Health Guidance Levels for THC in CBD products

Safety Assessment & Regulatory Recommendations

A joint publication of the Centre for Medical Cannabis (CMC), The Association for the Cannabinoid Industry (ACI) and Conservative Drug Policy Reform Group (CDPRG).

The Centre for MEDICINAL CANNABIS

Association for the Cannabinoid Industry

CONSERVATIVE DRUG POLICY REFORM GROUP

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Executive Summary

Cannabidiol (CBD), extracted from the Cannabis Sativa plant, has attracted a rapidly growing consumer interest as a wellness product, with a **UK market size of about £300M per year, and an estimated 1.3M users**. Whilst CBD itself is not a controlled substance, there are at least 12 potential controlled contaminants in CBD products including various tetrahydrocannabinol (THC) com-pounds.

There is **widespread confusion** among the public and UK businesses relating to the control status of products containing hemp, CBD and other cannabinoids, however, the Home Office interpretation presumes that **all CBD products are controlled** even when no controlled contaminants are detectable. This presumption is incompatible with scientific convention and is likely to be incompatible with case law.

In most European countries, maximum levels have been agreed for controlled cannabinoids in products for consumer use. This ranges from 0.001 mg/kg (EU (EFSA) and Germany) to 0.007 mg/kg THC in consumer products (Switzerland and Croatia), as well as THC limits in CBD end products (ranging from 0.05% in the Netherlands to <3% in Guernsey).

To address the UK regulatory anomalies, this report has independently considered all the available data and **recommends a THC safety limit of 0.03%** or 21 µg per day, which is derived as follows:

- Food Standards Agency Committee on Toxicity level for safe consumption of CBD is 70 mg/day
- European Food Safety Agency panel on Contaminants in the Food Chain (2015) reported a safe acute reference dose for THC of 83 µg (approx. 1 µg/kg/day), and we find no evidence to dispute this.
- For potential for pharmacodynamic or pharmacokinetic effects of trace quantities of other phytochemicals in CBD products, add uncertainty factor of 2.
- Some consumers may use products at greater than the recommended daily allowance. Therefore, we suggest a further uncertainty factor of 2 to account for variations in use.
- Applying these additional uncertainty factors (2 x 2 = 4) to the EFSA ArFD yields a threshold limit of 21 µg, equivalent to 0.03% of the maximum daily dose of CBD.

We recommend that the proposed safety limit of 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 Δ^9THC). This level of THC is highly unlikely to produce a positive THC drug test.

Based on gap review of the available literature, we make the following **recommendations for research**: acute and chronic toxicity studies of purified and combination cannabinoid products in animals and human after oral, inhaled, sublingual, and topical administration; study of the demographics and consumption patterns of CBD users, and phase 4 style surveillance studies on CBD products.

On the basis of the literature review and safety assessments in this report, we make the following **policy recommendations**:

1. To except from control CBD-based products containing no more than 21 µg of cannabinol derivatives (THC and CBN compounds) or with a total concentration of not more than 0.03%.

2. To except from control the dried leaves and flowers of approved hemp strains where the finished preparation contains no more than 0.03% cannabinol derivatives.

3. That the FSA establish regulations to require manufacturers of CBD based products to include mandatory warning labels and track and report suspected adverse events through a pre approved consumer app.

4. That the Home Office urgently issues updated public guidance to clarify the legal controls on CBD products.

5.That the Home Office and FSA issue joint guidance to industry regarding the regulatory controls and requirements for the importation, exportation, manufacture and supply of CBD based novel and non-novel food products.

Key terms and abbreviations

ACMD	Advisory Council for the Misuse of Drugs
ARfD	Acute reference doses
BMDL	Benchmark Dose lower confidence Limit
CBC	Cannabichromene
CBCA	Cannabichromenic acid
CBD	Cannabidiol
CBDL	Cannabinodiol
CBE	Cannabielsoin
CBF	Cannabifuran
CBG	Cannabigerol
CBGA	Cannabigerolic acid
CBL	Cannabicyclol
CBNA	Cannabinolic acid
CBN-C1	Cannabiorcol
CBN-C2	Cannabinol-C2
CBN-C4	Cannabinol-C4
CBN-C5 (CBN)	Cannabinol
CBNM-C5 (CBNM)	Cannabinol methyl ether
CBMP	Cannabis-based medicinal product
CBPM	Cannabis-based product for medicinal use
CBDV or CBN-C3 (CBV)	Cannabivarin
cis-THC-C5 (cis-THC)	cis-Δ^9-tetrahydrocannabinol
CRfD	Chronic reference dose
ED_{50}	Median effective dose. The dose required to achieve 50% of the desired response in 50% of the population
EC_{50}	Half maximum effective concentration. The concentration of a drug at which 50% of its maximum response is observed
EFSA	European Food Safety Authority
EWDTS	European Workplace Drug Testing Society
FSA	Food Standard Agency
GC-MS	Gas chromatography–mass spectrometry
HPLC	High performance liquid chromatography
LC_{50}	Half lethal concentration. The concentration of a drug at which 50% mortality from toxicity is observed
LC-MS	Liquid chromatography–mass spectrometry
LD_{50}	Median lethal dose. The dose required to achieve 50% mortality from toxicity.
LOAEL	Lowest-observed adverse effect level
LOEL	Lowest dose at which any effect was observed
LOD	Limits of detection
LOQ	Limits of quantification
MDA	Misuse of Drugs Act
MDR	Misuse of Drugs Regulations
MHRA	Medicines and Healthcare products Regulatory Agency
MTD	Maximum tolerated dose
NOAEL	No-observed adverse effect level
NOEL	No Observed Effect Level
OTC	Over the counter
PMTDI	Provisional maximum tolerable daily intake
SD	Standard deviations
TD_{50}	Median Toxic dose of 50% for 50%: The dose required to get 50% of the population reporting this specific toxic effect
TDI	Tolerable daily intake
Δ^8-THC	Δ^8-tetrahydrocannabinol
Δ^9-THC	Δ^9-tetrahydrocannabinol
Δ^9-THC-C1	Δ^9-tetrahydrocannabiorcol
Δ^9THC-C4	Δ^9-tetrahydrocannabinol-C4
Δ^9THC-C5	Trans-Δ^9-tetrahydrocannabinol
THCA	Tetrahydrocannabinolic acid
THC-COOH	11-nor-9-carboxy-Δ^9 tetrahydrocannabinol
Δ^9THCV	Δ^9-tetrahydrocannabivarin
THCVA	Tetrahydrocannabivarin carboxylic acid
TTC	Threshold of toxicological concern
UF	Uncertainty factor

Purpose of the report

This report has been co-produced by the CMC, ACI and CDPRG to identify and address key issues relating to the regulation of the UK market in CBD-based products. The primary objectives of this report were to

1. assess the safe levels of long-term exposure to controlled contaminants in CBD-based commercial products

2. use safe exposure assessments to recommend regulatory limits for controlled contami-nants to define the conditions under which CBD-based commercial products should be exempt from control under UK drug legislation and

3. make recommendations for research to address the gaps in existing scientific knowledge

4. make policy recommendations.

Our research identified that of the potential controlled contaminants in CBD-based products, there is only a significant evidence based on which to make decisions on the main active compound of the cannabis plant, Δ^9-tetrahydrocannabinol (Δ^9THC). **Therefore, to address these objectives, the report considered the available relevant toxicity and clinical data for Δ^9THC to assess safe levels in food products.**

In preparation of this document, there are a number of influencing factors that were considered as part of the overall evaluation. These include:

- Current international legislation specifying controlled levels of THC
- Does existing animal toxicity data provide sufficient quality and content to derive NO-EL/ NOAEL/BMDL endpoints to support safety recommendations?
- Would existing data used in any analysis be acceptable to the appropriate authorities (HO, FSA)?
- Should this be underpinned by clinical data and adverse event reporting from randomised controlled clinical trials?
- What constitutes harm in terms of safety; is it derived from animal toxicity data, human adverse event profile from controlled clinical trials or MDA statements on societal issues from recreational use?

Scope and constraints

- This report is concerned primarily with commercial end-products, rather than crude and intermediate materials used during manufacture.
- The emphasis is on products designed for oral administration, but further work is needed to assess safe exposure limits and guide regulatory controls on products designed for other routes of administration.
- The majority of the relevant toxicological, experimental and clinical data is only available for Δ^9THC, and therefore only a recommendation for levels of Δ^9THC were made. Future research should investigate other cannabinoids of importance, including Δ^8THC and CBN, to determine their safety levels alone and in combination with other phytocannabinoids in CBD products.

1. Background

Cannabis species are known to contain over 500 compounds, including cannabinoids, flavonoids and terpenes [1]–[4]. The vast majority of these are not controlled drugs in the UK [5]. Non-controlled cannabinoids include cannabidiol-type compounds (CBD), cannabigerol-type compounds (CBG), cannabichromene-type compounds (CBC), cannabinodiol-type compounds (CBDL), cannabifuran-type compounds (CBF), cannabicyclol-type compounds (CBL), cannabielsoin-type compounds (CBE), and the acid precursors of these classes. The acid precursors of the controlled compounds THC and CBN are not explicitly controlled either, but they readily degrade to form controlled products, and are presumed to be controlled by the Home Office on this basis [6]. There are widespread claims that many of these compounds contribute to the purported medicinal and wellness benefits of cannabis-derived products [7], [8]. There is limited evidence currently available to support many of these claims, though some data does exist to indicate beneficial effects, particularly for CBD [3], [4], [9], [10].

CBD has attracted substantial and rapidly growing consumer interest as a wellness product, available on the UK market in a wide variety of forms, such as oils, tinctures, capsules, creams, food products and supplements, and e-liquids [11]. While no outright medicinal claims can be made by suppliers for over the counter (OTC) CBD products, allusions are typically made to the antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties of CBD that have been demonstrated to varying degrees in clinical and preclinical studies (e.g. see [12]).

In 2019, the CMC commissioned an independent market insight and research agency to conduct a bespoke piece of market sizing analysis for the CBD sector in the UK [11]. The size of the UK OTC CBD market at that time was estimated at £300M per year with an estimated 1.3M users. This is larger than the total UK Vitamin D (£145M) and Vitamin C market (£119M) combined. The market continues to grow rapidly and is expected to be just short of £1B in 2025. This would be equivalent to the entire UK herbal supplement market in 2016.

The majority of UK consumers of CBD products purchase them online, although they are widely available in pharmacies, health food stores, and supermarkets. Over 70% of UK consumers are purchasing tinctures, oils or capsules, which are the most commonly available formats. Other formulations on the market include topicals, e-liquids, and consumables (e.g. confectionary). Consumers who buy CBD products for medicinal reasons show a greater preference for oils, tinctures and capsules than consumers who are not medicinally motivated (82% vs. 63%) and tend to spend more (£59/month vs. £22/month). These trends indicate a higher average daily intake of CBD-based products by those who believe it helps them manage medical conditions.

Categorisation and regulation of CBD products

The regulatory classification of CBD products depends not only on the constitution of the product but also on its intended use throughout its life cycle. Products that are or which contain controlled drugs cannot be lawfully manufactured, supplied or possessed except under exempted, licensed or otherwise authorised conditions. In the UK, the relevant legislation under which dangerous or otherwise harmful drugs are controlled is the Misuse of Drugs Act 1971 and its associated regulations [13]. The manufacture, supply and possession of products that are not, or which do not contain controlled drugs may not be subject to any generalised prohibitions under drugs legislation, but other legislation and regulations may still apply depending on the intended and advertised uses of products (e.g. medicinal products, veterinary medicines, cosmetics, foods).

Products for human use that are presented, used, or intended for the treatment or prevention of disease, modification of physiological function, or to make a medical diagnosis, are regulated as medicinal products. Ingredients of medicinal products are also regulated, as 'active substances' or 'active pharmaceutical ingredients', by the relevant medicines authority, which in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA) [14].

In October, 2016, the MHRA announced that CBD-containing products that meet the definition of a medicinal product must have market authorisation before being supplied or advertised, unless ordered in accordance with 'specials' regulations under the conditions laid out under the Human Medicines Regulations 2012 [15]. A deadline of 31 December 2016 was set for CBD-containing medicinal products to have either achieved market authorisation or be removed from the market.

