

SMART Forensics Update



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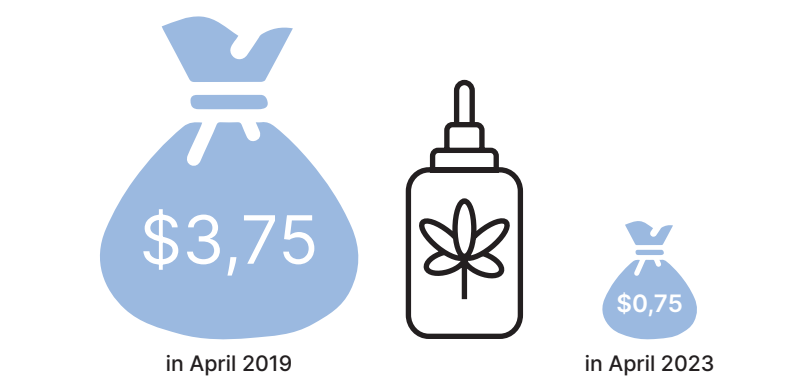
**Beyond plants:
semi-synthetics diversify
the cannabis market**

Introduction

In recent years, there has been a considerable expansion in the types of cannabis-based products available in illicit drug markets. In addition to herbal cannabis and cannabis resin (hashish) the variety of products that can now be purchased include e-liquids and oils for vaping and a wide range of edible products. Most of these products contain *delta-9-THC** (the main psychoactive component of cannabis) and/or cannabidiol (known as CBD, which is not considered to be psychoactive^(1,2)) in varying concentrations. The emergence of products containing a less well studied group of cannabinoids known as semi-synthetic cannabinoids is further increasing this diversity. Semi-synthetic cannabinoids are compounds which are manufactured by modifying cannabinoids that occur naturally in the cannabis plant (e.g. *delta-9-THC* or CBD) via relatively simple and inexpensive processes. Several of these semi-synthetic cannabinoids can be derived from CBD, though some can also be synthesized from THC.

The emergence of semi-synthetic cannabinoids is taking place in a context of comparatively low prices for CBD produced in large quantities from industrial hemp with a low-THC content for licit markets^(3, 4): After an initial rapid proliferation of CBD products sold within the lifestyle and health markets, wholesale prices of

Figure 1: CBD Biomass and Refined Hemp Oil Assessed Prices in the United States of America, April 2019 and April 2023



Note: Prices are expressed in dollars per percentage point of CBD oil per pound.
Source: [hempbenchmarks.com](https://www.hempbenchmarks.com). Accessible <https://www.hempbenchmarks.com/interactive/hempbenchmarks-historical-biomass-and-refined-hemp-oil-price-chart/>.

CBD have fallen drastically in recent years partly due to overproduction⁽⁵⁾. Analysis from Hemp Benchmarks® shows that in the United States of America, average monthly wholesale prices for CBD biomass dropped from over USD 3.5 per percentage points of CBD per pound (USD 7.7 per kg) in April 2019 to just about USD 0.5 in April 2022 and have remained at that level until at least April 2023⁽⁶⁾. Experts have suggested that the wide availability and low cost of CBD on the licit market bears risk to its diversion for the clandestine manufacture of semi-synthetic cannabinoids⁽⁷⁾. This report will focus on the semi-synthetic cannabinoids that, at the time of writing of this report,

have been reported to the UNODC's Early Warning Advisory (EWA) on new psychoactive substances as well as others that have been documented in the scientific literature and in drug markets. A brief description of these compounds, their molecular structure, and, where applicable, their control status under the United Nations Convention on Psychotropic Substances, 1971 is provided in table 2.

* Tetrahydrocannabinol (THC), along with some of its isomers and their stereochemical variants, are under international control in Schedule I of the Convention of Psychotropic Substances, 1971. Dronabinol ((-)-*trans-delta-9*-tetrahydrocannabinol, *delta-9-THC*), a specific isomer of THC, and its stereochemical variants are in Schedule II of the same Convention.

