Dear Sir/Madam,

We have collated a written submission that represents the thoughts of both ACI/CMC colleagues and its industry members.

1. The commission refers to the cannabinoids $\Delta^9$-THC, CBN and THCV. Are there any further phytocannabinoids which should be considered? If so, which cannabinoids and please provide evidence.

The Advisory Council for the Misuse of Drugs (ACMD) reviewed which of the 140 cannabinoids identified would be covered by the technical definition of ‘cannabinol derivatives’ and advised that a total of 12 are controlled under the definitions provided in the Misuse of Drugs Act (Table 1) [1]. Thus, we question why only $\Delta^9$-THC, CBN and THCV are being considered, and suggest that all 12 controlled cannabinoids are considered instead. Conversely, there is limited evidence about these controlled cannabinoids in the literature so further research may lead to higher confidence in this decision making. Furthermore, if this commission is focussed on safety and daily tolerable levels then all phytocannabinoids are important, not just the controlled cannabinoids.

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>$\Delta^9$-tetrahydrocannabinol</td>
<td>TCHV</td>
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<tr>
<td>$\Delta^9$-tetrahydrocannabinol-c4</td>
<td>THC-C1</td>
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<tr>
<td>$\Delta^9$-tetrahydrocannabinol-c4</td>
<td>THC-C4</td>
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<tr>
<td>trans-$\Delta^8$-tetrahydrocannabinol</td>
<td>THC-C5 (THC)</td>
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<tr>
<td>cis-$\Delta^8$-tetrahydrocannabinol</td>
<td>cis-THC-C5 (THC)</td>
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<tr>
<td>$\Delta^8$-tetrahydrocannabinol</td>
<td>$\Delta^8$-THC</td>
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<tr>
<td>Cannabigerol</td>
<td>CBN-C1</td>
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<tr>
<td>Cannabigerol-c2</td>
<td>CBN-C2</td>
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<tr>
<td>Cannabinol</td>
<td>CBN-C3 (CBV)</td>
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<td>Cannabinol-c4</td>
<td>CBN-C4</td>
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<tr>
<td>Cannabinol</td>
<td>CBN-C5 (CBN)</td>
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<tr>
<td>Cannabinol-methyl ether</td>
<td>CBNM-C5 (CBNM)</td>
</tr>
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</table>

Table 1: Cannabinoids controlled under the MDA and subsequent regulations

2. At what dose would each of these cannabinoids cause a psychoactive effect in humans? Are there any potential harmful effects at these doses?

$\Delta^9$-THC:

$\Delta^9$-THC has marked acute behavioural and physiological effects including anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication, and increased heart rate [2]. In the recently published paper “Health Guidance Levels for THC in CBD products” [3], it was concluded that the proposed THC safety limit of 0.03%, or 21 μg/day, accounts for the total controlled cannabinoid limit in CBD food and consumer products (i.e. including other THCs & CBN, which are less common and potent than $\Delta^9$-THC).
This level of THC is highly unlikely to produce a positive THC drug test. The majority of the relevant toxicological, experimental and clinical data is only available for Δ⁹-THC, and therefore only a recommendation for levels of Δ⁸-THC were made. However, future research should investigate other cannabinoids of importance, including Δ⁸-THC and CBN, to determine their safety levels alone and in combination with other phytocannabinoids in CBD products.

The Lowest-Observed-Adverse-Effect Level (LOAEL), for single and repeat administration, for Δ⁹-THC is 2.5 mg/day or 0.036 mg/kg/day (assuming a 70kg adult). Given the daily recommendation for CBD is 70mg, the THC content in a CBD product would have to be 3.5% to reach 2.5mg.

The EFSA expert Panel on Contaminants in the Food Chain derived a human Acute Reference Dose (ARfD) based on effects on Central Nervous System (CNS) and heart rate, and reported values were derived as follows:

- A LOAEL, for single and repeat administration, for Δ⁹-THC as 2.5 mg/day or 0.036 mg/kg/day (assuming a 70kg adult).
- An uncertainty factor (UF) of 3 to extrapolate from the LOAEL to No-Observed-Adverse-Effect Level (NOAEL).
- A further UF of 10 to allow for interindividual variances.
- With an overall UF of 30, the ARfD was considered to be 1 μg/kg body weight of Δ⁹-THC.

