4-Fluoromethcathinone (flephedrone; 4-FMC)

Critical Review Report

Agenda item 4.16

Expert Committee on Drug Dependence

Thirty-sixth Meeting

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Summary

(*R*/*S*)-1-(4-Fluorophenyl)-2-(methylamino)propan-1-one, also known as flephedrone or 4-FMC, has emerged in recent years as a recreational psychostimulant. Its synthesis was first published in 1952 in order to explore the potential for antithyroidal, antibacterial and bacteriostatic properties. Publications about the detection of 4-FMC obtained from Internet sources and test purchases started to appear from 2009 onwards. The first official notification submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by a European member state was 2008. Since then, it has been detected across the globe as a reflection of modern forms of trade within a globalised world. As was the case with many other emerging substances with psychoactive properties, commonly used terms include "legal highs", "bath salts" or "new psychoactive substances" (NPS) in the attempt to highlight the fact that many, if not most, did not originally fall under any legislative control and that detailed data on both pre-clinical and clinical levels were normally less well explored.

The amount of research data on 4-FMC is comparatively small in comparison with other cathinones such as 4-methyl-*N*-methylcathinone (mephedrone) or 3,4-methylenedioxypyrolvalerone (MDPV) but the currently available data suggest that the psychoactive and behavioural profile of 4-FMC, for example demonstrated by drug discrimination and *in-vitro* studies, show similarities to psychomotor stimulants such as cocaine, methcathinone and methamphetamine although it appears that it be less potent. It has been demonstrated that key targets of 4-FMC include monoamine transporters and that it functions as a catecholamine-selective substrate-type releaser of dopamine and norepinephrine.

While 4-FMC was a low potency partial agonist at the 5-HT_{1A} receptor, it was found to be an antagonist with very low potency at 5-HT_{2A} and 5-HT_{2C} receptors. 4-FMC was observed to act primarily as a substrate at the human dopamine (hDAT) and human norepinephrine transporter (hNET), with the latter being more pronounced than methamphetamine. In addition, it was observed to display appreciable affinity to the hα_{1A} adrenoceptor and rat trace amine-associated receptor 1.

The ability to induce DA release similar to methamphetamine-type substances known to act as hDAT substrates makes it likely that 4-FMC may show abuse potential. It seems conceivable that, especially at high dosage levels, extensive release of NE in combination with hα_{1A} adrenoceptor activation might also contribute to enhanced cardiotoxic effects, in addition to dopamine-mediated stimulation.

1. Substance identification

A. International Nonproprietary Name (INN)

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B. Chemical Abstract Service (CAS) Registry Number

447-40-5 (free base)
7589-35-7 (hydrochloride salt)
1419921-83-7 (1-(4-fluorophenyl-1,2,3,4,5,6-$^{13}C_6$) free base)
1286101-71-0 (N-CD_3 hydrochloride salt)
1286316-60-6 (N-CD_3 free base)

1388142-25-3 (*R*-enantiomer free base)
1388142-26-4 (*S*-enantiomer free base)

C. Other Names

4-FMC, flephedrone, 4-fluoromethcathinone, 4-flephedrone, 4-fluoro-*N*-methylcathinone, *p*-fluoromethcathinone, *p*-fluoro-*N*-methylcathinone

D. Trade Names

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E. Street Names

4-FMC, flephedrone.

F. Physical properties

4-FMC HCl is a white crystalline powder.

G. WHO Review History

4 - FMC was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 4 - FMC 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

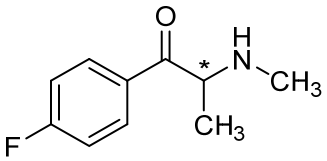
A. Chemical Name

IUPAC Name: (*R*/*S*)-1-(4-Fluorophenyl)-2-(methylamino)propan-1-one

CA Index Name:
(*R*/*S*)-1-(4-Fluorophenyl)-2-(methylamino)-1-propanone

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral centre

Molecular Formula: $C_{10}H_{12}FNO$ (base)
Molecular Weight: 181.21 g/mol
Melting point: 220-222 °C hydrochloride salt[1]

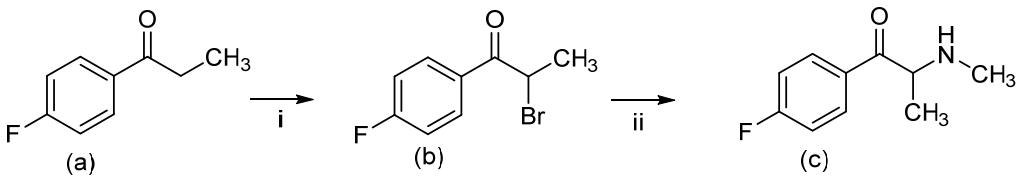
Boiling point:--
Fusion point: --

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-4-FMC and (*R*)-4-FMC, respectively. Currently, it appears that data about their optical rotation or potential to display distinguishable pharmacological properties have not been published. 4-FMC is most likely to be available as the racemic mixture.