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Manufacture of semi-synthetic cannabinoids

Cannabinoids, such as *delta*-10-THC, *delta*-8-THC, and hexahydrocannabinol (HHC) are classified as phytocannabinoids as they can occur naturally in low levels in the cannabis plant. However, they occur in low quantities in the cannabis plant and synthesis from the more abundant and readily available cannabinoids such as CBD

is necessary to manufacture enough for the illicit drug market. Others such as tetrahydrocannabinol acetate (THC-O) are not found naturally in the cannabis plant but can be similarly synthesized from THC. Whether occurring naturally in cannabis plants or not, these semi-synthetic cannabinoids are closely related to THC

or CBD in terms of their molecular structure. This is an important difference to synthetic cannabinoids, which are neither occurring in the cannabis plant nor are they derived from it (see [UNODC Global SMART Update vol. 13](#)).

Figure 2: Conversion of CBD to semi-synthetic cannabinoids

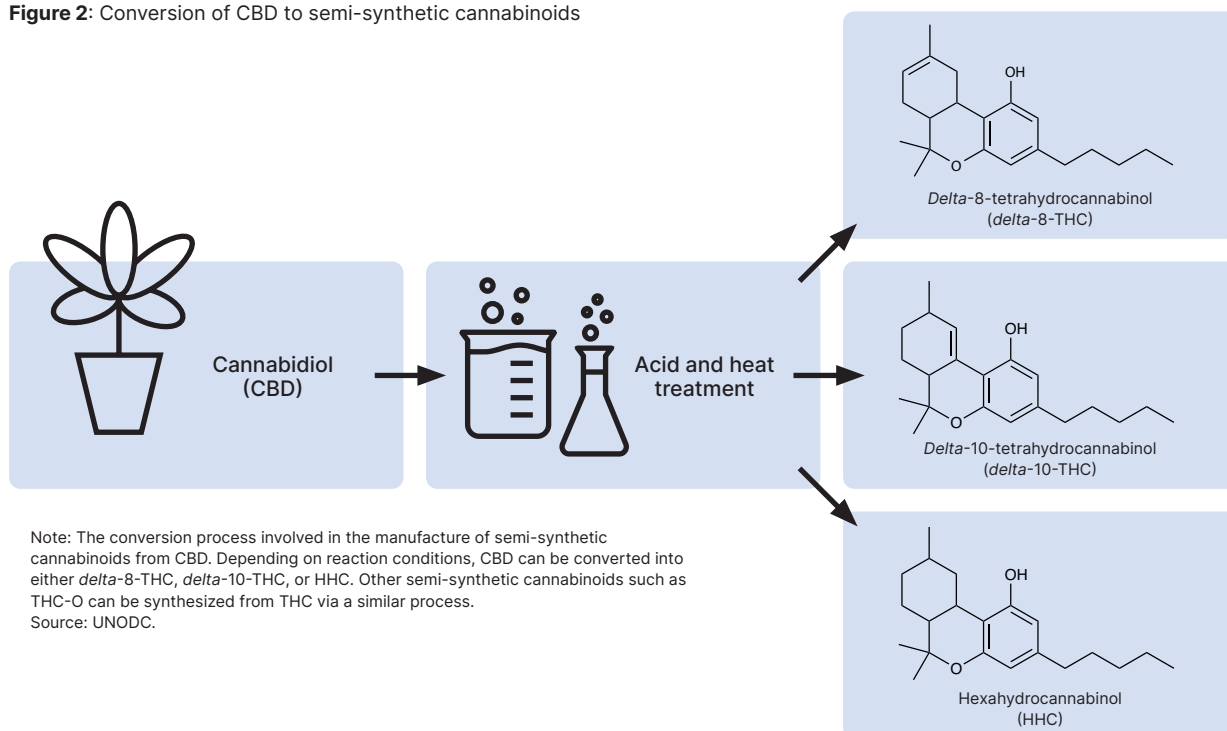


Photo: Examples of products containing semi-synthetic cannabinoids



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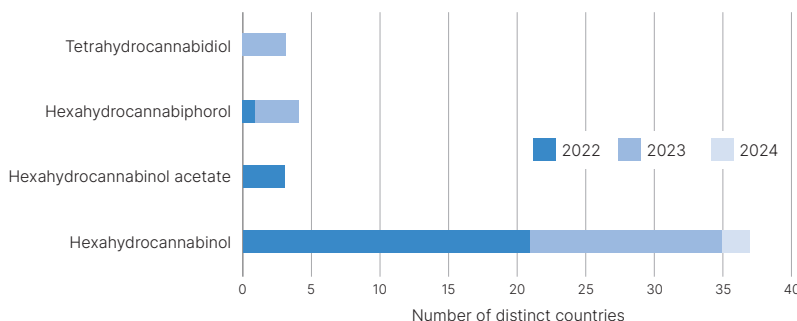
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Drug products containing semi-synthetic cannabinoids

As with THC products, semi-synthetic cannabinoids often appear in e-Liquids/vape-capsules and edible gummies or other types of confectionary but they can also be found in the form of herbal material. Products may also be sold in elaborately designed and branded packaging, some of which mimic the names of popular cannabis strains such as Purple Haze or Mango Kush. The composition of these products is not always consistent with what is stated on the label, and they may contain several cannabinoids in varying concentrations⁽⁸⁾. Some products are marketed using names such as cannabis lite or diet weed suggesting that effects are less intense compared to conventional cannabis products containing THC. Semi-synthetic cannabinoids have been identified by drug analysis lab-

Figure 3: Number of distinct countries reporting semi-synthetic cannabinoids in 2022-2024



Source: UNODC Early Warning Advisory (EWA) on New Psychoactive Substances, February 2024.

oratories in North America, Europe, South America and Southeast Asia and the number of different compounds as of countries reporting them is increasing^(7, 9, 10).