The EFSA paper states “Overall, the CONTAM Panel identified 2.5 mg per person as the lowest observed adverse effect dose of Δ⁹-THC orally administered in a single dose study. At this dose, single exposure in healthy volunteers had moderate effects (increased sedation, altered scale scores in the POMS, slightly impaired working memory performance and reduced diastolic blood pressure). The EFSA paper also states “A dose of 2.5 mg THC, corresponding to 0.04 mg THC/kg body weight (using a 60 kg body weight) was identified from human studies as the LOEL for psychotropic effects (including euphoria, dizziness, thinking abnormalities and somnolence, reduction in performance including reaction time, and memory function) after either single or repeated exposure.” [4].

Δ⁸-THC can also produce CNS effects in humans but it is less potent than Δ⁹-THC at a ratio of approximately 2:3 as assessed by mood scales and physiological observations [5]. In studies on oral administration, Δ⁸-THC produces lesser effects and has a slower onset and shorter duration of action compared to an equal dose of Δ⁹-THC.

CBD reduces the effects of Δ⁸-THC. A 2019 study identified vHipp pERK1–2 signaling as a critical neural nexus point mediating THC-induced affective disturbances which therefore suggests a potential mechanism by which CBD may counteract the psychotomimetic and psychotropic side effects of THC [6]. A study at King’s College London is investigating the optimum ratio of CBD:THC; it is predicted that the greater the CBD:THC ratio is, the less pronounced the cognitive, paranoid and psychotic effects will be for users [7]. However, a recent literature review found that currently there are minimal, substantial, reproducible conclusions surrounding the optimum CBD:THC ratio, and therefore “best practice” treatments of different diseases and their sequelae [8].

There is a small but growing body of evidence to support the positive effects of microdosing Δ⁹-THC, with studies suggesting protective effects against ischemia-reperfusion injury [25], myocardial ischemic damage [26], and treatment of age-related cognitive decline [27].
CBN:
In 1975, Karniol et. al investigated the interaction of Δ⁹-THC and CBN in man. Oral doses of Δ⁹-THC and CBN were administered and it was found that volunteers reported feeling drugged, drunk, dizzy, and drowsy under the Δ⁹-THC condition, but not under the CBN condition. With combined drug treatment, volunteers reported feeling more drugged, drunk, dizzy, and drowsy than under the Δ⁹-THC alone. None of the drug treatments produced significant changes on other items which included items on perception, emotion, cognition and sociability. It appears that CBN increases the effect of Δ⁹-THC on some aspects of physiological and psychological processes, but that these effects are small and cannot account for the greater potency which has been reported when plant material is used [9].

THCV:
THCV is a naturally occurring analog of Δ⁹-THC, but with different pharmacological effects: it is a CB1 antagonist therefore lacks the psychotropic actions of Δ⁹-THC. It has been given in humans in clinical studies up to 10mg/day and at the doses that have been tested in humans, no major side effects were reported, but findings have suggested a protective effect against Δ⁹-THC effects [10]. A study in 2016, investigated the efficacy and safety of CBD and THCV in patients with Type 2 Diabetes; patients were taking 5 mg twice a day, 4 patients (out of 12) reported decreased appetite and 2 reported diarrhoea [11].

We would like to clarify that something can be psychoactive without causing a euphoric ‘high’, for example, CBD. However, if you are referring to a substance being psychoactive via the CB1 receptor then the focus should be on CBN and Δ⁹-THC. Individual tolerance also plays an important role in the psychoactive effect of these cannabinoids. Additionally, psychoactive does not always equal harmful.

Further literature searching is required to reference the psychoactive effects in humans of all the psychoactive cannabinoids in Table 1. In addition, more research is required to determine controlled cannabinoid safety levels alone and in combination with other phytocannabinoids in CBD products.

