

5F-PB-22

Critical Review Report

Agenda Item 4.12

Expert Committee on Drug Dependence
Thirty-ninth Meeting
Geneva, 6-10 November 2017

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Summary

5F-PB-22 (quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate) is a synthetic cannabinoid receptor agonist (SCRA) that had no history in the scientific literature until its detection emerged in 2013. This substance has been encountered as a synthetic constituent found in herbal smoking mixtures that are sold under a variety of brand names. It is common for retailers to purchase bulk quantities of the synthetic substance and add the synthetic material to plant matter that is then distributed onto the market. However, 5F-PB-22 is also available in powdered form as a “research chemical”. Various UN Member States reported the identification of 5F-PB-22 first in 2013 and data obtained from law enforcement suggest that 5F-PB-22 emerged and peaked in 2013 and 2014 in the United States of America, which then dropped in the following years.

A small number of *in vitro* and *in vivo* studies are currently available but the data indicate that 5F-PB-22 binds to and activates human CB₁ and CB₂ receptors at low nanomolar concentrations, and that it induces a number of biological responses also triggered by the naturally occurring phytocannabinoid Δ⁹-THC. In some *in vitro* assays, 5F-PB-22 acted as a full at both cannabinoid receptors. 5F-PB-22 also fully substituted for Δ⁹-THC in the drug discrimination paradigm and was ~22 times more potent than the training drug, which suggests that 5F-PB-22 may have abuse liability similar to Δ⁹-THC and/or other internationally controlled synthetic cannabinoid receptor agonists.

Reports indicate an increasing trend for SCRA being implicated in mini epidemics that have been associated with severe adverse drug effects including deaths. Reported adverse drug reactions associated with a range of SCRA frequently include gastrointestinal (e.g. nausea/hyperemesis), neurological (e.g. hallucination, agitation, anxiety, paranoia, confusion, delusions, catatonia, lethargy, psychosis (including susceptible individuals)), cardiovascular (e.g. tachycardia, hypertension) and renal (e.g. acute kidney failure) features.

The total number of cases reported in the scientific literature that make a causal link with 5F-PB-22 is very small. Intoxications and deaths associated with 5F-PB-22 have been reported but very few details are available. ‘Driving Under the Influence’ cases linked to 5F-PB-22 intoxication revealed significant impairment.

Although not specific to 5F-PB-22, there are indications that socially vulnerable and stigmatized drug users for example found in homeless and prison populations, are increasingly associated with problematic use of SCRA products. Heavy use of SCRA has been associated with problematic withdrawal symptoms and further research is needed to investigate the underlying mechanisms. Epidemiological data, such as prevalence of use, abuse and dependence information specifically related to 5F-PB-22 could not be identified.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available.

B. Chemical Abstract Service (CAS) Registry Number

1400742-41-7 (free base)

C. Other Chemical Names

1-(5-Fluoropentyl)-1*H*-indole-3-carboxylic acid 8-quinolinyl ester;
8-Quinolinyl ester-1-(5-fluoropentyl)-1*H*-indole-3-carboxylic acid

D. Trade Names

Not available.

E. Street Names

5F-PB-22; 5-fluoro-PB-22; 5F-QUPIC; QCBL-2201;¹ PB-22F;¹ MN-25F;¹ QUPIC
N-(5-fluoropentyl) analog.

F. Physical Appearance

5F-PB-22 has been described as a crystalline solid,² white powder³ and off-white/tan crystalline solid.⁴

G. WHO Review History

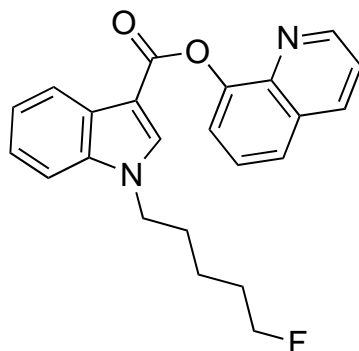
5F-PB-22 has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 5F-PB-22 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any 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: Quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate

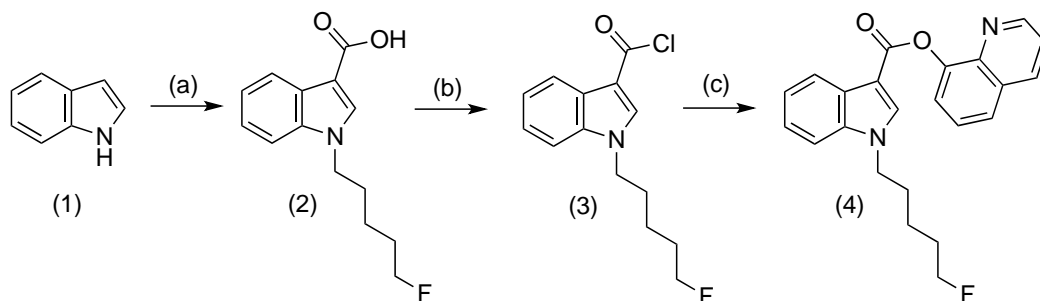
CA Index Name: 1*H*-Indole-3-carboxylic acid, 1-(5-fluoropentyl)-, 8-quinolinyl ester

B. Chemical Structure**Free base:****Molecular Formula:** C₂₃H₂₁FN₂O₂**Molecular Weight:** 376.43 g/mol**C. Stereoisomers**

Not applicable.

D. Methods and Ease of Illicit Manufacturing

The preparation of 5F-PB-22 is straightforward and follows standard procedures starting from indole (1). Indole *N*-alkylation followed by indole acylation and saponification provides the carboxylic acid intermediate (2). Conversion to the acid chloride intermediate (3) is then followed by reaction with 8-hydroxyquinoline to yield the ester product 5F-PB-22 (4).⁴



(a) NaH (2.0 equiv), Br(CH₂)₄F, DMF, 0 °C to rt, then (CF₃CO)₂O, 0 °C to rt, 1 h; next step: KOH, MeOH, PhMe, reflux, 2 h; (b) (f) (COCl)₂, DMF (cat.), CH₂Cl₂, rt, 1 h; (c) 8-hydroxyquinoline, Et₃N, CH₂Cl₂, rt, 24 h.⁴

E. Chemical PropertiesMelting point: 117.4 °C;³ 116–117 °C⁴Boiling point: Information could not be identified.Solubility: ~0.25 mg/mL in dimethylformamide/phosphate buffered saline (1:3; pH 7.2); ~11 mg/mL in dimethylsulfoxide; ~16 mg/mL in dimethylformamide.²

F. Identification and Analysis

Chemical and analytical data are available. 5F-PB-22 has also been employed for analytical purposes and featured in a range of routine methods of analysis associated with forensic and clinical investigations (Annex 2). The analytical determination of synthetic cannabinoid receptor agonists such as 5F-PB-22 in biological fluids can be a challenge, for example in cases where analytical methodologies are not specifically designed to detect these substances. In some instances (e.g. analysis of urine), the detection of metabolites may be the preferred approach. A number of 5F-PB-22 isomers are possible, for example by replacing 8-hydroxyquinoline (section 2D above) with various regioisomers of hydroxyquinoline and hydroxyisoquinoline. Whether any of these compounds circulate on the drug market has not been reported but the ability to differentiate between them analytically might be important for clinical and forensic purposes.⁵

3. Ease of Convertibility Into Controlled Substances

No information has been found. However, 5F-PB-22 can be easily converted back to the carboxylic acid intermediate (Section 2D, compound (2)), which can then be transformed into many other synthetic cannabinoid receptor agonists (SCRAs). It seems conceivable that the carboxylic acid intermediate might also be convertible into a ketone function, found for example in AM-2201, i.e. [1-(5-fluoropentyl)-1*H*-indole-3-yl](naphthalen-1-yl)methanone, which is listed in Schedule II of the Convention on Psychotropic Substances 1971.