Legal status of semi-synthetic cannabinoids

In several countries, semi-synthetic cannabinoid products have been marketed as 'legal alternatives' to cannabis in shops or online^(11, 12). While some specific isomers of THC, e.g. *delta*-8-THC and *delta*-10-THC are both under Schedule I of the United Nations Convention on Psychotropic Substances of 1971, THC-O and tetrahydrocannabinol (THCP), HHC, hexahydrocannabinol acetate (HHC-O), hexahydrocannabinol (HHCP) and tetrahydrocannabinol (H4-CBD) currently fall outside of the scope of this Convention⁽¹³⁾. At the national level, the legal landscape is evolving rapidly as several countries have been widening the scope of existing national drug laws. For example, HHC, HHC-O, HHC-P, THC-O and/or THC-P have recently been placed under control in Austria⁽¹⁴⁾, France⁽¹⁵⁾, Japan⁽¹⁶⁾ and Switzerland⁽¹⁷⁾. The legal status of H4-CBD as an analogue of CBD may vary from country to country.

Photo: Vending machine advertising "CBD and HHC alternatives"



Note: Some products on sale were branded as "CBD++ flowers HHC alternatives". The actual content of these products is not known. Credit: UNODC.

What are the effects of semi-synthetic cannabinoids?

As semi-synthetic cannabinoids have only recently emerged in drug products, there is a lack of robust, well-controlled studies on their pharmacological activity, toxicological properties, and potential for producing harmful effects. Similarly to THC^(18, 19), *delta*-8-THC and HHC act as partial agonists of the CB1 receptor. Data from animal experiments and *in vitro* studies suggest that their pharmacological effects are broadly like those of THC⁽²⁰⁻²²⁾. While no human pharmacological data has been reported for HHC, small-scale clinical studies comparing the effects of *delta*-8-THC with THC suggest that the effects of *delta*-8-THC are similar but weaker than those of THC⁽²¹⁾. A recent clinical case study involving three participants also showed similar results⁽²³⁾.

Measured on a behavioural assay in rhesus monkeys, THC-O showed considerably less activity compared to THC and the onset of effects was

delayed suggesting that THC-O may act as a prodrug for THC^(22, 24, 25). One study has shown that compared to THC, THCP displayed a 33-times greater binding affinity at the human CB1 receptor *in vitro* and induced THC-like cannabimimetic behavioral activity in mice⁽²⁶⁾.