D. Synthesis

The first synthesis of 4-FMC has been published in 1952 by Kraft and Dengel following the scheme shown below.[1] This key procedure includes the α-bromination (step i) of the propan-1-one precursor (a) and formation of the 2-bromoppropan-1-one intermediate (b). Reaction with *N*-methylamine (step ii) gives 4-FMC (c) which may then be converted into a range of salts. One of several alternatives may include the oxidation of the ephedrine-type 2-(methylamino)propan-1-ol precursor as well.



E. Chemical description

4-FMC, i.e. (*R*/*S*)-1-(4-fluorophenyl)-2-(methylamino)propan-1-one, contains a 2-amino-1-phenylpropan-1-one nucleus which forms the structural basis for many cathinone-based substances that are known to interact with a range of targets found, for example, in the central nervous system.

F. Chemical properties

4-FMC HCl is a water-soluble white crystalline powder. During preparation of the hydrochloride salt, a blue and brown colour formation was temporarily observed.[1]

G. Chemical identification

4-FMC, as well as many other cathinones, has been repeatedly characterized in recent years. The first report that described its identification in a sample obtained from an internet supplier was published in 2009 by Archer. Confirmation was obtained from synthesis and analytical characterisation by gas chromatography-mass spectrometry (GC-MS), attenuated total reflectance (ATR) Fourier transform (FT) infrared (IR) spectroscopy and ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance spectroscopy (NMR).[2] In addition to similar data, the first GC chemical ionisation mass spectrum was published in 2010.[3] 4-FMC was reported to give a purple (ninhydrin reagent) or orange colour when using the Dragendorff's reagent (+ 10% H_2SO_4) and a full scan ultraviolet (UV) spectrum was provided (amongst similar data mentioned above) in a 2010 forensic report from Tokyo on test purchases in 2009.[4] Electrospray ionisation mass spectrometry data were first published in 2011.[5,6] Several immunoassays have

been described for the detection of 4-FMC and other cathinones. Under certain conditions, examples of cross-reactivity have been described.[7,8]

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

Similar to other well-established psychostimulants, a key principle involved in the molecular mechanisms of 4-FMC is the interaction with transport proteins that lead to the elevation of extracellular neurotransmitter levels, most notably, dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT), respectively.

However, an important question relates to the ability of a psychostimulant to act as a monoamine re-uptake inhibitor (e.g. cocaine-like) or as a substrate-type releaser (amphetamine-like). In the latter case, this may be achieved by transporter-mediated translocation of the drug into the cytoplasm in exchange of the monoamine which may be exacerbated by additional release from vesicular storage, thus leading to increasing monoamine availability for further release.[9] The key targets of interest normally include the evaluation of drug action at the dopamine (DAT), norepinephrine (NET) and serotonin (SERT) transporters. Recently published research demonstrated that 4-FMC acted as a substrate, rather than an uptake blocker which is a property also shared with cathinone, methcathinone, mephedrone and methylone, respectively.[10-12]

4.1. Pharmacodynamics

In-vitro pharmacology

Simmler et al.[11] found that 4-FMC displayed the ability to inhibit monoamine transporters with IC_{50} values in the low µM range with ~ 26-fold selectivity to hNET (0.246 µM) over hDAT (6.35 µM) in HEK cells (Table 1). In comparison, some of the IC_{50} values observed with other substances were as follows: MDMA (hNET = 0.447, hDAT = 17 µM), cocaine (hNET = 0.451, hDAT = 0.768 µM), methamphetamine (hNET = 0.064, hDAT = 1.05 µM), respectively. However, 4-FMC seemed somewhat catecholamine-selective since the IC_{50} value for hSERT was > 10 µM. As expected, both cocaine and MDMA, were able to show a higher potency for hSERT inhibition with IC_{50} of 2.37 µM and 1.36 µM, respectively.[11] Similar selectivities with regards to [^{3}H]monoamine uptake inhibition, i.e. hNET > hDAT > hSERT, have been observed by Eshleman et al.. The authors also demonstrated that 4-FMC (EC_{50} = 1.53 µM, E_{max} = 194%) released more [^{3}H]NE than methamphetamine (EC_{50} = 0.128 µM, E_{max} = 92.7%) which showed a closer proximity to methcathinone (EC_{50} = 0.228 µM, E_{max} = 149%) even though 4-FMC was less potent in comparison. [10]

