UR-144

Critical-Review Report

Agenda item 4.8

Expert Committee on Drug Dependence

Thirty-sixth Meeting

Geneva, 16-20 June 2014
Acknowledgments

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Summary

UR-144 is a synthetic cannabinoid receptor agonist (SCRA) and has affinity for CB₁ and CB₂ receptors. It has a high selectivity for the CB₂-receptors.

UR-144 is a psychoactive substance and has effects similar to delta-9-tetrahydrocannabinol (THC), though slightly less potent than THC. UR-144 has been detected in herbal products marketed under a variety of names.

In mice, UR-144 is moderately potent in reducing in a time- and dose-dependent manner the locomotor activity (ID₅₀-value 7.8 mg/kg), induces an anti-nociceptive effect, and decreases rectal temperature and ring immobility with potencies several-fold greater than THC. In mice, UR-144 substituted for THC in a THC discrimination study (ED₅₀-value 7.1 to 7.4 µmol/kg intra-peritoneal), an effect antagonized by rimonabant.

Detailed information on the toxic effects of UR-144 is not available. In general, SCRAs may produce nausea, vomiting, agitation, hallucinations, panic attacks, tachycardia, hypertension, and occasionally chest pain, myoclonia, acute psychosis, and seizures. Intoxications have led to hospital admissions, but the psychoactive SCRA is rarely identified.

Human studies on abuse and dependence potential of UR-144 have not been performed, but considering the rodent studies and the close pharmacological resemblance of UR-144 to THC, abuse of UR-144 is likely to occur.
1. **Substance identification**

   **A. International Nonproprietary Name (INN)**
   
   Not applicable.

   **B. Chemical Abstract Service (CAS) Registry Number**
   
   1199934-44-6

   **C. Other Names**
   
   (1-pentylindol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
   (1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
   TMCP-018, KM-X1, MN-001, YX-17

   **D. Trade Names**
   
   No information available.

   **E. Street Names**
   
   Not known.

   **F. Physical properties**
   
   In pure form, UR-144 is a white powder.

   **G. WHO Review History**
   
   UR-144 was not previously pre reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO’s attention that UR-144 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. **Chemistry**

   **A. Chemical Name**
   
   **IUPAC Name:** (1-pentyl-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
   
   **CA Index Name:** -
B. Chemical Structure

Free base:

![Chemical Structure Diagram]

Molecular Formula: $C_{21}H_{29}NO$
Molecular Weight: 311.5
Melting point: 68 °C
Boiling point: -
Fusion point: -

C. Stereoisomers

No stereoisomers exist.

D. Synthesis

The general synthesis of N-side chain indole-3-yl cycloalkyl ketones has been described.11,23

E. Chemical description

UR-144 is an indole-3-yl cycloalkyl ketone. It has structural resemblance with other synthetic cannabinoids with a core indole structure, such as the Schedule I substances JWH-018 and AM2201.

F. Chemical properties

No data available.

G. Chemical identification

A forensic standard of UR-144 is available. UR-144 can be identified using NMR, GC-MS or IR spectroscopy.7 A commercial ELISA immunoassay to detect UR-144 in urine is available (Tulip Biolabs, Inc.) and an immunoassay that detects several UR synthetic cannabinoids has been developed by Immunalysis Inc. (Pomona, USA).

3. Ease of convertibility into controlled substances

Based on its structure, it is not likely that UR-144 can be converted into a controlled substance.
4. General pharmacology

4.1. Pharmacodynamics

UR-144 belongs to the category of synthetic cannabinoid receptor agonists (SCRAs). SCRAs mimic the effects of delta-9-tetrahydrocannabinol (THC) by binding to the CB1 and CB2 cannabinoid receptors in the brain and peripheral organs.

In the early 1990s, two cannabinoid receptors have been identified and named CB1 and CB2. CB1 is primarily localized in the central nervous system (CNS), and CB2 in cells mainly associated with the immune system, such as macrophages, lymph nodes, spleen, and microglia cells.12;20;22;30 CB1 receptors are mainly found in the CNS-regions involved in cognition, short-term memory, movement and motor function.4 Activation of the CB1 receptor by THC or SCRAs modulates amongst others neurotransmitter release in many inhibitory and excitatory synapses in the brain. These effects are mediated through CB1 receptor coupled G-protein activation and finally result in decreased activity of cAMP-dependent protein kinases.

