Cannabinoids – a Tutorial Review Psychoactivity, Regulation, Common and IUPAC Nomenclature, Structures and Abbreviations in Relation to Cannabidiol (CBD) Products

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Summary

Public Analysts and other forensic scientists frequently deal with the analysis of cannabis or cannabinoids, the nomenclature and abbreviations for which can be confusing. More recently, cannabidiol, (CBD), has gained salience as an ingredient in food supplements and in some cosmetic products. Apart from medicines with a market authorisation (eg Epidiolex and Sativex) which contain CBD, CBD-containing edible products must be regarded as food or as a food supplement. In the light of Food Standards Agency (FSA) advice after 31 March 2021 only certain CBD products for which the FSA has a valid application will be allowed to remain on the market. They must also be compositionally safe, correctly labelled, and must not contain substances that fall under controlled drugs legislation in the light of any extant or future Home Office guidance. It is to be anticipated that surveillance and, if necessary, enforcement action will take place against any non-compliant CBD products on the market after 31 March 2021. Wide variation in compliance with label claims as to the content of CBD in products has been recorded and the presence of controlled cannabinoids is a known risk.

In this paper cannabis and cannabinoid psychoactivity, regulation, control and medicinal use are reviewed together with developments in CBD regulation as a novel food. Cannabinoid nomenclature and structure are described with an overview of the common abbreviations. Analytical approaches are discussed however analysis of cannabinoids at low concentrations in complex food matrices is challenging and requires either extensive sample clean-up or the sensitivity allowed by mass spectrometric detection. The intention signalled by government to amend the Misuse of Drugs Act, 2001 to permit CBD products containing no more than a defined percentage trace concentration of certain controlled cannabinoids is welcomed to aid clarity. This should also influence better availability of appropriate cannabinoid reference standards. Harmonisation of target priority cannabinoids, analytical approaches and reporting conventions and better understanding of laboratory capability are recommended to assist appropriate numerical definition of the "trace" cannabinoid threshold and regulation of CBD-products.

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Introduction

Cannabis, *Cannabis sativa* L (Linnaeus), a single species with several varieties (including *Cannabis sativa* L subsp *sativa*, and *C sativa* L subsp *indica*), is a plant known since antiquity as a source of fuel, textiles, paper, rope and for medicinal or intoxicating recreational purposes[1]. The latter applications stem from the presence of the cannabinoids, a characteristic class of secondary metabolites produced by the cannabis plant, several of which are psychoactive. Public Analysts and other forensic scientists can meet with cannabis in a number of ways. They can be presented with it as a herbal specimen or as a resin or extract (cannabis oil) to be identified microscopically or chemically respectively. They can also be required to detect, identify and quantify cannabinoids in these matrices or in blood, urine or food and food supplements.

More recently interest in cannabinoids has increased owing to limited prescribing by specialist medical practitioners for a small range of clinical applications and the much more widespread availability of cannabidiol (CBD). In January 2019 CBD extracts were confirmed[2] as novel foods subject to approval. Hence, to assist Public Analysts and trade laboratories, we present here an overview of psychoactivity, nomenclature, structures, regulation, and analysis. The illicit synthetic cannabinoids (eg "spice")[3], whilst retaining sufficient structural similarity to psychoactive cannabis plant-derived cannabinoids to bind to cannabinoid receptors, are regulated mainly as new psychoactive substances and not dealt with here.

Cannabis, a scheduled illicit drug, contains a characteristic class of secondary metabolites, phytocannabinoids, of which the most well-known is the psychoactive compound (-) Δ^9-trans-tetrahydrocannabinol (THC). The cannabis plant produces (-) Δ^9-trans-tetrahydrocannabinolic acid (tetrahydrocannabinolic acid, THCA) and cannabidiolic acid (cannabidiol acid, CBDA) however decarboxylation of each with light, air or (especially) heat forms THC or CBD respectively. Oxidation of THC produces cannabinol (CBN). The principal mode of exposure to THC is inhalation after partial combustion for example by smoking herbal cannabis or resin mixed with tobacco. Some 50% of the THC in a "joint" of herbal cannabis is absorbed in the lungs after inhalation with rapid transfer to the bloodstream and on to the brain. Effects are observed within minutes. Bioavailability of THC after oral ingestion is some 25-30% less than from smoking the same dose owing in part to first-pass metabolism in the liver. After oral ingestion effects are seen in 0.5-2 hours. Its lipophilicity means THC accumulates in fatty tissues and is released over time. The THC content of cannabis varies considerably with source; moreover, in herbal specimens, a marked increase in THC content was seen over time from 1-3% in the mid-20th century to 6-29% as more potent varieties were produced after about 1980. Cannabis resin contains higher amounts again, from 10% to 20% and cannabis oils from 15% to over 65%. The major metabolite of THC is 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC), itself psychoactive, which is in turn oxidised to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (11-COOH-Δ^9-THC or THC-COOH, or Carboxy-THC) which is not psychoactive[4-8].

Cannabis has been recently legalised with certain restrictions in some jurisdictions[9]. Moreover, CBD which is not psychoactive (ie does not produce the psychological, psychomotor, or cognitive effects that are characteristic for THC)[10], is not scheduled as a controlled drug, has limited regulation as a medicine and is widely available in retail outlets and on the internet in the UK and elsewhere[11,12]. CBD-containing products include beverages (beer, spirits, wine, coffee and soft drinks), edible oils,

tinctures, drops, syrup, chewables (gum drops) and chocolate. CBD is commercially extracted from selected varieties of *Cannabis sativa* L, including industrial hemp, which usefully contains much less THC, and the CBD may then be dissolved in an edible oil for consumption[13]. Cannabis, its resin and hemp contain variable amounts of a large number of potentially-extractable compounds, some of which are psychoactive[6,7]. Improvements to the extraction procedure for CBD has given rise to several research publications[14-18] and to numerous patents for industrial processes[19-27].

Psychoactivity

Psychoactivity is a central feature of cannabis. A pure form of THC, the main psychoactive cannabinoid was isolated and structurally characterised in 1964[28]. The known psychoactivity of THC was at first thought to arise solely from its lipophilicity paralleling the pharmacology of anaesthetics. A series of studies led to the discovery in 1988 of a cannabinoid receptor, CB_1, (mainly) in the brain. Discovery of a partially-homologous receptor CB_2 in peripheral tissues followed. An endogenous ligand for the CB_1 receptor was identified, an amide of arachidonic acid, arachidonoyl ethanolamide (named anandamide) leading to a wealth of studies on the characterisation of endogenous cannabinoids[29].

Of the many known cannabinoids, only Δ^9THC, (and its 11-hydroxy *in vivo* metabolite), Δ^8THC (and presumably its 11-hydroxy *in vivo* metabolite) and, to some extent, cannabinol (CBN) bind significantly to the ligand-recognising site of these receptors[30] with the well-known acute psychological effects of euphoria, dysphoria, sedation and altered perception[4]. Stemming from the 1971 UN Convention on Psychotropic Substances, the World Health Organization (WHO) approached assessment of emerging substances for psychoactivity based on evidence of dependence, and central nervous system (CNS) stimulation or depression, that result in hallucinations or disturbances in motor function or cognitive, behaviour, perception or mood. WHO also took into account potential for abuse and ill effects similar to those of substances already scheduled by the UN Convention and the balance between public health or social problems and usefulness as a medicine[31]. A current WHO definition, which also refers to "psychotropic drug" includes[32]:

> *psychoactive substances are substances that, when taken in or administered into one's system, affect mental processes, eg cognition … "Psychoactive" does not necessarily imply dependence-producing*

With the advent around 2008 of new substances, mainly synthetic cannabinoids collectively known as "new psychoactive substances", intended to mimic the effects of traditional controlled drugs further control legislation was required. In the UK the Psychoactive Substances Act 2016[33,34] created offences including producing, suppling, and possession with intent to supply, psychoactive substances. The Act excludes legitimate substances such as food, alcohol, tobacco, nicotine, caffeine and medical products from the scope of the offence, as well as controlled drugs, which continue to be regulated by the Misuse of Drugs Act 1971.

The Act defines "psychoactive substance" as:

> *1 any substance which:*
> *(a) is capable of producing a psychoactive effect in a person who consumes it*
> *(b) is not an exempted substance*
>
> *2 for the purposes of this Act a substance produces a psychoactive effect in a person if, by stimulating or depressing the person's central nervous system, it affects the person's mental functioning or emotional state; and references to a substance's psychoactive effects are to be read accordingly*

The Explanatory Notes to the Psychoactive Substances Act elaborate on this with the following description (paragraph 38) reminiscent of early WHO considerations:

> *The main effect of psychoactive substances is on a person's brain, the major part of the central nervous system. By speeding up or slowing down activity on the central nervous system, psychoactive substances cause an alteration in the individual's state of consciousness by producing a range of effects including, (but not limited to): hallucinations, changes in alertness, perception of time and space, mood or empathy with others and drowsiness*

Further detail about psychoactivity testing is set out in the Home Office's Forensic Strategy[35]. The strategy includes *in-vitro* receptor binding and functional assays to assess if receptor-binding elicits a response (receptors include cannabinoid, opioid, GABA and others). Interestingly this appears to be the first time pharmacological action rather than chemical analysis has been used in modern forensic toxicology.

