# 5F-APINACA (5F-AKB-48)

# Review Report

## Agenda item 4.10

**Expert Committee on Drug Dependence**

**Thirty-eighth Meeting**

**Geneva, 14-18 November 2016**

World Health Organization

# Contents

# Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Policy Access and Use team. The WHO Secretariat would like to thank the following people for their contribution in producing this critical review report: Dr. Jan van Amsterdam and Dr. Ed Pennings, The Netherlands (literature search, review and drafting) and Dr. Stephanie Kershaw, Geneva, Switzerland (editing and questionnaire report drafting).

# Summary

5F-APINACA (5F-AKB-48) is an analogue of APINACA (AKB-48) fluorinated on the terminal carbon of the pentyl side chain. It belongs to the category of synthetic cannabinoid receptor agonists (SCRAs), which have affinity for $CB_1$ and $CB_2$ receptors with activation of the former accounting for the psychoactive effects of these substances. 5F-APINACA is a psychoactive substance and has effects similar to $\Delta^9$-THC, which, in accordance with the Convention on Psychotropic Substances of 1971, is listed as Schedule I substance.

5F-APINACA binds with nanomolar affinity to $CB_1$ and $CB_2$ receptors ($K_i$ -value of 1.94 and 0.27 nM, respectively), i.e. with a two-fold and 265-fold higher affinity as compared to THC. 5F-APINACA stimulates $CB_1$-induced [$^{35}$S]GTP$_\gamma$S binding with high potency and efficacy, and at 0.1 mg/kg i.v. it increases dopamine transmission in the nucleus accumbens. 5F-APINACA is mainly metabolized by hydroxylation and loss of the fluorine from the N-pentyl side chain.
Detailed information on the toxic effects of 5F-APINACA is not available. In general, SCRAs may produce nausea, vomiting, agitation, hallucinations, panic attacks, tachycardia, hypertension, and occasionally chest pain, acute psychosis, and seizures. Clinical signs of toxicity (chest pain, tachycardia, hypertension, and agitation) following smoking of 5F-APINACA usually resolve within 4 to 10 h and may require treatment with benzodiazepines. 5F-APINACA smoking has been associated with myocardial infarction. One non-fatal case was reported in a young man following smoking of 5F-APINACA 4 h before the onset of chest pain. Five similar cases were reported after use of other adamantyl-substituted SCRAs.

Long term use of 5F-APINACA is characterized by loss of appetite, cognitive impairment, breathlessness, cardiac conditions requiring medication, skin ablations, tooth decay, lethargy, apathy, tremors and insomnia, which are all exacerbated when attempting to reduce use.
Studies on abuse and dependence potential of 5F-APINACA have not been performed, but users reported a rapidly developing dependence (tolerance, compulsive re-dosing, craving). A variety of withdrawal symptoms have been reported, such as chest pains and pressure, tachycardia and palpitations, ongoing insomnia (for over 3 weeks), anxiety, agitation and paranoia.
No therapeutic or medical use has been described for 5F-APINACA and 5F-APINACA is neither marketed as medicinal product, nor used for industrial purposes.

For recreational use, herbs containing cannabinoids such as 5F-APINACA are smoked, often mixed with tobacco in joints, bongs and pipes. 5F-APINACA has been detected in commercial products send to or sold in Czech Republic, France, Portugal, the US and the UK. 5F-APINACA is not controlled world-wide so that in various countries products containing 5F-APINACA are legally marketed in head shops and via the Internet. In other countries, like Bulgaria, Brazil, some European member states (e.g., France, Latvia, the UK), Korea, and the US, 5F-APINACA was detected in seizures by customs or police. 5F-APINACA is a controlled substance in countries, like Australia, Canada, Germany, Czech Republic, China, Denmark, Latvia, Estonia, Moldova, New Zealand, the UK and the US.

# 1. Substance identification

## *A. International Nonproprietary Name (INN)*

Not applicable.

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

1400742-13-3

## *C. Other Chemical Names*

5F-AKB-48, 5F-AKB48, 5F-APINACA, 5F-APINAKA, AKB-48F, 5-fluoro AKB48, APINACA N-(5-fluoropentyl) analogue.

## *D. Trade Names*

Under the guise of herbal incense products, 5F-APINACA is present in 'Sweet Leaf C-Liquid', 5F-AKB-48 - C -Liquid, Aladin Black 3rd Edition, Aladin Legend 3rd Edition, Super snake green, Super snake white, Black by LIBIDO, Aladdin black 3rd, Cat eye, Annihilation, Psyclone and Exodus Damnation. In Ireland, a variety of products (herbal mixtures) containing 5F-AKB-48 were in circulation.[1]
Other products containing 5F-APINACA are: Annihilation Vol II, Berries, Berry Bomb, Black Mamba, Blueberry Kush, Blue Cheese, Bubblegum Kush, Bud Factory - Blueberry Boom, Bud Factory - Classic Bud, Bud Factory - Pineapple Haze, Clockwork Orange, Cotton Candy, Exodus Damnation, Exodus Nightshade, Fiji Wild, Genesis, Gold Seal, Head Trip, (happy) Joker - blueberry, (happy) Joker – juicy fruit, K2 - Black Edition, Kronic - Black Label (cumyl ring analogue), Kronic - Pineapple Express (cumyl ring analogue), Layer Cake, Lemon Haze, Pandora's Box, Pandora's Box Unleashed, Paradox Fusion, Psyclone (clown design), Psyclone (pink and white), Rapture, Spellbound, Sweet Leaf, Vertex, Viper, Voodoo, Voodoo Gold, White Widow, Dutchy, Puff Adder, Exodus, Exodus Damnation and Green Crack.[2] 5F-APINACA has also been detected in the e-liquids "Buddha Blues" and "Green fried".[3,4]

## *E. Street Names*

See section D.

## *F. Physical Appearance*

White powder.

## *G. WHO Review History*

5F-APINACA has not been previously pre-reviewed or critically reviewed by the Expert Committee on Drug Dependence of the WHO. A direct critical review is proposed based on information brought to WHO's attention that 5F-APINACA is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party.[66] 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

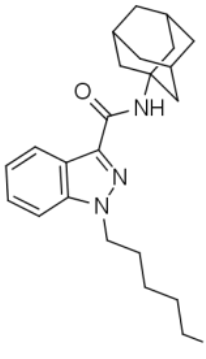
## *A. Chemical Name*

**IUPAC Name:**
N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide.

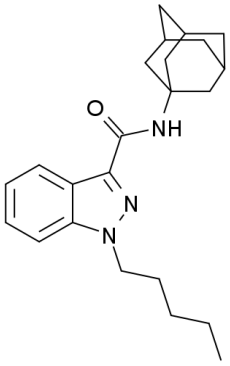
**CA Index Name:**
Not applicable.

## *B. Chemical Structure*

**Free base:**




5F-APINACA (5F-AKB-48)




AKB-48

**Molecular Formula:** $C_{23}H_{30}FN_3O$
**Molecular Weight:** 383

## *C. Stereoisomers*

No optical isomers.

