

APINACA
Critical Review Report
Agenda item 4.9

Expert Committee on Drug Dependence
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Summary

There is little information available for APINACA. It belongs to the category of synthetic cannabinoid receptor agonists (SCRAs), which have affinity for CB1 and CB2 receptors. APINACA binds to CB1 and CB2 receptors with two-fold higher affinity for the CB2-subtype (IC₅₀-value of 824 and 430 nM, respectively). However, the binding affinity of APINACA to both receptor subtypes is at least 15-fold lower as compared to delta-9-tetrahydrocannabinol (THC). APINACA was moderately potent in reducing in a time- and dose-dependent manner the locomotor activity (ID₅₀-value 2.2 mg/kg) in mice.

APINACA is a psychoactive substance and has effects similar to THC. It has been detected in herbal products marketed under a variety of names via the Internet and in specialised shops. The quantity of APINACA among the different packages may vary considerably.

Detailed information on the toxic effects of APINACA 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.

Studies on abuse and dependence potential of APINACA have not been performed, but considering its close pharmacological resemblance to THC, abuse of APINACA is likely to occur.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not applicable.

B. *Chemical Abstract Service (CAS) Registry Number*

1345973-53-6

C. *Other Names*

AKB-48

N-adamantyl-1-pentylindazole-3-carboxamide

N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide

1-pentyl-N-tricyclo[3.3.1.1^{3,7}]dec-1-yl-1H-indazole-3-carboxamide

D. *Trade Names*

No information available.

E. *Street Names*

No information available.

F. *Physical properties*

In pure form, APINACA is a white powder. It is soluble in methanol and ethanol.

G. *WHO Review History*

APINACA was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that APINACA 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

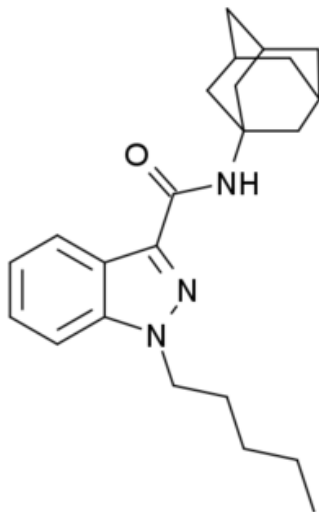
A. *Chemical Name*

IUPAC Name: 1-pentyl-N-tricyclo[3.3.1.^{13,7}]dec-1-yl-1H-indazole-3-carboxamide

CA Index Name: N/A

B. Chemical Structure

Free base:



APINACA

Molecular Formula:	C ₂₃ H ₃₁ N ₃ O
Molecular Weight:	365.2
Melting point:	63.6 °C
Boiling point:	-
Fusion point:	-

C. Stereoisomers

No stereoisomers exist.

D. Synthesis

No information available.

E. Chemical description

APINACA is a new type synthetic cannabinoid receptor agonist that has a core indazole structure and a carboxamide-adamantyl group attached to the indazole ring.

F. Chemical propertiesIn pure form, APINACA is a white powder.⁵**G. Chemical identification**

APINACA can be identified by NMR, infrared spectroscopy (FTIR) and GC-MS.^{1;5}

3. Ease of convertibility into controlled substances

Based on its structure, it is not likely that APINACA can be converted into a controlled substance.

4. General pharmacology

4.1. Pharmacodynamics

APINACA is a new type of synthetic cannabinoid receptor agonist (SCRA). SCRAs mimic the effects of delta-9-tetrahydrocannabinol (THC) by binding to the cannabinoid receptors CB₁ and CB₂ in the brain and in 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.^{11;14;16;21} CB₁ receptors are mainly found in the CNS-regions involved in cognition, short-term memory, movement and motor function.³ 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.

