World Health Organization

Critical review report

Hexahydrocannabinol

Expert Committee on Drug Dependence

Forty-seventh Meeting

Geneva, 14–18 October 2024

This report contains the views of an international group of experts, which do not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Executive summary

Hexahydrocannabinol (HHC) is a semi-synthetic cannabinoid that is typically synthesized from cannabidiol as a precursor, although it is also found in trace amounts as a phytocannabinoid in certain cannabis strains. Two epimers are contained in the marketed product: (9*R*)-hexahydrocannabinol and (9*S*)-hexahydrocannabinol, with an average (9*R*):(9*S*) ratio of 1.4:1. Although hexahydrocannabinol was discovered in 1940, it did not emerge onto the market until September 2021 in the USA, followed by its appearance and rapid distribution in Europe in May 2022.

Hexahydrocannabinol is administered by several routes: inhalation, oral and sublingual. Formulations for oral consumption include tinctures and edible products. Hexahydrocannabinol has also been detected in electronic cigarette cartridges and has been sprayed on hemp plant material for smoking. While information on dosage is sparse, websites that advertise the product for sale recommend doses ranging from 5 to 60 mg. Self-reported use of doses of 50–100 mg have been reported by poison centres in France, although analytical confirmation is lacking.

Like many cannabinoids, hexahydrocannabinol is highly lipophilic, suggesting its ready absorption and distribution to the brain and periphery. It undergoes extensive hepatic phase-I biotransformation involving oxidation and hydroxylation, followed by phase-II glucuronidation. Major identified phase-I metabolites identified in blood and urine include 11-hydroxy-9*R*-hexahydrocannabinol (11-OH-9*R*-HHC) and 11-nor-carboxy-9R-hexahydrocannabinol (9*R*-HHC-COOH). The corresponding epimers of these metabolites (11-OH-9*S*- hexahydrocannabinol and 9*S*-HHC-COOH) are usually detected at lower concentrations. As hexahydrocannabinol metabolites are cross-reactive with 11-nor-carboxy-tetrahydrocannabinol (THC-COOH), a major Δ^9-THC metabolite, in non-targeted immunoassays, a false positive reading for THC-COOH may be obtained in the absence of Δ^9-THC consumption due to the presence of hexahydrocannabinol.

Recent in-vitro and in-vivo studies suggest that the psychoactivity of the substance is due primarily to the (9*R*)-hexahydrocannabinol configuration. This epimer has CB1 receptor binding affinity, which is comparable to that obtained with Δ^9-tetrahydrocannabinol, as well as similar affinity for the CB2 receptor. In contrast, the CB1 receptor affinity for 9S-hexahydrocannabinol is 12 times lower. In a functional assay, both hexahydrocannabinol epimers were partial agonists (as is Δ^9-THC), but (9*R*)-hexahydrocannabinol was 17 times more potent than (9*S*)-hexahydrocannabinol in activating CB1 receptors. In tests in which psychoactive cannabinoids produce characteristic effects in mice, (9*R*)-hexahydrocannabinol decreased locomotion, increased antinoception, and showed trends towards causing catalepsy and hypothermia. (9*S*)-hexahydrocannabinol had no effect in any of the tests.

Hexahydrocannabinol showed little toxicity in vitro. It was not mutagenic in the Ames test, did not block HERG-encoded channels in HEK293 cells and was not cytotoxic to human hepatocytes. Potential cytotoxicity was observed in human lung fibroblasts; however, this effect was seen only at high concentrations (> 10 μM) and was comparable to the effect reported with the control, chlorpromazine.

People who use hexahydrocannabinol have described effects such as relaxation, euphoria, calming, sleepiness and hunger. While some people reported that they used hexahydrocannabinol

specifically for its euphoric effects, others reported using it for self-medication for anxiety, pain relief, sleep difficulty or to treat symptoms of withdrawal from cannabis or benzodiazepines. Undesired effects such as withdrawal (e.g. sleep difficulty, depressed mood), psychosis and uncontrolled tremors have also been noted. Serious adverse effects have been reported by medical authorities in several cases. Between January 2022 and May 2023, three patients with analytically confirmed sole exposure to hexahydrocannabinol were hospitalized in France with moderate to severe symptoms that involved several physiological systems, including cardiovascular, gastrointestinal, neurological, psychiatric and respiratory. Other cases occurred in Czechia, where 12 children who consumed hexahydrocannabinol-containing sweets were admitted to hospital. Hexahydrocannabinol was suspected of precipitating the onset of psychosis in two individuals in Ireland.

Hexahydrocannabinol has been confirmed analytically in blood samples from drivers suspected of driving under the influence of cannabis in Germany and Sweden. In early 2023, the positivity rate of hexahydrocannabinol detection in Swedish drivers who were stopped on suspicion of cannabis use increased sharply, from 5% in January to 14% in February/March and to 50% in April/May. This reported increase is consistent with a large rise in the number of posts that mentioned hexahydrocannabinol on a Swedish Internet chat site during 2022 and 2023. By the end of 2022, hexahydrocannabinol had been detected in 70% of European Union Member States. Countries in which hexahydrocannabinol has been identified include Austria, Belgium, Bulgaria, Colombia, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Latvia, Lithuania, Netherlands (Kingdom of the), Norway, Poland, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the United Kingdom and the USA. It is regulated under psychoactive drug control regulations in at least 11 countries.

1. Substance identification

A International Nonproprietary Name (INN)

Not assigned

B Chemical Abstracts Service (CAS) Registry Number

6692-85-9; 1972-09-4 (unspecified stereochemistry)
36403-90-4 (6a*R*,9*R*,10a*R*) isomer (9*R*-isomer)
36403-91-5 (6a*R*,9*S*,10a*R*) isomer (9*S*-isomer)
59042-47-6 [6a*S*-(6aα,9β,10aα)]- isomer
69855-11-4 [6a*R*-(6aα,9α,10aα)]-isomer
69855-12-5 [6a*R*-(6aα,9β,10aα)]-isomer
69880-65-5 [6a*S*-(6aα,9β,10aβ)]-isomer
103476-58-0 (6a*S*,9*S*,10a*S*)-isomer
69855-14-7 *rel*-(6a*R*,9*R*,10a*R*)-isomer
23050-51-3 *rel*-(6a*R*,9*R*,10a*S*)-isomer
58617-32-6 (6aα,9β,10aα)-isomer
146338-70-7 *rel*-(6a*R*,9*S*,10a*R*)-isomer
946512-74-9 rel-(6aR,10aR)-isomer
2891843-77-7 (6a*R*,10a*R*)-isomer

C Other chemical names

Unspecified stereochemistry

HHC (the acronym "HHC" has also been used for 9-nor-9-hydroxyhexahydrocannabinol and for hexahydrocurcumin) *(1)*
Hexahydrocannabinol
Hexahydro-CBN
HXC