4.1.1 Receptor binding studies

In 2006, a variety of N-side chain indole-3-yl cycloalkyl ketones showing selectivity to bind to CB2-receptors has been patented by Abbott Laboratories.23 UR-144 showed a high binding affinity to both CB1 and CB2 receptors (Table 1).32 The binding affinity of UR-144 (compound nr. 46) within a series of 70 indole ligands was evaluated at human recombinant CB1 (hCB1) and CB2 (hCB2) receptors using [3H]CP-55,940 as the radioligand.11 In this study, UR-144 showed 83-fold selectivity to bind to CB2-receptors,11 indicating that UR-144 is a highly CB2-selective ligand. Using the same radioligand, Wiley et al. (2013) found a 6-fold selectivity for the CB2-receptor.32 UR-144 also displaced the radiolabeled agonist [3H]CP-55,940 much more readily from the CB1 receptor than the radiolabeled CB1-selective antagonist [3H]rimonabant (apparent Ki was 29 and 368 nM, respectively).32 The US Drug Enforcement Administration (DEA) reported a Ki-value for UR-144 at CB1 receptors of 28.9 nM.6

Table 1. Binding affinity of UR-144 and THC (mean ± SEM) to CB1 and CB2 receptors.6;11;32

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ki-value (nM)</th>
<th>Ratio*</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CB1</td>
<td>CB2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UR-144</td>
<td>29 ± 0.9</td>
<td>4.5 ± 1.7</td>
<td>6.4</td>
<td>a</td>
</tr>
<tr>
<td>UR-144**</td>
<td>368</td>
<td></td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>UR-144</td>
<td>150</td>
<td>1.8</td>
<td>83</td>
<td>a</td>
</tr>
<tr>
<td>THC</td>
<td>28.9</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC</td>
<td>40.7</td>
<td>36.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THC</td>
<td>67</td>
<td>36</td>
<td>1.86</td>
<td>a</td>
</tr>
<tr>
<td>THC</td>
<td>15.3</td>
<td>25.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: Ratio: Ki CB1 / Ki CB2; ** Ki of THC in this study was 764 nM; a: displacement of [3H]CP-55,940; b: displacement of [3H]rimonabant (SR 141716)
4.1.1  Functional studies

In mice, UR-144 produced dose-dependent effects as a full agonist, which were blocked by the cannabinoid antagonist rimonabant. The effects (cf. Table 2) included antinociception, catalepsy, hypothermia and inhibition of locomotor activity.32 In another study, UR-144 (10 and 30 mg/kg) depressed the locomotor activity in mice in a time- and dose-dependent manner and with an ID50-value of 7.8 mg/kg.6

In a human embryonic kidney (HEK-293) cell line expressing CB2 receptors, UR-144 behaved as a full agonist in calcium mobilization, considering its almost maximal response (93%). Compared to other ligands in this series, the potency of UR-144 to mobilize calcium (EC50-value of 29-43 nM) was relatively high.11 In a functional assay mediated by CB1-receptors (not specified, but presumably the GTPγ[35S] binding assay), UR-144 showed agonistic activity with an IC50-value of 1295 nM.6

Using a functional assay that determines the change in the intracellular levels of the radiolabeled CB1 ([3H]Win55-212-2) and CB2 agonists ([3H]CP55-940), it was shown that UR-144 inhibited the internalization of CB1 and CB2 receptors. The IC50 values (nM ± standard error) for UR-144 were 27.2 ± 6.6 (CB1) and 83.6 ± 22 (CB2).5 This indicates a selectivity of only 3 for CB1, whereas others have previously shown a 83-fold selectivity in binding to the two receptors.11

UR-144 stimulated GTPγ[35S] turnover through both the hCB1 receptor and the hCB2 receptor at nanomolar concentrations, indicating that UR-144 acts as an agonist at both receptor subtypes. Mean EC50-value ± SEM for stimulation by UR-144 of the CB1 receptor was 98 ± 20.4 nM, and 334 ± 171 nM of the CB2 receptor. At both receptors UR-144 acted as full agonist.13;32

Table 2. ED50-values in µmol/kg in the mouse tetrad test.31;32

<table>
<thead>
<tr>
<th>Compound</th>
<th>SA</th>
<th>% MPE</th>
<th>RT</th>
<th>RI</th>
<th>AP</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>UR-144</td>
<td>1.0</td>
<td>(0.55-2.25)</td>
<td>2.6</td>
<td>(1.83-4.05)</td>
<td>0.6</td>
<td>(0.51-0.74)</td>
</tr>
<tr>
<td>THC</td>
<td>15</td>
<td>(4.8-41.9)</td>
<td>12</td>
<td>(9.3-16.8)</td>
<td>4</td>
<td>(2.8-6.5)</td>
</tr>
<tr>
<td>THC</td>
<td>0.92</td>
<td>(0.58-1.78)</td>
<td>2.7</td>
<td>(1.8-3.6)</td>
<td>2.5</td>
<td>(1.9-3.1)</td>
</tr>
</tbody>
</table>

ED50: dose at which half maximal effect occurred; SA: spontaneous activity; %MPE: % maximum possible anti-nociceptive effect; RT: rectal temperature; RI: ring immobility; NT: not tested; AP: averaged potency; 95% confidence intervals are given in parentheses.