The Advisory Council on the Misuse of Drugs, (ACMD), commenting on alkyl nitrites ("poppers"), reached a consensus view that a psychoactive substance has a direct action on the brain and that substances having peripheral effects, such as those caused by alkyl nitrites, do not directly stimulate or depress the central nervous system. Alkyl nitrites dilate blood vessels hence increasing blood flow and this is generally believed to result in the release of nitric oxide causing vasodilation by relaxation of smooth muscle in blood vessels[36].

Regulation of Cannabis and Cannabinoids

International Regulation

Cannabis and cannabis resin are listed for control in Schedule I (which adds "and extracts and tinctures of cannabis") and Schedule IV of the United Nations Single Convention on Narcotic Drugs 1961 as amended by the 1972 Protocol (the "Single Convention")[37]. The UN Commission on Narcotic Drugs (UNCND) recently took a number of decisions on the international control of cannabis and cannabis-related substances. The UNCND accepted a WHO recommendation to delete cannabis and

cannabis resin from Schedule IV of the 1961 Convention, but to maintain it in Schedule I. Other WHO recommendations were rejected, including one to add a footnote to Schedule I to read:

> *Preparations containing predominantly cannabidiol and not more than 0.2 per cent of delta-9-tetrahydrocannabinol are not under international control*

The recommendation had arisen from the fortieth meeting of the WHO Expert Committee on Drug Dependence, which *inter alia* considered a critical review of CBD. The Committee recognised that medicines such as Epidiolex, produced as preparations of the cannabis plant, will contain trace amounts of Δ^9-THC, (0.15% Δ^9-THC in the case of Epidiolex) although it was also recognised that analysis of Δ^9-THC at this concentration may be difficult in some jurisdictions[38].

UK Regulation

The main UK legislative provisions for controlled drugs are briefly described here as they apply at the time of writing (early 2021). The territorial extent of the Misuse of Drugs Act 1971 is UK-wide however devolved equivalents of subordinate regulations must be considered although not recorded here. Furthermore detailed provisions on controlled drug management or drug-driving measures have also not been considered.

The Misuse of Drugs Act

In the UK illicit drugs are regarded as compounds of no medical value and with a high risk of misuse. Illicit drugs are regulated by the Misuse of Drugs Act 1971[39] (MDA 1971) which, subject to subordinate regulations, prohibits the production, importation, exportation, possession and supply of controlled drugs, which are specified, by virtue of Section 2 (S 2) of the Act, in its Schedule 2. The expressions "Class A", "Class B" and "Class C" drugs refer to those specified in Parts I, II or III respectively of Schedule 2 [S 2(1)(b)].

Cannabinol and its derivatives, including any of their ethers or esters, cannabis and cannabis resin and nabilone (a synthetic cannabinoid, see below) are listed in Schedule 2 Part II, ie Class B drugs.

Part IV of Schedule 2 contains the definition of cannabinol derivatives:

> *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*

S 37 of MDA 1971 (Interpretation) defines "cannabis" as:

> *any plant of the genus Cannabis or any part of any such plant (by whatever name designated) or any of the following, after separation from the rest of the plant, namely (a) mature stalk of any such plant, (b) fibre produced from mature stalk of any such plant, and (c) seed of any such plant*

"Cannabis resin" is defined as:

> *the separated resin, whether crude or purified, obtained from any plant of the genus Cannabis*

The Advisory Council on the Misuse of Drugs (ACMD) was established pursuant to S1 of MDA 1971 which sets out ACMD's remit and duties.

The Misuse of Drugs Regulations

Subordinate regulations made under MDA 1971 provide more detail on the control of illicit drugs. Thus cannabis, including its resin and cannabinoids, are listed for more detailed control in the Misuse of Drugs Regulations 2001[40] (MDR 2001) which revoke and re-enact, with amendments previous such regulations. MDR 2001 sets out detailed rules for the cultivation, possession or trade in controlled substances (cannabis and certain cannabinoids), essentially unlawful except for legitimate purposes permitted by a Home Office licence. They make provision in relation to record keeping, the furnishing of information concerning controlled drugs and for the supervision of the destruction of such drugs. MDR 2001 make changes to the MDA 1971 Schedules but without affecting cannabis or cannabinoids and introduce and define cannabis-based product for medicinal use in humans.

MDR 2001 introduced certain exemptions including that in regulation 2 (Interpretation) which defines an "exempt product". This has significance for the marketing of CBD-containing products that contain detectable amounts of other cannabinoids.

The definition of an exempt product is three limbed:

> *a preparation or other product consisting of one or more component 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*
> *(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*

All three limbs of the exemption should be considered but the implications of (c) which introduced a "1 mg" threshold amount for controlled cannabinoids (among other controlled drugs) are explored in further detail below.

An ACMD paper of December 2016 sets out the probable controlled cannabinoids as of that date[41].

Medicinal Use

In a 2018 amendment to MDR 2001[42] unlicensed cannabis products were moved from Schedule 1 to Schedule 2 which made cannabis-based medicinal products available to be prescribed for medicinal use. MDR 2001 had already included Sativex, a cannabis-based buccal spray. Following a review by the UK Government's Chief Medical Adviser and the ACMD a defined category of cannabis-based products for medicinal use in humans became available without the need for a Home Office licence. The prohibition on their use by smoking, except for research purposes was retained. The definition introduced into MDR 2001 for cannabis-based products for medicinal use in humans, consists of three limbs:

(a) it is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative, (other than Dronabinol, [synthetic THC] or its stereoisomers)
(b) it is produced for medicinal use in humans
(c) it is a medicinal product or a substance or preparation for use as an ingredient of, or in the production of, a medicinal product

Any cannabis-based substance falling outside of this definition (for example, a cannabis-based product classified as a medicine but produced for recreational use) will remain a Schedule 1 drug. Moreover, as at the time there were no such medicinal products with a marketing authorisation (previously "product licence") prescribing is limited to three routes:

(a) Without a marketing authorisation the medicine can only be prescribed by a doctor on the Specialist Register of the General Medical Council
(b) Use is permitted in certain clinical trials
(c) If covered by a marketing authorisation (where its quality, safety and efficacy have been established for indicated uses) it can be prescribed as appropriate by any General Practitioner

At the time of writing there are two cannabis related medicinal products with UK marketing authorisations. Sativex, an oromucosal spray, is indicated for the treatment of certain effects of multiple sclerosis and contains 38-44mg/mL (3.8-4.4%) and 35-42mg/mL (3.5-4.2%) of two extracts from *Cannabis sativa* L, (leaf and flower) corresponding to 27mg/mL (2.7%) THC and 25mg/mL (2.5%) CBD[43]. This corresponds to the MDR 2001 Schedule 4 entry for a liquid formulation containing a botanical extract of cannabis with a concentration of not more than 30mg/mL of CBD and not more than 30 mg/mL THC. The second is Epidiolex oral solution containing 100mg/mL (10%) CBD indicated for the treatment of certain seizure syndromes associated with epilepsy[44]. This appears to correspond with the MDR 2001 Schedule 5 entry for a liquid formulation containing CBD obtained by extraction and purification from cannabis where the concentration of THC is not more than 0.1mg/mL (100 mg/L, 0.01%) and CBD is 95-105mg/mL (9.5-10.5%). The National Institute for Health and Care Excellence (NICE) notes the availability of Nabilone, a synthetic cannabinoid mimicking THC indicated for nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics[45]. Marinol (containing synthetic THC) is licensed in the USA and may be prescribed in the UK on a named patient basis.

Lastly, for interest, Schedule 1 of MDR 2001 also contains an entry for 3–Dimethylheptyl–11–hydroxyhexahydrocannabinol.

Regulation of CBD

As noted above CBD is not a controlled drug, is included in several authorised medicinal products and products containing CBD are widely offered for sale. Against this background the Food Standards Agency (and it is thought, other European food agencies) applied to the European Commission for clarification of CBD as a novel food pursuant to Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015[46]. A novel food is a food that has not been consumed to any significant degree in the EU before 15 May 1997 (when the first novel food legislation entered into force). The FSA submission related to a CBD isolate (purity >98%) dissolved in MCT oil (medium-chain triglyceride) with concentrations of CBD in the product of 500mg, 1000mg and 1500mg per 10mL (5, 10 and 15%). The CBD it was noted is extracted using ethanol as the solvent and the product is intended to be used as a food supplement[47].