Table 1 shows that 4-FMC acted as a subtype-type dopamine (DA) and norepinephrine (NE) releaser (EC_{50} DAT = 17.8 and 12.5 µM; EC_{50} NET = 1.53 µM) while high concentrations (EC_{50} > 39 and 33 µM) were required to elicit SERT-mediated [^{3}H]5-HT release. This also meant that 4-FMC also showed a preference for catecholamine release which differentiated this substance from other releasers that would show an additional 5-HT component (e.g. mephedrone and methylone).[10-12] Table 1 also summarises the key data obtained from additional *in-vitro* studies such as receptor binding and functional activity studies. For example, 4-FMC was shown to display an appreciable

affinity to the 5-HT_{2A} (K_i = 1.4 μM, [^{3}H]ketanserin and spiperone) and α_{1A} adrenoceptor (K_i = 1.52 μM, [^{3}H]prazosin and risperidone). While 4-FMC was a low potency partial agonist at the 5-HT_{1A} receptor, it was found to be an antagonist with very low potency at the 5-HT_{2A} and 5-HT_{2C} receptors. Direct effects on dopamine receptors were not observed.[10] Activation of the α_{1A} adrenoceptor, on the other hand, has been associated with stimulant-induced vasoconstriction and hyperthermia.[11] The fact that 4-FMC was observed to act primarily as a hDAT and hNET substrate, with the latter being more pronounced than methamphetamine, led to the suggestion that a extensive NE activity might contribute not only to cardiotoxic effects but also precipitation of panic attacks which appear to be frequently observed in acute intoxications with a number of cathinones.[10]

In-vivo pharmacology

Currently, it appears that two *in-vivo* studies have been published on 4-FMC (Table 2). Marusich et al.[13] have explored a range of cathinone analogs and their impact on a number of behavioural measures (locomotor activity, rotorod, functional observational battery) in male ICR mice (Table 2). Similar cocaine, MDPV and mephedrone, a steady attenuation of initially high levels of activity were observed following intraperitoneal 4-FMC administration which translated to a rapid on- and offset.[13] An important approach when evaluating abuse liability may also come from drug discrimination studies in animals trained to distinguish a training drug from saline. Gatch et al.[14] confirmed that 4-FMC showed discriminative stimulus effects in cocaine- and methamphetamine-trained mice (Table 2). Interestingly, with regards to locomotor activity, 4-FMC initially produced depressant effects before stimulant effects were observed which might be relevant when assessing psychostimulant effects in humans (Table 2).

Table 1. 4-FMC *in-vitro* uptake and release data [a]

Uptake [a]			Release [b]			Affinity			Ref
DAT IC_{50}/nM	NET IC_{50}/nM	SERT IC_{50}/nM	DAT EC_{50}/µM (E_{max} %)	NET EC_{50}/µM (E_{max} %)	SERT EC_{50}/µM (E_{max} %)	DAT K_i/µM	NET K_i/µM	SERT K_i/µM	
273	127	> 10 µM	17.8 µM (98)	1.53 µM (194)	39 µM (39.3)	10.4 [f]	35 [f]	> 100 µM [f]	Eshleman et al.[10]
6350	246	>10000	> 12.5 µM	--	> 33 µM	12.2 [g]	>25 [g]	>30 [g]	Simmler et al.[11]