4. General Pharmacology

A. Routes of administration and dosage

5F-PB-22, in its pure form but mostly as a synthetic constituent added to a plant matrix (e.g. damiana (*Turnera diffusa*) or marshmallow (*Althaea officinalis*), is normally smoked but reliable data about dosage are unavailable. The variations in drug composition and quantities frequently observed with many smoking mixtures (e.g.^{6, 7}) make such estimation impossible for users despite of information may be displayed on a product label. Speculative doses (presumably based on smoking/inhalation) have been suggested: 1 mg (threshold); 1-3 mg (light); 3-5 mg (common); 5-8 mg (strong).⁸

B. Pharmacokinetics

Information from clinical studies in humans is not available. A number of reports have been published that describe the biotransformation of 5F-PB-22 under *in vitro* conditions, either using human liver microsomes,⁹ pooled cryopreserved human hepatocytes,¹⁰ recombinant human carboxylesterases,¹¹ or incubation studies using the fungus *Cunninghamella elegans*.¹² The incubation with human hepatocytes resulted in the detection of 22 phase I and phase II metabolites with the ester hydrolysis product (1-(5-fluoropentyl)-1*H*-indole-3-carboxylic acid, 5F-PI-COOH) being the most dominant species, which has also been observed during an incubation study with human liver microseomes.⁹ Other transformations, either

alone or in combination, included hydroxylation and dihydroxylation, oxidative defluorination, carboxylation, epoxide hydrolysis and conjugation with glucuronic acid or cysteine. In addition to 5F-PI-COOH, two other major metabolites that originated via ester hydrolysis included 5F-PI-COOH-glucuronide indole hydroxylated 5F-PI-COOH. One major species still retaining the ester function originated from oxidative defluorination (to carboxylic acid at the terminal 5'-carbon of the pentyl chain) whereas another was identified as the 5'-OH-PB-22-glucuronide.¹⁰ It was also demonstrated that some of the 5F-PB-22 metabolites were identical to the products arising from metabolism of the defluorinated analog (PB-22).¹⁰ The ester hydrolysis product 5F-PI-COOH has also been detected in smoke condensates, which reflects pyrolysis-induced formation¹³ although it is unclear whether this carboxylic acid derivative would enter the brain for eliciting psychoactive effects. Interestingly, it has also been demonstrated that the detection of both 5F-PI-COOH and 5'-OH-PB-22 in human hair samples can result from external contamination rather than ingestion.¹³ An incubation of 5F-BB-22 (10 μ M) with human recombinant carboxylesterases (CES1b/CES1A1 and CES2) in human serum (37 °C, 10 min) confirmed that these enzymes facilitated the ester hydrolysis.¹¹ The correct identification of the parent molecule associated with drug intake can be challenging if one considers that structurally related metabolites might also show seemingly similar analytical features depending on the procedures used for their detection and identification. An example of this has recently been described where metabolites originally thought to originate from 5F-PB-22 were confirmed to arise from methyl 2-[[1-(5-fluoropentyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (5F-MDMB-PICA) instead.¹⁴ The identification of metabolites is also important to evaluate the question whether these could play a role in mediating the biological effects. It was recently reported that the 5F-PB-22 metabolite 5'-OH-PB-22 maintained the ability to activate both hCB₁ and hCB₂ receptors. Under the investigated *in vitro* conditions (Table 1), the 5'-COOH-PB-22 metabolite also displayed some activation (hCB₁: 25.8%; hCB₂: 43.5%) whereas the hydrolyzed 5F-PI-COOH metabolite was inactive.¹⁵

C. *Pharmacodynamics*

A number of *in vitro* and *in vivo* studies have been carried out, which suggest that 5F-PB-22, a SCRA, binds to and activates CB₁ and CB₂ receptors, and that it induces a number of biological responses that are also triggered by the naturally occurring phytocannabinoid Δ^9 -THC and other internationally controlled SCRA (Tables 1 and 2).

In vitro data:

5F-PB-22 was more potent than Δ^9 -THC in the ability to activate G-protein-gated inwardly rectifying K⁺ channels (GIRKs) in mouse AtT20 neuroblastoma cells transfected with human CB₁ and CB₁ receptors. 5F-PB-22 was 101 times (hCB₁) and 5.6 times (hCB₂) more potent than WIN-55,212-2 and showed similar efficacy as a full agonist. In comparison to Δ^9 -THC, 5F-PB22 was 89 times more potent (hCB₁). As a partial agonist, Δ^9 -THC only elicited 51% activation (hCB₁) compared to a 13% efficacy (hCB₂) that could only be achieved at a concentration of 10 μ M. In this assay, the full agonist JWH-018 was 2.8 times more potent (hCB₁) than

WIN-55,212-2 (similar efficacy) although the latter was 2 times more potent than the former (hCB₂) with comparable efficacy (Table 1).⁴

When using the [³⁵S]GTP γ S turnover assay, it was reported that 5F-PB-22 acted as an agonist at the CB₁ receptor (rat/mouse cortical homogenates). This compound was 5.5 times (rat CB₁) and 9.5 times (mouse CB₁) more potent than JWH-018. Relative to basal levels, 5F-PB-22 was also more effective than JWH-018 (Table 1). Activation was absent in CB₁ knockout mice and also abolished following co-incubation with CB₁ receptor antagonist/inverse agonist AM-251.¹⁸

A G-protein coupled receptor activation assay, operating via drug-induced β -arrestin 2/CB₁/CB₂ interaction, revealed that 5F-PB-22 was 45.5 times (hCB₁) and 18.3 times (hCB₂) more potent than JWH-018. Furthermore, 5F-PB-22 was also 2.8 times (hCB₁) and 1.32 times (hCB₂) more effective. In this study, it was also demonstrated that two main 5F-PB-22 metabolites, namely the ester hydrolysis product 1-(5-fluoropentyl)-1*H*-indole-3-carboxylic acid (5F-PI-COOH) and quinolin-8-yl 1-(5-hydroxypentyl)-1*H*-indole-3-carboxylate (5'-OH-PB-22) retained activity (Table 1).¹⁵ Recently published data showed that 5F-PB-22 had sub-nanomolar affinity toward hCB₁ and that its potency to activate the hCB₁ receptor was 416 times higher than that measured for the internationally controlled SCRA XLR-11.*¹⁶

Agonist-mediated inhibition of forskolin stimulated cAMP levels monitored in HEK-293 cells expressing the hCB₁ receptor and compared relative to WIN-55,212-2, 5F-PB-22 was determined to be a full agonist together with the SCRAs JWH-018 and XLR-11 whereas CP-55,940 and HU-210 were identified as partial agonists. 5F-PB-22 was 2 times more potent than WIN-55,212-2; 100 times more potent than XLR-11 and 6.3 times more potent than JWH-018. Under these assay conditions, JWH-073 was inactive (Table 1).¹⁷ From the perspective of evaluating living cellular functional responses to drug administration, hCB₁-induced suppression of Ca²⁺ spiking was investigated in cultured rat hippocampal neurons (fluorescence detection and multi-electrode experiments). 5F-PB-22 induced significant overall suppression of Ca²⁺ spiking together with other SCRAs. HU-210 did not produce a suppression using the same concentration.¹⁷ In multi-electrode experiments, 5F-PB-22 caused significant suppression at 10 μ M and overall at 1 μ M; effects were partially reversed by rimonabant.¹⁹

* XLR-11: [1-(5-Fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone.

Table 1. 5F-PB-22 <i>in-vitro</i> data	Ref
<p>Functional activity: ^a 5F-PB-22 at hCB₁: EC₅₀ = 2.8 nM (E_{max} = 108%); hCB₂: EC₅₀ = 11 nM (E_{max} = 101%) WIN-55,212-2 at hCB₁: EC₅₀ = 284 nM (E_{max} = 100%); hCB₂: EC₅₀ = 62 nM (E_{max} = 100%) Δ⁹-THC at hCB₁: EC₅₀ = 250 nM (E_{max} = 51%); hCB₂: EC₅₀ = 1157 nM (E_{max} = 13% at 10,000 nM) JWH-018 at hCB₁: EC₅₀ = 102 nM (E_{max} = 107%); hCB₂: EC₅₀ = 133 nM (E_{max} = 95%)</p>	Banister et al. ⁴
<p>Receptor binding: ^b 5F-PB-22 at hCB₁: IC₅₀/K_i = 0.27 nM XLR-11 at hCB₁: IC₅₀/K_i = 7.92 nM UR-144 at hCB₁: IC₅₀/K_i = 578.5 nM.</p> <p>Functional activity: ^b 5F-PB-22 at hCB₁: EC₅₀ = 0.95 nM (E_{max} = 98.31%) XLR-11 at hCB₁: EC₅₀ = 359 nM (E_{max} = 104.95%) UR-144 at hCB₁: EC₅₀ = 1295 nM (E_{max} = 95.28%).</p>	Gatch et al. ¹⁶
<p>Functional activity: ^c CB reporter assay 5F-PB-22 at hCB₁: EC₅₀ = 0.84 nM (E_{max} = 278.8%); hCB₂: EC₅₀ = 0.70 nM (E_{max} = 131.9%) JWH-018 at hCB₁: EC₅₀ = 38.2 nM (E_{max} = 100%); hCB₂: EC₅₀ = 12.8 nM (E_{max} = 100%) JWH-122 at hCB₁: EC₅₀ = 71.7 nM (E_{max} = 173.4%); hCB₂: EC₅₀ = 9.2 nM (E_{max} = 94.0%) MAM-2201 at hCB₁: EC₅₀ = 60.5 nM (E_{max} = 174.7%); hCB₂: EC₅₀ = 2.7 nM (E_{max} = 97.4%)</p> <p>Activation of 5F-PB-22 metabolites: 5F-PI-COOH at hCB₁: E_{max} = 3.1%; hCB₂: E_{max} = 4.6% (not significantly different from basal levels) 5'-OH-PB-22 at hCB₁: E_{max} = 171.0%; hCB₂: E_{max} = 142.3% 5'-COOH-PB-22 at hCB₁: E_{max} = 25.8%; hCB₂: E_{max} = 43.5%</p>	Cannaert et al. ¹⁵
<p>Functional activity (hCB₁): ^d</p> <p>Inhibition of forskolin stimulated cAMP levels: Efficacy relative to WIN-55,212-2: EC₅₀ = 79 nM (E_{max} = 65%).</p> <p>5F-PB-22: EC₅₀ = 39.8 nM (E_{max} = 67%), full agonist. CP-55,940: EC₅₀ = 316 nM (E_{max} = 47%), partial agonist. HU-210: EC₅₀ = 1585 nM (E_{max} = 35%), partial agonist. JWH-018: EC₅₀ = 251 nM (E_{max} = 55%), full agonist. JWH-073: no activity. XLR-11: EC₅₀ = 3981 nM (E_{max} = 65%), full agonist. AB-PINACA: EC₅₀ = 79 nM (E_{max} = 69%), full agonist.</p> <p>hCB₁-induced suppression of Ca²⁺ spiking in cultured rat hippocampal neurons: Compared to addition of blank.</p> <p>5F-PB-22: significant suppression of Ca²⁺ spiking at 10 μM. WIN-55,212-2: significant suppression at 10 μM. CP-55,940: significant suppression at 10 μM. HU-210: no suppression at 10 μM. XLR-11: significant suppression at 1 μM and 10 μM (significant more suppression than AB-PINACA) AB-PINACA: significant suppression at 10 μM.</p>	Costain et al. ¹⁷
<p>Receptor binding/rCB₁ ([³H]CP-55,940): ^e 5F-PB-22: K_i = 0.13 nM 5F-AKB-48: K_i = 0.87 nM JWH-018: K_i = 3.38 nM</p>	De Luca et al. ¹⁸