As a result, the European Commission Novel Foods catalogue[48] was updated in January 2019 and currently reads:

> *Cannabis sativa* L
> *In the European Union, the cultivation of Cannabis sativa L varieties is permitted provided they are registered in the EU's "Common Catalogue of Varieties of Agricultural Plant Species" and the tetrahydrocannabinol (THC) content does not exceed 0.2% (w/w). Some products derived from the Cannabis sativa plant or plant parts such as seeds, seed oil, hemp seed flour, defatted hemp seed have a history of consumption in the EU and, therefore, are not novel. Other specific national legislation may restrict the placing on the market of this product as a food or food ingredient in some Member States. Therefore, it is recommended to check with the national competent authorities*

The Novel Foods catalogue entry for Cannabidiol redirects to the entry for Cannabinoids which reads: (nb psychoactive compounds have been underlined by the authors for information)

> *The hemp plant* (*Cannabis sativa* L) *contains a number of cannabinoids and the most common ones are as follows: delta-9-tetrahydrocannabinol (Δ9-THC), its precursor in hemp, delta-9-tetrahydrocannabinolic acid A (Δ9-THCA-A), delta-9-tetrahydrocannabinolic acid B (Δ9-THCA-B), delta-8-tetrahydrocannabinol (Δ8-THC), cannabidiol (CBD), its precursor in hemp cannabidiolic acid (CBDA), cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), and delta-9-tetrahydrocannabivarin (Δ9-THCV). Without prejudice to the information provided in the novel food catalogue for the entry relating to Cannabis sativa L, extracts of Cannabis sativa L and derived products containing cannabinoids are considered novel foods as a history of consumption has not been demonstrated. This applies to both the extracts themselves and any products to which they are added as an ingredient (such as hemp seed oil). This also applies to extracts of*

> *other plants containing cannabinoids. Synthetically obtained cannabinoids are considered as novel*

Thus, before a CBD-containing food may be placed on the market in the EU (as a food or food ingredient) a safety assessment under the Novel Food Regulation is required and it must be pre-authorised by separate formal processes in the UK and EU prior to placing on the market. As a result, the Food Standards Agency has stipulated that businesses in the UK must submit, and have fully validated, novel food authorisation applications for their CBD products by 31 March 2021. After this date, only certain products for which the FSA has a valid application will be allowed to remain on the market. As a pragmatic approach, existing CBD products may continue on the market until the above deadline provided they are not incorrectly labelled, are not unsafe and do not contain substances that fall under controlled drugs legislation. Significant aspects with regard to CBD products, therefore, are their CBD and other cannabinoid concentrations. No new CBD extracts or isolates should be sold until they have the necessary authorisation[49].

Tallon (2020)[50] helpfully reviewed the regulation of CBD in the UK and EU. Among the considerations raised were psychoactive cannabinoid contamination of CBD, the European Food Safety Authority (EFSA) acute reference dose (ARfD) of 1µg/kg body weight (bw) for THC and emerging CBD authorisations as medicines that may influence regulatory attitudes to its use in foods. Tallon[50] also speculated on CBD as psychoactive in its own right based on a suggested CNS effect in stressed animal models secondary to reduction of increases in heart rate and blood pressure. That the noted CNS effect was seen only in pathological situations and bearing in mind ACMD's view on amyl nitrite it seems unlikely to alter the view of CBD as non-psychoactive unless further data emerge.

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has considered CBD on a number of occasions and summarised their views and that of the Food Standards Agency in July 2020. FSA advice is that, until further data are available, 1mg/kg bw/day of CBD represents a pragmatic upper level of intake above which there would be clear concerns about safety. As a precaution, FSA recommends that CBD should not be consumed by pregnant or breastfeeding women or by people taking medication. FSA further note that the CBD intake deemed acceptable will ultimately be determined by an individual's weight and health status[51]. For a male individual of 70 kg weight a daily intake of CBD of 70mg represents a pragmatic upper limit. By way of illustration a product containing CBD at 500mg/10mL (5%) would deliver 70mg of CBD in 1.4 mL of the product.

An increasing number of studies have assessed the quality of CBD-containing products. For example, fourteen commercially available CBD oils in Europe were assessed by LC-MS and by GC-MS. Of these nine had CBD concentrations that differed in some instances notably from the declared amounts, five samples were within ±10% of the declared concentrations, and questions were raised with regard to their oxidation stability[52]. For five mail-ordered samples the percentage of label-claimed contents ranged from 81-200%[53]. Variations in the chemical complexity of the bioactive constituents in cannabis oils indicate the need for a standardised and well-defined analytical approach[6,54]. The Food Safety Authority of Ireland (FSAI) published in early 2020 the results of a survey of CBD products. FSAI found the majority of products analysed were in breach of various articles of food law and some posed potential safety risks for consumers. Of the products tested 37% had a THC content that could

result in safety limits set by EFSA being significantly exceeded and the implicated batches of these products were recalled. In addition, it was found that the analytically-determined CBD content in over 40% of samples varied significantly (>50%) from the declared CBD content[55]. A 2020 survey of UK over-the-counter cannabidiol (CBD) products reported 38% (11/29) were within 10% of their advertised CBD content and 55% exhibited measurable LC-UV(DAD) concentrations of common, including controlled, cannabinoids[56].

Published Guidance

The MHRA has included guidance on CBD in its publication "Guidance Note 8 – a guide to what is a medicinal product"[57]. A set of Home Office guidance documents relating to drugs licensing is available[58]. The Home Office "Low THC Cannabis (Industrial Hemp) Licensing Factsheet"[59] describes the background to applying for a licence that may be issued for the cultivation of cannabis plants with a low THC content for the production of hemp fibre for industrial purposes or the obtaining of seeds which are then pressed for their oil. A second Home Office fact sheet[60] provides guidance on UK measures applicable to cannabis, cannabidiol (CBD) and controlled cannabinoids. This is aimed at existing and prospective licensees and not intended as a guide to consumer products. The guidance expands on the MDR 2001 definition of an exempt product and the "one milligram" cannabinoid threshold. Analytical results are usually expressed as a concentration (amount per volume) hence harmonised agreement on the volume, and which cannabinoids (or their sum) contribute to the threshold are desirable. Further discussion and guidance on these issues is available from the Government Chemist[61].

In January 2021 the Minister of State for Crime and Policing at the Home Office asked the ACMD for advice on CBD products. The Government appears to be minded to amend MDR 2001 to permit CBD products containing no more than a defined trace (eg between 0.0001 and 0.01%w/w) of certain controlled cannabinoids and to amend the definition of an "exempt product". The precise percentage will be determined following further scientific advice including on analysis. The Minister also referred to the current limited availability of reference standards, as a result of which analytical capability is likely to be best focused on the quantification of THCV, Δ^9-THC, CBN and Δ^9THCA-A rather than all controlled cannabinoids that could be permitted to be present in trace amounts[62].

No attempt has been made to survey control or guidance in jurisdictions other than the UK. However maximum recommended thresholds for THC in a number of jurisdictions are reported by Skoczinski *et al*., 2019[63] in a critique of a 2018 German survey[64] asserting excessive THC levels in many hemp-containing foods. Skoczinski *et al*., report thresholds for THC, either as such or as "total THC" including THCA between 0.005mgkg^{-1} and 34mgkg$^{-1.}$ The lowest (0.005mgkg^{-1}) applies to German alcoholic or non-alcoholic beverages and typical thresholds are in the range 0.02mgkg^{-1} to 10mgkg^{-1}. Attention[53] was drawn to the control of THC in foods in Italy which in advance of any EU law has limited the sum of THC and THCA in hemp (seeds, flour and oil), and supplements containing foodstuffs derived from hemp, to not more than 2.0mg/kg[65].

Biosynthesis

A number of precursors in the cannabis plant lead to the biosynthesis of geranyl phosphate and 2,4-dihydroxy-6-pentylbenzoate (conjugate base of olivetolic acid) which take part in an enzymatically mediated reaction producing cannabigerolic acid, (cannabigerolate ion)[5] which is further transformed into Δ^9-tetrahydrocannabinolate and cannabidiolate. For a more exact treatment of cannabinoid biosynthesis readers are referred to the appropriate page of the internet version of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB), in consultation with the IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN)[66].

Cannabinoids – Nomenclature, Structure and Psychoactivity

There are over 550 identified components in *C sativa* L among them are at least 110 phytocannabinoids. The phytocomplex compositions vary between the various cannabis genotypes[5]. The most studied of them are THC, CBD and CBN[29]. Lists of the principal cannabinoids are subject to opinion and with the nature of the questions raised about products being examined[6,7,52,54,67].