Additional 4-FMC *in-vitro* data	
Inhibition of [^{3}H]DHTB binding to hVMAT2 [c]: K_i > 1 mM. Comparison (K_i/µM): MDMA = 661; methamphetamine = 920; MDPV = 990. Inhibition of hVMAT2 [^{3}H]5-HT uptake [d]: IC_{50} = 178 µM. Comparison (IC_{50}/µM): MDMA = 5.8; methamphetamine = 4.72; MDPV > 100. hVMAT2 [^{3}H]NE release assay [e]: EC_{50} = > 100 µM with efficacy (E) of 24.9% [f]. Comparison: EC_{50} = 114 µM, E = 63% (MDMA); EC_{50} = 79 µM, E = 95.% (methamphetamine); EC_{50} = 148 µM, E = 35.8% (MDPV). Inhibition of binding to 5-HT receptors [g]: K_i h5-HT_{1A} = 71.6 µM; K_i h5-HT_{2A} = 10.0 µM; K_i h5-HT_{2C} = 12.6 µM. Comparison with LSD: K_i h5-HT_{1A} = 1.32 nM; K_i h5-HT_{2A} = 0.15 nM; K_i h5-HT_{2C} = 1.29 nM; comparison with MDPV: K_i h5-HT_{1A} = 14.8 µM; K_i h5-HT_{2A} = 207 µM; K_i h5-HT_{2C} = 107 µM. 4-FMC did not show any measureable affinity for dopamine receptor subtypes up to 10 µM. Potency and efficacy at 5-HT receptors [h]: h5-HT_{1A}: EC_{50} = 156.0 µM, E = 70.7%; h5-HT_{2A}: IC_{50} = 23.6 µM, E = 97%; h5-HT_{2C}: IC_{50} >1 mM, E = 15%. Comparison: LSD h5-HT_{1A}: EC_{50} = 5.8 nM, E = 107.8%; ketanserin h5-HT_{2A}: IC_{50} = 2.98 nM, E = 95.9%; SB-242084 h5-HT_{2C}: IC_{50} = 0.28 nM, E = 86.5%. Comparison MDPV: EC_{50} = 60.8 µM, E = 69%; h5-HT_{2A}: IC_{50} = 270 µM, E = 67.7%; h5-HT_{2C}: IC_{50} >1 mM, E = 24.5%. Inhibition of [^{3}H](+)-pentazocine binding to hSigma1 [i]: K_i = 24.2 µM. Comparison: haloperidol K_i = 0.94 nM; MDMA K_i = 19.4 µM; methamphetamine K_i = 3.18 µM; MDPV K_i = 4.4 µM.	Eshleman et al.[10]
Receptor binding profiles [j]: K_i (µM): 5-HT_{1A} >20; 5-HT_{2A} 1.4; 5-HT_{2C} >13; α_{1A} 1.52; α_{2A} >20; D_1 >13.6; D_2 >30; D_3 >17.7; H_1 >14.4; TA_{1rat} = 5.4; TA_{1mouse} >10. Comparison. MDPV: K_i (µM): 5-HT_{1A} 10.29; 5-HT_{2A} >13; 5-HT_{2C} >13; α_{1A} >6; α_{2A} >20; D_1 >13.6; D_2 >30; D_3 >9.2; H_1 >14.4; TA_{1rat} = 7.2; TA_{1mouse} >10. Cytotoxicity: None detected under conditions used [j].	Simmler et al.[11]

[a] Ref[10]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Ref[11]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT).

[b] Ref[10]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); data normalised to maximal effects of methamphetamine (hDAT and hNET) and *p*-chloroamphetamine (hSERT); Ref[11]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); release expressed as percent reduction in monoamine cell content at maximal drug concentration (100 mM) compared with controls.

[c] hVMAT2: human vesicular monoamine transporter type 2 (HEK-hVMAT2); [^{3}H]DHTB (7-10 nM): (+)-alpha-dihydrotetrabenazine; reserpine K_i = 0.147 µM (inhibition of [^{3}H]DHTB binding); reserpine IC_{50} = 6.6 nM (inhibition of [^{3}H]5-HT uptake).

[d] HEK-hVMAT2 using 40 nM [^{3}H]5-HT.

[e] HEK-hVMAT2 using 125 nM [^{3}H]NE (less non-transporter-mediated leakage than 5-HT and DA).

[f] Release efficacy relative to maximum response elicited by 100 µM or 1 mM methamphetamine.

[g] HEK-h5-HT_{1A} (0.5 nM [^{3}H]8OH-DPAT); HEK-h5-HT2A (0.1 nM [^{125}I]DOI); HEK-h5-HT_{2C} (0.07 nM [^{125}I]DOI).

