



Government Chemist Guidance

Analytical Limits for Controlled Cannabinoids in Specified Products Containing Cannabidiol (CBD)

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Scope

This advice applies to materials and products used in the supply or manufacture of cosmetic products¹ or novel foods² as defined by the relevant legislation.

Background

Cannabidiol (CBD) is a non-psychoactive cannabinoid³ present in the cannabis plant (*Cannabis sativa* L) along with many other cannabinoids that may either exhibit psychoactive or non-psychoactive properties.

CBD plant extract or plant isolates are preparations identified as ingredients in some cosmetic products or food supplements supplied to the UK market.

The process of extracting or isolating CBD from the cannabis plant is likely to co-extract other cannabinoids depending on the efficiency of the extraction process and could unintentionally include other non-psychoactive or, more significantly, psychoactive cannabinoid substances.

The UK Misuse of Drugs Act⁴ (MDA) with its subordinate regulations prohibit the supply of certain psychoactive cannabinoid substances depending on which part of the cannabis plant has been used⁵. To aid understanding of the legislation the Home Office produced general guidance in relation to the supply of products containing CBD titled '*Drug Licensing Factsheet-Cannabis, CBD and other cannabinoids*⁶. The factsheet explains '*some products may, in limited circumstances, be considered 'exempt' from control, notwithstanding their 'controlled drug' content... The exemption is a three-limbed definition but for the*

¹ Original UK law: Cosmetic Products Regulations 1978 No. 1354, with extensive amendments. The current UK measure is the Cosmetic Products Enforcement Regulations 2013, No. 1478 providing for the enforcement of Regulation [\(EC\) No 1223/2009](#) of the European Parliament of the Council of 20 November 2009 on cosmetic products (recast) (the "EU Cosmetics Regulation", please consult EUR-Lex (<https://eur-lex.europa.eu/homepage.html>) for the most recent text consolidating amendments of the EU regulation).

² The Novel Foods (England) Regulations 2018, No. 154, with devolved equivalents

³ Cannabinoid: a compound found in the cannabis plant, strictly, 'phytocannabinoid' to distinguish from synthetic and other compounds of the same structure.

⁴ 'MDA', Misuse of Drugs Act 1971, UK Public General Acts 1971 c. 38, <https://www.legislation.gov.uk/ukpga/1971/38/contents>

⁵ See MDA, Section 37, 'Interpretation'

⁶ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/825872/factsheet-cannabis-cbd-and-cannabinoids-2019.pdf *Note Intended as general guidance only; it is not legal advice.*

purposes of this note the relevant limb is '(c)', "...provided '(c) no one component part of the product or preparation contains more than one milligram of the controlled drug..."⁷

The 'controlled drug' content 'threshold' of one milligram when considering the exemption provides a content measurement enabling manufacturers using CBD derived plant extracts or isolates in preparations or products to demonstrate a *de minimis* inadvertent presence of psychoactive cannabinoid substances that might not contravene legislation.

Although a *de minimis* amount of one milligram (0.001 g) for the 'controlled drug' in a product or preparation appears straightforward, it presents difficulties in interpretation and analysis.

- (1) The 'controlled drug' could comprise one or more prohibited psychoactive cannabinoid compounds.
- (2) Determination of content is necessarily made indirectly by measuring concentration, which is amount per given mass or volume.

There is uncertainty over whether the 'controlled drug' content 'threshold' of one milligram applies to each illicit cannabinoid or the total sum of illicit cannabinoids given there are a number of prohibited psychoactive cannabinoids. As the legislation is unclear, a worst-case approach has been taken for measurement purposes in this guidance to assume the 1 mg threshold covers all psychoactive cannabinoids, although in practice only a limited number of psychoactive cannabinoids are determined analytically to assess compliance. This means the content threshold will be the sum of compounds, requiring each compound to be determined at a sufficiently low level to decide whether, or not, the summation of compounds exceeds the one milligram content threshold. Concentration measurements become more difficult because increasingly more sensitive methods are required to detect lower concentrations to demonstrate the one milligram content has not been exceeded.

1. Psychoactive Cannabinoid Compounds

The MDA does not identify the individual psychoactive cannabinoids, referring to a generic definition whereby *"Cannabinol derivatives means the following substances, except where contained in cannabis or cannabis resin, namely tetrahydro derivatives of cannabinol and 3-alkyl homologues of cannabinol or of its tetrahydro derivatives"*.

Twelve stereoisomeric cannabinoid compounds are identified⁸ as naturally present in the cannabis plant corresponding to the MDA generic definition for prohibited psychoactive cannabinoids and could be present in the CBD extract or isolate technically requiring determination as shown in Table 1.

