ACMD

Advisory Council on the Misuse of Drugs

‘Semi-synthetic’ Cannabinoids: Cannabinoids related to tetrahydro-cannabinol and cannabidiol

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1. Introduction

1.1. This report describes a group of compounds that are similar in chemical structure to tetrahydrocannabinol (THC), one isomer of which, Δ9-THC, is the main psychoactive chemical found in the cannabis plant. Like Δ9-THC, many of these compounds are psychoactive. Some are semi-synthetic, that is to say produced by alteration of the chemical structure of a naturally occurring compound, usually cannabidiol (CBD). For this reason, the compounds are usually referred to in the literature as 'semi-synthetic cannabinoids' (SSCs). Some similar compounds, however, can be made using either a semi-synthetic or a fully-synthetic approach, while others can only be made using fully-synthetic methods. For simplicity the term 'semi-synthetic cannabinoids' is used in this report for all of these compounds. The report also discusses tetrahydrocannabinol acid (THCA), which is a naturally occurring compound (phytocannabinoid) found in the cannabis plant.

1.2. CBD itself is not psychoactive and does not appear to have misuse potential [WHO, 2017]. It is not a controlled drug via the Misuse of Drugs Act 1971 (MDA) and is not subject to the provisions of the Psychoactive Substances Act 2016 (PSA) in the United Kingdom (UK). Manipulation of the structure, however, can produce various SSCs that may not yet be under international control, but that have similar psychoactive properties to tetrahydrocannabinols, especially Δ9-THC. In the UK, Δ9-THC is controlled as a Class B substance by virtue of a generic control of cannabinol derivatives within the MDA (see para 4.9 of this report) and is similarly listed in Schedule 1 of the Misuse of Drugs Regulations of 2001 (MDR).

1.3. Two major factors have encouraged the recent emergence of SSCs into recreational drug markets:

(a) an oversupply of CBD for the commercial market, in part caused by the relaxation of legislation relating to hemp production in the USA in 2018 [UNODC, 2024a]. This could be further exacerbated by a recent increase in the Δ9-THC content allowed in hemp in the European Union [EUDA, 2024a].

(b) recent restrictions on the international availability of potent and fully-synthetic cannabinoid receptor agonists (SCRAs) from Chinese manufacturers following their generic legal control by the Chinese government in 2021. Further information about SCRAs is available in previous ACMD reports [ACMD, 2020a; ACMD, 2023].

1.4. CBD can be extracted from legally-cultivated low-THC cannabis (hemp) and used as a starting point for the synthesis of Δ9-THC or other cannabinoids. An important example is hexahydrocannabinol (HHC), a compound that (unlike most fully synthetic SCRAs) is structurally similar to Δ9-THC, but which (until recently) was not legally controlled in many countries. HHC is currently not controlled via the MDA in the UK, but, as a psychoactive substance, would be captured by the PSA.

1.5. HHC was first detected in drug markets in the United States of America (USA) in 2021 and has subsequently been identified in many countries internationally including in the majority of European Union member states. It was initially trafficked to Europe from the USA, but there is evidence of more recent manufacture within Europe. Although HHC has been described as a phytocannabinoid, as it is present naturally in the cannabis plant, it is only found there in very low concentrations [UNODC, 2024a].

1.6. Following manufacture of HHC, further modifications can be made, including acetylating HHC to form HHCO-acetate, which has alleged increased potency.

1.7. Cannabinoids with different side-chain lengths cannot be formed from CBD. They are instead synthesised from commonly available and inexpensive precursors. HHC itself can be synthesised by combining the chemicals citronellal and olivetol. Replacing the olivetol with materials with different side-chains results in other variants (homologues) with differing side-chain lengths, such as hexahydrocannabiphorol (HHCP), with a seven-carbon side-chain, which is alleged to be significantly more potent than Δ9-THC. As these compounds are not developed from cannabis-derived natural materials, technically they are fully synthetic rather than semi-synthetic cannabinoids.

1.8. Related variants of CBD have appeared in recreational drug markets internationally [Janssens et al., 2024] and are also available for purchase online in the UK. The most commonly encountered example is tetrahydrocannabidiol (H4-CBD), which is reported to bind only weakly to CB1 receptors [Ben-Shabat et al., 2006], although user fora have suggested mild cannabis-like effects from use.

1.9. A compound structurally related to Δ9-THC that is not currently controlled via the MDA is THCA. This is included in this review because of its structural similarity and ease of conversion to THC and its recent detection in seizures of crystals and in vape canisters in the UK. Although not itself psychoactive and not currently controlled via the MDA, THCA is converted easily to psychoactive Δ9-THC by application of heat (pyrolysis), such as by smoking or vaping.

1.10. This review has been conducted to examine the current illicit use of SSCs and THCA in the UK with the aims of:

- identifying the specific compounds causing (or appearing capable of causing) health and social harms, including examples that are not captured by the current generic definition for cannabinoids;
- documenting available evidence on the pharmacology, health, and social harms of these compounds;
- considering the appropriate classification of currently uncontrolled examples under the Misuse of Drugs Act 1971.

2. Legitimate Use

2.1. There are some licensed medicines that contain cannabinoids related to those under consideration in this report:

Epidyolex® oral solution (Class B, Schedule 5) contains cannabidiol (CBD), but is scheduled via the MDR because it may also include a low concentration of Δ9-THC as an impurity [Home Office, 2020]. It is licensed in the UK for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) or tuberous sclerosis complex.

Sativex® oromucosal spray (Class B, Schedule 4 Pt 1), containing CBD and Δ9-THC, is licensed in the UK for symptom improvement in adults with moderate-to-severe spasticity due to multiple sclerosis.

Dronabinol, a medicine containing a synthetic form of the most active stereoisomer of Δ9-THC, is licensed in some other countries. For example, in the USA dronabinol (*Marinol®*) is licensed for the treatment of anorexia and weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS) and of nausea and vomiting associated with cancer chemotherapy in patients unresponsive to conventional antiemetic treatments. Although not currently licensed in the UK, dronabinol can be imported for prescription on a named patient basis and is listed in the MDA and MDR as a Class B and Schedule 2 compound, respectively.

Cannabis-based products for medicinal use (CBPMs)[1] in humans remain listed in Class B of the MDA but were moved to Schedule 2 of the MDR, with additional access and administration restrictions, in 2018. This allows the supply of either an investigational medicinal product for use in a clinical trial in humans, or a medicinal product with a marketing authorisation, under either the prescription or direction of a clinician on the General Medical Council's Specialist Register. The Regulations prohibit smoking of cannabis or cannabis-based products for medicinal use [Home Office, 2018].

2.2. Other than those discussed above, there are no medicinal products licensed in the UK containing other cannabinoids discussed in this report and the Medicines and Healthcare products Regulatory Agency (MHRA) have confirmed that they are not aware of any clinical trials, licensed or pending licensing applications or import license applications for any of them. The MHRA, however, is not made aware of unlicensed medicines being manufactured in the UK. The presence of some of these compounds in small amounts in CBPMs cannot be excluded and neither can the possibility that they (or related compounds) might be developed for therapeutic use in the future [Ujváry, 2024]. Potential indications include nausea and vomiting, pain,

[1] The UK government has defined "a cannabis-based product for medicinal use in humans" as a preparation or other product, other than one to which paragraph 5 of part 1 of Schedule 4 applies, which (a) is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers); (b) is produced for medicinal use in humans; and (c) is (i) a medicinal product, or (ii) a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product;".

inflammation, muscle spasticity and cancer [Abrahamov et al., 1995; Thapa et al., 2010; Rock et al., 2013; Moreno-Sanz, 2016; Persson et al., 2024].

2.3. The ACMD is not aware of other legitimate uses for SSCs or THCA, except as reference standards for laboratory analysis or for research.

2.4. Industrial hemp is grown to produce fibre and/or seeds from plant varieties intended to have a much lower THC content, rather than for any psychoactive or therapeutic effect. Products made from industrial hemp have a wide range of legitimate industrial uses, including in the construction, paper and textiles industries, and could potentially have environmental benefits through promoting carbon capture.

3. Chemistry

3.1. The term semi-synthetic cannabinoids (SSCs) now encompasses compounds that can be synthesised from naturally occurring phytocannabinoids, but also includes close structural analogues that are chemically synthesised from other material. They are structurally unrelated to the synthetic cannabinoids (SCs), sometimes also called synthetic cannabinoid receptor agonists (SCRAs), that are commonly referred to as 'Spice'. Some important examples of SSCs are listed in Annex A, together with acronyms, chemical names and structures.

3.2. SSCs are closely related in structure to Δ9-THC, with some of the simplest analogues being manufactured directly from Δ9-THC or (more commonly) from readily available CBD. The chemical modifications are typically straightforward, using standard, widely available chemicals and give access to a range of psychoactive compounds [Caprari et al., 2024; UNODC, 2024a].

3.3. Treatment of CBD with acid results in a mixture of the natural phytocannabinoid Δ9-THC, along with the semi-synthetic compound Δ8-THC, with one or other being formed in greater amounts depending on the precise conditions used [Ujváry, 2024].

3.4. Hydrogenation of either Δ9-THC or Δ8-THC (or a combination of the two) provides HHC as a mixture of the *R*- and *S*- isomers at C9. This is one of the simplest routes to HHC. However, there are also a variety of simple, fully-synthetic routes, for example from olivetol plus citronellal. If necessary, the fully-synthetic approach can be used for the stereoselective synthesis of the individual 9*S* and 9*R* isomers, with the latter having the more potent cannabinoid activity [Russo et al., 2023; Ujváry, 2024]. Of note, the ratio of *R* to *S* HHC isomers appears consistent within different containers of the same batch of marketed drug product, potentially providing a method for batch identification [Janssen et al., 2024].

3.5. Hydrogenated forms of CBD, such as H2-CBD and H4-CBD, are also being marketed [EMCDDA, 2023], with the latter reported to act as a CB2 receptor agonist [Janssens et al., 2024]. It also has measurable binding at CB1 receptors [Ben-Shabat et al., 2006; Morales et al., 2017], but it does not appear to activate these receptors. Anecdotal reports from users of H4-CBD have reported mild effects "like a 2:1 CBD:THC blend".

3.6. The availability of synthetic routes to HHC and Δ9-THC also allows for the production of analogues where the alkyl side-chain has been altered. This is achieved by replacing olivetol with materials having different side-chain lengths. Of these analogues, compounds having a 6 (e.g. HHCH) or 7 (e.g. HHCP) carbon side-chain are reported to be more potent than those with the standard 5 carbon side-chain [Caprari et al., 2024; Ujváry, 2024]. Compounds with 8 (e.g. HHC-C8) or 9 carbon side chains (e.g. HHC-C9) have also recently been identified in illicit drug markets.

3.7. The phenolic hydroxyl group present in all SSCs can easily be derivatised, with acetates already being encountered, for example Δ9-THCO-acetate, HHCO-acetate and HHCPO-acetate. The delayed onset of activity of these acetyl derivatives may indicate a requirement for hydrolysis back to the parent phenol before cannabinoid activity occurs. Other esters and ethers have been detected in the USA and elsewhere and these might be expected to display different rates of onset and duration of activity [Caprari et al., 2024; Ujváry, 2024].

3.8. THCA is a phytocannabinoid, i.e. it is naturally present in varying amounts in the cannabis plant. Whilst it is not psychoactive in itself, it is gradually decarboxylated to Δ9-THC during the process of drying the plant. This decarboxylation is accelerated by the application of heat in the range 105 to 120 ºC, such as during smoking or vaping or by cooking of cannabis edibles, so that Δ9-THC is then delivered directly to the user. As such, THCA can be considered a Δ9-THC precursor.

3.9. Pure THCA forms white crystals ('diamonds'). Two isomers of THCA are recognised, THCA-A (2-COOH-THC), which predominates in the cannabis plant, and THCA-B (4-COOH-THC), which is more stable and crystallises more easily [McPartland et al., 2017].

3.10. 11-Hydroxy-THC is a well-known and active metabolite of Δ9-THC with pronounced Δ9-THC-like clinical effects [Lemberger et al., 1973]. The activity of 11-hydroxy-THC at CB1 receptors and *in vivo*, in mice, also confirms a THC-like profile [Zagzoog et al., 2022]. Likewise, 11-hydroxy-HHC other 11-hydroxy analogues, such as 11-hydroxy-HHC-DMH (HU-243), are also known to be potent CB1 agonists [Ujváry, 2024]. All are accessible by a variety of synthetic methods, though these tend to involve a multistep synthesis, even when starting from related cannabinoid structures.

3.11. Variants of THC, where the double bond is moved (e.g. Δ8-THC), where the side-chain is a different alkyl chain (e.g. THCH, THCP), involving the formation of ethers or esters (e.g. THCO-acetate) or combinations of these changes (e.g. THCPO-acetate) are all covered by the current UK generic control. In contrast, the hexahydro variants such as HHC, HHCO-acetate and HHCPO-acetate are not covered by the current generic control (see below) and neither are 11-hydroxy derivatives or acids such as the THCA isomers.

4. Current Legal Status

International conventions

4.1. The cannabis plant and derived substances such as cannabis resin are listed in Schedule 1 of the 1961 United Nations Single Convention on Narcotic Drugs, while some individual cannabinoid chemicals are listed in the 1971 United Nations Convention on Psychotropic Substances [UNODC, 2016].

4.2. Δ9-Tetrahydrocannabinol (Δ9-THC), which has a double bond between the C9 and C10 atoms of the cyclohexene ring, is listed in Schedule 2 of the 1971 Convention, as is dronabinol, one of the stereoisomers of pure Δ9-THC, which has medicinal indications. However, the five isomers of Δ9-THC that have the double bond at the five other locations within the cyclohexene ring (including Δ8-THC), together with a sixth isomer with the double bond outside the ring between the 9- and the 11- carbon atoms, are listed by name in Schedule 1 of the Convention. Two closely-related variants of THC, 1,1-dimethylheptyl (DMHP) and parahexyl, are also listed in Schedule 1. Both compounds have the double bond of the cyclohexene ring at the 6a(10a) position and have the pentyl sidechain of THC replaced by DMHP and by hexyl (parahexyl) [UNODC, 2016].

4.3. Stereoisomers of 1971 Convention Schedule 1 substances are automatically included and the Schedule 2 entry for Δ9-THC specifically includes its stereochemical variants.

4.4. The hydrogenated derivative of THC, HHC was placed under Schedule 2 of the 1971 Convention by the Commission on Narcotic Drugs in March 2025, having been reviewed [WHO, 2024a] and recommended for inclusion by the WHO's Expert Committee on Drug Dependence [WHO, 2024b].

4.5. All signatories to the UN's drug conventions, such as the United Kingdom, are generally obliged to control appropriately the listed materials under their national legislation[2].