Medicinal products for use in animals are regulated in the UK by the Veterinary Medicines Directorate (VMD). In September 2018, the VMD announced that all CBD-containing products intended for use in animals would henceforth be regulated as veterinary medicines and could not be lawfully sold or supplied in the UK without a marketing authorisation [16]. This decision applied to all CBD-containing products for use in animals and not merely those for which medicinal claims were made. The administration of an unauthorised medicinal product to an animal without a valid prescription is an offence under the Veterinary Medicines Regulations 2013 [17].

Oral CBD products which are not for medicinal use, sometimes referred to as 'wellness' products, are regulated as novel food products. Novel foods are food products for which no significant history of consumption within the EU can be shown prior to May, 1997 [18]. In January 2019, the European Union's catalogue of novel foods was updated to clarify that extracts of cannabis and derived products containing cannabis were considered novel [19]. The UK foods regulator, the Food Standards Agency (FSA), subsequently accepted the EU recommendation. In February 2020, the FSA announced a deadline of 31 March 2021, for suppliers of CBD food products and food ingredients to have either submitted fully-validated novel food applications or to have removed their products from the market [20]. It is not permitted for new CBD food products to be brought to market until they are authorised by the FSA as novel foods, unless they had already been on the market prior to February, 2020. The FSA will accept formal applications for novel food authorisation when the Brexit transition period comes to an end in January, 2021.

CBD products that are not for medicinal use, veterinary use, or non-medicinal oral use are categorised and regulated according to their specific intended use. Cosmetic products are regulated in the UK under the Cosmetic Products Enforcement Regulations 2013 [21]. It is only lawful to market CBD cosmetics in the UK if the CBD derives from either synthetic manufacture or from extraction from the non-controlled parts of the hemp plant, namely the seeds or stalk [22]. Non-nicotine liquids containing CBD for vaporisation are regulated under EU legislation, the General Product Safety Directive (GPSD) 2001/95/EC, and the national legislation enacted to implement these regulations. In the UK, that national legislation is the General Product Safety Regulations 2005 [23].

Controlled contaminants in CBD products

Pure isolated CBD is not controlled under the Misuse of Drugs Act 1971 (MDA) and subsequent regulations [6], [13]. The MDA specifies the following as being controlled drugs under Class B:

- Cannabis ("any plant of the genus Cannabis or any part of any such plant" other than the seeds, mature stalk or fibre after separation);
- cannabis resin ("the separated resin, whether crude or purified, obtained from any plant of the genus Cannabis"); and
- cannabinol derivatives ("tetrahydro derivatives of cannabinol and 3-alpha homologues of cannabinol or of its tetrahydro derivatives").

At least 140 cannabinoids have so far been identified as being present in Cannabis species. The Advisory Council for the Misuse of Drugs (ACMD) have reviewed which of these cannabinoids would be covered by the technical definition of 'cannabinol derivatives' and have advised that a total of 12 are controlled under the definitions provided in the MDA (Table 1) [5]. Under that interpretation, a large majority of the cannabinoids identified in the plant are not subject to control in the UK.

Cannabinoid	Abbreviation
Δ^9-tetrahydrocannabivarin	TCHV
Δ^9-tetrahydrocannabiorcol	THC-C1
Δ^9-tetrahydrocannabinol-C4	THC-C4
trans-Δ^9-tetrahydrocannabinol	THC-C5 (THC)
cis-Δ^9-tetrahydrocannabinol	cis-THC-C5 (THC)
Δ^8-tetrahydrocannabinol	Δ^8-THC
Cannabiorcol	CBN-C1
Cannabiorcol-C2	CBN-C2
Cannabivarin	CBN-C3 (CBV)
Cannabinol-C4	CBN-C4
Cannabinol	CBN-C5 (CBN)
Cannabinol methyl ether	CBNM-C5 (CBNM)

Table 1: Cannabinoids controlled under the MDA and subsequent regulations

It is possible for controlled cannabinoids to be present as contaminants in CBD products, depending on storage conditions, the source materials, and extraction and production processes that were used in manufacture. These can be categorised as process-related contaminants, which may arise from the starting materials or from reactions during production, and degradation-related contaminants, which may result from reactions that occur in the finished product after manufacture (see Table 2).

Impurity	Type	
Organic	Degradation-related	Degradation Excipient interactions Residue interactions Container interactions
	Process-related	Excipient interactions Starting materials By-products Intermediates Reagents, ligands & catalysts
Solvents	Organic liquid Inorganic liquid	
Solvents	Reagents, ligands & catalysts Heavy metals or other residal metals Inorganic salts Other materials	

Table 2: Categorisation of contaminants

Crude starting materials used in the manufacture of plant-based CBD products, which accounts for the vast majority of products on the consumer market, are likely to contain traces of Δ^9THC, Δ^8THC, CBN and possibly other controlled cannabinoids as process-related contaminants [24], [25]. The concentration of these contaminants in the starting products will vary depending on the genetics and cultivation of the plant, the extraction processes, and storage conditions.

Unless specifically removed during the manufacturing process, controlled contaminants may also be present in finished CBD products available on the market. A CMC 2019 analysis of 29 of the most popular CBD products in the UK identified a range of contaminants present among the samples, including controlled substances (Δ^9-THC, CBN and THCV), precursors to controlled substances (tetrahydrocannabinolic acid (THCA) and tetrahydrocannabivarin carboxylic acid (THCVA)) and non-controlled substances (cannabigerol (CBG), cannabigerolic acid (CBGA), cannabichromene (CBC), and cannabichromenic acid (CBCA)) [26], as has also been observed in many other countries [27]–[29].

Poorly refined hemp CBD extracts manufactured by solvent-based or supercritical CO2 extraction methods with no further purification are particularly likely to contain controlled co/ntaminants. However, manufacturing processes that employ more effective techniques to remove unwanted compounds, including multi-step recrystallisation and advanced chromatography, may result in higher quality end products containing no detectable levels of contaminants, depending on the type and quality of the methods used. Analytic methods used in the detection, identification and characterisation of contaminants are discussed later in this report.

A variety of degradation-related contaminants may also exist in finished products, and their concentrations may change over time depending on the degradation rates and pathways of the compounds present at the time of packaging. Products that contain unremoved traces of non-controlled precursor acids may readily degrade to form controlled cannabinoids during storage; cannabinolic acid (CBNA) and THCA decompose to form CBN and THC, respectively, by decarboxylation catalysed by light or heat. On the basis of these degradation pathways, the Home Office presume that products containing THCA and CBNA would be controlled, as stated in the following excerpt from the department's factsheet on Cannabis, CBD and other cannabinoids [6];

> *"THC-A and its control status. THCA as an isolated substance, in its pure form, would not be controlled under the MDA 1971 / MDR 2001.*

However, it is understood that THC-A readily degrades both naturally, and with a catalyst or environmental change (e.g. ingestion) to THC which is a Schedule 1 controlled cannabinoid. Against this background, the presumption is similarly one of caution, namely that THCA will become a controlled substance by virtue of its degradation."

Δ^9THC has been shown to be sensitive to oxidation, heat, light and is unstable in acid solutions [30]–[32]. THC is oxidised to CBN over time, and this degradation represents the primary deactivation pathway in cannabis products, since CBN does not produce the characteristic psychoactive effects of THC [33]. In studies on the effects of long-term storage conditions on the cannabinoid concentration of seized cannabis products, Δ^9THC steadily and progressively decays, resulting in a corresponding increase in CBN and other oxidative derivatives [34]–[36]. These degradation pathways for Δ^9THC are shown in Fig 1.

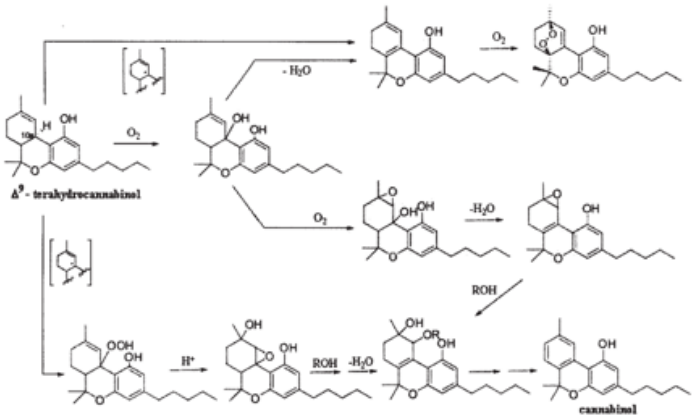

Figure 1. Degradation pathways for Δ^9THC (taken from Trofin et al., 2012 [34])

CBD is also sensitive to oxidation, heat, light, and unstable in acid or base solutions [37]–[39]. The common pathways for the degradation of CBD in storage are shown in Fig 2. In the presence of oxygen, CBD will readily oxidize to form a number of monomeric and dimeric hydroxyquinones. The oxidation of CBD in solution is catalysed by light and heat, so CBD products should be protected against both in storage to improve stability. While oxidative degradation may reduce the levels of CBD present in products, causing discrepancies between the true content and the labelled content depending on storage conditions, the products of this pathway are not controlled under UK law.

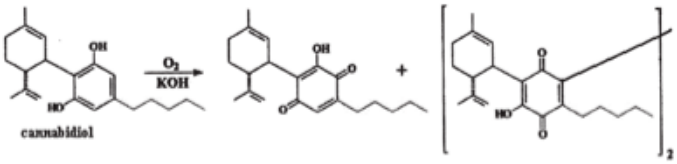

Figure 2. Degradation pathways for Δ^9THC (taken from Trofin et al., 2012 [34])

Analytic methods for impurity control in CBD products

Several hundred phytochemicals have been identified in cannabis plant extracts. The concentration and combination of these compounds can vary widely between plant strains and depending on cultivation conditions. The quantitative analysis of a pure chemical is relatively straightforward. However, cannabis and cannabis-derived products contain multiple compounds, making their analysis more complicated. The analytical challenges associated with quantifying any cannabinoid with absolute precision require a thorough understanding of—

i) the analytical instrumentation used for quantification;

ii) the techniques of sample preparation (particularly important for cannabinoid testing as most cannabinoids are sensitive to light, temperature and air);

iii) the degradation profile of cannabinoids present in the sample; and

iv) the effects of environmental factors including temperature, air & humidity.

Analytical instrumentation can determine the presence of impurities in a sample at high levels of specificity and sensitivity, but even the most accurate analytic tests cannot absolutely exclude the presence of a substance. Certain limits are built into analytic methodologies, defining the concentrations below which it becomes statistically meaningless to prove the existence or amount of a contaminant. These are called the limits of detection (LOD) and quantification (LOQ). The detection limit is a crucial factor in determining whether a molecule can be identified and quantified with an acceptable level of confidence. If standards of high quality and purity are available, protocols of validating detection limit are straightforward.

Generally, each testing laboratory develops its own methods and incorporates the limit of detection (LOD) for the procedure.

The LOD is the smallest signal from the analyte that can be reliably detected against the background noise from the instrumental system. It marks the threshold at which a compound can be determined to be present in a sample with a defined statistical confidence. There are various ways of establishing the LOD based on different statistical measures, but the simplest and most commonly used approach is to estimate the lowest concentration tested that has a peak signal height that is greater than or equal to the average of a blank sample (no analyte) plus three standard deviations (SD) of the blank. The acceptance criterion is that the LOD has to be less than 20% of the LOQ.

The LOQ is the smallest signal from the analyte that can be reliably measured against the background noise from the instrumental system. It marks the threshold at which the amount of a compound can be quantified at defined levels of imprecision and accuracy. There are various ways of measuring the LOQ based on different statistical measures, but the simplest and most commonly used is a signal 10 times the average background noise.

