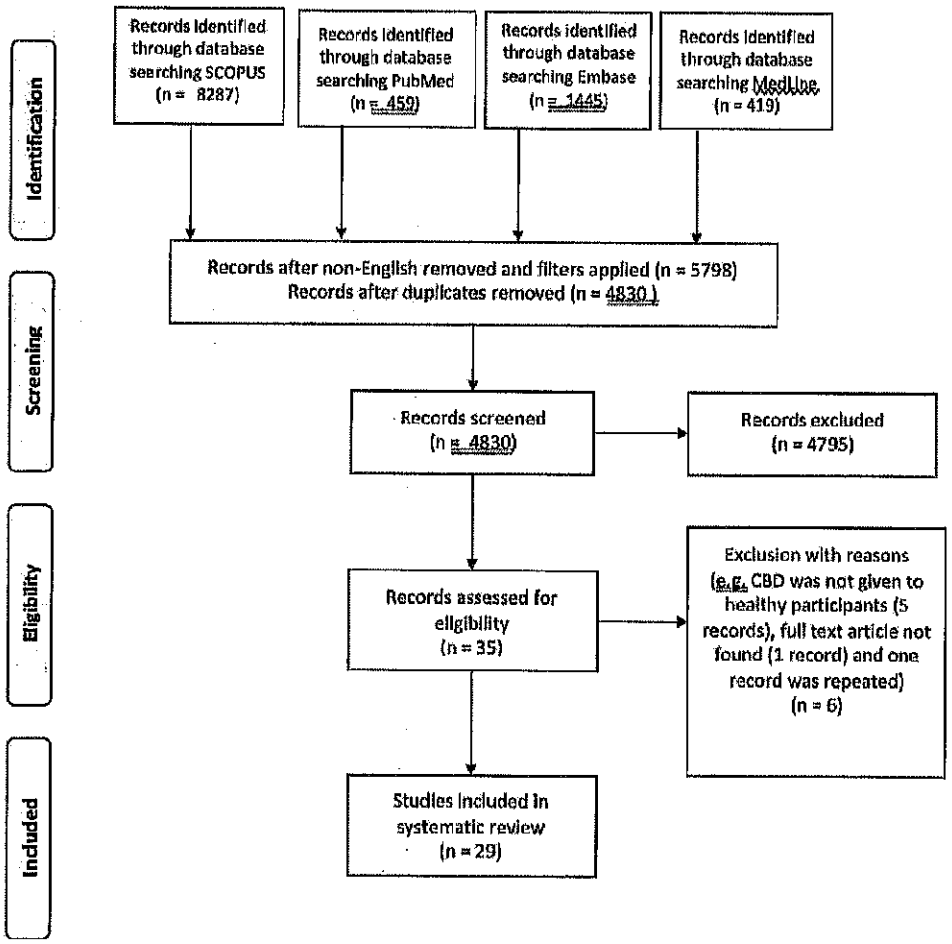


Figure 16: Prisma design employed as part of systematic review of human toxicological analysis [redacted]

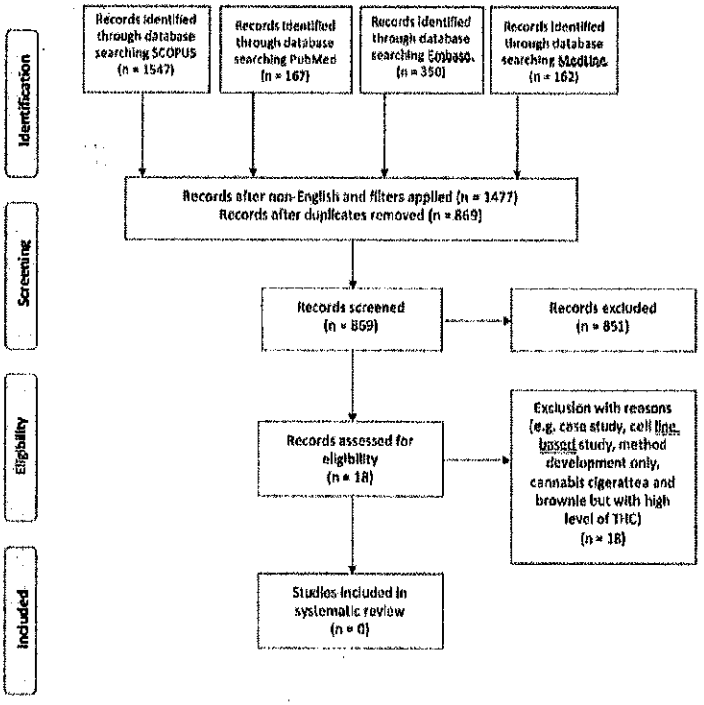


Figure 17: Prisma design employed as part of systematic review of human toxicological analysis [redacted]

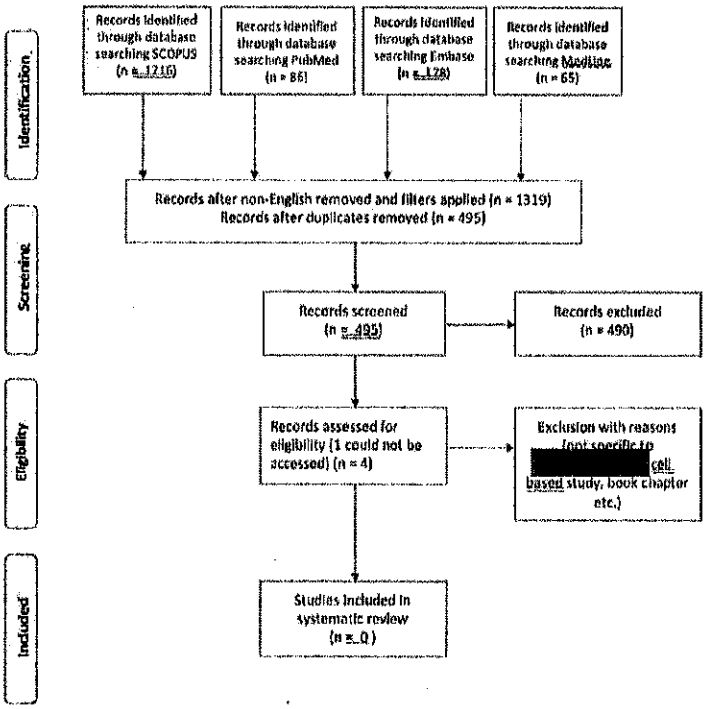


Figure 18: Prisma design employed as part of systematic review of human toxicological analysis [redacted]

[redacted]

Table 19 shows an overview of the human studies identified from the systematic review [redacted] 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); [redacted] ECG (electrocardiogram)

NB: Taylor 2018[129] – Food Effect study not included as no placebo

NB: Patrician 2019[130] – TurboCBD not included as prepared in mixture with other compounds

NB: Taylor 2019[131] – participants with mild, moderate or severe hepatic impairment were not included; not placebo-controlled

NB: Hundal 2018[132] – 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).[133] No significant effect of cannabidiol [redacted] 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.[134] [redacted]

[129] *Supra* 62

[130] Patrician A, Versic-Bratincevic M, Mijacika T, Banic I, Marendic M, Sutlović D, Dujić Ž, Ainslie PN. Examination of a New Delivery Approach for Oral Cannabidiol in Healthy Subjects: A Randomized, Double-Blinded, Placebo-Controlled Pharmacokinetics Study. Adv Ther. 2019;36(11):3196-3210

[131] *Supra* 61

[132] Hundal H, Lister R, Evans N, Antley A, Englund A, Murray RM, Freeman D, Morrison PD. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. J Psychopharmacol. 2018;32(3):276-282

[133] *Supra* 62

[134] Gong H Jr, Tashkin DP, Simmons MS, Calvarese B, Shapiro BJ. Acute and subacute bronchial effects of oral cannabinoids. Clin Pharmacol Ther. 1984 Jan;35(1):26-32

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. [redacted]

Note: The article written by Singh N (1978, 'Effect of cannabinol on human behaviour', *Indian Journal of Physiology and Pharmacology*, 22(2):176–177) is not available (including abstract), despite all the journal archives from January 1957–present being available and accessible (https://ijpp.com/ijpp_archives_new.php/).

[redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Taylor, L., Gidal, B., Blakey, G., Tayo, B., & Morrison, G. (2018). *A phase i, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects.* Taylor 2018		Randomised Double Blind Placebo Controlled	18-45 year Male (17) and female (19)	Single dose: 0.25 to 24 hour Multiple dose: 7 days	CBD from *Cannabis sativa* L plant Pharmaceutical formulation in oral solution (100mg/ml) Source: Endoidex (US); GW Pharmaceuticals (UK) Delivered orally using syringe	Single dose: 1500, 3000, 4500 or 6000 mg Multiple dose: 750 or 1500 mg (twice daily for 6 days, once on day 7)	No	electrocardiogram (ECG) physical examination sleep disruption (numerical-rating scale) Epworth Sleepiness Scale Cannabis Withdrawal Scale MedDRA terms (adverse events (AE))	No clinically significant change in ECG or physical examination No consistent effect on sleep No evidence of drug withdrawal No severe or serious AEs Mild and moderate AEs observed: Single dose: CBD (3000 mg+) caused greater proportion of subjects to experience diarrhoea (3000 mg:83.3%; 4500 mg:50%; 6000 mg:66.7% versus placebo:25%) No impact on other GI disorders (nausea, abdominal discomfort) CBD (1500 mg+) caused greater proportion of subjects to experience headache (1500 mg:16.7%; 3000 mg:16.7%; 4500 mg:66.7%; 6000 mg:33.3% versus placebo:0%) and dizziness (1500 mg: 16.7%; 3000 mg:0%; 4500 mg:16.7%; 6000 mg:33.3% versus placebo:0%) Multiple dose: CBD caused a greater proportion of subjects to experience diarrhoea and nausea CBD caused a greater proportion of subjects to experience headache, dizziness and presyncope At 1500 mg CBD, 33.3% subjects noted a rash compared to 0% in placebo and 750 mg dose groups
Gong Jr. H., Tashkin D.P., Simmons M.S., Calvarese, B., & Shapiro B.J. (1984). *Acute and subacute bronchial effects of oral cannabinoids.* Gong Jr 1984		Randomised Double Blind Crossover Placebo Controlled	21-32 year All male (59) Habitual marijuana smokers, 3-4 day detox prior to study	Dose-response: 1 to 6 hour Acute: 24 and 48 hour Sub-acute: 19 days	CBD CBN Suspended in sesame oil Gelatin capsules Source: National Institute on Drug Abuse	Dose-response: 100, 600 or 1200 mg CBD or CBN Acute: 600 mg CBN or 1200 mg CBD Sub-acute: 600 mg CBN or 1200 mg CBD	No	Systolic and diastolic blood pressure Heart rate Respiratory rate Specific airway conductance Intoxication level (self-reported)	No significant effect of CBN or CBD, versus placebo, at any dose on any of the safety-related parameters in either the dose-response (a), acute (b) or sub-acute (c) studies.

Table 19: Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Taylor, L., Crockett, J., Tayo, B., & Morrison, G. (2019). *A phase I, open-label, parallel-group, single-dose trial of the pharmacokinetics and safety of cannabidiol (CBD) in subjects with mild to severe hepatic impairment.*	Taylor 2019	Open Label Parallel Group	49-66 year Male (4) and female (4)	48 hour	CBD from *Cannabis sativa* L plant Pharmaceutical formulation in oral solution (100mg/ml) Source: Epidiolex (US); GW Pharmaceuticals (UK)	200 mg	No but sample size based on guidance from US Food and Drug Administration and European Medicines Agency	electrocardiogram (ECG) physical examination MedDRA terms (adverse events (AE))	No clinically significant change in ECG, physical examination or AEs
Hundal H., Lister R., Evans N., Antley A., England A., Murray R.M., (2018). *The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group.*	Hundal 2018	Randomised Double Blind Placebo Controlled	18-50 year Male (8) and female (8)	130 mins	Synthetic CBD Pure CBD solubilised in sublingual Et and Labrafil M1944CS Hard gelatin capsule Source: GW Pharmaceuticals (UK)	600 mg	Yes – for whole study (32 participants) – data recorded here from baseline group only)	Persecutory ideation and psychotic-like experiences Affect Cognition Heart rate Blood pressure Salivary cortisol	No significant effect of CBD, versus placebo, on persecutory ideation and psychotic-like experiences, affect, cognition or physiological measures
Patrician A., Versic-Bratincevic M., Mihaljevic T., Barac I., Marendic M., et al. (2019). *Examination of a new delivery approach for oral cannabidiol in healthy subjects: A randomized, double-blinded, placebo-controlled pharmacokinetics study.*	Patrician 2019	Randomised Double Blind Crossover Placebo Controlled	20-28 year All male (12)	0.5-6 hour	Generic CBD from organic multi-spectrum hemp oil Source: Endoca	45 mg CBD (from 150 mg hemp oil) 90 mg CBD (from 300 mg hemp oil)	No	Heart rate Blood pressure Respiratory rate End-tidal PCO_2 Cerebral perfusion Cognition Haematology (haemoglobin, haematocrit, blood cells, platelet count) Inflammation markers (erythrocyte sedimentation rate, C-reactive protein) Metabolic markers (insulin, glucose)	No significant effect of CBD at 45 or 90 mg, versus placebo, on cardiovascular /respiratory measures, cognition, haematology, inflammation or metabolic markers
Hobbs J.M., Vazquez A.R., Bentlan N.D., Trotter R.E., McMillan T.V., Freedman K.E., et al. (2020). *Evaluation of pharmacokinetics and acute anti-inflammatory potential of two oral cannabidiol preparations in healthy adults.*	Hobbs 2020	Randomized Double Blind Parallel arm	22-51 year Male (4) and female (6) 3-day CBD containing products detox prior to study	0.5-6 hour	99.1% CBD 2.5% CBD powder with MCT oil, modified food starch and sorbitol either: emulsified and homogenised (water-soluble CBD) or Non emulsified and non-homogenised (lipid-soluble CBD) Source – Calibar CBD, from hemp plants.	30 mg	No	Blood pressure Inflammation markers (TNF-alpha and IL-10 in peripheral blood mononuclear cells)	No significant effect of either water- or lipid-soluble CBD, compared to baseline levels, on blood pressure, heart rate, pulse pressure or TNF-alpha and IL-10 in peripheral blood mononuclear cells (HR and PP data not included).

Table 19: Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Consroe, P., Carlini, E. A., Zwicker, A. P., & Lucerda, L. A. (1979). *Interaction of cannabidiol and alcohol in humans.*	Consroe 1979	Randomized Double Blind Crossover Placebo Controlled	21-33 year Male (6) and female (4)	0.5-6 hour	99% pure crystalline cannabidiol. Gelatin capsule Source – chemist (R Mechoulam, Israel)	200 mg	No	Attention and concentration (cancellation test; differential aptitude test) Internal perception function (time production task) Motor speed (finger tap test)	No significant effect of CBD, versus glucose placebo, on attention and concentration, internal perception function or motor speed
Appiah-Kusi, E., Petros, N., Wilson, R., Colizzi, M., Bossong, M. G., Valmaggia, L., et al. (2020). *Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis.*	Appiah-Kusi 2020	Randomised Placebo controlled Between groups Double blind study	23-29 years Male (12) and female (13)	One week	STI Pharmaceuticals, UK.	600 mg per day for a week	No	Serum cortisol response and anxiety response to the Trier Social Stress Test.	No impact of CBD, versus placebo, on cortisol response to Trier test.
Arndt D.L., & De Wit, H. (2017). *Cannabidiol does not dampen responses to emotional stimuli in healthy adults.*	Arndt 2017	Double blind Randomised Placebo-controlled	18-35 year Male (19) and female (19) 24 CBD detox prior to study.)	2.5 hr	CBD (300 mg/ml solution) Source: Insys Therapeutics, Inc (IND 125302)	300, 600, 900 mg CBD or placebo single oral dose. CBD was 300 mg/ml solution	No	Heart rate, blood pressure, profile of moods, behavioural tasks	No effect on mean arterial pressure, mood states, attentional bias, emotional stroop or emotion identification at any concentration. Significant increase in heart rate with 900 mg CBD versus placebo.
Belgrave, B. E., Bird, K. D., Chesher, G. B., Jackson, D. M., Lubbie, K. E., Starmer, G. A., et al. (1979). *The effect of cannabidiol, alone and in combination with ethanol, on human performance*	Belgrave 1979	Randomised Double blind Placebo controlled	18-24 year Male (11) and female (4) 1 hr after light breakfast	100 min, 160 min and 220 min Experiment was conducted on 4 successive week ends.	320 µg/kg Source – not specified	CBD dissolved in sesame oil and sealed into caps containing 2.5, 5.0 and 10.0 mg. Each subject – 4 capsules (adjusted dose 320 µg/kg)	No	Standing steadiness test (eyes open and closed), visual reaction time, auditory reaction time and complex reaction time, the Vienna Determination to measure coordination and attention task and Boggles word construction test. Subjective assessment of intoxication and pulse rate.	CBD was inactive. No decrements were recorded in any of the factors and no changes in pulse rate were observed. CBD did not produce a subjective effect not did it effect the intoxication ratings produced by ethanol.

