



Critical Review Report: APINACA (AKB-48)

Expert Committee on Drug Dependence
Forty-second Meeting
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Executive Summary

APINACA (CAS: 1345973-53-6), N-(adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide, is a synthetic cannabinoid that does not have stereoisomers and is not readily converted into other controlled substances. APINACA is also known as AKB-48. This compound was reviewed by the WHO Expert Committee on Drug Dependence at its 36th Meeting on June 16-20, 2014 in Geneva, Switzerland. The present critical report represents an update of this earlier report.

The most likely route of administration for APINACA (AKB-48) in humans is inhalation via smoking the chemical after it has been sprayed on plant material or vaping it after formulation in liquid. Dosage required for pharmacological effects in humans is unknown. Little is known about its absorption, distribution, elimination or time course. Pharmacokinetic investigation has focused on metabolism, with an emphasis on identifying unique metabolites that may be used for forensic purposes. Based upon results of experiments in human liver cells and analysis of urine from verified users, APINACA (AKB-48) undergoes extensive biotransformation catalyzed by cytochrome P450 enzymes (primarily CYP34A) prior to elimination of metabolites in the urine. Primary metabolism of APINACA (AKB-48) includes mono-, di-, and trihydroxylation of the adamantyl moiety.

APINACA (AKB-48) binds to hCB₁ and hCB₂ receptors, with K_i = 3.24 and 1.68 nM, respectively. Functional activity at both receptors was also indicated by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) in hCB₁ and hCB₂ receptors (IC₅₀ = 5.39 and 2.13 nM, respectively). It was a full agonist at both receptors. Consistent with its activation of CB₁ receptors, APINACA (AKB-48) produced an *in vivo* pharmacological profile in mice that was typical of psychoactive cannabinoids, including suppression of locomotor activity, antinociception, hypothermia and catalepsy. Rimonabant reversal suggested that these effects were CB₁ receptor-mediated. APINACA (AKB-48) also stimulated extracellular dopamine release in the nucleus accumbens (NAc) shell, but not in the striatum, in freely moving mice. Although its dependence potential has not been evaluated, APINACA (AKB-48) was tested in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle, where it fully substituted (ED₅₀ = 0.21 mg/kg). Full substitution occurred over a time frame of 15-120 min, with substitution decreasing to 50% by 4 h after intraperitoneal injection. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans. APINACA (AKB-48) has not been examined for its abuse potential in self-administration in animals nor has it been evaluated in humans.

Systematic preclinical evaluation of the toxicology of APINACA (AKB-48) has not been undertaken, although it has been tested in two studies. In the first study, acute APINACA (AKB-48) (tested over the dose range of 0.1 – 6 mg/kg, *i.p.*) produced increases in a number of neurological signs in male ICR mice, including spontaneous and handling-induced convulsions, hyperreflexia, myoclonias, tail elevation, and spontaneous aggressiveness. These neurological signs were most prominent at the 6 mg/kg dose but occurred only in some mice (25-50%), albeit the authors cautioned that higher doses may be needed to induce these responses in increased numbers of mice. All neurological effects were prevented by pre-administration of a CB₁ receptor antagonist. In the second study,

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APINACA (AKB-48) was shown to decrease viability of SH-SY5Y cells (human bone marrow neuroblastoma cell line) in a concentration-dependent manner, with an IC₅₀ of 160.91 μM.

APINACA (AKB-48) is a synthetic cannabinoid that likely shares a profile of centrally mediated effects with other synthetic cannabinoids, including THC-like intoxication. Examination of the in vivo effects of this compound specifically is limited, and formal surveys of adverse reactions in humans consequent to acute administration of APINACA (AKB-48) specifically are lacking. Specific information on the nature and magnitude of public health problems associated with APINACA (AKB-48) also is not available; however, it is a synthetic cannabinoid, a class of chemicals that have become a global issue with potential for serious public health problems. While the magnitude of these challenges is difficult to determine, issues that have been reported with synthetic cannabinoids include impaired driving, acute psychiatric distress, polysubstance abuse, and increased aggressiveness.