Validation of detection levels

Thresholds to be used for the reporting, identification and qualification of known impurities in specific drug compounds with established medicinal uses are typically provided in pharmacopoeial monographs. There is no official monograph available for CBD in either the British Pharmacopoeia or the European Pharmacopoeia. A monograph for synthetically produced CBD is provided in the German Drug Codex (DAC), but there is no equivalent monograph for hemp-derived CBD. It lays out a validated protocol to test for impurities by high performance liquid chromatography (HPLC) at the following thresholds:

- Unspecified impurities: maximum 0.10% each.
- Sum of all impurities: maximum 0.5%.
- Report threshold: 0.05%
- Specified impurities (i.e. THC) reporting limit: 0.0003%

The ACI have investigated HPLC methodology in detail and have established validated LOD /LOQ for Δ9THC and for other 11-12 other cannabinoids using certified reference material to produce a validated HPLC method for the analysis of CBD samples. ACI are now further working to establish validated analytical methodology using liquid chromatography–mass spectrometry (LC-MS), a more sensitive analytical technique capable of establishing lower LOD/LOQ for quantifying controlled contaminants in CBD-containing products. This work has been done in collaboration with the Laboratory of Government Chemists and is expected to be finalised by the end of 2020. The results will be compared with other techniques including high resolution nuclear magnetic resonance (NMR) and gas chromatography–mass spectrometry (GC-MS) in the near future.

Challenges for UK regulators

Narcotics and other toxins are found naturally in many plant species. Some toxin-bearing plants are used as ingredients in the manufacture of products for human use. Others may grow as weeds among food or industrial crops and may get mixed in accidentally at harvest. As a result, plant toxins may be detectable in a range of end-products for human use, including opium alkaloids in poppy seeds, cyanide in apricot kernels, and ergot alkaloids and tropane alkaloids in cereal products. To protect consumer safety, maximum levels have been established for many of these toxins and these are defined either in legislation or non-statutory regulations [40].

The plant toxins of interest in this report are controlled cannabinoids present in many hemp products and CBD extracts. In most European countries, maximum levels have been agreed for controlled cannabinoids in products for consumer use. No such levels have yet been established for products on sale in the UK, meaning that all contaminated products likely qualify as controlled substances under UK drugs legislation. Nevertheless, CBD products are widely available and generate hundreds of millions of pounds in sales annually. Independent laboratory analyses have consistently found detectable levels of controlled cannabinoids in most, but not all, CBD-based consumer products on sale in the UK [26], Germany [28], Europe [29], and the US [27].

It is possible that these contaminated products may be responsible for some reported side-effects and adverse reactions to CBD products [28], but this hypothesis has not been empirically established, and is quite unlikely given the very low levels of compounds other than CBD.

The inconsistencies in the quality and purity of products on the market relate to the range of methods and materials used by manufacturers to extract and purify CBD, differences in storage conditions throughout the supply chain, and a lack of appropriate regulatory oversight and enforcement. At present, there is little regulation of quality management. The novel food authorisation process requires manufacturers to submit a dossier of evidence on the toxicology, characterisation and stability of products, ensuring high standards of quality, but no CBD food products have yet been authorised by the FSA for supply in the UK because applications cannot be processed until January, 2021. In the EU, no hemp-derived CBD products have been granted authorisation by the EFSA and applications are currently closed for this category of product due to concerns about their status as a narcotic under the UN Drug Conventions. There is no mandatory pre-marketing approval or other appropriate quality control regulations for non-food CBD products, such as e-liquids and cosmetics.

Regulators face the challenge of balancing public health and consumer safety against the social and economic benefit to the UK associated with the growth of a legitimate CBD wellness market. The current Home Office policy on CBD recognises the quality concerns and is intended to limit the manufacture, supply and possession of controlled drugs to authorised and lawful operations only, in order to prevent both criminal activity and the potentially harmful effects of exposure to controlled drugs. However, there continues to be widespread uncertainty regarding the controlled status of CBD-based and hemp-based products among regulators, manufacturers and consumers alike. The clarification and/or refinement of existing legal and regulatory approaches may need to be considered to address misinterpretations and reconcile the differing positions of regulators.

For instance, the leaves and flowers of hemp plants are widely sold and supplied as ingredients of herbal teas and smoking products by UK retailers ranging from small business owners to national supermarket chains, despite such products being classified as controlled drugs in the MDA under the definition of 'Cannabis' irrespective of THC content. These retail operations have resulted in multiple arrests and prosecutions of suppliers, including owners of otherwise legitimate taxpaying businesses. There is no public data presently available on the number of law enforcement investigations into activities of this sort, nor on the outcomes of resultant proceedings. There is a plausible concern that law enforcement action may not target all offenders equally, as has previously been identified in the inconsistent policing of other cannabis-related offences across different forces and among different demographics [41]–[44]. The ongoing availability of products that contain controlled parts of the hemp plant in UK stores indicates that this legal issue is still not widely understood in the private sector. To prevent criminal justice inequalities, protect consumers, and reduce offending by businesses, UK regulators may wish to consider means of clarifying and communicating current regulations to retailers.

There is also widespread ambiguity regarding the control status of hemp-based CBD extracts. Arguably, many hemp-derived CBD products might be classified as controlled drugs in the MDA under the definition of 'cannabis resin' where the resinous products of the plant are the basis of the extraction ("whether crude or purified"). However, the most pressing ambiguity regarding the control status of CBD products relates to the analytic methods and thresholds that would be appropriate to accurately and consistently distinguish products containing only non-controlled elements from products containing trace amounts of controlled contaminants. This issue relates directly to the absence of regulated maximum limits in the UK.

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 [45]:

> ""exempt product" means a preparation or other product consisting of one or more components parts, any of which contains a controlled drug, where—

a) the preparation or other product is not designed for administration of the controlled drug to a human being or animal;

b) the controlled drug in any component part is packaged in such a form, or in combination with other active or inert substances in such a manner, that it cannot be recovered by readily applicable means or in a yield which constitutes a risk to health; and

c) no one component part of the product or preparation contains more than one milligram of the controlled drug or one microgram in the case of lysergide or any other N-alkyl derivative of lysergamide".

The limbs of this provision are independent from one another and must all be satisfied for a product to be exempt for control. It was inserted into the MDR in 1999 by Statutory Instrument (SI) 1999/1404, which was accompanied by an explanatory memorandum stating the intention of exempting "products used for scientific or diagnostic purposes which contain an extremely small amount and proportion of controlled drugs" [46]. In 2017, a letter from the ACMD to the Home Office observed that the SI was "intended to facilitate the use of test kits for testing biological samples for traces of controlled drugs" [47]. Although the provision was not meant to apply to products for human consumption, claiming 'exempt product' status is the most common justification put forward by manufacturers of CBD products containing controlled substances. The legitimacy of this justification is discussed below.

In recognition of the wide range of quality and purity of CBD products on the market, the Home Office have published a Factsheet on Cannabis, CBD and cannabinoids [6], which states that:

"If a CBD 'product' contained any controlled cannabinoids, unintentionally or otherwise (e.g. THC or THCV), then it is highly likely that the product would be controlled. It is our understanding that it is very difficult to isolate pure CBD, and in our experience many products in fact do not fully disclose their contents or provide a full spectrum analysis at an appropriate level of sensitivity to accurately and consistently determine their true content or control status.

Against this background, the presumption has to be one of caution; that is, that a CBD containing product would be controlled under the MDA 1971 / MDR 2001 as a result of its other cannabinoid content."

The presumption made by the Home Office is that pure isolated CBD does not exist and that all CBD products on the market would be controlled as Class B, Schedule 1 drugs, unless a product meets the definition of either of a cannabis-based product for medicinal use (CBPM), or an exempt product. Schedule 1 drugs cannot be lawfully supplied or possessed except under a Home Office license. CBPMs are controlled under Class B, Schedule 2, and cannot be lawfully supplied except under a valid prescription or at the direction of a specialist physician, under the terms laid out in SI 2018/1055 [48]. Under the current Home Office interpretation, therefore, non-medicinal CBD products could only be lawfully supplied on the consumer market if they fulfil all three limbs of an exempt product. It is not clear whether the same presumption of control is also made in regard to non-novel hemp-based food products, such as hemp seeds and oils, although evidence exists that these products can sometimes also contain controlled contaminants [38], [49]–[51].

The manufacture of CBD products in the UK is likely to require the importation, possession and use of crude starting products which, in bulk form, may exceed the threshold of 1mg of controlled contaminants per container stated in the third limb of the exempt product definition. Equally, end products that satisfy the 1mg threshold at a specific container volume may exceed the threshold when stored in bulk. Therefore, manufacturers and distributors may both require Schedule 1 Home Office licences in order to conduct bulk operations lawfully. To our knowledge, there are no companies involved in the UK supply of non-medicinal CBD products for consumer sale that hold controlled drug licences to cover those activities. Nonetheless, this commercial activity is widespread, and there has been no reported law enforcement action taken against companies for conducting these operations without a Home Office licence, other than the proceedings brought against some suppliers of hemp flowers as mentioned earlier.

As quoted above, the Home Office factsheet states that *"many products in fact do not fully disclose their contents or provide a full spectrum analysis at an appropriate level of sensitivity to accurately and consistently determine their true content or control status"* [6].

This statement implies that there is an appropriate level of sensitivity at which the purity and control status of a product could be accurately determined, but the Home Office Minister for Crime and Policing has stated that the department *"has made no assessment of limits of detection in relation to testing for the presence of controlled cannabinoids in CBD products"* [52].

In the absence of such an assessment, the presumption of control exists even when the presence of controlled contaminants is not detectable at the most sensitive levels of detection achievable by analytic laboratories, because the controlled elements are presumed to be present at levels below the limit of detection. Home Office guidance states that "CBD as an isolated substance, in its pure form, would not be controlled". In practice, it is not possible to demonstrate or define the existence of the non-controlled element—pure, isolated CBD—without specifying a threshold under which contaminants would be presumed not to exist. The presumption of control is problematic from a scientific perspective because it cannot be disproven. Furthermore, it would define all manufacturers, distributors, suppliers and consumers currently participating in the UK CBD market as criminal offenders, unless operating under Home Office license or meeting the conditions laid out under the exempt product criteria. Enforcing this would create an extremely challenging situation for police forces, prosecutors, the industry, and the British public.

The problem is complicated further by the fact that all three limbs of the exempt product criteria must be satisfied for a product to be eligible for exemption. All CBD products are presumed by the Home Office to contain controlled contaminants, which means that even those products that have no detectable levels of controlled contaminants must comply with limbs (a) and (b). There is some ambiguity regarding the conditions under which CBD products would be considered fully compliant with exempt product criteria, since the provision was originally brought into law to facilitate products used for scientific testing, rather than consumer products for administration in humans. In particular, there is little guidance presently available to clarify the conditions under which a product would satisfy limb (a), which requires that the product is not designed for administration of the controlled drug to a human being or animal. The term 'administration' is not defined by the MDR or the MDA, but the Minister for Crime and Policing has stated that the following definition provided under the Human Medicines Regulations 2012 would likely apply:

> "administer" means administer to a human being—
>
> (a) orally, by injection, or by introduction into the body in any other way; or
>
> (b) by external application (whether or not by direct application to the body) [52]"

Under this definition, administration would not only cover the consumption of food products but also the inhalation of vaping products and the topical application of cosmetics. Therefore, the great majority of CBD products on the market are designed for administration to humans.

Compliance with limb (a) depends on whether or not the product is designed for the administration of the controlled element specifically, but there remains ambiguity as to the circumstances under which the controlled elements that are presumed to exist in a CBD product would be considered to be administered by design or merely present as unintentional and undesirable contaminants. There has been no assessment of limits of detection that would be sufficient and appropriate to define pure CBD and no public guidance is available to clarify the concentration thresholds at which a controlled element would be considered part of a product's designed constitution. The Home Office factsheet provides the following information in regard to limb (a):

> *"It is likely that the product will be subjected to regulation as a medicinal product (or to an equivalent UK regulatory standard) as a way of demonstrating that there is no intention of administering the controlled drug element of the product (referred to in (a)). The purpose and intended method of administration of a product may affect this"* [6].

Products on the CBD consumer market are typically food supplements, vaping liquids for e-cigarettes, and cosmetics. These categories of product are not regulated as medicinal products and no regulatory processes are currently active in the UK to assess the safety and quality of such products to an equivalent standard. The FSA has a procedure in place to assess novel food applications for authorisation, but it cannot process these applications until 2021.