4.6. CBD and its derivatives are not listed in the UN conventions.

National control of cannabinoids

United Kingdom

4.7. Cannabis itself is a Class B controlled drug under the MDA, listed in Schedule 1 of the MDR 2001) and designated under the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015. Cannabis-based products for medicinal use in

[2] Control under the MDA may not be necessary if it can be demonstrated that the broad aims of the Convention are still being met, no other obligations on international control decisions are being undermined and there is a clear rationale as to why control under the MDA is not appropriate. There is scope for the UK to conduct other regimes to provide controls that would also (dependent on substance) appear convention compliant (such as leaving those substances subject to the provisions of the PSA).

humans (CBPMs) were introduced under Schedule 2 to the MDR in 2018 [Home Office, 2018].

4.8. Licences are available for the cultivation and use of non-controlled parts of cannabis plants (seeds and fibre/mature stalk only) with a low Δ9-THC content for legitimate industrial purposes. These include the production of hemp fibre or the obtaining of seeds, which can then be pressed for their oil [Home Office, 2024]. The threshold for the definition of low Δ9-THC has been 0.2% by dry weight, but the ACMD has recently supported the proposal that this threshold should be increased to 0.3%, to bring the UK in line with the situation in many other countries including the European Union, USA, Canada and China [ACMD, 2024a]. Cultivation of cannabis for other purposes, for example, for use in production of cannabis-based medicines, requires a controlled drug licence.

4.9. The MDA includes in Part II of Schedule 2 (Class B drugs) a generic control of cannabinol derivatives, using the following wording

"..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."

4.10. This means that, for example, Δ8-tetrahydro variants are controlled in the same way as Δ9- materials and that variants with alkyl chains other than pentyl at the 3-position, such as tetrahydrocannabihexol (THCH) which has a six-carbon hexyl chain and tetrahydrocannabutol (THCB, also known as JWH-130), which has a four-carbon butyl chain, are also controlled.

4.11. In addition, Paragraph 2 of Part II of Schedule 2 of the MDA extends control to include esters and ethers of controlled cannabinol derivatives, so materials such as THC acetate (THCO-acetate) and THC methyl ester (THCM) are also controlled.

4.12. Cannabinol itself is listed separately within the MDA as a Class B drug, while the MDR lists cannabinol and its derivatives as Schedule 1 materials, with the exception of dronabinol, which is listed in Schedule 2.

4.13. One HHC variant listed individually in the MDA is 3-(1,1-dimethylheptyl)-11-hydroxy-hexahydrocannabinol, also known as HU-243, which is a potent CB1 receptor agonist. Other hexahydro derivatives of cannabinol and derivatives of cannabidiol (CBD) are not covered by the current MDA generic but, if psychoactive, are subject to the PSA.

4.14. Acid forms of cannabinoids, such as the THC acids THCA-A and THCA-B, are not named in the MDA and are also not covered by the UK cannabinoid generic and so are not controlled by the MDA. THCA has long been known as a non-psychoactive precursor to THC within the cannabis plant; as the plant itself is controlled, it was not thought necessary to control THCA specifically. Although acting as direct precursors to cannabinoids when their carboxylic groups are lost, if they do not of themselves demonstrate significant psychoactivity (see para 5.9), they will also not be subject to the provisions of the PSA.

4.15. The 11-hydroxy (11-OH) variants of THC, which have a hydroxyl group attached to the methyl group at the 11-position are not covered by the generic control. These were previously only regarded as potently active metabolites of cannabinoids, but are now encountered in vaping products, especially 11-OH-THC. One 11-OH variant,

HU-210 (the 11-OH-3-dimethylheptyl derivative of THC) is already specifically named as a Class B drug in the MDA and related materials can also be expected to be strong agonists. A summary of compounds detected in Europe and/or the UK and their current legal status under the MDA can be found later in this report in Table 1 in the section on 'UK prevalence'.

Other countries

4.16. As the number of psychoactive cannabinol and cannabidiol variants being identified in the drug market has increased, other countries have expanded their controls to address them by naming specific cannabinol and cannabidiol variants as being controlled and, in some cases, introducing their own generic controls. Examples of other countries' recent introduction of controls on such materials by name are listed in Annex B.

4.17. Broad generic controls on THC-related materials have been introduced by, for example, France, Germany and Switzerland. The French generic, enacted in June 2024, is based on a benzo[c]chromene core, while the German and Swiss generics, introduced at around the same time, are based on the closely related benzo[c]chromen-1-ol core. In France, acid forms of cannabinoids, such as THCA-A and THCA-B, are controlled by virtue of the French generic control (see Annex B). Details of these generic controls, which are facilitated by those countries' ability to include diagrams of chemical structures within their legislation, are also included in Annex B.

4.18. In the USA, measurements to assess the THC content of herbal cannabis to establish whether the material qualifies as being low-THC cannabis (hemp) have to include both the ∆9-THC and the ∆9-THCA in order to allow for the potential conversion of ∆9-THCA to ∆9-THC in storage and fermentation, or by heating [Moreno-Sanz, 2016]. The total ∆9-THC content is to be either measured post-decarboxylation or calculated by measuring both the THC and the THCA and including the THCA quantitation after applying a conversion factor of 0.877 to allow for the proportion of the weight of ∆9-THCA lost in the decarboxylation process, based on the molecular weights of the two materials (US Agriculture Improvement Act, 2018).

5. Pharmacology and toxicology

5.1. Based on the close similarity in chemical structure to the naturally occurring cannabinoid Δ9-THC, the main psychoactive constituent of the cannabis plant, the pharmacology and toxicology of SSCs is expected to be similar. Exogenous cannabinoid administration may result in toxicity as a consequence of overstimulation of the endocannabinoid system (see below) leading to neurotransmitter modulation [Kelly & Nappe, 2023].

5.2. A key factor associated with the emergence of SSCs, and a major difference when considering the conventional (smoked) use of recreational cannabis, is the presentation of different usage forms. As opposed to smoking cannabis, where it is difficult to inhale very substantial doses and users are often familiar with anticipated effects, other usage forms, such as edible materials and vaping cartridges, do not pose such inherent limitations in dosing. One factor is the high concentrations of the cannabinoid(s) that may be involved. In addition, the slower onset of effects after ingestion of edibles makes dose titration more challenging and may result in users re-dosing before the full effects of the original dose have been experienced.

Δ9-THC

5.3. Δ9-THC exerts its pharmacological effects by stimulating G protein-coupled type 1 (CB1) and type 2 (CB2) cannabinoid receptors via binding to their primary functionally important (‘orthosteric’) binding sites. Intoxicating effects of Δ9-THC are primarily mediated via CB1 receptors, which are especially abundant in the brain (frontal cortex, hippocampus, basal ganglia, hypothalamus, cerebellum) and spinal cord [Chayasirisobhon, 2020] and are located on both inhibitory GABAergic and excitatory glutamatergic neurons. CB1 receptor activation results in a suppression of cyclic AMP production and inhibits the release from the neuron of other neurotransmitters. It also results in Gi/o protein-mediated activation of A-type and inwardly rectifying potassium currents, and inhibition of N-type and P/Q-type calcium currents [Pertwee & Cascio, 2015]. Δ9-THC is a partial agonist at CB1 receptors, and therefore cannot fully activate the receptor, in contrast to some recently encountered fully-synthetic cannabinoid receptor agonists [Ligresti et al., 2016; Iversen, 2019; Akram et al., 2019]. CB2 receptors are found on white blood cells and other immune cells and are thought to be involved in modulating immune function. CB2 receptors are also found on glial cells and their expression in the brain is increased in unhealthy states [Chayasirisobhon, 2020]. Both CB1 and CB2 receptors are also found widely in the cardiovascular system [Iversen, 2019].

5.4. As well as being active in its own right, metabolites of Δ9-THC also have cannabinoid activity. For example, 11-OH-THC, which is formed as a result of hepatic Δ9-THC metabolism, penetrates the blood–brain barrier more easily than Δ9-THC and has pronounced activity at the CB1 receptor. It appears in higher concentrations in the blood after oral ingestion of THC compared to smoking [Huestis, 2007; Zagzoog et al., 2024].

5.5. There are natural substances within the body (endocannabinoids) that bind to CB1 and CB2 receptors (cannabinoid 'ligands'), specifically N-arachidonoylethanolamine (AEA, also known as ‘anandamide’) and 2-arachidonoylglycerol (2-AG). The precise physiological role of these ligands and their interaction with cannabinoid receptors is not yet fully understood.

5.6. In addition to orthosteric binding sites for agonists like Δ9-THC, CB1 receptors also contain so-called 'allosteric' binding sites. Several small molecule allosteric modulators have now been identified, that can affect (either positively or negatively) the binding of and/or the response to an orthosteric agonist.

5.7. Adding to the complexity of their pharmacology, cannabinoids can also interact with a wide range of other receptor systems, transporters, enzymes and channels, other than CB1 and CB2 receptors. For example, the orphan G protein-coupled receptor-55 (GPR55) is activated by Δ9-THC and other cannabinoids [Lauckner et al, 2008], whilst CBD provides functional antagonism and this may be relevant to its anticonvulsant effects [Gray, 2020]. A further example is the transient receptor potential vanilloid 1 (TRPV1) receptor, which is expressed on sensory neurons and is involved in pain perception. Δ9-THC has also been shown to act as an allosteric modulator of μ and δ opioid receptors located in neuronal membranes. These various effects may have relevance to the analgesic actions of cannabinoids. A detailed account of cannabinoid pharmacology is beyond the scope of this report, but reviews are available elsewhere [Chayasirisobhon, 2020].

5.8. The rate of absorption of Δ9-THC depends on the route of exposure, with peak serum concentrations achieved in less than 30 minutes after inhalation and at 2-4 hours after ingestion. As a result, toxicity from ingestion appears later and can persist for longer. Due to its high fat solubility, Δ9-THC has a high volume of distribution and accumulates in fat, especially after chronic use. Δ9-THC also crosses the placenta and concentrates in breast milk [Kelly & Nappe, 2023].

Cannabidiol (CBD)

5.9. Cannabidiol (CBD), unlike Δ9-THC, is not psychoactive and does not exhibit effects indicative of any abuse or dependence potential [WHO, 2017]. It does, however, have beneficial anti-epileptic effects in the treatment of some specific childhood epilepsy syndromes such as Dravet syndrome and Lennox-Gastaut syndrome (LGS). It has been suggested that CBD may act as an allosteric modulator of CB1 receptor function [ACMD, 2021].

THCA

5.10. Studying the pharmacology of THCA is challenging because spontaneous decarboxylation results in contamination with Δ9-THC, which then contributes to observed effects. Taking this into account, THCA is reported to demonstrate very much lower binding affinity to CB1 and CB2 receptors than Δ9-THC and very weak agonist properties at the CB1 receptor [McPartland et al., 2017]. Other studies, however, have reported more potent CB1 receptor binding and several animal studies have suggested peripheral cannabimimetic effects, but without central psychoactive effects [Rock et al., 2013; Moreno-Sanz, 2016]. This lack of central effects may be explained by the poor penetration of the blood brain barrier by THCA, likely due to effective exclusion by efflux transporters of the ATP-binding cassette family [Moreno-Sanz, 2016].

5.11. Both THC and THCA are found in oral fluid, blood and urine after smoking THCA preparations. The evidence indicates that the presence of THC results from decarboxylation during smoking and that little decarboxylation occurs within the body. THCA is metabolised to its 11-OH intermediate and then oxidised to the 11-carboxylic metabolite (THCA-COOH).

5.12. *In vitro* experiments have suggested other pharmacological effects of THCA at low micromolar concentrations that could have potential therapeutic value, such as activation of TRPA1 and TRPV4 channels and blockade of TRPM8 channels [Moreno-Sanz, 2016].

The emergence of SSCs

5.13. Besides THC and CBD, there are many other (psychoactive or non-psychoactive) constituents that may be present in cannabis products, including THC isomers (e.g. Δ8-THC, cis-Δ9-THC, etc.), homologues with shortened or elongated alkyl chains, analogues (e.g. HHC, HHCP, etc), CBD-type cannabinoids and many others [Janssens et al., 2024]. Agricultural selection has already been successful in generating strains that are exceptionally rich in minor phytocannabinoids. More recently, an oversupply of CBD-rich products has resulted in CBD being used to synthetically generate other cannabinoids [Ujváry, 2024].

5.14. The cannabinoids that can be derived following chemical conversion of natural products are being referred to here as SSCs. Some of these may be present at minor levels in natural cannabis (and may actually be considered 'hemp-derived'), others do not occur (or have not been found) naturally. Either way, the term SSCs is used here to refer to what can be referred to as 'natural cannabinoid-inspired products'.

5.15. Many of the SSCs bind to and modulate the activity of CB1 and/or CB2, as assessed via *in vitro* and/or *in vivo* testing. The extent to which this modulation takes place differs per compound and depends on the test used. When interpreting historical data, one should bear in mind that in not all instances the purity or composition of a preparation was detailed. In addition, different (in vitro) assays may yield different outcomes, depending on the read-out or assay principle used.

5.16. Compounds binding to CB receptors may act as agonists, antagonists (blocking receptor activation), or inverse agonists (reducing baseline levels of receptor activation). Pharmacological characterisation typically entails the derivation of efficacy and the potency. Efficacy refers to the extent to which the CB receptor can be activated (relative to a reference compound). For example, THC is a weak partial agonist relative to synthetic cannabinoids like CP-55,940. A compound's potency refers to the concentration at which the half-maximum effect is reached and is typically expressed as the EC50 (effective concentration resulting in 50% efficacy).

5.17. Limited information is available on the toxicokinetics of SSCs, which may vary with specific compound. Toxicological effects of illicitly obtained SSCs might also result from impurities of adulteration with other substances [Kelly & Nappe, 2023]

HHC

5.18. HHC is a THC analogue and one of the more prevalent SSCs. Two diastereomers can be distinguished, i.e. 9β-HHC (the *R* isomer) and 9α-HHC (the *S* isomer). Products available on the recreational drug market are mixtures of both isomers. While some studies have evaluated the effects of pure isomers, others have assessed the effect of mixtures, complicating interpretation. The available information on the pharmacology of HHC, described in more detail elsewhere [Graziano et al, 2023; EMCDDA, 2023; Ujváry, 2024; Nasrallah & Garg, 2024; Janssens et al., 2024, Persson et al., 2024; WHO, 2024a], is consistent with the following:

5.19. HHC binds to and is a partial agonist at human CB1 and CB2 receptors, with 9(*R*)-HHC having a higher affinity and being more potent than 9(*S*)-HHC at both receptors. Some assays also showed a higher efficacy for the 9(*R*) isomer [Nasrallah & Garg, 2024; Janssens et al., 2024; Persson et al., 2024].