Table 19. Results of systematic review [redacted]

Table 19. Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Bhattacharyya, S., Fusar-Poli, P., Borgwardt, S., Martin-Santos, R., Nosarti, C., O'Carroll, C., et al. (2009). *Modulation of mediotemporal and ventrostriatal function in humans by Δ9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis.*	Bhattacharyya 2009	Double-blind, randomized, placebo-controlled, Repeated-measures, within-subject design	15 people, mean age 26.7 years, no gender detail 2 hrs before session light breakfast	1, 2 and 3 hour study	A gelatine capsule containing 600 mg CBD, 99.9% pure (source: THC-Pharm, Frankfurt, Germany)	600 mg CBD	No	Visual Analog Mood scale, State-Trait Anxiety Inventory by Spielberger, Analog Intoxication Scale, and Positive and Negative Syndrome Scale(PANSS).Heart rate and blood pressure	No significant effect was noted of either drug on heart rate, blood pressure, or performance in the verbal paired associate learning task as measured by recall score.
Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., et al. (2010). *Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology.*	Bhattacharyya 2010	Placebo controlled, double-blind, repeated measures, within-subject design	Male (18) and Female (3) 2 hrs before session light breakfast	1, 2 and 3 hour study	source: THC-Pharm	600 mg CBD Gelatin capsule	No	Visual Analog Mood scale, State-Trait Anxiety Inventory by Spielberger, Analog Intoxication Scale, and Positive and Negative Syndrome Scale (PANSS).Heart rate and blood pressure	There was no change in psychotic symptoms, and a trend for a reduction in subjective anxiety was found. No significant effects on behavioural performance of the verbal memory, viewing fearful faces or the response inhibition.
Bird, K. D., Boleyn, T., Chesher, G. B., Jackson, D. M., Starmer, G. A., & Teo, R. K. C. (1980). *Intercannabinoid and cannabinoid-ethanol interactions and their effects on human performance.*	Bird, 1980	Double blind Placebo controlled	18-35 years Male (122) and females (39)	6 successive weeks ends (i.e 12 days) 100 min after cannabinoid administration and then at hourly intervals, 2, 3 4 hours	Source – Not specified	CBN, CBD were dissolved in sesame oil and sealed into caps containing 2.5, 5.0. 10.0 or 20.0 mg. Each subject was given six capsules with the dosage of CBD and CBN adjusted to deliver approx. 320 ug/kg.	No	Standing steadiness (eyes open and closed): visual, auditory and complex reaction times, the Vienna Determination Apparatus (VDA), the pursuit – rotor (error and time off target) Pulse rates	No suggestion of systematic effects involving CBN or CBD.

Table 19. Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Watkins, P., Church, R., Li, J., & Knappertz, V. (2020). *Cannabidiol and Abnormal Liver Chemistries in Healthy Adults: Results of a Phase I Clinical Trial*	Watkins 2020	A phase I, open-label, fixed single-sequence DDI trial	18-60 years, male (6) and female (10)	23 days	CBD from *Cannabis sativa L* plant Pharmaceutical formulation in oral solution (100mg/ml) Source: Epidiolex (US); GW Pharmaceuticals (UK)	The following regime was followed over the 23 day period for all: • 2 days – 250 mg x2 per day • 2 days – 700 mg (am) and 250 mg (pm) • 2 days – 500 mg • 2 days – 750 mg (am) and 500 mg (pm) • 16 days – maintenance at 750 mg per day First and last day administered CBD with 200 mg caffeine	No	Treatment emergent adverse effects (AEs) and liver enzyme (alanine aminotransferase, ALT) analysis	Treatment emergent adverse effects (AEs) in 88% of which 31% were mild and 50% were moderate in severity. The most common AEs were GI disorders such as diarrhea (50%) and abdominal discomfort (31%) 38% of participants displayed elevated liver test (ALT > 2x upper limit of normal) 31% of participants displayed elevated liver test consistent with drug-induced liver injury (ALT > 3x upper limit of normal) 31% of participants displayed elevated liver test consistent with drug-induced liver injury (ALT > 5x upper limit of normal)
Bloomfield, M. A. P., Green, S. F., Hindocha, C., Yamamori, Y., Yim, J. L. L., Jones, A. P. M., et al. (2020). *The effects of acute cannabidiol on cerebral blood flow and its relationship to memory: An arterial spin labelling magnetic resonance imaging study.*	Bloomfield, 2020	Randomised, crossover, Double-blind design, Placebo controlled	19-29 year Male (6) Female (9)	3 hr	Synthetic CBD (99.9% purity) obtained from STI Pharmaceuticals (Brentwood, UK) and manufactured by Nova Laboratories (Leicester, UK).	600 mg CBD, Size 2 gelatin capsules contained microcrystalline cellulose filler and CBD	A sensitivity power analysis conducted using G*Power 3 (Faul et al., 2007) indicated that our sample size would provide 80% power to detect a large effect size (Cohen's d = 0.8) at an alpha of 0.05.	Regional cerebral blood flour and memory assessment	CBD increased CBF in the hippocampus. There were no differences in memory task performance, but there was a significant correlation whereby greater CBD-induced increases in orbitofrontal CBF were associated with reduced reaction time on the 2-back working memory task

Table 19. Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Borgwardt, S. J., Allen, P., Bhattacharyya, S., Fusar-Poli, P., Crippa, J. A., Seal, M. L., et al. (2008). *Neural basis of Δ-9-tetrahydrocannabinol and cannabidiol: Effects during response inhibition*	Borgwardt, 2008	Double blind, placebo-controlled, pseudo-randomised, withing subject study	20-42 years, male (15) No cannabis use in the past month	1 hour, 2 hours and 2 hours	Source – not specified	600 mg CBD	No	Blood pressure, Visual Analogue Mood Scale (VAMS), Spielberger state Trait Anxiety Inventory (STAI) and a visual analogue intoxication scale (AIS) and positive and Negative Symptoms Scale (PANSS)	Relative to placebo, CBD deactivated the left insula and the left superior and transverse temporal gyri. CBD was not associated with any significant increases in regional activation relative to placebo.
Crippa, J. A. d. S., Zuardi, A. W., Garrido, G. E. J., Wichert-Ana, L., Guarnieri, R., Ferrari, L., et al. (2004). *Effects of cannabidiol (CBD) on regional cerebral blood flow.*	Crippa, 2004	Randomised, placebo-controlled, double blind	25-42 year 10 male	60, 75 and 110 min	CBD in powder 99.9% pure Source - THC-Pharm,	400 mg CBD Sciatic capsules.	No	Visual Analogue Mood Scale (VAMS) - anxiety, physical sedation, mental sedation, and other feelings and attitudes	Decreased subjective anxiety and increased mental sedation (visual analogue mood scale) with CBD compared to placebo.
Fusar-Poli, P., Allen, P., Bhattacharyya, S., Crippa, J. A., Mechelli, A., Borgwardt, S., et al. (2010). *Modulation of effective connectivity during emotional processing by Δ9-tetrahydrocannabinol and cannabidiol*	Fusar-Poli, 2010	Double-blind, pseudo-randomized, placebo-controlled, repeated-measures,	20-42 year Male (15) cannabis detox for 1 month	1-3 hour	600 mg CBD oral administration 99.9% pure source: THC-Pharm	600 mg CBD	No	Recorded electrodermal skin conductance responses and event-related functional magnetic resonance imaging (fMRI)	CBD had a significant effect on connectivity between anterior cingulate cortex (emotional brain) / ACC and amygdala --> brain connectivity during emotional processing of fearful stimuli.
Grimm, O., Löffler, M., Kamping, S., Hartmann, A., Rohleder, C., Leweke, M., et al. (2018). *Probing the endocannabinoid system in healthy volunteers: Cannabidiol alters fronto-striatal resting-state connectivity*	Grimm, 2018	observer-blind, placebo-controlled, randomized, three-period cross-over study	Male (16)	75 min	Source - not stated	600mg CBD capsule or placebo	No	State anxiety, positive and negative affect, subjective valence and arousal ratings, and dissociative symptoms	Compared state anxiety, positive and negative affect, subjective valence and arousal ratings as well as dissociative symptoms. No significant effect on these scales was found for CBD with placebo. CBD lead to an increase of fronto-striatal connectivity in comparison to placebo.

Table 19. Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Karniol, I. G., Shirakawa, I., Kasinski, N., Pfeferman, A., & Carlini, E. A. (1974). *Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man.*	Karniol, 1974,	21-34 years, Male (40)	6 days	45, 95 and 180 min after ingestion and again 55, 95, 155 and 185 min	CBD Source: Makor Chemicals Ltd, Israel	15, 30 or 60 mg CBD		Time production tasks psychological effects of drug action were graded from 0 to 4	15-60 mg of CBD alone provoked no effects. No significant change in pulse rate at 50 or 70 mins after drug consumption.
Lawn, W., Hill, J., Hindocha, C., Yim, J., Yamamori, Y., Jones, G., et al. (2020). *The acute effects of cannabidiol on the neural correlates of reward anticipation and feedback in healthy volunteers*	Lawn, 2020	double-blind, placebo-controlled, repeated-measures design	19-36 year Male (11) and female (12)	2 , 7 hr experiments	Pure synthetic (-)-CBD Source: STI pharmaceuticals Opaque capsules. Swallowed 12 capsules to give 600 mg.	50 mg capsules, participants swallowed all 12 capsules at their own pace under invigilation of the experiment er therefore 600 mg dose	A power calculation was conducted using G*Power (version 3.1.9.2).	Whole brain analysis fMRI data analysis, behavioural results	There was no significant effect of CBD on brain activity -- reward anticipation, reward feedback, and MRI.
Linares I.M., Zuardi A.W., Pereira L.C., Queiroz R.H., Mechoulam R., Guimaraes F.S., et al. (2019). *Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test.*	Linares, 2019	double-blind Randomised design	57 male 19 – 27 year	1.5 hour	CBD (150, 300 or 600 mg) Powder form (99.9% purity) Source: STI-Pharm	150 and 300 and 600 mg. Dissolved in corn oil Gelatin capsules	No	Psychological measurements Visual Analogue Mood scale (VAMS)	300mg CBD showed lower anxiety than placebo. No significant phase, group, or group-phase interaction effects were found for the VAMS factors sedation, cognitive impairment, or distress. Neither the task nor the drug affected any other VAMS dimensions.