Accordingly, no CBD food supplements currently on the market have yet been authorised by UK regulators. An interpretation of the above to mean that FSA authorisation would have to be achieved for a product to meet the conditions of limb (a) would imply that there are no products currently on the CBD food market that would qualify as exempt. With no equivalent regulatory authorisations in place for cosmetics and vaping liquids, it would follow that there may be no products currently on those markets that would qualify either. **Such an interpretation would define the entire non-medicinal CBD UK market as unlawful, but there has been no known enforcement action taken against companies on this basis.**

No formal statement has been provided to the CBD food industry by the FSA or Home Office to clarify the licencing requirements that are, or will be, required to produce, store and supply CBD food products in the UK. That the FSA has continued to permit the continued sale of CBD food products that were on the market prior to February, 2020, suggests that no presumption of control is currently being made by that regulator. It has not been publicly confirmed how Home Office regulations and FSA regulations will reconcile in practice once novel foods authorisations are processed. Businesses preparing applications for novel food authorisation are not being advised that they may need to demonstrate compliance with exempt product criteria, nor that they may require Schedule 1 licenses to lawfully manufacture or distribute in bulk in the UK. No clear regulatory position has yet been confirmed and communicated to industry regarding the circumstances under which Home Office licences would be required for the production and supply of other categories of non-medicinal CBD product either. **As a result, it remains unclear whether commercial activity on any of these markets is in full compliance with current Government regulations.**

There is no process of applying for a certificate of exemption from the Home Office other than requesting a Letter of No Objection (LONO) to signify permission to import or export a product. There is no explicit regulatory requirement for food products, vaping liquids or cosmetics to be authorised as being exempt from control prior to being placed on the market. Other than a number of arrests of importers and vendors of hemp flowers, there has been almost no law enforcement action yet taken against businesses involved in the manufacture and supply of CBD products, even when specific companies have been identified by national newspapers for supplying products contaminated with controlled elements. Accordingly, there seems to be some disconnection between the interpretations presently taken by the Home Office, other regulatory bodies, and law enforcement in regard to non-medicinal CBD products. This likely reflects the different roles played by each of these public bodies.

The control status of a product would ultimately be a decision for the courts. In regard to the meaning of 'possession' as an offence under the MDA, the courts have identified both a physical and a mental element. The physical element involves evidence that something was in the custody or control of an individual, and the mental element involves the individual knowing that the thing existed and that they had it. The individual may be in possession of the thing if these elements are satisfied, even if the individual did not know the identity or the control status of the possessed thing. In Lambert [2001] UKHL 37, per Lord Hope, Lord Slynn of Hadley stated the following:

> *"This means in a case like the present that the prosecution must prove that the accused had a bag with something in it in his custody or control; and that the something in the bag was a controlled drug. It is not necessary for the prosecution to prove that the accused knew that the thing was a controlled drug let alone a particular controlled drug"* [53].

On that basis, if proceedings were brought against a member of the public for the possession of a non-medicinal CBD product that happened to contain controlled contaminants, it is plausible that the criminal offence of possessing a Class B drug may be argued to have been committed, even if the individual had bought the product from a supermarket and was unaware of its control status. While such a situation seems highly improbable at the current time, it illustrates the **urgent need to clarify the legal and regulatory controls on products in the UK CBD market.**

The physical element of possession requires evidence that the quantity of the controlled drug amounts to something—but does not need to amount to a quantity that is usable.

In Marriott [1971] 1 All ER 595, the defendant was ruled to not be in possession of cannabis resin on a penknife, since the quantity was so small as to be detectable only by forensic analysis. In Boyesen [1982] AC 768, Lord Scarman stated that "if it is visible, tangible and measurable, it is certainly something" [54]. Therefore, in regard to highly purified CBD-based products in which controlled contaminants are not detectable, it seems improbable that the physical element of the offence could be established.

Unless the product is exempt, the current legal limit for the permitted levels of controlled cannabinoids in CBD products is zero. However, the technical definition of zero in this regard has not been clarified, either by regulators or by the courts, and the burden of proof that is placed on CBD manufacturers by an absolute presumption of control is not consistent with the actual capability of analytic methods. Regulations or guidance to define maximum limits would eliminate many of the challenges and ambiguities described above. These limits would need to protect the health and safety of the UK public while being practical and achievable for manufacturers to comply with.

Summary of key regulatory issues

In summary, the key regulatory issues in the CBD market at the present time are as follows:

- There is little quality management of products on the CBD market: many products are contaminated with trace amounts of controlled drugs and many products do not accurately or reliably disclose their contents.
- There is widespread confusion among the public and UK businesses relating to the control status of products containing hemp, CBD and other cannabinoids. There are also substantial disparities in the interpretation of 'exempt product' status between stakeholders.
- The Home Office consider all CBD products to be controlled unless shown to be exempt, but this interpretation does not seem to be shared by law enforcement.
- The Home Office interpretation presumes that CBD products are controlled even when no controlled contaminants are detectable. This presumption is incompatible with scientific convention and is likely to be incompatible with case law.
- There is no guidance at present on the Home Office licensing requirements expected of CBD novel foods manufacturers. Applicants for novel food authorisation are not being advised by the FSA that they must also apply for Home Office authorisation.
- The Home Office are not presently granting controlled drug licenses for the manufacture of CBD food products, which prevents legitimate businesses from competing with less reputable companies that do not seek regulatory oversight. This has the effect of reducing the quality and regulatory control of the market.

2. Safe exposure assessments

Drug laws in the UK and internationally are intended to prevent avoidable harms to society and the individual by limiting the availability of harmful or otherwise dangerous drugs. As such, the health and safety of the British consumer must be the primary concern in the assessment of regulatory limits for controlled contaminants in products designed for human administration. These limits must be consistent with analytic instrumentation and methodologies, but most importantly they must reflect evidence-based safety thresholds. Safety thresholds define the safe levels at which contaminants that are known or suspected to be potentially harmful in products for human or animal use can be administered over a defined period of exposure.

Safety assessments identify relevant biological parameters or endpoints which signal the toxic or otherwise undesirable pharmacodynamic effects of the contaminant. For each parameter, a reference point (or point of departure) is derived from the available toxicological, clinical and experimental data. These reference points indicate the dose levels at which the contaminant is unlikely to cause specific undesirable effects. Depending on the reliability and applicability of the available data, a number of uncertainty factors may then be applied to reference points to account for missing data, to ensure the prevention of harm to the population of interest. Health guidance values, representing the permissible levels at which exposure to the contaminant can be reliably presumed to not cause harm, are equal to the lowest value calculated after applying uncertainty factors to each reference point. These values are typically presented as units of substance weight/kilograms of body weight and can be used to determine permissible concentrations (%) of a contaminant in a product. The final concentration threshold must be equal to or higher than the achievable LOQ in order to be applied in practice.

A number of different types of reference point can be determined. The most reliable reference point derives from the benchmark dose of a compound, or the dose that corresponds to a low but measurable change in a given biological parameter. The benchmark dose (lower confidence limit) (BMDL), represents the lower dose limit with a defined statistical confidence to account for the quality of the data. The advantage of this type of reference point is that it accounts for both the dose-response curve of a compound and for uncertainties due to study quality. However, this model is only compatible with specific dose-response data involving at least three dosing groups and one control group. Where compatible data for a particular biological parameter is not available for BMDL modelling, a no-observed adverse effect level (NOAEL) may be used as the reference point, representing the largest concentration or amount of a substance that causes no adverse effect as compared to the control group. The least reliable reference point is the lowest-observed adverse effect level (LOAEL), where data is available to determine the lowest concentration or amount of a substance that causes an adverse change, but not the dose at which no change is observed. LOAEL data cannot reliably be used to determine the NOAEL, but additional uncertainty factors can be applied to estimate a NOAEL on a precautionary basis.

Uncertainty factors are safety margins applied to account for limitations in the available data, such as the extrapolation of dose-response data between species, variability between individuals, extrapolation of long term effects of exposure from studies with a short duration, or extrapolation from a LOAEL or otherwise low quality reference point. Additional uncertainty factors may be appropriate if the compound of interest is known or suspected to cause serious toxicity.

A wide range of health guidance values also exist depending on the classification of the product and the period of predicted exposure. Acute reference doses (ARfD) may be used as guidance values to account for acute exposure to a substance, while values such as the tolerable daily intake (TDI), acceptable daily intake (ADI) or chronic reference dose (CRfD) account for longer-term or lifetime exposure. Approaches such as the threshold of toxicological concern (TTC) may be used where specific toxicological data is lacking.

Previous hazard and exposure assessments of Δ^9-THC in consumer products

A number of safety assessments have been conducted by food regulators overseas to establish health guidance values for Δ^9-THC in products for human use. These values, which define the maximum amounts of THC that are expected to not cause harm when consumed by humans on a daily basis, are derived by applying uncertainty factors to estimated LOAEL/NOAEL estimates for particular biological, psychological or behavioural endpoints, as previously described.

Australia and New Zealand

In 2002, Food Standards Australia New Zealand (FSANZ) assessed the safety of THC in novel foods derived from industrial hemp [55]. The evaluation concluded that, while the majority of available human toxicological data on THC derived from studies in which the route of administration was inhalation, there was adequate toxicological data on oral administration to establish a tolerable daily intake (TDI) threshold of 6 µg/kg body weight (bw). The assessment found no evidence that low-dose human exposure to THC would be associated with an increased risk of reproductive and developmental toxicity, genotoxicity or carcinogenicity. Accordingly, the endpoint used in the analysis was skill performance in humans, which was found to be a more sensitive marker than psychotropic effects.

The basis of the 2002 FSANZ TDI was a human dose-response study of oral THC at total dose levels of 0, 5, 10, 15 and 20mg by Chesher et al. (2009), which reported no observed intoxication-related effects and a slight but reversible effect on skill performance at the lowest dose (5mg) [56]. A threshold effect dose of 60 µg/kg bw was determined using the highest bodyweight individual in the study, to which an uncertainty factor of 10 was applied to account for potential variability in sensitivity to THC between individuals, thus deriving the TDI of 6 µg/kg bw. FSANZ justified the use of acute human data, without additional uncertainty factors to account for longer periods of exposure, by noting that the known development of tolerance to THC would plausibly decrease the effects of the same dose over an extended period.

In 2012, FSANZ conducted an updated hazard assessment to evaluate relevant data that had been published after the 2002 evaluation, including a 2009 review by Zuurman et al. (2009) that included 10 post-1998 human studies on the effects of THC following oral administration [57], [58]. None of these 10 studies provided human data at doses lower than the 5mg threshold effect dose established by Chesher et al. (1990). However, the Zuurman review reported that the subjective report of feeling 'high' was the most sensitive marker of the effects of THC, contrary to the previous finding by Chesher et al. that skill performance was most sensitive [59]. FSANZ revised its analysis of the dose-response data on the basis that skill performance data at the lowest dose was not statistically robust, and concluded that the threshold effect dose of 5mg represented a NOAEL in humans. The FSANZ 2012 assessment upheld the TDI of 6 µg/kg bw.

European Union

In 2011, the European Food Safety Authority (EFSA) Panel on Additives and Products or Substrates used in Animal Feed (FEEDAP Panel) published a scientific opinion on the safety of hemp for use in animal feed [60]. The panel identified a LOEL (the lowest dose at which any effect was observed) of 2.5 mg THC for psychotropic and other central nervous system effects in humans, and applied an uncertainty factor of 100 to derive a provisional maximum tolerable daily intake (PMTDI) of 0.4 ug/kg bw. A maximum THC content of 10 mg/kg product weight (0.001%) was recommended for hemp-derived animal feed materials, to protect consumers of dairy products from accidental exposure.

In 2015, the EFSA Panel on Contaminants in the Food Chain (CONTAM) conducted a hazard assessment of THC in milk and other foods of animal origin [61]. The panel reviewed a selection of clinical and non-clinical reports, including studies in humans and in animals, focusing on health-relevant effects of orally administered Δ^9-THC at low doses and threshold doses. Central nervous system effects, such as mood alteration and sedation, were identified as the most sensitive relevant endpoint. The assessment found that the available data in humans was not adequate for benchmark dose level (BMDL) modelling and that effects were observable at the lowest investigated doses. An Acute Reference Dose (ARfD) of 1 ug THC/kg bw was established by applying a combined uncertainty factor of 30 to the LOAEL of 2.5 mg.