5.20. *In vivo*, 9(*R*)-HHC is clearly the more active isomer [Andersson et al., 2011; EMCDDA, 2023]. It is currently not clear to what extent the active 11-OH metabolite contributes to activity *in vivo.*

5.21. While the intrinsic CB1 receptor activation potential of 9(*R*)-HHC may be higher than that of Δ9-THC (as assessed *in vitro*), this does not translate to the *in vivo* situation (animal models), where 9(*R*)-HHC is less-to-slightly-less potent than THC.

5.22. Limited information is available about the pharmacokinetics of HHC. Like other cannabinoids, including Δ9-THC, it is highly lipid soluble (calculated logP 7.93) and therefore likely to accumulate in fatty tissue and be readily absorbed and distributed through cellular membranes, including the blood–brain barrier [WHO, 2024]. Different time courses for the concentration-time curves of 9(*R*)- and 9(*S*)-HHC were observed in human volunteers after smoking a 50:50 mix. The 9(*R*)- isomer was absorbed more rapidly and achieved substantially higher concentrations than the 9(*S*)- isomer. Both isomers were eliminated with similar half-lives (1.3 and 1.6 h for the 9(*R*)- and 9(*S*)- isomers, respectively [Di Trana et al., 2024]). 11-OH-HHC can also be detected as a minor metabolite of Δ9-THC [Jørgensen et al., 2023].

5.23. Metabolism studies (*in vitro* as well as *in vivo*, from volunteers and cases) have demonstrated that HHC is subject to oxidative metabolism, resulting in the formation of several hydroxylated metabolites, including the active 11-OH metabolite. Not all studies reported 11-nor-9-carboxy-HHC (9*R*-HHCCOOH) as a major metabolite in urine [Schirmer et al., 2023; Di Trana et al., 2024; Kronstrand et al., 2024; WHO, 2024].

5.24. In a controlled self-administration experiment involving a single volunteer for each route, vaping 15 mg of HHC resulted in mild cannabimimetic effects that lasted for about 2 hours, but ingestion of 20 mg orally did not produce any noticeable effects [Schirmer et al., 2023]. Reports on the effects perceived by users reportedly using HHC suggest similar effects and adverse effects to those of Δ9-THC [Ferretti, 2023; Labadie et al., 2024].

5.25. Very limited information is available on the toxicology of HHC. Studies of racemic HHC demonstrated little evidence of mutagenicity, hERG[3] channel blockade, or human hepatocyte cytotoxicity. Potential cytotoxicity was observed in human lung fibroblasts, but only at very high concentrations (>10 μM) and was no more severe than with the control drug chlorpromazine [EMCDDA, 2023]. It should be noted that there may also be toxic effects from impurities or contaminants arising from the process of manufacture.

5.26. As for HHCP, the (*R*)-isomer is more active at the CB1 receptor than the (*S*)-isomer [Janssens et al., 2024]. The (*R*)-isomers of both HHC and HHCP exerted higher

[3] The human ether-a-go-go-related gene (hERG) encoded channel is important for cardiac repolarization.

maximal CB1 activity compared to Δ9-THC, making them potentially more harmful and relevant to monitor.

THC Isomers

5.27. Of the Δ9-THC isomers, Δ8-THC is undoubtedly the best known and has been studied in the greatest detail. It can be manufactured from CBD but is also present in small amounts in the cannabis plant [LoParco et al., 2023]. Other isomers include Δ6 (9(*S*)- Δ6a,10a-THC and 9(*R*)- Δ6a,10a-THC), Δ7 (9(*S*)- Δ 7-THC, 9(*R*)-Δ7-THC), Δ10 ((6a*R*, 9*S*)-Δ10-THC, (6a*R*, 9*R*)-Δ10-THC), Δ8-iso-THC, Δ4(8)-iso-THC and exo-THC.

5.28. Metabolism studies revealed that, similar to Δ9-THC, Δ8-THC also yields an active 11-OH metabolite. Like Δ9-THC, Δ8-THC and its 11-OH metabolite bind to CB1 receptors with a Ki (inhibitory constant for binding) in the nanomolar range. Δ8-THC also inhibits cAMP accumulation and produces cannabimimetic effects in animals [Tagen & Klumpers, 2022].

5.29. A recent *in vivo* study in human volunteers (oral and vaped Δ8-THC) revealed dosing-dependent psychoactive effects. Following oral administration to humans (in brownies), maximum effects of Δ8-THC were seen after about 3 hours. Following vaping, maximal effects occurred much more rapidly (within minutes). A higher dose was needed for Δ8-THC to exhibit similar effects to THC, and the effects following vaping were more marked than those following oral administration [Vandrey et al., 2023]. Consistent with this, regular users of Δ8-THC, Δ9-THC and CBD reported Δ8-THC had less intense effects compared to Δ9-THC but they also reported adverse effects less commonly [Bergeria et al., 2023].

5.30. Apart from Δ8-THC, most of the data available for the other isomers stems from relatively limited *in vitro* studies, evaluating the cannabinoid receptor activating potential of the isomers. In these studies, the THC isomers exhibited similar (e.g. Δ8-THC), reduced (e.g. Δ10-THC), or even lack of (e.g. Δ4(8)-iso-THC) CB1 activation, when compared to Δ9-THC. Exo-THC was characterised by a considerably higher efficacy than Δ9-THC, but with a low potency [Janssens et al., 2024].

THC Homologues with varying chain lengths

5.31. Multiple THC homologues have been reported, varying in the length of the typical carbon tail seen in natural cannabinoids. THC has a C5 tail, but homologues with C1, C2, C3, C4, C6, C7 or C8 tails have been reported. Most of these have only been evaluated using *in vitro* tests.

5.32. Shortening the tail (C1 to C4) results in reduced efficacy, while C6 and C8 tail-containing homologues of both Δ8- and Δ9-THC showed a similar or higher efficacy at CB1 receptors. Heptyl (C7)-containing homologues were less active than the corresponding C5 compounds [Janssens et al., 2024].

5.33. THCP has been shown to have a high CB1 receptor affinity and was shown to have cannabimimetic effects in the mouse tetrad assay [Citti et al., 2019].

HHC Homologues

5.34. As with THC homologues, the biological activity of HHC homologues varies with side-chain length. This activity is, as yet, not well characterised but it is clear that homologues with C5, C6 and C7 side- chain lengths are highly active CB1 receptor agonists [EMCDDA, 2023; Ujvary, 2023; Janssens et al., 2024].

5.35. Similar to observations for HHC, the 9(*R*)-isomer of HHCP was shown to be more potent at CB1 than the 9(*S*)-isomer. Both were partial agonists [Janssens et al., 2024; Persson et al., 2024].

5.36. HHCP is metabolised primarily by glucuronidation, hydroxylation and dehydrogenation. Mono or di-hydrogenated and glucuronide metabolites appear suitable as biomarkers for HHCP use [Lindbom et al., 2025].

SSC Ethers and acetates

5.37. The (*R*)-isomer of HHCO-acetate activated the CB1 receptor at lower potency compared to HHC and HHCP, while the (*S*)-isomer showed no activity [Persson et al., 2024].

5.38. Studies using hepatic microsomes, however, have shown that HHCO-acetate and HHCP-O are rapidly metabolised to HHC and HHCP, respectively. The data suggest that the activity of these esters can actually (primarily) be attributed to their hydrolysed equivalents [Lindbom et al., 2025].

5.39. Of potential toxicological relevance is that heating of acetates may lead to ketenes, which are reactive, alkylating compounds (see ‘Health Harms’ section).

6. Misuse

International perspective

6.1. The initial rise in availability of SSCs in the United States stems from the enactment of the US Agriculture Improvement Act of 2018, commonly known as the 2018 Farm Bill, which declared hemp, i.e. any product of the *Cannabis sativa* plant with a Δ9-THC concentration of no more than 0.3 percent, to be legal. Its passage into US law prompted mass production of CBD and encouraged its over-the-counter sale. The market for CBD products rapidly became saturated, prompting a fall in price and the use of surplus CBD to synthesise compounds similar in structure to THC that also have CB1 receptor activity [UNODC, 2024a].

6.2. Use may also have been encouraged by increasing recognition of the adverse health effects of potent and fully-synthetic cannabinoid receptor agonists (SCRAs) and recent restrictions on their international availability from Chinese manufacturers following their generic legal control in that country in 2021 [ACMD, 2023].

6.3. The earliest manufactured SSC to appear in the USA was Δ8-THC around September 2019. This compound was, at least initially, not considered by many suppliers to be a controlled (Schedule 1) compound in the USA because it was thought to fall under the definition of 'hemp'. Several other Δ8-THC homologues subsequently appeared, including Δ8-THCB, Δ8-THCH, Δ8-THCP and Δ8-THC-C8 [Janssens et al., 2024]. Subsequently, the US Drug Enforcement Administration (DEA) clarified that Δ8-THC was a controlled Schedule 1 material in the USA because it did not meet the hemp definition, not being a natural component of the cannabis plant. This prompted the search for other unscheduled SSCs that could be sold as legal alternatives to cannabis [Caprari et al., 2024; EMCDDA, 2023; Zawatsky et al., 2024; EUDA, 2024a].

6.4. HHC is a compound originally synthesised in 1940 [Adams et al., 1940; Todd, 1940] that can also be detected in the cannabis plant at very low concentrations (around 0.1%). It began to appear in US drug markets around September 2021 [European Commission, 2024]. It was first detected in Europe in May 2022 in a branded tincture containing HHC and cannabinol (CBN) seized by Danish police, which was being sold as a sleep aid (*CBN Night*). Since then, HHC has been sold openly in Europe as a ‘legal’ replacement for cannabis, with currently marketed products typically containing a mix of the 9(*S*)- and 9(*R*)-HHC isomers [EMCDDA, 2023; Ujváry, 2024].

6.5. More than 50 seizures of HHC-containing materials had been made in Europe by 2023 and HHC had been identified in a range of products in 24 European countries by February 2024 [EUDA, 2024]. These included low-THC cannabis flower, resin, liquid, sweets (gummies, marshmallows), other unspecified herbal material, liquids, disposable vapes, pens, e-liquids and e-liquid cartridges. Most HHC-containing vape cartridges fitted a range of commercially available e-cigarettes. Many HHC vapes were sold as branded products with attractive and brightly coloured designs, but unbranded products were also available. Cannabis flower fortified with HHC was also on sale with product names associated with popular cannabis strains such as *Afghan Kush, Amnesia, Bubble Gum Kush, Strawberry Kush, Pineapple Express* and *Purple Haze*. Associated marketing alluded to similar effects as obtained with the original THC strains. Large-scale seizures have included HHC-containing oils originating from the USA and low-THC cannabis flower containing HHC that looks like illicit

cannabis and has a similar cost [EMCDDA, 2023; EUDA, 2024; WHO, 2024; UNODC, 2024a]. Seizures of HHC made in 2022 included 47 kg of herbal material and 96 litres of HHC-containing liquids [EUDA, 2024a]. Concentrates being sold can have an HHC content as high as 50–70% [European Commission, 2024].

6.6. Following on from the appearance of HHC, other structurally related SSCs have also appeared in drug markets across the world, including in North America, Europe, South America and Southeast Asia [UNODC, 2024a]. The nine compounds identified in Europe by April 2024 were HHC, HHCO-acetate, HHCP, H4-CBD, Δ9-THCP, HHCH, Δ8-THCP, Δ9-THCB and 9-OH-HHC [Persson et al., 2024]. Further details of compounds detected in Europe, their dates of first identification in Europe and the UK and their current status under the UK MDA are shown in Table 1. For each group, compounds are listed by date of first detection in European countries reporting to EUDA, to illustrate the rapid evolution of compounds being identified.

6.7. HHCP was first notified in Europe in November 2022 by Slovenia and had been detected in four other European Union countries by March 2023 [EMCDDA, 2023; Lindbom et al., 2025].

6.8. In the United States, acetates of Δ8-THC and Δ9-THC, CBN, THCP, HHC, and HHCP were found in various ratios in vape products or concentrated oils [Ujváry, 2024].

6.9. The acetate of HHC, HHCO-acetate was first identified in Europe in a sample of plant material seized in Hungary in August 2022 [EMCDDA, 2023; Ujváry, 2024] and had appeared in at least three other European Union countries by March 2023, [EMCDDA 2023] where HHCO-acetate has been sold in bulk, in cartridges and as refill liquids for vaping [Ujváry, 2024].

6.10. There were 18 SSCs reported in a UNODC Early Warning Advisory between 2022 and 2024, out of a total of 40 synthetic cannabinoids identified in material seized internationally. Those compounds reported by the largest numbers of countries were HHC, HHCP, H4-CBD, Δ9-THCP and HHCO-acetate [UNODC, 2024b].

6.11. In Europe, SSC products have been sold in a range of ‘brick-and-mortar’ and online shops, particularly those specialising in selling low-THC cannabis, CBD products and vapes ('smoke shops'). Sales via the internet and even from vending machines also occur. Marketing material can make direct comparisons to the effects of cannabis [Persson et al., 2024; EMCDDA, 2023]. Suppliers claim that these products are legal, as well as being natural and organic, providing potentially misleading reassurance about their safety [Zawatsky et al., 2024]. Some are manufactured in the United States and imported, but there is also evidence of large-scale production within Europe [EUDA, 2024].

6.12. In Denmark, a prevalence study of SSCs in seized drug samples demonstrated an increase in numbers containing SSCs from the third quarter of 2021, with a further substantial increase in late 2022 and early 2023. Samples analysed included plant material (41%), edibles (27%), hashish (15%), concentrates (10%), e-cigarette products (6%) and dermal products (1%). Compounds identified in declining order of frequency were HHC, H4-CBD, Δ8-THC, HHCO-acetate, HHCP and THCP [Jørgensen et al., 2024].

6.13. In a paper submitted in April 2023 from Germany, the authors describe the detection of both 9(*R*)- and 9(*S*)-HHC in 17 of 321 serum or plasma samples taken from drivers

in Lower Saxony suspected of driving under the influence of cannabis. The concentration ratios of 9(*R*)- to 9(*S*)-HHC in these samples ranged from 1.6 to 2.8. Of note, immunological screening tests did not detect HHC, except when the concentration was high, neither did analogues such as H4-CBD cause cross-reactivity. The authors concluded that mass spectrometry (LC-MS/MS) is required for reliable detection, but samples may not be subject to that if initial screening by point-of-care testing is negative [Höfert et al., 2024; Kronstrand et al., 2024; WHO, 2024].

6.14. In the Czech Republic, the main reported problem associated with SSCs has been the sale of 'edibles' such as gummy bears, chocolate, cookies, and beverages containing an SSC such as HHC, HHCO-acetate or THCP [European Commission, 2024].