<p><u>[³⁵S]GTPγS turnover:</u> ^e</p> <p>5F-PB-22: rCB₁: EC₅₀ = 3.7 nM (E_{max} = 203%); mouse cortex CB₁: EC₅₀ = 4 nM (E_{max} = 183%) 5F-AKB-48: rCB₁: EC₅₀ = 31 nM (E_{max} = 190%); mouse cortex CB₁: EC₅₀ = 28 nM (E_{max} = 167%) JWH-018: rCB₁: EC₅₀ = 20.2 nM (E_{max} = 163%); mouse cortex CB₁: EC₅₀ = 38 nM (E_{max} = 158%) Activation of G-proteins absent in CB₁-KO mice; response also abolished when test drugs co-incubated with CB₁ receptor antagonist/inverse agonist AM-251.</p>	
<p><u>Functional activity (hCB1):</u> ^f</p> <p><u>hCB1-induced suppression of Ca₂₊ spiking in cultured rat hippocampal neurons (multi-electrode experiments):</u> Percent change in number of spontaneous spikes before and after addition of 0.1% DMSO. 5F-PB-22 (10 μM) caused significant decrease in spontaneous activity at all time points at 10 μM; overall decrease at 1 μM. Rimonabant (5 μM) significantly reversed 5F-PB-22-induced suppression (10 μM) at the first three time-matched recordings and overall. WIN-55,212-2 (10 μM), WIN-55,212-3 (10 μM), HU-210 (10 μM), CP-55,940 (10 μM) suppressed overall activity. JWH-018 (10 μM and 1 μM), XLR-11(10 μM), JWH-250 (10 μM), and MAM-2201 (10 μM and 1 μM) suppressed overall activity. AB-PINACA caused significant suppression overall at both 10 μM and 1 μM but not at all investigated time points. “Overall“ suppression determined at the end of the recording time. For some compounds, suppression was not always considered significant at a number of earlier time points, thus, indicating suppression occurring at longer incubation times.</p>	Tauskela et al. ¹⁹
<p>^a Ref^d: hCB1 and hCB2 receptors in stably transfected mouse AtT20 neuroblastoma cells; FLIPR membrane potential assay (blue) used for quantitative determination of K⁺ flux (hyperpolarization) linked to G-protein activation: G-protein-gated inwardly rectifying K⁺ channels (GIRKs); plates were incubated at ambient CO₂ for 45 min at 37 °C; receptor activation and stimulation of cellular hyperpolarization led to decrease in fluorescence response. Comparison of test drugs was normalized against WIN-55,212-2 response (set at 100% efficacy).</p> <p>^b Ref¹⁶: Assays carried out by NovaScreen (PerkinElmer, Waltham, Massachusetts, USA) under contract with the National Institute on Drug Abuse Addiction Treatment Discovery Program; hCB₁ receptors expressed in HEK-293 (binding) and CHO cells (functional activity). Further details not reported.</p> <p>^c Ref¹⁵: Application of NanoLuc binary technology (Promega): G-protein coupled receptor (GCPR) activation monitored via ligand-induced interaction of β-arrestin 2 with hCB₁ and hCB₂ receptors; transient transfection in HEK-293T cells; increase in bioluminescence measured via luciferase activity following CB-βarr2 interaction; cells transfected with either CB₁-LgBiT/SmBiT-βarr2 combination or the CB₂- SmBiT/LgBiT-βarr2 combination; efficacy reported relative to JWH-018 set at 100%; test drug concentrations for efficacy tests was 1 μM. Several synthetic cannabinoid receptor agonist metabolites, e.g. originating from JWH-018, JWH-122, JWH-210, MAM-2201, EAM-2201, PB-22, 5F-PB22, retained the ability to activate the CB receptors.</p> <p>^d Ref¹⁷: GloSensor™ cAMP assay; agonist-mediated inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP) levels was monitored in live HEK293T cells transfected with human cannabinoid receptor 1 gene (CNR1) and pGloSensor-22F; efficacy determinations (% inhibition) relative to full agonist WIN-55,212-2. Synthetic cannabinoids were added 12 min prior to the addition of 10 μM forskolin. Luminescence was determined 15 min after forskolin addition; data were normalized to vehicle readings. Low-density primary hippocampal neuron cultures were loaded with a Ca²⁺ indicator and exposed to low Mg²⁺ buffer to induce spontaneous, transient increases in intracellular Ca²⁺ levels (Ca²⁺ spikes). Post-drug frequencies were normalized to pre-drug frequencies and post-drug % inhibition was calculated relative to the pre-drug condition.</p> <p>^e Ref¹⁸: Receptor binding: male Sprague-Dawley rat cortical homogenates; membranes incubated with [³H]CP-55,940 (0.5 nM) for 1 h at 30 °C; [³⁵S]GTPγS binding assay: rat and mouse cortical membranes used; mouse and rat brain membranes incubated with test drugs at 30 °C in assay buffer containing 0.1% BSA in the presence of 0.05 nM [³⁵S]GTPγS and 30 μM GDP; final volume of 1 mL and incubation for 60 min; stimulation expressed relative to basal levels. For stimulation experiments test drugs (1 μM) added alone or in combination with CB₁ receptor antagonist/inverse agonist AM-251 (0.1 μM).</p> <p>^f Ref¹⁹: Hippocampal neurons plated at high density; each multi-electrode array served as its own internal control: two 20 min baseline recordings were performed prior to acquiring four 20 min recordings with a cannabinoid or DMSO vehicle present; online extracellular spike detection was used; activity was monitored over a total 80 min exposure of a cannabinoid, in 20 min recording sessions.</p>	

In vivo data:

Currently available data suggest that 5F-PB-22 induces responses in animals that are also seen with Δ^9 -THC and other SCRAs, such as suppression of locomotor activity and decreased body temperature. 5F-PB-22 was 45 times more potent than Δ^9 -THC; 41 times more potent than XLR-11 and 31 times more potent than UR-144[†] in resulting in decreased locomotor activity (Table 2).¹⁶ Furthermore, 5F-PB-22 was found to fully substitute for Δ^9 -THC using the drug discrimination paradigm in mice where it was found to be 22 times more potent than the training drug. Microdialysis studies (nucleus accumbens shell) in male Sprague–Dawley rats revealed a modest increase in extracellular dopamine levels (~150%) (Table 2).¹⁸