## *D. Methods and Ease of Illicit Manufacturing*

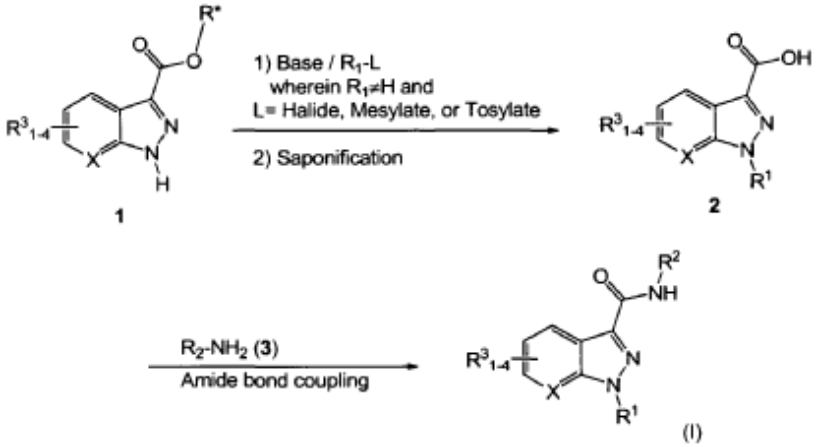



Figure 1. Route of synthesis of 5F-APINACA

Starting compound 1 (see Fig. 1), wherein X is carbon and R* is a carboxyl protecting group such as alkyl or aryl, can be treated with a base and an alkylating

agent $R_1$-L where L is a leaving group and $R_1$ the fluoropentyl group. The desired $N_1$-alkylated regio-isomer is isolated in pure form by either chromatographic separation, or by recrystallization from the crude product mixture. Saponification of the alkylated product with an aqueous base gives compound 2. Compound 2 may be coupled with an amine 3 by using reaction conditions well known for peptide synthesis, where specific agents (e.g. carbodiimides) are applied to activate the negatively charged oxygen into a better leaving group, to give a compound of formula (I). $R_2$ is the adamantly group.

### *E. Chemical Properties*

| | |
|---|---|
| Melting point: | 54.9 °C |
| Boiling point: | not reported |
| Solubility: | sparingly soluble in water; propylene glycol: 2 mg/ml; DMF: 30 mg/ml; ethanol: 30 mg/ml; DMSO: 5 mg/ml. |

### *F. Identification and Analysis*

UV-Visible spectrum: $\lambda_{max}$ at 209 and 302 nm.[5] IR-spectrum: Forendex,[6] MS,[7] GC-MS[8], HPLC-TOF, FTIR-ATR.[9]

## 3. Ease of Convertibility Into Controlled Substances

Based on its chemical structure it is not likely that 5F-APINACA can be easily converted into another controlled substance.

## 4. General Pharmacology

### *A. Routes of administration and dosage*

On the non-commercial, but not peer-reviewed German website "NeuePsychoaktiveSubstanzen.de"[10] users are informed about new psychoactive substances (not peer reviewed). The website provided the following information:

- Usual dose for recreational use is 1-2 mg (inhalation/oral)
- The effect of 5F-APINACA builds up relatively quickly and disappears also rapidly. The duration is shorter than AKB-48. 5F-APINACA is generally regarded as very short-acting cannabinoid, even if it can sometimes cause a very long 'afterglow'.

### *B. Pharmacokinetics*

No pharmacokinetic studies have been described in scientific literature. The website "NeuePsychoaktiveSubstanzen.de" provides the following information:

- Inhalation: Effects within 30-60 minutes with a peak effect at 10-30 minutes; afterglow: 15-90 minutes.
- Oral route: Effects within 45-180 minutes with a peak effect at 15-60 minutes; afterglow: 60-180 minutes.

*Metabolism*

The metabolism of 5F-APINACA is complex and extensive, involving mono-, di-,

and trihydroxylation, N-dealkylation, oxidative loss of fluorine, and carboxylation of the pentyl chain. Holm et al.[11] identified 16 phase-I metabolites in an authentic human urine sample.

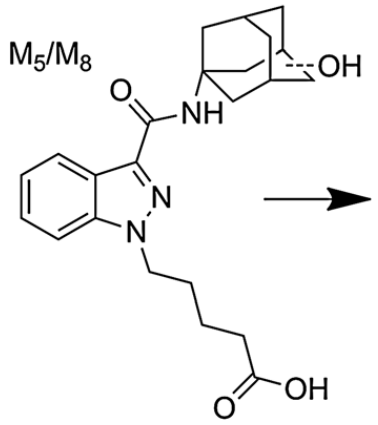



Figure 2. Structure of 5F-APINACA-hydroxy-adamantyl-N-pentanoic acid, the most prominent metabolite of 5F-APINACA

The most prominent metabolite was 5F-APINACA-hydroxy-adamantyl-N-pentanoic acid (Figure 2).[11] Human liver microsomal incubations confirmed the formation of mono- di-, and trihydroxylated metabolites having the hydroxyl groups on the adamantyl ring and the pentyl-indazole moiety.

### *C. Pharmacodynamics*

*In-vitro studies*

5F-APINACA belongs to the synthetic cannabinoid receptor agonists (SCRAs), which have affinity for $CB_1$ and $CB_2$ receptors[12] with activation of the former accounting for the psychoactivity of these substances.[13] While its molecular structure differs only slightly from that of AKB-48 by the addition of fluorine at the terminal carbon of the pentyl chain, the effects are reported to be significantly more potent than those of the parent compound.[14] Consumers appreciated the quality and potency ('the quick high') of 5F-APINACA.[1]

According to the DEA, the binding affinity of AKB-48 to $CB_1$ receptors is higher than that of $\Delta^9$-THC.[12] Based on structure-activity relationship studies, DEA previously expected that 5F-APINACA would bind to $CB_1$ receptors as well.[12] Like quinolones with adamantyl-carboxamide moieties,[15] 5F-APINACA has a higher affinity for the $CB_2$ receptor than for the $CB_1$ receptor. Both DEA's[12] and Pasquini's group[15] suggestions were recently confirmed by Hess et al. (2016)[17] (see below).

In a study of the agonist activity of several SCRAs at $CB_1$ and $CB_2$ receptors, the fluorinated analogues generally showed a 2 to 5-fold higher activity at the $CB_1$ receptor than their corresponding des-fluoro analogues.[16]

In the functional cAMP accumulation assay, Hess et al. (2016)[17] found that most of the tested SCRAs had similar or less activity at the $CB_1$ receptor than at the $CB_2$ receptor, but 5F-APINACA activated the $CB_1$ receptor more strongly than the $CB_2$

receptor (data not shown in Table 1).[17] Affinities of 5F-APINACA and related SCRAs are given in Table 1, together with the $EC_{50}$ data from the studies of Banister et al. (2015; 2016).[18,19]

Table 1. Affinities of synthetic cannabinoids at human $CB_1$ and $CB_2$ receptors. $K_i \pm$ SEM (nM; versus 0.1 nM [$^3$H]CP55,940) and $EC_{50}$ values (nM) from functional assays.[17]

| Compound | Human $CB_1$ | Human $CB_2$ | Reference |
|---|---|---|---|
| 5F-APINACA | 1.94 ± 0.55 | 0.27 ± 0.04 | 17 |
| THC | 3.87 ± 0.91; $EC_{50}$=250 | 71.6 ± 2.4; $EC_{50}$=1157 | 16,17 |
| FUB-AKB-48 | 1.06 ± 0.29 | 0.17 ± 0.02 | 17 |
| APICA | 6.52 ± 3.73; $EC_{50}$=128 | 1.22 ± 0.14; $EC_{50}$=29 | 16,17 |
| STS-135 | 2.51 ± 0.35; $EC_{50}$=51 | 0.79 ± 0.07; $EC_{50}$=13 | 16,17 |
| 5F-AB001 | 12.3 ± 3.0 | 1.47 ± 1.03 | 17 |
| RCS-4 | 26.6 ± 6.6; $EC_{50}$=145 | 2.86 ± 0.39; $EC_{50}$=145 | 17,18 |
| UR-144 | 55.9 ± 6.5; $EC_{50}$=421 | 1.49 ± 0.25; $EC_{50}$=72 | 16,17 |

Functional assay: cAMP accumulation in the presence of forskolin (10 μM). STS-135 is the indole analogue of 5F-APINACA (an indazole); both contain a 5-fluoro-*n*-pentyl and an adamantyl group.