Detection of APINACA (AKB-48) has been reported in the United States, Romania, Italy, United Kingdom, Czech Republic, Australia, New Zealand, Latvia, Croatia, Denmark Spain, Belgium, Hungary, Germany, Sweden, and Bulgaria; however, underreporting is likely due to lack of routine screening for the compound. Most incidents occurred prior to 2015, with the most recent incident reported in the IONICS platform in August 2017. Synthesis of the compound occurs predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped.

Currently, APINACA (AKB-48) is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances, although its closely related analog 5F-APINACA is controlled under this convention. The previous ECDD critical report for APINACA (AKB-48) stated that it is controlled as a schedule I substance in the United States (final ruling 2016)¹ and is also 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). It is also considered a controlled substance in China.

1. Substance identification

A. International Nonproprietary Name (INN)

N/A

B. Chemical Abstract Service (CAS) Registry Number

1345973-53-6

C. Other Chemical Names

APINACA (AKB-48)

APINACA

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

N/A

E. Street Names

Street names specific for APINACA (AKB-48) are not known.

F. Physical Appearance

In pure form, APINACA (AKB-48) is a white powder.

G. WHO Review History

APINACA (AKB-48) was reviewed at the 36th meeting of WHO Expert Committee on Drug Dependence, held in Geneva, Switzerland, 16-20 June 2014. The present critical review represents an update of this previous review.

2. Chemistry

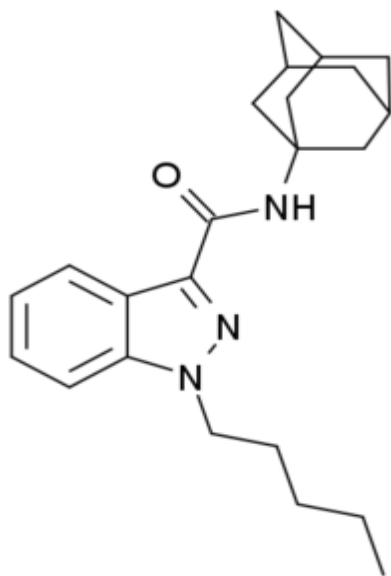
A. Chemical Name

IUPAC Name: N-(adamantan-1-yl)-1-pentyl-1H-indazole-3-carboxamide

CA Index Name: N/A

B. Chemical Structure

Figure 1: Chemical structure of APINACA (AKB-48)



Molecular Formula: C₂₃H₃₁N₃O

Molecular Weight:
365.2 g/mol

C. Stereoisomers

None identified.

D. Methods and Ease of Illicit Manufacturing

No information is available on methods for synthesis or ease of illicit manufacturing.

E. Chemical Properties

Melting point 63.6 °C²

Boiling point 568.3±23.0 °C at 760 mmHg

Solubility Methanol

F. Identification and Analysis

Various methods have been used to identify and/or analyze APINACA (AKB-48). These methods have included gas chromatography-mass spectrometer (GC-MS),^{3,4} liquid chromatography-mass

spectrometer-mass spectrometer (LC-MS-MS),⁵ gas chromatography-electron ionization-mass spectrometry (GC-EI-MS),⁶ direct infusion electrospray ionization Fourier transform ion cyclotron mass spectrometry technique (ESI-FT-ICR MS),⁷ ultra-high pressure liquid chromatography–quadrupole time of flight–mass spectrometry (UHPLC–QTOF–MS),⁸ near infrared (NIR) spectroscopy coupled to chemometrics calibration,⁹ nontargeted liquid chromatography, high-resolution, quadrupole/time-of-flight mass spectrometric (LC-QTOF),¹⁰ and GC/MS followed by liquid chromatography/high-resolution mass spectrometry (LC/HRMS).¹¹

3. Ease of Convertibility Into Controlled Substances

Ease of its convertibility into a controlled, but non-cannabinoid substance, is low. However, conversion of APINACA (AKB-48) into another psychoactive synthetic cannabinoid with a core indazole structure is possible, especially given the large number of possible substituents that could be substituted for the pentyl side chain with retention of nM affinity for the CB₁ receptor.¹²

