German Federal Institute for Risk Assessment

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5 Oktober 2023

Hexahydrocannabinol (HHC) in foodstuffs: Indications of psychoactive effects

Hexahydrocannabinol (HHC) belongs to the cannabanoid substance group. Its chemical structure is similar to that of Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive cannabinoid in the plant *Cannabis sativa L*. However, unlike Δ^9-THC, it is found only in small amounts in the plant and is produced mainly artificially (synthetically). It first appeared on the US drug market in late 2021. In Europe, findings were first reported in May 2022. By December 2022, HHC products were found in 70% of EU member states.

Among other things, HHC is used in liquids for e-cigarettes or offered in the form of HHC oils. However, it is also found in products that consumers may perceive as foodstuffs – including wine-gum-like products and food supplements. Hexahydrocannabinol is offered as a "legal substitute" for cannabis or Δ^9-THC because it is currently not subject to the German Narcotics Act, the New Psychoactive Substances Act (NpSG), or the relevant international drug control conventions. However, in the EU, HHC is now monitored as a new psychoactive substance by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

The scientific data on HHC is still insufficient – both in terms of toxicity (poisonousness) and its other effects on humans. However, there are some findings from animal and cell culture studies as well as testimonials from people who consumed HCC. These suggest that HHC, especially in its β-HHC form, can induce effects similar to those of Δ^9-THC. However, somewhat higher doses are probably required. According to current knowledge, the HHC contents in products perceived as foodstuffs (e.g. wine gums with 25 mg of HHC per piece) could thus be sufficient to induce a state of euphoria in those who consume them. The health effects of excessive intake (even accidentally by children) cannot yet be assessed with certainty. However, the occurrence of serious intoxication must be considered because of the risk of confusion with foodstuffs.

BfR Risk Profile | Opinion [number/year]

Hexahydrocannabinol in foodstuffs

A Affected persons	General population, children				
B Probability of adverse health effects from the consumption of foodstuffs containing HHC [1]	Very low	Low	Middle	**High**	Very high
C Severity of impairment to health when consuming foodstuffs containing HHC [2]	No impairment	**Slight impairment [reversible]**	**Moderate impairment [reversible]**	Severe impairment [reversible/irreversible]	
D Validity of available data [3]	High: The most important data are available and are internally consistent	Medium: Some important data are missing or inconsistent	**Low: A large volume of important data is missing or inconsistent**		
E Controllability by the consumer [4]	Control not necessary	Controllable with precautionary measures	**Controllable by avoidance**	Not controllable	

Fields with a dark grey background indicate the properties of the risk assessed in this Opinion
(for more details, see the text of Opinion number [number/year] from the BfR dated [day/month/year]).

Explanations
The risk profile is intended to visualise the risk outlined in the BfR Opinion. The profile is not intended to be used to com pare risks. The risk profile should be read only in conjunction with the corresponding Opinion.

Row B – Probability of the impairment to health:
[1] - Ingestion of foodstuffs containing HHC at the levels commonly offered on the market is highly likely to cause adverse health effects in the sense of psychoactive effects
Row C – Severity of the impairment to health:
[2] - The severity of the impairment to health depends on the amount of HHC ingested. Based on current knowledge, mild to moderate adverse effects are likely to occur; however, these are reversible.
Row D – Validity of available data:
[3] – The validity of the available data is low. Overall, the data provide conclusive indications of the psychoactive properties of HHC; however, toxicological data beyond this are currently lacking.

1 Object of the assessment

Hexahydrocannabinol (HHC)-containing products that can be perceived as foodstuffs by consumers (e.g. in the form of wine gum-like products) are currently available on the German market. The German Federal Institute for Risk Assessment (BfR) has therefore carried out a toxicological assessment of HHC in foodstuffs.

2 Result

Hexahydrocannabinol (HHC) has been found in various products on the European market since 2022. These include products that consumers may perceive as foodstuffs (e.g. wine gum-like products). The HHC used in this process is probably produced semi-synthetically from cannabidiol (CBD).