[h] HEK-h5-HT_{1A} stimulation of [^{35}S]GTPγS binding; agonist efficacy relative to 100 nM 5-HT; HEK-h5-HT_{2A} and HEK-h5-HT_{2C} stimulation of inositol monophosphate (IP-1) formation; tested in presence of 100 nM 5-HT and normalized to inhibitory efficacy of 10 µM ketanserin (h5-HT_{2A} receptors) or 100 nM SB-242084 (h5-HT_{2C} receptors). On average, 5-HT-(100 nM) stimulated 640 nM IP-1 in h5-HT_{2A}, 1920 nM IP-1 in h5-HT_{2C} cells.

Table 1. 4-FMC *in-vitro* uptake and release data [a]			
Uptake [a]	**Release** [b]	**Affinity**	**Ref**

[i] Cos-7-hSigma1 using 1.3 nM [^{3}H](+)-pentazocine.

[j] [^{3}H]-8-OH-DPAT and indatraline (5-HT_{1A} , [^{3}H]ketanserin and spiperone (5-HT_{2A}), [^{3}H]mesulergine and mianserin (5-HT_{2C}), [^{3}H]prazosin and risperidone (α1 adrenoceptor), [^{3}H]rauwolscine and phentolamine (α2 adrenergic receptor), [^{3}H]SCH 23390 and butaclamol (DA_{D1}), [^{3}H]spiperone and spiperone (DA_{D2} and DA_{D3}), [^{3}H]pyrilamine and clozapine (H_1) and [^{3}H]-RO5166017 and RO5166017 (TA_1).

[k] Cell membrane integrity tested by measurement of adenylate kinase release from damaged cells via bioluminescence detection (after 4 h of incubation at 37°C). Drug concentrations were 10 and 100 μM.

Table 2. Summary of animal data published on 4-FMC	
Behaviour	**Reference**
Locomotor activity [a,b]: compared to saline, 4-FMC (30 mg/kg) caused significant increases in beam breaks during the first 70 min (attenuation of initial stimulant effects occurred at 40-90 min) whereas 17 mg/kg increased activity only during the first 20 min (attenuation 20-90 min); locomotor activity not affected at 10 mg/kg. Rotarod test / apparatus (motor coordination) [a]: no effect in time spent on the rotarod with 4-FMC. Functional observational battery (FOB) [a,c]: significant increases in some observational measures related to stimulant action (ranging from 17-30 mg/kg to 10-56 mg/kg): circling, hyperactivity, head weaving, head circling, and stimulation. No effect noted for ataxia, exploration, convulsions, salivation, and compulsive movements.	Marusich et al. [13]
Locomotor activity [d]: maximal stimulant first occurred 40-70 min after injection of 10 mg/kg (ED_{50} of significant stimulant effects = 2.04 mg/k); initial depression of locomotor activity between 10-30 min at 10 mg/kg (occurred within 20 min and lasted 20 min), followed by stimulation; stimulation occurred within 50 min and lasted 90 min; ED_{50} methamphetamine 0.30 mg/kg (doses 0.5 and 2 mg/kg); ED_{50} cocaine 7.24 mg/kg (doses 10, 20 and 40 mg/kg). Drug discrimination [e]: full substitution in cocaine-trained rats (ED_{50} 4-FMC 3.24 mg/kg; ED_{50} cocaine 3.09 mg/kg) and methamphetamine-trained rats (ED_{50} 4-FMC 2.69 mg/kg; ED_{50} methamphetamine 0.37 mg/kg).	Gatch et al.[14]

[a] Male ICR mice; substances administered intraperitoneally.

[b] Beam breaks in open field activity chambers.

[c] 20 Minutes post-injection of test drug. Behavioural profile with emphasis on detection of potential safety concerns; adapted from Environmental Protection Agency. Observations included a range of behaviour, such as locomotion, ataxia, exploration, convulsions, circling, hyperactivity, salivation, stereotyped head weaving, head circling, other stereotyped compulsive movements and stimulation.

[d] Male Swiss Webster mice; locomotor activity counts in horizontal plane (ambulation counts); horizontal activity measured for 8 hours; locomotor activity: (0.3, 1, 3, 10, or 30 mg/kg); behavioural observations recorded at 30, 120, and 480 min after 30 mg/kg 4-FMC administration.

[e] Male Sprague-Dawley rats; learned to discriminate methamphetamine (1 mg/kg, i.p., ED_{50} 0.37 mg/kg) or cocaine (10 mg/kg, i.p., ED_{50} 3.09 mg/kg) from saline; 4-FMC (0.5-10 mg/kg) administered 60 min before start of test session.