The nomenclature of the cannabinoids can be confusing. Schoenfeld[68] and Raman and Joshi[69] have described the historical origins. Of the up to five different atom-numbering systems developed for cannabinoids[70] two came to prominence. One regarded the molecules as substituted monoterpenes while the other, preferred by Chemical Abstracts, is based on the formal chemical rules for numbering dibenzopyran-type compounds, which is illustrated in Figure 1. Thus, in the literature the cannabinoids may be described as "C_{21} terpenophenolics", stemming from their biogenetic origin, or, similarly, "aryl-substituted meroterpenes" ("mero" = "partial"), more easily seen in the structures of CBGA and CBG (Table 1). Recognising that terpenes exhibit carbon skeletons formally derived from isoprene (CH_2=C(CH_3)CH=CH_2), the presence of 1,3-benzenediol (resorcinol) in eg CBD and the alternating carbonyl and methylene groups exhibited by many cannabinoids they may also described as isoprenylated resorcinyl polyketides.

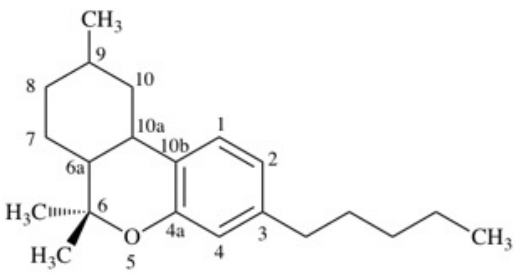


Figure 1: Dibenzopyran Numbering

Note: in various cannabinoids the pyran ring may not be formed, both other rings may or may not be aromatic, the side chain at C-3 may be shortened and other structural variations may occur

The pivotal role of cannabinol, CBN, as the starting point for cannabinoid nomenclature and regulation stems from its from its early isolation (1896[71]). CBN arises from successive oxidation of THCA and THC (Figure 2) and is an artefact probably not present in fresh cannabis extracts. The isolation and identification of CBN from aged samples by relatively harsh techniques explains it pre-eminent position[68].

Important structural variations in cannabinoids include (from left to right in Figure 1):

(a) *At C-3 the pentyl side chain may be shortened in some cannabinoids attracting the suffix Cn (n being the number of carbons in the side chain) except for propyl analogues when the term "varin" and letter "V" are often used eg Tetrahydrocannabivarin (THCV)*
(b) *Cannabinoids containing a carboxyl group on the aromatic ring attract an "A" (Acid) in their capitalised acronym, and may be described as an "A" or "B" acid depending on whether the carboxyl group is attached to C-2 or C-4, ie ortho or para to the hydroxyl at C-1 in THCA-A or THCA-B[72]*
(c) *For some cannabinoids the pyran ring is not formed (e.g. CBDA and CBD).*
(d) *The now redundant Δ notation denotes unsaturation and although it is no longer required in the IUPAC nomenclature it persists to describe a double bond, eg at C-9 in THC, (Δ^9...)*
(e) *Cannabichromene, CBC, first isolated and characterised in 1966[73,74] exhibits the pyran ring hence benzopyran moiety (for which the older term "chromene" remains valid) but isoprenyl cyclisation is absent*
(f) *In some cannabinoids (cannabinol, cannabinodiol) the cyclised isoprenyl ring is fully aromatised*

Isomerism is also relevant for many of the cannabinoids. *Cis-trans* isomerism is variable with CBD and THC exhibiting *trans*-geometry whereas most of the CBG-type exhibit a *cis*- configuration. Most natural cannabinoids have two chiral centres at atoms 10a and 6a (Figure 1). A single enantiomer, the (*R,R*)-form is generally found in the cannabinoids, as for many natural products[75]. In THC under harsh conditions the double bond at C-9 (Figure 1) may isomerise to the C-8 position, Δ^9 to Δ^8 isomerism.

In addition, in reports from forensic toxicologists it is common to see abbreviations such as 11-COOH-Δ^9-THC, THC-COOH, THC-carboxylic acid, and Carboxy-THC all referring to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol, IUPAC name 1-hydroxy-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid.

Despite Schoenfield's[67] scholarly condemnation 40 years ago of capitalised acronyms their utility has led to ubiquitous prevalence albeit at the risk of confusion, in part the reason for the present paper. Thus Figure 2, based on the WHO critical review of 2018[76]summarises the common capitalised acronyms for the major cannabinoids and illustrates their interrelations.

Table 1 contains a list of the most important cannabinoids for regulation with their abbreviations, names, CAS No, IUPAC nomenclature, structures, their physiological activities and other brief relevant remarks. Further information on individual compounds is readily available via their PubChem (https://pubchem.ncbi.nlm.nih.gov/) web pages. Hanuš *et al*[30] describe in some detail

the isoprenylated resorcinyl polyketide structural motifs and give a unified critical inventory of the phytocannabinoids.

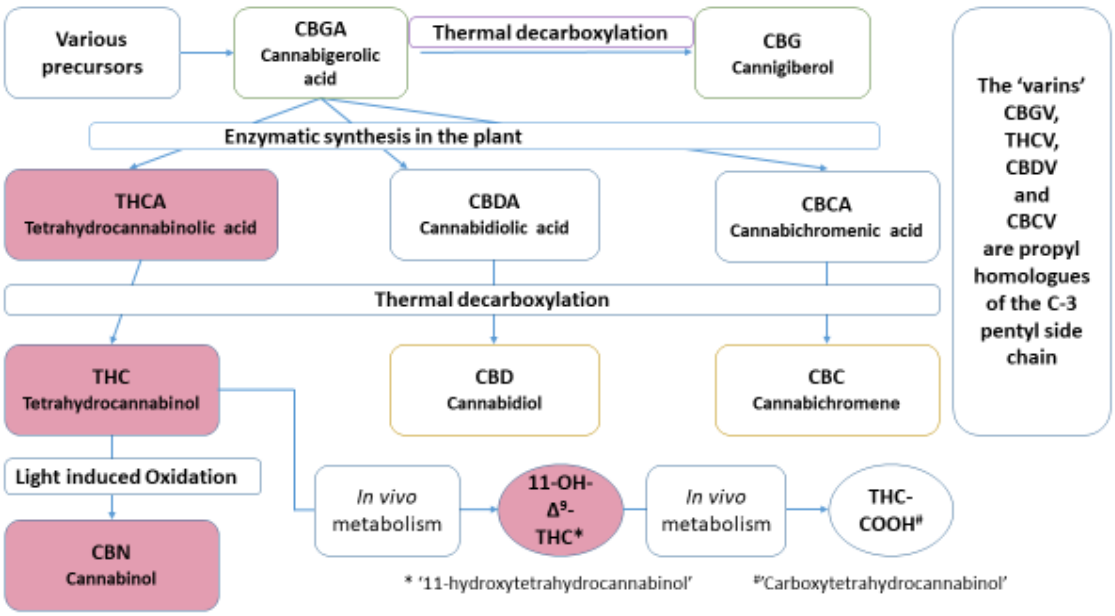
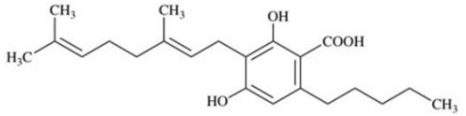
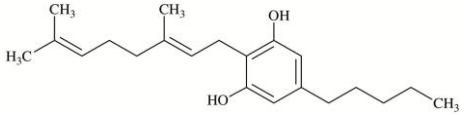
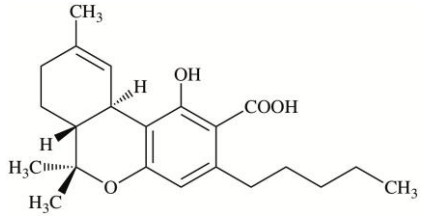
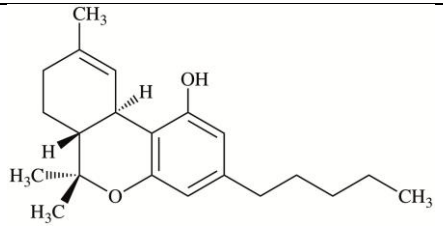