So far, HHC has not been sufficiently characterised with respect to its toxicological properties. In particular, there are no data regarding the acute or chronic toxicity of the substance. There are also no reliable knowledge on the effects of HHC in humans. Findings from animal experiments and *in vitro studies* as well as the anecdotal reports of HHC users on the Internet have led to the following conclusions:

→ The data available indicate that β-HHC in particular has a psychoactive potential. On the other hand, the cannabimimetic activity of α-HHC, seems to be considerably lower.

→ There is evidence that the effects of β-HHC are similar to those of Δ^9-tetrahydrocannabinol (Δ^9-THC); however, the potency is probably somewhat lower. This means that slightly higher doses are needed in order to achieve an effect comparable to that of ingesting Δ^9-THC.

→ According to the current state of knowledge, the HHC contents in products that can be perceived as foodstuffs by consumers (e.g. wine gums with 25 mg/piece) are sufficient to induce a state of euphoria in the consumer.

→ Because of the differences in the cannabimimetic activity of β-HHC and α-HHC, it is to be expected that the effects after consumption of HHC-containing products with different epimer content may differ.

→ The effects of an excessive intake (also accidentally by children) cannot be assessed with certainty. However, the occurrence of serious intoxication must be considered because of the risk of confusion with foodstuffs.

→ Products containing HHC can, in principle, also be contaminated with residues from the extraction, synthesis by-products, and other phytocannabinoids as well as residues of the catalysts used in the synthesis. However, whether this results in health risks can be assessed only in a specific individual case.

3 Rationale

3.1 Background

Hexahydrocannabinol (HHC) appeared on the US drug market in late 2021. In Europe, it was first observed in May 2022; by December 2022, HHC products were found in 70% of EU member states. Among other things, HHC is used in liquids for e-cigarettes or offered in the form of HHC oils. However, it is also found in products that consumers may perceive as foodstuffs – including wine-gum-like products and food supplements. Hexahydrocannabinol is openly offered as a "legal substitute" for cannabis or Δ^9-tetrahydrocannabinol (Δ^9-THC) (EMCDDA 2023).

Unlike Δ^9-THC as well as other tetrahydrocannabinol derivatives, HHC as a hexahydro derivative does not fall under the international conventions on the regulation of drug cultivation, drug trafficking, and drug consumption. It is also not subject to the German Narcotics Act (UN 1961, 1971, 1988; DE 2023). However, in the European Union (EU), HHC is now monitored as a new psychoactive substance by the *European Monitoring Centre for Drugs and Drug Addiction* (EMCDDA). The EMCDDA published a comprehensive report on HHC in spring 2023 (EMCDDA 2023).

3.2 Agent

HHC (IUPAC: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol, CAS: 6692-85-9, molar mass: 316.48 g/mol) was first described in the scientific literature in 1940. The structure resembles that of Δ^9-THC, the most psychoactive cannabinoid in *Cannabis sativa* L.. Only the double bond between C9 and C10 is missing. Hexahydrocannabinol can be present stereochemically in the form of the two epimers: 9β-HHC and 9α-HHC (Ujváry 2023).