Table 2 shows that as compared with the non-fluorinated analogue AKB-48, 5F-APINACA showed a higher affinity for mouse $CB_1$ and $CB_2$ receptors and functional activity.[20]

Table 2. Binding and functional parameters (mean ± SEM) of AKB-48 and 5F-APINACA on human and mouse $CB_1$ and $CB_2$ receptors, in comparison to $\Delta^9$-THC and JWH-018.

| Compound | h$CB_1$ CHO membranes[a] | h$CB_2$ CHO membranes[a] | Mouse cortex membranes $CB_1$[a] | Mouse spleen membranes $CB_2$[a] | h$CB_1$ CHO cells[b] | h$CB_2$ CHO cells[b] |
|---|---|---|---|---|---|---|
| | $K_i$ (nM) | $K_i$ (nM) | $K_i$ (nM) | $K_i$ (nM) | $IC_{50}$ (nM) | $IC_{50}$ (nM) |
| $\Delta^9$-THC | 28.35 ± 2.43 | 37.82 ± 3.14 | 39.21 ± 2.88 | 45.57 ± 4.18 | 44.76 ± 4.68 | 56.24 ± 5.12 |
| JWH-018 | 9.62 ± 0.79 | 8.55 ± 0.73 | 5.79 ± 0.63 | 7.24 ± 0.65 | 13.88 ± 1.19 | 11.54 ± 1.06 |
| AKB-48 | 3.24 ± 0.28 | 1.68 ± 0.12 | 5.34 ± 0.44 | 1.93 ± 0.14 | 5.39 ± 0.47 | 2.13 ± 0.21 |
| 5F-APINACA | 1.82 ± 0.15 | 0.82 ± 0.07 | 3.87 ± 0.27 | 1.24 ± 0.07 | 2.57 ± 0.19 | 1.94 ± 0.14 |

[a] [$^3$H]-CP-55,940 competition binding experiments; [b] cyclic AMP experiments performed in CHO cells transfected with human $CB_1$ or $CB_2$ receptors.

5F-APINACA behaved as full agonists as demonstrated by the capability to completely inhibit the forskolin-stimulated cAMP production.[20]
5F-APINACA (0.01, 0.03, 0.1 and 0.3 mg/kg i.p.) dose-dependently increased extracellular DA release in nucleus accumbens shell of awake and freely moving mice. 5F-APINACA at 0.03 mg/kg induced a prolonged release of DA (up to 180

min) that reached the maximum at 30–60 min after drug administration (maximal increase of about +75 %).[20]

*In-vivo studies*

In vivo dopaminergic stimulant properties and in vitro affinity at rat cerebral cortex $CB_1$ receptors (displacement of [$^3$H]CP55,940), agonist potency (stimulation of $CB_1$-induced [$^{35}$S]GTP$_\gamma$S) and DA transmission in the nucleus accumbens in vivo of a series of cannabinoids, including 5F-APINACA, were assessed by De Luca et al.[21] 5F-APINACA showed high affinity to $CB_1$ receptors and stimulated in a concentration dependent and saturable manner [$^{35}$S]GTP$_\gamma$S binding, whereas no activation of G protein was observed in cortical membranes of $CB_1$ knockout mice. $K_i$ of binding of 5F-APINACA to $CB_1$ receptors was 0.87 ± 0.14 nM, which was 3.8 times lower than that of JWH-018 (3.38 nM); potency ($EC_{50}$ 31.0 ± 7.5 nM) and efficacy ($E_{max}$ 190% ± 11% over basal activity) as $CB_1$ agonist were slightly lower and higher, respectively, as compared to JWH-018 ($EC_{50}$, 20.2 nM; $E_{max}$, 163%). The functional effect of all the cannabinoids tested was drastically reduced by the $CB_1$ antagonist/inverse agonist AM251 (0.1 µM). The cannabinoids increased DA transmission in the accumbens shell at doses consistent with their in vitro affinity for $CB_1$ receptors (5F-APINACA, 0.1 mg/kg i.v.) which was also reversed by AM251.[17]

At 3 mg/kg i.p., 5F-APINACA induced a greater degree of tail elevation than AKB-48. AKB-48 (3 and 6 mg/kg i.p.) and 5F-APINACA (1, 3, and 6 mg/kg i.p.) induced spontaneous and stimulated aggressiveness in mice. AKB-48 and 5F-APINACA (6 mg/kg i.p.) caused spontaneous aggressiveness in 90, 50 and 100 % of treated animals, respectively. 5F-APINACA at 6 mg/kg induced a stimulated aggressiveness with higher duration than AKB-48 at the same dose. 5F-APINACA at 1 and 3 mg/kg, respectively, stimulated aggressive behavior in 30% and 70% of treated mice. The effect induced at 3 mg/kg was greater than that caused by AKB-48 at the same dose.[20] The observed neurological changes were prevented by the pre-treatment with the selective $CB_1$ receptor antagonist AM251 (6 mg/kg, i.p. injected 20 min before AKB-48 and 5F-APINACA administration).[20]

5F-APINACA induced a prolonged and significant hypothermia at both 3 and 6 mg/kg in mice, but was ineffective in the lower dose range of 0.01–1 mg/kg which was prevented by the pre-treatment with AM251.[20]

5F-APINACA (0.01–6 mg/kg i.p.) increased the threshold to acute mechanical and thermal pain stimulus in mice in the tail pinch and tail withdrawal test, respectively and the effects were prolonged up to 5 h after injection. The analgesic effects were prevented by the pre-treatment with AM251.[20] 5F-APINACA induced at the highest dose tested (3 and 6 mg/kg i.p.) a prolonged and significant impairment of locomotion in the accelerod test. Furthermore, 5F-APINACA at 6 mg/kg also affected spontaneous locomotor activity as at this dose it reduced the total distance travelled and increased at 1 and 6 mg/kg the immobility time in mice.[20]

# 5. Toxicology

*Animal studies*

The genotoxic potency of two groups of synthetic cannabinoids (SCRAs), i.e., aminoalkylindoles (AM-2201 and UR-144) and 1-alkylindazoles (5F-APINACA and AM-2201-IC) was evaluated in single cell gel electrophoresis and micronucleus assays, and in Salmonella/microsome assays.[22] All drugs except AM-2201 caused DNA-migration and all four SCRAs inhibited cell division and significant induction of micronuclei reflecting structural and numerical chromosomal aberrations (Lowest Observed Effect Level for both effects: 50 - 75 μM). Both groups elevated the levels of nucleoplasmatic bridges which are formed from di-centric chromosomes (chromosome with two centromeres), but the frequencies of nuclear buds were not affected.[22] The results in the Salmonella assays were negative. These findings show that these SCRAs cause chromosomal damage without inducing gene mutations (negative results in Salmonella assays in absence and presence of metabolic activation).