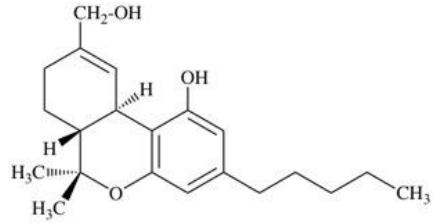
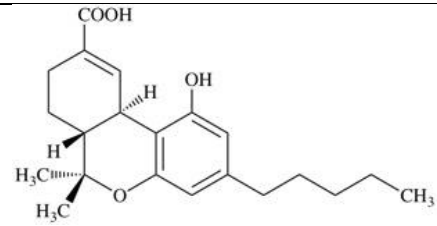
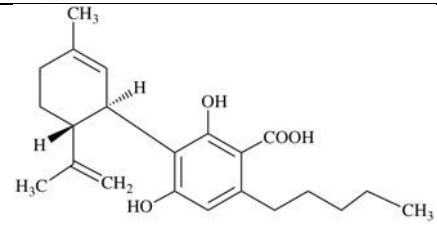
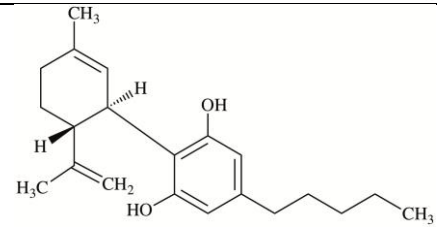
Figure 2: Illustration of the Relationships between some Principal Cannabinoids

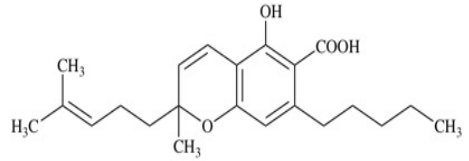
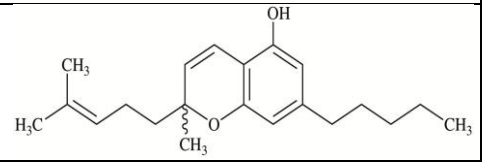
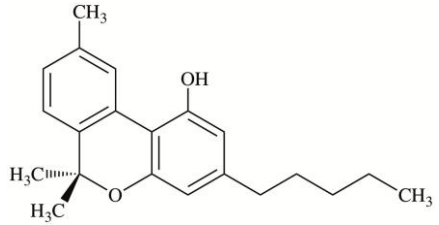
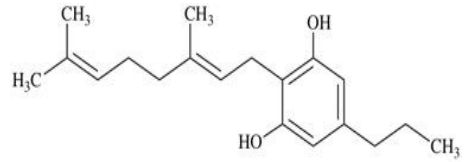
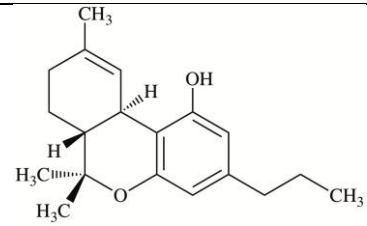
Note: pink shading indicates psychoactivity - see also Table 1

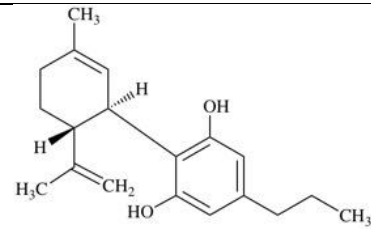
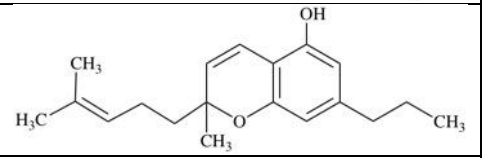
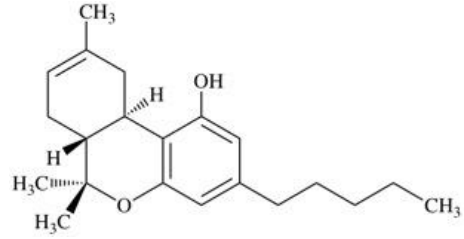
Lastly in this section it must be remembered that cannabis contains many compounds besides cannabinoids, including mono- and sesquiterpenes that contribute to the odour of the drug, sugars, hydrocarbons, steroids, flavonoids, nitrogenous compounds and amino acids. Analytically this represents a highly-complex matrix to say nothing of the pesticides, mycotoxins, heavy metals and other contaminants that may also occur in the plant and find their way into its extracts.

Table 1: Cannabinoids of Regulatory Interest: Abbreviations, Common Names, CAS No, Physiological Activity, IUPAC Nomenclature and Structures

Abbreviation	Common Name	CAS no.	Remarks and Activity[1,5,41,67,73]	IUPAC nomenclature (dibenzopyran rules)	Structure
CBGA	Cannabigerolic acid	25555-57-1	The starting point for phytocannabinoids in the cannabis plant	3-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-2,4-dihydroxy-6-pentylbenzoic acid	
CBG	Cannabigerol	25654-31-3	The first isolated cannabinoid. Appetite enhancer, antibacterial, antioxidant, neuroprotective	2-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-5-pentylbenzene-1,3-diol	
THCA	Tetrahydrocannabinolic acid	23978-85-0	Not psychoactive*	(6a*R*,10a*R*)-1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-2-carboxylic acid	
THC	Δ^9-tetrahydrocannabinol *or* Δ^9-THC	5957-75-5	Main active component of cannabis, formed by (thermal) decarboxylation of THCA	(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol	

Abbreviation	**Common Name**	**CAS no.**	**Remarks and Activity**[1,5,41,67,73]	**IUPAC nomenclature (dibenzopyran rules)**	**Structure**
11-OH-Δ^9-THC	11-hydroxy-Δ^9-tetrahydrocannabinol *or* 11-Hydroxy-THC	26108-40-7	Major *in vivo* metabolite of THC, psychoactive*	(6a*R*,10a*R*)-9-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol	
THC-COOH	(-)-11-nor-9-carboxy-Δ^9-tetrahydrocannabinol *or* 11-Nor-9-carboxy-delta-9-tetrahydrocannabinol	56354-06-4	Major *in vivo* metabolite of 11-OH-Δ^9-THC, not psychoactive	1-hydroxy-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-9-carboxylic acid	
CBDA	Cannabidiolic acid *or* cannabidiol acid	1244-58-2	Carboxylated form, not psychoactive,	2,4-dihydroxy-3-[(1*R*,6*R*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl]-6-pentylbenzoic acid	
CBD	Cannabidiol	13956-29-1	Not psychoactive	2-[(1*R*,6*R*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol	

Abbreviation	**Common Name**	**CAS no.**	**Remarks and Activity**[1,5,41,67,73]	**IUPAC nomenclature (dibenzopyran rules)**	**Structure**
CBCA	Cannabichromenic acid	20408-52-0	Not psychoactive	5-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-7-pentyl-2*H*-1-benzopyran-6-carboxylic acid	
CBC	Cannabichromene *or* Cannanbichrome	20675-51-8	Not psychoactive	*rac*-2-methylpent-3-1-yl)-7-pentyl-2*H*-1-benzopyran-5-ol	
CBN	Cannabinol	521-35-7	Psychoactive* owing to weak effect on central nervous system, derives from the oxidation of Δ^9-THC	6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol	
CBGV	Cannabigerovarin	55824-11-8	Propyl homologue of the C-3-pentyl side-chain	2-[(2*E*)-3,7-dimethylocta-2,6-dien-1-yl]-5-propylbenzene-1,3-diol	
THCV	Tetrahydrocannabivarin *or* Δ^9-tetrahydrocannabivarin	28172-17-0	Psychoactive*, numerous effects listed, propyl homologue of the C-3-pentyl side-chain	(6a*R*,10a*R*)-6,6,9-trimethyl-3-propyl-6a,7,8,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol	

Abbreviation	**Common Name**	**CAS no.**	**Remarks and Activity**[1,5,41,67,73]	**IUPAC nomenclature (dibenzopyran rules)**	**Structure**
CBDV	Cannabidivarin	24274-48-4	Propyl homologue of the C-3-pentyl side-chain	2-[(1*R*,6*R*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl]-5-propylbenzene-1,3-diol	
CBCV	Cannabichromevarin	57130-04-8	Propyl homologue of the C-3-pentyl side-chain	(+)-2-methyl-2-(4-methylpent-3-enyl)-7-propyl-2*H*-1-benzopyran-5-ol	
Δ^8-THC	Δ^8-tetrahydrocannabinol	5957-75-5	Isomer of Δ^9-THC resulting from variation in the position of the double bond in the alicyclic carbon ring, may be an isolation artefact	(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,10,10a-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-1-ol	