Dose-response data in rats was found to be adequate for BMDL modelling, but the values derived by this approach were more than 700 times greater than the ARfD. Accordingly, the panel concluded that the ARfD could be assumed to be protective in both acute and chronic exposure conditions.

In 2020, EFSA published an assessment of acute exposure to THC to include a range of non-dairy food products that were not assessed in the 2015 CONTAM assessment. It concluded that the ARfD of 1 µg/kg bw was exceeded in high-consumption models of most hemp derived food products [62].

Switzerland

In 1995, the Swiss Federal Office of Public Health (Bundesamt für Gesundheit (BAG)) assessed safe exposure limits for THC [63]. Using the endpoint of psychotropic effects, the BAG assessment determined a TDI of 7 µg/kg bw, derived from a threshold effect dose of 5 mg in a 70 kg human, with an uncertainty factor of 10 applied to account for accumulation of THC in the body over longer periods of exposure.

Germany

In 1997, the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) published a recommended daily intake of 1-2 µg THC/kg bw [64]. The BgVV assessment identified effects on the central nervous system as the most sensitive relevant endpoint and established the daily intake value by applying an uncertainty factor of 20-40 to a LOEL of 40 µg/kg bw. In 2000, assuming average daily consumption amounts of different types of food product, BgVV established maximum THC levels of 5 ug/kg for non-alcoholic and alcoholic beverages (0.0000005%), 5 mg/kg for edible oils (0.0005%) and 0.150 mg/kg for all other foods (0.000015%) [65]. In 2018, the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung (BfR)) published an updated exposure assessment which concluded that the consumption of hemp-containing foods could plausibly result in exposure to THC at levels that exceed the ARfD of 1 µg/kg bw established by EFSA in 2015 [66].

Croatia

In 2011, the Croatian Food Agency (Hrvatska Agencija za Hranu (HAH)) published a scientific opinion on the health impact of hemp-derived food products [67].

The HAH opinion provided an acceptable daily intake of 7 µg THC/kg bw, based on earlier estimates published by Grotenhermen et al. in 2001 [68]. The Grotenhermen assessment, which was not peer-reviewed, applied an uncertainty factor of 20 to a NOAEL for psychomotor effects in humans of 140 µg/kg bw.

Region	Assessor	Reference point (mg)	Uncertainty factors	Health guidance value (mg/kg bw)
Australia & New Zealand	FSANZ	5	10	0.006
EU	EFSA	2.5 2.5	30 100	0.001 0.004
Germany	BgVV	2.5	20-40	0.001-0.002
Switzerland	BAG	5	10	0.007
Croatia	HAH	10	20	0.007

Table 3. Summary of safety assessments and health guidance values for THC in consumer products across the world

Regulations on CBD products in Europe

In the majority of Europe, it is legal for industry hemp products to be sold provided they contain 0.2% THC or less (see Table 4). However, as of January 2019, the European Food Safety Authority (EFSA) announced that food products containing CBD products would be classified as Novel Foods under Act (EU) 2015/2283, and would require authorisation prior to being placed on the market [69], [70]. Companies are therefore required to file a novel food application and have this approved by the EFSA before legally being able to sell such products. The EFSA announcements notwithstanding, regulations surrounding THC limits, as well as CBD inclusion in other products is largely unclear with many European countries adopting their own individual regulations.

In Austria, whilst unauthorised CBD-based edibles and medicines may not be sold, cannabis flower extracts with less than 0.3% THC can be sold when labelled as aroma products, as products classed essential oil are still permitted [71]. Belgium permits the purchase of CBD flowers with a THC content of less than 0.2% in tobacco products and is taxed as such [71], [72].

As per EU law, CBD (including CBD oil) is not permitted in food products unless authorised as a novel food. According to the Danish Veterinary and Food Administration (DVFA), CBD products with a THC content below 0.2% can be marketed without being in breach of the executive order on euphoriant substances [73]. Bulgaria's Ministry of Agriculture, Food and Forestry, and the Bulgarian Food Safety Agency issued Free Certificate of Sale for products produced by Kannaway, claiming they are "traditional foods", in order to bypass the current EU legislation (Law on Foodstuffs of Republic of Bulgaria and of Regulation (EC) No 852/2004 of European Parliament and the Council on the hygiene of foodstuffs) [74].

Jurisdiction	THC limit in CBD end products
Guernsey Jersey	<3%
Switzerland	<1%
Austria Luxembourg Czech republic	<0.3%
Poland Greece Spain Belgium Romania Germany Denmark	<0.2%
Netherlands	<0.05%
France Sweden Norway UK Slovakia	Not permitted
Bulgaria Italy	Not clear

Table 4. THC limits in CBD end products in Europe

Under EU regulation, CBD may only be used in cosmetics provided the extract does not derive from the fruiting tops of the cannabis plant, and products are subject to cosmetic safety regulations (Regulation (EU) No 1223/2009) [71]. In the UK, The Cosmetic, Toiletry and Perfumery Association states that whilst CBD alone is not subjected to the control drugs act and whilst plant derived CBD can be used in cosmetic products it must not be obtained from the flowering or fruiting tops of the cannabis plant [22].

World Health Organisation recommendations

At the 40th meeting of the World Health Organisation (WHO) Expert Committee on Drug Dependence (ECDD), the committee discussed a critical review report on CBD [75]. WHO subsequently made recommendations to the Secretary General of the UN that pure CBD should not be scheduled within the UN Drug Control Conventions and that a footnote be added to the 1961 Single Convention on Narcotic Drugs to read:

> *"Preparations containing predominantly cannabidiol and not more than 0.2 percent of delta-9-tetrahydrocannabinol are not under international control"* [76].

In a Questions and Answers consultation published by the UN Office on Drugs and Crime in October 2019 [77], WHO made the following clarifications in regard to the recommended 0.2% threshold:

- *"The word predominantly was used to describe the proportion of CBD and this was intended to mean that almost all of the content was CBD. The Committee considered that the percentage of CBD to be used in practice could be left to individual Member States in consultation with INCB."*
- *"The value of 0.2% for THC was specified as WHO had requests from Member States to indicate what maximum percentage was considered appropriate and to ensure that the currently registered CBD medication [Epidyolex] was exempted from control. That medication has a THC content not greater than 0.15% by weight as a proportion of the total weight of plant material."*
- *"The specified level of 0.2% is by dry weight as a proportion of the total weight of cannabis plant material. This was done intentionally as different manufacturers (or the same manufacturer in different countries) may add different amounts and types of excipients to the material extracted from the plant. Different amounts of excipients will result in different final percentages of delta-9-THC for the same amount of delta-9-THC. What is important is the amount of delta-9-THC relative to the amount of cannabidiol (and other minor plant constituents that will be present in the product). By specifying the level of delta-9-THC as a proportion of the total weight of cannabis plant material, irrespective of the amount of excipients added, this is achieved."*

- *"The Committee also acknowledged that chemical analysis of Δ9-THC to an accuracy of 0.15% may be difficult for some Member States and hence ECDD adopted a limit of 0.2%. On the basis of the Committee's recommendation, even for a maximum adult dose of CBD, the level of THC (max. 0.2%) will be below the level that would produce significant effects."*
- *"It is only possible to experience effects of THC by consumption of very high doses of CBD that would produce significant adverse effects from the CBD itself such as weakness, diarrhoea, general malaise and insomnia.*
- *These effects make it extremely unlikely that anyone would do this on more than one occasion and therefore abuse and dependence of THC from CBD products with less than 0.2% of delta-9-THC is therefore not a significant concern."*
- *"The wording of the footnote encompasses both medicinal and non-medicinal products."* [75]

On December 2, 2020, the 53 member States of the UN Commission on Narcotic Drugs (CND) voted on the WHO recommendations at its 63rd reconvened session on December 2, 2020. The CND did not elect to implement the recommendation to remove CBD products with less than 0.2% THC from international control.

3. ACI/CMC & CPDRG Safety Assessment

In order to make a recommendation on safe THC levels in CBD products, this group undertook a series of systematic literature reviews to identify the pertinent literature according to the following methodology.

Methodology

To identify the key literature, we carried out literature searches, searched clinical trials.com, handsearched relevant literature, and searched any data available on approved THC products. From these searches, we looked to identify any literature relating to toxicology, toxicity, genotoxicity, dose-responses and adverse events (from clinical trial data).

1. Pubmed search strings:

- (THC OR delta-9-tetrahydrocannabinol OR tetrahydrocannabinol OR delta-9-THC OR Δ9-THC or Δ-9-THC or Δ9-tetrahydrocannabinol or Δ-9-tetrahydrocannabinol OR marinol OR dronabinol) AND (pharmacokinetics OR "dose-response" OR "dose response" OR titration OR LOAEL OR LOEL OR NOAEL OR NOEL OR BMDL OR "dose dependent" OR "dose-dependent" OR EC50 OR ED50 OR MTD OR *toxic OR toxicology OR *toxicity OR teratogenicity OR *natal development) AND (review)
- (THC OR delta-9-tetrahydrocannabinol OR tetrahydrocannabinol OR delta-9-THC OR Δ9-THC or Δ-9-THC or Δ9-tetrahydrocannabinol or Δ-9-tetrahydrocannabinol OR marinol OR dronabinol) AND (pharmacokinetics OR "dose-response" OR "dose response" OR titration OR LOAEL OR LOEL OR NOAEL OR NOEL OR BMDL OR "dose dependent" OR "dose-dependent" OR EC50 OR ED50)
- (delta-8-tetrahydrocannabinol OR delta-8-THC or Δ8-THC or Δ-8-THC or Δ8-tetrahydrocannabinol or Δ-8-tetrahydrocannabinol) AND (pharmacokinetics OR "dose-response" OR "dose response" OR titration OR LOAEL OR LOEL OR NOAEL OR NOEL OR BMDL OR "dose dependent" OR "dose-dependent" OR EC50 OR ED50 OR LD50 OR LC50 OR TD50)
- (cannabinol OR CBN) AND (pharmacokinetics OR "dose-response" OR "dose response" OR titration OR LOAEL OR LOEL OR NOAEL OR NOEL OR BMDL OR "dose dependent" OR "dose-dependent" OR EC50 OR ED50 OR LD50 OR LC50 OR TD50)

2. Clinicaltrials.gov was searched for the terms 'THC, tetrahydrocannabinol, delta-8-THC, cannabinol' for completed trials in humans with results which haven't been published under peer review (as far as we are aware), which identified 4 studies:

NCT identifier	Cannabinoid & dose	Protocol	Study title	Relevant results
NCT00314808	Dronabinol (THC)	Dronabinol 5 mg BID administered 24 hours prior to, during, and 48 hours after completion of oral/intravenous chemotherapy for a maximum of 2 consecutive cycles	A Pilot Study of Dronabinol for Adult Patients With Primary Gliomas	Tolerability rate: 60% Unacceptable Toxicity Rate: 0% Serious adverse events: 3.03% Other adverse events: 36.36%
NCT02472847	Dronabinol (THC)	In a randomized, double-blind, placebo-controlled, between-subjects design, the investigators will couple a standard Pavlovian fear extinction paradigm in fMRI with an acute pharmacological challenge with oral dronabinol (synthetic THC; 7.5mg once orally) or placebo 2 hours prior to extinction learning.	A Pilot Study of Dronabinol for Adult Patients With Primary Gliomas	Tolerability rate: 60% Unacceptable Toxicity Rate: 0% Serious adverse events: 3.03% Other adverse events: 36.36%
NCT00757822	Dronabinol (THC)	Dronabinol (5 mg) administered po 30-60 min prior start of surgery.	Prevention of Postoperative Nausea and Vomiting (PONV) in Surgical Patients	Serious adverse events: 14.13% Other adverse events: 2.17%
NCT01786109	Dronabinol (THC)	One dose of dronabinol (2.5 or 5 mg) taken orally with water.	Effect of a Cannabinoid Agonist on Colonic Sensory Functions in Patients With Irritable Bowel Syndrome	Serious adverse events: 0% Other adverse events 2.5 mg: 41.67% Other adverse events 5 mg: 54.17% (placebo AEs = 37.04%)

3. Relevant review articles and the reference lists of final included studies were handsearched for any articles that may have been missed by the search terms.

