Critical Review Report:
CUMYL-PEGACLONE

Expert Committee on Drug Dependence
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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.
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Executive summary

CUMYL-PEGACLONE (SGT-151; CAS: 2160555-55-3), 5-pentyl-2-(2-phenylpropan-2-yl)pyrido[4,3-b]indol-1-one, is a synthetic cannabinoid derived from combining a cumyl group with pentyl and gamma-carbol ine-1-one. It is structurally related to cumyl-PICA (SGT-56), which is covered by international patent WO 2014/167530 A1. A synthesis method has been published for CUMYL-PEGACLONE. The compound is not readily converted into other controlled substances and has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

CUMYL-PEGACLONE has been identified in seized material formulated for smoking. The dosage required to elicit pharmacological effects in humans is unknown. Apart from studies examining its metabolism, investigation of the pharmacokinetics of CUMYL-PEGACLONE has been sparse. Like many other synthetic cannabinoids, CUMYL-PEGACLONE is extensively metabolized and presence of the parent product has not been reported in authentic urine samples. Of the identified metabolites, two monohydroxylated metabolites (M20 and M09) predominate and may serve as forensic markers of CUMYL-PEGACLONE use. A thermal degradation product of CUMYL-PEGACLONE has also been identified: N-pentyl-γ-carbolinone.

CUMYL-PEGACLONE binds to both human cannabinoid receptors hCB1 and hCB2, with similar low nanomolar affinities. At CB1 receptors, it acts as a full and potent agonist, increasing [35S]-GTPγS binding and decreasing forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP). CUMYL-PEGACLONE also produced pronounced biased agonism at the CB1 receptor through recruitment of mini-Gi and β-arrestin2.

CUMYL-PEGACLONE has not been evaluated preclinically for pharmacological or toxicological effects. Nor has its abuse and dependence potential been assessed. While the presence of CUMYL-PEGACLONE in postmortem femoral vein blood samples from six individuals has been reported, other drugs were also detected in these samples. Hence, the degree to which CUMYL-PEGACLONE contributed to the deaths could not be definitively stated. In addition, two adolescents experienced seizures after smoking herbal product laced with (analytically confirmed) CUMYL-PEGACLONE.

CUMYL-PEGACLONE was first identified in samples seized by authorities in Germany in 2016 as part of the European Union (EU) SPICE Profiling initiative. While the magnitude of its illicit manufacture and trafficking is unknown, its detection was reported in 16 countries in the EU and in Japan from 2017 to 2019. Currently, CUMYL-PEGACLONE is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances. In 2018, CUMYL-PEGACLONE became controlled under the German Narcotics Law. The chemical is also federally controlled under the psychoactive substance laws of Canada, Sweden and the United Kingdom.
1. Substance identification
   A. International Nonproprietary Name (INN)
      NA
   B. Chemical Abstract Service (CAS) Registry Number
      2160555-55-3
   C. Other chemical names
      SGT-151
   D. Trade names
      NA
   E. Street names
      CUMYL-PEGACLONE has been identified in products labelled Desert (2). In addition, it has been confirmed analytically in products labelled Spice Gold, Mary Joy, Mind Trip, Joker, K2, Karamel Sutra, CM, Monkees Go Bananas, Vertex, Crazy Monkees, and KMA (3).
   F. Physical appearance
      CUMYL-PEGACLONE has been described as a crystalline solid (4) and a white powder (5).
   G. WHO review history
      CUMYL-PEGACLONE has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry
   A. Chemical name
      IUPAC name: 5-pentyl-2-(2-phenylpropan-2-yl)pyrido[4,3-b]indol-1-one
      CA Index Name: NA
   B. Chemical structure
      Molecular formula: C_{25}H_{28}N_{2}O
      Molecular weight: 372.5 g/mol
C. **Stereoisomers**

No stereoisomers of CUMYL-PEGACLONE have been identified.

D. **Methods and ease of illicit manufacturing**

A synthesis method for CUMYL-PEGACLONE and derivatives has been published by Janssens et al. (6)

E. **Chemical properties**

- **Melting point**
  No data

- **Boiling point**
  No data

- **Solubility**
  No data

F. **Identification and analysis**

Ultraviolet (UV)-visible spectrum: $\lambda_{\text{max}}$ at 252 nM (4).

Various methods have been used to identify and/or analyse CUMYL-PEGACLONE. These have included gas chromatography-mass spectrometry (GC-MS) (2, 3, 7), gas chromatography–solid state infrared analysis (GC–sIR) (2), liquid chromatography–electrospray ionization–quadrupole time of flight-mass spectrometry (LC–ESI–qToF–MS) (2), nuclear magnetic resonance (NMR) spectrometry (2, 7), high-performance liquid chromatography – diode array detection (HPLC-DAD) (3), ultra-high-performance liquid chromatography – quadrupole linear ion trap mass spectrometry (UHPLC-QTRAP) (8) and liquid chromatography-tandem mass spectrometry (LC–MS–MS) (9).