APINACA has been detected in illegal products in Japan.¹⁷ Preclinical or clinical studies characterizing APINACA's pharmacological and toxicological profile or pharmacokinetics are, however, not available.¹⁰

Analogues of APINACA in which a Cl-, I-, or CN-group is introduced at the terminal carbon of the pentyl moiety exhibit high affinity for CB₁ and CB₂ receptors; their K_i values in nM for CB₁ and CB₂ receptors are 1.7/1.3, 0.6/0.2, and 2.3/0.3, respectively.¹³ It is, therefore, likely that APINACA has a similar cannabimimetic activity as these analogues. Recently, it was shown that APINACA has a two-fold higher affinity at the human recombinant CB₂ receptor compared to CB₁ (IC₅₀-value of 430 and 824 nM, respectively) (cf. Table 1).¹⁸ The K_i-value of APINACA at CB₁ receptors reported by the Drug Enforcement Agency (USA) was 304 nM. As compared to THC, these values implicate a 12-30 fold lower binding affinity to CB₁-receptors and a 12-17 fold lower binding affinity to CB₂-receptors. APINACA (3 to 30 mg/kg) was shown to reduce the locomotor activity (ID₅₀-value 2.2 mg/kg) in mice in a time- and dose-dependent manner which reflects a moderate potency.⁴ In another functional assay (assay was not further specified, but refers probably to the GTPγ³⁵S assay), APINACA shows agonist activity with an IC₅₀-value of 585 nM.⁴

Table 1. Binding affinity of APINACA and THC (mean ± SEM) to CB₁ and CB₂ receptors.^{4;18}

Compound	K _i CB ₁ (nM) ^a	K _i CB ₂ (nM) ^a	Ratio	Method	Reference
APINACA (IC ₅₀ -value)	824	430	1.9	a	18
APINACA (K _i -value)	304.5				4
THC	40.7	36.4			2
THC	15.3	25.1			15
THC	67	36	1.86	a	22

^a CB₁: displacement of CP-55,940 at rat brain membranes; CB₂: cloned human receptor preparation; ratio: K_i CB₁ / K_i CB₂

4.2. Routes of administration and dosage

As a substitute for cannabis, APINACA is smoked or sometimes ingested. The dose required for the desired effect(s) is unknown.

4.3. Pharmacokinetics

A study of the metabolism of APINACA in human hepatocytes yielded 17 metabolites of APINACA. Eleven major metabolites were monohydroxylated, dihydroxylated, and trihydroxylated products, and several glucuronide conjugates. Oxidation occurred both on the adamantyl ring and on the aliphatic side chain.¹⁰

5. Toxicology

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

6. Adverse reactions in humans

It is not possible to draw conclusions about the toxicity of APINACA in humans because no toxicity data are available following overdosing of APINACA. In general, acute symptoms of SCRA intoxications include tachycardia, hypertension, nausea/vomiting, hypokalemia, agitation, hallucinations, somnolence, mydriasis, chest pain, myoclonia, seizures, and acute psychotic reactions. Symptoms usually disappear within a few hours. Most of the symptoms are similar to those after high-dose cannabis, except for agitation and seizures which are usually not seen after high doses of cannabis.¹²

7. Dependence potential

No study data on the dependence potential of APINACA is available.

8. Abuse potential

No study data on the abuse potential of APINACA in humans is available. The initial indication of evidence of abuse appeared in 2011 upon the identification of APINACA in products, with evidence of abuse of UR-144 and XLR11 appearing in 2012.⁴

Considering the close pharmacological resemblance of APINACA to THC, abuse of APINACA is likely to occur.

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

APINACA does not have any therapeutic application.

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing authorizations (as a medicine)

APINACA is not marketed as a medicine.

12. Industrial use

No industrial use known.

13. Non-medical use, abuse and dependence

APINACA has been encountered as adulterants in herbal products that are marketed as herbal incense and promoted as legal alternatives to marijuana. However, the extent of the use of these products (either or not containing APINACA) is largely unknown.⁶

Please 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 APINACA, like other SCRA, is used as 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.⁶ There appears to be a wide variety of herbal products containing a variety and varying quantities of SCRA.⁶

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

15. Licit production, consumption and international trade

No data available.

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

16. Illicit manufacture and traffic and related information

No data about the manufacture is available.