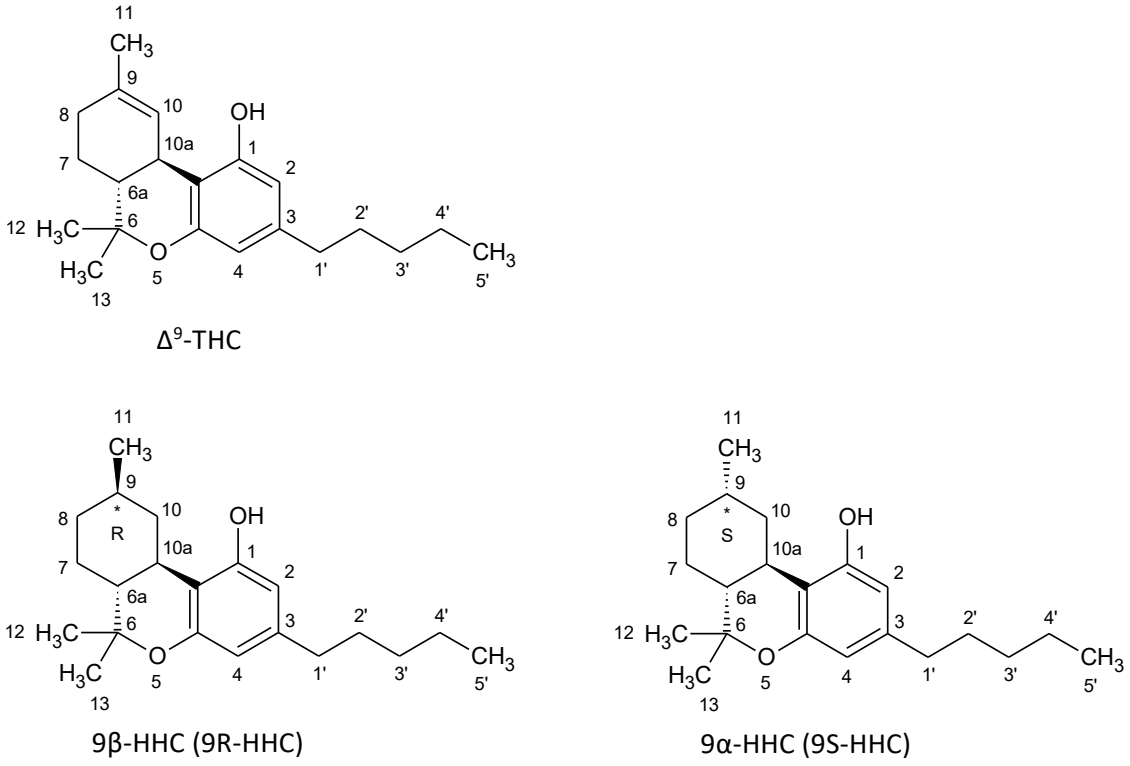

Figure 1: Structural formulae of Δ^9-THC, 9β-HHC and 9α-HHC, numbering according to IUPAC

Hexahydrocannabinol is not naturally biosynthesised in *Cannabis sativa* L. However, trace amounts of the compound have been detected in the hemp plant. In this occurrence, it is likely a degradation product of Δ^9-THC. On a larger scale, production is probably semi-synthetic, starting from cannabidiol (CBD), which is obtained from commercial hemp, among others. In the first step, CBD is acid-catalysed into Δ^8-THC and Δ^9-THC. This is then hydrogenated to HHC in a second step. Semi-synthetic production typically results in a mixture of the epimers 9β-HHC and 9α-HHC. However, the ratio can vary depending on the synthesis method. The compound can also be made fully synthetically. However, this is

probably not particularly common on a larger scale because of the higher costs. Depending on the synthetic method, various by-products can occur. The exact production method of the HHC available on the market is not known (Ujváry 2023).

3.3 Toxicological assessment

So far, HHC has not been sufficiently characterised with respect to its toxicological properties. In particular, there are no data regarding the acute or chronic toxicity of the compound. There is also no reliable knowledge on the effects of HHC in humans. However, findings from animal experiments and *in vitro* studies as well as the anecdotal reports of HHC users on the Internet indicate that β-HHC in particular mediates effects similar to those of the structurally similar Δ^9-THC.

3.3.1 Toxicokinetics

Findings on the toxicokinetics of HHC are limited. Because of the chemical structure, HHC as well as the structurally similar cannabinoids can be assumed to be highly lipophilic. This suggests a high absorption rate after oral ingestion, a strong plasma protein binding, and an accumulation in fatty tissue (Ujváry 2023).