3. **Ease of convertibility into controlled substances**

Convertibility into a controlled, but non-cannabinoid substance, is unlikely.

4. **General pharmacology**

A. **Routes of administration and dosage**

The primary route of administration for CUMYL-PEGACLONE is presumed to be the same as for other synthetic cannabinoids: inhalation via smoking or vaping after the chemical has been sprayed onto herbal material or solubilized in vehicle for vaping. Samples obtained for research from online purchases (3, 10) or law enforcement seizures (2, 7, 11) comprised “herbal material”, from which CUMYL-PEGACLONE was identified after extraction. Users have also reported formulation of an e-liquid form of CUMYL-PEGACLONE (12-14). The dosage of CUMYL-PEGACLONE required for pharmacological effects in humans
is unknown, although forensic analysis of postmortem serum samples revealed concentrations ranging from 0.38 to 34.9 nM (0.14–13 ng/mL) (10).

B. Pharmacokinetics

No information on the absorption and distribution of CUMYL-PEGACLONE is available. Several studies have examined its metabolism, with emphasis on the identification of biomarker(s) that could serve in forensic investigations as indicators of use. Like many other synthetic cannabinoids, CUMYL-PEGACLONE is extensively metabolized, and parent product is not detected in authentic urine samples (5, 8). Analysis of authentic urine samples revealed 22 distinct phase I metabolites resulting from various chemical reactions, including mono- and di-hydroxylation, dehydrogenation, N-dealkylation, degradation of the pentyl side-chain to a propionic acid metabolite, and carbonyl formation at the pentyl side-chain (8). Of these metabolites, 16 were further confirmed with a pooled human liver microsome assay (8). Of these, two monohydroxylated metabolites were most abundant and may serve as forensic markers of use (8). A separate study identified three major metabolites through analysis of pooled human liver microsomes: OH-SGT-151, di-OH-SGT-151, and N-dealkyl SGT-151 (5).

In addition to metabolites, a thermal degradation product of CUMYL-PEGACLONE has been identified: N-pentyl-γ-carbolinone (15). Although its activity has not been investigated, the degradant may be present in biological samples after methods of use that involve high heat (e.g. smoking or vaping).

C. Pharmacodynamics

CUMYL-PEGACLONE binds to both human type 1 cannabinoid (hCB1) and hCB2 receptors (expressed in Chinese hamster ovary (CHO) cells) with similar affinities: $K_{i} (\text{CB}1) = 1.37 \pm 0.24 \text{nM}$ and $K_{i} (\text{CB}2) = 2.09 \pm 0.33 \text{nM}$ (2). Binding affinity to hCB1 receptors (expressed in human embryo kidney cells) was also reported to be in the low nanomolar range: $K_{i} = 0.36 \text{nM}$ (16) and $K_{i} = 4.57 \text{nM}$ (17). When evaluated for functional activation of the CB1 receptor, CUMYL-PEGACLONE was shown to be a full and potent agonist and increased $[^{35}\text{S}]$GTP$\gamma$S binding (half maximal effective concentration (EC$_{50}$) = 1.62 nM; $E_{\text{max}}$ = 143% over basal activity) (16), and decreased forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP) (2), with EC$_{50}$ = 0.114 nM; $E_{\text{max}}$ = 109% (17). In two studies, CUMYL-PEGACLONE also produced pronounced biased agonism at the CB1 receptor through recruitment of mini-G$\alpha$ (EC$_{50}$ = 0.07 nM and $E_{\text{max}}$ = 260.9% (18); EC$_{50}$ = 0.17 nM and $E_{\text{max}}$ = 194% (6)) and $\beta$-arrestin2 (EC$_{50}$ = 0.09 nM; $E_{\text{max}}$ = 655.1% (18); EC$_{50}$ = 0.23 nM and $E_{\text{max}}$ = 344% (6)). CUMYL-PEGACLONE has not been evaluated in vivo.

5. Toxicology

Preclinical toxicology studies on CUMYL-PEGACLONE have not been conducted.

6. Adverse reactions in humans

Although adverse reactions to CUMYL-PEGACLONE have not been widely reported (10), some information was available. For example, analysis of postmortem femoral vein blood samples from six individuals revealed the presence of CUMYL-PEGACLONE. However, the presence of other drugs (e.g. opioids, benzodiazepines, alcohol, and/or other synthetic
cannabinoids) was also noted in five of the six cases (10). Hence, the degree to which CUMYL-PEGACLONE contributed to the deaths could not be determined definitively. Other cases in which CUMYL-PEGACLONE was identified in the serum of the dead person have been reported in Australia (19, 20). CUMYL-PEGACLONE was deemed to be a causal or contributory factor in 4 of the 12 reported deaths (20). In addition, two adolescents experienced seizures after smoking herbal product laced with (analytically confirmed) CUMYL-PEGACLONE (5).