4.2. Routes of administration and dosage

Not applicable.

4.3. Pharmacokinetics

Detailed studies appear to be unavailable at the time of writing. The case report provide by Thornton et al.[15] currently offers the only description of 4-FMC levels in serum and urine following nasal insufflation of a white powder confirmed to contain a mixture of 4-FMC, MDPV and caffeine (Table 3). 4-FMC levels detected in serum and urine were 346 and 257 ng/ml following, according to the patient's recollection, insufflation of 1 g of powdered material 30-60 min prior to presentation at the emergency department. Powder analysis revealed the presence of 4-FMC (142 µg/mg), MDPV (143 µg/mg) and caffeine (102 µg/mg). Studies in animals have shown (Table 2) that the initial phase following 4-FMC administration was characterised by depression of locomotor activity[14] whereas a large, rapid initial increases in locomotor activity has been observed by others.[13]

5. Toxicology

A recently carried out assay for cell membrane integrity measuring adenylate kinase release from damaged cells via bioluminescence detection (after 4 h of incubation at 37°C, drug concentrations 10 and 100 µM) did not reveal any indications for cytotoxicity under the conditions used[11] and further studies are warranted. Eshleman et al. suggested that the serum concentrations found in the Thornton et al. case report[15] (Table 3) might have been sufficient to block DA and NE uptake and elicit NE release[10] which may have been consistent with mild sympathomimetic features mentioned by Thornton et al.. It is currently not known how these biofluid levels correspond to concentrations present in the brain.

6. Adverse reactions in humans

It appears that the only case report involving 4-FMC was published in 2012 by Thornton et al. who describe a patient who presented with psychosis and a mild sympathomimetic syndrome (Table 3). Analytical confirmation revealed that the white powder consisted of a 4-FMC/MDPV/caffeine mixture and agitation was treated with intravenously administered droperidol and lorazepam.[15] However, it is impossible to separate the individual contribution derived from 4-FMC from MDPV, which is a powerful, catecholamine-selective transport inhibitor[16] with a known potential to cause severe adverse reactions in humans.[17]

Table 3. Summary of case report on 4-FMC/MDPV intoxication by Thornton et al.[15]

- 23 Year old male with psychiatric history (previous prescriptions for clonazepam, quetiapine, aripiprazole, valproic acid and lithium) admitted to emergency department.
- Bizarre behaviour, suicidality and hallucinations.
- Patient indicated insufflation of 1g of unknown white powder 30-60 min prior to presentation.
- Due to agitation, patient was physically and chemically restrained
- Intravenous administration of 6 mg lorazepam and 2.4 mg of droperidol in total over 90 min. Patient remained sedated in the next 5 hours.
- Basic metabolic panel was normal.
- Psychiatric evaluation offered differential diagnosis of schizoaffective disorder, bipolar disorder or psychosis secondary to "bath salt".
- Patient discharged within 8 hours of presentation.
- Serum, urine and product analysed by LC-MS. Product: MDPV (143 µg/mg), 4-FMC (142 µg/mg) and caffeine (102 µg/mg).
- MDPV in serum and urine: 186 and 136 ng/ml.
- 4-FMC in serum and urine: 346 and 257 ng/ml.
- Caffeine in serum and urine: 387 and 367 ng/ml.
- Urine immunoassay (ONLINE DAT II) positive for tetrahydrocannabinoids (cutoff 100 ng/mL).
- Serum screens negative for ethanol, acetaminophen, lithium and valproic acid.

7. Dependence potential

Data on dependence potential of 4-FMC are currently absent from the literature.

8. Abuse potential

Detailed clinical studies in humans are not available in the scientific literature and data on prevalence of 4-FMC use in the general population are not obtainable at this stage. Pre-clinical data currently available show that 4-FMC shows a number of features that are consistently observed with some classical psychostimulants (e.g. substrate at hDAT and hNET) or DAT/SERT selectivity profile (methamphetamine-like cathinones) (see sections above) which suggests the possibility of abuse liability. For example, 4-FMC (EC_{50} = 17.8 µM) was found to be 45-fold less potent than methamphetamine (EC_{50} = 0.40 µM) in its ability to induce hDAT-mediated [^{3}H]DA release[10] which indicated that 4-FMC may be a less potent psychostimulant in humans. Animal studies have so far indicated that 4-FMC results in a number of increased behavioral activities also observed with classical psychostimulants (see sections above). The observation of fast on- and offsets associated with 4-FMC and locomotor activity in mice[13] could suggest a potential for re-dosing in humans but further studies are required to address these issues. Gatch et al., on the other hand, reported initial depression of locomotor activity and delayed onset of action.[14] Further studies, e.g. self-administration in rodents, are necessary to elucidate these mechanisms in more detail.