Findings from studies on the metabolism of 9β-HHC using microsomal preparations from rat, guinea pig, rabbit, hamster, and mouse showed a hydroxylation pattern similar to that known for Δ^9-THC with hydroxylations at C11, C8, and C4 as well as the pentyl side chain (Harvey & Brown 1991). The study focused on monohydroxylated metabolites; other Phase I and Phase II metabolites were not reported.

The pharmacologically active 11-hydroxy metabolite of Δ^9-THC is further metabolically converted into the pharmacologically inactive compound 11-nor-9-carboxy-THC, which is excreted in the urine as a relatively hydrophilic metabolite and is also detected by many drug tests. It is currently unknown whether 11-hydroxy-HHC can also be oxidised to acid. It is discussed in the scientific literature that the primary hydroxyl group in HHC might be less well converted to acid than the allylic hydroxyl group in Δ^9-THC. This could lead to a prolonged half-life compared with 11-hydroxy-$^{\Delta}$9-THC. Because animal studies indicate a comparable or even stronger psychoactive potency of 11-hydroxy-HHC compared with Δ^9-THC (Skinner *et al.* 1979; Järbe *et al.* 1986), this could also be associated with a prolonged half-life (Ujváry 2023). However, reliable data on this is currently lacking.

3.3.2 Data on toxicology

3.3.2.1 Findings from *in vitro* studies

Hexahydrocannabinol has been studied in a number of *in vitro* test systems. In addition to cannabimimetic properties, other endpoints were addressed (e.g. antiproliferative properties in tumour cell lines and binding affinity to opioid receptors). An overview of published studies can be found in the EMCDDA report and in a review paper by Ujváry (EMCDDA 2023; Ujváry 2023). Within the scope of the present opinion, only the essential findings regarding the cannabimimetic (i.e. the Δ^9-THC-like) activity of HHC as well as a study on safety pharmacology are described.

A recently published *in silico* analysis on *molecular docking* shows that HHC and Δ^9-THC should have binding affinities comparable to the CB1 and CB2 receptor (Aviz-Amador *et al.* 2021).

Andersson et al. used HEK 293 cells expressing the human cannabinoid receptors CB_1R or CB_2R to investigate whether and to what extent 9β-HHC and 9α-HHC (test concentration: 100 µM) lead to an activation of these receptors. Receptor activation was reported only semi-quantitatively as a decrease in forskolin-induced cAMP accumulation. Both epimers caused an activation of CB_1R and CB_2R in this test system; the effect size was similar to that of the Δ^8-THC also investigated (Andersson *et al.* 2011).

Another study was recently conducted at the Swedish National Board of Forensic Medicine and is described in the EMCDDA report. In this study, CB_1R-expressing transfected cells were used. It was shown that 9β-HHC acts as a partial agonist at CB_1R (EMCDDA 2023).

In 2023, Nasrallah and Garg published a study that investigated both the binding affinity *(radioligand binding assay*) and functional activity *(G-protein coupled receptor (GPCR) functional assay*) of 9β-HHC and 9α-HHC at CB_1R and CB_2R. This showed that both the binding affinity and the functional activity at CB_1R and CB_2R for β-HHC are comparable to that of Δ^9-THC. In this study, 9α-HHC showed about tenfold lower binding activity and functional activity (Nasrallah & Garg 2023).

The comparison of the spatial structure basically shows that 9β-HHC and Δ^9-THC are quite similar, whereas 9α-HHC differs considerably in parts (Ujváry 2023). A cannabimimetic activity is therefore particularly plausible for 9β-HHC. This observation underlines the experimental results.