9R-isomer

(6a*R*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol (ACI)
6*H*-Dibenzo[*b,d*]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, [6a*R*-(6aα,9α,10aβ)]- (ZCI)
6*H*-Dibenzo[*b,d*]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, stereoisomer (8CI)
(–)-Hexahydrocannabinol
(–)-*trans*-Hexahydrocannabinol
trans-(6a*R*,9*R*,10a*R*)-HHC
9β-Hexahydrocannabinol
11β-Hexahydrocannabinol
9β-HHC
9(*R*)-HHC
11β-HHC

(−) NL-105

(9S)-isomer

(6a*R*,9*S*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[b,d]pyran-1-ol (ACI)
6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, [6a*R*-(6aα,9β,10aβ)]- (9CI)
6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, stereoisomer (8CI)
9α-Hexahydrocannabinol
11α-Hexahydrocannabinol
9α-HHC
9(*S*)-HHC
trans-(6a*R*,9*S*,10a*R*)-HHC
11α-HHC
(−) NL-106

D Trade names

Currently marketed hexahydrocannabinol is semi-synthetic and is typically a mixture of the 9S and 9R epimers. It is sold under the trade names HHC, Hexahydrocannabinol, Hexahydro-CBN and HXC. As an analytical standard it is sold under the trade names 9(S)-Hexahydrocannabinol (9S-HHC) and 9(R)-Hexahydrocannabinol (9R-HHC) *(2,3)*.

E Street names

Hexahydrocannabinol products are currently available on the market in various forms, including low-THC cannabis flowers and resins infused or sprayed with hexahydrocannabinol, disposable vape pens, e-liquids and cartridges for electronic cigarettes, edibles such as gummies and marshmallows, tinctures resembling dietary supplements and hexahydrocannabinol distillate oils *(1,4).*

Hexahydrocannabinol-containing products are packaged in attractive, brightly coloured, sophisticated designs. Low-THC cannabis flowers with hexahydrocannabinol are marketed under popular cannabis strain names such as Afghan Kush, Amnesia, BubbleGum Kush, Strawberry Kush, Pineapple Express and Purple Haze, likely to suggest effects similar to those of the strains *(1,4)*.

*F **Physical appearance***

Hexahydrocannabinol has been described as a colourless viscous oil or resin *(5,6)* that tends to dark orange after exposure to oxygen, with a slightly floral odour *(4)*.

G WHO review history

Hexahydrocannabinol has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name:
6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (unspecified stereochemistry)
(6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (9*S* isomer)
(6a*R*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (9*R* isomer)

CA Index name:
6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-(7CI, 8CI, 9CI, ACI) (unspecified stereochemistry)
6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, (6a*R*,9*S*,10a*R*)- (ACI) (9*S* isomer)
6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, (6a*R*,9*R*,10a*R*)- (9CI, ACI) (9*R* isomer)

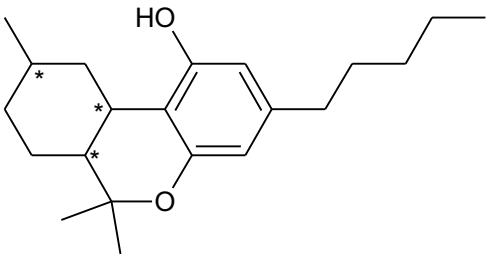
Canonical SMILES:
OC=1C=C(C=C2OC(C)(C)C3CCC(C)CC3C12)CCCCC (unspecified stereochemistry)
OC1=C2[C@]3([C@](C(C)(C)OC2=CC(CCCCC)=C1)(CC[C@H](C)C3)[H])[H] (9*S* isomer)
OC1=C2[C@]3([C@](C(C)(C)OC2=CC(CCCCC)=C1)(CC[C@@H](C)C3)[H])[H] (9*R* isomer)

InChI:
InChI=1S/C21H32O2/c1-5-6-7-8-15-12-18(22)20-16-11-14(2)9-10-17(16)21(3,4)23-19(20)13-15/h12-14,16-17,22H,5-11H2,1-4H3 (unspecified stereochemistry)
InChI=1S/C21H32O2/c1-5-6-7-8-15-12-18(22)20-16-11-14(2)9-10-17(16)21(3,4)23-19(20)13-15/h12-14,16-17,22H,5-11H2,1-4H3/t14-,16+,17+/m0/s1 (9*S* isomer)
InChI=1S/C21H32O2/c1-5-6-7-8-15-12-18(22)20-16-11-14(2)9-10-17(16)21(3,4)23-19(20)13-15/h12-14,16-17,22H,5-11H2,1-4H3/t14-,16-,17-/m1/s1 (9*R* isomer)

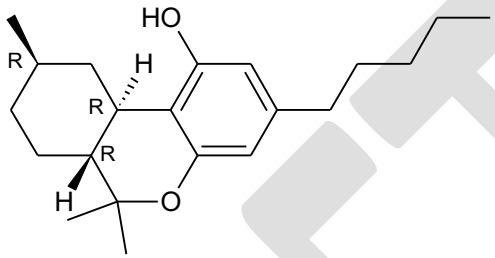
InChI key:
XKRHRBJLCLXSGE-UHFFFAOYSA-N (unspecified stereochemistry)
XKRHRBJLCLXSGE-USXIJHARSA-N (9*S* isomer)
XKRHRBJLCLXSGE-DJIMGWMZSA-N (9*R* isomer)

B Chemical structure

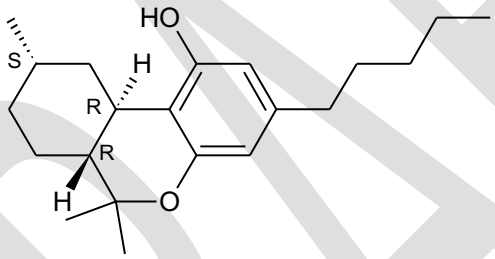
Free base:



Unspecified stereochemistry



(6a*R*,9*R*,10a*R*)-isomer (9*R*-HHC)

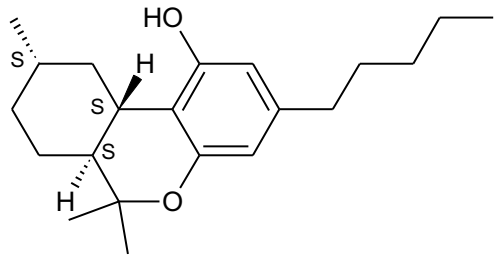


(6a*R*,9*S*,10a*R*)-isomer (9S-HHC)

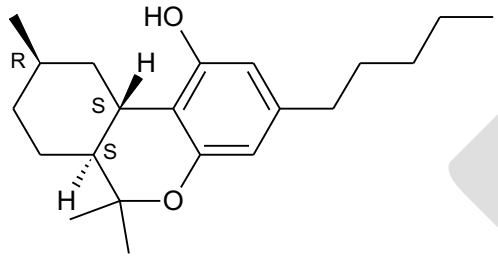
Molecular formula: $C_{21}H_{32}O_2$
Molecular weight: 316.48 g/mol