3. What are the conditions that precursors of cannabinoids such as Δ⁹-THCA-A might be transformed into controlled cannabinoids?

Figure 1: Decarboxylation reaction of THCA to THC [24]

Heat, light, and air are the oxidation conditions that can lead to degradation of cannabinoid precursors such as in Figure 1.
Section 3. ‘Ease of Convertibility into Controlled Substances’ in the 2018 WHO CANNABIDIOL (CBD) Critical Review Report details the conditions in which CBD has been found to transform into Δ⁹-THC, specifically in relation to the acidic conditions of the human stomach. This has been demonstrated under some lab based conditions, however, they concluded that overall there is no evidence that this transformation occurs in humans after oral CBD administration. Furthermore, there is no evidence that oral CBD administration in humans results in clinically relevant THC-like subjective or physiological effects, or appreciable plasma concentrations of THC or its metabolites [12].

More recently, a human clinical study definitively looked at whether CBD could convert into THC in the body and concluded that oral CBD does not convert to Δ⁸-THC or Δ⁹-THC in humans [13].

The decarboxylation of THCA-A, CBDA and CBGA into Δ⁹-THC, CBD and CBG, respectively, was investigated in 2016 and whilst decarboxylation at different temperatures displayed an exponential relationship between concentration and time, the conditions of this study were not reflective of the conditions of the human body and thus conclusions cannot be drawn about the potential for decarboxylation in humans [14].

To conclude, severe chemical acid transformation would not occur in the body. Any degradation issues would be covered by stability testing, which in the UK, is a prerequisite for novel food authorisation for CBD products. However, this question reinforces the need to consider more than the three cannabinoids mentioned in Question 1.

4. What is the combined level of the psychoactive cannabinoids that would not produce a psychoactive effect (in other words maximum combined dose of active ingredients) given the standard use of consumer CBD products?

If it is assumed at least 2.5 mg of THC is required to get the psychoactive “high” (lowest-observed adverse effect level (LOAEL) being 2.5mg, assigned by EFSA, 2015), and all other compounds are less potent than THC, then it would be safe to say that if the total amount of all controlled compounds is less than 2.5mg, you are unlikely to get ‘high’. Additionally, CBD may offset the psychoactive effects of CB1 activation [6] therefore the psychoactive effect will be dependent on the CBD:THC ratio. More research and evidence is required to define the exact levels that specific combinations of controlled cannabinoids would not produce a psychoactive effect.

Again we refer you to our recent paper, “Health Guidance Levels for THC in CBD products” [3], which recommends a THC safety limit of 0.03% or 21μg per day, and details how this conclusion was drawn; 0.03% accounts for the total controlled cannabinoid limit in CBD food and consumer products (i.e. including other THCs & CBN, which are less common and potent than Δ⁹-THC).

Moreover, consumer CBD products should not contain any controlled cannabinoids under current legislation.

5. Are you aware of any evidence of CBD products causing adverse reactions or harms which might be attributable to cannabinoid impurities? If so, please attach such evidence.

The adverse effects of CBD have been well-researched, with much of the literature and the available data from clinical trials suggests that CBD is well tolerated and has relatively few serious adverse effects.
It is noted, however, that interactions with other medications should be monitored carefully as drug-drug interactions have the potential to cause adverse effects that CBD alone does not produce [15,16].

A toxicological study (OECD 408) by ACI, ADSL and Covance is currently underway and results will be available in September 2021. Additionally, ValidCare recently completed a toxicological study that found no evidence of liver toxicity in the 839 adults who consumed oral CBD [17].

With regards to cannabinoid impurities, currently we are not aware of any data to show that they cause adverse reactions or harm, as collecting this evidence would require large, multi-faceted studies to investigate specific impurities and combinations thereof. Furthermore, impurities such as residual solvents, pesticides and heavy metals are controlled in consumer products thus should not be present at levels to cause adverse reactions.