H4-CBD is sometimes advertised as not being psychoactive, although this cannot be confirmed based on available scientific studies. The only pharmacological study available is an *in vitro* study exploring its potential therapeutic benefits which found that H4-CBD exhibited much greater binding affinity for the CB1 receptor compared to CBD (which displays very low affinity for these receptors)⁽²⁷⁾. However, higher binding affinity does not necessarily result in higher efficacy or effect in humans.

Although lacking the control over administered doses that is possible with clinical studies, information about behavioral effects can also be

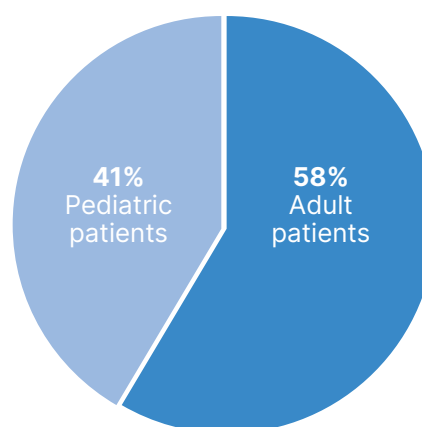
inferred from interview-based studies in which users report their own experiences of using drug products. In such studies users report that the acute effects of *delta*-8-THC are similar in type but of lower magnitude (or “less intense”) compared to THC and less likely to produce undesired effects (e.g. anxiety and paranoia)^(12, 28). Desired effects of *delta*-8-THC reported by users include relaxation, euphoria and relief from various mental/physical health conditions including stress, anxiety, and pain^(12, 28). Similar effects have also been reported for THC-O⁽²⁹⁾ and HHC⁽³⁰⁾ while no studies on the self-reported effects of the other semi-synthetic cannabinoids have yet been published. Thus, there is insufficient scientific evidence available to associate individual semi-synthetic cannabinoids with specific psychoactive effects⁽²⁹⁾.

Health implications of semi-synthetic cannabinoids

Since semi-synthetic cannabinoids first emerged in drug markets, several incidences of adverse effects following their use have been reported. As products containing semi-synthetic cannabinoids often appear in the form of edibles and are sold in misleading packaging (e.g. resembling popular non-drug confectionery products), the risk of accidental exposure is high, particularly among young children. Between 1st January 2021 and 28th February 2022, the US National Poison Centre received 2,362 cases who reported exposure to *delta*-8-THC products and 41% of these were pediatric patients (i.e. under the age of 18). In total, 70% of cases required health care facility evaluation and pediatric patients represented 45% of these cases. Furthermore, 40% of all cases involved unintentional exposure to *delta*-8-THC, and 82% of these unintentional exposures affected pediatric patients⁽³¹⁾.

Adverse effects from *delta*-8-THC and other semi-synthetic cannabinoid products have also been re-

Figure 4: Proportion of *delta*-8-THC exposure cases reported to the US National Poison Centre involving adult and pediatric (under the age of 18) patients between 1st January 2021 and 28th February 2022 (n=2,362).



Source: United States Food & Drug Administration (2022): 5 Things to Know about *Delta*-8 Tetrahydrocannabinol – *Delta*-8 THC.

ported in scientific literature. Like THC, the most commonly reported adverse effects include respiratory problems, reduced blood pressure and heart rate, confusion, sedation or reduced consciousness and decreased psychomotor activity^(9, 28, 29).