C Stereoisomers

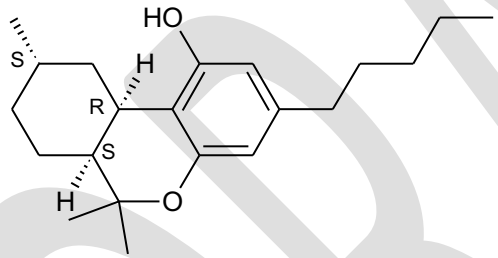
As hexahydrocannabinol has three stereogenic carbon atoms (6a, 9 and 10a), eight stereoisomers with four pairs of enantiomers are possible. The structures shown above depict hexahydrocannabinol of unspecified stereochemistry and the two diastereomers (epimers), in which the configurations of the 6a and 10a carbon atoms are identical to those of (–)-*trans*-Δ^9-THC (6aR,7,8,10a*R*-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol). These two epimers (9*R*-hexahydrocannabinol and 9*S*- hexahydrocannabinol) are the expected main components of HHC-containing products manufactured from cannabidiol. The chemical structures of the other stereoisomers are shown below.



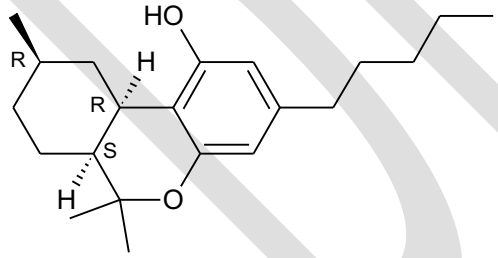
(6a*S*,9*S*,10a*S*)-isomer



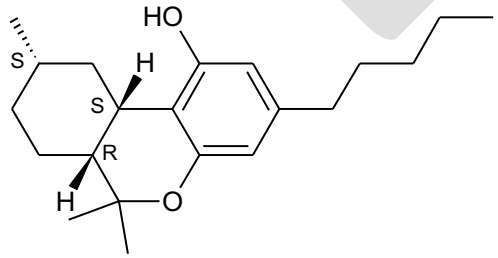
(6a*S*,9*R*,10a*S*)-isomer



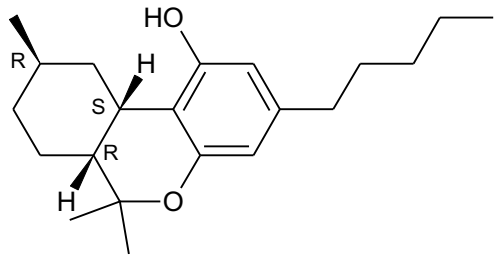
(6a*S*,9*S*,10a*R*)-isomer



(6a*S*,9*R*,10a*R*)-isomer



(6a*R*,9*S*,10a*S*)-isomer



(6a*R*,9*R*,10a*S*)-isomer

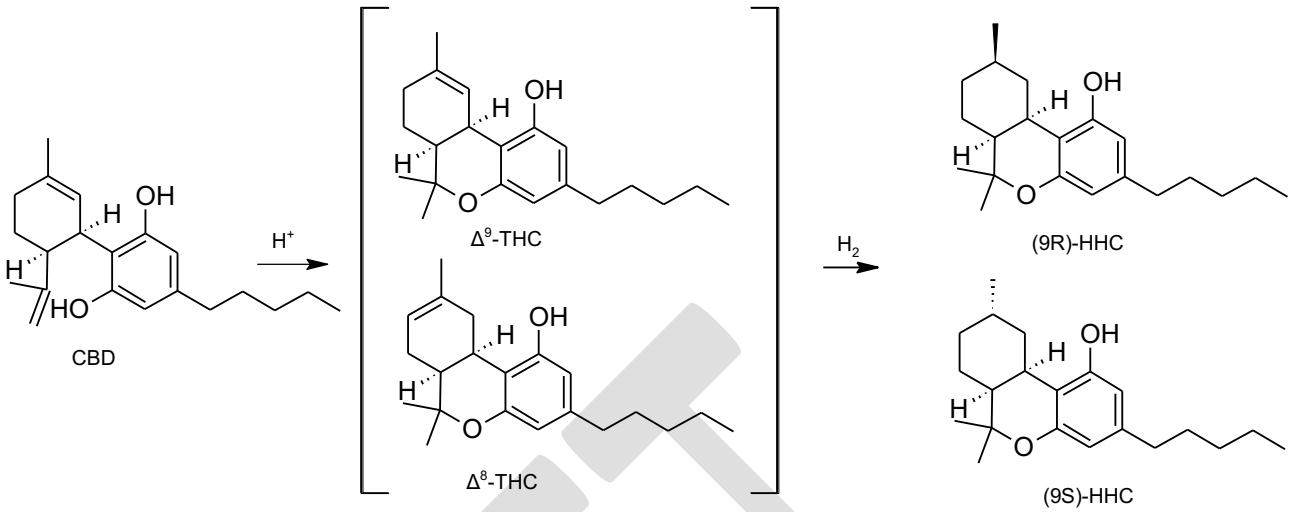
D Methods and ease of illicit manufacture

Although the technical methods of large-scale production of hexahydrocannabinol are not well known, it is suggested to be derived from (–)-*trans*-cannabidiol (CBD) through a two-step synthesis *(1,4)*.

The first step involves acid-catalysed cyclization of CBD, which leads to either Δ^9-THC, Δ^8-THC or a mixture of the two isomers, with various by-products *(1)*. The ratio of the two THC isomers and the amount and chemical nature of the byproducts depend on the reaction conditions *(7)*. Gaoni & Mechoulam *(8)* obtained Δ^9-THC by treating CBD with hydrochloric acid as a catalyst for a short time, while Δ^8-THC was obtained when CBD was treated with *p*-toluenesulfonic acid for longer. More recently, an in-depth study of the product composition of the cyclization of CBD was conducted with various protic and Lewis acids in different solvents *(9)*.

In the second step, reduction of the double bond on the terpene group of Δ^9-THC/Δ^8-THC results in a mixture of the two (9*R*)- and (9*S*)- hexahydrocannabinol epimers. The ratio of the two epimers depends mainly on the starting reactant (Δ^9-THC or Δ^8-THC) and the catalyst used *(1,4,7)*. Catalytic hydrogenation of Δ^9-THC with a platinum catalyst leads to an excess of the 9*R*- hexahydrocannabinol isomer over the 9*S* isomer, while use of a palladium catalyst reverses the ratio, resulting in an excess of the 9*S* epimer over the 9*R* epimer *(7,10)*. In contrast, hydrogenation of Δ^8-THC with a platinum catalyst favours production of the 9*S*- hexahydrocannabinol isomer over the 9*R*- hexahydrocannabinol isomer in a 3:1 ratio *(7,8,11)*. Recently, tri(acetylacetonato)iron(III) was reported as the hydrogen atom donor catalyst for radical reduction reactions in combination with thiophenol and sylilbenzene to reduce Δ^8-THC, resulting in an epimeric ratio of 11:1 ((9*R*)-hexahydrocannabinol:(9*S*)- hexahydrocannabinol) *(12)*.