⁷ The Misuse of Drugs Regulations 2001, UK SI 3998, Regulation 2 (interpretation) 2(1) 'exempt product' (c), <https://www.legislation.gov.uk/uksi/2001/3998/regulation/2>

⁸ Advisory Council on the Misuse of Drugs, 2016, Phytocannabinoids, A review of the generic definition December 2016, Table 1, page 9 and Appendix 1

Table 1. List of prohibited psychoactive cannabinoids

#	Name
1	Trans-delta-9-tetrahydrocannabinol-C5
2	Cis-delta-9-tetrahydrocannabinol-C5
3	Delta-9-tetrahydrocannabinol-C4
4	Delta-9-tetrahydrocannabinol-C3 (Delta-9-tetrahydrocannabivarin)
5	Delta-9-tetrahydrocannabinol-C1
6	Delta-8-tetrahydrocannabinol
7	Cannabinol-C1
8	Cannabinol-C2
9	Cannabinol-C3
10	Cannabinol-C4
11	Cannabinol-C5
12	Cannabinol methyl ether-C5

It should be noted there are also precursors of the prohibited cannabinoids present in the plant that can transform into the prohibited cannabinoids under conditions of heat requiring consideration during analysis and this includes delta-9-tetrahydrocannabinolic acid (Δ^9 -THCA).

It is possible to individually determine all twelve stereoisomeric cannabinoid compounds using a combination of different techniques provided there are reference standards of known purity available. This, however, presents analytical challenges as well as being costly in determining individually all twelve stereoisomeric cannabinoid compounds where the presence of certain stereoisomeric cannabinoid compounds will be infinitesimal in both the plant and extract.

To address these analytical issues in a proportionate way there is usually selection and grouping of the cannabinoid compounds to be able to efficiently quantify the prohibited psychoactive cannabinoids as shown in Table 2.

Table 2. List of grouped prohibited psychoactive cannabinoids

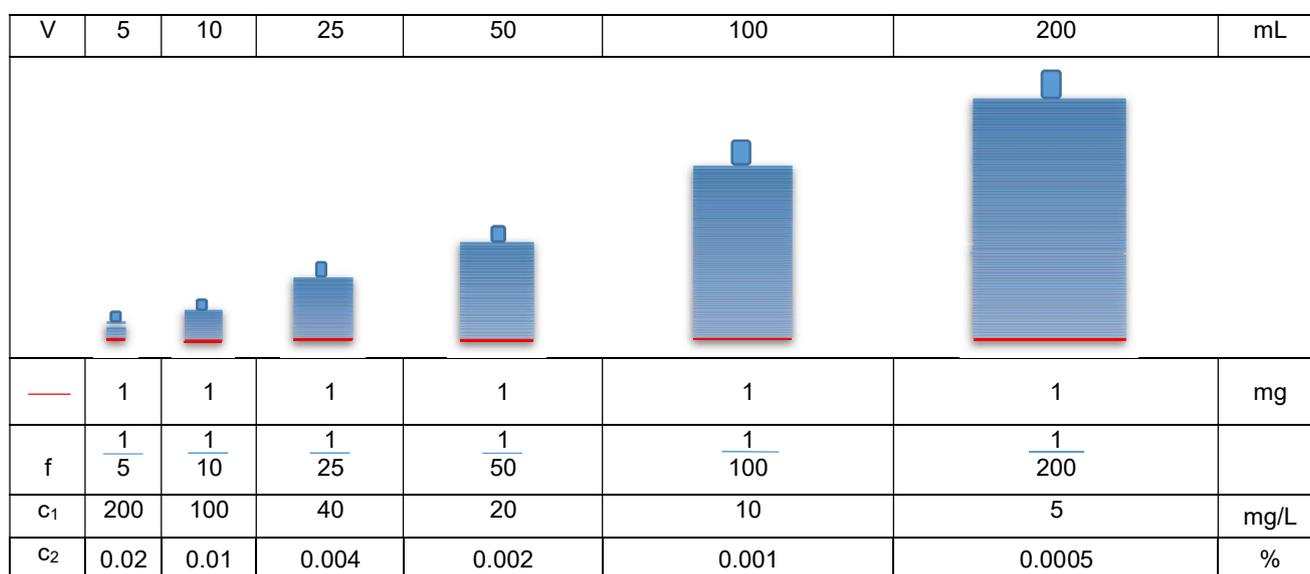
Group	#	Name
A	1-3, 5	Delta-9-tetrahydrocannabinol (Δ^9 -THC)
B	4	Delta-9-tetrahydrocannabivarin (Δ^9 -THCV)
C	6	Delta-8-tetrahydrocannabinol (Δ^8 -THC)
D	7-11	Cannabinol (CBN)
E	12	Cannabinol methyl ether-C5

2. Concentration

The accepted view⁵ is that the applicable unit of measure for the 1mg 'threshold' is the 'container' (i.e. bottle or packet) and not the 'typical dose' (of any product). Consider a product consisting of 10 mL liquid containing just one milligram of a 'controlled drug' i.e. having a concentration of $0.001\text{g}/10\text{mL} = 0.0001\text{ g/mL}$ (or 0.1 mg/mL). Similarly consider a product consisting of 100 mL liquid again containing one milligram of 'controlled drug', i.e. having a concentration threshold of $0.001\text{g}/100\text{ mL} = 0.00001\text{ g/mL}$ (or 0.01 mg/mL). In both situations, there will be a total of one milligram of the 'controlled drug' in the liquid but in the case of the 100 mL product the detection system will have to be ten times more sensitive than for the 10 mL product for the manufacturer to be able demonstrate the content threshold has not been exceeded.