In 2022, Collins et al. published a study (*non-peer-reviewed preprint*) that addressed various endpoints regarding the toxic potential of HHC. Hexahydrocannabinol was tested as a mixture of the epimers 9β-HHC and 9α-HHC. The mutagenic potential was investigated in the bacterial reverse mutation test (Ames test). According to the authors, HHC was negative. However, the test is not sufficiently reported. The validity of this statement can therefore not be conclusively assessed. In addition, the patch-clamp technique was used to investigate whether HHC can lead to inactivation of the hERG channel. No activity was shown here; at present, it cannot be assumed that HHC has a QT-time prolonging potential in the heart. Further tests showed that HHC has a cytotoxic effect on human lung fibroblasts (IC_{50} = 14.4 µM), whereas no relevant cytotoxic effect was observed on human hepatocytes up to a concentration of 50 µM (Collins *et al.* 2022).

3.3.2.2 Findings from animal studies

The focus of the animal studies was to clarify the cannabimimetic activity of HHC.

The first studies on this subject date back to the 1940s and addressed the cannabimimetic effect of HHC in the Gayer test (decrease of the corneal reflex in rabbits) (Russell *et al.* 1941) and in the ataxia test in dogs (Adams *et al.* 1940; Adams *et al.* 1942) after intravenous application of the test substance. In both studies, an activity of the test substance that was slightly weaker than THC (approx. 20–50%) was observed. However, the studies are difficult to interpret because the purity and isomeric ratios of HHC and THC were not characterised. In addition, the Gayer test is no longer considered a suitable test for determining cannabimimetic activity (EMCDDA 2023).

A few decades later, the cannabimimetic effect of HHC was investigated in a comprehensive study on rhesus monkeys. In this, the behaviour of animals after intravenous administration of 9β-HHC (doses: 0.1, 0.5, and 1 mg/kg body weight (BW)) or 9α-HHC (doses: 1, 2, and 5

mg/kg BW) was assessed using Norton's score. Administration of 9β-HHC resulted in stupor, ataxia, immobility, and stooped posture as well as reduced response to external stimuli in the animals. The potency of 9β-HHC was about half that of Δ^9-THC; the activity of 9α-HHC was about 10-fold lower compared to 9β-HHC. The authors noted that the substances were not completely isotopically pure. The effects of 9α-HHC could thus also have been caused by low levels of 9β-HHC (Edery *et al.* 1971; Mechoulam *et al.* 1980).

Another study investigated the effects of several cannabinoids on the endpoints locomotor activity, *postural arrest*, body temperature, and pain sensation *(hot plate test*) in mice after intraperitoneal application of HHC as a mixture (about 1:1) of the two epimers 9β-HHC and 9α-HHC. The potency of HHC was about one order of magnitude or more lower than that of Δ^9-THC depending on the endpoint; however, unlike Δ^9-THC, HHC showed no analgesic effect in this study (Skinner *et al.* 1979).

Intravenous administration of Δ^9-THC is known to induce convulsions in the *New Zealand White* rabbit (Martin *et al.* 1977). Consroe et al. therefore investigated different cannabinoids in this animal model. Compared with Δ^9-THC, HHC showed a potency of about 50% (Consroe *et al.* 1982).

In a study published in 2023, Russo et al. investigated the cannabimimetic potential of 9β-HHC and 9α-HHC after intraperitoneal application to mice in the tetrad test (locomotor activity, catalepsy, body temperature, pain sensation; dose: 10 mg/kg BW). A non-significant cataleptic effect as well as a non-significant decrease in body temperature was recorded in the 9β-HHC group. In addition, a significant analgesic effect and a significant decrease in locomotor activity were observed in this group. In contrast, there was no relevant change in the animals treated with 9α-HHC compared with the control animals. In this study, no Δ^9-THC group was included (Russo *et al.* 2023).

There are currently no studies that have investigated the effects of HHC after oral administration. Studies on classical toxicological endpoints regarding the acute and chronic toxicity of HHC are also lacking.