Psychotic-like symptoms have also been observed in case studies including paranoia, hallucinations, and panic attacks⁽³²⁻³⁴⁾. The acute clinical management of intoxication and adverse effects will be similar to the treatment of other types of cannabi-

- noid toxicity with a focus on providing supportive care and symptomatic relief. Health care and emergency service providers need to be aware that due to the risk of unintended exposure, such symptoms may also be present in patients not reporting drug exposure. Furthermore, semi-synthetic cannabinoid may contain other cannabinoids (including THC and synthetic cannabinoid receptor agonists⁽²²⁾) as well as other potentially harmful contaminants and impurities^(3, 35). Additionally, vapes/e-Liquids containing semi-synthetic cannabinoids may contain cannabinoid acetates which could lead to the formation

Table 1: Self-reported effects of semi-synthetic cannabinoids

Self-reported desired effects	Self-reported undesired effects
<ul style="list-style-type: none"> • Relaxation • Euphoria • Relief from stress, anxiety, pain and other mental/physical health conditions 	<ul style="list-style-type: none"> • Respiratory problems • Confusion • Increased heart rate • Increased blood pressure • Reduced psychomotor activity • Sedation or reduced consciousness • Psychotic like symptoms (including paranoia and panic attacks)

Source: Please see endnotes 9, 28, 29 and 32-34 for further information.

of harmful by-products causing respiratory problems similar to those observed during the E-cigarette or vaping use-associated lung injury

(EVALI) outbreak in the United States of America in 2019^(3, 8, 36).

Challenges in the detection and identification of semi-synthetic cannabinoids

The growing number of cannabinoid compounds in drug markets presents important challenges for conducting both preliminary screening and confirmatory analysis of both seized materials and biological specimens. Due to their structural similarity, semi-synthetic cannabinoids may be detected by standard THC screening methods. However, common screening methods are not designed to differentiate between THC and semi-synthetic cannabinoids and they may lead to false-positive results when THC or one of its scheduled isomers or variants is not present. Identification of individual compounds can even be challenging with high resolution analytical methods, particularly when found in complex mixtures and matrices, and instrument parameters may need to be optimized for clearer separation of cannabinoid analogues.

Urine drug screening for THC in workplace or criminal justice settings typically involves the use of immunoassays which test for the presence of its main secondary metabolite, *delta*-9-THC-COOH. Studies assessing the sensitivity of commercially available urine THC immunoassay screening kits have shown cross-reactivity with other cannabinoid analogs including *delta*-8-THC, *delta*-10-THC and HHC (and/or their metabolites)^(37, 38) which may lead to false-positive results. If such screening methods are intended to be used as a preliminary indication

of recent THC exposure specifically, further confirmatory analyses using more advanced analytical methods (described below) are needed to discriminate between individual cannabinoid compounds.

Currently, no studies have evaluated the effectiveness of common field-based screening methods (i.e. presumptive tests) to detect semi-synthetic cannabinoids in seized material. Specific colorimetric tests for semi-synthetic cannabinoids are currently not available. Thus, more research is needed to determine the sensitivity and specificity of commonly used colorimetric test with regard to semi-synthetic cannabinoids. Other commonly used field-based drug detection methods utilize handheld or portable devices based on Raman or infrared spectroscopy. Whilst the results obtained with these devices are not suitable for evidentiary or validity purposes, the sensitivity and specificity of these methods can be higher than presumptive colour tests. However, currently no spectral data acquired via these methods has been reported for semi-synthetic cannabinoids, and it is not clear whether detection or discrimination from other cannabinoids is possible. As with colorimetric tests, the presence of semi-synthetic cannabinoids in drug samples may result in a false-positive indication of THC, however, this has not yet been assessed or reported in the scientific literature.

The identification and confirmatory analysis of cannabinoids in biological specimens and drug products typically involves the use of high-performance liquid chromatography (HPLC) or liquid or gas chromatography coupled with mass spectrometry (LC-MS & GC-MS)⁽³⁹⁾. While compounds can be separated chromatographically and the identification of HHC and *delta*-8-THC (and their metabolites) by relative retention time via LC-MS and GC-MS has been reported in several studies^(22, 37, 40, 41), issues with separation and peak interference have also been reported^(40, 41). Laboratories may need to adapt their methods according to their national legal frameworks and carry out appropriate method validation to make sure their choice of analytical scheme is adequate for their particular needs with respect to semi-synthetic cannabinoids.