The effect of increasing volume resulting in decreasing concentration are shown in Figure 1.

Figure 1 Concentration of 1 mg of cannabinoid with increasing volume



v = volume of solution/container in millilitres (mL)

— = 1 milligram (mg) of cannabinoid

f = fraction of the mass of cannabinoid to the volume of solution

c₁ = concentration of cannabinoid in milligrams per litre (mg/L)

c₂ = concentration of cannabinoid as a percent (%)

3. Combining Factors

As previously shown the 'controlled drug' may not consist of a single compound but could include all twelve psychoactive cannabinoid compounds that when added together may exceed the one milligram threshold. Consequently, each psychoactive cannabinoid compound requires detection at a lower concentration.

There is no wholly satisfactory solution to this problem as psychoactive cannabinoid compounds can be present in varying proportions, so analytically the detection system should measure at least one-twelfth of the one-milligram content threshold (0.0833 mg or 0.0000833 g) for each compound (if present in equal amounts).

Combining the effects of the number of psychoactive cannabinoid compounds with varying quantities of preparation or products will provide the minimum concentration a detection system will need to achieve. Moreover factors such as matrix effects and measurement uncertainty need to be considered to be sure of detection.

4. Calculation

The concentration of the 'controlled drug' will be dependent on the quantity of preparation or product where, for the purpose of this guidance, it is the retail pack size placed on the market where CBD is listed as an ingredient.

As explained in Section 3 (Combining Factors) the analyst is required to have an analytical system sufficient to determine the one-milligram content threshold. Where each of the twelve prohibited psychoactive cannabinoid compounds present in a container they could each contribute > 0.0833 mg to the total content of prohibited psychoactive cannabinoid compounds potentially exceeding the 1 mg content threshold.

As measurements are made in relation to the volume or mass at the lowest level of the cannabinoid compound required to be determined divided by the volume or mass in the container. For example 0.0833 mg in 10 g of liquid or solid in a container will require a minimum concentration to be determined as follows:

$$\frac{\text{Weight of cannabinoid compound}}{\text{Quantity of liquid/solid}} = \frac{0.0833 \text{ mg}}{10 \text{ g}} = 0.00833 \text{ mg/g}$$

The minimum required detectable concentration should not be confused with the limit of quantitation (LoQ) which is the lowest detectable concentration for an analytical system based on a validated method which takes into account uncertainties in measurement. It is expected the LOQ of an analytical system will need to be below the minimum required detectable concentration. In a recently published paper⁹ determining cannabinoids in cannabis and hemp products using liquid chromatography with a tandem- mass spectrometer detector (LC-MS/MS) the quantification of samples ranged from 0.002 to 200 mg/g.

For cosmetic products containing CBD, the quantity of product generally found on the market ranged from 200 mL for body lotions, 30 mL for a face washes and 15 g for lip balms.

The minimum required detection limit for an individual prohibited psychoactive cannabinoid in the identified cosmetic product shown in Table 3.

⁹ McRae, G. and Melanson, J.E., 2020. Quantitative determination and validation of 17 cannabinoids in cannabis and hemp using liquid chromatography-tandem mass spectrometry. *Analytical and bioanalytical chemistry*, 412, 7381-7393.

Table 3. Minimum Required Detectable Concentration for Different Quantities of Cosmetic Products

Product	Quantity	Minimum Detectable Concentration
Body lotion	200 mL	< 0.0004 mg/mL
Face wash	30 mL	< 0.0028 mg/mL
Lip balm	15 g	< 0.0055 mg/g

Novel foods containing CBD covers a wide range of products including 'gummy bears' each weighing 6 g where 30 'gummy bears' are in a container (180 g), 30 mL oral sprays, 10 mL oral liquids and capsules weighing 15 mg where 30 capsules are in a container (450 mg). The minimum required detection limit for an individual prohibited psychoactive cannabinoid in the identified novel food product shown in Table 4.

Table 4. Minimum Required Detectable Concentration for Different Quantities of Novel Foods

Product	Quantity	Minimum Detectable Concentration
Gummy Bears	180 g	< 0.0005 mg/g
Oral spray	30 mL	< 0.0028 mg/mL
Oral liquids	10 mL	< 0.00833 mg/mL
Nutritional capsules	450 mg	< 0.185 mg/g

In considering whether an analytical system is sufficiently sensitive to measure the minimum detectable concentration, it is necessary to increase sensitivity as the container size increases to have certainty the 1 mg threshold has not been exceeded.

5. Acknowledgements and disclaimer

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