The presence of both (9*R*)- and (9*S*)- hexahydrocannabinol epimers in various commercial hexahydrocannabinol products and of impurities of Δ^9-THC and Δ^8-THC has led some authors to suggest that the synthetic pathway used to manufacture commercial hexahydrocannabinol starts from CBD, a process that is relatively simple and does not require sophisticated equipment or highly trained personnel *(4,7)*.



Scheme 1
Synthesis of HHC. Step 1: Cyclization of CBD. Step 2: Hydrogenation of Δ^9-THC/Δ^8-THC.

A second approach for the synthesis of hexahydrocannabinol is total synthesis, with small molecules of both natural and synthetic origin as starting materials *(4)*. This approach has the advantage over synthesis with CBD as the starting material that it allows for production of single stereoisomers or hexahydrocannabinol analogues *(1,4,13)*. The first total synthesis of hexahydrocannabinol was proposed by Adams et al. in 1940 *(5)* through hydrogenation of $\Delta^{6a,7}$-THC. The first total stereoselective synthesis of (9*R*)- hexahydrocannabinol and its (9*S*)-isomer was performed by Tietze et al. *(14)*, starting with 5-pentylcyclohexane-1,3-dione and optically pure citronellal via an intramolecular Diels-Alder reaction and aldol condensation, followed by aromatization and elimination. The reaction was later modified by using olivetol, which eliminates the use of toxic selenium reagents in the aromatization step. Specifically, the one-step condensation reaction of (*R*)-citronellal with olivetol in the presence of diethylaluminium chloride *(15,16)* or ethylenediamine diacetate/triethylamine *(17)* leads to (9*R*)- hexahydrocannabinol in good yields and with stereochemical purity > 76% *(1,4)*. This synthetic method has the advantage that it is applicable for the production of hexahydrocannabinol analogues such as hexahydrocannabiphorol (hexahydrocannabinol-P) or hexahydrocannabihexol (hexahydrocannabinol-H), with olivetol homologues with seven- or six-carbon chains, respectively *(1,4,13)*. The total synthesis of hexahydrocannabinol is, however, a more complex method than the semi-synthetic process starting from CBD. Moreover, it requires more sophisticated equipment and more specialized personnel.

E Chemical properties

Melting-point: No information was found.

Boiling-point
153–155 °C (0.1 mm Hg) (unspecified stereochemistry) *(1,4,5)*
174–177 °C (0.1 mm Hg) (unspecified stereochemistry) *(8)*

Solubility

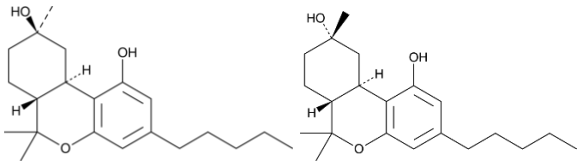
There is little information on the solubility of HHC, but data on structurally related phytocannabinoids suggest high lipid solubility and poor water solubility *(1,4)*. A solubility of 10 mg/mL in acetonitrile has been reported for both 9*R* and 9*S* epimers *(2,3)*.

Optical rotation

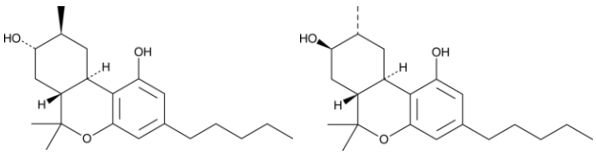
$[\alpha]_D$ −85.4 (c. 0.30, $CHCl_3$) (9R-HHC) *(17)*
$[\alpha]_D$ −107 ($CHCl_3$) (9R-HHC) *(8)*
$[\alpha]_D$ −109 ($CHCl_3$) (9S-HHC) *(8)*

F Identification and analysis

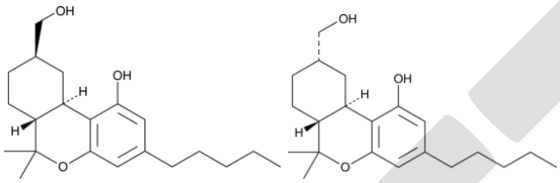
Synthetic (9*R*)- hexahydrocannabinol and (9*S*)- hexahydrocannabinol were both characterized, and optical rotatory properties *(8,17)*, ultraviolet (UV) properties *(7)*, proton magnetic resonance (^{1}H NMR) properties *(7,10,11)*, carbon magnetic resonance (^{13}C NMR) properties *(7,10,18)*, infrared (IR) properties *(8,16,17)* and mass spectrometry (MS) properties *(2,3,7)* have been reported. UV-visible spectroscopy reveals the hexahydrocannabinol spectrum, with primary absorption peaks at wavelengths of 272 and 282 nm *(4,7,13)*. ^{1}H-NMR spectroscopy can differentiate the two epimers by analysing the chemical shifts of protons near the phenolic group, which are affected by solvent interactions *(1,4,7,10,13)*. ^{13}C-NMR spectroscopy distinguishes the 9*S*- and 9*R*- stereoisomers from the chemical shifts of carbon atoms in the cycloalkane segment, the 9*R* epimer displaying a downfield shift for all carbon atoms except C6a *(1,4,7,10,13)*. Hence, this technique is essential for structural identification. As the MS fragmentation patterns of the 9*S* and 9*R* hexahydrocannabinol epimers are almost identical, the stereochemical composition of samples is determined by coupling MS with a chromatographic technique such as gas chromatography (GC) or liquid chromatography (LC), followed by confirmation with a standard of known epimeric purity *(1,4,13)*. Pure 9*R*- hexahydrocannabinol and its labelled version (9(*R*)-hexahydrocannabinol -d_9), 9*S*-HHC, eight metabolites ((±)-9(*S*)-hydroxy HHC, (±)-9(*R*)-hydroxy hexahydrocannabinol, 8(*S*)-hydroxy-9(*S*)- hexahydrocannabinol, 8(*R*)-hydroxy-9(*R*)-hexahydrocannabinol, 11-hydroxy-9(*R*)- hexahydrocannabinol, 11-hydroxy-9(*S*)-hexahydrocannabinol, 11-nor-9(*R*)-carboxy- hexahydrocannabinol and 11-nor-9(*S*)-carboxy- hexahydrocannabinol), are available as reference materials from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(2,3)*.



