European Monitoring Centre for Drugs and Drug Addiction

EU EARLY WARNING SYSTEM FORMAL NOTIFICATION

Date issued	05 December 2022	RCS ID	EU-EWS-RCS-FN-2022-0035
Issued by	EMCDDA	Transmitted by	Action on New Drugs Sector, EMCDDA
Subject	Formal notification of (6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-yl) acetate (hexahydrocannabinol acetate; HHC acetate) as a new psychoactive substance under the terms of Regulation (EC) No 1920/2006 and Council Framework Decision 2004/757/JHA		

1. Read me first

This document provides formal notification of the analytical identification of (6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-yl) acetate (hexahydrocannabinol acetate; HHC acetate) for the first time in Europe.

Semi-synthetic cannabinoids have recently emerged in a wide range of cannabis products. The internationally controlled semi-synthetic cannabinoid, delta-8-THC, has been detected in e-liquids, gummies and infused beverages, for example, and has been associated with reported cases of adverse events in the United States during 2020 and 2021.

We kindly request that you report any detections of related semi-synthetic cannabinoids as soon as possible so that we can assess, notify, and better understand these rapid developments in the market.

Please report any additional data you have on this substance to: ews@emcdda.europa.eu

2. Data use restrictions

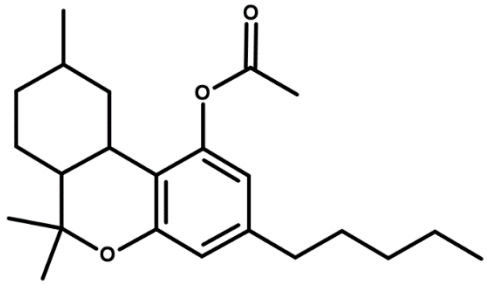
As with all formal notifications issued by the EU EWS remember that they may contain information that could be regarded as sensitive. Should you provide some of the information in this notification to other groups we would ask that you exercise your best judgment on what information needs to be provided. If you have any questions in this respect, please contact us.

3. Names of substance and other identifiers

- IUPAC name: (6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-yl) acetate
- Common name: hexahydrocannabinol acetate; HHC acetate
- Other names: acetyl-hexahydrocannabinol; O-acetyl-hexahydrocannabinol; HHC-O-acetate; HHCO; HHC-O; HHCOA; HHCOAc; HHC-OAc
- Chemical formula: $C_{23}H_{34}O_3$
- Molecular weight: 358.51

- CAS Registry number: not registered.
- InChIKey: ZAZIHGFBNRVMAI-UHFFFAOYSA-N

Molecular structure



4. Substance classification

Cannabinoids

5. Detection

Type: Seizure

6. Chemistry and Analysis

Chemical classification: unclassified

HHC acetate is a semi-synthetic cannabinoid and the acetate derivative of hexahydrocannabinol (HHC), formally notified in October 2022 and placed under intensive monitoring as of 7 November 2022. HHC acetate can be synthesised via acetylation of the phenol moiety present in HHC [1]. Phenyl acetate, part of the substructure of HHC acetate, converts to ketene (a highly reactive poisonous gas) and phenol under thermolytic conditions [1].

HHC acetate is structurally related to delta-8-THC acetate and delta-9-THC acetate; delta-9-THC acetate has reportedly been 'investigated as an incapacitating agent by the U.S. military as part of the Edgewood Arsenal experiments between 1949 and 1975' [1].

Reference standards are available for '9(*R*)-hexahydrocannabinol acetate' and '9(*S*)-hexahydrocannabinol acetate' and both substances are reported to be soluble in acetonitrile (10 mg/ml) [2,3].

HHC acetate contains three stereogenic centres and therefore eight possible stereoisomers may exist.

7. Pharmacology and toxicology

Pharmacological classification: cannabinoid

There is no information available on the pharmacology and toxicology of HHC acetate. Based on its structural similarity to hexahydrocannabinol (HHC), HHC acetate is expected to act as a cannabinoid receptor agonist.

Munger et al. recently hypothesised that vaping cannabinoid acetates could lead to ketene exposure, since cannabinoid acetates and vitamin E acetate both contain phenyl acetate moieties [1]. This hypothesis followed from previous published work in 2019 on the reported formation of ketene after vaping of vitamin E acetate, which led to the consideration of ketene as a possible 'causative agent of e-cigarette or vaping use-associated lung injury (EVALI)' [1,4]. Munger et al. found that 'ketene was consistently observed in vaped condensates', from delta-8-THC acetate, CBN acetate and CBD acetate, as well as from a commercial delta-8-THC acetate product purchased online [1].

It is likely that in the body HHC acetate will be hydrolysed to HHC [5].

8. References

[1] Munger KR, et al. Vaping cannabinoid acetates leads to ketene formation. Chemical Research in Toxicology. 2022;35(7):1202-5.
[2] https://www.caymanchem.com/product/35368/9(r)-hexahydrocannabinol-acetate
[3] https://www.caymanchem.com/product/35369/9(s)-hexahydrocannabinol-acetate
[4] Wu D, et al. Potential for release of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate. Proceedings of the National Academy of Sciences. 2020;117(12):6349-55.
[5] Ujváry I. The emergence of semi-synthetic cannabinoids - A new class of NPS? 22nd Annual meeting of the Reitox Early Warning System Network. 7–8 June 2022.