Table 2. <i>In vivo</i> assay data for 5F-PB-22	
Behavior / physiology / neurochemistry	Ref
<p><u>Body temperature:</u> ^a 5F-PB-22: hypothermic effect (0.3-3 mg/kg) (> 1.5 °C) was observed. Maximum drop in body temperature observed within the first hour of the 6 h monitoring period. Mean maximal hypothermia (at 3 mg/kg) was comparable to that induced by JWH-018.</p> <p>Rimonabant partially reversed hypothermic effects but CB₂ receptor antagonist SR-144528 had only negligible effects on drug-induced hypothermia.</p> <p><u>Heart rate:</u> ^a 5F-PB-22: significant decrease in heart rate but more variable than body temperature data, possibly reflecting multiple determinants.</p>	Banister et al. ⁴
<p><u>Locomotor activity:</u> ^b 5F-PB-22 (ED₅₀ = 0.25 mg/kg), Δ^9-THC (ED₅₀ = 11.14 mg/kg), XLR-11 (ED₅₀ = 10.29 mg/kg), and UR-144 (ED₅₀ = 7.68 mg/kg) decreased locomotor activity as dose increased.</p> <p>Depressant effects of 5F-PB-22 (0.5 and 1.0 mg/kg) occurred within 10 min after injection and lasted 140 min. Maximal depressant effects were observed 0-30 min.</p> <p>Depressant effects of Δ^9-THC occurred within 10-50 min after injection and lasted 90-140 min. Maximal depressant effects were observed 30-60 min after 10 and 30 mg/kg.</p> <p>Depressant effects of XLR-11 occurred within 10 min after administration and lasted 40-60 min. Maximal depressant effects of 10 and 30 mg/kg occurred 10-40 min after injection.</p> <p>Depressant effects of UR-144 occurred within 10 min after administration and lasted 60-90 min. Maximal depressant effects of 10 and 30 mg/kg occurred 10-40 min after injection.</p> <p><u>Drug discrimination:</u> ^c 5F-PB-22 (ED₅₀ = 0.039 mg/kg), Δ^9-THC (ED₅₀ = 0.85 mg/kg), XLR-11 (ED₅₀ = 0.18 mg/kg), and UR-144 (ED₅₀ = 0.45 mg/kg), amongst other synthetic cannabinoids tested, fully substituted for the discriminative stimulus effect of Δ^9-THC (3 mg/kg).</p> <p>5F-PB-22 (0.5 mg/kg) fully substituted from 30 to 60 min after administration, and drug-appropriate responding was attenuated at the 120 min point; rates of responding decreased at 5, 15, 30 and 60 min with marked suppression at 15 min after administration.</p> <p>XLR-11 (1 mg/kg) fully substituted from 5 to 15 min after administration, and drug-appropriate</p>	Gatch et al. ¹⁶

[†] UR-144: (1-Pentyl-1*H*-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone

<p>responding was nearly absent by 60 min. No effect of UR-144 on the response rate was observed.</p> <p>UR-144 (2.5 mg/kg) fully substituted at 15 and 60 min after administration, and drug-appropriate responding was diminished to <40% after 4 h. No effect of UR-144 on the response rate was observed.</p> <p>No other adverse effects were observed at the doses and time points tested.</p>	
<p><i>In vivo</i> microdialysis:^d</p> <p>5F-PB-22 administration (0.01 mg/kg, i.v.) led to a moderate but significant increase in extracellular dopamine levels in the nucleus accumbens shell dialysate at the 30 min (~145%) and 40 min (~150%) point (relative to basal levels). In comparison, 5F-AKB-48 induced comparable increases at the 60, 10 and 150 min time point.</p>	De Luca et al. ¹⁸
<p>^a Ref⁴: male Wistar rats; biotelemetry transmitters placed in the peritoneal cavity; drugs administered (i.p.) in an ascending dose sequence (0.1, 0.3, 1, 3 mg/kg) (10 mg/kg if required) at the same time of day; data for heart rate and body temperature gathered at 1000 Hz (15 or 30 min bins). Data were recorded for 6 h post-injection.</p> <p>^b Ref¹⁶: Locomotor activity: male ND4 Swiss-Webster mice (~8 weeks old); 16 infrared beams were located in the horizontal direction; dose range tested: Δ^9-THC (1-30 mg/kg), 5F-PB-22 (0.1-1 mg/kg), UR-144 (1-30 mg/kg), XLR-11 (1-30 mg/kg), and others, immediately before testing. Horizontal activity (interruption of photocell beams, ambulation counts) was measured for 8 h within 10-min periods; behavioural observations of each mouse were recorded at 30, 120, and 480 min after the highest dose tested.</p> <p>^c Ref¹⁶: Drug discrimination: male Sprague-Dawley rats; trained to discriminate Δ^9-THC (3 mg/kg) from vehicle using a two-lever choice methodology; each training session lasted 10 min; test drugs (amongst others): intraperitoneal injections of 5F-PB-22 (0.01-0.5 mg/kg, 30 min before start of session), UR-144 (0.1-5 mg/kg, 30 min before start) and XLR-11 (0.05-1 mg/kg, 15 min before start). Δ^9-THC (3 mg/kg) controls were tested before the start of each compound evaluation. A repeated-measures design was used for time-course experiments.</p> <p>^d Ref.¹⁸ Male Sprague-Dawley rats; vertical dialysis probes implanted in nucleus accumbens (NAc) shell and core and medial pre-frontal cortex (mPFC); test drugs administered intravenously; 5F-PB-22: 0.01 mg/kg; 5F-AKB-48: 0.1 mg/kg; STS-135: 0.15 mg/kg; CB₁ receptor antagonist/inverse agonist AM-251 administered intraperitoneally (1 mg/kg); dopamine levels determined by HPLC-ECD; only the NAc shell dialysate was analyzed after 5F-PB-22 treatment.</p>	

5. Toxicology

5F-PB-22, XLR-11 (1-500 μ M, 24 h) and their pyrolysis products (10 mg of test drug burned and pyrolysis products isolated by solid phase extraction) were studied for exposure to SH-SY5Y, HepG2 and H9c2 cell lines and cell viability was assessed by the MTT and sulforhodamine B assay (SRB). 5F-PB-22 was found to reduce viability of cardiac and neuronal cells whereas XLR-11 decreased viability of all three cell lines tested at lower concentrations. The pyrolysis products arising from 5F-PB-22 were stated to be more toxic than 5F-PB-22 and affected all assessed cell types. The XLR-11 pyrolysis products were stated to be less toxic than XLR-11 in the three cell lines.²⁰ Any other information related to acute and chronic preclinical toxicology could not be identified.

6. Adverse Reactions in Humans

Reports associated with the presence of 5F-PB-22 in drug products and biofluids is summarized in Table 3. The total number of cases reported in the scientific literature that make a specific causal link with 5F-PB-22 is small.

Table 3. Case reports associated with the involvement of 5F-PB-22 reported in the scientific literature.				
Year	Cases	Patient, age	Comments (examples)	Ref
2014	1	M, 17	One of four death cases analyzed between July and October 2013; ^a began ‘gasping for air and fell to the ground’ in the morning following consumption of alcohol and other drugs including synthetic cannabinoids and pronounced dead at medical center; autopsy did not reveal significant injuries or natural diseases. Toxicology findings: femoral blood concentration for 5F-PB-22 of 1.1 ng/mL, an ethanol concentration of 0.033 g/dL, amiodarone (administered during resuscitative efforts) and caffeine.	Behonick et al. ²¹
2014	1	M, 27	One of four death cases analyzed between July and October 2013; arrived at emergency room ‘appearing quite ill and diaphoretic’. Patient confirmed history of marijuana use of several times per week. Evaluation indicated severe liver injury, severe coagulopathy, acute kidney injury, acute respiratory failure, hypoxemia, severe anion gap, metabolic and lactic acidosis; clinical condition deteriorated over the next 12 h; progressed to critically ill status due to circulatory failure, respiratory failure, central nervous system failure, renal failure and severe metabolic derangement. Autopsy revealed cause of death to be fulminant liver failure in the setting of THC (marijuana) and 5F-PB-22 (synthetic cannabinoid) exposure. The manner of death was certified as undetermined. Toxicology findings: a pair of hospital serum specimens obtained a day before death (~9.5 h apart) indicated presence of THCCOOH (246 and 176 ng/mL); piperacillin, levofloxacin (presumably reflecting treatment) also detected. A different serum specimen, collected ~7 h before death revealed 5F-PB-22 at 1.3 ng/mL and lorazepam (19.5 ng/mL) (presumably reflecting treatment).	Behonick et al. ²¹
2014	1	M, 18	One of four death cases analyzed between July and October 2013; pronounced dead at home following a night of partying; reported to have consumed numerous beers, mixed alcoholic beverages and smoked synthetic marijuana (K2/Spice); later discovered unresponsive, not breathing, cool to the touch and pulseless; autopsy: bilateral pulmonary vasocongestion and congestion in the abdominal organs (liver, spleen and kidneys); concentration of 1.5 ng/mL 5F-PB-22 determined in iliac blood; cause of death was attributed to sudden death, in association with synthetic cannabinoid use; manner of death classified as accident.	Behonick et al. ²¹
2014	1	M, 19	One of four death cases analyzed between July and October 2013; was found dead after returning from a party. Autopsy: included bilateral pulmonary edema, necrotizing granulomatous inflammation with histoplasma microorganisms and congestion of viscera. Toxicology findings: 5F-PB-22 at 1.5 ng/mL in superior vena cava blood; stated cause of death was suspected acute drug intoxication using the synthetic cannabinoid 5F-PB-22. The manner of death was accident.	Behonick et al. ²¹
2014	6	NR ^b	Report sent to DEA from the Mansfield Division of Police Forensic Science Laboratory in Mansfield, Ohio (USA); was stated to have included incident/investigative public narratives and descriptions of physical symptoms and observations of users such as unconsciousness, agitation, violent behavior; details not reported. Timeframe: January to May 2013.	DEA ²²
2014	2	M, 17 M, 18	Seventeen-year-old male’s cause of death listed “5F- PB-22 intoxication.” Autopsy findings of 18 year old male reported as a fatal cardiac arrhythmia and/or fatal seizure in association with 5F-PB-22 use. Three separate postmortem cases stated to be under investigation. Whether any of these cases are similar to the ones published by Behonick et al. ²¹ is not clear.	DEA ²²
2015	1	M, 23	Recreationally smoked a synthetic cannabinoid cigarette (trade name K2) at home and 6 h later suffered what his wife described as generalized tonic-clonic seizure activity, including urinary incontinence and tongue lacerations; presented later at emergency department with nausea, dry mouth, and vomiting. Neurologic and cardiopulmonary examination was normal; patient experienced second episode of seizure activity three h after discharge. Use history: smoking synthetic cannabinoids more or less daily for the previous several years with no history of seizures. Blood biochemistry was normal except for potassium of 3.3 mM. Two plasma samples were taken (5.5 and 8.3 h after the last exposure) and analyzed. 5.5 h / 8.3 h samples (pg/mL): BB-22 (97/94), AM-2233 (148/125); PB-22 (75.84); 5F-	Schep et al. ²³