In contrast to $\Delta^9$-THC, high doses (3 and 6 mg/kg, i.p.) of AKB-48 and 5F-APINACA induced spontaneous and handling-induced convulsions, hyperreflexia and myoclonias in mice; specifically 5F-APINACA administered at 3 and 6 mg/kg induced convulsions in 30 and 90 % of treated animals, respectively. 5F-APINACA at 6 mg/kg induced seizures with longer duration but with similar latency as those produced by AKB-48.[20] 5F-APINACA at 3 and 6 mg/kg i.p. induced hyperreflexia in 30 and 75 % of mice, respectively which lasted shorter as seen following AKB-48 at 6 mg/kg. 5F-APINACA at 3 and 6 mg/kg i.p. induced myoclonia in 90 and 100 % of treated animals with longer latency and duration than those produced by AKB-48. These neurological changes were blocked by the pre-treatment with the selective $CB_1$ receptor antagonist AM251 (6 mg/kg, i.p. injected 20 min before AKB-48 and 5F-APINACA administration).[20]

Systemic administration of 5F-APINACA (0.01–6 mg/kg i.p.) dose-dependently reduced the visual object response in mice at all doses tested and the effect persisted up to 5 h of observation only for the highest doses of substance 3 and 6 mg/kg i.p. (prevented by pre-treatment with AM 251 at 6 mg/kg i.p.). 5F-APINACA inhibited the acoustic response in a prolonged manner and the effect appeared to be higher than that induced by AKB-48 at the same doses where the inhibitory effect persisted up to 5 h (prevented by pre-treatment with AM 251 at 6 mg/kg i.p.). The pinnae, corneal and vibrissae reflexes were dose-dependently reduced by 5F-APINACA (3-6 mg/kg i.p.) (prevented by the pre-treatment with AM 251 at 6 mg/kg i.p.).[20] 5F-APINACA induced a marked catalepsy at 3 and 6 mg/kg, and the effects remained up to 270 min. The effects were prevented by the pre-treatment with AM 251 which alone did not induce akinesia and catalepsy.[20]

*Human studies*

Only little is known about the toxicity of 5F-APINACA in humans because few toxicity data are available following (over)dosing of 5F-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.[23] Symptoms usually disappear within a few hours. Most of the symptoms are similar to those after the use of cannabis in high-dose, except for agitation and seizures which are usually not seen after high doses of cannabis.[24]

Anxiety, paranoia, dry mouth, headache, hyperthermia have been reported by users of 5F-

APINACA on blogs and forums. It cannot be excluded that 5F-APINACA increases one's disposition to mental illness and psychosis, as has been observed following smoking of other synthetic cannabinoids.[23,25]

A case of acute toxicity after inhalation of 5F-APINACA was reported from Australia.[26] A previously healthy 29-year-old male presented to the emergency department with chest pain and agitation after smoking herbal marijuana containing 5F-APINACA. This was the first time he had smoked this product and denied co-ingestion of alcohol or other substances. Within minutes of smoking the product, the patient developed chest pain, and on arrival in emergency department he had a hypertension (blood pressure 170/95); tachycardia (110 bpm); respiratory rate, 20; saturation, 100% on room air; pupils, 5 mm, equal and reactive; light hypothermia, 36.5 °C; and a reduced Glasgow Coma Scale of 14 (E4, V4, M6). The patient was extremely agitated, unable to keep still, twitching and clutching his chest due to discomfort. After rehydration, 4 mg midazolam i.v. and 1 hour later further 1 mg of midazolam i.v. followed by 5 mg of oral diazepam for ongoing agitation he subsequently improved over a period of 2 hours and became alert and coherent.

Electrolytes, full blood count, liver function tests, and serial cardiac enzymes were within normal limits. Electrocardiogram showed sinus rhythm with no ischemic changes. Chest X-ray was unremarkable. After overnight observation and return to normal vital signs, the patient was discharged without complications, including at 1 month follow up.[26]

Synthetic cannabinoid receptor agonists (SCRAs) were detected in blood of patients presenting from January to July 2015 to an emergency department in London with acute drug toxicity. Blood of 18 out of 179 (10%) patients was positive for SCRAs and 5F-APINACA was the most common SCRA detected (13 samples, concentration 0.05-7.6 ng/ml). No specific clinical signs related to 5F-APINACA were reported.[27]

A 19-year-old female developed seizures and showed tachycardia (HR 128), agitation, visual hallucinations and sustained ankle clonus (20–30 beats) 1–2 hours after she had smoked two herbal mixtures (“cannabis tea” and “mushroom tea”) and ingested two LSD blotters. Symptoms resolved within 13 hours after treatment with midazolam (1 mg i.v.) and no further supportive care was required. Plasma, blood, and urine analysis confirmed the presence of 5F-APINACA and 5F-PB-22. The patient also reported therapeutic use of both fluoxetine and citalopram for depression.[28]

Myocardial infarction was reported in a 26-year-old man who had smoked 5F-APINACA 4 h before the onset of chest pain (not confirmed in specimen). He habitually smoked AKB-48 and 5F-APINACA.[29] The patient smoked around 2.5 g of synthetic cannabinoid per week, almost every day for the past three years and in the last 6 weeks 5F-APINACA. The pain was associated with shortness of breath and not relieved by sublingual glyceryl trinitrate spray. The electrocardiogram (ECG) in the ambulance revealed lateral ST-depression and, in the emergency department, a second ECG showed inferior ST-elevation. On examination the patient was cold peripherally, sweaty and clammy. Blood pressure, temperature, heart rate, oxygen saturation and an arterial blood gas were unremarkable. Jugular venous pressure was not clinically elevated, heart sounds were normal and the chest was clear. The 5F-APINACA induced myocardial infarction was associated with angiographic evidence of coronary occlusion. The patient was treated with antiplatelet agents and post-treatment angiogram shows almost complete resolution of the filling defects.

Rook et al. (2016)[30] reported on four patients admitted to the Poisons Unit of Birmingham City Hospital (UK) from a nearby prison within a 6-h period. Three of the four patients had a reduced level of consciousness and one had suffered a tonic-clonic seizure, which lasted eight minutes and was terminated by the paramedics with diazepam 8 mg i.v. The other three patients were observed to have intermittent limb shaking. Three of the four patients had a sinus tachycardia at presentation (140, 142 and 160 bpm). All four patients were intermittently agitated, disorientated and aggressive, but did not require sedation. Two of the four patients admitted to smoking "Black Mamba", which is known to have a variable content of SCRAs. In all four cases, the presence of a third generation SCRA incorporating an adamantyl group (these include STS-135, AKB-48 and 5F-APINACA) in urine was analytically confirmed. In addition to the synthetic cannabinoid, one patient also had dihydromorphine, amitriptyline, nortriptyline and protriptyline detected; the second had 6-monoacetyl-morphine, morphine, pregabalin, mirtazapine (prescribed) and buprenorphine (prescribed) detected; the third had olanzapine detected (prescribed); the fourth had methadone and metabolites (prescribed) present. All patients recovered completely over a maximum of 4 h and were returned to prison.[30]

A recent report refers to a 39-year-old Caucasian man admitted to the hospital after an out-of-hospital cardiac arrest. ECG and elevated cardiac enzymes revealed ST-elevation myocardial infarction. Although he initially denied illicit drug use, a third party confirmed he had smoked "Black Mamba" during three hours before the onset of his symptoms. Normal coronary perfusion was restored after thrombectomy and coronary artery stenting. Subsequent urine testing confirmed the presence of an adamantyl synthetic cannabinoid, whilst cannabis, cocaine, amphetamines and other drugs of abuse were not detected. He was discharged with anti-platelet therapy.[31]

Four French men (aged 21 to 37 years) were hospitalized following a consumption of different products purchased over the Internet which contained a number of synthetic cannabinoids, including 5F-APINACA (concentrations not given).[4]

*Driving under the influence of drug (DUID) cases*

5F-APINACA was found in one DUID case and both APINACA and 5F-APINACA in three DUID cases reported by the Norwegian Institute of Public Health. 5F-APINACA and APINACA concentrations in whole blood were 0.9 and 2.2 ng/ml in case 1; 6.5 and 0.24 ng/ml in case 2 and 2.2 and 24.5 ng/ml in case 3, respectively. Case 4 had a 5F-APINACA concentration of 5.3 ng/ml. The range of 5F-APINACA concentrations in these four cases was 0.9–6.5 ng/ml (median, 3.75 ng/ml).[32]

*Fatal cases*

Only one case of a fatal 5F-APINACA intoxication has been described.[33] This case involved a 25-year-old man, suffering from diabetic ketoacidosis. Ten synthetic cannabinoids were detected in femoral blood, including 5F-APINACA (0.51 ng/ml), AB-CHMINACA (2.8 ng/ml) and AB-FUBINACA 0.97 ng/ml. Other synthetic cannabinoids were < 0.19 ng/ml. Apart from synthetic cannabinoids, no further drugs or medicinal drugs (insulins) could be detected. Alcohol was absent in blood and urine samples.[33] Heart blood contained only traces (<0.1 ng/ml) of 5F-APINACA. In urine, metabolites of UR-144 or its 5-fluorinated analogue XLR-11 could be detected which indicates previous consumption of one of those drugs, but further discrimination was not possible.