6.15. In Sweden, online interest in HHC increased substantially in the spring of 2023, as evidenced by increasing numbers of internet posts. Prior to July 2023, when they were controlled, HHC and HHC-P were widely available for sale over-the-counter in shops. After their legal control, there were increased sales of other analogues that remained uncontrolled, such as HHCO-acetate and THCP [Helander et al., 2024]. After January 2023, an increasing proportion of forensic samples submitted for routine cannabis screening that had provided a preliminary positive for cannabis use (THC-COOH) were subsequently confirmed negative by LC-MS/MS. These screening tests were shown to exhibit cross-reactivity with SSCs. Subsequently the samples were shown to contain HHCO-acetate, HHCH and THCP by LC-MS/MS [Helander et al., 2024]. Similarly, HHC or its metabolites were detected by LC-MS/MS in 32 of 145 (22%) blood samples that were collected from Swedes suspected of driving under the influence of drugs between January and May 2023. The samples used in this study screened positive for cannabis by ELISA but Δ9-THC, THC-COOH and 11-OH-THC were not subsequently detected by LC-MS/MS. The specific compounds identified were 9(*R*)-HHC-COOH (32 samples), 9(*R*)-HHC (24), 9(*S*)-HHC (15) and 11-OH 9(*R*)-HHC (12), while 9(*S*)-HHC-COOH and 8(*R*)-OH-9R-HHC were not identified in any samples [Kronstrand et al., 2024].

United Kingdom prevalence

6.16. The ACMD wrote to a range of stakeholders in April 2024, including public health authorities, forensic service providers and academic researchers. Quantitative information was requested about SSCs recently identified in drug seizures by law enforcement or customs staff, submitted sample analysis, samples from those attending emergency departments with drug toxicity and forensic analysis of drug-related deaths.

6.17. Detailed results are provided in Annex C, but in summary, UK stakeholders have reported the detection of five different SSCs. Initially Δ8- and Δ9-THCP, compounds already controlled via the MDA, were identified during 2022, with the uncontrolled compounds HHC, HHCO-acetate and HHCP detected in 2023 (Table 1). By far the largest numbers of detections were for HHC.

6.18. Very little information is available about the involvement of SSCs in episodes of human toxicology in the UK, either non-fatal (for example emergency department presentations) or fatal (for example post-mortem toxicology screening). It should be emphasised that UK detection rates are likely to underestimate substantially the prevalence of SSCs in these episodes because analytical methods used for forensic samples may not identify these newly emerging compounds. Several stakeholders have confirmed that this is the case for their analytical methods (Annex C).

6.19. Several websites can be accessed via the open internet that claim to sell SSCs, including with shipment to UK buyers.

6.20. Eurofins have reported the detection of THCA-A in 5 cases as a clear ('diamonds') or brown crystalline powder (total weight 550g) during 2024 and 1 case in 2023. This compound has also been detected in single cases of herbal material and 'crumble', which is a waxy preparation that can be crumbled between the fingers then inhaled by smoking in a joint or after vaporisation using a vape pen or a 'dab ring' ('dabbing'). Eurofins have also recently analysed a cannabis cigarette ('joint') that had been rolled in THCA crystals.

Table 1. Semi-synthetic cannabinoids identified in Europe and their current status under the UK Misuse of Drugs Act 1971. In each group, compounds are ranked by date of first detection in European countries reporting to EUDA.

Semi-synthetic cannabinoid	First notified to EUDA		UK detections		MDA controlled[1]
	Detection date	Notification date	Number	Year of first detection	
HHC and derivatives					
HHC	May 2022	Oct 2022	108	2023	No
HHCO	Aug 2022	Dec 2022	1	2023	No
HHCP	Nov 2022	Jan 2023	1	2023	No
9-OH-HHC	Dec 2022	Apr 2024	0	-	No
HHCH	Jun 2023	Sep 2023	0	-	No
HHCP-O-acetate	Feb 2024	Aug 2024	0	-	No
10-OH-HHC	June 2024	Dec 2024	0	-	No
10-OH-HHCP	July 2024	Dec 2024	0	-	No
HHC-C8	June 2024	-	0	2024	No
HHC-C9	Dec 2024	Apr 2025	0	-	No
THC derivatives					
Δ8-THCP	Mar 2023	Mar 2024	5	2022	Yes
Δ9-THCP	Jul 2023	Sep 2023	10	2022	Yes
THCB	Oct 2023	Mar 2024	0	-	Yes
Δ8-THCH	Oct 2023	May 2024	0	-	Yes
Δ8-THCM	Dec 2023	Jun 2024	0	-	Yes
Δ9-THCP-O-acetate	Dec 2023	Aug 2024	0	-	Yes
Δ8-THC-C8	Feb 2024	Aug 2024	0	-	Yes
Δ8-THCB-O-acetate	Mar 2024	Aug 2024	0	-	Yes
Δ9-THC-C8	Feb 2024	Aug 2024	0	-	Yes
Δ9 THCH	Apr 2024	Aug 2024	0	-	Yes
Δ8-THC-O-acetate	Apr 2024	Aug 2024	10	2023	Yes
Δ8-THCV	Apr 2024	Oct 2024	0	-	Yes
Δ9-THC-O-acetate	Aug 2024	Dec 2024	0	-	Yes
Δ9-THC-methylcarbonate	Sep 2024	Dec 2024	0	-	Yes
THC precursors					
THCA	*	*	6	2023	No
CBD derivatives					
H4-CBD	Dec 2022	Apr 2023	0	-	No

[1]All compounds controlled via the MDA are Class B Schedule 1. Uncontrolled compounds that are psychoactive are subject to the PSA.
*THCAs are not regarded as NPS by EUDA and detections therefore are not notified.

Desired effects

6.21. There are very few studies of the psychological or behavioural effects of SSCs [EMCDDA, 2023] but their chemical and pharmacological similarity to Δ9-THC makes it likely they would have similar effects [WHO, 2024]. Self-reported desired effects of SSCs include relaxation and euphoria as well as relief from stress, anxiety, pain and other mental or physical health conditions [O'Mahoney et al., 2024; Persson et al., 2024; UNODC, 2024a; WHO, 2024]. Effects are reported to commence 30 minutes to 1 hour after ingestion [European Commission, 2024].

6.22. For HHC specifically, effects are reported to be similar to those of cannabis and include relaxation, euphoria, calming, sleepiness and hunger. People have also used HHC to treat their pain, anxiety or stress and to assist in withdrawal from cannabis or benzodiazepines [Caprari., 2024; Labadie et al., 2024; O'Mahoney et al., 2024; Persson et al., 2024; WHO, 2024].

6.23. There is also little information available on typical doses of SSCs used, but these are likely to be similar to or a bit larger than typical doses of Δ9-THC. Recommended doses varying from 5 to 60 mg have been reported [WHO, 2024]. No studies are yet available that give information on dose-response relationships. There may be some contribution towards the effects of HHC from active metabolites such as 11-OH-HHC.

6.24. User fora have suggested that HHCO-acetate is 1.5 times more potent than HHC. Users have reported sedation, relaxation, anxiolytic and antidepressant effects, removal of overwhelming thoughts, more relaxed sleep, blissfulness and openness to new sensations and ideas. Users of vape cartridges have commented that HHCO-acetate takes a little more time than other cannabinoids to produce effects. This is consistent with the inactivity of HHCO-acetate *in vitro* and the need for enzymatic hydrolysis *in vivo* to release the bioactive phenol [Caprari et al., 2024].

6.25. The majority of users report that vaping HHCP gives milder effects than vaping Δ9-THC, but that ingesting HHCP edibles can produce substantial effects. Anxiolytic properties, relief, a happy experience, uplifting effects, better mood, great feelings and good times have all been reported after HHCP use, and euphoria has sometimes been described as intense. Interpretation of these reports, however, is challenging because HHCP is provided as tinctures, vape cartridges and gummies that may also contain other compounds [Caprari et al., 2024].

Motivations for use

6.26. There is limited information available about the reasons people seek to use SSCs, but their pharmacological similarity to Δ9-THC may make them attractive to some cannabis users. They may be presented by retailers (or perceived by users) as being legal alternatives to cannabis. The possibility of evading point-of-care drug testing may also be considered advantageous.

6.27. Some SSC users have suggested that SSCs are less intoxicating than cannabis, although there are no controlled data available to confirm this. As a result, they have occasionally been referred to as 'cannabis lite', although the same term is also used to refer to low-Δ9-THC cannabis products.

6.28. The toxic effects of fully synthetic cannabinoid receptor agonists (‘Spice’ compounds) are increasingly well known and some users may consider SSCs to be safer alternatives [Persson et al., 2024], although there is no direct evidence of this. In some cases, users are not aware that the product that they have used contained an SSC [Guyon et al., 2024].

User profiles

6.29. There is also very little information available about the profiles of people who use SSCs.

6.30. A US-based online survey conducted in February and March 2022 obtained responses from 109 people (age range 20-72 years; 70 males, 39 females) who self-reported HHC use at least once in the previous 6 months. Respondents reported using HHC relatively frequently (~10 days during the past month) with the most common motivations being a desire to relax, enjoy its effects and/or to ‘get high’. A minority used HHC for medical indications, including anxiety (13), pain (10), post-traumatic stress disorder (6), depression (4) and insomnia (1). Reported beneficial effects included relaxation and euphoria [Ferretti et al., 2023].

6.31. In a retrospective study of those with undesired effects conducted by French Poisons Centres, the median age of those affected was 36 years (IQR 28-43), with males predominating. The results of this study are described in more detail in the ‘Health Harms’ section [Labadie et al., 2024].

Dependency, treatment and recovery

6.32. The abuse liability of SSCs has not been studied in any detail [EMCDDA, 2023] but pharmacological and behavioural studies in animals suggest similar properties to THC. Withdrawal features have been described by some users, as described under ‘Health Harms’.

7. Health Harms

7.1. Interpreting reported health harms with SSCs is challenging because analytical confirmation is not available in many cases, in part because sample analysis is rarely performed in the clinical management of people with suspected drug toxicity. The possibility that the drugs used have been misidentified or that other substances contribute to the clinical effects cannot be excluded. Health harms may be worsened by the modes of use including ingestion and vaping, as dosing may be less self-limiting than with smoking.

7.2. Self-reported undesired effects of SSCs include respiratory problems, confusion, increased heart rate and/or blood pressure, reduced psychomotor activity, sedation or reduced consciousness and psychotic-like symptoms (including paranoia and panic attacks) [UNODC, 2024a].

7.3. In a small online survey involving 109 US self-reported users of HHC in the United States, 17% of the respondents reported adverse effects, mostly sleepiness, red eyes, dry mouth and stomach problems. Of interest, 22% of the 54 individuals who ceased using HHC reported withdrawal symptoms such as sleeping difficulties and depressed mood [Ferretti et al., 2023].

7.4. French poisons centres conducted a retrospective observational study of cases self-reporting HHC exposure to them between January 2022 and May 2023. There were 37 cases, with all presenting after September 2022 and 19 in the final month of data collection. Routes of exposure were ingestion (24 cases), inhalation (smoke or vape, 10 cases), inhalation and ingestion together (2 cases) and sublingual (1 case). The reason for use was reported by 21 cases and was for the treatment of anxiety/obtain wellbeing in 10 (48%), to combat pain in 4 (19%), to support cannabis or benzodiazepine withdrawal in 2, (9%) 'wanted to try it' in 2 (9%), and to treat insomnia in one (4%). Two cases (9%) thought they were buying another product. The form of the HHC used was reported in 33 cases as follows: gummies (8), e-liquid (7), oil (5), unspecified liquid (5), joint (3), resin (2), chocolate (1), cake (1), space cake (1) and puffer (1). The site of purchase was reported for 20 and was via the internet in 12, from a specialist CBD shop in 6, a tobacconist in one and an e-liquid shop in one. Doses used were reported to range from 50 to 100 mg.

7.5. Documented clinical features were as follows:

- *neurological* (85%), most commonly dizziness, somnolence, trembling, agitation, headaches, dysarthria, confusion, euphoria, paraesthesia or muscle contractions
- *cardiovascular* (61%), especially tachycardia, palpitations or chest pain
- *gastrointestinal* (33%), especially vomiting, nausea, or abdominal pain
- *psychiatric* (27%), most commonly anxiety, hallucinations, or delirium
- *ocular* (21%) commonly mydriasis (dilated pupils) or blurred vision.
- *Other*, with effects reported in more than one person being breathlessness, dry mouth or mucous membranes, asthenia (lack of energy) and muscle pain.

7.6. Hospitalisation was required in 24 (59%) cases, with all recovering and a mean length of hospital stay of 13h (range 1-28h). One patient required sedation due to extreme agitation. There were 13 patients who were not admitted and were monitored at home.

7.7. Analysis of the drug product and/or biological samples was only conducted in 6 cases, but HHC was identified in all cases in samples of drug product, blood and/or urine and was detected in at least one biological sample in all but one patient. In that case, urine analysis was not performed, and the blood sample was taken more than 24h after exposure. One of the products analysed also contained Δ8-THC and another both Δ8- and Δ9-THC. A third sample also contained S-hexacannabinol, R-HHC, cannabidiol and cannabinol. No other recreational substances were detected [Labadie et al., 2024].

7.8. Separately, a case report from Paris described a regular consumer of HHC products with severe adverse effects including loss of consciousness, tonic-clonic seizures, metabolic acidosis and rhabdomyolysis after use of vape containing HHC. Exposure was confirmed by a plasma HHC concentration of 11 ng/ml plasma on admission to hospital [Thiebot et al, 2024].

7.9. A further report describes 6 cases of HHC users reported to the Bordeaux Addictovigilance Center (age range 16-60 years), with all experiencing psychoactive effects such as confusion or hallucinations after inhalation using vapes (3) or ingestion of gummies (2) or ‘space cake’ (1). Other documented effects included mydriasis, myoclonus and extrapyramidal symptoms. The product used was sold as HHC to 3 cases but as CBD to 2 and THC to one case [Guyon et al., 2024].

7.10. In some cases, SSC exposures have involved young people, including children [Ferretti et al., 2023]. For example, between June 2022 and the beginning of February 2024, the Czech poison centre recorded 170 cases of self-reported exposure to SSCs, mainly in children and adolescents. In January 2024 alone, eight cases of HHC overdose of children and adolescents occurred in the Karlovy Vary Region, with at least one child being admitted to an intensive care unit [European Commission, 2024]. In Plzeň, 11 children were treated in connection with HHC exposure over 3 months. One adult female required mechanical ventilation and over one weekend three adults required intensive care. Emergency services have also already been called due to intoxicated primary school pupils. Children and adolescents often use SSCs in the form of gummy bears, which are sold under the designation of 'collector's items', even via vending machines [European Commission, 2024].