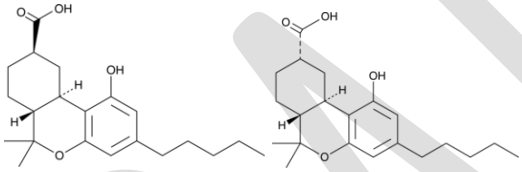
(±)-9(*S*)-Hydroxy Hexahydrocannabinol (±) and 9(*R*)--hydroxy Hexahydrocannabinol



8(*S*)-Hydroxy-9(*S*)-hexahydrocannabinol and 8(*R*)-hydroxy-9(*R*)-hexahydrocannabinol



11-Hydroxy-9(*R*)-hexahydrocannabinol and 11-hydroxy-9(*S*)-hexahydrocannabinol



11-nor-9(*R*)-carboxy-Hexahydrocannabinol 11-nor-9(*S*)-carboxy-Hexahydrocannabinol

Fig. 1
Commercially available hexahydrocannabinol metabolites

Source: Cayman Chemical *(2,3)*

Several thin-layer chromatography *(8,10,14)*, GC *(10,18,19)* and LC *(7,10,18,20–24)* analytical methods coupled with detectors such as UV and MS have been published. These methods can readily separate the 9*S* and 9*R* hexahydrocannabinol epimers *(1,4,7,13)*. Early research was conducted to explore the relations between chemical structure and GC retention times for different cannabis constituents and synthetic cannabinoids, including hexahydrocannabinol, with both unmodified and trimethylsilyl (TMS)-derivatized analytes *(10,18,19)*. LC has also proven effective in separating these cannabinoids and the hexahydrocannabinol epimers *(1,4,7,13)*. Recently, LC-MS/MS bioanalytical methods with reversed-phase or chiral stationary phases have been developed to detect (9*R*)- hexahydrocannabinol and (9*S*)-hexahydrocannabinol and their metabolites in human blood, oral fluid and urine *(20,21,23–25).* Several radioimmunoassay methods designed mainly for detection of cannabis cross-react with other phytocannabinoids and their metabolites, including hexahydrocannabinol, regardless of epimeric purity *(1,4,13)*. Derne et al. *(26)* suggested that, in the absence of concomitant THC, the vast majority of

hexahydrocannabinol in users may not be detected by immunoassays; only comprehensive instrumental analytical techniques will accurately assess the spread of recreational use of hexahydrocannabinol.

3. Ease of conversion into controlled substances

The published literature does not indicate whether hexahydrocannabinol can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

Several routes of administration have been used to take hexahydrocannabinol, including inhalation, oral and sublingual *(1,25,27–29)*. Formulations for oral consumption include tinctures and edibles. Hexahydrocannabinol has been detected in electronic cigarette cartridges and sprayed on hemp plant material for smoking. This information was derived from self-reports by people who use hexahydrocannabinol and from reports on the formulation of marketed products and seized material.

No reliable information on standard doses was identified. Websites that advertise hexahydrocannabinol products for sale recommend different doses according to the experience of the person who intends to use the product (e.g. 5–12 mg for "beginners", 12–30 mg for "intermediate" and 30–≥ 60 mg for "pros" *(30,31)*. Doses of 50–100 mg were self-reported in a study of cases referred to poisoning centres in France, the onset of symptoms occurring 10–240 min (mean, 101 min) after consumption *(29)*. While the amount of hexahydrocannabinol per unit (e.g. liquid cartridge, edible) is often listed on branded products, the accuracy of this information is uncertain, as analytical verification of these amounts is not usually provided.

B Pharmacokinetics

Like many cannabinoids, hexahydrocannabinol has a low topological polar surface area (calculated to be 29.46, a value that is identical to that of Δ^9- and Δ^8-tetrahydrocannabinol). This value suggests high lipophilicity, which facilitates absorption and distribution through cellular membranes, including penetration of the blood–brain barrier *(1)*. No other information on the absorption and distribution of hexahydrocannabinol was found.

The results of recent studies on the metabolism of hexahydrocannabinol in humans have shown that the compound undergoes extensive hepatic metabolism. While the relative proportions of different metabolites reported differ between studies, analysis of blood and urine samples in all the studies revealed phase-I reactions of oxidation and hydroxylation, primarily at C11 and at the pentyl side-chain positions on the molecule *(20,24,32,33)*. The major metabolites identified were 11-hydroxy-9*R*-hexahydrocannabinol and 11-nor-carboxy-9R-hexahydrocannabinol (9*R*-HHC-COOH). The corresponding epimers of these metabolites were not identified as

frequently or were detected at lower concentrations *(20,24,34)*. As studies have reported higher amounts of 9*R*- hexahydrocannabinol than 9*S*-hexahydrocannabinol in sampled products purchased on the drug market *(7,12),* the findings may have been due to less 9*S*- hexahydrocannabinol in the consumed product. In addition, faster elimination of 9*S*- hexahydrocannabinol than of 9*R*-hexahydrocannabinol has been reported after consumption of a 50:50 racemic mixture of the two epimers *(20)*. In urine, 4'OH- hexahydrocannabinol was identified as a potentially unique and abundant phase-I metabolite that could serve as a marker for exposure *(33)*. Phase-II metabolites resulting from glucuronidation of the C1 hydroxyl group have also been reported *(34)*.

Analysis of absorption and elimination after smoking of a 50:50 mix of (9*R*)- and (9*S*)-hexahydrocannabinol showed different time courses for the two epimers, (9*R*)-hexahydrocannabinol being absorbed more efficiently *(20)*. At every time point during the 3-h measurement period, the serum concentrations of (9*R*)-hexahydrocannabinol exceeded those of (9*S*)-hexahydrocannabinol, with mean maximum concentrations (C_{max}) of 7.9 ng/mL and 2.3 ng/mL, respectively. The apparent half-lives of the epimers were similar (1.3 and 1.6 h for 9*R*-hexahydrocannabinol and 9*S*-HHC, respectively).

Analysis by non-targeted immunoassays of blood samples from people with suspected cannabis exposure showed cross-reactivity of hexahydrocannabinol metabolites with 11-nor-carboxy-tetrahydrocannabinol (THC-COOH), a major Δ^9-tetrahydrocannabinol metabolite *(24,34,35)*. The results suggest that exposure to hexahydrocannabinol could cause a positive reading for THC-COOH without consumption of Δ^9-tetrahydrocannabinol.

C Pharmacodynamics

Hexahydrocannabinol is a semi-synthetic cannabinoid that may also be present naturally in the cannabis plant in trace amounts. The most likely epimers contained in unapproved marketed products are (9*R*)-hexahydrocannabinol and (9*S*)-hexahydrocannabinol, with an average (9*R*):(9*S*) ratio of 1.4:1 *(12)*. Although hexahydrocannabinol was discovered in 1940 *(5)*, it has received relatively little research attention, especially as compared with well-known cannabinoids such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol. Further, interpretation of early pharmacological studies is complicated by the unknown purity or composition of the substance and lack of procedures to measure cannabinoid receptor binding and functioning *(4,13)*. Hence, this review focuses on the results of more recent studies of pharmacodynamics.