Table 19. Results of systematic review [redacted]

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Linares, I. M. P., Guimaraes, F. S., Eckeli, A., Crippa, A. C. S., Zuardi, A. W., Souza, J. D., et al. (2018). *No acute effects of cannabidiol on the sleep-wake cycle of healthy subjects: A randomized, double-blind, placebo-controlled, crossover study*	Linares, 2018,	Randomized, double blind, and crossover mode	20-37 year Male (12) female (14)	0.5 – 8 hour	CBD 300 mg (99.9% purity) Source: STI-Pharm	300 mg CBD Dissolved in corn oil Gelatin, capsules	No	Polysomnographic recordings	No significant effect of CBD, versus placebo, on total sleep time, REM (rapid eye movement) onset, apnea index, hypopnea index. No significant changes in the subjective and cognitive measures collected during the two nights of polysomnographic exams.
McCartney, D., Benson, M. J., Suraev, A. S., Irwin, C., Arkell, T. R., Grunstein, R. R., et al. (2020). *The effect of cannabidiol on simulated car driving performance: A randomised, double-blind, placebo-controlled, crossover, dose-ranging clinical trial protocol*	McCartney, 2020	Randomised Double-blind Placebo-controlled Cross-over	18-65 years, 16 male and female	45 min and 210 min duration	Oral formulation containing 100 mg/ml CBD in MCT oil. Source: GD Cann®–C; GD Pharma Pty Ltd	15, 300, 1500 mg CBD	Power calculated using Cohen dz.	Simulated car driving performance, psychomotor vigilance and cognitive and psychomotor impairment	No significant effect of CBD, versus placebo, on cognitive function or psychomotor vigilance or cognitive and psychomotor impairment
Perkins D., Butler J., Ong K., Nguyen T.H., Cox S., Francis B., et al. (2020). *A phase 1, randomised, placebo-controlled, dose escalation study to investigate the safety, tolerability and pharmacokinetics of cannabidiol in fed healthy volunteers.*	Perkins, 2020	Randomised Double-blinded Placebo-controlled Single-dose escalation study.	18-48 years, Male (14) and female (4)	1 hour to 15 days duration	Cannabidiol (100g/L) plus soybean oil, sweetener (0.3g/L). 99.6% CBD Source: Monash Institute of Pharmaceutical Sciences.	Single dose of CBD 5 or 10 or 100 mg/kg	No	Safety and tolerability, Treatment emergent adverse effects (AEs)	Oral lipid-based 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, as did placebo (5mg/kg 4 AEs, 10mg /kg 1 AE, 20mg/kg 8 AEs, placebo 4 AEs)
Sultan, S. R., O'Sullivan, S. E., & England, T. J. (2020). *The effects of acute and sustained cannabidiol dosing for seven days on the haemodynamics in healthy men: A randomised controlled trial.*	Sultan 2020	A randomised, placebo controlled, double-blind, parallel group trial	26 healthy men Cannabis detox for at least 2 months prior	2 hour to 7 days.	600 mg CBD Source: Ethixia Organics	600 mg CBD or placebo	No	blood pressure and arterial stiffness participants were asked to perform isometric handgrip (IHG) stress exercise for 3 minutes	There was no significant difference in aortic BP or arterial stiffness from CBD treatment compared to placebo, for acute dosing however there was significantly lowered mean arterial pressure. CBD dosing for 7 days significantly reduced arterial stiffness and internal carotid artery diameter but had no effect on mean arterial pressure.

Reference (author, year, title of study)	Study report provided in the application dossier (name of file)	Study design	Study population	Duration of the study	Tested material	Dosage	Power calculations performed	Safety related parameters investigated	Summarised results
Taylor, L., Crockett, J., Tayo, B., Checketts, D., & Sommerville, K. (2020). *Abrupt withdrawal of cannabidiol (CBD): A randomized trial*	Taylor, 2020	Randomized, double-blind trial, with a single-blind baseline assessment with matched placebo	18-45 years, male (24) and female (15)	14-28 days	Highly purified CBD derived *from Cannabis sativa L.* plant Oral solution (100 mg/ml) Source - Epidiolex, GW Research Ltd.	750 mg CBD for 28 days, twice daily for 2 weeks and 4 weeks	No	Adverse effects using MedDRA terms	There were differences in adverse effects between CBD and placebo mild (19 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 (9 in CBD 28 days, versus 0 in CBD 14 days and 1 in placebo)
Woelfl, T., Rohleder, C., Mueller, J.K., Lange, B., Reuter., et al. (2020). *Effects of Cannabidiol and Delta-9-tetrahydrocannabinol on emotion, cognition and attention*	Woelfl 2020	Randomized, double-blind trial, with parallel groups and placebo control	19-36 years, male (60)	235 min	800 mg CBD capsules Source: STI-Pharm	4 x 200 mg CBD or placebo	Yes – 80% power, 2-sided type I error 5%, two-sample Wilcoxon rank sum test, no multiplicity correction	Six emotional categories including performance-related activity, general well-being and emotional excitability	CBD treatment (CBD/PLA) had no significant effect on any of the six emotional categories: 1. Performance-related activity 2. General inactivation 3. Extroversion 4. General well-being 5. Emotional excitability 6. Depressiveness
Williams, N., Ewell., T., Abbotts, K., Harms, K., Woelfel K., et al. (2021). *Comparison of Five Oral Cannabidiol Preparations in Adult Humans: Pharmacokinetics, Body Composition, and Heart Rate Variability*	Williams 2021	A randomized, double-blind, repeated measures cross-over study design	21-62 years, male (9) and female (6)	1 hour to 4 hours	CBD in 5 different preparations: CBD tincture based, CBD powder in water, 5% CBD concentrated liquid, 20% CBD concentrated liquid, and 5% CBD concentrated powder Source: Cellnec Foods	One preparation at 30 mg CBD standardised dose in 227 ml water or placebo	No	Heart rate variability and blood pressure	CBD treatment, in any preparation, has no significant effect on heart rate variability or blood pressure

Table 19. Results of systematic review [redacted]

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 [redacted] 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.[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.

[135] *Supra* 134

2.10.2 Genotoxicity (overview)

In accordance with EFSA guidance on genotoxic testing strategies from its Scientific Committee[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 [redacted] in 2021 using test material with batch number 103501b. The aim of the study was to assess gene mutations.

The AMES test was conducted [redacted]

[136] EFSA Scientific Committee. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379

[137] Mortelmans K, Zeiger E. The Ames Salmonella/microsome mutagenicity assay. Mutat Res. 2000;455:29–60.

[138] Gatehouse D. Bacterial mutagenicity assays: test methods. Methods Mol Biol 2012;817:2134.

[redacted]

[redacted]

Table 20: Summary table of results from the mutagenicity study [redacted]

2.10.2.2 Genotoxicity – in vitro 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).

[redacted]

[redacted]

[redacted]

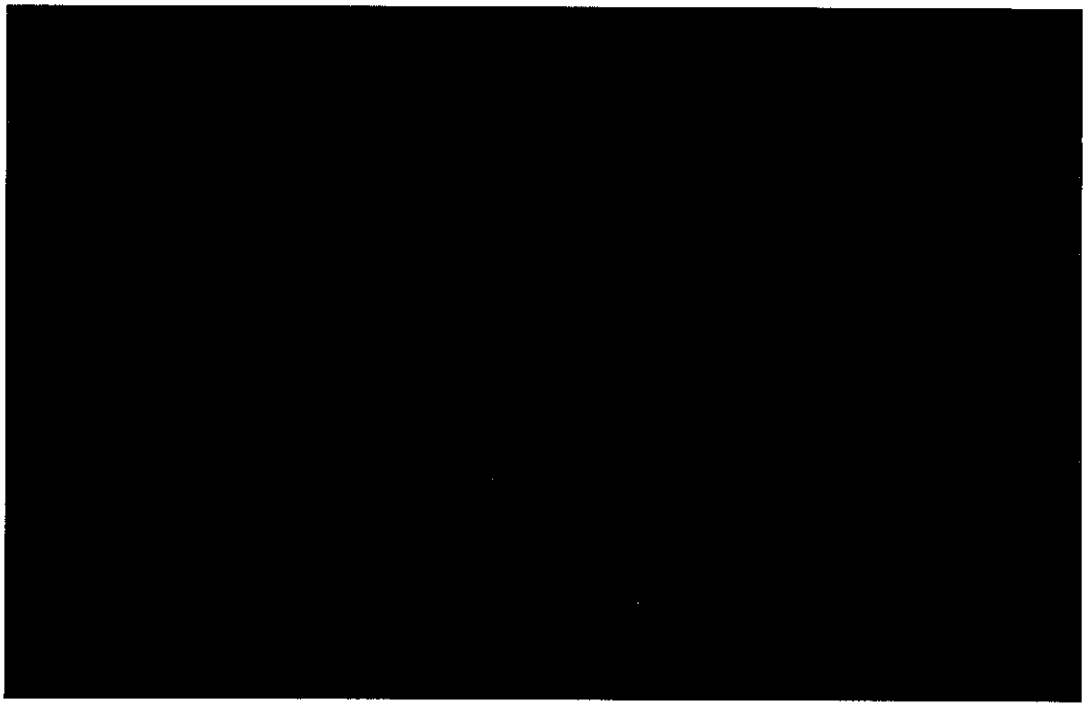


Table 21: Summary table of results from the micronucleus study (MN) [redacted]

[redacted]

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. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 22: Results of 14 d DRF testing [redacted]

[redacted]

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. [redacted]

[redacted]

[redacted]

[139] *Supra* note 3, Section 2.10.3

[140] EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to food), 2012. Guidance for submission for food additive evaluations. EFSA Journal 2012;10(7):2760, 60 pp. doi:10.2903/j.efsa.2012.2760

[141] Traul KA, Driedger A, Ingle DL, Nakhasi D. Review of the toxicologic properties of medium-chain triglycerides. Food Chem Toxicol. 2000;38(1):79-98.