7. **Dependence potential**
   
   **A. Animal studies**
   
   No in vivo animal studies to evaluate the dependence potential of CUMYL-PEGACLONE have been conducted.

   **B. Human studies**
   
   No human studies to evaluate the dependence potential of CUMYL-PEGACLONE have been conducted.

8. **Abuse potential**
   
   **A. Animal studies**
   
   No in vivo animal studies to evaluate the abuse potential of CUMYL-PEGACLONE have been conducted.

   **B. Human studies**
   
   No human studies to evaluate the abuse potential of CUMYL-PEGACLONE have been conducted.

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

10. **Listing on the WHO Model List of Essential Medicines**
    
    CUMYL-PEGACLONE is not included on the WHO Model List of Essential Medicines.

11. **Marketing authorizations (as a medicinal product)**
    
    CUMYL-PEGACLONE has no marketing authorizations as a medicinal product.

12. **Industrial use**
    
    NA

13. **Nonmedical use, abuse and dependence**
    
    CUMYL-PEGACLONE began to appear on the German market in late 2016, shortly after the enactment of the German law on new psychoactive substances. This law banned substances based upon generic structural features of previously identified synthetic substances of abuse. For cannabinoids, banned features included compounds with indole, indazole and benzimidazole cores. Because CUMYL-PEGACLONE contained a γ-carbolinone
core that had not been observed previously, it is hypothesized that it was developed to circumvent the new German law (10). Within the first year of enforcement of these new legal restrictions, results of surveillance under the auspices of the European Union (EU) SPICE Profiling initiative revealed that, of the biological samples that contained any synthetic cannabinoid, CUMYL-PEGACLONE was identified in about 30% of urine samples from December 2016 to September 2017 (8) and in 29% of blood/serum samples from January to December 2017 (10). CUMYL-PEGACLONE was also present in 25% of product samples evaluated over the same period, second only to 5F-ADB in frequency of detection (10). While some biological and product samples contained other synthetic cannabinoids, in other samples CUMYL-PEGACLONE was the only synthetic cannabinoid identified.

A search of three user websites (Erowid, Bluelight and Reddit (subreddit/r/research chemicals)) revealed only a few mentions of CUMYL-PEGACLONE (SGT-151). Most threads consisted of user queries about the substance. A single user’s description of the effects was available: “The effects come on very fast and only last about 1 hour. It produces some euphoria, a relaxed but not ‘out of it’ – feeling. Some dissociation was also felt at the end of the experience. Also all the usual suspects: red eyes, dry mouth, munchies” (14).

The prevalence of chronic use and dependence on CUMYL-PEGACLONE has not been reported.

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

No specific information on the nature and magnitude of public health problems associated with use of CUMYL-PEGACLONE is available. One case report identified CUMYL-PEGACLONE in samples obtained from two adolescents who experienced seizures after smoking a cigarette that had been laced with CUMYL-PEGACLONE without their knowledge, suggesting that the chemical could cause harm to others if administered without their knowledge or consent. Adverse effects experienced by individual users have been described in section 6 of this document.

15. Licit production, consumption and international trade

NA

16. Illicit manufacture and traffic and related information

CUMYL-PEGACLONE was first identified in samples seized by authorities in Germany in 2016 as part of the EU SPICE Profiling initiative (2). The extent of its illicit manufacture and trafficking is unknown. However, as with other synthetic cannabinoids, underreporting is likely to be due to lack of routine screening for specific compounds. In addition to Germany (2 reports in 2017; 1 report each in 2018 and 2019), the United Nations Office on Drugs and Crime (UNODC) reported detection of CUMYL-PEGACLONE in the following countries from 2017 to 2019:

- Austria (2 reports in 2019)
- Belgium (2 reports in 2019)
- Croatia (1 report in 2017)
17. **Current international controls and their impact**

CUMYL-PEGACLONE is not currently under any international controls.

18. **Current and past national controls**

In 2018, CUMYL-PEGACLONE became controlled under the German Narcotics Law. The chemical is also federally controlled under the psychoactive substance laws of Canada and the United Kingdom. Sweden entered CUMYL-PEGACLONE into its list of controlled substances in 2019.

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

None.
References


Data were obtained from 105 Member States (19 African Region, 13 Eastern Mediterranean Region, 40 European Region, 16 Region of the Americas, seven South-East Asia Region and 10 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three African Region, two Eastern Mediterranean Region, two European Region, three Region of the Americas, one South-East Asia Region and two Western Pacific Region), leaving 92 active countries. Of these, 30 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on CUMYL-PEGACLONE

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of countries without information</th>
<th>Number of countries with information on substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa Region</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>European Region</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total 92</td>
<td>62</td>
<td>30</td>
</tr>
</tbody>
</table>

LEGITIMATE USE

No countries reported approved human medical products or veterinary products containing CUMYL-PEGACLONE.