Recent in-vitro and in-vivo studies suggest that the psychoactivity of the substance is due primarily to the (9*R*)-hexahydrocannabinol configuration. In vivo, a single dose (10 mg/kg) of each epimer of hexahydrocannabinol was assessed in a tetrad of tests in which psychoactive cannabinoids produce characteristic effects. Whereas the (9*R*)-hexahydrocannabinol decreased locomotion, increased antinoception and showed trends to producing catalepsy and hypothermia, (9*S*)-hexahydrocannabinol had no effect in any of the tests *(7)*.

In-vitro binding affinity (K_i) for (9*R*)-hexahydrocannabinol for human CB1 and CB2 receptors expressed in Chinese hamster ovary cells were 15 ± 0.8 nM and 13 ± 0.4 nM, respectively. In comparison, the CB1 and CB2 binding affinities of Δ^9-THC in the same study were 15 ± 4.4 nM and 9.1 ± 3.6 nM, respectively. In contrast, the affinities for (9*S*)-hexahydrocannabinol were substantially lower than those of both the (9*R*)-epimer and Δ^9-THC (Ki = 176 ± 3.3 nM for CB1 receptors and 105 ± 26 nM for CB2 receptors) *(12)*. In a functional assay of inhibition of forskolin-stimulated cAMP, both hexahydrocannabinol epimers were partial agonists (as is Δ^9-THC), but (9*R*)-hexahydrocannabinol was 17 times more potent than (9*S*)-hexahydrocannabinol in activating CB1 receptors (EC_{50} = 3.4 ± 1.5 nM and 57 ± 19 nM, respectively) and nine times more potent in activating CB2 receptors (EC_{50} = 6.2 ± 2.1 nM and 56 ± 10 nM, respectively) *(12*). The results of other functional assays showed that (9*R*)-hexahydrocannabinol directly activated CB1 receptor G-proteins, stimulated GPK3 and β-arrestin2 pathways, enhanced internalization of activated CB1 receptors and produced low levels of ERK1/2 phosphorylation *(36)*. The effectiveness varied among the assays in a pattern different from that produced by Δ^9-THC, suggesting biased intracellular signalling in CB1 receptor pathways. Like Δ^9-THC, hexahydrocannabinol has been shown to activate transient receptor potential ankyrin 1 (TRPA1) receptors *(15)*.

5. Toxicology

The preclinical toxicology of hexahydrocannabinol (racemic mixture of *R*- and *S*-epimers) was examined in a single study *(37)*. In the systems evaluated, hexahydrocannabinol showed little toxicity in vitro. It was not mutagenic in an Ames test, it did not block HERG-encoded channels in HEK293 cells, and it was not cytotoxicity in human hepatocytes. Potential cytotoxicity was observed in human lung fibroblasts but only at high concentrations (> 10 μM) and was comparable to the effect reported with the control, chlorpromazine.

6. Adverse reactions in humans

Between January 2022 and May 2023, three patients with analytically confirmed exposure only to hexahydrocannabinol were hospitalized in France *(29)*. The patients had moderate to severe symptoms involving several physiological systems, including cardiovascular (palpitations, chest pain, tachycardia), gastrointestinal (nausea, vomiting), neurological (dizziness, tremors, spatiotemporal disorientation, dyskinesia, convulsions), psychiatric (anxiety, agitation) and respiratory (respiratory pause and discomfort) systems *(29,38)*. Hexahydrocannabinol was also suspected of precipitating the onset of psychosis in two individuals in Ireland *(39)*.

People who used hexahydrocannabinol have described effects such as relaxation, euphoria, calming, sleepiness and hunger *(40)*. While some people reported that they used hexahydrocannabinol specifically for its euphoric effects, others reported using the substance as self-medication for anxiety, pain relief, sleep difficulty or to treat symptoms of withdrawal from cannabis or benzodiazepines *(13,29)*. Undesired effects such as withdrawal effects (e.g. sleep difficulty, depressed mood), psychosis and uncontrolled

tremors have also been noted *(13,35,40)*. Self-reported experiences of the psychological effects of hexahydrocannabinol should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7. Dependence potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

8. Abuse potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are no known therapeutic uses of hexahydrocannabinol.

10. Listing on the WHO Model List of Essential Medicines

Hexahydrocannabinol is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Hexahydrocannabinol has no known marketing authorizations.

12. Industrial use

Hexahydrocannabinol has no known industrial use.

13. Non-medical use, abuse and dependence

Hexahydrocannabinol is a semi-synthetic cannabinoid that is most commonly synthesized from cannabidiol as a precursor. It was first detected in the USA in 2021, but its use quickly spread to other countries. Reports on online forums by people who use drugs provide evidence that hexahydrocannabinol has been used intentionally for its intoxicating effects (see section 6). The presence of this substance had been reported in at least 31 countries (see section 16 for listing). The prevalence of chronic use and dependence of hexahydrocannabinol has not been reported.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

In Europe, hexahydrocannabinol has been associated with cases of hospitalization and driving under the influence. Between January 2022 and May 2023, 37 cases of self-reported use of hexahydrocannabinol presented to French poison centres *(29)*. A wide variety of symptoms were reported, including neurological (e.g. dizziness, headache, paresthesia), cardiovascular (e.g. palpitations, sinus tachycardia, chest pain), gastrointestinal (e.g. nausea/vomiting, abdominal pain) and psychiatric (e.g. anxiety, hallucinations/delirium) *(29)*; however, analytical confirmation of hexahydrocannabinol consumption was obtained in only six cases, and hexahydrocannabinol was the sole substance in three of these individuals *(29,38)*. These three patients showed moderate to severe symptoms leading to admission to an emergency department. Other cases of hospitalization have occurred in Czechia, where 12 children who consumed HHC-containing sweets were admitted *(41)*. Hexahydrocannabinol has also been suspected of precipitating the onset of psychosis in two individuals in Ireland *(39)*.