APINACA has been seized as a pure substance and as a substance spiked on herbal products. Between January 2010 and April 2013, 525 reports from forensic laboratories were identified in the National Forensic Laboratory Information System (NFLIS) regarding APINACA. In addition, in the System to Retrieve Information from Drug Evidence (STRIDE), a DEA program, 40 cases and 112 records were identified involving APINACA between January 2009 and April 2013.⁴ 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 AKB48.⁴ In Japan, APINACA has been identified in currently sold designer drugs.^{17;19} To the EMCDDA, seizures containing APINACA have been reported from Romania, Italy, United Kingdom, Czech Republic, Latvia, Croatia, Denmark Spain, Belgium, Hungary, Germany, Sweden, and Bulgaria.⁷

The global emergence retrieved from the UNODC Early Warning Advisory on NPS is listed in Table 2.²⁰

Table 2. Global emergence of APINACA.²⁰

List of countries (13)	
Austria	Latvia
Canada	Lithuania
Croatia	Romania
France	Sweden
Germany	United Kingdom
Hungary	United States
Italy	

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

17. Current international controls and their impact

APINACA is currently not under international control.

18. Current and past national controls

APINACA is a schedule I controlled substance under the US Federal Controlled Substances Act.⁸ It is under national control in Denmark (2013), Germany (2013), Hungary (2012), Lithuania (2013), Latvia (2013), Slovakia (2013), and Japan (2012); and under temporary control in New Zealand (2012).⁹

Please 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

No remarks.

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of APINACA

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 Apinaca (AKB 48). Of these, only 27 respondents (AFR 1, AMR 5, EUR 18, WPR 3) had information on this substance.

LEGITIMATE USE

None reported Apinaca was currently authorized or in the process of being authorized/registered as a medical product in their country. Three respondents stated that this substance was used in medical and scientific research or as analytical standard. There was no use stated for animal/veterinary care

HARMFUL USE

Sixteen respondents confirmed that there was recreational/harmful use of AKB 48; common route of administration being oral in 2, inhaling/sniffing in 9 and oral, injection, inhaling/sniffing in 1 response. Eight respondents stated this was obtained only via trafficking, 1 via clandestine manufacturing and 4 via trafficking and clandestine manufacturing. Seven respondents reported on the common formulations of AKB 48 available with 6 reporting powder, and 1 powder and liquid forms. Three respondents also mention that AKB 48 is often smoked and six that AKB 48 is often found in herbal mixtures. When asked if AKB 48 was used by any special populations 6 responded only in the general population and 1 responded that it was used by the general population and in clubs. One emergency room visit due to AKB 48 was reported in 2013. Five respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by AKB 48. These included vomiting, hallucination, disorientation, anxiety, agitation, paranoia, panic attacks, concentration and coordination difficulty, xerostomia, seizures, elevated blood pressure, tachycardia and loss of consciousness. One respondent reported drug related crimes involving postal delivery of NPS.

Additional information ‘in 2012, the American Association of Poison Control Centers (AAPCC) reported receiving an excess of 5,200 exposure calls corresponding to products purportedly laced with synthetic cannabinoids, although the data provided does not generally include biological sample testing that would confirm to which cannabinoids the user was exposed. There is concern regarding the possibility of serotonin syndrome related to synthetic cannabinoids of the indole structural class (e.g. UR-144 and AKB48) due to the similarity to serotonin (Wells and Ott, 2011).’

CONTROL

Of those with information on the substance 20 reported that AKB 48 was controlled under legislation that was intended to regulate its availability - 10 under “controlled substance act”, 5 under “medicines law”, 3 “temporary ban” and 1 under “other” type of legislation. Only 3 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving Apinaca, three respondents reported clandestine manufacture. Eight

respondents reported processing into the consumer product, 11 reported trafficking, 1 reported diversion and 11 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	56 (2)	876 (11)
Total quantity seized (kg)	21.30 (1 – all synthetic cannabinoids)	5.69 (5) includes other cannabinoids as well
Others seized		Additional seizures of plant material and herbal substances reported

IMPACT OF SCHEDULING

Twenty-three respondents reported that if AKB 48 was placed under international control, they would have the laboratory capacity to identify the substance. It has no reported medical use.