4. Any data on THC products already approved was searched using https://www.pharmacompass.com/manufacturers-suppliers-exporters/thc and the FDA and EMA websites.

Inclusion criteria for studies were those that indicated the THC dose and endpoint; cannabis-naïve participants (if human); a dosing group in which only the cannabinoid was administered; and administration by oral, inhalation, topical or intranasal routes.

Exclusion criteria were those where the cannabinoid was administered in combination with other drugs; non-naïve participants (if human); a non-relevant route of administration; duplicated study; or non-English publication.

It should be noted that most of the literature found through these searches around THC relates to its pharmacological effects and not toxicology or safety. No studies were found relating to the toxicological effects of Δ^8THC or CBN.

Toxicology literature results

The searches did not reveal an extensive literature database of detailed animal toxicity information. Key papers to emerge in relation to animal toxicity studies are detailed in Table 5.

The EFSA expert Panel on Contaminants in the Food Chain derived a human ARfD based on effects on CND and heart rate and reported values derived as follows:

- A LOAEL, for single and repeat administration, for Δ^9-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 NOAEL
- A further UF of 10 to allow for interindividual variances
- With an overall UF of 30, the ARfD was considered to be 1 mg/kg bw of Δ^9-THC

The CONTAM Panel also derived and reported a BMDL10 (Lowest 10% CL) using rodent data from the NTP report. of 0.73 mg/kg/day Δ^9THC. This was approximately 700-fold greater that their ARfD. The considered view of the CONTAM Panel was that, as the ARfD value was approximately 700-fold lower that the animal based $BMDL_{10}$, then the use of 1 mg/kg bw/day of Δ^9THC or lower would be unlikely to pose or be associated with any health concerns.

	Study	Ref	Findings	Implications to current report
1	Thompson, Harris Rosenkrantz, Ulrich H. Schaeppi And Monique C. Braude. Toxicology and Applied Pharmacology, 25, 363-372 (1973) Comparison of Acute Oral Toxicity of Cannabinoids in Rats, Dogs and Monkeys. Toxicol Appl Pharmacol	[78]	For preclinical toxicologic evaluation, Δ^9THC, Δ^8-THC, and Cannabis extract were administered p.o. to rats, dogs and monkeys as solutions in either absolute ethanol, sesame oil, or sesame oil with 2.5-9.0 % ethanol. The measure of toxicity was the LD50 and for rats (two strains) within the dosage range of 225-3600 mg/kg, Δ^9THC and Δ^8-THC produced the same lethality, while both isomers were approximately twice as potent as the Cannabis extract. In dogs and monkeys, single oral doses of Δ^9THC and Δ^8-THC between 3000 and 9000 mg/kg were non-lethal. In all species there were general signs of marked toxicity some of which were consistent with significant CNS effects.	For the purposes of this report, the acute toxicity data is of less critical relevance but for the purposes of completeness are included.
2	Thompson, Marcusm. Mason, Harris Rosenkrantz and Monique C. Braude. Toxicology and Applied Pharmacology, 25, 373-390 (1973). Chronic Oral Toxicity of Cannabinoids in Rats. Toxicol Appl Pharmacol.	[79]	In the chronic rat toxicity study, Δ9THC and Δ8THC were evaluated in Fischer rats. The compounds were administered po for 119 consecutive days at doses of 50, 250, 400 or 500 mg/kg/day (which included some lethal doses). There was a dose- related decrease in body weigh in all groups, limited hematological and blood chemistry effects. Weights were decreased in some organs suggesting endocrinological effects, but this was not reflected in histopathology.	The data in these papers, whilst having intrinsic value in profiling the toxicity of Δ9THC, does not constitute a level of detail or quality that would be suitable for the derivation of NOAEL or BMDL.

> Continued overleaf

	Study	Ref	Findings	Implications to current report
3	P. C. Chan, r. C. Sills, a. G. Braun, J. K. Haseman, and J. R. Bucher. Fundam. Appl. Toxicol. 30, 109-117. (1996). Toxicity and Carcinogenicity of A9 -Tetrahydrocannabinol in Fischer Rats and B6C3F1 Mice	[80]	Δ^9THC in corn oil was administered by gavage to male and female Fischer rats and B6C3F1 mice at 0, 5, 15, 50, 150, or 500 mg/kg, 5 days a week for 13 weeks and for 13-week plus a 9-week recovery period. In all studies, mean body weights were lower than controls. This was not reflected in food consumptions and probably indicated increased activity and metabolism. Convulsions and hyperactivity were observed; the onset and frequency of which were dose related. Δ^9THC administration for 13 weeks induced testicular atrophy and uterine and ovarian hypoplasia; the lesions persisted in a 9-week recovery period. There was no evidence that Δ^9THC was carcinogenic in rats or mice.	The data available in this paper, whilst having intrinsic value in profiling the toxicity of Δ^9THC, does not constitute a level of detail or quality that would be suitable for the derivation of NOAEL or BMDL.
4	P Beaulieu. Pain Res Manage 10(Suppl A):23A-26A. (2005)[79]	[81]	This is a review paper covering several aspects of preciously reported findings of several cannabinoids given by different routes of administration.	The data in this paper is minimal and does not offer anything of value for the derivation of NOAEL or BMDL.
5	Katarina Černe. Arh Hig Rada Toksikol; 71:1-11 (2020). Toxicological properties of Δ^9 tetrahydrocannabinol and cannabidiol	[82]	This is a recent and more comprehensive summary review of the current state of non-clinical (and clinical) toxicology knowledge of THC and CBD.	Useful overview document. The data in this paper is minimal but useful back reference to other papers are listed (including the ones listed above). There is no direct data usable for the derivation of NOAEL or BMDL.
6	Marinol (capsules) NDA 18651 (Dronabinol) - Summary Basis of Approval 1985		The summary basis of approval for Mariniol (dronabinol) is a heavily redacted photocopied old FDA document of poor quality. However, it does summarise a very comprehensive evaluation of Δ^8THC and Δ^9THC. The studies include both rodent and non-rodent general toxicology studies (including some non-human primate studies), with durations of up to 3 months. A range of reproduction toxicity studies in rodents are also reported.	This is a very useful background document in understanding the animal toxicity profile of THC. However, it is not considered that the data presented in this document is in a form that could be analysed in a way that would permit the derivation of a BMDL.
7	WHO Expert Committee on Drug Dependence Critical Review. Delta-9-tetrahydrocannabinol. (2018)	[83]	The Toxicology Section (section 3 p55 -66), is relatively short, with an emphasis on human information and much less on animal data. The key areas of comment include lethal doses in animals, cardiovascular and respiratory effects in humans, effects on the immune system in in vitro and animal studies with, apparent lack of effect in some human evaluations. Also covered are mutagenicity and reproduction studies in animals with cross reference to a report by the US National Toxicology Programme series of studies.	It should be noted that this report reflects the views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization. This is a very comprehensive summary of current knowledge of Δ^9THC including section on Chemistry, Pharmacology, Toxicology, Therapeutic use and Epidemiology.
8	Toxicology and Carcinogenesis Studies Of 1-Trans-Delta^9-Tetrahydrocannabinol (Cas No. 1972-08-3) In F344/N Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series No446 (1996)[82]	[84]	This report contains a significant amount of detailed information from rat and mouse studies conducted under the direction of the US NTP. It details a series of 13 week studies, without and with recovery in rats and mice that served as dose range finding studies for subsequent 2 year oncogenicity studies. The 13 week studies in rats cover a dose range that spans a NOEL at the low dose and mortality at the high dose. The mouse studies indicate a lower sensitivity but with some comparable effects. For both species data is available on clinical observations, body weights, food consumption, clinical pathology, haematology, organ weights and histopathology. From the 2 year carcinogenicity studies, in addition to full tumour analysis data (demonstratively negative and of little value to the current project), there is similar data sets plus some plasma exposure data. In addition, there is further detailed evaluation of mutagenicity and the effects on reproductive organs that are attributed to endocrinological perturbation.	This report and data set is by far the most comprehensive that has been published on Δ^9THC. It has been produced by recognised competent laboratories in the US and evaluated by recognised experts in the field. It was conducted to a level that appears to be GLP quality, even if that designation has not been claimed in the report. It is considered that the information provided would be of value in any BMDL analysis.
9	Scientific Opinion on the risks for human health related to the presence of tetrahydrocannabinol (THC) in milk and other food of animal origin. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal, 2015;13(6):4141[59]	[61]	Seminal review paper of information available up to the time of publication (2015), supporting the propositions in this document. It is both the most comprehensive and the most conservative of the international safety assessments. The EFSA paper includes detailed risk assessment based on key safety parameters including animal toxicity derived BMDL and ARfD based on clinical safety data. For the animal data calculations, the expert panel relied on the above referenced report from the US NTP studies.	The findings of the EFSA paper will form the basis of recommendations later in this document, but for completeness, each of the other publications above were reviewed and assessed for suitability of contributory data. It is important to note that this paper is primarily aimed at risk assessment for THC derived from milk and other animal derived food products resulting from the feeding of livestock with hemp-based materials.

Table 5. Key animal THC toxicity studies

Clinical and experimental research

The literature search found that 15 human studies where THC was administered were published in or after 2015. These studies were further reviewed to identify any changes in the evidence base since the publication of the EFSA CONTAM Panel's report.

3 studies reported the effects of THC in humans at doses equal to or lower than the 2.5mg/day LOAEL used by the CONTAM Panel as the reference point for their analysis. An additional 3 clinical studies were identified from a citation search and added for review. Two of these studies reported a daily dose above 2.5mg/day but are included for two reasons: (1) the drug was administered in multiple daily doses of 1.5mg each; and (2) because the study population were thought to be particularly vulnerable to adverse events (elderly patients with dementia).

There were no clinically relevant changes or serious adverse effects reported at doses of THC less than the EFSA's stated LOAEL of 2.5mg/day in any clinical or experimental studies published since 2015.

Relative to placebo, no clinically significant adverse effects were reported at daily doses of 1.68 mg [85]; 1.5 mg [86], [87]; 2.25 mg [88]; 2.5 mg [89]; or 3.0 mg [87], [90]. Previous safety assessments have identified the subjective feeling of being 'high' and related CNS effects as the most sensitive markers of the effect of THC in humans. In the two studies that reported measures of a subjective high, no significant effect was seen relative to placebo at doses of 0.75 mg, 1.5 mg or 2.25mg [86], [88].

Taking these studies into consideration, there are no identified studies in humans published since 2015 that would justify lowering the 2.5mg LOAEL reported by EFSA [61]. Several studies report no adverse effects at doses between 0.75 mg – 2.25 mg, supporting the uncertainty factor of 3 used in the EFSA report to derive an estimated NOAEL of 0.83 mg/day. While the studies summarised above had sample sizes too small to draw firm conclusions from, the available evidence suggests that these reference points may not be inappropriate even in vulnerable populations, including children and older adults with dementia.