Hexahydrocannabinol has been confirmed analytically in blood samples from drivers suspected of driving under the influence of cannabis in Germany and Sweden *(24,33)*, although neither report provided details of the effects of the substance on the drivers' behaviour. In early 2023, the rate of hexahydrocannabinol detection among Swedish drivers who were stopped on suspicion of cannabis use increased sharply, from 5% in January to 14% in February–March and to 50% in April–May *(24)*. In addition, Helander et al. *(35)* reported that the percentage of Swedish drivers who had false positive tests for Δ^9-THC increased from < 2% before the spring of 2023 to > 10% by June 2023. The presumed reason for the false positives is the cross-reactivity of immunoassays used for detection of metabolites of Δ^9-THC and hexahydrocannabinol (see section 4B). This reported increase is consistent with the dramatic rise in the number of posts mentioning hexahydrocannabinol on a Swedish Internet chat site during 2023 *(35)*. The posts primarily addressed online dealers and products intended for smoking or vaping and on the likelihood of testing positive for Δ^9-THC after ingestion or inhalation of hexahydrocannabinol.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

Hexahydrocannabinol emerged on the drug market in the USA in September 2021, followed by its appearance and rapid expansion in Europe in May 2022 *(1)*. By December 2022, hexahydrocannabinol had been detected in 70% of the European Union Member States. Countries in which hexahydrocannabinol has been identified are Austria, Belgium, Bulgaria, Colombia, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Latvia, Lithuania, Netherlands (Kingdom of the), Norway, Poland, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the United Kingdom and the USA *(1,25,40,42)*.

The 2023 technical report of the European Monitoring Centre for Drugs and Drug Addiction on hexahydrocannabino *(1)* cited reports of 50 seizures by customs and law enforcement personnel, comprising a total of 70.7 kg of material. The formulations included low-THC cannabis flower, resin, liquid and hexahydrocannabinol-containing food products. While most of the seizures were of small amounts, at least three involved larger quantities, suggesting more extensive trafficking.

17. Current international controls and their impact

Hexahydrocannabinol is not currently under international control.

18. Current and past national controls

Hexahydrocannabinol is regulated under psychoactive drug control regulations in Austria, Belgium, Czechia, Denmark, France, Italy, Japan, Lithuania, Luxembourg, Sweden and the United Kingdom *(25,41,43)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No other matters were identified.

References

1. Hexahydrocannabinol (HHC) and related substances. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2023 (https://www.euda.europa.eu/publications/technical-reports/hhc-and-related-substances_en).
2. 9(R)-Hexahydrocannabinol. Ann Arbor (MI): Cayman Chemical; 2024 https://www.caymanchem.com/product/27500, accessed 30 May 2024).
3. 9(S)-Hexahydrocannabinol. Ann Arbor (MI): Cayman Chemical; 2024 https://www.caymanchem.com/product/27500, accessed 30 May 2024).
4. Ujváry I. Hexahydrocannabinol and closely related semi-synthetic cannabinoids: A comprehensive review. Drug Test Anal. 2024;16:127–61. doi:10.1002/dta.3519.
5. Adams R, Pease DC, Can CK, Clark JS. Structure of cannabidiol. VI. Isomerization of cannabidiol to tetrahydrocannabinol, a physiologically active product. Conversion of cannabidiol to cannabinol. J Am Chem Soc. 1940;62:2402–5. doi:10.1021/JA01866A040.
6. Hively RL, Mosher WA, Hoffmann FW. Isolation of *trans*-Δ6-tetrahydrocannabinol from marijuana. J Am Chem Soc. 1966;88:1832–3. doi:10.1021/ja00960a056.
7. Russo F, Vandelli MA, Biagini G, Schmid M, Luongo L, Perrone M et al. Synthesis and pharmacological activity of the epimers of hexahydrocannabinol (HHC). Sci Rep. 2023;13:11061. doi:10.1038/s41598-023-38188-5.
8. Gaoni Y, Mechoulam R. Hashish – VII: The isomerization of cannabidiol to tetrahydrocannabinols. Tetrahedron. 1966;22:1481–8. doi:10.1016/S0040-4020(01)99446-3.
9. Marzullo P, Foschi F, Coppini DA, Fanchini F, Magnani L, Rusconi S et al. Cannabidiol as the substrate in acid-catalyzed intramolecular cyclization. J Nat Prod. 2020;83:2894–901. doi:10.1021/acs.jnatprod.0c00436.

10. Casati S, Rota P, Bergamaschi RF, Palmisano E, La Rocca P, Ravelli A et al. Hexahydrocannabinol on the light cannabis market: the latest “new” entry. Cannabis Cannabinoid Res. 2024;9:622–8. 10.1089/can.2022.0253
11. Archer RA, Boyd DB, Demarco PV, Tyminski IJ, Allinger NL. Structural studies of cannabinoids. A theoretical and proton magnetic resonance analysis. J Am Chem Soc. 1970;92:5200–6. doi:10.1021/ja00720a033.
12. Nasrallah DJ, Garg NK. Studies pertaining to the emerging cannabinoid hexahydrocannabinol (HHC). ACS Chem Biol. 2023;18:2023–9. doi:10.1021/acschembio.3c00254.
13. Caprari C, Ferri E, Vandelli MA, Citti C, Cannazza G. An emerging trend in novel psychoactive substances (NPSs): designer THC. J Cannabis Res. 2024;6:21. doi:10.1186/s42238-024-00226-y.
14. Tietze LF, von Kiedrowski G, Berger B. Stereo- and regioselective synthesis of enantiomerically pure (+)- and (−)-hexahydrocannabinol by intramolecular cycloaddition. Angew Chem Int Ed English. 1982;21:221–2.
15. Andersson DA, Gentry C, Alenmyr L, Killander D, Lewis SE, Andersson DA et al. TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Δ9-tetrahydrocannabiorcol. Nat Commun. 2011;2:551. doi:10.1038/ncomms1559.
16. Cornia M, Casiraghi G, Casnati G, Zetta L. A concise stereocontrolled route to hexahydrocannabinol and relatives. Gazz Chim Ital. 1989;119:329–33 (https://hdl.handle.net/11381/1996006).
17. Lee YR, Xia L. Efficient one-pot synthetic approaches for cannabinoid analogues and their application to biologically interesting (−)-hexahydrocannabinol and (+)-hexahydrocannabinol. Tetrahedron Lett. 2008;49:3283–7. doi:10.1016/j.tetlet.2008.03.075.
18. Collins A, Ramirez G, Tesfatsion T, Ray K, Caudill S, Cruces W. Synthesis and characterization of the diastereomers of HHC and H4CBD. Nat Prod Commun. 2023;18:1934578X231158910. doi:10.1177/1934578X231158910.
19. Vree TB, Breimer DD, van Ginneken CA, van Rossum JM. Gas chromatography of cannabinoids. Gas chromatographic behaviour of *cis*- and *trans*-tetrahydrocannabinol and isotetrahydrocannabinol. J Chromatogr. 1973;79:81–90. doi:10.1016/s0021-9673(01)85276-6.
20. Di Trana A, di Giorgi A, Sprega G, Carlier J, Kobidze G, Montanari E et al. Disposition of hexahydrocannabinol epimers and their metabolites in biological matrices following a single administration of smoked hexahydrocannabinol: a preliminary study. Pharmaceuticals (Basel). 2024;17(2):249. doi:10.3390/ph17020249.
21. Graziano S, Varì MR, Pichini S, Busardo FP, Cassano T, di Trana A. Hexahydrocannabinol pharmacology, toxicology, and analysis: the first evidence for a recent new psychoactive substance. Curr Neuropharmacol. 2023;21(12):2424–30. doi:10.2174/1570159X21666230623104624.
22. Hill DW, Langner KJ. HPLC photodiode array UV detection for toxicological drug analysis. J Liquid Chromatog Related Technol. 1987;10:377–409. doi.org/10.1080/01483918708066724
23. Kobidze G, Sprega G, Montanari E, Taoussi O, Bambaggiotti G, Fede M et al. The first LC-MS/MS stereoselective bioanalytical methods to quantitatively detect 9R- and 9S-hexahydrocannabinols and their metabolites in human blood, oral fluid and urine. J Pharm Biomed Anal. 2024;240:115918. doi:10.1016/j.jpba.2023.115918.
24. Kronstrand R, Roman M, Green H, Truver MT. Quantitation of hexahydrocannabinol (HHC) and metabolites in blood from DUID cases. J Anal Toxicol. 2024;48(4):235–41. doi:10.1093/jat/bkae030.
25. Tanaka R, Kikura-Hanajiri R. Identification of hexahydrocannabinol (HHC), dihydro-iso-tetrahydrocannabinol (dihydro-iso-THC) and hexahydrocannabiphorol (HHCP) in electronic