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

Not known.

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing authorizations (as a medicine)

Not available.

12. Industrial use

Not known.

13. Non-medical use, abuse and dependence

Household surveys that specifically probe for prevalence of 4-FMC do currently not appear to be available in the published literature.

Oral dosage levels have been tentatively suggested to range between 15-50 mg (threshold) and 150-300+ mg (strong) whereas threshold levels obtained from nasal insufflation were suggested to range between 5-25 mg (strong: 75-200 mg). The total duration of intoxication may last between 1.5-4 hours (p.o.) or 1-2.5 hours via nasal insufflation.[18,19] Other reports indicate that dosage levels may range from 100-200 mg orally, with an optimal dose of 150mg intranasally, and 150 mg to 350 mg rectally. Rectal administration as a gel capsule has also been reported.[20]

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

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

The Drug Enforcement Administration, after reviewing the scientific literature, 3-factor analysis, consultation of NFLIS, law enforcement, Customs and Border Protection and other sources, confirmed that 4-MEC appeared to be sufficiently prevalent to pose a public health risk.[21]

15. Licit production, consumption and international trade

No information available.
Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

16. Illicit manufacture and traffic and related information

As of 11.03.2014, reports have been received from the European early-warning system on new drugs that 4-FMC was encountered in seizures or as a used substance in Italy, Germany, Hungary, Poland, Czech Republic, Croatia, Bulgaria, France, Belgium, Ireland, Austria, Finland. Denmark was the first country to submit a notification in

September 2008.[20] The Drug Enforcement Administration concluded that prevalence of use and distribution of 4-FMC warranted inclusion into Schedule 1 of the Controlled Substances Act as part of temporary placement.[22]

Responses obtained to the UNODC questionnaire on NPS (up to 2012) revealed that 4-FMC was ranked fifth with regards to numbers of reports (35) received. This was only superseded by mephedrone (68 reports), MDPV (61 reports), methylone (53 reports) and 4-MEC (38).[23]

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

17. Current international controls and their impact

Not applicable in terms of medical use.

18. Current and past national controls

The EMCDDA received confirmation that 4-FMC is controlled in the following countries[20]:

- Bulgaria via amendments to the National Drug Law; came into force on 09 February 2011
- Croatia (amendments to the List of drugs, psychotropic substances, plants used to produce drugs and substances that can be used in the production of drugs (precursors) (OG 19/11) (February 2011)
- Czech Republic via amendment of the Act n. 167/1998 on addictive substances; came into force on 22 April 2011
- Denmark: 4-FMC added to lists of controlled substances (List B))
- Finland (in accordance with section 83 of the Medicines Act (395/1987); Finnish Medicines Agency)
- France: controlled since 27 July 2012
- Germany (by adoption of the 26th Amending Regulation on Narcotic Drugs, i.e. 26. Betäubungsmittelrechts-Änderungsverordnung, BtMÄndV; came into force 26 July 2012 and permanently placed under schedule II (narcotics eligible for trade but not for medical prescription) of the German Narcotics Act (Betäubungsmittelgesetz, BtMG))
- Hungary (as of 3 April 2012, via generic definition, new Schedule C list, i.e. Annex 1 of Government Decree 66/2012 (IV. 2.))
- Ireland via generic definition, Misuse of Drugs Act 1977 (controlled drugs) (2011, S.I. No. 551, 2011)
- Lithuania via amendment to Republic of Lithuania Law on the Control of Narcotic Drugs and Psychotropic Substances
- Poland (as of 8 June 2011) amendment of the act of law on counteracting drug addiction from 15 April 2011
- Portugal (Portaria nº 154/2013, 17 April 2013)

- Romania (Governmental decision, came into force 15 February 2010)
- Slovakia (List of hazardous substances in Annex, § 2; came into force on 1 October 2013)
- Slovenia (via amendment of Decree on classification of illicit drugs, published on 22 July 2013 in Official Gazette of RS No. 62/2013; came into force 15 days afterwards
- Sweden (classified as narcotics since 1 October 2010)
- Turkey (Law on Control of Narcotic Substances no 2313, 22 May 2013)
- United Kingdom via generic definition under 1971 Misuse of Drugs Act 1971; came into force 16 April 2010
- USA: 4-FMC and nine other cathinones have been placed under temporary control (Schedule 1) of the Controlled Substances Act.[22]
- Singapore, via generic definition, placed 4-FMC under temporary control (Misuse of Drugs (Amendment) Act 2012, No. 30 of 2012)

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

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

Not applicable.