7.11. HHC was suspected of precipitating the onset of psychosis in two males in Ireland who presented with psychotic features. One had been a heavy cannabis user over 3 years but had switched to daily use of an HHC vape 2 months earlier, supplemented by occasional use of edibles. He had previously infrequently used benzodiazepines, codeine, and 3,4-methylenedioxymethamphetamine (MDMA) but not in the weeks prior to his presentation. He improved with treatment including antipsychotic therapy and was free of psychosis after five months without need for ongoing antipsychotic treatment. The second patient, having been diagnosed with cannabis-induced psychosis 28 months previously, had a second episode of psychosis 2 weeks after he purchased HHC vape to treat anxiety. He also improved with antipsychotic treatment [O'Mahoney et al., 2024].

7.12. Users have also reported panic attacks after consuming edibles containing HHCO-acetate, with subsequent chronic depressive mood lasting for a few weeks. Effects from use of 11-OH-HHC were reported to be similar to those of HHC. Slower onset but longer lasting effects were reported after use of HHCPO-acetate, including relaxation, euphoria, pain relief, 'warm body vibrations' and creative inspiration [Caprari et al., 2024].

7.13. EUDA reported an outbreak of poisonings in Hungary in 2024 involving 'gummies' containing Δ9-THC-C8 and Δ8-THC-C8. Reported clinical features included prolonged sedation, hallucinations, tremors, agitation and confusion. No fatal cases were recorded [EUDA, 2024b].

7.14. A recent paper from Denmark has described 2 cases of intoxication after oral ingestion of hexahydrocannabioctyl (HHC-C8). Observed clinical features included loss of consciousness, respiratory acidosis, recurring seizures with subsequent recovery over several days [Thomsen et al., 2025]. The related compound HHC-C9 (sometimes also referred to as 'CC9') has also recently been identified in Europe (Italy and Malta) in vapes, edibles and herbal material, with some packaging labelled 'THC' and some 'CC9' [University of Malta, 2025]. This compound is also available for sale on some websites.

7.15. In the absence of adequate purification of the product, there is a potential risk of harms from contaminants or by-products of manufacture such as other cannabinoids or traces of heavy metals [EMCDDA, 2023]. There is currently no information available to confirm or refute this possibility.

7.16. In the late summer of 2019, there was an outbreak in the USA of an acute lung condition in people inhaling drugs via vapes. This was termed e-cigarette or vaping product use-associated lung injury (EVALI) and it resulted in many hospitalisations and deaths [CDC, 2020; Rebuli et al., 2023]. In most cases the vapes that had been used contained Δ9-THC and a subset of samples possessed profiles indicating CBD-based routes of production, such as high concentrations of Δ8-THC and olivetol [Zawatsky et al., 2024]. The lung injury was linked to vaping products that contained vitamin E acetate (VEA) and it was suggested that heating of VEA generates ketene (ethernone), which is toxic to the lungs, although the role of other toxic or sensitising chemicals remains uncertain [CDC, 2020]. Of note, cannabinoid acetates such as HHCO-acetate may also generate ketene when heated, although amounts involved appear low [EMCDDA, 2023; Caprari et al., 2024; Munger et al., 2022; Munger et al., 2024], and there are no reports to date of EVALI related to the inhalation using vapes of any of the compounds reviewed in this report.

8. Social Harms

8.1. There is currently limited direct evidence of the social harms associated with SSCs. These are likely to be similar to those of other cannabinoids, with many also applying to other drug groups.

8.2. At present, direct evidence that SSC use might increase the risk of exclusion from education, educational disengagement, and underachievement (qualifications) is lacking. However, a survey of people who used Δ8-THC and compared the effects with those of Δ9-THC [Kruger & Kruger, 2022] found that 81% experienced difficulty concentrating and 80% experienced difficulties with short-term memory following use of Δ8-THC, although overall the effects of Δ9-THC were rated more intense and longer-lasting. Meta-analytical evidence indicates that cannabis use is associated with lower school grades, lower school completion, lower university enrolment, lower postsecondary degree attainment, and higher school dropout and absenteeism [Chan et al., 2024]. Based on these findings, similar (but potentially weaker) associations could be expected for SSCs.

8.3. The pharmacology and effect profile of SSCs indicates that they could affect employment performance through cognitive impairment and effects on mood and mental health (e.g., relaxation, euphoria, anxiety, and paranoia [Kruger & Kruger, 2022]. This might result in loss of employment; lack of and under-employment; loss of income and low wages; and tangible losses through workplace discrimination (identification as a person who uses drugs).

8.4. Loss of accommodation can be a direct or indirect consequence of the use of some drugs. Due to the pharmacology and effect profile of SSCs, direct effects on housing may be less likely than with some other drugs, but indirect effects on housing from loss of employment, conviction/imprisonment or breakdown in relationships could become more likely for users if these compounds were controlled.

8.5. Chronic and increasing use of cannabis are predictors of adult antisocial behaviour [Brook et al., 2011]. It is plausible that this would also be the case for SSCs although there is currently no evidence to support an increase in antisocial behaviour amongst regular SSC users.

8.6. An increased risk of road traffic collisions may occur from use of SSCs by drivers, because of their intoxicating effects. Evidence of the increasing prevalence of SSC use amongst those suspected of driving under the influence of drugs in Germany and Sweden is presented in more detail in the section on Misuse (Paragraphs 6.13 and 6.15).

8.7. As for other drugs, the legal control of previously uncontrolled SSCs could affect users receiving cautions and/or convictions by exclusion from education and loss of employment, housing or liberty. Secondary escalation of criminality and drug use could also occur through involvement in the criminal justice system.

9. Conclusions

9.1. Several SSCs have been detected in drug markets internationally since 2019. Many of these are also available for purchase in a variety of forms in the UK, including sweets and vapes, and some have been detected in UK drug seizures. The possibilities that the data provided for this report underestimates the prevalence of these compounds in the UK or that other examples are in circulation in the UK cannot be excluded with confidence, especially due to limitations in sample testing for emerging NPS.

9.2. Many of the SSCs detected internationally are already controlled as Class B compounds under the MDA via the current UK generic text, including THC homologues (compounds with shorter or longer chain lengths) and their esters and ethers. The hexahydro derivatives of cannabinol, derivatives of cannabidiol (CBD), 11-OH compounds and THCA are not currently captured, although psychoactive examples are subject to the provisions of the PSA. Several of these uncontrolled substances have been reported in the UK, specifically HHC, HHCO, HHCP and THCA; of these, HHC has been detected most often.

9.3. There is accumulating evidence of the similarity in pharmacology as well as chemistry of many of these uncontrolled examples to Δ9-THC, the major psychoactive constituent of the cannabis plant, with evidence of their agonist activity at CB1 cannabinoid receptors.

9.4. There is also increasing evidence of their human psychoactivity and of associated health harms, including neurological (e.g. somnolence), cardiovascular (e.g. rapid heart rate, increased blood pressure, palpitations, chest pain), gastrointestinal (e.g. nausea and vomiting, abdominal pain), psychiatric (e.g. anxiety, hallucinations, delirium, psychosis, panic attacks) and ocular (mydriasis, red eyes, blurred vision) effects. There are also reports of withdrawal symptoms. Materials with psychoactivity similar to that of Δ9-THC are liable to have similar effects on psychomotor activity, for example, on driving ability. As with many other illicitly produced substances, there may also be health risks from contaminants or from by-products of manufacture.

9.5. More severe effects have occasionally been reported such as tonic-clonic seizures, metabolic acidosis and rhabdomyolysis. Some affected people have required hospital admission and occasionally mechanical ventilation. Adverse effects have also been reported to affect children and adolescents. Serious toxicity, however, appears uncommon and to date there have been very few UK detections reported in people experiencing clinical toxicity or drug-related deaths, although these are likely to be underestimated by current limitations in sample testing. The possibility that some of the reported adverse effects might be caused by co-used substances cannot be excluded.

9.6. Much of the information on health harms is preliminary and uncontrolled and often lacks analytical confirmation. Coupled with the pharmacological evidence of cannabimimetic effects, however, it does, provide sufficient indication of a potential risk to public health to justify control of selected psychoactive compounds under the MDA. Those compounds currently providing the highest risk are those that have already been detected in the UK, especially HHC in view of the frequency of detection. Other structurally related compounds, however, are likely to appear in the UK in the future, especially those that have already been detected in other countries.

9.7. It was not previously thought necessary to control THC acids as these are components of the cannabis plant that is already controlled. In view of its recent appearance in drug markets as pure material ('diamonds') in solid form for smoking or in liquids for vaping, control of these compounds is now necessary.

9.8. For the hydrogenated forms of CBD such as H4-CBD, there is currently less evidence of psychoactivity and health harms and currently insufficient justification for control of via the MDA at present. Any emerging evidence of the psychoactivity of these compounds, however, should be kept under review.

Legislative options

9.9. If SSCs are controlled via the MDA, it is appropriate that the level of control should be consistent with that of other cannabinoids, such as Δ9-THC, its stereoisomer dronabinol and other THC isomers, which are placed in Class B. The ACMD previously recommended that cannabis should be reclassified to Class C, although the then government decided that it should remain in Class B. The working group, however, considered that, irrespective of the debate in relation to cannabis, Class B was more appropriate for SSCs considering the following:

(a) their similarity to cannabinoids already in Class B;
(b) the additional risks arising from routes of administration (e.g., ingestion, vaping) that are less likely than smoking to limit the dose consumed, combined with the unpredictable purity of the products used; and
(c) their potential provision to children and young people as sweets/gummies or vapes.

9.10. The possibility that SSCs or structurally related compounds might be developed as medicines in the future cannot be excluded, but none of the uncontrolled SSCs identified in this report are currently licensed as medicines in the UK or elsewhere and we are not aware of any currently being developed for this purpose. It is therefore appropriate that they should be listed in Schedule 1 of the MDR, as are the SSCs that are already controlled via the generic text in the Act. Their placement in Schedule 1 does not preclude their involvement in research in the UK, although an appropriate licence would be required.

9.11. Some of the compounds considered in this report may not have potent psychoactive effects in their own right until they are converted to psychoactive products, either before (e.g. by heating) or after (e.g. by metabolism) ingestion. THCA is an example of the former group and acetates examples of the latter. As such, some of these precursor compounds may not be subject to the provisions of the PSA. For these, control of those associated with risk of harm via the MDA is especially necessary. The control of precursors under the MDA has been used previously, for example the cocaine precursor ecgonine and its derivatives are, like cocaine, controlled in Class A.

9.12. Control of compounds via the MDA can be achieved by naming specific compounds or by using generic text. The latter would capture compounds of current concern as well as possible chemical variants. The current cannabinoid generic text has already been successful in controlling many recently emerging SSCs, but modifications are needed to capture uncontrolled variants associated with potential harms. The generic approach is preferred to the option of naming specific compounds, as it is more likely to be 'future-proof', but it does risk capturing other compounds that have potential legitimate uses, including as medicines or in research. It is, therefore, essential to

consult with stakeholders, including academia and the chemical and pharmaceutical industries, to ensure that any proposed legislation does not produce unintended barriers to research or legitimate commercial activity.

9.13. Should it not be possible to modify the generic text to capture currently uncontrolled variants without compromising legitimate research or commercial activity, these variants could be listed by name. In any event, as the process of consultation and legislation can be lengthy, the listing of compounds of immediate concern by name in the MDA should be considered, pending changes to the generic text coming into law.

Other options

9.14. As with other new psychoactive substances, it is important that information is available for users and health professionals about SSCs, their health and social harms and their legal status.

9.15. It is also important that there is adequate infrastructure in the UK for the detection of newly emerging NPS and their possible health harms. Coroners/procurators fiscal should be aware of prevalent and emerging NPS and consider their potential involvement when investigating possible drug-related deaths. Forensic laboratories analysing seized or submitted drug materials, as well as patient or post-mortem samples, should be able to detect prevalent and emerging NPS. If there are limitations in what can be detected by the assays used, this should be made clear in their reports. Minimum standards for post-mortem toxicology testing and reporting would be advantageous. There should be ongoing collection and dissemination of information about drugs detected in the UK between public health agencies, coroners/procurators fiscal, toxicology laboratories and health professionals working with people who use drugs. To facilitate this, there may sometimes be a need to share reference standards, analytical methods and structural information between laboratories. It is also essential that adequate funding for all of this is made available. The ACMD has made recommendations along these lines in previous reports in relation to specific groups of NPS [ACMD, 2020a; 2020c; 2022; 2024b; 2024c] and although these are not being repeated here, they remain important.

10. Recommendations

Changes to the Misuse of Drugs Act 1971

The ACMD advises that there is sufficient actual or potential risk of harms from the misuse of SSCs in the UK to justify control of currently uncontrolled compounds via the MDA, with the level of control commensurate with that of Δ9-THC and its derivatives that are already controlled, i.e. Class B.

The compounds involved are not currently licensed as medicines and should therefore be included in Schedule 1 of the MDR and Schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015, to which 7(4) of the Misuse of Drugs Act 1971 applies. This scheduling can be reviewed should any of these compounds subsequently become licensed as a medicine for human or veterinary use.

Control via the MDA can be achieved by listing specific compounds by name, or by broadening the current cannabinoid generic text. The latter is preferred as a more future-proof long-term approach as it makes the development of new uncontrolled cannabinoids more difficult (but not necessarily impossible), but does carry a risk of capturing compounds of current or future legitimate use. Consultation with stakeholders including academia and the chemical and pharmaceutical industries is therefore essential before changes are enacted.

As the process of consultation can take considerable time, the ACMD advises that currently uncontrolled SSCs that have been detected in the UK or Europe should be controlled by name as soon as possible, because they pose a significant immediate risk to public health.

RECOMMENDATION 1a: The following compounds should be included as named compounds in the MDA as Class B and in the MDR as Schedule 1 compounds. They should also be listed in Schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015.

Hexahydro-derivatives

- Hexahydrocannabinol (HHC)
- Hexahydrocannabiphorol (HHCP)
- Hexahydrocannabihexol (HHCH)
- 9-Hydroxyhexahydrocannabinol (9-OH-HHC)
- 10-Hydroxyhexahydrocannabinol(10-OH-HHC)
- 11-Hydroxyhexahydrocannabinol (11-OH-HHC)
- 10-Hydroxyhexahydrocannabiphorol (10-OH-HHCP)
- Hexahydrocannabinol-C8 (HHC-C8)
- Hexahydrocannabinol-C9 (HHC-C9)

THC derivatives

- 11-Hydroxy tetrahydrocannabinol (11-OH-THC)

THC precursors (cannabinoid acids)

- Tetrahydrocannabinolic acid A (THCA-A)
- Tetrahydrocannabinolic acid B (THCA-B)

Note that:

(a) Chemical names are given in Annex A.
(b) There are also potential harms associated with Hexahydrocannabinol-O-acetate (HHC-acetate, HHCO-acetate) and Hexahydrocannabiphorol acetate (HHCPO-acetate). It is not necessary to list the acetates separately, as these will automatically be covered by the "esters and ethers" clause in the legislation.