			PB-22 (85/91), JWH-122 (<i>N</i> -cyclohexylmethyl) (9/13).	
"Clusters of cases of adverse health effects or severe toxic effects and deaths associated with synthetic cannabinoid product use." Analysis of clinical samples; details not reported. Locations: USA. July 2013: One fatal and one non-fatal intoxication detected in Davenport, IA. October 2013: One fatal and one non-fatal intoxication detected in Waverly, NE				Trecki et al. ²⁴
2016	1	F, 19	Reported to have purchased three products from a headshop: two new psychoactive substances (sachets of "cannabis tea" and "mushroom tea") as well as two LSD blotters. After the "cannabis tea" was smoked and the two LSD blotters and "mushroom tea" were ingested, the patient became tachycardic (HR 128), developed seizures, agitation, visual hallucinations as well as suspected serotonergic toxicity (sustained ankle clonus 20-30 beats) 1-2 hours after use. Patient was treated with 1 mg of intravenous midazolam and symptoms/signs resolved within 13 h. Patient had medical history of depression, treated with fluoxetine and citalopram. Samples collected from patient at 5 h (plasma) and 17 h (blood and urine) post exposure. Toxicology findings: initial plasma sample (5 h) contained 5F-PB-22 (200 pg/mL) and two 5F-AKB-48 metabolites (5F-AKB-48 adamantyl hydroxy (900 pg/mL) and 5F-AKB-48 desfluoro hydroxypentyl (5000 pg/mL)), citalopram (10-20 ng/mL), diazepam 10-20 ng/mL and fluoxetine metabolites. Seventeen hours: 5F-PB-22 (40 pg/mL), two 5F-AKB-48 metabolites (150 pg/mL and 800 pg/mL), citalopram (10-20 ng/mL), fluoxetine (20-30 ng/mL) and diazepam (40-50 ng/mL). Urine sample (17 h) contained metabolites of 5F-AKB-48 (1-5 ng/mL range), citalopram (approx. 250 ng/mL), fluoxetine 40 ng/mL and diazepam metabolites (oxazepam 200 ng/mL, temazepam 100 ng/mL) and zolpidem metabolites (10-50 ng/mL). The detection of diazepam and zolpidem might have indicated potential adulteration of drugs (not given during treatment and not reported by user).	Abouchédid et al. ²⁵
2017	1	M, 36	Presenting at emergency department between January-July 2015. Self reported use: "Black Mamba" and crack. Observations at admission: heart rate: 55 bpm; temp: 35.6 °C; Glasgow coma scale: 14; length of stay: 3.0 h. Serum analysis (ng/mL): 5F-AKB-48: 4 and 32 for metabolites; 5F-PB-22: 0.2.	Abouchédid et al. ²⁶
2017	1	M, 22	Presenting at emergency department between January-July 2015. Self reported use: "Herbal A" and alcohol. Observations at admission: heart rate: 52 bpm; temp: 35.8 °C; Glasgow coma scale: 14; length of stay: 1.7 h. Serum analysis (ng/mL): 5F-AKB-48: 2 and 6.8 for metabolites; BB-22: 0.06; 5F-PB-22: 0.4.	Abouchédid et al. ²⁶
2017	1	M, 18	Presenting at emergency department between January-July 2015. Self reported use: Unknown. Observations at admission: heart rate: 74 bpm; temp: 36.4 °C; Glasgow coma scale: 15; length of stay: 2.5 h. Serum analysis (ng/mL): 5F-AKB-48: 0.4 and 2.4 for metabolites; 5F-PB-22: 0.36.	Abouchédid et al. ²⁶
2017	1	M, 38	Presenting at emergency department between January-July 2015. Self reported use: Unknown. Observations at admission: heart rate: 96 bpm; temp: 35.4 °C; Glasgow coma scale: 15; length of stay: 7.8 h. Serum analysis (ng/mL): 5F-AKB-48: 0.08 and 0.4 for metabolites; 5F-PB-22: 0.03. Other drug detected: carbamazepine.	Abouchédid et al. ²⁶
2017	1	F, 24	Presenting at emergency department between January-July 2015. Self reported use: "Pirate vertex" and alcohol. Observations at admission: heart rate: 128 bpm and agitation; length of stay: 3.1 h. Serum analysis (ng/mL): 5F-AKB-48: 7.6 and 3 for metabolites; 5F-PB-22: 0.08; AB-CHMINACA: 0.280. Other drugs detected: quetiapine, citalopram/escitalopram and metabolites, lorazepam.	Abouchédid et al. ²⁶
2017	1	M, 44	Presenting at emergency department between January-July 2015. Self reported use: cocaine and cannabis. Observations at admission: heart rate: 72 bpm; temp: 37 °C; Glasgow coma scale: 15; seizure, psychosis; length of stay: 4.9 h. Serum analysis (ng/mL): main drug detected: cocaine and metabolite; levamisole/tetramisole; 5F-AKB-48: 0.45 and 1.2 for metabolites; 5F-PB-22: 0.08.	Abouchédid et al. ²⁶
2017	1	F, 24	Presenting at emergency department between January-July 2015. Self reported use: white powder. Observations at admission: heart rate: 79 bpm; temp: 35.5 °C; Glasgow coma scale: 15; chest pain; length of stay: 2.3 h. Serum analysis (ng/mL): main drugs detected: ethylphenidate and methiopropamine; also levamisole/tetramisole; 5F-AKB-48: 0.4 and 0.6 for metabolites; 5F-PB-22: 0.08.	Abouchédid et al. ²⁶

2017	15	NR	Review of cases associated with motor vehicle collisions and ingestion of synthetic cannabinoid receptor agonists in Japan. Time frame: 2012-2014, with 5F-PB-22 being dominant between spring and winter 2013; not detected before of after that time period. Detection of 5F-PB-22 in 6 case samples: range 0.274-0.93 ng/mL (n = 5), median 0.35 ng/mL. In three cases, further information was available: a) driver looked emotionless and kept flooring accelerator pedal even after the crash; driver had no memory of the crash; b) driver lost consciousness; recovered after 3.5 h but had no memory of the crash; c) driver did not step off the accelerator pedal after crash and kept on moving the steering wheel and gear lever in a stereotyped manner; driver had no memory of abnormal driving. NNE-1 was also detected together with 5F-PB-22.	Kaneko ²⁷
<p>^a It appears that some of the case data were also published by Bottei in an abstract form.²⁸</p> <p>^b NR: not reported.</p>				

7. Dependence Potential

A. *Animal Studies*

No information available.

B. *Human Studies*

Three male (aged 17-38 years) and three female (aged 20-42 years) dependent users (included based on the Severity of Dependence Screener) of herbal mixtures containing 5F-AKB-48[‡] and 5F-PB-22 were interviewed following a structured interview guide. Users reported agitation, suicidal ideation and self-harm ideologies, and incidences of sibling and peer suicide during times of withdrawal and when attempted to restricted use or self-detoxify. The urge to re-dose has been reported by the users.²⁹ However, it was not reported whether 5F-PB-22 was present in the herbal mixtures and biofluids.

8. Abuse Potential

A. *Animal Studies*

As summarized in Tables 1 and 2 (Section 4C), 5F-PB-22 was shown to share some cannabinoid-like properties, such as binding to and activation of CB₁ and CB₂ receptors and depression of locomotor activity. A moderate increase in extracellular dopamine levels have been identified in an *in vivo* microdialysis study (nucleus accumbens shell) using conscious rats. One drug discrimination study revealed that 5F-PB-22 (more potently) substituted fully for Δ⁹-THC although a decrease in response rates was also observed (Table 2). These data indicate that 5F-PB-22 may have abuse liability and further studies are warranted to investigate this further.

B. *Human Studies*

See 7B.

[‡] 5F-AKB-48: *N*-(Adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide

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

5F-PB-22 is not known to have any therapeutic applications.

10. Listing on the WHO Model List of Essential Medicines

5F-PB-22 is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)

5F-PB-22 is not marketed as a medicine.

12. Industrial Use

5F-PB-22 has no reported industrial use.