Two countries (one European Region, one Region of the Americas) reported CUMYL-PEGACLONE being currently used in medical or scientific research (excluding use as an analytical standard).

No countries reported CUMYL-PEGACLONE being used in industrial or other non-medical or non-scientific use.

No countries reported approved therapeutic indications for CUMYL-PEGACLONE.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

Eight countries (six European Region, two Western Pacific Region) reported that CUMYL-PEGACLONE is being misused or abused for its psychoactive properties/recreational use.
The most common known route of administration reported was smoking (Table 2).

Table 2. Common routes of administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>1</td>
</tr>
<tr>
<td>Injection</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation</td>
<td>2</td>
</tr>
<tr>
<td>Sniffing</td>
<td>0</td>
</tr>
<tr>
<td>Smoking</td>
<td>7</td>
</tr>
<tr>
<td>Don’t know</td>
<td>15</td>
</tr>
</tbody>
</table>

To the above, one country added, “...most likely smoking”.

The most common known formulation of CUMYL-PEGACLONE reported was powder (Table 3).

Table 3. Common formulations reported by countries

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>4</td>
</tr>
<tr>
<td>Tablets</td>
<td>1</td>
</tr>
<tr>
<td>Liquid for oral use</td>
<td>1</td>
</tr>
<tr>
<td>Solution for injection</td>
<td>0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>14</td>
</tr>
</tbody>
</table>

To the above, countries added:
- tobacco leaves laced with substance
- herbal material/herbal plants for smoking.

Eight countries reported the level of negative health impact due to CUMYL-PEGACLONE’s non-medical consumption as “serious” or “substantial” (Table 4).

Table 4. Numbers of countries reporting levels of negative health impact of CUMYL-PEGACLONE

<table>
<thead>
<tr>
<th>Serious</th>
<th>Substantial</th>
<th>Negligible</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

One country (European Region) reported, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers, etc.”. Another country (European Region) noted the “Small magnitude of the problem. Extent increasing over the last years”.
One country (European Region) reported emergency room/department admissions related to the non-medical use of CUMYL-PEGACLONE.

As for reported adverse effects, one country (European Region) noted, “Several severe intoxications; adverse reactions: can lead to sudden tiredness”.

No countries reported users of CUMYL-PEGACLONE presenting for drug dependence treatment.

Regarding mortality, only one country (European Region) reported deaths involving CUMYL-PEGACLONE:
- three fatal cases where other substances were also involved (2017).

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

Thirteen countries responded that CUMYL-PEGACLONE is currently controlled under national legislation to regulate its availability.

Table 5 shows the main reported activities involving CUMYL-PEGACLONE.

Table 5. Reported illicit activities involving CUMYL-PEGACLONE

<table>
<thead>
<tr>
<th>Activities</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smuggling from other countries</td>
<td>3</td>
</tr>
<tr>
<td>Manufacture of substance by chemical synthesis</td>
<td>0</td>
</tr>
<tr>
<td>Manufacture of substance by extraction from other products</td>
<td>0</td>
</tr>
<tr>
<td>Production of consumer products containing the substance</td>
<td>0</td>
</tr>
<tr>
<td>Trafficking</td>
<td>3</td>
</tr>
<tr>
<td>Diversion from legal supply chain</td>
<td>0</td>
</tr>
<tr>
<td>Internet sales – seller or website located in country</td>
<td>1</td>
</tr>
<tr>
<td>Internet sales – from abroad to buyers in country</td>
<td>2</td>
</tr>
<tr>
<td>Internet sales – other, or location of sellers and website unknown</td>
<td>4</td>
</tr>
<tr>
<td>Direct sales to people who use the substance</td>
<td>0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>18</td>
</tr>
</tbody>
</table>

To the above, countries added:
- trafficking through postal services
- not currently, but trends suggest smuggling, production and Internet sales.
Seven countries (seven European Region) reported seizures (Table 6).

Table 6. Reported seizures of CUMYL-PEGACLONE

<table>
<thead>
<tr>
<th>Year</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>32</td>
</tr>
<tr>
<td>2019</td>
<td>182</td>
</tr>
<tr>
<td>2018</td>
<td>1148</td>
</tr>
<tr>
<td>Total</td>
<td>1362</td>
</tr>
</tbody>
</table>

Twenty-four countries have forensic laboratory capacity to analyse CUMYL-PEGACLONE.

One country (European Region) noted, “Forensic laboratories have the capacity to analyse CUMYL-PEGACLONE if reference material is available”.