[142] *Supra* Note 62

[redacted]

[redacted]

Table 23: Main OECD 408 [redacted]

[redacted]

Table 24: Recovery group [redacted]

[redacted]

[143] *Supra* Note 75

[144] Łebkowska-Wieruszewska B, Stefanelli F, Chericoni S, Owen H, Poapolathep A, Lisowski A, Giorgi M. Pharmacokinetics of Bedrocan®, a cannabis oil extract, in fasting and fed dogs: An explorative study. Res Vet Sci. 2019 Apr;123:26-28.

[145] Lim SY, Sharan S, Woo S. Model-Based Analysis of Cannabidiol Dose-Exposure Relationship and Bioavailability. Pharmacotherapy. 2020;40(4):291-300

[redacted]

2.10.3.2.1 Results

[redacted]

[redacted]

Table 25: Summary of selected bodyweight, organ weight and observational findings [redacted]

[redacted]

[redacted]

[redacted]

Table 26: Summary of selected clinical chemistry findings [redacted]

[redacted]

[redacted]

[redacted]

Table 27: Summary of selected bodyweights and organ weight [redacted]

[redacted]

[redacted]

Table 28: Summary of selected observational finding[redacted]

[redacted]

[redacted]

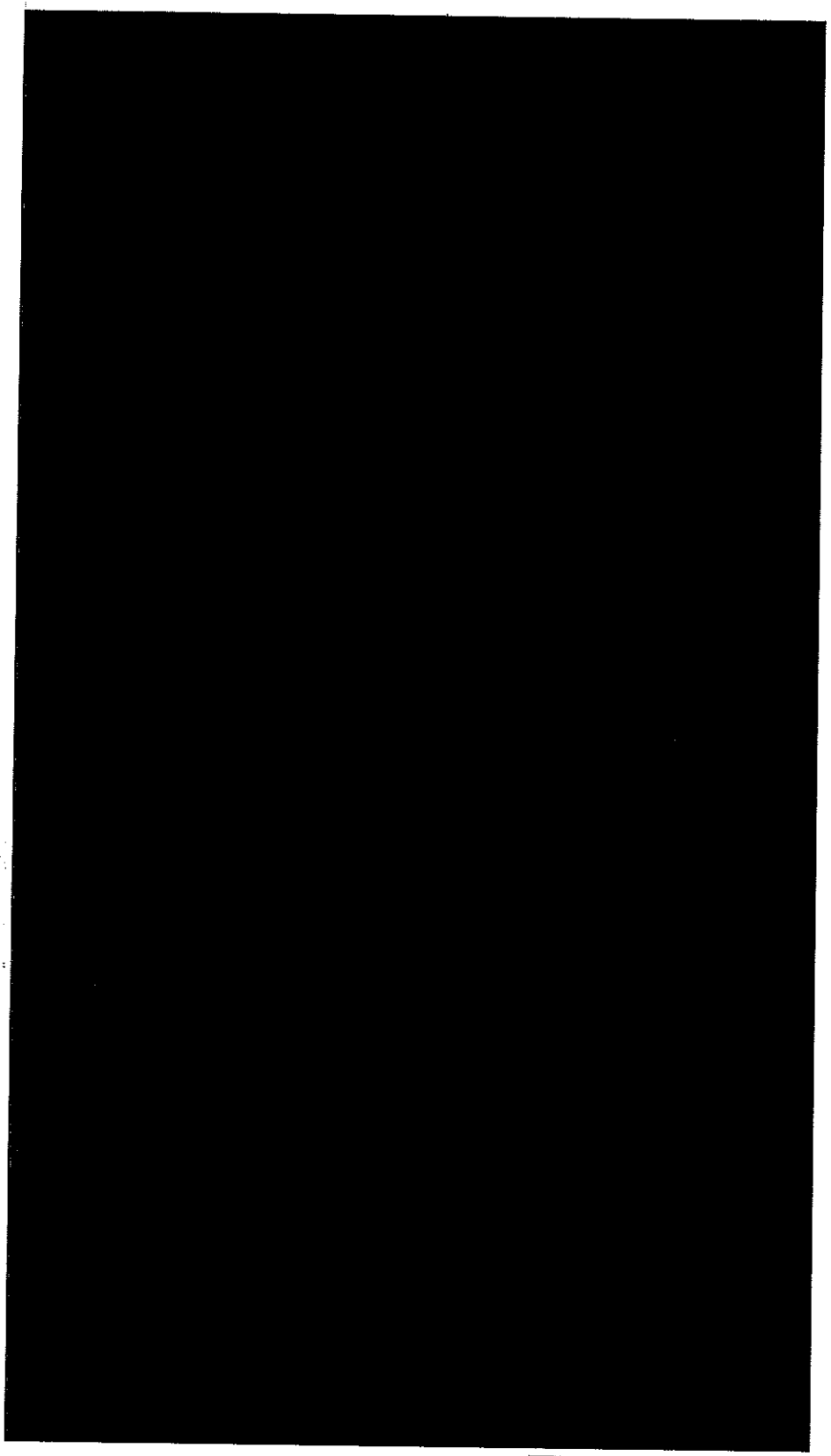


Table 29: Summary of selected clinical chemistry findings

[redacted]

2.10.4 Recovery and additional histopathology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.10.5 Reproductive and development toxicity – Prenatal DRF trial

In a recent publication from the Committee on Toxicology (COT)[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,[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.

[redacted]

[redacted]

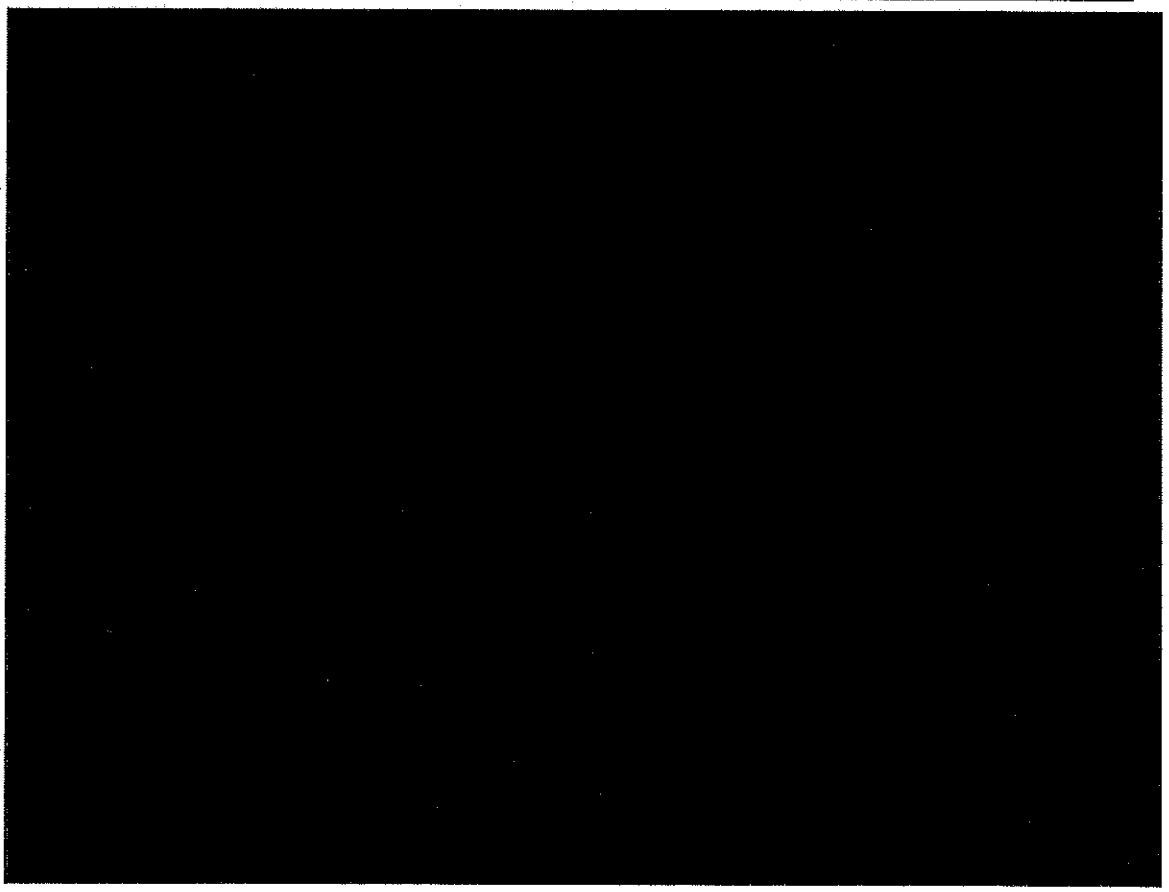
[redacted]