Table 2 shows that UR-144 induces spontaneous activity (SA) and an anti-nociceptive effect (%MPE), and decreases rectal temperature (RT) and ring immobility (RI) with 3 to 15-fold greater potency relative to THC.32

In summary, these results demonstrate that in vitro and in vivo UR-144 shares the pharmacological properties of THC.32 However, as compared to THC, UR-144 is a highly selective CB2-agonist.
4.2. Routes of administration and dosage

UR-144 is usually smoked and sometimes ingested. The dose required for the desired effect(s) is unknown.

4.3. Pharmacokinetics

The metabolism of UR-144 has not been systematically studied, but mono-hydroxylated metabolites seem to be most abundant in vitro and in vivo. Analysis of urine from mice treated with UR-144 revealed that UR-144 is extensively metabolised and predominantly excreted in the urine as glucuronide conjugates.

5. Toxicology

No pre-clinical safety data are available about the toxicity, reproductive impact and mutagenic/carcinogenic potential of UR-144.

6. Adverse reactions in humans

In general, toxic effects of SCRs include tachycardia, nausea/vomiting, somnolence, mydriasis, and hypokalemia. Less frequent are reduced or missing pupillary light reflex, agitation, vertigo, paraesthesia, aphasia, dysphasia, generalised seizures, myoclonia or muscle jerking, hypopnoea with hypoxemia and aspiration with respiratory insufficiency. Most symptoms cease within a few hours.

The about two-fold lower affinity of UR-144 to the CB₁ receptor as compared to THC (cf. Table 1) may imply that UR-144 is less psychoactive than cannabis. Due to the low psychotropic effect, abusers might increase the dose, which can cause unexpected toxic side effects.

In a series (closely similar and probably overlapping with the previously reported series of the same group), UR-144 was one of the twelve different SCRs detected in serum samples of 25 emergency department (ED) patients with analytically verified consumption of synthetic cannabinoids. UR-144 was found in three serum samples. In 65% of the cases, more than one SCRA was identified and at maximum 8 different SCRs were identified in one patient. Symptoms of intoxication were similar to those reported by this group before.

In another study of this group, the cases of four additional ED patients were presented. In these four cases, six SCRs (JWH-122, JWH-018, JWH-210, MAM-2201, UR-144, and JWH-081) were detected in the blood or the urine. In the serum of case 2 (a 17-year-old male), UR-144 (0.24 ng/ml) together with MAM-2201 (0.15 ng/ml) was detected. In the urine of this patient (case 2) the N-(5-OH-pentyl) metabolite of JWH-122 (1.6 ng/ml) and the N-(5-carboxypentyl) metabolite of JWH-018 (0.11 ng/ml) along with two metabolites of UR-144 were detected. Clinical symptoms in this patient were pronounced sinus tachycardia (160 beats/min), mydriasis, anisocoria, retrograde amnesia, and a mild somnolence which resolved within 12 h of admission. According to the authors, it is unlikely that the clinical symptoms seen were evoked by UR-144, because UR-144 possesses relatively low affinity for the CB₁ receptor.
A previously healthy 26-year-old male was presented to the emergency department with one day of abdominal pain, nausea, vomiting and lower back pain. He had smoked “Mr. Happy”, a product which contained 61 mg/g of UR-144 and 69 mg/g of its fluorinated analogue XLR-11. He stated that he had used this product two or three times a day for approximately one year and that he had used the product on the morning of his presentation. In his blood, 6 ng/ml of UR-144 and 35 ng/ml of XLR-11 were detected. The man had elevated serum creatinine values and was diagnosed with acute kidney injury of unknown aetiology. Twenty-three days later his serum creatinine had normalised. It is unclear whether and how UR-144 and/or XLR-11 contributed to the kidney injury.\textsuperscript{2,26}

Right after smoking of a joint, a 36-year old man collapsed and was transferred to the hospital. Upon arrival, the man suffered seizures and died several hours later.