13. Non-Medical Use, Abuse and Dependence

Household or subpopulation surveys that specifically probe for prevalence of 5F-PB-22 could not be identified in the currently available literature. Epidemiological data, such as prevalence of use, abuse and dependence information, are not available specifically for 5F-PB-22. However, heavy use of synthetic cannabinoid receptor agonists has been associated with problematic withdrawal symptoms (e.g.²⁹⁻³¹) and further research is needed to investigate the underlying mechanisms.

Also see 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 majority of available synthetic cannabinoid products (including those containing 5F-PB-22) is sold in the form of herbal mixtures, and designed for smoking purposes. It is common for retailers to purchase bulk quantities of the synthetic substance and to add the synthetic material to a variety of vegetable matter as the plant base. Products sold as herbal smoking mixtures frequently change in drug composition and quantity, often without indications on product labels, which results in challenges to unambiguously correlate harms to public health with a specific drug such as 5F-PB-22.

The consumption of these products might be attractive to a variety of users, such as regular users of cannabis and those who might wish to avoid drug-testing procedures resulting in positive cannabis findings. Ease of access, and perceived lack of control might equally be of interest to some users. The high potency associated with many synthetic cannabinoids carries the risk of accidental overdose and potentially severe adverse events but information specific to 5F-PB-22 is limited. As highlighted in Section 6 (Table 3), the ingestion of 5F-PB-22 products has been implicated in cases of impaired driving and motor

vehicle collisions,²⁷ which adds a public health dimension. Although not specific to 5F-PB-22, there are indications that socially vulnerable and stigmatized drug users, for example found in homeless and prison populations, are increasingly associated with problematic use of synthetic cannabinoid receptor agonist products.³²⁻³⁵

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

15. Licit Production, Consumption and International Trade

5F-PB-22 is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses could not be identified.

16. Illicit Manufacture and Traffic and Related Information

Reports have been received from the European Early-Warning System on new psychoactive substances that 5F-PB-22 (first detected in 2013) was encountered in seizures and collected specimen (herbal mixtures or powders) in Belgium, Sweden, Latvia, Germany, Denmark, United Kingdom, Romania, Turkey, Lithuania, Croatia, Luxembourg, France, Hungary, Norway, Italy, Czech Republic, Bulgaria and Spain.³⁶

5F-PB-22 detections started to appear and peaked in United States of America (USA) in 2013. The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA, registered a drop in reports from 2015 onward (Table 4), presumably as a consequence of issuing an order to temporarily schedule 5F-PB-22 into Schedule I of the Controlled Substances Act.³⁷⁻³⁹ 5F-PB-22 has also been seized in kilogram quantities.²²

Table 4. Number of reports received by the U.S. National Forensic Laboratory Information System (NFLIS) related to detections of 5F-PB-22 in law enforcement operations.					
Year ^a	Numbers	XLR-11	MDMA	Meth ^b	Ref
2013 (MY)	544	11,273	2,423	100,045	NFLIS ⁴⁰
2013 (AR)	1,952	19,243	4,798	206,784	NFLIS ⁴¹
2014 (MY) ^c	708	6,316	2,224	117,318	NFLIS ⁴²
2014 (AR)	1,067	11,001	4,902	236,175	NFLIS ⁴³
2015 (MY)	184	3,769	2,421	133,374	NFLIS ⁴⁴
2015 (AR)	408	6,973	5,188	277,823	NFLIS ⁴⁵
2016 (MY)	NR ^d	1,409	2,901	155,535	NFLIS ⁴⁶

^a MY: mid-year report (January to June); AR: annual report (January to December).
^b Meth: methamphetamine.
^c Revised March 2016.
^d Not reported but 5F-PB-22 related numbers might have been covered under the item "other synthetic cannabinoids".

Detections of 5F-PB-22 have also been reported to UNODC's Early Warning Advisory on New Psychoactive Substances.⁴⁷ 5F-PB-22 was reported by 28 countries in 2013, 27 countries in 2014, 29 countries in 2015, and 7 countries in 2016 (as of 08 August 2017).

17. Current International Controls and Their Impact

5F-PB-22 is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

Refer to 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

Not applicable.

References

1. Shevyrin V, Melkozerov V, Nevero A, Eltsov O, Shafran Y. Analytical characterization of some synthetic cannabinoids, derivatives of indole-3-carboxylic acid. *Forensic Sci Int* 2013;232:1-10. doi:10.1016/j.forsciint.2013.06.011.
2. Cayman. Safety data sheet. 5-Fluoro PB-22. Revision 15 August 2013. Cayman Chemical Company, Ann Arbor, M, USA. Available at: <https://www.caymanchem.com/msdss/14095m.pdf>. 2013.
3. SWGDRUG. 5-Fluoro-PB-22 Monograph. Latest revision 16 December 2013. Available at: <http://www.swgdrug.org/Monographs/5FPB22.pdf>.
4. 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;6:1445-58. doi:10.1021/acchemneuro.5b00107.
5. Kohyama E, Chikumoto T, Tada H, Kitaichi K, Ito T. Analytical differentiation of quinolinyl- and isoquinolinyl-substituted 1-(5-fluoropentyl)-1H-indole-3-carboxylates: 5F-PB-22 and its ten isomers. *Forensic Toxicol* 2017;35:56-65. doi:10.1007/s11419-016-0334-9.
6. Moosmann B, Angerer V, Auwärter V. Inhomogeneities in herbal mixtures: a serious risk for consumers. *J Anal Toxicol* 2015;33:54-60. doi:10.1007/s11419-014-0247-4.
7. Frinculescu A, Lyall CL, Ramsey J, Miserez B. Variation in commercial smoking mixtures containing third-generation synthetic cannabinoids. *Drug Test Anal* 2017;9:327-33. doi:10.1002/dta.1975.
8. 5F-PB-22. Basic information. Available at: <http://drugs.tripsit.me/5f-pb-22>.
9. Takayama T, Suzuki M, Todoroki K, Inoue K, Min JZ, Kikura-Hanajiri R et al. UPLC/ESI-MS/MS-based determination of metabolism of several new illicit drugs, ADB-FUBINACA, AB-FUBINACA, AB-PINACA, QUPIC, 5F-QUPIC and α -PVT, by human liver microsome. *Biomed Chromatogr* 2014;28:831-8. doi:10.1002/bmc.3155.
10. Wohlfarth A, Gandhi AS, Pang S, Zhu M, Scheidweiler KB, Huestis MA. Metabolism of synthetic cannabinoids PB-22 and its 5-fluoro analog, 5F-PB-22, by human hepatocyte incubation and high-resolution mass spectrometry. *Anal Bioanal Chem* 2014;406:1763-80. doi:10.1007/s00216-014-7668-0.
11. Thomsen R, Nielsen LM, Holm NB, Rasmussen HB, Linnet K. Synthetic cannabimimetic agents metabolized by carboxylesterases. *Drug Test Anal* 2015;7:565-76. doi:10.1002/dta.1731.
12. Watanabe S, Kuzhiumparambil U, Nguyen MA, Cameron J, Fu S. Metabolic profile of synthetic cannabinoids 5F-PB-22, PB-22, XLR-11 and UR-144 by *Cunninghamella elegans*. *AAPS Journal* 2017;19:1148-62. doi:10.1208/s12248-017-0078-4.

13. Franz F, Angerer V, Hermanns-Clausen M, Auwärter V, Moosmann B. Metabolites of synthetic cannabinoids in hair--proof of consumption or false friends for interpretation? *Anal Bioanal Chem* 2016;408:3445-52. doi:10.1007/s00216-016-9422-2.
14. Mogler L, Franz F, Rentsch D, Angerer V, Weinfurter G, Longworth M et al. Detection of the recently emerged synthetic cannabinoid 5F-MDMB-PICA in 'legal high' products and human urine samples. *Drug Test Anal* 2017. doi:10.1002/dta.2201.
15. Cannaert A, Storme J, Franz F, Auwarter V, Stove CP. Detection and activity profiling of synthetic cannabinoids and their metabolites with a newly developed bioassay. *Anal Chem* 2016;88:11476-85. doi:10.1021/acs.analchem.6b02600.
16. Gatch MB, Forster MJ. Δ^9 -Tetrahydrocannabinol-like effects of novel synthetic cannabinoids found on the gray market. *Behav Pharmacol* 2015;26:460-8. doi:10.1097/fbp.0000000000000150.
17. Costain WJ, Tauskela JS, Rasquinha I, Comas T, Hewitt M, Marleau V et al. Pharmacological characterization of emerging synthetic cannabinoids in HEK293T cells and hippocampal neurons. *Eur J Pharmacol* 2016;786:234-45. doi:10.1016/j.ejphar.2016.05.040.
18. 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. doi:10.1016/j.neuropharm.2015.11.017.
19. Tauskela JS, Comas T, Hewitt M, Aylsworth A, Zhao X, Martina M et al. Effect of synthetic cannabinoids on spontaneous neuronal activity: evaluation using Ca²⁺ spiking and multi-electrode arrays. *Eur J Pharmacol* 2016;786:148-60. doi:10.1016/j.ejphar.2016.05.038.
20. Carvalho AS, Fontes A, Santos N, Araujo A, Guedes P, Cavadas C et al. 5F-PB-22 and XLR-11, two consumed synthetic cannabinoids, present a distinct toxicity profile in neuronal, hepatic and cardiac cells. *Toxicol Lett* 2016;258S:S127.
21. Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M et al. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. *J Anal Toxicol* 2014;38:559-62. doi:10.1093/jat/bku048.
22. Drug Enforcement Administration. Quinolin-8-yl 1-pentyl-1*H*-indole-3-carboxylate (PB-22; QUPIC), quinolin-8-yl 1-(5-fluoropentyl)-1*H*-indole-3-carboxylate (5-fluoro-PB-22; 5F-PB-22), *N*-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide (AB-FUBINACA) and *N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide (ADB-PINACA). Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5, and 6) for Temporary Scheduling. Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537. January 2014. Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537. January 2014. Available at: <https://www.regulations.gov/document?D=DEA-2014-0003-0002>.