***** Psychoactive (in the sense of THC) or otherwise and other common human physiological activity

Analytical Methods

The purity of CBD extracts is important due to the need to ensure the absence, or the near absence, of controlled, psychoactive/intoxicant components and of their precursors in products for reasons of human health and legal compliance. A range of methods has been developed for cannabinoids. These encompass sampling, presumptive colour tests and immunoassays, TLC, GC-FID, GC-MS and LC-UV (PAD and DAD), HPTLC with UV and MS, LC-MS/MS; (see glossary below). LC methods resolve precursor cannabinoid acids (eg THCA, CBDA and CBCA) from their derivatives. However in typical GC methods the acid analogues are thermally oxidised (Figure 2) to their derivatives (eg THC, CBD and CBC) and hence not detected[77-83]. A review covering the literature from 2010 to 2019 emphasised the utility of UPLC-MS approaches[84]. A recent LC-MS/MS study demonstrated validation of the quantification of 17 cannabinoids in cannabis and hemp from 2–200,000 $mgkg^{-1}$ (0.0002 to 20.0%) in matrix with good precision and accuracy[85]. A single-laboratory validation of a LC–DAD method for quantification of 12 major cannabinoids in *Cannabis* dried plant materials, concentrates and oils was reported in 2019. The method is approved under AOAC First Action for dried plant materials, including hemp, as AOAC 2018.11. LOQs were in the range 0.003–0.10% (w/w), depending on the analyte and matrix and both DAD–UV and MS detection could be deployed. During method validation, high-resolution quadrupole time-of-flight MS was connected in series to the LC–DAD instrument to provide high confidence identification of target analytes and as a tool for monitoring other cannabinoids for which reference standards were not available[86]. Commission Recommendation (EU) 2016/2115 of 1 December 2016 on the monitoring of cannabinoids in food[87] advocates clean up followed by LC-MS or GC-MS that allows the determination of Δ^9-THC separately and its precursors and other cannabinoids in hemp-containing food products. Nevertheless, more work is required on current analytical methods for the testing and compliance of CBD products both for consumer confidence and potential enforcement of regulations. Method validation is needed in a range of edible matrices, with considerably better detection capability and, if possible, standardisation of methods and reporting conventions.

Conclusions

For good reasons the psychoactive cannabinoids and hence cannabis remain controlled internationally, federally in the USA and in most individual jurisdictions. Where legalisation for non-medicinal recreational purposes has to any extent taken place public health advantages and disadvantages remain to be fully explored[9,88]. Outwith market authorisation for medicinal purposes CBD edible products fall to be regarded as food or as a food supplement. In the light of FSA advice after 31 March 2021 only certain CBD-products for which the FSA has a valid application will be allowed to remain on the market in the UK. They must also be compositionally safe, correctly labelled and must not contain substances that fall under controlled drugs legislation in the light of any Home Office guidance. For CBD products recorded variations in CBD content and controlled cannabinoid contamination may well be of concern to regulatory and enforcement bodies. It is to be anticipated that surveillance and, if necessary, enforcement action will take place against any non-compliant CBD products on the market after 31 March 2021. It is timely therefore that this review should be available with the common names, abbreviations, IUPAC nomenclature, structures, regulation, psychoactivity and analytical methodology for the principal cannabinoids.

Analytically, the AOAC method 2018.11 of LC- DAD analysis may be a reasonable starting point, in view of its extensive validation study by Vaclavik *et al*[83] although the LoQ's estimated for cannabinoid-containing oils range from 0.003%w/w (for CBN) to 0.01%w/w (for CBD). As Vaclavik *et al* note[86] analysis of cannabinoids at low concentrations in complex food matrices is challenging and requires either extensive sample clean-up or, as the European Commission recommend[87], the specificity allowed by mass spectrometric detection. The intention signalled by government to amend MDR 2001 to permit CBD products containing no more than a defined trace (eg between 0.0001 and 0.01%w/w) of certain controlled cannabinoids and to amend the definition of an exempt product is welcomed to aid clarity. This should also influence better availability of appropriate cannabinoid reference standards. Harmonisation of target priority cannabinoids, analytical approaches and reporting conventions and better understanding of laboratory capability are recommended to assist appropriate numerical definition of the "trace" cannabinoid threshold and regulation of CBD-products.

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Glossary

GABA	Gamma-aminobutyric acid, a neurotransmitter
GC	Gas chromatography
GC-FID	GC with flame ionisation detection
GC-MS	GC with mass spectrometric detection
HPTLC	High performance thin layer chromatography
IDMS	Isotope dilution mass spectrometry
LC	Liquid chromatography, also HPLC, high performance LC, UPLC, ultra-performance LC
LC–DAD	Liquid chromatography, diode array detection, a form of LC-UV
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LC-PDA	LC with pulsed amperometric detection
LC-UV	Liquid chromatography with ultra violet detection

Official Food Analyst	A person qualified under the Food Safety (Sampling and Qualifications) Regulations (1990 and/or 2013) (see also Public Analyst)
Port Health Authority	Special type of local authority created to ease administration at seaports where the port area is covered by more than one local authority, responsible for carrying out checks on food and feed consignments
Public Analyst	Analytical scientist appointed under statute by UK local authorities to provide an official food or feed control function and scientific advice for the enforcement of many acts of Parliament
TLC	Thin layer chromatography
UV	Ultraviolet
Tandem mass spectrometry	Use of linked mass spectrometers; molecules of interest can be broken up after the first stage to allow more detailed characterisation by analysing their fragments in the second

References

1 *Cannabis - The Genus Cannabis*, Ed David T Brown, Harwood Academic Publishers, 1998, Taylor & Francis e-Library, 2003

2 Food Standards Agency, FSA, 2020, Novel Foods Authorisation Guidance; Novel Foods Authorisation Requirements and What you Need to Submit as Part of a Novel Food Application https://www.food.gov.uk/business-guidance/regulated-products/novel-foods-guidance (Accessed 06.01.2021)

3 B Mills, A Yepes and K Nugent, 2015, Synthetic Cannabinoids; The American Journal of the Medical Sciences, **350(1)**, 59-62

4 CH Ashton, 2001, Pharmacology and Effects of Cannabis: a Brief Review; The British Journal of Psychiatry, **178(2)**, 101-106

5 WHO, Critical Review: Cannabis and Cannabis Resin, World Health Organisation, Geneva (2018)

6 TWM Davis, CG Farmilo and M Osadchuk, 1963, Identification and Origin Determinations of Cannabis by Gas and Paper Chromatography; Analytical Chemistry, **35(6)**, 751-755

7 R Lewis, S Ward, R Johnson and DT Burns, 2005, Distribution of the Principal Cannabinoids within Bars of Compressed Cannabis Resin; Analytica Chimica Acta, **538(1-2)**, 399-405

8 C Citti, B Pacchetti, MA Vandelli, F Forni and G Cannazza, 2018, Analysis of Cannabinoids in Commercial Hemp Seed Oil and Decarboxylation Kinetics Studies of Cannabidiolic Acid (CBDA); Journal of Pharmaceutical and Biomedical Analysis, **149**, 532-540

9 W Hall, D Stjepanović, J Caulkins, M Lynskey, J Leung, G Campbell and L Degenhardt, 2019, Public Health Implications of Legalising the Production and Sale of Cannabis for Medicinal and Recreational Use; The Lancet, **394(10208),** 1580-1590

10 F Grotenhermen, E Russo and AW Zuardi, 2017, Even High Doses of Oral Cannabidiol do not Cause THC-like Effects in Humans: Comment on Merrick et al Cannabis and Cannabinoid Research 2016; **1(1)**: 102–112, DOI: 10.1089/can 2015.0004 Cannabis and Cannabinoid Research, ***2*(1)**, 1-4

11 European Monitoring Centre for Drugs and Drug Addiction (2018), Medical Use of Cannabis and Cannabinoids: Questions and Answers for Policymaking; Publications Office of the European Union, Luxembourg

12 TP Freeman, C Hindocha, BF Green, MA Bloomfield, 2019, Medicinal Use of Cannabis Based Products and Cannabinoids; British Medical Journal, 2019 Apr 4;365

13 A Hazekamp, 2018, The Rrouble with CBD Oil; Med Cannabis & Cannabinoids, **1**, 65-72

14 TM Attard, C Bainier, M Reinaud, A Lanot, SJ McQueen-Mason, AJ Hunt, Utilisation of Supercritical Fluids for the Effective Extraction of Waxes and Cannabidiol (CBD) from Hemp Wastes; Industrial Crops and Products, 2018 Feb 1, **112,**38-46

15 R Deidda, HT Avohou, R Baronti, PL Davolio, B Pasquini, M Del Bubba, C Hubert, P Hubert, S Orlandini, S Furlanetto, 2019, Analytical Quality by Design: Development and Control Strategy for a LC Method to Evaluate the Cannabinoids Content in Cannabis Olive Oil Extracts; Journal of Pharmaceutical and Biomedical Analysis, Mar 20, **166,** 326-335

16 S Marzorati, D Friscione, E Picchi, L Verotta, 2020, Cannabidiol from Inflorescences of *Cannabis sativa L*: Green Extraction and Purification Processes; Industrial Crops and Products, Nov 1, **155,** 112816

17 D Fiorini, S Scortichini, G Bonacucina, NG Greco, E Mazzara, R Petrelli, J Torresi, F Maggi, M Cespi, 2020, Cannabidiol-Enriched Hemp Essential Oil Obtained by an Optimized Microwave-assisted Extraction Using a Central Composite Design; Industrial Crops and Products, Oct 15, **154,** 112688