3.3.2.3 Findings from reports of user experiences on the Internet

A cursory Internet search has revealed after ingesting HHC, users report experiencing effects similar to those of Δ^9-THC. The exact effects seem to vary from person to person. The strength of the effect is mostly described as somewhat weaker than with Δ^9-THC. However, the reports consistently mention clearly perceptible intoxicating effects.

Although such experience reports cannot be used to make a scientifically reliable statement, the descriptions indicate that intoxicating effects may be caused by the products on the market.

3.3.2.4 Other toxicological aspects

The exact synthesis methods and manufacturing conditions of HHC are not known for individual products. However, it can generally be assumed that HHC is primarily obtained semi-synthetically from CBD. The conversion of CBD to Δ^8-THC and Δ^9-THC is the first step. Numerous studies have shown that various by-products are also formed. The exact pattern of the resulting products differs depending on the exact manufacturing conditions. Unless adequate purification takes place, the final HHC products may be contaminated with residues from the extraction, by-products, and other phytocannabinoids as well as residues

from the catalysts used. However, there are no analytical data available for such products so far (EMCDDA 2023; Ujváry 2023). Whether this results in health risks can generally be assessed only in a specific individual case.

Furthermore, it must be taken into account that the purity of HHC products may deviate from the manufacturer's specifications. For example, one HHC product sold in the US contained Δ8-THC, Δ^9-THC, and $\Delta^{6a,10a}$-THC but no HHC (Sams 2020).

3.3.3 Exposure

The BfR does not yet have comprehensive knowledge about the levels of HHC in products that can be perceived as foodstuffs by consumers. Two products presented in the EMCDDA report have a content of 25 mg per wine gum or marshmallow according to the product declaration (EMCDDA 2023). A cursory Internet search yielded numerous hits for other products with the HHC content often stated as 25 mg per wine gum or higher.

3.4 Risk management options, recommended measures

So far, HHC has not been sufficiently characterised with respect to its toxicological properties. In particular, there are no data regarding the acute or chronic toxicity of the substance. There is also no reliable evidence on the effects of HHC in humans. Findings from animal experiments and *in vitro studies* as well as the anecdotal reports of HHC users on the Internet have led to the following conclusions:

- → The data available indicate that β-HHC in particular has a psychoactive potential. On the other hand, the cannabimimetic activity of α-HHC, seems to be considerably lower.
- → There is evidence that the effects of β-HHC are similar to those of Δ^9-tetrahydrocannabinol (Δ^9-THC); however, the potency is probably somewhat lower. This means that slightly higher doses are needed in order to achieve an effect comparable to that of ingesting Δ^9-THC.
- → According to the current state of knowledge, the HHC contents in products that can be perceived as foodstuffs by consumers (e.g. wine gums with 25 mg/piece) are sufficient to induce a state of euphoria in the consumer.
- → Because of the differences in the cannabimimetic activity of β-HHC and α-HHC, it is to be expected that the effects after consumption of HHC-containing products with different epimer content may differ.
- → The effects of an excessive intake (also accidentally by children) cannot be assessed with certainty. However, the occurrence of serious intoxication must be considered because of the risk of confusion with foodstuffs.
- → Products containing HHC can, in principle, also be contaminated with residues from the extraction, synthesis by-products, and other phytocannabinoids as well as residues of the catalysts used in the synthesis. However, whether this results in health risks can be assessed only in a specific individual case.

Further information on the substance-related risks of foodstuffs in the website of the BfR.

Topic page on the assessment of the substance-related risks of foodstuffs:
https://www.bfr.bund.de/de/bewertung_der_stofflichen_risiken_von_lebensmitteln-432.html

Frequently asked questions about health risks of foodstuffs and feed containing hemp:
https://www.bfr.bund.de/de/fragen_und_antworten_zu_den_gesundheitlichen_risiken_von_hanfhaltigen_lebensmitteln_und_futtermitteln-277052.html

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About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the States ('Laender') on questions of food, chemicals and product safety.
The BfR conducts independent research on topics that are closely linked to its assessment tasks.

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