4. General Pharmacology

A. *Routes of administration and dosage*

The primary route of administration for APINACA (AKB-48) is presumed to be the same as for other synthetic cannabinoids: inhalation via smoking or vaping. Inhalation of smoke from chemical sprayed on herbal material is the most common route of administration for synthetic cannabinoids.¹³ Dosage required for pharmacological effects in humans is unknown. In a small sample of drivers tested for driving under the influence, concentrations ranging from 0.24 to 24.5 µg/L of APINACA (AKB-48) were measured in blood;¹⁴ however, the researchers urged caution due to the large variation in analysis. In addition, this study did not determine the amount or time of administration.

B. *Pharmacokinetics*

The previous ECDD report on APINACA (AKB-48) cited one study in human hepatocytes that yielded 17 metabolites of APINACA (AKB-48).¹⁵ Monohydroxylated, dihydroxylated, and trihydroxylated products, and several glucuronide conjugates comprised eleven of the major metabolites. Oxidation occurred both on the adamantyl ring and on the aliphatic side chain. Since the time of the first critical report, additional APINACA (AKB-48) metabolites (n=41 total) have been identified in human liver microsomes and in human urine samples, with several specific to APINACA (AKB-48) (vs. its fluorinated analog 5F-APINACA).¹⁶ Holm et al.¹⁷ demonstrated that the primary hepatic enzyme involved in the metabolism of APINACA (AKB-48) is CYP3A4.

C. *Pharmacodynamics*

In the previous ECDD report on APINACA (AKB-48),² the binding affinity of APINACA (AKB-48) for CB₁ receptors was reported as K_i = 304.5 nM in hCB₁ receptors expressed in HEK-293 cells, with the binding assay performed by NovaScreen (PerkinElmer, Waltham, Massachusetts, USA) under contract with the National Institute on Drug Abuse Addiction Treatment Discovery Program.¹⁸ This K_i value is inconsistent with the higher potency of APINACA (AKB-48) (compared to THC) for

producing *in vivo* cannabimimetic effects. In another publication, however, binding affinities (K_i) in human CB_1 and CB_2 receptors expressed in Chinese hamster ovary (CHO) cells were 3.24 and 1.68 nM, respectively.¹⁹ In the same study, comparable CB_1 and CB_2 receptor affinities (K_i) were reported in mouse cortex (5.34 nM) and spleen (1.93 nM), respectively. Further, functional activity at both receptors was indicated by inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) in hCB_1 and hCB_2 receptors expressed in CHO cells (IC_{50} = 5.39 and 2.13 nM, respectively)¹⁹ and in hCB_1 receptors expressed in HEK293T cells.²⁰ At each receptor, APINACA (AKB-48) acted as a full agonist.

In mice, APINACA (AKB-48) produced a cannabinoid pharmacological profile in the classic tetrad battery of tests.¹⁹ Hence, it suppressed locomotor activity and produced antinociception, hypothermia and catalepsy. Suppression of locomotion in male mice was also observed in a second study, with an ED_{50} of 2.18 mg/kg and onset of effects at 10-20 min after intraperitoneal injection and duration of 70-100 min.¹⁸ APINACA (AKB-48) also stimulated extracellular dopamine release in the nucleus accumbens (NAc) shell in freely moving mice.^{19, 21} Increased release of dopamine into the extracellular space of the NAc shell is characteristic of drugs with reinforcing properties, an effect that is reversed by CB_1 receptor antagonism and does not appear to be related to direct action at the dopamine active transporter (DAT).²² In contrast, APINACA (AKB-48) did not stimulate dopamine release in the striatum.²¹