	Study	Ref	Design	Adverse event findings
1	Ahmed et al., 2015.	[86]	Randomized, double-blind, placebo-controlled, crossover trial for older adults with dementia (N = 10; mean age 77.3 ± 5.6). For 12 weeks, participants randomly received oral THC (0.75 mg during weeks 1–6; 1.5 mg during weeks 7–12) or placebo twice daily for 3 days.	Relative to placebo, neither dose of THC had any effect on feeling 'high' and external perception as measured by the Visual Analog Scale (VAS); body sway (eyes-open); or diastolic blood pressure. Body sway-(eyes-closed) increased at 1.5 mg but not 0.75 mg. Statistically significant increases in internal perception (VAS), heart rate, and systolic blood pressure relative to placebo were reported at the 0.75 mg dose, but were not considered clinically relevant as they were small and not associated with adverse events.
2	Van den Elsen et al. 2015a.	[87]	Randomised, double-blind, placebo-controlled, repeated crossover trial for older adults with dementia (N = 22; mean age 76.4 ± 5.3), consisting of six treatment blocks of 2 weeks each. Within each block THC (0.75 mg twice daily in blocks 1-3 and 1.5 mg twice daily in blocks 4-6) and placebo were administered in random order for 3 consecutive days, followed by a 4-day washout.	THC was well tolerated as assessed by adverse event monitoring, vital signs and mobility. There were no serious adverse events in any group and no significant difference in the incidence of adverse events between groups. In total, 184 AEs of mild to moderate severity occurred during the crossover study period, similarly distributed over the THC (91 AEs) and placebo (93 AEs) conditions. Relative to placebo, no statistically significant effects were reported on diastolic blood pressure, heart rate, agitated behaviour or caregiver burden at either dose. High dose THC (1.5 mg) but not low dose (0.75 mg) increased SBD by 2.6 mmHg compared to placebo within four hours after first tablet intake.
3	Van den Elsen et al. 2015b.	[88]	Randomised, double-blind, placebo-controlled trial for adults with dementia (N = 50). Participants were randomised to groups receiving either placebo or THC at doses of 0.75 mg three times daily.	THC was well tolerated at this dose. The number of patients experiencing adverse events and the frequency of adverse events were similar in both groups. Known THC-mediated AEs, such as dizziness, somnolence, and falls, were more frequently reported during placebo treatment. None of the participants reported a feeling "high," nor was behaving "high" observed by caregivers or research staff.

> Continued overleaf

	Study	Ref	Design	Adverse event findings
4	Kuhlen et al., 2016.	[85]	Open-label uncontrolled retrospective study of dronabinol in paediatric participants with spasticity (N = 16; aged 1.3-26.6 years, median 12.7 years). The starting dose was 0.83 mg (one drop) twice daily for all patients. The dose escalation was stopped as soon as a treatment effect was clinically assessed. Therapeutic doses varied from 0.08 to 1.0 mg/kg/d with a median of 0.33 mg/kg/d. Only 1 patient (11.3 years, 21kg bodyweight) received a maximum daily dose less than 2.5 mg (1.68 mg) for a total duration of 118 days.	No adverse effects were reported for this patient. With an escalating dosage scheme, no side effects lasting more than one week were seen in any patient. However, restlessness and vomiting occurred as side effects in the case of two patients, who received maximum dose of 0.19 mg/kg (8.17 mg/day) and 0.07 mg/kd (3.15 mg/day). None of the children in cohort were verbally communicative, so psychological effects could not be assessed. THC was well tolerated with 15/16 participants requiring >2.5 mg/day to reach therapeutic effects and no side effects reported below that dose.
5	Van den Elsen et al. 2017.	[90]	Randomised, double-blind, crossover study to evaluate the effects of THC on mobility in dementia patients (N = 18; median age 77 years). Participants received 1.5 mg of oral THC twice daily and placebo, in random order, for three days, separated by a four-day washout.	THC was well tolerated by patients. There was no difference in the occurrence of adverse events observed between 1.5 mg of THC twice daily compared to placebo. Nor were there differences in mobility-related adverse events (e.g. dizziness, somnolence and balance disorders) between groups and no falls occurred after administration of THC.
6	Carley et al., 2018.	[89]		The most frequently reported verbatim adverse effects included sleepiness/drowsiness (N = 25; 8% of total AEs reported), headache (N = 24; 8%), nausea/vomiting (N = 23; 8%), and dizziness/ lightheadedness (N = 12; 4%). There were no statistically significant differences in the frequency of these adverse events between groups: the average number of adverse events reported by the 73 participants was 4.1 ± 4.0 and this did not differ from placebo (3.4 ± 2.9) among participants receiving either 2.5 mg/ day (2.8 ± 3.6) or 10 mg/day (5.8 ± 4.7) of dronabinol.

Table 6. THC clinical trials published since 2015

ACI/CMC & CDPRG Recommended safe exposure limit

Based on the above research, our assessments if that the literature view supports the findings of the EFSA CONTAM Panel (2015), which reported an ArFD of 83 mg (approximately 1mg/kg bw/day) [61]. This value was considered by the Panel to be appropriate as a safety threshold for both acute and chronic exposure to THC without further adjustments, since health guidance levels drawn from toxicological data suggested safety at doses that were higher than the ArFD by orders of magnitude. Our review has identified no evidence to dispute this position.

We concur with and present additional evidence to support the EFSA Panel's use of 2.5 mg/day as a LOAEL reference point with an uncertainty factor of 3 to derive a NOAEL. The Panel applied a further uncertainty factor of 10 to account for variations between individuals. This document has identified additional uncertainties in the data.

The first relates to the unknown effects of cannabinoids in combination. Human and animal studies suggest that CBD may attenuate some of the acute effects of THC, particularly in regard to THC-associated impairments in memory and cognition. However, other preclinical studies suggest that CBD may potentiate some effects of THC [91]. In CBD-based food and consumer products, a combination of controlled and non-controlled cannabinoids may be present at trace levels, and data is not yet available on what the combined effects might be. It is possible that different cannabinoids would compete for the same receptor sites antagonistically, but it is also possible that some combination could have synergistic effects. As such, we provisionally suggest an additional uncertainty factor of 2 to account for unknown polypharmacological effects.

The FSA have stated that CBD-containing food supplements should not be used at doses in excess of 70mg/day. However, it is possible that some consumers will use products at greater than the recommended daily allowance.

Equivalent restrictions have not been placed on other types of products on the CBD market, such as e-liquids, and it is plausible that consumers of may also consume these products at doses in excess of 70mg/day. Therefore, we provisionally suggest a further uncertainty factor of 2 to account for variations in use.

Applying these additional uncertainty factors (2 x 2 = 4) to the EFSA ArFD yields a threshold limit of 21mg, equivalent to 0.03% of the maximum daily dose of CBD permitted by the FSA (70mg). This limit employs the validated LOAEL of 2.5 mg/day with a total uncertainty factor of 120 (10 x 3 x 2 x 2). On the basis of the available evidence, it is highly likely that this safety limit would be sufficient to protect consumers from any potential harms of Δ^9-THC present at trace amounts in CBD products.

Other controlled cannabinoids may also be present as trace contaminants in CBD products, most notably CBN and Δ^8-THC. Like Δ^9-THC, CBN produces central nervous system (CNS) effects, but it is a mildly psychoactive weak partial agonist at the CB1 and CB2 receptors causing a maximal effect of approximately half the effect of Δ^9-THC at the same dose and less than half the maximal effect of Δ^9-THC [92]. In 1946, some of the earliest pharmacological observations of cannabinoids revealed that CBN, unlike Δ^9-THC, only induced catalepsy in mice at very high, lethal doses [93]. It is now widely recognised that the ability of cannabinoids to produce signs of catalepsy in rodents correlates well with their psychotropic activity, and these findings have since been interpreted as early evidence of the relatively low potency of CBN as a psychoactive drug [94].

CBN is a relatively minor constituent in fresh cannabis-derived material [33]. In fibre-type (low-THC) hemp plants, CBN has been detected at lower trace concentrations than THC at 2-7µg CBN/g (parts per million) in seeds compared to 3-29 µg THC/g; and at 0-47 µg CBN/g in the plant stem compared to 196-475 µg THC/g [95], [96]. We did not identify any data on the concentrations of CBN in the leaves or flowers of fibre-type hemp plants. In drug-type cannabis plants, however, the ratio of THC:CBN in the leaves and flowers is approximately 75:1 and 160:1, respectively [97]. CBN is present at relatively low levels in both the raw cannabis plant and in finished CBD extracts.

An analysis of the content of CBD and other phytocannabinoids in 29 over-the-counter cannabidiol products available in the United Kingdom found that much fewer products contained detectable traces of CBN than contained Δ^9-THC (7/29 vs 15/29), and that the mean concentration of CBN was lower than Δ^9-THC (0.01% vs 0.034%) [26].

Δ8-THC can also produce CNS effects in humans but it is less potent than Δ^9-THC at a ratio of approximately 2:3 as assessed by mood scales and physiological observations [98]. In studies on oral administration, Δ^8-THC produces lesser effects and has a slower onset and shorter duration of action compared to an equal dose of Δ^9-THC. The concentrations of Δ^8-THC in hemp plants is generally considered to be extremely low relative to other cannabinoids, and it is not thought to contribute substantially to the activity of cannabis-based products [99]. In the aforementioned analysis of 29 CBD products available in the United Kingdom, only 1/29 product had detectable levels of Δ^8-THC [26]. The concentration of Δ^8-THC was 0.02%, compared to 0.04% Δ^9-THC in the same product. The overall mean concentration of Δ^8-THC in the tested samples was 0.001%.

CBN and Δ^8-THC are typically present in hemp varieties at lower concentrations than Δ9-THC and both cannabinoids are thought to be less active than Δ^9-THC, although reliable dose-response data in humans is limited. We did not identify any evidence to suggest that the safety limits for these controlled cannabinoids would be smaller than the limit proposed for Δ^9-THC. Accordingly, we recommend that the proposed safety limit of 0.03% accounts for the total controlled cannabinoid limit in CBD food and consumer products (i.e. Δ^9-THC + Δ^8-THC + CBN). In effect, this limit should represent 'zero controlled cannabinoids' since exposure at or below this concentration would produce no toxic or psychoactive effects in humans. This threshold is above the LOD/LOQ achievable by most analytic laboratories and is therefore practical for regulators to implement and for manufacturers to comply with, while protecting the health and safety of UK consumers at a high level of confidence.

Implication for THC drug testing

Urine is currently the most widely tested matrix for drug tests. It is preferred due to higher concentration, longer detection time of metabolites, and ease of sampling compared to other bodily samples such as saliva, blood, hair and nail [100]. The European Workplace Drug Testing Society (EWDTS) have published European Guidelines for Workplace Drug Testing in Urine, designed to establish best practice procedures for laboratories [101]. These guidelines set protocols for the collection, analysis, quality assurance, and interpretation of drug testing in urine.

The first stage of analysis involves initial screening tests to indicate the possible presence of a drug in a sample at a predefined cut-off level. Urinary drug testing techniques for identifying cannabinoid exposure typically use the metabolite 11-nor-9-carboxy-Δ^9tetrahydrocannabinol (THC-COOH) as the target analyte [102]. The screening cut-off level recommended by EWDTS and federally mandated in the US for THC-COOH is 50 ng/mL. Acceptable screening techniques include immunoassays, gas chromatography (GC), high performance liquid chromatography (HPLC), capillary zone electrophoresis, and all chromatographic techniques coupled to mass spectrometry.

To assess whether the proposed safe exposure limit of 21 µg THC/day would protect consumers of CBD products against the possibility of false-positive results on a drug test, we performed an further literature search for studies on urinary cannabinoids after oral administration of THC at doses below 1mg/day. We could not identify any research studies that investigated the detectability of cannabis metabolites after repeated exposure to oral doses of THC that were equal to or lower than the proposed safe exposure limit. However, we did identify published data relating to repeated exposure at higher daily doses ranging from 90 – 600 µg THC/day.

In 2001, a study by Leson and colleagues evaluated the impact of extended daily oral ingestion of hemp oils with low doses of THC on the creatinine normalized urinary levels of THC-COOH [103]. Fifteen THC-naive adults received four different daily doses ranging from 90 to 600 µg THC over four successive 10-day periods, with doses increasing stepwise after each condition. Urine specimens were collected at baseline, on days 9 and 10 of each exposure period, and at 1 and 3 days after the last dose. Urine specimens were tested for THC-COOH by radioimmunoassay and using GC/MS. At daily doses of 90, 190, 290 and 450 µg THC/day, none of the specimens screened positive for THC-COOH by immunoassay at the 50 ng/mL screening cut-off. One specimen screened positive by immunoassay following the highest daily dose of 600 ug THC. There were no specimens from any participant at any dose that were confirmed to be positive by GC/MS at the 15 ng/mL cut-off, and the highest level of THC-COOH reported was 5.2 ng/mL after a daily dose of 600 ug THC. At daily doses of 90 and 190 µg THC, 100% of samples were found to contain metabolite levels at less than or equal to 2.5 ng/mL.