RECOMMENDATION 1b: Following appropriate consultation, the UK generic text for cannabinoids in the MDA should be updated so that psychoactive SSCs that are not currently captured are included in the MDA as Class B and in the MDR as Schedule 1 compounds. They should also be listed in Schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015.

Suggested alterations to the current cannabinoid generic text are provided in Annex D.

Lead: Home Office

Measure of outcome: The inclusion of the described compounds in Class B of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001 by adjustment of the cannabinoid generic (following appropriate consultation) or as named compounds.

Education and training

The ACMD is concerned that users of SSCs may not be aware of their potential harms or their legal status. This may also apply to younger people who might use these drugs and their parents or carers.

Similarly, healthcare professionals who encounter users may not be aware of or familiar with these compounds and this might compromise clinical management of those experiencing adverse effects.

Retailers of SSCs may not be aware that SSCs are either already controlled via the MDA or will soon become so. They need to be informed so that they do not inadvertently break the law by import or supply of controlled drugs.

RECOMMENDATION 2: More detailed information on the legal status and adverse effects of SSCs should be made available to people who use drugs, the public and staff who may encounter drug users, especially those working in health, and social care.

The public facing websites "Frank" (England), "Know the Score" (Scotland) and "DAN24/7" (Wales) do not appear to include information about these compounds and should be updated to include this, especially for those compounds already prevalent in the UK.

The National Police Chief's Council has established a cannabis edibles group which provides information to parents. This may be a useful way to pass on information to parents about SSCs, their adverse health effects and their legal status.

Information should be provided to schools about the illicit substances that may be found in vapes, their legal status and their potential adverse health effects.

Retailers of vapes and other products that may contain SSCs should be provided with information about their legal status.

Healthcare professionals can register to access comprehensive evidence-based online information and clinical management advice about potentially toxic substances, including illicit drugs, via the TOXBASE website, provided by the National Poisons Information Service (NPIS) and funded by the UK Health Security Agency (UKHSA). While TOXBASE provides information about THC, cannabis and SCRA, searches for the SSC described in this report yield negative results. Information about the SSCs described in this report should be included.

Leads: Office for Health Improvement and Disparities, National Poisons Information Service, UK Health Security Agency, Betsi Cadwaladr University Health Board, Scottish Government Population Health Directorate, National Police Chief's Council, Department for Business and Trade, Department for Education, Scottish Government – Learning Directorate, Welsh Government – Department for Education and Welsh Language, Department of Education (Northern Ireland).

Measure of outcome: Communication of appropriate online and written information to target groups.

Research

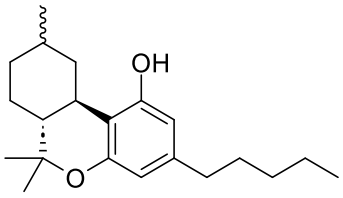
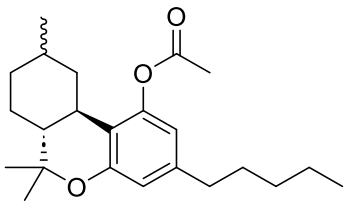
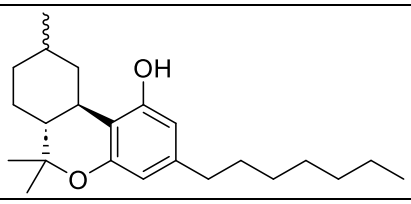
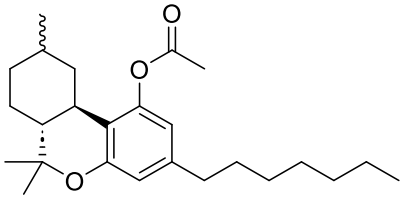
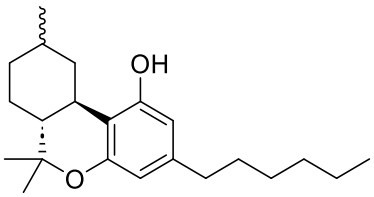
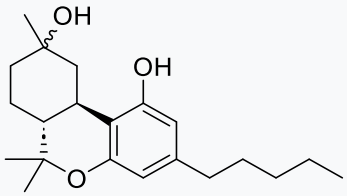
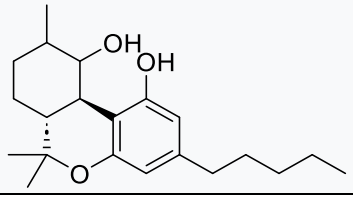
There is conflicting evidence of the psychoactivity of hydrogenated CBD derivatives, especially H4-CBD, a compound that the ACMD has not recommended for control via the MDA. It is therefore important to establish the status of H4-CBD under the PSA.

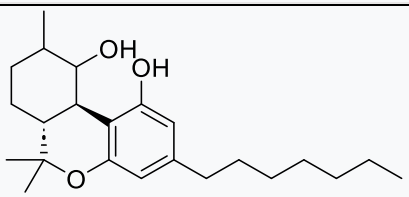
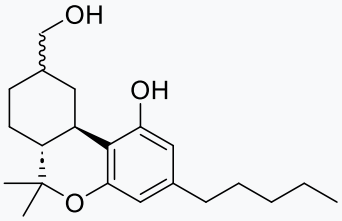
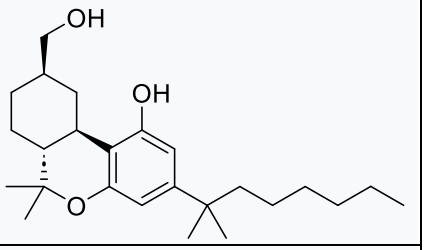
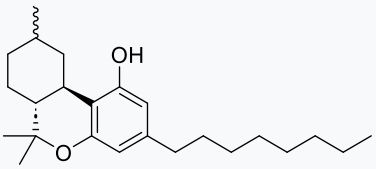
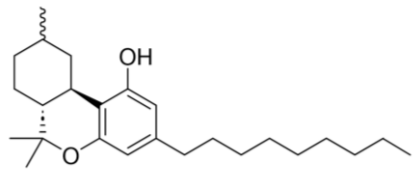
RECOMMENDATION 3: The status of H4-CBD under the PSA should be established using the standard *in vitro* testing panel

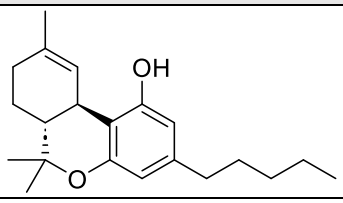
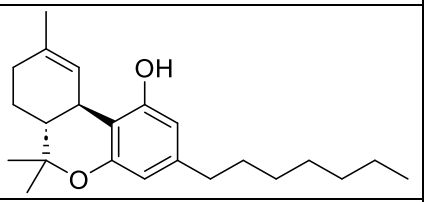
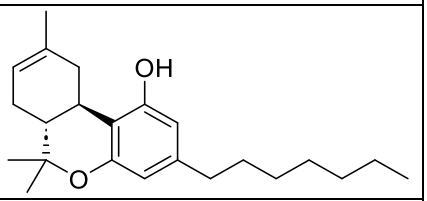
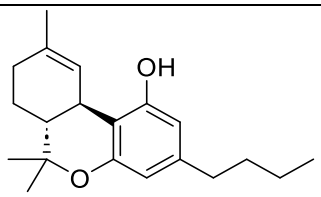
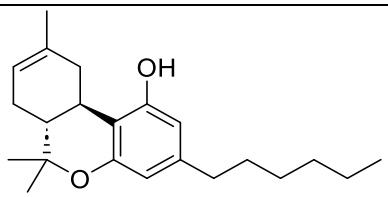
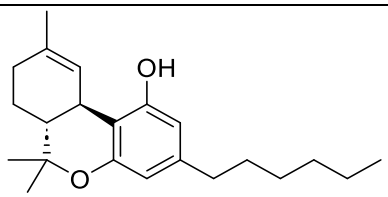
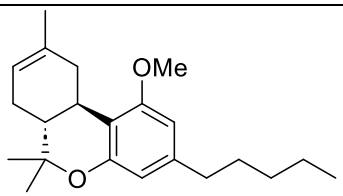
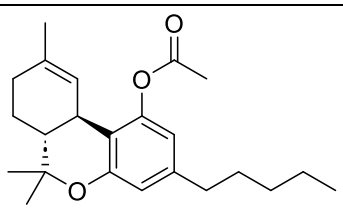
Leads: Home Office.

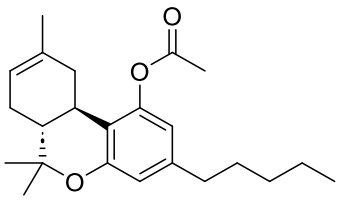
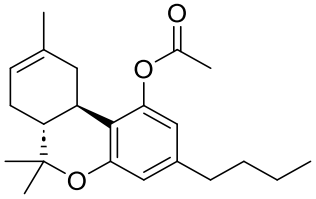
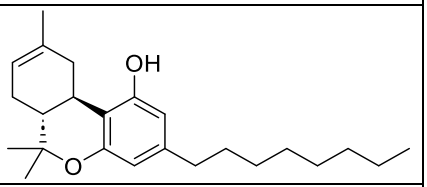
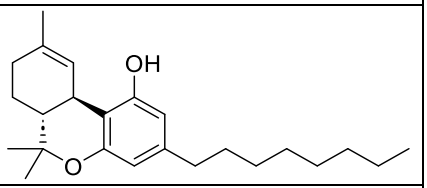
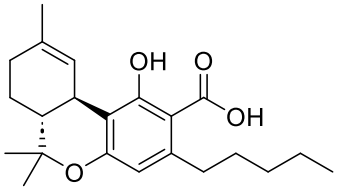
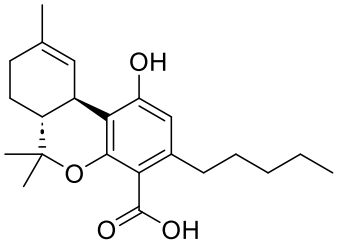
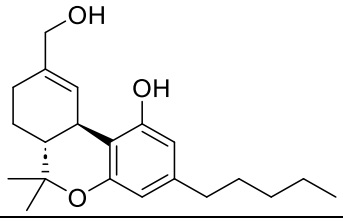
Measure of outcome: Availability of panel testing report.

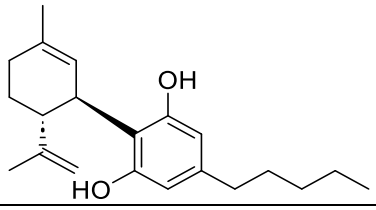
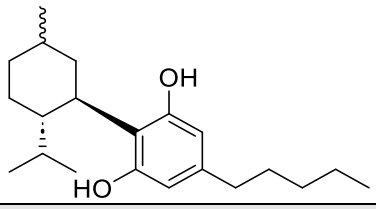
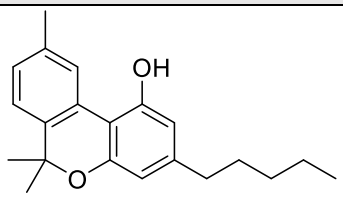
Annex A: Compound synonyms and structures

Common name	Chemical name	2D Structure
HHC and derivatives		
Hexahydrocannabinol (HHC)	(6*aR*, 10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,8,9,10,10*a*-hexahydrobenzo[*c*]chromen-1-ol	
Hexahydrocannabinol-O-acetate (HHC-acetate, HHCO-acetate)	[(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,8,9,10,10*a*-hexahydrobenzo[*c*]chromen-1-yl] acetate	
Hexahydrocannabiphorol (HHCP)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-heptyl-6*a*,7,8,9,10,10*a*-hexahydrobenzo[*c*]chromen-1-ol	
Hexahydrocannabiphorol acetate (HHCPO-acetate)	(6*aR*,10*aR*)-3-Heptyl-6,6,9-trimethyl-6*a*,7,8,9,10,10*a*-hexahydro-6*H*-benzo[*c*]chromen-1-yl acetate	
Hexahydrocannabihexol (HHCH)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-hexyl-6*a*,7,8,9,10,10*a*-hexahydrobenzo[*c*]chromen-1-ol	
9-Hydroxyhexahydrocannabinol (9-OH-HHC)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6a,7,8,9,10,10*a*-hexahydro-6*aH*-benzo[*c*]chromene-1,9-diol	
10-Hydroxyhexahydrocannabinol (10-OH-HHC)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,8,9,10,10*a*-hexahydro-6*H*-benzo[*c*]chromene-1,10-diol	

Common name	Chemical name	2D Structure
HHC and derivatives (cont.)		
10-Hydroxyhexahydrocannabiphorol (10-OH-HHCP)	(6*aR*,10*aR*)-3-Heptyl-6,6,9-trimethyl-6a,7,8,9,10,10*a*-hexahydro-6H-benzo[*c*]chromene-1,10-diol	
11-Hydroxyhexahydrocannabinol (11-OH-HHC)	(6*aR*,10*aR*)-9-(Hydroxymethyl)-6,6-dimethyl-3-pentyl-6*a*,7,8,9,10,10*a*-hexahydro-6*H*-benzo[*c*]chromen-1-ol	
11-Hydroxy-HHC-DMH (HU-243)	(6*aR*,9*R*,10*aR*)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6*a*,7,8,9,10,10*a*-hexahydro-6*H*-benzo[*c*]chromen-1-ol	
Hexahydrocannabinol-C8 (HHC-C8)	6,6,9-Trimethyl-3-octyl-6*a*,7,8,9,10,10*a*-hexahydro-benzo[*c*]chromen-1-ol)	
Hexahydrocannabinol-C9 (HHC-C9)	3-nonyl-6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol	

Common name	Chemical name	2D Structure
THC and derivatives		
Tetrahydrocannabinol (Δ9-THC)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	
Tetrahydrocannabiphorol (Δ9-THCP)	(6*aR*,10*aR*)-3-Heptyl-6,6,9-trimethyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	
Δ8-THCP	(6*aR*,10*aR*)-3-Heptyl-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	
Tetrahydrocannabutol (Δ9-THCB)	(6*aR*,10*aR*)-3-Butyl-6,6,9-trimethyl-6*a*,7,8,10*a*-tetrahydro-6H-benzo[*c*]chromen-1-ol	
Δ8-Tetrahydrocannabihexol (THCH)	(6*aR*,10*aR*)-3-Hexyl-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	
Δ9-THCH	(6*aR*,10*aR*)-3-Hexyl-6a,7,8,10*a*-tetrahydro-6,6,9-trimethyl-6H-dibenzo[*b*,*d*]pyran-1-ol	
Δ8-Tetrahydrocannabinol methyl ether (Δ8-THCM)	(6*aR*,10*aR*)-1-Methoxy-6,6,9-trimethyl-3-pentyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[*c*]chromene	
Δ9-Tetrahydrocannabinol acetate (Δ9-THC-O-acetate)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6H-benzo[*c*]chromen-1-yl acetate	