18 T Moreno, F Montanes, SJ Tallon, T Fenton, JW King, 2020, Extraction of Cannabinoids from Hemp (*Cannabis sativa L*) Using High Pressure Solvents: an Overview of Different Processing Options; The Journal of Supercritical Fluids, **2,** 104850

19 P Wu, Method for the Extraction of Cannabidiol (CBD) from Industrial Cannabis Sativa; China, CN10304994 A 2019-10-08

20 J Liu, J Fan, W Zhai, Cannabidiol (CBD)-based Extraction Method of Smoke Oil from Cannabis sativa; China, CN119819435 A 2020-02-21

21 Z Wang, SL Lui, FB Zhigao, L Kong, Process for Treating Industrial Cannabis Leaves with Microorganisms to Increase Extraction Rate of Cannabidiol; China, CN110041172 A 2019-07-23

22 D Yao, L Wan, D Yao, Y Li, Method of Extracting Cannabidiol (CBD) from Industrial Cannabis Sativa; China, CN1105657 A 2019-08-23

23 F Brusa, F Baratta, Method for the Extraction of d-9-tetrahydrocannabinol and Cannabidiol from Cannabis Inflorescences; European Patent Organisation, EP3666280 A1 2020-06-17

24 K Wang, Y Xu, Y Gao, H Wang, J Yu, Extraction and Separation Method of Cannabidiol (CBD) with High Purity; China, CN108314608 A 2018-07-24

25 JS Held, K Stanis, Extraction of Compounds from Cannabis; World Intellectual Property Organisation, WO2018125857 A1 2018-07-05

26 Y Luan, S Zheng, Z Li, X Li, Method of Extracting and Separating Cannabidiol from Cannabis Sativa; China, CN110066216 A 2019-07-30

27 T Verzura, B Blackman, Methods for the Extraction of Botanical Drug Substances Comprising Cannabinoids for use in Treatment of Chronic Pain and Other Disorders; United States, US20160106705 A1 2016-04-21

28 Y Gaoni, R Mechoulam, Isolation, Structure and Partial Synthesis of an Active Constituent of Hashish; Journal of the American Chemical Society, 1964 Apr, **86(8),** 1646-7

29 BR Martin, R Mechoulam, RK Razdan, 1999, Discovery and Characterization of Endogenous Cannabinoids; Life Sciences, Jul 9, **65(6-7),** 573-95

30 LO Hanuš, SM Meyer, E Muñoz, O Taglialatela-Scafati, G Appendino, 2016, Phytocannabinoids: a Unified Critical Inventory; Natural Product Reports. **33(12),** 1357-92

31 MJ Barratt, K Seear, K Lancaster, 2017, A Critical Examination of the Definition of "Psychoactive Effect" in Australian Drug Legislation; International Journal of Drug Policy, **1,40,** 16-25

32 WHO, Management of Substance Abuse, Terminology and Classification; https://www.who.int/substance_abuse/terminology/psychoactive_substances/en/ (Accessed 10.01.2021)

33 Psychoactive Substances Act 2016, UK Public General Acts2016 c2; http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted (Accessed 10.01.2021)

34 MJ Walker, 2019, Food and Feed Law: Compendium of UK Food and Feed Legislation with Associated Context and Changes during July – September 2019; Section 2.16 Psychoactive substances, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857812/Foodfeedlaw_July_Sept2019_final.pdf (Accessed 11.01.2021)

35 Home Office, 2016, Circular 004/2016: Psychoactive Substances Act 2016; https://www.gov.uk/government/publications/circular-0042016-psychoactive-substances-act-2016 and Forensic Strategy https://www.gov.uk/government/publications/circular-0042016-psychoactive-substances-act-2016 (Accessed 11.01.2021)

36 Advisory Council on the Misuse of Drugs, (ACMD), 2016; ACMD Review of Alkyl Nitrites ("poppers"), https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/508179/Poppersadvice.pdf (Accessed 11.01.2021)

37 United Nations Treaty Collection, https://treaties.un.org/pages/ViewDetails.aspx?src=IND&mtdsg_no=VI-18&chapter=6&clang=_en (Status as at 24th October 2020, viewed 24th October 2020), and see https://www.unodc.org/pdf/convention_1961_en.pdf (viewed 24th October 2020)

38 UN Commission on Narcotic Drugs, December 2020, Press Statement – 2 December 2020; CND Votes on Recommendations for Cannabis and Cannabis-Related Substances https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_63Reconvened/Press_statement_CND_2_December.pdf, and see also the Summary Note by the Secretariat https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_62Reconvened/ECN72020_CRP19_V2006823.pdf (Accessed 11.01.2021)

39 Misuse of Drugs Act 1971, c 38 to which there have been many amendments, a version correct to the date indicated is available at https://www.legislation.gov.uk/ukpga/1971/38/contents (accessed 24th October 2020)

40 Misuse of Drugs Regulations 2001, SI 3998, which has been amended many times, a version updated with amendments is available (correct to 24th June 2020) at https://www.legislation.gov.uk/uksi/2001/3998 (Accessed 25th October 2020)

41 Advisory Council on the Misuse of Drugs, ACMD, 2016, Phytocannabinoids, A Review of the Generic Definition, https://www.gov.uk/government/publications/plant-cannabinoids-acmd-report (Accessed 18.01.2021)

42 The Misuse of Drugs (Amendments) (Cannabis and Licence Fees) (England, Wales and Scotland) Regulations 2018, No 1055, and see for details of the policy background the Explanatory Memorandum to these Regulations.

43 See, for example, The Electronic Medicines Compendium (emc), Summary of Product Characteristics, Sativex Oromucosal Spray; https://www.medicines.org.uk/emc/product/602 (accessed 27th October 2020)

44 See, for example, The Electronic Medicines Compendium (emc), Summary of Product Characteristics, Epidyolex 100 mg/ml Oral Solution; https://www.medicines.org.uk/emc/product/10781/smpc (accessed 27th October 2020)

45 The National Institute for Health and Care Excellence (NICE), Nabilone; https://bnf.nice.org.uk/drug/nabilone.html (accessed 27th October 2020)

46 Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods; http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.327.01.0001.01.ENG&toc=OJ:L:2015:327:TOC

47 European Commission, Consultation Process on Novel Foods, CBD Isolate (purity >98%); https://ec.europa.eu/food/sites/food/files/safety/docs/novel-food_consult-status_cbd-isolate_uk-fsa.pdf (accessed 27th October 2020)

48 The European Commission Novel Foods Catalogue; https://ec.europa.eu/food/safety/novel_food/catalogue_en and

https://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm (accessed 27th October 2020)

49 Food Standards Agency, FSA, 2020, Cannabidiol (CBD) Guidance, Business Guidance on Cannabidiol (CBD) as a Novel Food. Last updated 31 December 2020; https://www.food.gov.uk/business-guidance/cannabidiol-cbd (Accessed 12.01.2021)

50 MJ Tallon, (2020) *Cannabis sativa* L and its Extracts: Regulation of Cannabidiol in the European Union and United Kingdom; *Journal of Dietary Supplements*, ***17*(5),** 503-516

51 Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), July 2020, Position Paper on the Potential Risk of CBD in CBD Food Products; https://cot.food.gov.uk/sites/default/files/2020-08/cbdpositionpaper290720_accessibleinadobepro.pdf (Accessed 12.01.2021)

52 R Pavlovic, G Nenna, L Calvi, S Panseri, G Borgonovo, L Giupponi, G Cannazza, A Giorgi, Quality Traits of "Cannabidiol Oils": Cannabinoids Content, Terpene Fingerprint and Oxidation Stability of European Commercially Available Preparations; Molecules, 2018 May, **23(5),** 1230

53 SHIMADZU, Application News, HPLC-018; The Determination of CBD and General Cannabinoid Content in Hemp Oils using HPLC with UV detection, (2018)

54 L Calvi, D Pentimalli, S Panseri, L Giupponi, F Gelmini, G Beretta, D Vitali, M Bruno, E Zilio, R Pavlovic, A Giorgi, Comprehensive Quality Evaluation of Medical *Cannabis Sativa* L. Inflorescence and Macerated Oils based on HS-SPME Coupled to GC–MS and LC-HRMS (q-exactive orbitrap®) Approach; Journal of Pharmaceutical and Biomedical Analysis, 2018 Feb 20, **150,** 208-19

55 Food Safety Authority of Ireland, FSAI, Survey Regulatory Issues with Hemp-based Food and Food Supplements on the Irish Market, Food Safety Authority of Ireland, Dublin, (2020); https://www.fsai.ie/news_centre/press_releases/cbd_food_supplement_survey_130220.html (Accessed 27th October 2020)