cigarette cartridge products. Forensic Toxicol. 2024;42:71–81. doi:10.1007/s11419-023-00667-9.
26. Derne AS, Pape E, Jouzeau JY, Kolodziej A, Gambier N, Scala-Bertola J. Immunological detection of hexahydrocannabinol (HHC) in oral fluid. Drug Test Anal. 2024;16(6):638–40. doi:10.1002/dta.3595.
27. HHC (hexahydrocannabinol) and its effects. Prague: RastaKoala.com; 2024 (https://www.rastakoala.com/blog/detail/hhc-hexahydrocannabinol-and-its-activities, accessed 31 July 2024).
28. Hexahydrocannabinol (HHC) in foodstuffs: indications of psychoactive effects: BfR Opinion No. 044/2023. Berlin: Bundesinstitut für Risikobwertung; 2023. doi: 10.17590/20231128-134714-0.
29. Labadie M, Nardon A, Castaing N, Bragança C, Daveluy A, Gaulier JM et al. Hexahydrocannabinol poisoning reported to French poison centres. Clin Toxicol (Phila). 2024;62:112–9. doi:10.1080/15563650.2024.2318409.
30. HHC dosage: How much should you take? Tomball (TX): Natural Ways CBD; 2024 https://www.naturalwayscbd.com/blog/hhc-dosage/, accessed 31 July 2024).
31. How much HHC should I take? Find the right dosage. Toronto (ONT): Herb; 2024 (https://herb.co/guides/hhc-dosage-guide-how-much-should-i-take, accessed 31 July 2024).
32. Manier SK, Valdiviezo JA, Vollmer AC, Eckstein N, Meyer MR. Analytical toxicology of the semi-synthetic cannabinoid hexahydrocannabinol studied in human samples, pooled human liver S9 fraction, rat samples and drug products using HPLC-HRMS-MS. J Anal Toxicol. 2023;47:818–25. doi:10.1093/jat/bkad079.
33. Schirmer W, Auwärter V, Kaudewitz J, Schürch S, Weinmann W. Identification of human hexahydrocannabinol metabolites in urine. Eur J Mass Spectrom (Chichester). 2023;29(5–6):326–37. doi:10.1177/14690667231200139.
34. Höfert L, Becker S, Dressler J, Baumann S. Quantification of (9R)- and (9S)-hexa hydrocannabinol (HHC) via GC-MS in serum/plasma samples from drivers suspected of cannabis consumption and immunological detection of HHC and related substances in serum, urine, and saliva. Drug Test Anal. 2024;16:489–97. doi:10.1002/dta.3570.
35. Pitterl F, Pavlic M, Liu J, Oberacher H. Insights into the human metabolism of hexahydrocannabinol by non-targeted liquid chromatography-high-resolution tandem mass spectrometry. J Anal Toxicol. 2024;48(5):350–8. doi:10.1093/jat/bkae022.
36. Helander A, Johansson M, Villén T, Andersson A. Appearance of hexahydrocannabinols as recreational drugs and implications for cannabis drug testing – focus on HHC, HHC-P, HHC-O and HHC-H. Scand J Clin Lab Invest. 2024;84:125–32. doi:10.1080/00365513.2024.2340039.
37. Durydivka O, Palivec P, Gazdarica M, Mackie K, Blahos J, Kuchar M. Hexahydrocannabinol (HHC) and Δ(9)-tetrahydrocannabinol (Δ(9)-THC) driven activation of cannabinoid receptor 1 results in biased intracellular signaling. Sci Rep. 2024;14:9181. doi:10.1038/s41598-024-58845-7.
38. Collins A, Tesfatsion TT, Ramirez GA, Ray KP, Cruces W. Nonclinical in vitro safety assessment summary of hemp derived (R/S)-hexahydrocannabinol ((R/S)-HHC). Cannabis Sci Technol. 2022;5:23–7. doi:10.212023/rs.3.rs-2299264/v1.
39. Guyon J, Paradis C, Titier K, Braganca C, Peyre A, Nardon A et al. Letter to the Editor: The cannabinoid consumed is not necessarily the one expected: recent experience with hexahydrocannabinol. Cannabis Cannabinoid Res. 2023 16 August. doi:10.1089/can.2023.0154.

40. O'Mahoney B, O'Malley A, Kerrigan O, McDonald C. HHC-induced psychosis: a case series of psychotic illness triggered by a widely available semisynthetic cannabinoid. Ir J Psychol Med. 2024;1–4. doi:10.1017/ipm.2024.3.
41. Ferretti ML, Gournay LR, Bingaman MG, Leen-Feldner EW. A survey study of individuals using hexahydrocannabinol cannabis products: use patterns and perceived effects. Cannabis Cannabinoid Res. 2023. doi:10.1089/can.2023.0143.
42. Holt E. Czech Republic latest country to ban hexahydrocannabinol. Lancet. 2024;403(10427):604. doi:10.1016/S0140-6736(24)00307-6.
43. Early Warning Advisory (EWA) on New Psychoactive Substances: Hexahydrocannabinol. Vienna: United Nations Office on Drugs and Crime; 2024 https://www.unodc.org/LSS/Home/NPS, accessed 2 August 2024).
44. Hexahydrocannabinol. Wikipedia.; 2024 (https://en.wikipedia.org/wiki/Hexahydrocannabinol#:~:text=Previously%2C%20the%20German%20expert%20committee,Russia%2C%20but%20THCP%20is%20banned, accessed 31 July 2024).