Common name	Chemical name	2D Structure
THC and derivatives (Cont.)		
Δ8-Tetrahydrocannabinol acetate (Δ8-THC-O-acetate)	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-pentyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-yl acetate	
Δ8-Tetrahydrocannabutol acetate (Δ8-THCB-O-acetate)	(6*aR*,10*aR*)-3-Butyl-6,6,9-trimethyl-6*a*,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-yl acetate	
Δ8-THC-C8	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-octyl-6*a*,7,10,10*a*-tetrahydro-6H-benzo[*c*]chromen-1-ol	
Δ9-THC-C8	(6*aR*,10*aR*)-6,6,9-Trimethyl-3-octyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	
Δ9-Tetrahydrocannabinolic acid-A isomer (THCA-A)	(6*aR*,10*aR*)-1-Hydroxy-6,6,9-trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromene-2-carboxylic acid	
Δ9-Tetrahydrocannabinolic acid-B isomer (THCA-B)	(6*aR*,10*aR*)-1-Hydroxy-6,6,9-trimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromene-4-carboxylic acid	
11-Hydroxy-Δ9-THC	(6*aR*,10*aR*)-9-(Hydroxymethyl)-6,6-dimethyl-3-pentyl-6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	

Common name	Chemical name	2D Structure
CBD and derivatives		
Cannabidiol (CBD)	2-[(1*R*,6*R*)-6-Isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol	
Tetrahydrocannabidiol (H4-CBD)	2-((1*R*,2*S*)-2-Isopropyl-5-methylcyclohexyl)-5-pentylbenzene-1,3-diol	
Others		
Cannabinol (CBN)	6,6,9-Trimethyl-3-pentyl-benzo[*c*]chromen-1-ol	

Annex B: International Legislative Control of Semi-synthetic cannabinoids

As the number of psychoactive cannabinol and cannabidiol variants identified in the drug market has increased, other countries have expanded their drug controls to address them by naming specific cannabinol and cannabidiol variants as being controlled and, in some cases, introducing generic controls. Examples of other countries' recent introduction of controls on such materials include:-

Canada – in December 2023, Health Canada issued guidance that products containing 'intoxicating cannabinoids other than Δ9-THC' are subject to the same statutory requirements as those containing Δ9-THC, such as not containing more than specified total amounts of active materials per unit.

Czech Republic – controlled HHC, HHCO-acetate (HHC acetate) and THCP in March 2024 and in June 2024 expanded control to cover THCB, THCH, THC-C8 as well as HHCP, HHCH, HHCB and HHC-C8.

France – controlled HHC, HHCO-acetate and HHCP in June 2023 and both H2-CBD (dihydrocannabidiol)[4] and H4-CBD (tetrahydrocannabidiol) in June 2024, when a broad generic control on THC and HHC variants was also introduced (see below for details of generic controls).

Germany – has introduced an extremely broad generic control on THC and HHC variants (see below).

Italy – controlled HHC, HHCO-acetate and HHC-P in July 2023 and HHCH and Δ9-THCP in March 2024.

Denmark – controlled HHC in May 2023, followed by H4-CBD, HHCP and all seven isomers of THCP in January 2024 and in September 2024 introduced a generic control covering any derivatives of THC and HHC which are not already specifically listed (see below).

Japan – introduced a series of specific controls, on Δ9-THCP and HHC in March 2022, Δ8- and Δ9-THC-O and HHCO-acetate in March 2023, Δ8- and Δ9-THCH (hexyl-THC) in August 2023 and HHC-H in December 2023. In May 2024 a set of three generic controls were added in order to control a range of variants of Δ8- and Δ9-THC and of HHC (see below). In August 2024, these controls were further extended by specific control of Δ8- and Δ9-THCOP (propionates) and of HHCPM (HHCP methyl ester).

Malta – in September 2024 a ban on the sale of HHC-containing products was announced resulting from concerns that colourful edible materials such as 'gummy bears' and lollipops were attractive to children.

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[4] Note: H2-CBD is an ambiguous term, as the hydrogens can be added either to saturate the cyclohexene ring or to hydrogenate the isopropenyl group. Commercial products are likely to consist of a mixture of these materials.

Sweden – controlled HHC, HHC-P, HHCO-acetate and Δ8- and Δ9-THCP in July 2023, as well as the acetates of Δ8- and Δ9-THC, and each of THC's isomers where the cyclohexene double bond is situated around the cyclohexene ring.

Switzerland – controlled HHC in March 2023 and HHC-P, Δ8- and Δ9-THCP and H4-CBD in October 2023. More recently, a generic control has been introduced (see below) and olivetol has been designated as a precursor chemical.

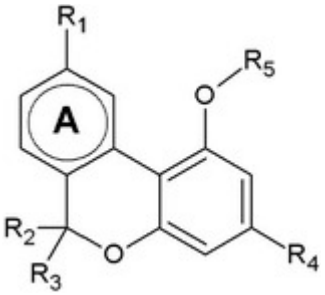
Generic controls

The following examples of generic controls have some common features. The German, Swiss, French and Japanese controls all use a similar 6H-benzo(*c*)chromene or 6*H*-benzo(*c*)chromen-1-ol type core structure, but with different substituents specified so that the scope of the different generics vary. The German generic has the broadest scope, the Japanese the most narrow. However, considered together, they indicate the range of substances thought to merit control.

German generic (translated from the Federal Law Gazette, 2024, Part 1 No 210, 26th June 2024):-

"2.3 Compounds derived from 6H-benzo(c)chromen-1-ol (6H-dibenzo(b,d)pyran-1-ol)

This independent group of cannabimimetics/synthetic cannabinoids, which are not composed according to the modular structure described under 2.1 and 2.2 above *[NOTE, NOT IN TEXT: these two paragraphs describe a range of SCRA structures]*, includes those substances that have a core structure described under 2.3.1 which are modified with the substituents described under 2.3.2 and have a maximum molecular weight of 600.



2.3.1 Core structure

The core structure includes compounds derived from 6H-benzo(c)chromen-1-ol (6H-dibenzo(b,d)pyran-1-ol) regardless of the degree of hydrogenation of the aromatic ring A and the position of any double bonds remaining therein. The compounds can be substituted at the marked positions (R1 to R5) with the atoms and groups listed under 2.3.2.

2.3.2 Substituents at positions R1 to R5

a) R1 can consist of hydrogen or one of the following groups, hydroxymethyl, methyl or a hydrocarbon chain, saturated or unsaturated, branched or unbranched, containing up to 10 carbon atoms. These groups can be substituted by hydrogen, fluorine, chlorine, bromine or iodine.

b) R2 and R3 can consist of hydrogen, methyl groups or alkyl chains branched or unbranched, containing up to 5 carbon atoms. These groups can be substituted by hydrogen, fluorine, chlorine, bromine or iodine.

c) R4 can consist of hydrogen, methyl or a hydrocarbon chain, saturated or unsaturated, branched or unbranched, containing up to 12 carbon atoms. These groups can be substituted by hydrogen, fluorine, chlorine, bromine or iodine.

d) R5 can consist of hydrogen or one of the following groups:-

alkylcarbonyl (branched or unbranched, alkyl radical up to 7 carbon atoms),

cycloalkylmethylcarbonyl with three to seven ring atoms, including polycycles,

arylcarbonyl with three to six ring atoms, including polycycles and heterocycles,

arylmethylcarbonyl with three to six ring atoms, including polycycles and heterocycles.

In the polycycles, each ring can have three to seven ring atoms.

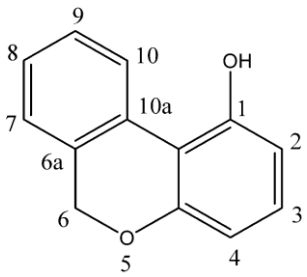
In addition to carbon atoms, heterocycles may contain oxygen, nitrogen and sulphur atoms in the ring.

A free valence of a nitrogen atom in a ring can carry a hydrogen atom or a methyl or ethyl group."

Swiss generic

"Synthetic cannabinoids 2

Any substance (except controlled substances in schedules a, b, d and f) *[Note: not in text, these are generic controls on families of SCRA]* whose structure is derived from 6H-benzo(c)chromen-1-ol (6H-dibenzo(b,d)pyran-1-ol), regardless of the degree of hydrogenation of the non-phenolic benzo ring, by substitution:



– at positions 3, 6 and 9 by any alkyl groups.

These structures may additionally be substituted in one or more of the following ways:

– at any position to any extent by alkyl, alkoxy, halogen and hydroxy groups.

Industrial and scientific use is exempt from control. Private use is not exempt from control."

French generic

"Any substance derived from the benzo[c]chromene nucleus, whether un- or partially or fully hydrogenated on the A ring (defined as the unsaturated ring bearing the methyl in position 9 of said nucleus in tetrahydrocannabinol), substituted or not at one of the following locations on the nucleus:

[Note : the numbering system used here is the same as that in the Swiss generic above]

In position 1 by a hydroxyl function, esterified or not, or an alkoxy function;

In position 2 or 4 by a carboxyl function;*

[This means that acid derivatives, such as THCA-A and THCA-B, are controlled]*

In position 3 by an adamantyl substituent or by an alkyl, alkenyl, alkynyl, cyanoalkyl, haloalkyl, cyanoalkynyl, haloalkynyl, alkoxy chain, whether this chain is itself substituted or not by one or more alkyl substituents, cyclic or not, whether these cycles or heterocycles are themselves saturated or not;

In position 6 by one or two alkyl groups

In position 9 by a ketone, alkyl, hydroxyalkyl or alkoxy function."

Danish generic

"B346a. Dibenzopyran group

Any chemical compound that is structurally derived from 6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-ol or stereoisomers thereof by one or more of the following modifications:

a) Addition of a double bond in Ring 1

b) Substitution at the 3-position of the aromatic ring with an arbitrary substituent (R1)"

This approach, therefore, differs from the French and German generics by using a hexahydro core, but subparagraph (a) then allows for the addition of a double bond to the cyclohexyl ring to form a tetrahydro core. Notably, subparagraph (b) permits any substituent at all.

Japanese generics

Under Japanese law, Δ8- and Δ9-THC are classified as narcotics. Certain variants of Δ9- and Δ8-THC together with HHC and certain variants of HHC are classified as Designated Substances (i.e. controlled NPS).

Three generics address variants of the three materials, each based on the 6,6,9-trimethyl-[6H]-benzo[c]chromene core, with either Δ8- or Δ9- tetra-hydrogenation of the 'A' ring (THCs) or hexahydrogenation (HHCs), combined with straight alkyl chains of between 3 and 8 carbons at the 3- position, with either hydroxy or acetoxy at the 1- position.

For THC variants, this defined scope covers Δ8- and Δ9- forms of THCV, THCB, THCH, THCP and THCjd (octyl) as well as their O-acetate derivatives

For HHC variants, this means that HHCV, HHCB, HHC, HHCH, HHCP and HHCjd (HHC-octyl) are controlled, as are their O-acetates (HHCVO, etc).

Annex C: UK Stakeholder Responses

The ACMD sought quantitative information about SSCs from a range of stakeholders in April 2024. These included public health authorities, forensic service providers and research studies. Their responses are detailed below.

It should be noted that these detections may underestimate the prevalence of SSCs in the UK as not all laboratories use assays that that would detect all of these compounds.

Drug seizures or submitted sample analysis

There were several data sets involving drug seizures of submitted sample analysis where SSCs were detected. These are summarised in Table C1.

Table C1. Summary of responses from stakeholders - Submitted Sample analysis

Organisation	Type of data	Findings
Eurofins Forensic Services	Provide a comprehensive forensic analysis service to police forces, legal and criminal justice organisations throughout the UK.	Detection of HHC reported in 2 drug seizures in 2023 and 50 in 2024. Δ8-THC-O-acetate detected in 10 drug seizures in 2024.
Emerging Drugs and Technologies Programme (EDAT)	Data from non-adopted drug seizures	Detections of SSCs made in 4 samples, all during the 2023/4 financial year: 1 vape sample that contained HHC, HHC-P and HHCO-acetate; 1 resin sample that contained HHC only; 2 resin samples containing HHC and THC.
Border Force	Data from seizures at the UK Border. Testing at point of seizure has not always proven to be accurate and not all products are referred for further testing.	[REDACTED][5]
Scottish Prison Service	Data obtained from the analysis of anonymised non-judicial drug seizures from Scottish Prisons using gas chromatography-mass spectrometry (GC-MS).	6 samples reported that contained HHC, 2 collected in 2023 (one vape pod, one brown resinous material) and 4 during 2024 (one each of a brown powder, a brown resinous material, a vape pod and a piece of infused paper)
Scottish Police Authority (SPA) Forensic Services	Analysis of drugs seized in Scotland	HHC identified in 7 samples in 2023 (mostly described a sticky brown materials) and 33 in 2024 (a mix of brown powders and confectionary).
RADAR	Samples from Scottish prisons	HHC present in 2 samples in 2023 and 2 samples in 2024.

[5] This data has been redacted from the published version of this report.

		Δ8-THC in single cases in 2023 and 2024.
Forensic Service of Northern Ireland (FSNI)	Detections are related to submitted suspected controlle1d drug seizures.	HHC detected in 2 samples in 2023 and 11 samples in 2024. Overall, 4 were plant material or resin, 3 were sweets and 6 were vapes.
Office for Health Improvement and Disparities (OHID)	Samples from drug seizures	HHC detected in 1 sample in 2022, 5 samples in 2023 and 8 samples in 2024.

Nil returns were obtained from the following:

- The Welsh Emerging Drugs and Identification of Novel Substances Project (WEDINOS), which analyses samples of drug samples submitted anonymously by users from across the UK, has only recently validated their HHC assay.
- TICTAC Communications Ltd, which analyses drugs either seized, or voluntarily placed in amnesty bins at UK festivals, have not identified any of these compounds.
- The MANchester DRug Analysis & Knowledge Exchange (MANDRAKE), which performs forensic/chemical analysis of seized samples, have not identified any of these compounds.

No data were received from:

- SOCOTEC
- National Crime Agency, which does not hold the data requested

Emergency department and poisons centre data

LGC Ltd have reported a single detection of HHC during 2023 in a clinical sample sent from a hospital in the East Midlands. No further information is available.