23. Schep LJ, Slaughter RJ, Hudson S, Place R, Watts M. Delayed seizure-like activity following analytically confirmed use of previously unreported synthetic cannabinoid analogues. *Hum Exp Toxicol* 2015;34:557-60. doi:10.1177/0960327114550886.
24. Trecki J, Gerona RR, Schwartz MD. Synthetic Cannabinoid-Related Illnesses and Deaths. *N Engl J Med* 2015;373:103-7. doi:10.1056/NEJMp1505328.
25. Abouchedid R, Ho JH, Hudson S, Dines A, Archer JR, Wood DM et al. Acute toxicity associated with use of 5F-derivations of synthetic cannabinoid receptor agonists with analytical confirmation. *J Med Toxicol* 2016;12:396-401. doi:10.1007/s13181-016-0571-7.
26. Abouchedid R, Hudson S, Thurtle N, Yamamoto T, Ho JH, Bailey G et al. Analytical confirmation of synthetic cannabinoids in a cohort of 179 presentations with acute recreational drug toxicity to an Emergency Department in London, UK in the first half of 2015. *Clin Toxicol* 2017;55:338-45. doi:10.1080/15563650.2017.1287373.
27. Kaneko S. Motor vehicle collisions caused by the 'super-strength' synthetic cannabinoids, MAM-2201, 5F-PB-22, 5F-AB-PINACA, 5F-AMB and 5F-ADB in Japan experienced from 2012 to 2014. *Forensic Toxicol* 2017;35:244-51. doi:10.1007/s11419-017-0369-6.
28. Bottei E. First report of drug concentrations of the synthetic cannabinoid 5F-PB-22 found on post-mortem testing. *Clin Toxicol* 2014;52:750.
29. 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 Mental Health Addict* 2017;15:565-79. doi:10.1007/s11469-016-9650-x.
30. Macfarlane V, Christie G. Synthetic cannabinoid withdrawal: a new demand on detoxification services. *Drug Alcohol Rev* 2015;34:147-53. doi:10.1111/dar.12225.
31. Cooper ZD. Adverse effects of synthetic cannabinoids: management of acute toxicity and withdrawal. *Curr Psychiatry Rep* 2016;18:52. doi:10.1007/s11920-016-0694-1.
32. Blackman S, Bradley R. From niche to stigma-Headshops to prison: Exploring the rise and fall of synthetic cannabinoid use among young adults. *Int J Drug Policy* 2017;40:70-7. doi:10.1016/j.drugpo.2016.10.015.
33. Joseph AM, Manseau MW, Lalane M, Rajparia A, Lewis CF. Characteristics associated with synthetic cannabinoid use among patients treated in a public psychiatric emergency setting. *Am J Drug Alcohol Abuse* 2017;43:117-22. doi:10.1080/00952990.2016.1240799.
34. Ralphs R, Williams L, Askew R, Norton A. Adding Spice to the Porridge: The development of a synthetic cannabinoid market in an English prison. *Int J Drug Policy* 2017;40:57-69. doi:10.1016/j.drugpo.2016.10.003.
35. Springer YP, Gerona R, Scheunemann E, Shafer SL, Lin T, Banister SD et al. Increase in adverse reactions associated with use of synthetic cannabinoids - Anchorage, Alaska, 2015-2016. *MMWR Morb Mortal Wkly Rep* 2016;65:1108-11. doi:10.15585/mmwr.mm6540a4.

36. AM-2201 carboxylate analogue quinolinyl derivative / 5F-PB-22. The European Union Early Warning System, the Reitox National Focal Points in the EU Member States, Turkey and Norway, as well as the Europol National Units and their networks. Early-warning system on new drugs (EDND). European Monitoring Centre for Drugs and Drug Addiction Database on New Drugs (EDND). Cais do Sodré, 1249-289 Lisbon, Portugal.
37. U.S. Drug Enforcement Administration; Department of Justice. Schedules of controlled substances: temporary placement of four synthetic cannabinoids into Schedule I. Final order. *Fed Regist* 2014;79:7577-82.
38. U.S. Drug Enforcement Administration; Department of Justice. Schedules of controlled substances: extension of temporary placement of PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA in Schedule I of the Controlled Substances Act. Final order. *Fed Regist* 2016;81:6175-7.
39. U.S. Drug Enforcement Administration; Department of Justice. Schedules of controlled substances: placement of PB-22, 5F-PB-22, AB-FUBINACA and ADB-PINACA into Schedule I. Final rule. *Fed Regist* 2016;81:61130-3.
40. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). 2013 Mid-Year Report. Springfield, VA: U.S. Drug Enforcement Administration. Available at: <https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2013MY.pdf>. 2014.
41. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). Year 2013 Annual Report. Springfield, VA: U.S. Drug Enforcement Administration. Available at: <https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2013AR.pdf>. 2014.
42. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). Midyear Report 2014 (revised March 2016). Springfield, VA: U.S. Drug Enforcement Administration. Available at: <https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2014MY.pdf>. 2015.
43. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). Year 2014 Annual Report. Springfield, VA: U.S. Drug Enforcement Administration. Available at: <https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2014AR.pdf>. 2015.
44. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). Midyear Report 2015. Springfield, VA: U.S. Drug Enforcement Administration. Available at: https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS_MidYear2015.pdf. 2016.

45. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). Year 2015 Annual Report. Springfield, VA: U.S. Drug Enforcement Administration. Available at: <https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2015AR.pdf>. 2016.
46. U.S. Drug Enforcement Administration; Diversion Control Division. National Forensic Laboratory Information System (NFLIS). Midyear Report 2016. Springfield, VA: U.S. Drug Enforcement Administration. Available at: https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS_MidYear2016.pdf. 2017.
47. UNODC. UNODC Early Warning Advisory on New Psychoactive Substances. Available at: <https://www.unodc.org/LSS/Home/NPS> [08 August 2017]. 2017.

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of 5F-PB-22

Please refer to separate Annex 1 document published on ECDD website

Annex 2: Studies associated with the detection and chemical analysis of 5F-PB-22 (amongst other substances) published in the scientific literature.

Techniques ^a	Comment	Reference
GC-HR-MS, LC-QTOF-MS/MS, NMR, FT-IR	Characterization of seized/collected compounds.	Shevyrin et al. ^{1, 2}
Melting point, ¹ H-NMR, GC-MS, ATR-FT-IR	Characterization of reference material.	SWGDRUG ³
LC-QqQ-MS/MS	Postmortem blood and antemortem serum analyses.	Behonick et al. ⁴
Not reported	Postmortem analysis (presumably identical cases described by Behonick et al. ⁴)	Bottei ⁵
¹ H-NMR	Analysis of reference material.	Huang et al. ⁶
LC-QqQ-MS/MS	<i>In vitro</i> metabolism studies using human liver microsomes.	Takayama et al. ⁷
Not reported.	Analysis of products purchased between November 2013 and May 2014 in Japan.	Uchiyama et al. ⁸
LC-QqQ-TOF-MS	<i>In vitro</i> metabolism studies using pooled human hepatocytes.	Wohlfarth et al. ⁹
Melting point, NMR, ESI-MS, elemental analysis	Synthesis and use in pharmacological investigations.	Banister et al. ¹⁰
LC-TOF-MS, GC-MS	Analysis of reference material.	Marginean et al. ¹¹
LC-Q-Orbitrap-MS	Plasma analysis following intoxication case.	Schep et al. ¹²
LC-Q-Orbitrap-MS/MS	<i>In vitro</i> metabolism studies using human liver microsomes and recombinant carboxylesterases.	Thomsen et al. ¹³
Not reported	Summary of cases related to acute intoxications.	Trecki et al. ¹⁴
LC-Q-Orbitrap-MS/MS	Plasma, blood and urine analysis following intoxication case.	Abouchedid et al. ¹⁵
LC-QqQ-MS/MS	Analysis of urine samples.	Cannaert et al. ¹⁶
Voltammetry	Detection of reference material spiked in artificial saliva.	Dronova et al. ¹⁷
LC-QqQ-MS/MS	Analysis of hair samples.	Franz et al. ¹⁸
LC-MS/MS	Analysis of serum and urine samples obtained from acute intoxication cases.	Müller et al. ¹⁹
DART-MS, LC-QTOF-MS	Analysis of reference material and method application to samples.	Nie et al. ²⁰
LC-Q-Orbitrap	Analysis of serum samples following acute intoxications.	Abouchedid et al. ²¹
GC-MS, ¹ H-NMR	Analysis of herbal mixtures.	Frinculescu et al. ²²
Not reported	Review of cases involving motor vehicle collisions in 2013 and blood analysis.	Kaneko ²³
GC-MS(/MS), LC-PDA, LC-MS	Characterization of 5F-PB-22 and regioisomers and analysis of herbal mixtures.	Kohyama et al. ²⁴
GC-cold-EI-MS	Analysis of reference material.	Smolianitski-Fabian et al. ²⁵
LC-QTOF-MS/MS	Metabolism studies using the fungus <i>Cunninghamella elegans</i> .	Watanabe et al. ²⁶