56 JP Liebling, NJ Clarkson, BW Gibbs, AS Yates, SE O'Sullivan, An Analysis of Over-the-Counter Cannabidiol Products in the United Kingdom; Cannabis and Cannabinoid Research, 2020 Apr 1

57 MHRA Guidance Note 8 March 2020, A Guide to what is a Medicinal Product, Appendix10 Guidance on Cannabidiol (CBD) Products; https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872742/GN8_FINAL_10_03_2020__combined_.pdf (Accessed 27th October 2020)

58 Home Office Drugs Licensing Guidance Collection; https://www.gov.uk/government/collections/drugs-licensing#applying-for-a-licence-companies (Accessed 27th October 2020)

59 Home Office Drugs Licensing & Compliance, Low THC Cannabis (Industrial Hemp) Licensing Factsheet- January 2020 v 1.4; https://www.gov.uk/government/publications/industrial-hemp-licensing-guidance (Accessed 27th October 2020)

60 Home Office Fact Sheet, Drug Licensing Factsheet- Cannabis, CBD and other Cannabinoids; https://www.gov.uk/government/publications/cannabis-cbd-and-other-cannabinoids-drug-licensing-factsheet (Accessed 27th October 2020)

61 M Walker and I Axford, 2021, Government Chemist Guidance, Analytical Limits for Controlled Cannabinoids in Specified Products Containing Cannabidiol (CBD), January 2021; https://www.gov.uk/government/publications/guidance-on-analytical-limits-for-controlled-cannabinoids

62 Kit Malthouse MP, Minister of State, Home Office to Professor Bowen-Jones, Chair ACMD, 11 January 2021; https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/955153/Letter_from_Kit_Malthouse_to_ACMD_chair.pdf (Accessed 03.02.2021)

63 P Skoczinski, M Carus, F Grotenhermen, B Beitzke, D Kruse, 2019, Limit and Guideline Values for THC (tetrahydrocannabinol) in Hemp Foods; Nova Institute for the European Industrial Hemp Association, https://eiha.org/media/2019/06/19-06-18_Limit-and-guideline-values-for-THC-in-hemp-foods.pdf (Accessed 12.02.2021)

64 German Federal Institute for Risk Assessment (*Bundesinstitut für Risikobewertung*, BfR), 2018, Tetrahydrocannabinol Levels are too High in Many Hemp-containing Foods – Health Impairments are possible No. 034/2018, BfR Opinion No 034/2018 of 8 November 2018, DOI 10.17590/20181128-152745-0; https://www.bfr.bund.de/cm/349/tetrahydrocannabinol-levels-are-too-high-in-many-hemp-containing-foods-health-impairments-are-possible.pdf (Accessed 12.02.2021)

65 European Commission, 2018, Draft Regulation Laying Down the Definition of Maximum Levels of tetrahydrocannabinol (THC) in Food; Notification Number: 2018/546/I (Italy), https://ec.europa.eu/growth/tools-databases/tris/en/index.cfm/search/?trisaction=search.detail&year=2018&num=546&mLang=EN (Accessed 24.01.2021)

66 GP Moss, Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB), in consultation with the IUPAC-IUBMB Joint Commission on Biochemical Nomenclature (JCBN); Cannabinoid Biosynthesis, available at https://www.qmul.ac.uk/sbcs/iubmb/enzyme/reaction/misc/cannab.html, hosted by Queen Mary University of London, (Accessed 1st November 2020)

67 C Citti, G Ciccarella, D Braghiroli, C Parenti, MA Vandelli and G Cannazza, 2016, Medicinal Cannabis: Principal Cannabinoids Concentration and their Stability Evaluated by a High Performance Liquid Chromatography Coupled to Diode Array and Quadrupole Time of Flight Mass Spectrometry Method; Journal of Pharmaceutical and Biomedical Analysis, **128**, 201-209

68 R Schoenfeld, 1980, Has Nomenclature Gone to Pot?; Journal of Chemical Information and Computer Sciences, **20(2),** 65-68

69 A Raman and A Joshi, The Chemistry of Cannabis, Chapter 3 in Cannabis The Genus Cannabis, Ed DT Brown; Harwood Academic Publishers, 1998, Taylor & Francis e-Library, 2003

70 MA El Sohly, D Slade, 2005, Chemical Constituents of Marijuana: the Complex Mixture of Natural Cannabinoids; Life Sciences, **22,78(5),** 539-48

71 CE Turner, MA Elsohly, EG Boeren, 1980, Constituents of *Cannabis Sativa* L, XVII, A Review of the Natural Constituents; Journal of Natural Products, **43(2),** 169-234 (and references therein)

72 R Brenneisen, Chemistry and Analysis of Phytocannabinoids and Other Cannabis Constituents, in MA El Sohly, (*Ed*.); Marijuana and the Cannabinoids, Springer Science & Business Media, 2007 (Table 1, 20)

73 U Claussen, F Von Spulak and F Korte, 1966, Zur Chemischen Klassifizierung von Pflanzen XXXI, Haschisch X, Cannabichromen, ein Neuer Haschisch-inhalts-stoff (Chemical Classification of Plants XXXI Hashish 10 Cannabichromene, a New Hashish Component); Tetrahedron, **22(4)**, 1477-1479

74 Y Gaoni and R Mechoulam, 1966, Cannabichromene, a New Active Principle in Hashish; Chemical Communications (London), **1**, 20-21

75 G Mazzoccanti, OH Ismail, I D'Acquarica, C Villani, C Manzo, M Wilcox, A Cavazzini and F Gasparrini, 2017, Cannabis Through the Looking Glass: Chemo- and Enantio-Selective Separation of Phytocannabinoids by Enantioselective Ultra High Performance Supercritical Fluid Chromatography; Chemical Communications, ***53*(91),** 12262-12265

76 Reference 5, Section 1: Chemistry, page 12 Figure 2

77 United Nations Office on Drugs and Crime, UNODC, Recommended Methods for the Identification and Analysis of Cannabis and Cannabis Products; UN, New York, 2009

78 CAMAG, Application Note, A-108.1; Identification and Quantification of Different Cannabinoids in *Cannabis sativa*, 2017

79 SHIMADZU, Application News, HPLC-018; The Determination of CBD and General Cannabinoid Content in Hemp Oils using HPLC with UV Detection, 2018

80 LA Ciolino, TL Ranieri, AM Taylor, Commercial Cannabis Consumer Products Part 1: GC–MS Qualitative Analysis of Cannabis Cannabinoids; Forensic Science International, 2018 Aug 1, **289,** 429-437

81 LA Ciolino, TL Ranieri, AM Taylor AM, 2018, Commercial Cannabis Consumer Products Part 2: HPLC-DAD Quantitative Analysis of Cannabis Cannabinoids; Forensic Science International, 2018 Aug 1, **289,** 438-447

82 S Zivovinovic, R Alder, MD Allenspach, C Steuer, 2018, Determination of Cannabinoids in *Cannabis sativa* L Samples for Recreational, Medical and Forensic Purposes by Reversed-phase Liquid Chromatography - Ultraviolet Detection; Journal of Analytical Science and Technology, **9(1),** 1-10

83 A Nemeškalová, K Hájková, L Mikulů, D Sýkora, M Kuchař, 2020, Combination of UV and MS/MS detection for the LC Analysis of Cannabidiol-rich Products; Talanta, 2020 Nov 1, **219,** 121250

84 L Nahar, A Onder, SD Sarker, 2020, A Review on the Recent Advances in HPLC, UHPLC and UPLC Analyses of Naturally Occurring Cannabinoids (2010–2019); Phytochemical Analysis, 2020 Jul, **31(4),** 413-57

85 G McRae, JE Melanson, 2020, Quantitative Determination and Validation of 17 Cannabinoids in Cannabis and Hemp using Liquid Chromatography-Tandem Mass Spectrometry; Analytical and Bioanalytical Chemistry, 2020 Nov, **412(27),** 7381-93

86 L Vaclavik, F Benes, M Fenclova, J Hricko, A Krmela, V Svobodova, J Hajslova and K Mastovska, 2019, Quantitation of Cannabinoids in Cannabis Dried Plant Materials, Concentrates, and Oils Using Liquid Chromatography–Diode Array Detection Technique with Optional Mass Spectrometric Detection: Single-Laboratory Validation Study, First Action 2018.11; Journal of AOAC International, **102(6),** 1822-1833.

87 Commission Recommendation (EU) 2016/2115 of 1 December 2016 on the Monitoring of the Presence of Δ9-tetrahydrocannabinol, its Precursors and Other Cannabinoids in Food; OJ 2.12.2016 L327/103

88 JF Crépault, 2018, Cannabis Legalization in Canada: Reflections on Public Health and the Governance of Legal Psychoactive Substances; Frontiers in Public Health, 2018 Aug 6, **6** 220