No detections of SSCs have been reported by the following studies that have been analysing samples from patients attending emergency departments with suspected drug toxicity:

- The ASSIST (‘A Surveillance Study of Illicit Substance Toxicity’) study, collects anonymised clinical data and toxicology testing is performed on surplus serum samples that were taken as part of normal clinical care from emergency department patients in one hospital in Glasgow.

- The Identification Of Novel psychoActive substances (IONA) study collected clinical data and analysed biological samples (blood and/or urine) from consenting patients attending 39 participating UK emergency departments with suspected toxicity due to substance use between March 2015 and March 2023.

No response has been received to date from:

- The National Poisons Information Service (NPIS)

Involvement in drug-related deaths

Information on drug-related deaths is generally available from death registrations (collected separately in the various devolved administrations) and forensic analysis of samples taken at post-mortem.

Data received for SSCs is summarised in Table C2. As with many newly emerging compounds, however, there is very little information available, either because the analyses used in post-mortem toxicology do not include these compounds or information about them is not collected by statistical agencies.

Table C2. Summary of responses from stakeholders – death registrations and post-mortem forensic toxicology.

Organisation	Type of data	Findings
National Programme on Substance Use Mortality (NPSUM, formerly known as NPSAD)	Receives drug-related death reports made voluntarily by coroners across England, Wales and Northern Ireland, but not Scotland	No detections of SSCs reported to them
Office for National Statistics (ONS)	Publish annual numbers of drug-related poisonings in England and Wales where new psychoactive substances were mentioned on death certificates	SSCs are not typically included in postmortem screening and are not in the search terms used for cause of death, so no information is held.
National Records of Scotland (NRS)	Data on drug-related deaths in Scotland	No mentions of SSCs in records for deaths registered in Scotland from 2019 onwards. Death data for 2024, particularly when involving drugs, is provisional.
EU-MADNESS project	Detections in data provided by the National Records of Scotland for the period	No detections reported for the period 2013 to the end of the third quarter of 2024.
SPA PM toxicology	Detections in post-mortem forensic toxicology in Scotland	Do not test for SSC in post-mortem samples
NISRA	Data on drug-related deaths in Northern Ireland	No mentions to Sept 2024 of any SSC detected in post-mortem samples

No response has been received to date from:

- COPFS/Aberdeen (NHS Grampian)

Annex D: Possible revisions of the UK's cannabinoid controls

The novel cannabinoid-related materials considered in this report are of four types:-

- THC derivatives
- HHC and its derivatives
- Hydrogenated forms of CBD
- Cannabinoid acids

Some of these materials are outside the UK generic's current scope but produce similar psychoactive effects to THC and may, therefore, merit control under the MDA, rather than the PSA.

Hydrogenated forms of CBD such as H4-CBD are currently considered to have insufficient evidence of psychoactivity to merit control via the MDA.

Adding named materials to the MDA

Particular materials which have been widely identified in national and international drugs markets and which are considered to present sufficient risk of harm could simply be addressed by adding the individually named materials to the legislation, an approach already taken in a number of other countries. Based on reported potency and/or UK incidence these specific additions are:

- *THC derivatives:* 11-hydroxy THC
- *HHC and its derivatives*: HHC, HHCP, HHCH, 9-OH-HHC, 10-OH-HHC, 11-OH-HHC, 10-OH-HHCP, HHC-C8
- *Cannabinoid acids*: THCA-A, THCA-B

However, new variants can be expected to continue to emerge, so that an expansion of the generic control would potentially offer a more flexible response.

Broadening the scope of the UK generic

The current wording of the generic control on cannabinol derivatives within Part IV of Schedule 2 of the MDA is:-

"…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."

Materials that might be included in a revised generic.

THC derivatives

The current generic already covers THC isomers such as Δ8 variants and THC homologues with alkyl sidechains other than pentyl, such as THCP. In addition, the MDA's controls include any esters and ethers of these materials, so that most of the THC derivatives discussed in the report are already controlled by the generic.

One group of THC derivatives that is known to be psychoactive but is not covered by the generic is those that have a hydroxyl group attached to the methyl group at the 11-position. Originally only identified as potently active metabolites of cannabinoids, synthetic forms of 11-hydroxy materials (particularly 11-hydroxy-THC) are now being offered for sale as, for example, components of vaping products. One 11-hydroxy variant, HU-210 (the 11-hydroxy-

3-dimethylheptyl derivative of THC) is already specifically named as a Class B drug in the MDA and related materials can also be expected to be strong agonists.

HHC and its derivatives

Hexahydro forms of cannabinol are outside the scope of the current cannabinoid generic, but many would become controlled if the wording of the generic were to be expanded to include hexahydro as well as tetrahydro derivatives.

HU-243 (the 11-hydroxy-dimethylheptyl derivative of HHC) is known to be a potent CB1 agonist and is specifically named as a Class B drug in the MDA. 11-Hydroxy forms of related HHC derivatives are also likely to be potent agonists and could therefore be considered for inclusion.

Other hydroxy derivatives, such as 10-hydroxy variants, are also known to be psychoactive, have been identified as components of mixtures containing other SSCs and are being offered for sale by some webshops. However, their psychoactivity is reported to be relatively mild and they may therefore be more appropriate to remain under PSA control.

Cannabinoid acids

The acid forms of cannabinoids are reported to be essentially inactive but are direct precursors to active materials, requiring only the appliance of heat, such as in cooking, smoking, vaping or 'dabbing', to be converted by decarboxylation into active forms. The most commonly encountered examples of these materials are the THC acids THCA-A and THCA-B and these could be brought under control by specifically listing them within the MDA. Alternatively, materials of this type more generally could be brought under control by expanding the current generic to incorporate cannabinoids with acid groups at the 2- and 4- positions.

A possible expanded generic

New generic controls on SSCs introduced by other countries have been based around dibenzopyranol-type cores (see Annex B) to address derivatives of both THC and HHC. However, the UK's existing cannabinoid generic in Part IV of Schedule 2 of the MDA is already drafted to cover many THC derivatives and it can be broadened to cover many of the materials discussed here.

To allow for materials which are already listed, or which may become listed, by name in Part II of Schedule 2 of the MDA (Class B drugs) a revised wording for the UK generic to cover hexahydro, 11-hydroxy and acid forms would, therefore, be:-

"…the following substances, ***except where listed in 1(a) of Part II of Schedule 2 above and*** *except where contained in cannabis or cannabis resin, namely tetrahydro* ***or hexahydro*** *derivatives of cannabinol and 3-alkyl homologues of cannabinol or of its tetrahydro* ***or hexahydro*** *derivatives i****ncluding those derivatives substituted by a hydroxy group at the 11- position and those substituted by a carboxy group at the 2- or 4- position"***

If it is decided only to control the acid forms of THC, rather than those of other variants, the final words of the proposed generic after ***"…at the 11-position***" can be deleted and the two acids listed by name in Part II of Schedule 2 (Class B drugs) as:

Tetrahydrocannabinolic acid A (THC acid A, 1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6[H]-benzo(c)chromene-2-carboxylic acid), except where contained in cannabis or cannabis resin.

Tetrahydrocannabinolic acid B (THC acid B, 1-hydroxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6[H]-benzo(c)chromene-4-carboxylic acid), except where contained in cannabis or cannabis resin.

Annex E: List of Abbreviations Used In This Report

ACMD	Advisory Council On The Misuse Of Drugs
CBD	Cannabidiol
CBD-DMH	Dimethylheptyl cannabidiol
CDC	Centers for Disease Control
DEA	Drug Enforcement Administration
DMHP	Dimethylheptylpyran
DSTL	Defence Science and Technology Laboratory
ED	Emergency Department
EMCDDA	European Monitoring Centre for Drugs And Drug Addiction
ENDD	European New Drugs Database
EUDA	European Union Drugs Agency
EU-MADNESS	EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS
EVALI	E-cigarette or vaping product use-associated lung injury
FSNI	Forensic Science Northern Ireland
FTIR	Fourier Transfer Infrared Spectrometry
GC-MS	Gas Chromatography Mass Spectroscopy
IONA	Identification Of Novel Psychoactive Substances
IUPAC	International Union of Pure And Applied Chemistry
IV	Intravenously
HHC	Hexahydrocannabinol
HHCO-acetate	Hexahydrocannabinol acetate
HHC-H	Hexahydrocannabihexol
HHC-P	Hexahydrocannabiphorol
HHCP-O-acetate	Hexahydrocannabiphorol acetate
H2-CBD	Dihydrocannabidiol
H4-CBD	Tetrahydrocannabidiol
IQR	Inter-quartile range
MANDRAKE	Manchester Drug Analysis and Knowledge Exchange
MDA	Misuse Of Drugs Acts 1971
MDR	Misuse Of Drugs Regulations 2001
MHRA	Medicines And Healthcare Products Regulatory Agency

NCA	National Crime Agency
NISRA	Northern Ireland Statistics and Research Agency
NPIS	National Poisons Information Service
NPS	Novel Psychoactive Substances
NPSUM	The National Programme on Substance Use Mortality
NRS	National Records of Scotland
OH-	Hydroxy-
OHID	Office for Health Improvement and Disparities
ONS	Office for National Statistics
PHS	Drugs Team at Public Health Scotland
PM	Post-Mortem
PSA	Psychoactive Substances Act 2016
SCRAs	Synthetic Cannabinoid Receptor Agonists
SPA	Scottish Police Authority
SSC	Semi-synthetic cannabinoid
UN	United Nations
UNODC	United Nations Office on Drugs And Crime
THC	Tetrahydrocannabinol
THCA	Tetrahydrocannabinol acid
THC-B	Tetrahydrocannabutol
THCH	Tetrahydrocannabihexol
THC-O	Tetrahydrocannabinol Acetate
THCP	Tetrahydrocannabiphorol
THCP-O	Tetrahydrocannabiphorol acetate
WEDINOS	Welsh Emerging Drug & Identification Of Novel Substances
WHO	World Health Organization

Annex F: Chair and Members of ACMD Semi-Synthetic Cannabinoid Working Group

Chair of Working Group	
Professor Simon Thomas	Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Members of Working Group	
Mr Peter Cain	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Tom Freeman*	Reader, Department of Psychology Addiction and Mental Health Group, University of Bath
Dr John Corkery	Associate Professor in Research (Psychoactive Substances' Epidemiology, Toxicology and Mortality), University of Hertfordshire; mortality. Epidemiological lead for EU-MADNESS project
Professor Stephen Husbands	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	Professor of Pain Management, Faculty of Science, Nottingham University
Professor Christophe Stove*	Laboratory Manager of Toxicology, Professor in the Faculty of Pharmaceutical Sciences, Ghent University, Belgium
Mr Ric Treble	Retired Laboratory of the Government Chemist (LGC) Expert
Dr David Wood	Consultant Physician and Clinical Toxicologist, Guy's and St Thomas' NHS Foundation Trust and Reader in Clinical Toxicology at King's College London
Dr Carl Fletcher*	Principal Scientist at UK Border Force and DSTL

*denotes co-opted member of the Working Group

Annex G: ACMD Novel Psychoactive Substances (NPS) Committee Membership, At Time of Publication

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Mr Peter Cain**	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Caroline Copeland	Senior Lecturer in Pharmacology & Toxicology at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Dr John Corkery**	Associate Professor in Research (Psychoactive Substances' Epidemiology, Toxicology and Mortality), University of Hertfordshire; mortality. Epidemiological lead for EU-MADNESS project
Professor Colin Davidson	Professor of Neuropharmacology, University of Central Lancashire
Professor Amira Guirguis	Professor of Pharmacy, MPharm Programme Director and Deputy Pro Vice Chancellor at Swansea University
Dr Hilary Hamnett	Associate Professor in Forensic Science, University of Lincoln
Professor Graeme Henderson	Honorary Professor of Pharmacology, School of Physiology, Pharmacology & Neuroscience, University of Bristol
Professor Stephen Husbands	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	Professor in Clinical Pharmacy Practice at the University of Nottingham
Professor Fiona Measham**	Professor and Chair in Criminology at the University of Liverpool; Co-Founder and Co-Director of the Loop
Dr Lorna Nisbet	Senior Lecturer at the Leverhulme Research Centre for Forensic Science, University of Dundee
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Professor Simon Thomas	ACMD NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble**	Retired Laboratory of the Government Chemist (LGC) Expert
Dr David Wood	Consultant Physician and Clinical Toxicologist, Guy's and St Thomas' NHS Foundation Trust and Reader in Clinical Toxicology at King's College London

**denotes co-opted member of ACMD Novel Psychoactive Substances Committee

Annex H: ACMD Membership, At Time of Publication

Professor Judith Aldridge	Professor of Criminology at the University of Manchester
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Dr Caroline Copeland	Senior Lecturer in Pharmacology & Toxicology, King's College London and the Director of the National Programme on Substance Abuse Deaths
Professor Colin Davidson	Professor of Neuropharmacology, University of Central Lancashire
Professor Karen Ersche	Professor of Addiction Neuroscience at the Department of Psychiatry at the University of Cambridge
Mr Mohammed Fessal	Chief Pharmacist, Change Grow Live
Professor Amira Guirguis	Professor of Pharmacy, MPharm Programme Director and Deputy Pro Vice Chancellor at Swansea University
Dr Hilary Hamnett	Associate Professor in Forensic Science at the University of Lincoln
Mr Jason Harwin	Director and Co-founder of E-T-E Solutions Limited
Professor Graeme Henderson	Honorary Professor of Pharmacology, School of Physiology, Pharmacology & Neuroscience, University of Bristol
Professor Katy Holloway	Professor of Criminology, University of South Wales
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Mrs Fiona Spargo-Mabbs	Director and Founder, Daniel Sargo-Mabbs Foundation. Chair, Drug Education Forum

Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Professor Paul Stokes	Professor of Mood Disorders and Psychopharmacology, King's College, London
Professor Harry Sumnall	Professor in Substance Use, Liverpool John Moores University (LJMU)
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Professor Derek Tracy	Medical Director of West London NHS Trust
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Annex I: Range and Quality of Evidence

This report draws on evidence from peer-reviewed literature (UK and international publications) and government reports and considered international approaches when drafting its recommendations. The evidence gathered was considered in accordance with the ACMD's standard operating procedure for quality of evidence [ACMD, 2020b].

To evidence the identification and prevalence in the UK of the SSCs considered in this report, the ACMD's NPS Committee wrote to stakeholders requesting available data on SSCs they had encountered. Details of organisations contacted and responses received are provided in Annex C.

The ACMD also sought information on medicinal use of SSCs from the Medicines and Healthcare products Regulatory Agency (MHRA).

It is important to note that forensic analysis is inconsistent across the UK and as a result, some 'novel' compounds present in samples may not be identified. As a result, information being fed into reporting agencies that were approached may not be representative and it remains possible that some SSCs that are already in circulation in the UK have not yet been identified.

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