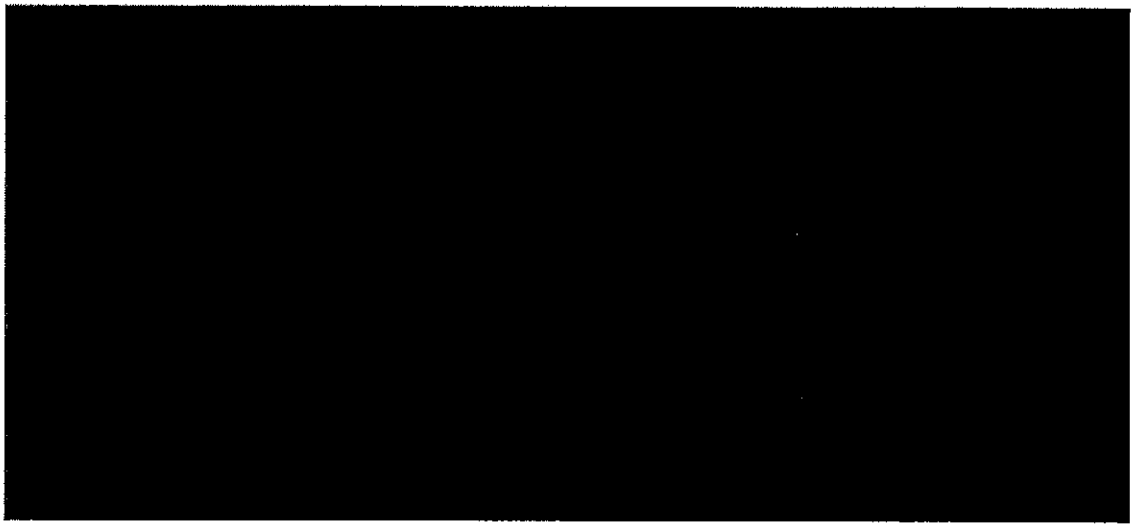
[146] Committee on Toxicity of Chemicals in food, consumer products and the environment: CBD UPDATE. TOX/2020/02. Accessed online at: https://cot.food.gov.uk/sites/default/files/tox202002cbd.pdf

[147] Committee on Toxicity of Chemicals in food, consumer products and the environment: Scoping paper on the potential adverse effects of CBD products. TOX/2019/32 Accessed online at: https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf

[148] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. OJ L 276, 20.10.2010, p. 33–79

[redacted]





[redacted]

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)[149] and Reich et al. (1982)[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.

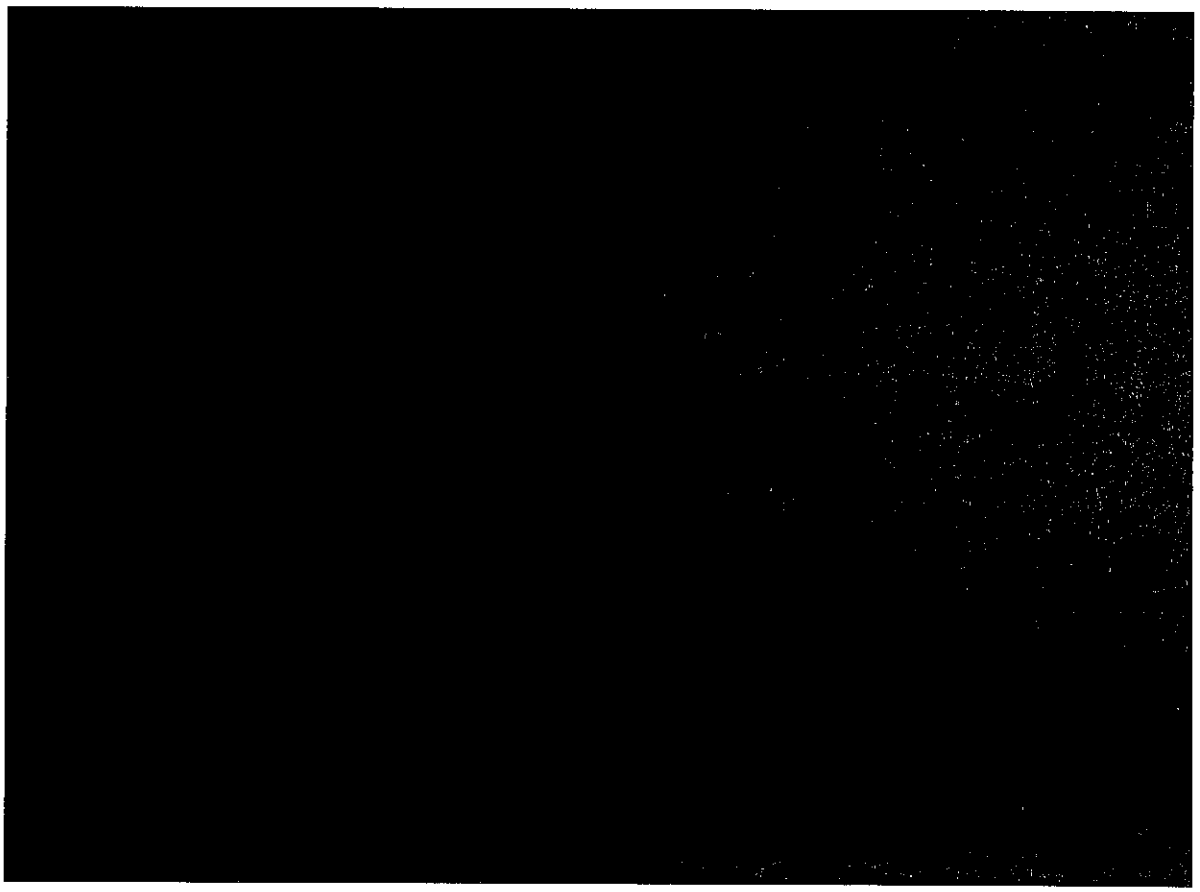
[redacted]

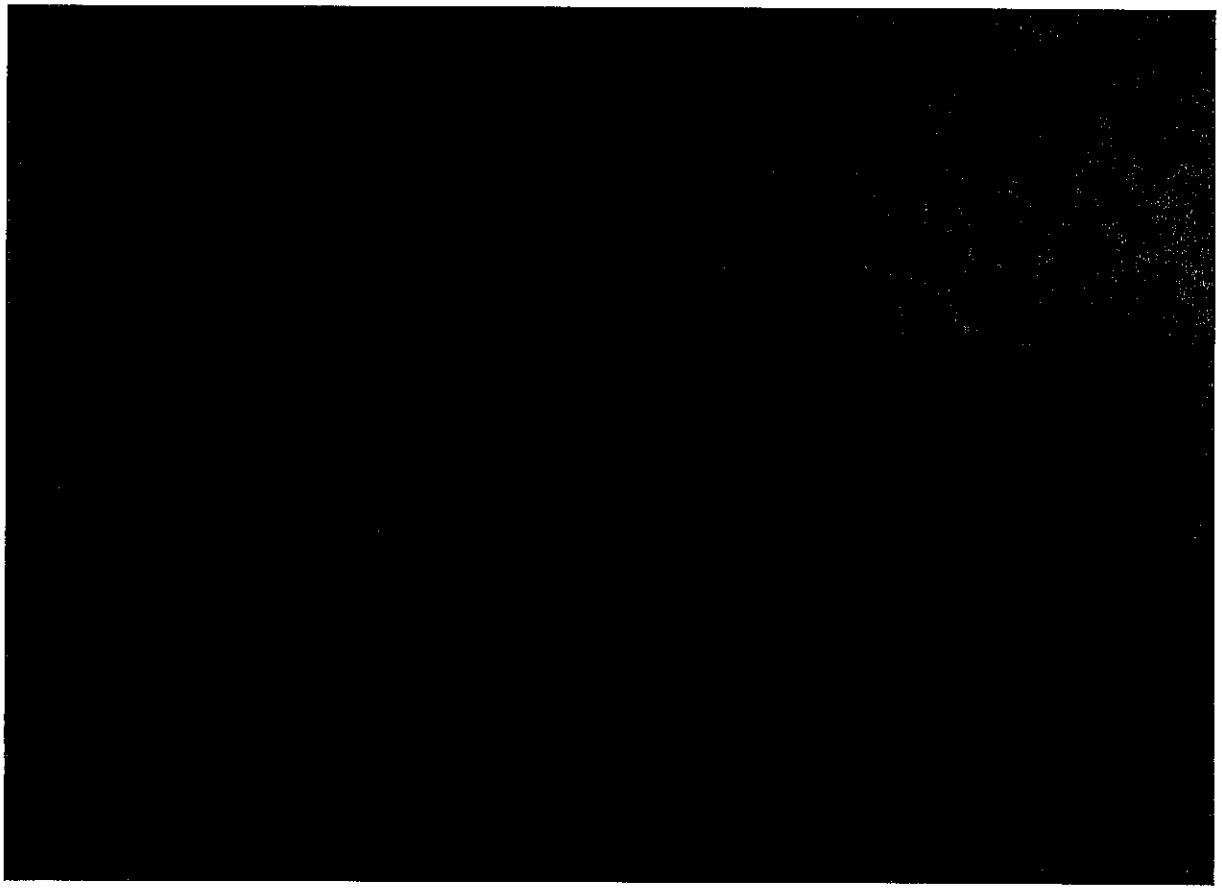
[redacted]

[149] Carvalho RK, Santos ML, Souza MR, Rocha TL, 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.