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Annex 1:
Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation 4 FMC

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

A total of 65 Member States answered the questionnaire for 4-fluoromethcathinone (flephedrone; 4-FMC). Of these, only 28 respondents (AMR 5, EUR 20, WPR 3)had information on this substance.

LEGITIMATE USE

None reported that 4-FMC was currently authorized or in the process of being authorized/registered as a medical product in their country. Four respondents reported that this substance was used in medical and scientific research. There was no use stated for 4-FMC in animal/veterinary care

HARMFUL USE

Fifteen respondents confirmed that there was recreational/harmful use of 4-FMC**.** Of these, four stated that the common route of administration was oral, six oral, inhaling/sniffing, and two oral, injection, inhaling/sniffing. On how 4-FMC was obtained, nine stated this was only via trafficking while three mentioned combinations of diversion, trafficking and clandestine manufacturing. Thirteen respondents reported on the common formulations of 4-FMC available with four reporting powder, seven powder and tablet, one powder and liquid and one liquid forms. When asked if 4-FMC was used by any special populations two each stated use in general population and in clubs; in clubs only and general population only – one specifies youth in general population. In 2012, 18 deaths for all cathinones were reported by one respondent as well as 3 emergency room visits in another. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by 4-FMC. These included a variety of symptoms and signs such as hallucinations, delusions, excitability, agitation, palpitation and other sympathomimetic effects, circulatory and CNS effects. Please also refer report on 4 MEC.

One respondent reports ‘available evidence on the overall public health risks associated with the use of synthetic cathinones indicates that 4-MEC, 4-MePPP, a-PVP, butylone, pentedrone, pentylone, 4-FMC, 3-FMC, naphyrone, and a-PBP can cause acute health problems leading to emergency department admissions, violent behaviors causing harm to self or others, or death. For example, individuals have presented at emergency departments following exposure to some of these synthetic cathinone substances or products containing them. Some of these synthetic cathinone substances have been directly or indirectly implicated in the death of individuals. For example, a 24-year-old female died after ingesting two capsules of what she believed to be ‘‘Ecstasy’’ but was subsequently confirmed to be a mixture of methylone and butylone. In 2011, there were 205 reports related to these 10 substances, and in 2012, there were 1,302 reports. From January to November 2013 there were 221 reports (excluding naphyrone). National Forensic Laboratory Information System (NFLIS) registered over 8,000 reports from state and local forensic laboratories identifying these substances in drug related exhibits for the period from January 2010 to November 2013 across 42 states. Specifically, in 2010, NFLIS registered 13 reports from 5 states containing many of these synthetic cathinone

substances. 8 In 2011, there were 800 reports from 32 states related to these substances registered in NFLIS, in 2012 there were 5,485 reports from 41 states, and from January to November 2013 there were 2,509 reports from 41 states.'

CONTROL

Of those with information on this substance 24 reported that 4-FMC was controlled under legislation that was intended to regulate its availability - 18 under "controlled substance act", three under "medicines law", one "temporary ban" and two under "analogue legislation". Four respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving 4-FMC, one country reported clandestine manufacture, five reported processing into the consumer product, 11 reported trafficking, 2 diversion and 11 countries an internet market.
Details on seizures are presented below.

	2011 (number of respondents)	**2012 (number of respondents)**
Total number of seizures	247 (10)	41 (9)
Total quantity seized (kg)	150.79 (5)	42.23 (13)
Total quantity seized (ampoules)	2 (1)	
Total quantity seized (L)		0.001 (1)
Total quantity seized (tablets/pills)	1,777 (3)	1,035 (2)

IMPACT OF SCHEDULING

Twenty-four respondents reported that if 4-FMC was placed under international control, they would have the laboratory capacity to identify the substance. There is no medical use reported.