In a double-blind, placebo controlled, randomized, clinical study conducted on a closed research ward, Gustafson and colleagues administered "low-doses" of 390 and 470 µg THC/day and "high doses" of 7500 and 14800 µg THC/day to seven adults with a history of cannabis use [104]. Participants were exposed to all five dosing conditions for five consecutive days each, with a 10-day washout period between conditions. A total of 4381 urine specimens were collected and analysed by immunoassay and GC/MS. At the screening stage, the mean rate of positive results by immunoassay were <0.2% after ingestion of the two low doses. Six out of seven participants had no positive screening results at the lowest dose of 390 µg THC/day. Of the 125 urine samples taken from the seventh participant during and after this dose, a single sample screened positive with the DRI immunoassay and two screened positive with the Emit II immunoassay. In the 470 µg/day dosing condition, one participant produced one positive sample and two participants produced two positive samples with the Emit II immunoassay, out of an average of more than 100 samples taken from each participant at this dose. However, GC/MS results showed much greater variability. Four of the seven participants produced at least one sample that tested above the 15 ng/mL confirmation cut-off after the lowest dose of 390 µg (a 3.1% detection rate), and two out of seven participants had at least one positive test result at the higher 470 µg dose (a 2.4% detection rate).

A third study used GC-MS to assess urinary metabolite levels after low daily doses of THC in commercially available hemp oils over seven days [51]. Four participants received doses below 1 mg, ranging from 97.2 to 546 µg. After administration of 540 µg THC, the peak urine concentration of one participant exceeded the 15 ng/mL confirmation cut-off for THC metabolites (21.1 ng/mL). All other samples for the remaining 4/5 participants were below the confirmation cut-off at peak concentration and samples from all participants were below the cut-off within a 48-hour cessation period. The peak metabolite concentration at the lowest dose (97.2 µg/day) was 5.2 ng/mL.

The available evidence suggests that positive drug test results for THC metabolites are possible but highly unlikely after exposure to THC at daily doses between 300-400 µg. At higher daily doses, the probability of positive results increases. We did not find evidence of positive results at either the screening or confirmation cut-offs for repeated daily doses of 290 µg THC and lower. However, sample sizes in the studies identified above were generally small and other research has identified significant inter-subject variability in the urinary excretion profile for THC metabolites [105], [106]. Accordingly, these data are not sufficient to conclusively assess the level of no-effect. To account for inter-subject variability, it is appropriate to apply an uncertainty factor of 10 to the value of 290 µg THC/day to reliably establish the level at which exposure would not result in the detection of THC metabolites in urine. As the resultant value (29 µg/day) is larger than the ARfD proposed in the previous section (21 µg/day), we conclude that the ARfD would protect consumers of CBD products against the possibility of false-positive results on a drug test.

4. Recommendations

Gap Review

The following gaps in the existing published or publicly available data were identified by the authors:

- Insufficient data to determine a NOAEL for Δ^9THC in CBD products. The LOAEL was derived from human studies using pure Δ^9-THC in humans.
- Insufficient data to assess possible interactions of cannabinoids (including synergistic/agonist or antagonist effects of other CNS active or non-narcotic cannabinoid molecules that may be present in food products).
- Insufficient data to reliably determine a reference point for Δ^8-THC or CBN in humans.
- Insufficient data to reliably determine the implications of different routes of administration that OTC CBD products can use (e.g. topical, inhalation, sublingual, buccal).
- Insufficient data on the level of controlled contaminants in OTC CBD products.
- Insufficient data to determine the real-world daily consumption rates of CBD products (and hence contaminants) by UK consumers.
- Insufficient toxicology and safety data in at-risk populations, e.g. children, pregnant women, people with psychotic disorders, etc.
- Insufficient long-term THC exposure toxicology data.

Research recommendations

Based on this gap review, we make the following recommendations for research:

1. The acute and chronic toxicity of combination cannabinoid preparations in animals.

We recommend controlled toxicology studies on the acute and chronic effects of purified cannabinoids (CBD, Δ^9THC, Δ^8THC, and CBN) and their combinations in animals. This could be extended to include other phytochemicals such as terpenes and flavonoids which may also interact with the health impact of each of the compounds in isolation.

These studies will generate data to characterize the toxicity profile of pure compounds and of polypharmacy cannabinoid combinations (which is more typical in the OTC CBD market) by identifying the impact on organ structure and/or functionality, including the severity and reversibility of toxicity, and dose-response effects.

2. The dose-response effects of purified Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, and cannabinol in adults after oral, inhaled, sublingual, and topical administration.

We recommend further non-clinical safety studies on the acute and chronic effects of purified Δ^9THC, Δ^8THC and CBN in humans at low daily dose. Appropriate dosing groups for Δ^9THC could include 0.1, 0.2, 0.4, 0.8, 1.6 and 3.2 mg/day. Investigations should cover all routes of administration of relevance to CBD-based consumer and food products in which traces of controlled cannabinoids could theoretically be present as contaminants. These studies would be valuable for the identification of consumer safety issues requiring further regulatory action. However, considering the lack of existing evidence for toxicologically relevant effects of Δ^9THC, Δ^8THC and CBN in humans at doses below 2.5 mg/day, this research may be limited value relative to the likely costs.

3. The dose-response effects of combination cannabinoid preparations in adults after oral, inhaled, sublingual, and topical administration.

We recommend randomised, placebo-controlled, double-blind studies on the acute and chronic effects of preparations containing a variety of combinations of CBD, Δ^9THC, Δ^8THC, CBN and other cannabinoids known or suspected to be present in commercially available products. Investigations should cover central nervous system and cardiovascular measures outcome, and all routes of administration of relevance to CBD-based consumer and food products. These studies will generate data to assess the pharmacokinetic and pharmacodynamic impact of interactions between multiple cannabinoids on their activity in humans.

4. The demographics and consumption patterns of CBD users in the UK.

We recommend qualitative and quantitative observational studies on consumers of commercially available CBD-based products in the UK to identify consumer characteristics and the amount and frequency of use.

These studies will help inform understanding of the actual daily intake of cannabinoid products for the identification and assessment of potential risks to the UK public. It is essential that appropriate labelling and certificates of analysis are available on OTC CBD products for this data to have real value.

5. Phase 4-style surveillance studies including adverse event monitoring

We recommend studies to monitor the safety, tolerability and comparative outcomes of CBD consumer products in real world settings, in much the same way that Phase 4 studies track post-marketing outcomes and safety issues with medicinal products, except that no assessment of effectiveness would be relevant to non-medicinal consumer products. There are a number of study designs that might be appropriate for this purpose, ranging from multi-arm prospective observational studies to consumer registries populated with user-generated data.

6. The pharmacokinetic characterization of cannabinoid metabolites in urine following acute and prolonged exposure to combination cannabinoid preparations in adults.

We recommend randomised, placebo-controlled, double-blind studies on the impact of preparations containing a variety of combinations of CBD, D9-THC, D8-THC, CBN and other cannabinoids known or suspected to be present in commercially available products on the urinary profile of cannabinoid metabolites in humans. These studies will assess the risk of false-positive drug tests occurring after consumption of CBD-based products.

Policy recommendations

On the basis of the literature review and safety assessments in this report, we make the following recommendations:

1. That the Home Office issue guidance and/or amend existing legislation, as needed, to exempt from control CBD-based products defined as—

Any preparation or any ingredient to be used in a preparation that is designed for the oral administration of cannabidiol, containing not more than 21 micrograms of cannabinol derivatives (THC and CBN compounds and their derivatives) or with a total concentration of not more than 0.03% cannabinol derivatives in undivided preparations.

We recommend that 0.03% is established as the 'threshold of zero impurities' for CBD products, based on our findings that lifetime exposure to contaminants at this limit would be indistinguishable from exposure to contaminants at 'true zero' in terms of toxicological and other relevant markers of drug action in humans.

The UK has obligations under the 1961 and 1971 UN Drug Conventions to limit the importation and exportation of controlled drugs to the estimated national requirements for scientific and medical purposes. These obligations require the UK to submit annual requirement estimates to the INCB. However, there would be no requirement to report on controlled cannabinoids as may be present only as trace contaminants in products for consumer sale, as is also the case in regard to the presence of traces of opium alkaloids in poppy seeds. The cultivation of low-THC cannabis would continue to be controlled under licence, monitored, and reported to the INCB.

Setting a permitted maximum level for controlled cannabinoids in consumer goods could be established through legislative change, such as by means of a statutory instrument amending the MDR 2001 after consultation with the Advisory Council for the Misuse of Drugs to exempt CBD-based products at defined thresholds. A maximum level could also be established simply by means of guidance from regulators without new legislation, as is presently the case in regard to the target level of 10 mg/kg agreed for the presence of morphine in poppy seeds.

2. That the Home Office consult the advice of the ACMD on rescheduling to Schedule 5 of the MDR 2001 products defined as—

Any preparation or any ingredient to be used in a preparation that is designed for the oral administration of cannabidiol, containing a total concentration of not less than 0.03% cannabinol derivatives and of not more than 0.2% cannabinol derivatives in undivided preparations.

The recommendation made by the World Health Organisation to remove CBD products with no more than 0.2% THC from control was made on the basis of abuse potential. The WHO Expert Committee on Drug Dependence stated that CBD products controlled at this limit would have a low potential for abuse.

These findings are consistent with the conclusions of the ACMD in regard to the medicinal product Epidyolex, which contains no more than 0.1% THC, and which was found by the committee to have a "a low risk of abuse potential, low risk of dependency, and low risk of diversion."[107]

As such, we recommend that CBD products containing between 0.03% and 0.2% controlled cannabinoids should be classified under Schedule 5 of the Misuse of Drugs Regulations 2001, and should be lawfully available for over-the-counter supply in the UK.

3. That the Home Office consider excepting from control the dried leaves and flowers of approved hemp strains, where—

A. the hemp plant has been lawfully grown in or imported to the UK under authorisation by the Home Office; and

B. the finished preparation contains no more than 0.03% cannabinol derivatives.

The safety assessment conducted in this report identifies the potential risks and safe exposure levels for cannabinoids in consumer products. These chemical-based safety limits apply equally regardless of which part of the plant the end-product contains. Accordingly, it would be appropriate to control all CBD-based consumer products under the same regulatory framework, including hemp flowers. Implementing this recommendation would necessitate legislative changes as the flowers of cannabis are currently controlled under the MDA 1971 irrespective of THC content. Furthermore, the 1961 UN Single Convention limits the cultivation of cannabis for industrial purposes to fibre and seed. In acknowledgment of these considerations, we recommend that this regulatory issue be considered separately to recommendation 1.

4. That the FSA establish regulations to require manufacturers of CBD-based novel and non-novel food products to include mandatory warning labels recommending against the use of those products by groups who may potentially be at heightened risks, including women who are pregnant or attempting pregnancy, children and young people, and individuals with a history of psychotic disorders.

5. That the FSA consider post-marketing surveillance approaches to identify potential real-world risks to consumers.

Appropriate measures would include requiring manufacturers and suppliers to track and report suspected adverse events through a pre-approved consumer app.

6. That the Home Office urgently issues updated public guidance to clarify the legal controls on the manufacture, supply and possession of products containing hemp, CBD and other cannabinoids to ensure a level regulatory playing field for the industry, to protect the health and safety of the British public, and to prevent unintended offending.

7. That the Home Office and FSA issue joint guidance to industry regarding the regulatory controls and requirements for the importation, exportation, manufacture and supply of CBD-based novel and non-novel food products.

5. Conclusion

In conclusion, our organisations feel that the current state of legality and regulation of over the counter CBD products is not fit for purpose and a sensible, safe level of THC and other controlled products of 0.03% or 21 µg per day could be instated in the UK on CBD products with appropriate warning labels. We acknowledge that further research is required to fully appreciate the long-term health impacts of cannabinoid molecules alone and in combination, and recommend that the safety levels of THC and other compounds be regularly revisited on the basis of new data.

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