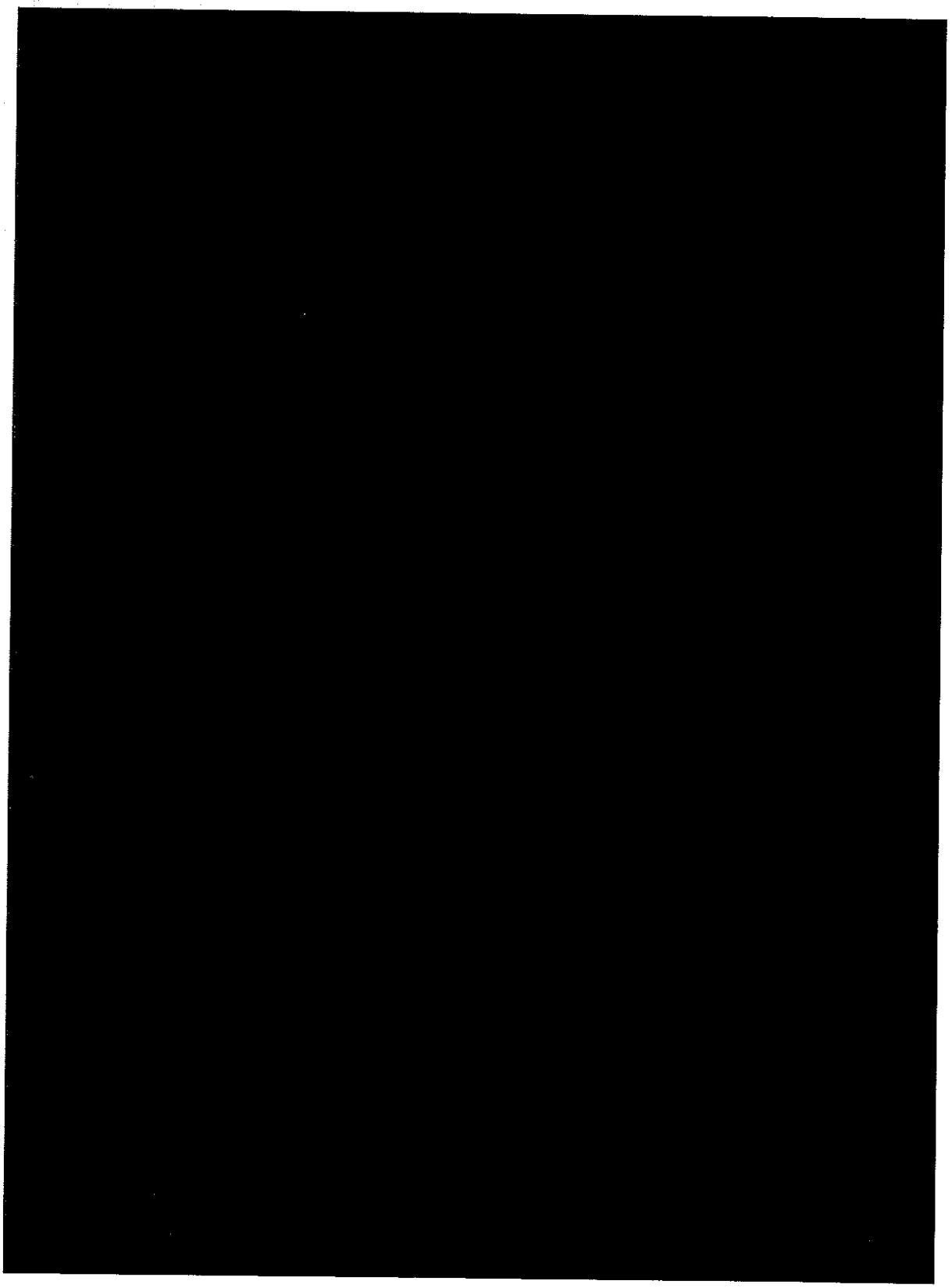
[150] Reich R, Laufer N, Lewysohn O, Cordova T, Ayalon D, Tsafriri A. In vitro effects of cannabinoids on follicular function in the rat. Biol Reprod. 1982 Aug;27(1):223-31.

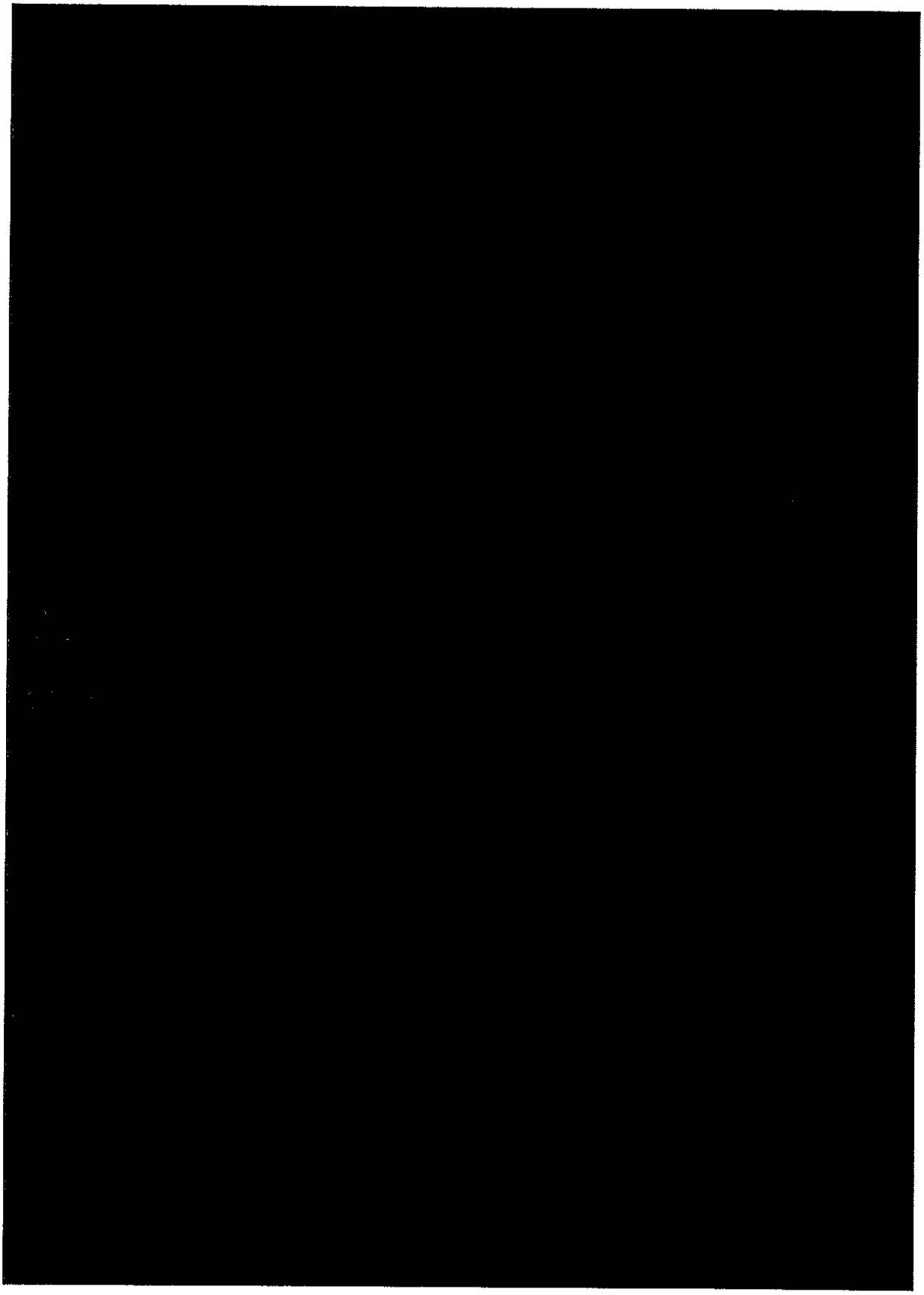
[redacted]





[redacted]





[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

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).[151]

There is a significant volume of data related to the medicine Epidiolex® 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)[152] and 2020 (TOX/2020/02).[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® data is also not readily accessible so we do not know what other impurities or residues are present in Epidiolex;® 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,[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.[155] [redacted]

[151] *Supra* note 4
[152] *Supra* note 147
[153] *Supra* note 146
[154] EMA. Committee for Medicinal Products for Human Use (CHMP)Assessment report. Epidyolex. International non-proprietary name: cannabidiol Procedure No. EMEA/H/C/004675/0000. EMA/458106/2019. https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf
[155] *Supra* note 146, para 159 and 162.