In 2019, a study analysed the impurities of 67 CBD products with respect to the non-legal conformity of CBD products regarding THC contamination, rather than harmful effects of cannabinoid impurities [18]. It found the safety, efficacy and purity of commercial CBD products was highly questionable, and all of the products in the sample showed various non-conformities to European food law. However, this study was completed in Germany and since its publication, the FSA have established the novel food regulation for CBD products in the UK, therefore this is not necessarily representative of the UK CBD market. Additionally, this study was strongly refuted in 2020 due to its ‘fundamental flaws’, omission of well-known findings and lack of sufficient scientific justification for their claims [19]. A 2020 UK based review summarised that at present, there is little evidence that over-the-counter CBD products have health benefits, and their safety has not been investigated enough: controlled trials of over-the-counter and low-dose CBD preparations are needed to resolve these issues [20]. Furthermore, cannabinoid impurities not only pose a potential physiological harm but also present social risks with regards to drug testing as explained eloquently by Close et al. 2021 [21].

6. For producers of CBD-containing products for supply to consumers, what certification of quality of CBD extracts from raw materials do you require or expect?

Certification of quality should confirm the percentage weight/weight purity of the CBD extracts. The FSA have set out standards of what is required for a CBD product to be able to be sold on the UK market. This includes Certificate of Analysis (CoAs) of cannabinoids (Lab report with validated LOQ limits which meet the legal requirements for controlled cannabinoids and other compositional testing in line with FSA requirements), CoAs for the presence of heavy metals, pesticides etc., Stability data, and Labelling details. More details of what is required for a novel food application can be seen on the FSA website [22]. It is our understanding that individual producers have their own quality control parameters such as batch testing, FDA enforced cGMP, and ensuring the laboratories they use are verified and independently certified. Mutual recognition of the cannabis testing methodology is required.

This individualised approach, and lack of standardisation and harmonisation of analytical methodology for cannabinoid testing, can lead to variability in the test results from one testing lab to another. This is why the ACI initiated the need for standardised technology for CBD industry as detailed in our report ‘Analytical methodology and related controlled cannabinoids & uncontrolled cannabinoids testing’. Standardisation of analytical methodologies and quality control parameters, outlined by regulators, would ensure a fully controlled industry and ensure the safety of CBD consumer products.
7. For which controlled phytocannabinoids are there reference standards available or likely to become available in the near future for their use in testing?

All controlled cannabinoids have reference standards, for example those laid out by Cerilliant Corp. (an ISO 17034 and ISO/IEC 17025 accredited and ISO 9001 certified manufacturer of certified reference standards and certified reference materials). Whilst the existence of these is well-known throughout the industry there are potential barriers to access including cost and sourceability.

Additional Comments

Products that contain in excess of 1mg of any controlled substance per container are classified as controlled drugs and can only be sold and supplied lawfully under Home Office licence, irrespective of the volume of the container. This 1mg threshold relates to the following definition of an 'exempt product' under the Misuse of Drugs Regulations (MDR) 2001 [23]. However, this blanket restriction of 1mg of controlled cannabinoids per container, poses logistical and bulk transportation challenges: when importing cannabinoid products into the UK, we are aware that the Home Office will use the LOQ figure provided in the analytical reports from the supplier. When these LOQs are added together for the controlled cannabinoids they frequently supersede the 1mg limit. As it stands, the order of magnitude for the LOQ to meet the 1mg limit of controlled cannabinoids per container would have to be 1000 times more sensitive to achieve this for bulk transportation. Our members who import into the UK are particularly impacted by this; they do not know many analytical companies that provide NMR detection and associated ppb detection for cannabinoids which adds another impractical element to the interpretation of the UK misuse of drugs act.

Consumer safety is the paramount priority but it seems that these arbitrary numbers assigned in the UK and its jurisdictions, are not backed by sufficient scientific evidence.

Any, and all, confidential information that is not available in the public domain, that was submitted to the ACMD, has been omitted from this public version of this report.

Signed,

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References


[18] “Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination?” by Lachenmeier et al. in the online Journal F1000Research 2020, 8:1394; Last updated 17 Feb 2020