Amphetamine and five SCRAs, including UR-144, were detected in the femoral blood post mortem.\textsuperscript{24} Concentrations were 0.39 ng/ml JWH-122; 1.5 ng/ml MAM-2201; 1.4 ng/ml AM-2201; 6.0 ng/ml UR-144; 0.1 ng/ml JWH-018; and 250 ng/ml amphetamine. The amphetamine level is not indicative for a fatal amphetamine intoxication and, presumably, the combination of amphetamine with SCRAs was the probable cause of death.

Kronstrand et al. (2013) presented eight cases of intoxications with SCRAs between 2011 and early 2013, where blood from subjects suspected of an innocent drug offence or driving under the influence of drugs (DUI) was analysed.\textsuperscript{19} Of 3,078 blood samples analysed, 28% were found positive for one or more SCRAs. UR-144 could be detected in 181 samples; mean (median) concentration was 1.26 (0.34) ng/g blood.

In summary, it is not possible to draw conclusions about the toxicity of UR-144 in humans, because in the studies available the signs of toxicity were only presented for the group of SCRAs detected and no toxicity data are presented following overdosing of UR-144 alone.

7. Dependence potential

No human studies to the dependence potential of UR-144 have been performed.

8. Abuse potential

In mice, UR-144 substituted for THC in a THC discrimination study (ED50-value 7.1 to 7.4 μmol/kg i.p.).\textsuperscript{6,32} This effect was antagonized by rimonabant.

Redwood Laboratories (California, USA) routinely testing specimen of illicit drugs users recently added UR-144 and XLR11 to their toxicological panel. Using this new panel, 300 randomly selected samples from December 2012 were re-analysed. The positivity of the 300 samples increased from 2.8% to 16% (39 additional samples positive for UR-144 and/or XLR11).\textsuperscript{6} NMS Laboratories (PA, USA) had a similar experience when 46 samples (collected in July 2012) and 28 samples (collected in December 2012) that had been positive for a synthetic drug compound, were re-analysed with a panel that included UR-144 and XLR11. In the total of 74 samples, 35 (47%) and 26 (35%) were positive for UR-144 and XLR11, respectively.\textsuperscript{6} A third
testing laboratory, Premier Integrity Solutions (KY, USA), reported that of 310 drug tests for SCRAs (collected between July 1, 2012 and December 20, 2012), 24 were positive for SCRAs, and 19 of these 24 were positive for UR-144.6

Specific studies to the abuse potential of UR-144 in humans have not been performed. Considering the close pharmacological resemblance of UR-144 to THC, abuse of UR-144 is likely to occur.

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

Pre-clinical studies of nociceptive and neuropathic pain have shown that CB2-selective ligands are analgesics without causing the adverse side effects linked with CB1 receptor activation.23 However, UR-144 has no therapeutic application. According to the FDA (US Food and Drug Administration) there are currently no approved or on-going drug applications for the medical use of UR-144.6

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing authorizations (as a medicine)

UR-144 is not marketed as a medicine.

12. Industrial use

No commercial or industrial use known.

13. Non-medical use, abuse and dependence

Non-medical use of UR-144 is reported in Austria, Poland, Canada, Portugal, France, Romania, Germany, Singapore, Hungary, Ukraine, Lithuania, United States, and Norway. However, the extent of its use is largely unknown.8

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

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

The general view is that UR 144, like other SCRAs, is used a substitute for cannabis. In general, adverse effects of SCRA intoxications are more intense than with cannabis, possibly because of their high activity and ease of overdosing.8 There appears to be a wide variety of herbal products containing a variety and varying quantities of SCRAs.8
Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

No data available.

16. Illicit manufacture and traffic and related information

As reported to the EMCDDA, UR-144 has been encountered in seized products in Latvia, Croatia, Spain, Denmark, Belgium, Germany, France, Slovenia, Turkey, United Kingdom, Sweden, Hungary, Norway, Poland, and Finland.\(^9\)

In Korea, UR-144 has been detected in seized herbal products (resin, herbals and powder).\(^3,18\)

In the USA, UR-144 has been seized as a pure substance and as a substance spiked on products that are marketed as herbal incense and promoted as legal alternatives to marijuana under a variety of names.\(^9\) Between January 2010 and April 2013, 5,356 reports from forensic laboratories were identified in the National Forensic Laboratory Information System (NFLIS) regarding UR-144. In addition, the System to Retrieve Information from Drug Evidence (STRIDE), a DEA program, 179 cases and 1,510 records were identified involving UR-144 between January 2009 and April 2013.\(^6\) Submissions to DEA laboratories from January 2012 through April 03 2013 have documented over 150 distinct packaging examples containing mixtures of UR-144, XLR11 and/or AKB-48.\(^6\)

In Japan, UR-144 has been identified in currently sold designer drugs.\(^27,28\) The number of seizures world-wide containing UR-144 is not known.