[redacted]

Additional data is accessible as submitted to the FDA,[156] 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 allermatch.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.[157]

Molecular weight	Genbank nucleotide	Genbank protein	Description
9 kDa	HE972341.1	CCK33472.1	Lipid transfer protein precursor, partial (chloroplast)
10 kDa	HE972341.1	P86838.1	Non-specific lipid-transfer protein
38 kDa	XM_030636673.1	XP_030492533.1	Thaumatin-like protein 1b
53 kDa	JP454288.1	YP_009123081.1	Ribulose 1,5-bisphosphate carboxylase/oxygenase large subunit (chloroplast)
54 kDa	JP462165.1	YP_009123080.1	ATP synthase CF1 beta subunit (chloroplast)
29 kDa	JP475070.1	XP_030482568.1	Oxygen-evolving enhancer protein 2, chloroplastic
49 kDa	JP458088.1	XP_030492156.1	Ribulose bisphosphate carboxylase/oxygenase activase, chloroplastic isoform X2
52 kDa	JP451043.1	XP_030504809.1	Ribulose bisphosphate carboxylase/oxygenase activase 2, chloroplastic-like
48 kDa	JP450816.1	XP_030507192.1	Glutamine synthetase leaf isozyme, chloroplastic
51 kDa	JP458176.1	PON58274.1	Phosphoglycerate kinase (Trema orientale)
47 kDa	JP473302.1	XP_030489218.1	Fluoride export protein 2-like isoform X1
48 kDa	JP452228.1	PON90495.1	Glyceraldehyde-3-phosphate dehydrogenase, type I (Trema orientale)

Table 39. Possible allergens in Cannabis sativa. Source: Jackson et al. 2020[158]

[156] https://www.regulations.gov/docket/FDA-2019-N-1482/document

[157] Rojas Pérez-Ezquerra, P., Sánchez-Morillas, L., Davila-Ferandez, G., Ruiz-Hornillos, F. J., Carrasco García, I., Herranzmañas, M., ... Bartolomé, B. (2015). Contact urticaria to Cannabis sativa due to a lipid transfer protein (LTP). Allergologia et Immunopathologia, 43(2), 231–233.

[158] Jackson B, Cleto E, Jelmy S. An emerging allergen: Cannabis sativa allergy in a climate of recent legalization. Allergy Asthma Clin Immunol. 2020 Jun 26;16:53

However, CS is an anemophilous plant that produces a large quantity of pollen (trizonporate) produced by inflorescence.[159] In Europe we have incidence of rhinitis and asthma symptoms attributed to environmental exposure.[160] 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,[161, 162] 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'.[163] These are suggested to be sensitisers in fruits,[164] 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.[165] This seems to be supported by the almost complete absence of reported allergy reports from consumers following consumption of CBD isolates in food form. [redacted]

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.[166]

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[159] Aboulaich N, Trigo MM, Bouziane H, Cabezudo B, Recio M, El Kadiri M, Ater M. Variations and origin of the atmospheric pollen of Cannabis detected in the province of Tetouan (NW Morocco): 2008-2010. Sci Total Environ. 2013 Jan 15;443:413-9

[160] Torre FD, Limonta A, Molinari A, Masala E, Vercelloni S, Torre ED. Cannabaceae pollen in the atmosphere of Brianza, Northen Italy. Eur Ann Allergy Clin Immunol. 2007 Jan;39(1):9-11.

[161] de Larramendi CH, Carnés J, García-Abujeta JL, García-Endrino A, Muñoz-Palomino E, Huertas AJ, Fernández-Caldas E, Ferrer A. Sensitization and allergy to Cannabis sativa leaves in a population of tomato (Lycopersicon esculentum)-sensitized patients. Int Arch Allergy Immunol. 2008;146(3):195-202

[162] Larramendi CH, López-Matas MÁ, Ferrer A, Huertas AJ, Pagán JA, Navarro LÁ, García-Abujeta JL, Andreu C, Carnés J. Prevalence of sensitization to Cannabis sativa. Lipid-transfer and thaumatin-like proteins are relevant allergens. Int Arch Allergy Immunol. 2013;162(2):115-22.

[163] Gamboa P, Sanchez-Monge R, Sanz ML, Palacín A, Salcedo G, Diaz-Perales A. Sensitization to Cannabis sativa caused by a novel allergenic lipid transfer protein, Can s 3. J Allergy Clin Immunol. 2007;120:1459–60.

[164] Enrique E, Ahrazem O, Bartra J, Latorre MD, Castelló JV, de Mateo JA, Montoya E, Malek T, Barber D, Salcedo G. Lipid transfer protein is involved in rhinoconjunctivitis and asthma produced by rice inhalation. J Allergy Clin Immunol. 2005 Oct;116(4):926-8.

[165] Mamone G, Picariello G, Ramondo A, Nicolai MA, Ferranti P. Production, digestibility and allergenicity of hemp (Cannabis sativa L.) protein isolates. Food Res Int. 2019 Jan;115:562-571.

[166] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004 Text with EEA relevance OJ L 304, 22.11.2011, p. 18–63

2.12 Conclusions

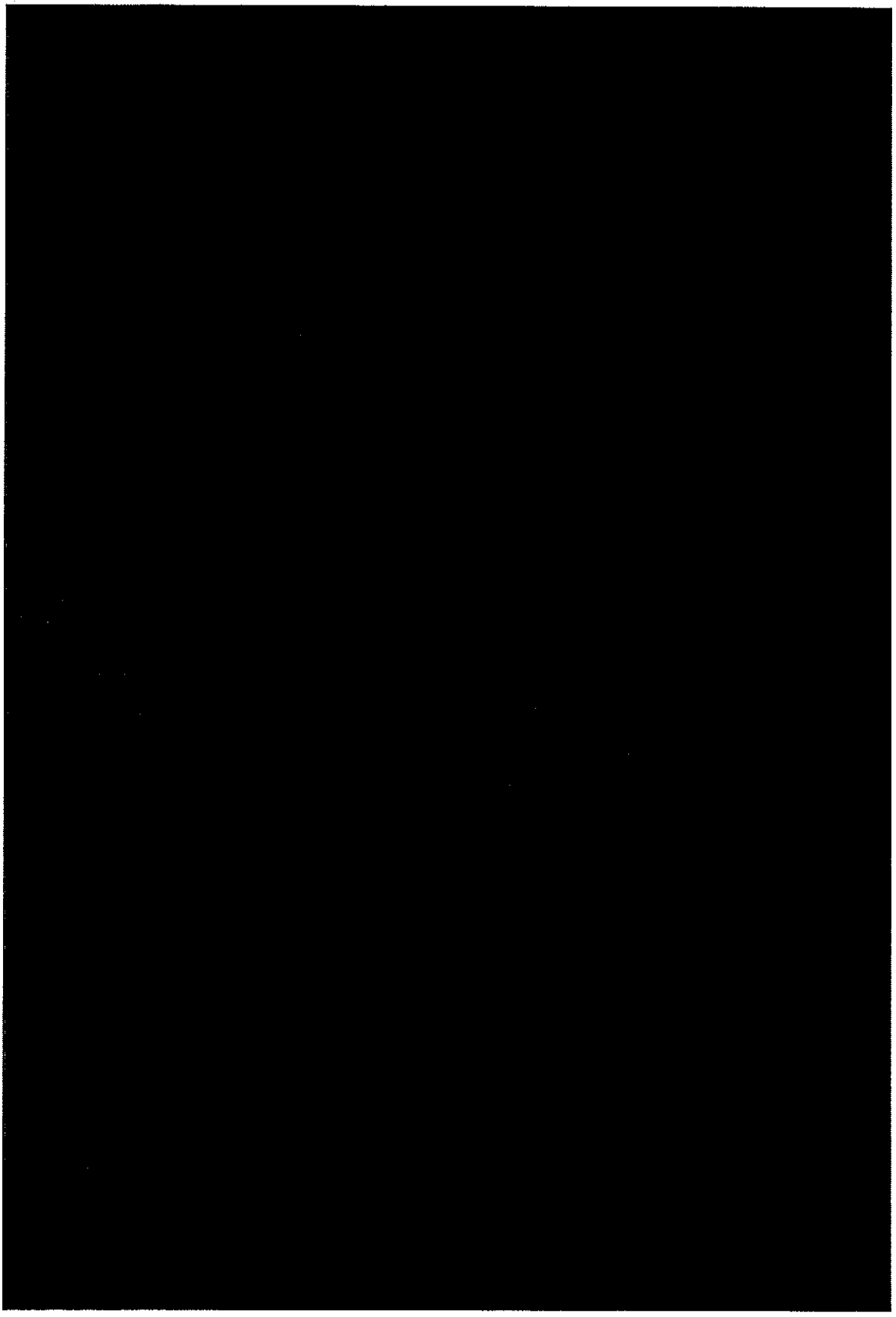
[redacted]

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. [redacted] 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.

[redacted] 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. [redacted]



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. [redacted]

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 [redacted] 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.

[redacted] 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 [redacted] supports the safe use under the proposed conditions of use.

[redacted]

3.0 ANNEXES TO THE DOSSIER

[redacted]

[redacted]

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	Tetrahydrocannabivarin
TK	Toxicokinetics
UB	Upper Bound
UF	Uncertainty Factor

[redacted]

UHPLC Ultra-high performance liquid chromatography

[redacted]

[redacted]

[redacted]