5. Toxicology

Systematic preclinical evaluation of the toxicology of APINACA (AKB-48) has not been undertaken. Two studies have examined specific aspects of toxicity induced by APINACA (AKB-48). In the first study, APINACA (AKB-48) was evaluated acutely in a battery of pharmacology/ toxicology assays designed to examine toxicology in the CNS.¹⁹ Results show that APINACA (AKB-48) (tested over the dose range of 0.1 – 6 mg/kg, *i.p.*) produced increases in a number of neurological signs in male ICR mice, including spontaneous and handling-induced convulsions, hyperreflexia, myoclonias, tail elevation, and spontaneous aggressiveness. These neurological signs were most prominent at the 6 mg/kg dose but occurred only in some mice (25-50%). The authors suggest that higher doses may be needed to induce these responses in increased numbers of mice. All neurological effects were prevented by pre-administration of a CB_1 receptor antagonist (AM-251), suggesting that they were mediated by activation of this receptor.¹⁹

The second study examined the cytotoxic effects of APINACA (AKB-48).²³ Results showed that APINACA (AKB-48) decreased viability of SH-SY5Y cells (human bone marrow neuroblastoma cell line) in a concentration-dependent manner, with an IC_{50} of 160.91 μ M. Whereas apoptotic effects were observed at low concentrations, higher concentrations were associated with both apoptotic and necrotic changes. Oxidative stress was hypothesized to be a potential mechanism for these effects.²³

6. Adverse Reactions in Humans

Formal surveys of adverse reactions in humans consequent to acute administration of APINACA (AKB-48) do not exist; however, the chemical and pharmacological data that are available suggest that it would produce adverse reactions that are similar to those reported for other synthetic cannabinoids. In humans, the acute psychological effects of synthetic cannabinoids may resemble those reported during acute intoxication with cannabis, ranging from a relaxed and unfocused euphoria to feelings of distress (e.g., confusion, anxiety, and fear). Time perception may be distorted, and in susceptible individuals, hallucinations, paranoia, and more serious psychiatric disorder may occur. Physical effects may include bloodshot eyes (as is characteristic of THC), tachycardia, somnolence, mydriasis, nausea, vomiting, seizures, and impaired motor performance. Because synthetic cannabinoids are usually more potent (and also may be more efficacious) than phytocannabinoids, their effects occur at lower doses, and overdose may be more common, as suggested by increased reports of deaths and serious adverse reactions compared to cannabis.^{13, 24-27} Since users usually are unaware of which synthetic cannabinoid is contained in a product, they may administer a chemical with greater potency than the chemical contained in previous products. Further, the chemical may not be evenly distributed throughout the plant material, creating “hot spots” containing higher concentrations of synthetic cannabinoid. For these reasons, dose (in THC equivalents) often exceeds intended dose. Contaminants (e.g., pesticides, heavy metals, rodent feces) may also be present and may contribute to adverse reactions.

Reports on the pharmacological effects of APINACA (AKB-48) in humans after chronic use are not available.

7. Dependence Potential

A. *Animal Studies*

No available data.

B. *Human Studies*

No available data.

8. Abuse Potential

A. *Animal Studies*

The abuse potential of APINACA (AKB-48) has been assessed in three animal studies of behavior. The first two studies examined the effects of APINACA (AKB-48) on dopamine release in the NAc shell in mice.^{19, 21} APINACA (AKB-48) stimulated extracellular dopamine release. Increased release of dopamine into the extracellular space of the NAc shell is characteristic of drugs with reinforcing properties.²² The third study employed a drug discrimination procedure to show that APINACA (AKB-48) fully substituted in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle (ED₅₀ = 0.21 mg/kg).²⁸ Full substitution occurred over a time frame of 15-120 min, with substitution decreasing to 50% by 4 h after intraperitoneal injection. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans.²⁹

B. Human Studies

No available data.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

No known medical / therapeutic usage.

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing Authorizations (as a Medicinal Product)

N/A

12. Industrial Use

N/A

13. Non-Medical Use, Abuse and Dependence

The prevalence of non-medical use of APINACA (AKB-48) has not been determined specifically, primarily because the chemicals contained in packages of synthetic cannabinoids are not labeled. Hence, users may not even know which synthetic cannabinoids they are using. Prevalence estimates for specific synthetic cannabinoids rely upon analysis of seized materials and bodily fluids of persons who appear in hospital or morgue following administration, both of which undoubtedly underestimate actual use. In a report covering the period from January 2016 to December 2017, synthetic cannabinoids represented the largest group of substances monitored by the European Union (EU) Early Warning System.¹³ Non-medical use and abuse of synthetic cannabinoids has also been reported outside of the EU, including in the United States, Australia, New Zealand, and Asia.³⁰⁻³⁴