Conclusions

Recent developments indicate that CBD is increasingly used as a precursor for substances such as *delta*-8-THC, which is under even stricter control than *delta*-9-THC at the international level, and for semi-synthetic cannabinoids not under international control. As the manufacture of semi-synthetic cannabinoids seems to be related to the already sizable CBD market, a further spread of products containing semi-synthetic cannabinoids could have a significant impact on use of cannabinoids and related public health problems. Of particular concern are products containing semi-synthetic cannabinoids in the form of sweets and other edibles, which target not only adult cannabis users looking for alternative products but also children and youth. The accessibility of products containing semi-synthetic cannabi-

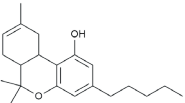
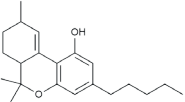
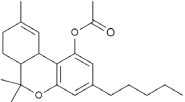
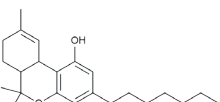
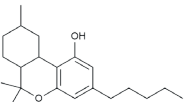
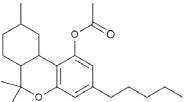
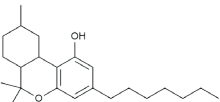
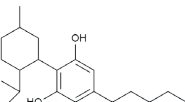
noids for children and adolescents, for example via vending machines, seem to be high in several countries, raising concerns about the protection of minors.

Misconceptions about the control status of semi-synthetic cannabinoids, some of which fall under international control, while others may or may not be subject to national controls in some countries, may contribute to a false sense of safety and legality among persons buying these products.

As semi-synthetic cannabinoids are not (yet) routinely analysed and reported by drug analysis and toxicology laboratories, their prevalence and public health impact may be underestimated and the growing range of semi-synthetic cannabinoids on the market poses serious challenges to detection and identification.

The emergence of semi-synthetic cannabinoids has added complexity to the drug policy discussion around cannabis. The implications of a sizeable, licit CBD market on public health and drug control efforts need to be researched more thoroughly. Previous claims that the wide availability of CBD does not have negative public health consequences may need to be revisited in the light of its role as a precursor for other cannabinoids. In this regards, countries are encouraged to make active use of early warning mechanisms on emerging drug-related threats to monitor the emergence of semi-synthetic cannabinoids, their forms of presentation, and the potential public health impact, specifically on children and youth.

Table 2: "Semi-synthetic cannabinoids" reported to UNODC or mentioned in the literature

Semi-synthetic cannabinoid	Molecular structure	Brief description	Schedule
<i>Delta</i> -8 tetrahydrocannabinol (<i>Delta</i> -8-THC)		A positional isomer of THC differing only in the placement of the carbon-carbon double bond on the cyclohexene ring (located between carbon atoms 8 and 9 rather than carbon atoms 9 and 10).	Schedule I of the UN 1971 convention on Psychotropic Substances
<i>Delta</i> -10-tetrahydrocannabinol (<i>Delta</i> -10-THC)		A positional isomer of THC differing only in the placement of the carbon-carbon double bond on the cyclohexene ring (located between carbon atoms 10 and 10a rather than carbon atoms 9 and 10).	Schedule I of the UN 1971 convention on Psychotropic Substances
Tetrahydrocannabinol acetate (THC-O, THC-O acetate)		The acetate ester of <i>delta</i> -9-THC.	Not scheduled
Tetrahydrocannabiphorol (THCP)		A homologue of <i>delta</i> -9-THC with an alkyl side chain length of 7 carbon atoms.	Not scheduled
Hexahydrocannabinol (HHC)		A derivative of THC in which the carbon-carbon double bond on the cyclohexene ring has been hydrogenated.	Not scheduled
Hexahydrocannabinol acetate (HHC-O, HHC-O-acetate)		The acetate ester of hexahydrocannabinol	Not scheduled
Hexahydrocannabiphorol (HHC-P)		A homologue of HHC with an alkyl side chain length of 7 carbon atoms.	Not scheduled
Tetrahydrocannabinol diol (H4-CBD)		A derivative of CBD, in which two carbon-carbon double bonds have been hydrogenated.	Not scheduled

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