Recent media reports have associated the use of two products with the brand names *Psyclone* and *Exodus Damnation*, containing a blend of the two highly potent synthetic cannabinoids 5F-APINACA and 5F-PB228, with heart attack and death in two men in the UK.[34,35] The relevance of these media messages cannot be evaluated without toxicological analyses.

## 6. Adverse Reactions in Humans

It is not possible to draw conclusions about adverse reactions to 5F-APINACA in humans because few toxicity data are available following overdosing. In general, acute symptoms of SCRA intoxications include tachycardia, hypertension, nausea/vomiting, hypokalemia, agitation, hallucinations, somnolence, mydriasis, chest pain, myoclonic seizures, and acute psychotic reactions. Symptoms usually disappear within a few hours. Most of the symptoms are similar to those after the use of cannabis in high-dose, except for agitation and seizures which are usually not seen after high doses of cannabis.[24] Anxiety, paranoia, dry mouth, headache, and hyperthermia have been reported on user blogs and forums by users of 5F-APINACA.

## 7. Dependence Potential

### *A. Animal Studies*

No studies using self-administration, conditioned place preference or discriminative behavior have been described.

### *B. Human Studies*

Herbal mixtures containing 5F-APINACA are rapidly addictive products as participants described quickly adopted dependent use patterns and routines.[1]
Following the use between one and four grams per day in first-time experimentation, the volume of use increased quickly.
Compulsive re-dosing occurred despite recognition of loss of control, awareness of tolerance and fears around adverse effects. The development of thoughts and cravings about smoking first thing in the morning developed rapidly following initial patterns of use of 5F-APINACA.[1]

*Withdrawal*
Acute physical withdrawal symptoms when attempting to restrict use, included chest pains, chest pressure, tachycardia and palpitations, lower extremity pain and spasms, nausea, sweating, diarrhea, and vomiting, which were easily resolved by resuming smoking of 5F-APINACA.
Psychological withdrawal symptoms included ongoing insomnia (for over 3 weeks), internal restlessness, urge to re-dose, anxiety, agitation and paranoia.

## 8. Abuse Potential

### *A. Animal Studies*

No studies about drug discrimination, place preference or self-administration of 5F-

APINACA have been reported.

### *B. Human Studies*

The website "NeuePsychoaktiveSubstanzen.de" provided the following information about 5F-APINACA: "Strong tolerance is reported which rapidly develops and decreases relatively slowly".[10]

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

There are no commercial or medical uses of 5F-APINACA.[36]

## 10. Listing on the WHO Model List of Essential Medicines

Not listed.

## 11. Marketing Authorizations (as a Medicinal Product)

5F-APINACA is not marketed or licensed as a medicinal drug.

## 12. Industrial Use

5F-APINACA is not used for industrial purposes.

## 13. Non-Medical Use, Abuse and Dependence

In general, herbs containing cannabinoids are smoked, often mixed with tobacco in joints, bongs and pipes. Like the majority of the other cannabinoids, 5F-APINACA can be vaporized in its pure powder form or laced onto a dried plant material and smoked out of a pipe. Additionally, 5F-APINACA can be consumed orally with the assistance of a carrier that is high in fat content such as whole milk, cream, butter, peanut butter, and olive oil. Long term use of 5F-APINACA was characterized by loss of appetite, cognitive impairment, breathlessness, cardiac conditions requiring medication, skin ablations, tooth decay, lethargy, apathy, tremors and insomnia, which were all exacerbated when attempting to reduce use.[1]

*Detection in commercial products*

| | |
|---|---|
| Czech Rep. | In 2014, 5F-APINACA was well available online.[37] |
| France | Of some 4400 samples purchased between 2012 and 2014 in Île de France (Fr) analyzed for content of NPS, 2% contained NPS with 5 samples containing only 5F-APINACA an 3 samples in combination with other NPS.[38] Analysis of herbal smoking mixtures by GC-MS showed that 5F-APINACA was present in 58 of the 69 samples. Of the 46 brands previously analyzed in 2014, 85% of samples were 5F-APINACA positive: 12 contained both 5F-APINACA and 5 F-PB-22 and 27 contained 5F-APINACA alone or in combination with other cannabinoids. In January 2015, 46 out of 113 brands analyzed contained 5F-APINACA (41%). Other cannabinoids, such as the |

non-fluorinated versions, were detected seven times (6%) in the same period.[39]

Portugal In 2014, 5F-APINACA was well available online.[37]

UK Routine analysis of 69 street samples from the UK received between January and September 2014 showed that the averaged concentration of 5F-APINACA varied from 31 to 272 mg per gram of the herbal mixture. The variation in concentration of 5F-APINACA within the brands (Pandora's Box, Puff Adder, Exodus, Clockwork Orange and Green Crack) was between 90 and 110%. However, pronounced variation was observed in "Dutchy" (concentration of 5F-APINACA varied between 75 and 130%) which may contribute to adverse effects experienced by the user.[39] From July 2014 to July 2015, 98 suspected materials for NPS including 50 herbal type, 16 hand rolled cigarettes and loose tobacco samples, 5 liquids, and 27 pills and powders were tested (87% was positive for NPS, and 15% for controlled drugs). In addition to methiopropamine and ethylphenidate, 5F-APINACA belonged to the three common NPS in 74% of the suspect materials (mainly in the herbal and tobacco types, but not in pills/powders).[40]

US Of all synthetic cannabinoids reported by DEA-operated National Forensic Laboratory Information System in the USA during the first half of 2013, AKB-48 and 5F-APINACA formed respectively 1.0 and 2.5 %.[41]

*Detection in specimen of drug users*

Sweden 5F-APINACA was detected in 8 out of 84 patients collected within the Swedish STRIDA project between years 2010 and 2013.[42] Blood levels in the four samples where only 5F-APINACA was found were 14.2, 6.6, 3.7, and 2.2 ng/ml.

UK 5F-APINACA was one of the NPS detected in 12 street urinals in London over an 18 month period from July 2013 to December 2014. As compared to e.g. mephedrone which was detected consistently every month, 5F-APINACA was 12 times less detected (2 months, detection rate 8%).[43]

US 5F-APINACA was not detected by the drug testing panels of (a) the Pretrial Services Agency for the District of Columbia who tested specimens of subjects on parole and probation (N=319), (b) Adult Drug Court (Denver, USA) (N=19), DC Juveniles (N=188) and (c) Tampa Juvenile Assessment Center (Florida, USA) (N=218).[44]

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

The general view is that 5F-APINACA, like other SCRAs, 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. There appears to be a wide variety of herbal products containing different SCRAs and varying quantities of SCRAs.

## 15. Licit Production, Consumption and International Trade

5F-APINACA is not controlled world-wide so that 5F-APINACA products (as herb

mixtures, powders, liquids) are legally marketed in head shops and via the Internet.

## 16. Illicit Manufacture and Traffic and Related Information

*Seizures*

| | |
|---|---|
| Bulgaria | Two new SCRAs were identified in 2013 for the first time in Bulgaria: 5F-APINACA (13 cases out of 80 cases; 16.2%), 5F-AKB-48 (nearly 3 kg) was seized in 12 cases.[45] |
| Brazil | Controlled substance according to Resolution No. 79 of May 23rd, 2016. List of prohibited substances in Brazil, List 2 - Psychotropic substances.[46] |
| EU | Between 2008 and 2013 there has been a 200-fold increase in the number of seizures of synthetic cannabinoids in the EU. In 2012, 5F-APINACA was first detected by EMCDDA and number of seizures in 2013 was 3,362 with a notable seizure of 114 kg of 5F-APINACA.[47] |
| France | 5F-APINACA was detected (number not given, total number seized was 56) in French seizures.[48] The French Customs reported two minor seizures of MDMB-CHMICA in 2015. Both seizures were post parcels, the first contained less than 1 g of MDMB-CHMICA mixed with 5F-APINACA and the second 12 g of such a mixture. No seizures were made in 2014.[49] Later in 2015, 5F-APINACA was detected in 4 bags.[50] |
| Latvia | One postal seizure was reported in 2015 which had arrived from the UK. In total 6.1 g of herbal mixture was seized containing MDMB-CHMICA and 5F-APINACA. In another case, Latvian authorities seized 115.6 g of MDMB-CHMICA as herbal mixture.[49] |
| Korea | From 2009 to June 2013 the Korean National Forensic Service noticed that halogenated synthetic cannabinoids were seized more frequently than the classical synthetic cannabinoids considering that 36 out of 43 cannabinoids detected in June 2013 were halogenated compounds which included amongst others 5F-APINACA.[51,52]<br>Both XLR-11 and 5F-APINACA were identified in the seized material of a suspected user apprehended by the police (February 2013 - September 2014), but none of the specific metabolites for XLR-11 and 5F-APINACA were detected in his urine.[53] |
| UK | Forensic analysis of 345 products seized from head shops from Aberdeen to Plymouth in Spring 2014 detected 11 different SCRAs, including 5F-APINACA which was seen most often (156 times).[54,55] Note that a high proportion (88%) of controlled drugs detected was sampled at festivals. |
| US | NFLIS (National Forensic Laboratory Information System) collects data on drugs seized by law enforcement in the US. DEA's System To Retrieve Information from Drug Evidence (STRIDE) reflects results of drug evidence from drug seizures, undercover drug buys, and other evidence analyzed at DEA laboratories across the US. In 2012, NFLIS and STRIDE databases contain 81 reports for 5F-APINACA.[12,36] According to NFLIS (National Forensic Laboratory Information System) which collects data on drugs seized by law enforcement, 860 reports were received concerning 5F-APINACA (2.45% of all synthetic cannabinoid reports) in 2013.[56] In 2014: NFLIS received 326 reports about 5F-AKB-48 (0.87% of all synthetic cannabinoid reports).[57] |

## 17. Current International Controls and Their Impact

5F-APINACA is not scheduled under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

## 18. Current and Past National Controls

| | |
|---|---|
| Australia | 5F-APINACA is scheduled in the Poison Act.[58] |
| Canada | 5F-APINACA is scheduled in Schedule II (Canada's Controlled Drugs and Substances Act).[55] |
| Germany | 5F-APINACA is scheduled in Anlage II of the German 'Betäubungsmittelgesetz' (BtMG, Narcotic Act) since July 2013 stating that controlled substances are tradable, but cannot be prescribed. |
| Czech Rep. | 5F-APINACA is scheduled as controlled substance.[59] |
| China | 5F-APINACA is scheduled as controlled substance since October 2015.[60] |
| Denmark | By decree on narcotics, 5F- APINACA is under control by the Danish Ministry of Health since 2013.[61] |
| Latvia | 5F-APINACA is scheduled as Schedule I drug.[59] |
| Estonia | 5F-APINACA is scheduled according to Estonian Narcotic Drugs and Psychotropic Substances and Their Precursors Act.[60] |
| Moldova | 5F-APINACA is scheduled as controlled substance.[62] |
| New Zealand | 5F-APINACA controlled as per 20 April 2013 in Temporary Class Drug Notice.[63] |
| UK | Synthetic cannabinoids are covered by the Psychoactive Substances Act[64] (illegal to produce, supply, or import this drug), which came into effect on May 26th, 2016.[65] |
| US | If intended for human consumption, 5F-APINACA may be treated as a "controlled substance analogue" under the CSA pursuant to 21 U.S.C §§802(32)(A) and 813.[12] |

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

No remarks.

# References


1. van Hout MC, Hearne E. User experiences of development of dependence on the synthetic cannabinoids, 5F-AKB48 and 5F-PB-22, and subsequent withdrawal syndromes. Int J Ment Health Addiction. 2016 (Epub ahead of print).
2. CREW. 2016. NPS at Crew Annual Report. 2015-2016. Available from: http://www.drogart.org/priponke/2455/20160524-nps-annual-report-2015-2016.html
3. Angerer V, Moosmann B, Franz F, Auwärter V. 2015. 5F-cumyl-PINACA in 'e-liquids' for electronic cigarettes - A new type of synthetic cannabinoid in a trendy product. 53rd Annual Meeting of the International Association of Forensic Toxicologists (TIAFT), Firenze, Italy. Available from: http://tinyurl.com/gmh9flf
4. Le Roux G, Bruneau C, Ferec S, Gegu C, Balter C, Roussel O, et al. Premiers cannabinoïdes de synthèse au centre antipoison et de toxicovigilance d'Angers: à propos de quatre cas. 23e congrès SFTA et 53e congrès STC, Abstract P43. Toxicologie Analytique et Clinique. 2015;27(2 (Suppl)):S63.
5. Cayman. 2013. Product information. AKB48 N-5-fluoropentyl analogue. Available from: https://www.caymanchem.com/pdfs/12065.pdf
6. Fordendex. 2016. 5F-AKB-48. IR spectrum. Available from: http://forendex.southernforensic.org/uploads/spectra/5F-AKB48_edit.pdf
7. Fordendex. 2016. 5F-AKB-48 MS spectrum Available from: http://forendex.southernforensic.org/uploads/spectra/5F-AKB48_edit.pdf
8. Cayman. 2012. 5F-AKB GC-MS. Available from: https://www.caymanchem.com/gcms/12065-0440921-GCMS.pdf
9. NFL (National Forensic Laboratory). 2015. Analytical report 5F-AKB48, Ljubljana, Slovenia. Available from: http://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/5F-AKB48-ID-1179-15-report_final.pdf
10. NeuePsychoaktiveSubstanzen.de. 2016. 5F-AKB-48 / 5F-APINACA - Synthetisches Cannabinoid. Available from: http://neuepsychoaktivesubstanzen.de/5f-akb-48/
11. Holm NB, Pedersen AJ, Dalsgaard PW, Linnet K. Metabolites of 5F-AKB-48, a synthetic cannabinoid receptor agonist, identified in human urine and liver microsomal preparations using liquid chromatography high-resolution mass spectrometry. Drug Test Anal. 2015;7(3):199-206.
12. DEA. 2013. Drug Enforcement Administration (DEA). Office of diversion control. AKB48 (APINACA) and 5F-AKB48 (5F-APINACA). Available from: http://ebookinga.com/pdf/akb48-apinaca-and-5f-akb48-5f-apinaca--96326527.html# or http://deadiversion.usdoj.gov/drug_chem_info/spice/akb48.pdf
13. Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry. 2001;58(4):322-8.
14. Drug Forum. 5F-AKB48. Available from: https://drugs-forum.com/forum/showwiki.php?title=5F-AKB48. 2014.
15. Pasquini S, De Rosa M, Pedani V, Mugnaini C, Guida F, Luongo L, et al. Investigations on the 4-quinolone-3-carboxylic acid motif. 4. Identification of new potent and selective ligands for the cannabinoid type 2 receptor with diverse substitution patterns and antihyperalgesic effects in mice. J Med Chem. 2011;54(15):5444-53.

16. Banister SD, Stuart J, Kevin RC, Edington A, Longworth M, Wilkinson SM, et al. Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. ACS Chem Neurosci. 2015;6(8):1445-58.
17. Hess C, Schoeder C, Pillaiyar Th, Madea C. Pharmacological evaluation of synthetic cannabinoids identified as constituents of spice. Forensic Toxicol. 2016;34:329-43.
18. Banister SD, Stuart J, Conroy T, Longworth.M., Manohar M, Beinat C, et al. Structure-activity relationships of synthetic cannabinoid designer drug RCS-4 and its regioisomers and C4 homologues. Forensic Toxicol. 2015;33:355-66.
19. Banister SD, Longworth.M., Kevin R, Sachdev S, Santiago M, Stuart J, et al. The pharmacology of valinate and tert-leucinate synthetic cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA, and their analogues. ACS Chem Neurosci. 2016 (Epub ahead of print).
20. Canazza I, Canazza I, Ossato A, Ossato A, Trapella C, Trapella C, et al. Effect of the novel synthetic cannabinoids AKB48 and 5F-AKB48 on "tetrad", sensorimotor, neurological and neurochemical responses in mice. In vitro and in vivo pharmacological studies. Psychopharmacology (Berl). 2016 (Epub ahead of print).
21. De Luca MA, Castelli MP, Loi B, Porcu A, Martorelli M, Miliano C, et al. Native CB1 receptor affinity, intrinsic activity and accumbens shell dopamine stimulant properties of third generation SPICE/K2 cannabinoids: BB-22, 5F-PB-22, 5F-AKB-48 and STS-135. Neuropharmacology. 2016;105:630-8.
22. Koller VJ, Ferk F, Al-Serori H, Misik M, Nersesyan A, Auwarter V, et al. Genotoxic properties of representatives of alkylindazoles and aminoalkyl-indoles which are consumed as synthetic cannabinoids. Food Chem Toxicol. 2015;80:130-6.
23. Castellanos D, Gralnik LM. Synthetic cannabinoids 2015: An update for pediatricians in clinical practice. World J Clin Pediatr. 2016;5(1):16-24.
24. Hermanns-Clausen M, Kneisel S, Szabo B, Auwarter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction. 2013;108(3):534-44.
25. van Amsterdam J, Brunt T, van den Brink W. The adverse health effects of synthetic cannabinoids with emphasis on psychosis-like effects. J Psychopharmacol. 2015;29(3):254-63.
26. Gunja N, Kuligowski K, Paul PG, Collins M, Anderson R, Kwan J. Acute agitation and chest pain from 5-fluoro-AKB48: A novel synthetic cannabinoid. Abstract 162 EAPCCT. Clin Toxicol. 2014;52:295-443. Available from: http://www.ismu.baikal.ru/src/downloads/5aeda28d_abstracts_brussels.pdf.
27. Abouchedid R, Thurtle N, Yamamoto T, Ho J, Bailey G, Hudson S, et al. Analytical confirmation of the synthetic cannabinoid receptor agonists (SCRAs) present in a cohort of presentations with acute recreational drug toxicity to an Emergency Department (ED) in London, UK (Abstract nr. 238). Clin Toxicol. 2016;54:472-3.
28. Abouchedid R, Ho JH, Hudson S, et al. Acute toxicity associated with use of 5F-derivations of synthetic cannabinoid receptor agonists with analytical confirmation. J Med Toxicol. 2016 (Epub ahead of print).
29. Walsh JL, Ossei-Gerning N, Harris BH. MI with multiple distal occlusions associated with use of the synthetic cannabinoid 5F-AKB48 (Abstract). Br J Cardiology. 2015;22:40.
30. Rook W, Ford L, Vale A. Four analytically confirmed cases of use of third-generation synthetic cannabinoid receptor agonists incorporating an adamantyl group. Clin Toxicol (Phila). 2016;54(6):533-4.
31. McIlroy G, Ford L, Khan JM. Acute myocardial infarction, associated with the use of a synthetic adamantyl-cannabinoid: a case report. BMC Pharmacol Toxicol. 2016;17:2.

32. Karinen R, Tuv SS, Oiestad EL, Vindenes V. Concentrations of APINACA, 5F-APINACA, UR-144 and its degradant product in blood samples from six impaired drivers compared to previous reported concentrations of other synthetic cannabinoids. Forensic Sci Int. 2015;246:98-103.
33. Hess C, Stockhausen S, Kernbach-Wighton G, Madea B. Death due to diabetic ketoacidosis: Induction by the consumption of synthetic cannabinoids? Forensic Sci Int. 2015;257:e6-11.
34. Daily Mail. 2013. Horrific cost of taking legal highs. Available from: http://tinyurl.com/zk6mvnr
35. Mirror. 2013. Man dies after smoking herbal incense sold as 'legal high'. Available from: http://www.mirror.co.uk/news/uk-news/man-dies-after-smoking-psyclone-2334291
36. DEA. 2013. Information on Synthetic Drugs. Synthetic Cannabinoids. Available from: http://www.deadiversion.usdoj.gov/drug_chem_info/index.html
37. Vavrincikova L, Fidesova H, Janikova B, Grund JP. 2016. New psychoactive substances among people who use drugs heavily. Towards effective and comprehensive health responses in Europe. Available from: http://www.npsineurope.eu/images/pdf/publication/NPS_5_country_rar_report.pdf
38. Cheze M, Hoizey G, Eliot E, Zamore J, Borlot AL, Toulourat R, et al. Nouvelles drogues: bilan à partir des saisies de produits analysés au laboratoire Toxlab sur la période 2012-014. Abstract P41 23e congrès SFTA et 53e congrès STC. Toxicologie Analytique et Clinique. 2015;27 (Suppl June):S62.
39. Frinculescu A, Frinculescu A, Lyall CL, Lyall CL, Ramsey J, Ramsey J, et al. Variation in commercial smoking mixtures containing third-generation synthetic cannabinoids Drug Test Anal. 2016 (Epub ahead of print).
40. Ford LT, Berg JD. Annals Express: Analysis of legal high materials by UPLC-MS/TOF as part of a toxicology vigilance system. What are the most popular novel psychoactive substances in the UK? pii: 0004563216651646. Annals Clin Biochem. 2016 (Epub ahead of print).
41. NFLIS (National Forensic Laboratory Information System). 2013. Annual Report. Thematic paper. U.S. Department of Justice, D. E. A., Office of Diversion Control. Available from: http://www.deadiversion.usdoj.gov/nflis/NFLIS2013AR.pdf
42. Tworek L. 2016. Development of a liquid chromatography - high resolution mass spectrometry method for multi-component screening of synthetic cannabinoids in blood. Available from: www.diva-portal.se/smash/get/diva2:936608/FULLTEXT01.pdf
43. Archer JRH, Hudson S, Yamamoto T, Abouchedid R, Thurtle N, Ho J, et al. Trend analysis of novel psychoactive substances (NPS) detected in pooled urine samples from street urinals in London, UK over 18 months (Abstract). Clin Toxicol. 2015;409:A88.
44. ONDCP (Office of National Drug Control Policy). 2015. Community Drug Early Warning System: The CDEWS-2 Replication Study. Available from: https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/finalreport_4_8_15v3.pdf
45. Andreeva-Gateva PA, Nankova VH, Angelova VT, Gatev TN. Synthetic cannabimimetics in Bulgaria 2010-2013. Drug Alcohol Depend. 2015;157:200-4.
46. MoH (Ministry of Health). 2016. Resolution No. 79 of May 23, 2016. List of prohibited substances in Brazil. List 2 - Psychotropic substances. Available from: http://www.lex.com.br/legis_27142279_RESOLUCAO_RDC_N_79_DE_23_DE_MAIO_DE_2016.aspx
47. EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2015. New psychoactive substances in Europe. An update from the EU Early Warning System (March

2015), Publications Office of the European Union, Luxembourg. Available from: www.emcdda.europa.eu/publications/2015/new-psychoactive-substances

48. Roussel O, Tensorer L, Bouvot X, Balter C, Sabini S. Le point sur les saisies de nouvelles drogues de synthèse. 23e congrès SFTA et 53e congrès STC Abstract O18. Toxicologie Analytique et Clinique. 2015;27(2, Supplement):S23.
49. EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2016. MDMB-CHMICA. EMCDDA-Europol Joint Report on a new psychoactive substance: methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA). EMCDDA-Interpol joint publication. Available from: http://www.emcdda.europa.eu/system/files/publications/2873/2016.4528_WEB.pdf
50. Richeval C, Humbert L, Lazes-Charmetant A, Martinez M, Nefau T, Gaulier JM, et al. Le stock incroyable d'une consommatrice hors norme de NPS. Toxicologie Analytique et Clinique. 24e congrès annuel de la Société Française de Toxicologie Analytique. Abstract O35. Toxicologie Analytique et Clinique. 2016;28 (2, Supplement):S28.
51. Chung H, Choi H, Heo S, Kim E, Lee J. Synthetic cannabinoids abused in South Korea: drug identifications by the National Forensic Service from 2009 to June 2013. Forensic Toxicol. 2014;32:82-8.
52. Chung H, Lee J, Kim E. Trends of novel psychoactive substances (NPSs) and their fatal cases. Forensic Toxicol. 2016;34:1-11.
53. Jang M, Shin I, Kim J, Yang W. Simultaneous quantification of 37 synthetic cannabinoid metabolites in human urine by liquid chromatography-tandem mass spectrometry. Forensic Toxicol. 2015;33:221-34.
54. FEWS. 2014. Annual Report on the Home Office Forensic Early Warning System (FEWS). A system to identify New Psychoactive Substances in the UK. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/344551/2014-08-12_-_FEWS_Annual_Report_Aug_2014_-_Final__2_.pdf
55. ACMD (Advisory Council on the Misuse of Drugs). 2014. 'Third generation' synthetic cannabinoids. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/380161/CannabinoidsReport.pdf
56. NFLIS (National Forensic Laboratory Information System). 2014. Annual report 2013. Available from: https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2013AR.pdf
57. NFLIS (National Forensic Laboratory Information System). 2015. Annual report 2014. Available from: https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2014AR.pdf
58. MHA (Minister for Health Australia). 2014. Poisons Act (Appendix A Amendment) Order 2014.
59. CZMoH (CZ Ministry of Health). 2013. List of no. 4 psychotropic substances. (Appendix 4 to the Government Regulation no. 463/2013 Coll.). Available from: http://www.mzcr.cz/Admin/_upload/files/3/Nov%C3%A9%20PL.pdf
60. CFDA (China Food and Drug Administration). 2015. China. 27 September 2015.
61. DMH (Danish Ministry of Health). 2013. Bekendtgørelse om ændring af bekendtgørelse om euforiserende stoffer. Available from: https://www.retsinformation.dk/pdfPrint.aspx?id=158765&exp=1
62. GRM (Guvernul Republicii Moldova). 2004. Available from: http://www.gov.md/sites/default/files/document/attachments/intr17_48.pdf

63. UNODC. 2013. Global SMART Update Volume 10, September 2013. Available from: https://www.unodc.org/documents/scientific/Global_SMART_Update_10_web.pdf
64. PSA (Psychoactive Substances Act). 2016. Available from: http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted/data.htm
65. Home Office. 2016. legislation.gov.uk. Psychoactive Substances Act 2016. Available from: http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted
66. WHO (World Health Organization). 2010. Guidance on the WHO review of psychoactive substances for international control. http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf?ua=1

# Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of 5F-APINACA

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 41 Member States (4 AFR, 2 EMR, 22 EUR, 7 PAH, 1 SEAR and 5 WPR) answered the questionnaire for 5F-APINACA. Of these, 24 respondents (1 AFR, 19 EUR, 2 PAH and 2 WPR) had information on this substance.

## LEGITIMATE USE

There were 24 countries that reported no approved medical products containing 5F-APINACA for human or veterinarian indications. There was also no reported industrial use in 19 countries.

5F-APINACA is currently being used in medical or scientific research in one country for metabolism and abuse potential research.

5F-APINACA was not reported to be used for any cultural, religious or ceremonial purposes in 18 countries.

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

There were 17 countries that reported 5F-APINACA as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are smoking (14 countries), inhalation (3 countries), oral (2 countries) and sniffing (1 country). The main route of administration for 5F-APINACA was reported as smoking (9 countries) and oral (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (6 countries) and tablets (1 country). There were 15 countries which reported of plant material impregnated with the 5F-APINACA being used as a formulation. One country commented that it is prepared this way to resemble cannabis. One country reported that it is also used as an e-liquid for vaping.

There were 10 countries which reported that the source of 5F-APINACA for non-medical/non-scientific use was smuggling.

Specified subpopulations known to misuse 5F-APINACA were identified as prison populations (3 countries) and the homeless (1 country). One country cited published reports that state that 18-34 year olds are predominant users; however, use is reported from ages 12-67.

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (1 country), substantial (2 countries) or serious (6 countries). For the countries that indicated a substantial or serious level of negative health-impact, they specified

that it was due to the association of 5F-APINACA with adverse effects (e.g. seizures, intoxications) and fatalities.

Three countries reported emergency room/department visits related to the non-medical use 5F-APINACA. A combined total of 4 cases were reported by 2 countries, however, no further details or time frame was provided. It was noted that one country had a single report about in-prison treatment.

The adverse effects which presented for 5F-APINACA at the emergency room/department included enlarged pupils, conjunctivitis, limpness, tachycardia, seizures, agitation, visual hallucination and serotonin syndrome.

In regards to the mortality rate, data was provided by 2 countries. The rate which included involvement of other substances was reported to be 1 case in 2014 and 1 case in 2015. The rate where it was unknown if other substances were involved was 1 case (year not specified).
One country commented each synthetic cannabinoid requires own standard, along with additional standards for metabolites to be detected by a forensic laboratory. Therefore it is highly probable that due to lack of standards and recognition by emergency physicians, overdoses and fatalities are under-reported.

One country reported that people presented to drug dependence treatment centers due to the use of 5F-APINACA, however, they were unsure if was specifically for this psychoactive substance, rather it is for synthetic cannabinoids generally.

## STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 19 countries reported that 5F-APINACA was under national control. The legislation the control is based upon included Medicines Act (2 countries), Controlled Substances Act (11 countries), Criminal Law Act (1 country), Analog Act (1 country) and other specific legislation (2 countries stated that it was specific legislation for new psychoactive substances). The control measures are a temporary provision in 3 countries. One country commented that the temporary measures are until end of 2016 and are likely to be controlled permanently after this.

One country reported that a challenge to implementing control for 5F-APINACA was that the Analog Act is often challenged in court cases.

The scope of the controls includes production (15 countries), manufacturing (17 countries), exporting (14 countries), importing (18 countries), distribution (18 countries), use (12 countries) and possession (15 countries).

Reported illicit activities involving MDMB-CHMICA include manufacture of the substance by chemical synthesis (1 country), production of consumer products (3 countries), trafficking (12 countries), smuggling (1 country), diversion (1 country), domestic internet sales (3 countries), internet sales from abroad (8 countries), internet sales from unknown locations (3 countries) and finally sales to people who use this substance (7 countries).

There were 17 countries which completed the section on the number of seizures. The combined number of seizures was 1819 (2014), 3001 (2015) and 149 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If 5F-APINACA was placed under international control, 23 countries responded that they would have the capacity to enforce the control at the national level. There were 23 countries which responded that they would have the forensic laboratory capacity to analyse the substance.