^a GC: gas chromatography; MS: mass spectrometry; MS/MS: tandem mass spectrometry; HR: high resolution; LC: liquid chromatography (various forms); Q: quadrupole; TOF: time-of-flight; NMR: nuclear magnetic resonance spectroscopy; FT-IR: Fourier transform infrared spectroscopy; ATR: attenuated total reflectance; QqQ: triple quadrupole; ESI: electrospray ionization; DART: direct analysis in real time; PDA: photo diode array detector.

References

1. Shevyrin V, Melkozerov V, Nevero A, Eltsov O, Shafran Y. Analytical characterization of some synthetic cannabinoids, derivatives of indole-3-carboxylic acid. *Forensic Sci Int* 2013;232:1-10. doi:10.1016/j.forsciint.2013.06.011.
2. Shevyrin V, Melkozerov V, Nevero A, Eltsov O, Shafran Y. Erratum to “Analytical characterization of some synthetic cannabinoids, derivatives of indole-3-carboxylic acid” [Forensic Sci. Int. 232 (2013) 1-10]. *Forensic Sci Int* 2013;232:151-2.
3. SWGDRUG. 5-Fluoro-PB-22 Monograph. Latest revision 16 December 2013. Available at: <http://www.swgdrug.org/Monographs/5FPB22.pdf>.
4. Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M et al. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. *J Anal Toxicol* 2014;38:559-62. doi:10.1093/jat/bku048.
5. Bottei E. First report of drug concentrations of the synthetic cannabinoid 5F-PB-22 found on post-mortem testing. *Clin Toxicol* 2014;52:750.
6. Huang L, Marino MA, Voyer B. Nuclear magnetic resonance implemented synthetic indole and indazole cannabinoid detection, identification, and quantification. WO 2014/176542 (A1). Hofstra University, Hempstead, New York, USA.; 2014.
7. Takayama T, Suzuki M, Todoroki K, Inoue K, Min JZ, Kikura-Hanajiri R et al. UPLC/ESI-MS/MS-based determination of metabolism of several new illicit drugs, ADB-FUBINACA, AB-FUBINACA, AB-PINACA, QUPIC, 5F-QUPIC and α -PVT, by human liver microsome. *Biomed Chromatogr* 2014;28:831-8. doi:10.1002/bmc.3155.
8. Uchiyama N, Shimokawa Y, Kawamura M, Kikura-Hanajiri R, Hakamatsuka T. Chemical analysis of a benzofuran derivative, 2-(2-ethylaminopropyl)benzofuran (2-EAPB), eight synthetic cannabinoids, five cathinone derivatives, and five other designer drugs newly detected in illegal products. *Forensic Toxicol* 2014;32:266-81. doi:10.1007/s11419-014-0238-5.
9. Wohlfarth A, Gandhi AS, Pang S, Zhu M, Scheidweiler KB, Huestis MA. Metabolism of synthetic cannabinoids PB-22 and its 5-fluoro analog, 5F-PB-22, by human hepatocyte incubation and high-resolution mass spectrometry. *Anal Bioanal Chem* 2014;406:1763-80. doi:10.1007/s00216-014-7668-0.
10. 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;6:1445-58. doi:10.1021/acschemneuro.5b00107.
11. Marginean I, Rowe WF, Lurie IS. The role of ultra high performance liquid chromatography with time of flight detection for the identification of synthetic cannabinoids in seized drugs. *Forensic Sci Int* 2015;249:83-91. doi:10.1016/j.forsciint.2015.01.013.

12. Schep LJ, Slaughter RJ, Hudson S, Place R, Watts M. Delayed seizure-like activity following analytically confirmed use of previously unreported synthetic cannabinoid analogues. *Hum Exp Toxicol* 2015;34:557-60. doi:10.1177/0960327114550886.
13. Thomsen R, Nielsen LM, Holm NB, Rasmussen HB, Linnet K. Synthetic cannabimimetic agents metabolized by carboxylesterases. *Drug Test Anal* 2015;7:565-76. doi:10.1002/dta.1731.
14. Trecki J, Gerona RR, Schwartz MD. Synthetic Cannabinoid-Related Illnesses and Deaths. *N Engl J Med* 2015;373:103-7. doi:10.1056/NEJMp1505328.
15. Abouchedid R, Ho JH, Hudson S, Dines A, Archer JR, Wood DM et al. Acute toxicity associated with use of 5F-derivations of synthetic cannabinoid receptor agonists with analytical confirmation. *J Med Toxicol* 2016;12:396-401. doi:10.1007/s13181-016-0571-7.
16. Cannaert A, Storme J, Franz F, Auwärter V, Stove CP. Detection and activity profiling of synthetic cannabinoids and their metabolites with a newly developed bioassay. *Anal Chem* 2016;88:11476-85. doi:10.1021/acs.analchem.6b02600.
17. Dronova M, Smolianitski E, Lev O. Electrooxidation of new synthetic cannabinoids: Voltammetric determination of drugs in seized street samples and artificial saliva. *Anal Chem* 2016;88:4487-94. doi:10.1021/acs.analchem.6b00368.
18. Franz F, Angerer V, Hermanns-Clausen M, Auwärter V, Moosmann B. Metabolites of synthetic cannabinoids in hair--proof of consumption or false friends for interpretation? *Anal Bioanal Chem* 2016;408:3445-52. doi:10.1007/s00216-016-9422-2.
19. Müller D, Angerer V, Auwärter V, Neurath H, Liebetrau G, Just S et al. Desoxypipradrol – eine neue (alte) Designerdroge: eine Fallserie. *Dtsch Med Wochenschr* 2016;141:951-3. doi:10.1055/s-0042-107537.
20. Nie H, Li X, Hua Z, Pan W, Bai Y, Fu X. Rapid screening and determination of 11 new psychoactive substances by direct analysis in real time mass spectrometry and liquid chromatography/quadrupole time-of-flight mass spectrometry. *Rapid Commun Mass Spectrom* 2016;30:141-6. doi:10.1002/rcm.7629.
21. Abouchedid R, Hudson S, Thurtle N, Yamamoto T, Ho JH, Bailey G et al. Analytical confirmation of synthetic cannabinoids in a cohort of 179 presentations with acute recreational drug toxicity to an Emergency Department in London, UK in the first half of 2015. *Clin Toxicol* 2017;55:338-45. doi:10.1080/15563650.2017.1287373.
22. Frinculescu A, Lyall CL, Ramsey J, Miserez B. Variation in commercial smoking mixtures containing third-generation synthetic cannabinoids. *Drug Test Anal* 2017;9:327-33. doi:10.1002/dta.1975.
23. Kaneko S. Motor vehicle collisions caused by the 'super-strength' synthetic cannabinoids, MAM-2201, 5F-PB-22, 5F-AB-PINACA, 5F-AMB and 5F-ADB in Japan experienced from 2012 to 2014. *Forensic Toxicol* 2017;35:244-51. doi:10.1007/s11419-017-0369-6.

24. Kohyama E, Chikumoto T, Tada H, Kitaichi K, Ito T. Analytical differentiation of quinolinyl- and isoquinolinyl-substituted 1-(5-fluoropentyl)-1H-indole-3-carboxylates: 5F-PB-22 and its ten isomers. *Forensic Toxicol* 2017;35:56-65. doi:10.1007/s11419-016-0334-9.
25. Smolianitski-Fabian E, Cohen E, Dronova M, Voloshenko-Rossin A, Lev O. Discrimination between closely related synthetic cannabinoids by GC-Cold-EI-MS. *Drug Test Anal* 2017. doi:10.1002/dta.2247.
26. Watanabe S, Kuzhiumparambil U, Nguyen MA, Cameron J, Fu S. Metabolic profile of synthetic cannabinoids 5F-PB-22, PB-22, XLR-11 and UR-144 by *Cunninghamella elegans*. *AAPS Journal* 2017;19:1148-62. doi:10.1208/s12248-017-0078-4.