No data about the manufacture is available. The global emergence retrieved from the UNODC Early Warning Advisory on NPS is listed in Table 3.\(^29\)

**Table 3.** Global emergence of UR-144.\(^29\)

<table>
<thead>
<tr>
<th>List of countries (13)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Poland</td>
</tr>
<tr>
<td>Canada</td>
<td>Portugal</td>
</tr>
<tr>
<td>France</td>
<td>Romania</td>
</tr>
<tr>
<td>Germany</td>
<td>Singapore</td>
</tr>
<tr>
<td>Hungary</td>
<td>Ukraine</td>
</tr>
<tr>
<td>Lithuania</td>
<td>United States</td>
</tr>
<tr>
<td>Norway</td>
<td></td>
</tr>
</tbody>
</table>

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.
17. **Current international controls and their impact**

UR-144 is currently not under international control.

18. **Current and past national controls**

UR-144 is a schedule I controlled substance under the US Federal Controlled Substances Act, and under national control in Germany (2012), Denmark, Hungary, Portugal, Slovakia, Slovenia, Turkey, and Russia. UR-144 has also been banned in the UK in 2013 along with RCS-4 and AM-2201.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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


6. Drug Enforcement Administration (2013). Background information and evaluation of 'three factor analysis' (factors 4, 5 and 6) for temporary scheduling. Available at http://165.189.64.111/Documents/Board%20Services/Agenda%20Materials/Controlled%20Substances/2013/20130425_agenda_SU2.pdf


27. Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y (2012). Identification of two new-type synthetic cannabinoids, N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide (APICA) and N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (APINACA), and detection of five synthetic cannabinoids, AM-1220, AM-2233, AM-1241, CB-13 (CRA-13), and AM-1248, as designer drugs in illegal products. Forensic Toxicol 30(2): 114-125


Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 66 Member States answered the questionnaire for UR-144. Of these, only 24 respondents (AFR 1, AMR 5, EUR 20, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that UR-144 was currently authorized or is in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in medical and scientific research or as analytical standard. None of the respondents stated that there was a use for animal/veterinary care.

HARMFUL USE

Nineteen respondents confirmed that there was recreational/harmful use of UR-144; the common route of administration was stated as inhaling/sniffing by 9, oral by 2, and oral/injection/inhaling/sniffing by a further two. Ten respondents stated this was obtained via trafficking, one via clandestine manufacturing, three via trafficking plus clandestine manufacturing and 2 via diversion plus trafficking. Eight reported powder as the common formulation available and one reported powder and liquid forms. Five respondents also state that UR-144 is used in herbal mixtures. Five stated that it was only used by the general population and 2 only in clubs while 1 respondent stated that it was used by both populations. One overdose death and 10 emergency room visits are reported by one respondent in 2012. Two emergency room visits are reported by another respondent. Five respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by UR-144 similar to other synthetic cannabinoids. Drug related crime is reported by one respondent.

CONTROL

Of those with information on this substance, 21 reported that UR-144 was controlled under legislation that was intended to regulate its availability; 13 under “controlled substance act”, 5 under “medicines law”, 1 “temporary ban” and 1 under “other” laws. Only 2 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving UR-144, three respondents reported clandestine manufacture. Eleven respondents reported processing into the consumer product, 15 reported trafficking, two reported diversion and 14 an internet market.
Details on seizures are presented below.

<table>
<thead>
<tr>
<th></th>
<th>2011 (number of respondents)</th>
<th>2012 (number of respondents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of seizures</td>
<td>12 (6)</td>
<td>6,681 (14)</td>
</tr>
<tr>
<td>Total quantity seized (kg)</td>
<td>21.3 (1) some include other cannabinoids</td>
<td>64.53 (10) some include other cannabinoids</td>
</tr>
<tr>
<td>Other seizures</td>
<td>wraps/pieces/bags (1)</td>
<td>wraps/pieces/bags (1) plant and herbal material are also reported</td>
</tr>
</tbody>
</table>

**IMPACT OF SCHEDULING**

Twenty-six respondents reported that if UR-144 was placed under international control, they would have the laboratory capacity to identify the substance. This has no reported medical use.