In a report that covered identifications from 2015-2018 (provided by the UNODC to the ECDD Secretariat), APINACA (AKB-48) was detected in 5 regions and 20 countries. Numbers of detections decreased over the time period, with 17 detections in 2015 and 1 detection in 2018. APINACA (AKB-48) was not listed in U.S. DEA Emerging Threat annual reports for years 2016-2018 nor in the mid-year report for 2019.

The prevalence of chronic use and dependence of synthetic cannabinoids has not been reported.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Although specific information on the nature and magnitude of public health problems associated with APINACA (AKB-48) is not available, misuse and abuse of synthetic cannabinoids is a global issue with potential for serious public health problems.^{13, 34, 35} The magnitude of these challenges is difficult to determine; however, newer compounds (i.e., “second and third generation” synthetic

cannabinoids) may have increased potential for harm.³⁶ Issues that have been reported include impaired driving,^{37, 38} acute psychiatric distress,^{39, 40} and polysubstance abuse with several synthetic cannabinoids and/or synthetic cannabinoids and other substances (e.g., alcohol).^{41, 42} Increased aggressiveness has also been reported with some of the newer compounds,⁴³ but a definitive causal link is lacking. This increase could conceivably be related to recent changes in the population consuming synthetic cannabinoids: i.e., increased use by incarcerated persons and the homeless,⁴⁴⁻⁴⁶ the former of whom might already be prone to be more aggressive. APINACA (AKB-48) has been detected in blood from a small sample of drivers at concentrations ranging from 0.24 to 24.5 µg/L (with a possibility that the upper concentration may be related to variant analytical method),¹⁴ suggesting that impaired driving could be a problem. Co-morbidity also may be an issue with synthetic cannabinoids in general (as suggested by emergency room reports and autopsies).⁴²

15. Licit Production, Consumption and International Trade

N/A

16. Illicit Manufacture and Traffic and Related Information

Synthesis of APINACA (AKB-48) (and many other synthetic cannabinoids) is believed to occur predominantly in chemical companies in China, with subsequent processing and packaging within the country to which it is shipped.¹³ This hypothesis is supported by the observation that shipments confiscated by law enforcement organizations frequently originate from China. Direct marketing and purchase over the internet also are common. There may also be trade within the European Union, as indicated by seizures of packages of synthetic cannabinoids.

The prior ECDD critical report on APINACA (AKB-48) indicated peak forensic identification of the substance occurred between January 2010 and April 2013, with 525 reports from forensic laboratories listed in the National Forensic Laboratory Information System (NFLIS). During this time frame, the EMCDDA revealed that seizures containing APINACA (AKB-48) were reported from Romania, Italy, United Kingdom, Czech Republic, Latvia, Croatia, Denmark Spain, Belgium, Hungary, Germany, Sweden, and Bulgaria.²

More recent email correspondence (August 13, 2019) from the International Narcotic Control Board Secretariat, United Nations Office on Drugs and Crime, to the ECDD Secretariat stated that survey of the IONICS platform revealed fourteen contact incidents with APINACA (AKB-48) (mostly seizures) to date. Thirteen of these incidents occurred in 2015, and the most recent incident was reported in August 2017. No newer incidents have been communicated thereafter. These incidents were reported from four countries (1 from Australia, 9 from New Zealand, 1 from United Kingdom and 3 from United States of America). As in the case for most synthetic cannabinoids, however, underreporting is likely due to lack of routine screening for the specific compound.

See Annex 1 for additional information on illicit manufacture and traffic in WHO Member States.

17. Current International Controls and Their Impact

APINACA (AKB-48) is not currently under international control.

18. Current and Past National Controls

The previous ECDD critical review report for APINACA (AKB-48) stated that it is controlled as a schedule I substance in the United States (2016)¹ and is also 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).² It is also considered a controlled substance in China.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances