4-Fluoroamphetamine

(4-FA)

Critical Review Report

Agenda item 5.4

Expert Committee on Drug Dependence

Thirty-seventh Meeting

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World Health Organization

Contents

Acknowledgements

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Summary

1-(4-Fluorophenyl)propan-2-amine (4-fluoroamphetamine, 4-FA) is a psychomotor stimulant that was first synthesized in the early 1940s. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) received the first formal notification of the detection of 4-FA in Europe in December 2008 although its presence has been noted since at least 2007. In Europe, it has been found in tablets sold as 'ecstasy'/MDMA, paste or powder sold as amphetamine. In addition, it can be obtained from Internet retailers as a 'research chemical' and it has also been detected as an adulterant present in other illicit controlled substances. 4-FA appears to be most commonly administered orally or by nasal insufflation (snorting). The EMCDDA has been notified of seizures from various locations in Europe since 2008.

Data indicate that 4-FA may be able to inhibit monoamine oxidase and that it functions as a substrate-type releasing agent of dopamine, norepinephrine and serotonin. It has been shown to display amphetamine-like features *in vivo* and *in vitro* and further research is warranted to investigate the extent to which 4-FA displays a potential for abuse and dependence in both animals in humans that is comparable to substances such as amphetamine, cocaine or related psychostimulants. Case report data in the scientific literature that unambiguously confirm a causal relationship between adverse effects of 4-FA and its presence in biofluids are limited to only a relatively small number of cases. In cases where this information is available, reported clinical features were associated with those of a sympathomimetic toxidrome. The EMCDDA has received reports from positive identifications in biofluids samples from 2009 onward. It has been reported that 4-FA might have established itself as a drug of choice in a surveyed convenience sample of 249 life-time users of 4-FA in one European country. Surveys that systematically assess the prevalence of use 4-FA within the general population are not available.

1. Substance identification

A. International Nonproprietary Name (INN)

None

B. Chemical Abstract Service (CAS) Registry Number

459-02-9 (free base)
64609-06-9 (hydrochloride salt)
72522-20-4 ((α*R*)-free base)
788123-23-9 ((α*S*)-free base)
127515-13-3 ((α*S*)- hydrochloride salt)
72522-24-8 ((α*R*)- hydrochloride salt)
1419922-92-1 (1,2,3,4,5,6-$^{13}C_6$-free base)
59963-24-5 (D-mannopyranose, 1-(hydrogen sulfate))
153506-17-3 (4-(fluoro-^{18}F))
72522-20-4 (*L*-leucine, *N*-acetyl- compd. with (α*R*)-4-fluoro-α-methylbenzeneethanamine, 1:1)
788123-23-9 (*L*-leucine, *N*-acetyl- compd. with (α*S*)-4-fluoro-α-methylbenzeneethanamine, 1:1)
1782279-11-1 (d_5-hydrochloride salt)
1783027-85-9 (d_5-free base)

C. Other Names

1-(4-Fluorophenyl)-2-propanamine, 1-(*p*-fluorophenyl)-2-aminopropane, 2-amino-1-(4'-fluorophenyl)propane, 2-amino-1-(4'-fluorophenyl)propane, 2-amino-1-(*p*-fluorophenyl)propane, 2-amino-1-(para-fluorophenyl)propane, *p*-fluoro-α-methylphenethylamine, 2-(4-fluorophenyl)-1-methylethylamine, 2-(4-fluoro-phenyl)-1-methyl-ethylamine, α-methyl-β-(4-fluorophenyl)ethylamine, α-methyl-β-(*p*-fluorophenyl)ethylamine, α-methyl-*p*-fluorophenethylamine, 1-(4-fluorophenyl)prop-2-ylamine, 1-(4-fluorophenyl)-2-propylamine, 1-(4-fluorobenzyl)ethylamine, 1-*p*-fluorophenyl-2-propylamine, *p*-fluoro-α-methyl-phenethylamine, *para*-fluoro-α-methyl-phenethylamine, 4-fluoro-α-methyl-phenethylamine, 4-fluoroamphetamine, *p*-fluoroamphetamine, parafluoroamphetamine, PFA, 4-F-A, PAL-303, p-FA, P-FMP, 4-FMP, 4FMP, 4-FA.

D. Trade Names

None

E. Street Names

Flux, Fifa.

F. Physical properties

4-FA HCl is a white crystalline powder.

G. WHO Review History

4-FA was not previously pre-reviewed or critically reviewed.

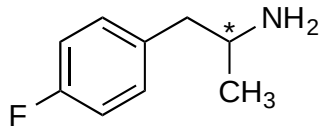
2. Chemistry

A. Chemical Name

IUPAC Name: 1-(4-Fluorophenyl)propan-2-amine
CA Index Name: 4-Fluoro-α-methyl-benzeneethanamine

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral centre

Molecular Formula: $C_9H_{12}FN$ (free base)
Molecular Weight: 153.20 g/mol
Melting point:
Hydrochloride salt: 156–157 °C (dry acetone)[1]
Hydrochloride salt: 152–154 °C[2]
Hydrochloride salt: 152–154 °C[3]
Hydrochloride salt: 152–154 °C[4]
(α*S*)-Hydrochloride salt: 195–198 °C[2]
(α*R*)-Hydrochloride salt: 195–197 °C[2]
Boiling point:
Free base: 95–96 °C (17 mmHg)[1]
Free base: 78 °C (10 mmHg)[2]
Free base: 96 °C (19.5 mmHg)[4]
Free base: 90 °C[3]

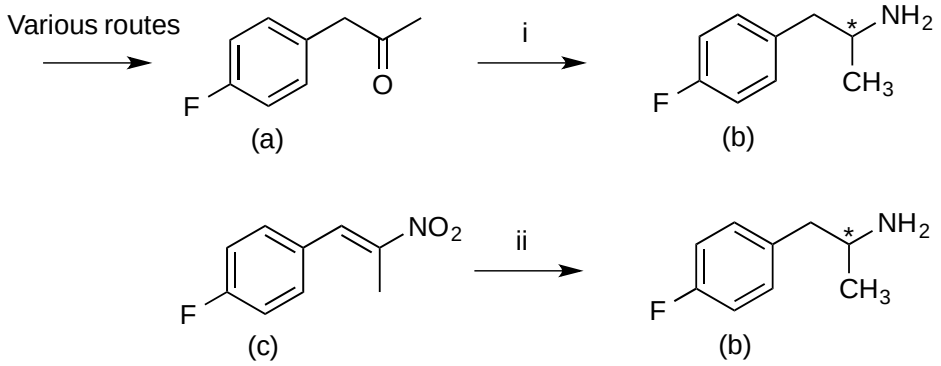
C. Stereoisomers

The presence of a chiral center at the α-carbon of the side chain gives rise to the enantiomeric pair of (*S*)-4-FA and (*R*)-4-FA, respectively. However, 4-FA is most likely to be available as the racemic mixture.

D. Synthesis

Methods of manufacturing:
4-FA may be obtained from a variety of synthetic methods that are commonly employed for the preparation of amphetamine (e.g.[5]). A classic approach might include the use of the 1-(4-fluorophenyl)propan-2-one (4-fluorobenzyl methyl ketone) (a) and exposure to reductive conditions (i) (e.g. using formamide[1]) to give

racemic 4-FA (b). Depending on the availability of starting materials, precursor (a) may be obtained from a variety of synthetic procedures. Another common approach includes the reduction of the nitroalkene intermediate 1-fluoro-4-(2-nitroprop-1-en-1-yl)benzene[2,6-9] (c) where 4-fluorobenzaldehyde may serve as the starting material. Enantiomerically pure forms of 4-FA have been prepared with the help of enzymes[8, 10-14] and a number of chemical methods have also been reported.[2, 9, 15-17] Alternative suggestions for the preparation of 4-FA have been published.[3, 4] The EMCDDA received information in 2009 about some 4-FA samples analyzed by the Forensic Science Service. The presence of specific impurities were associated with the Leuckart synthesis, which pointed to the possible use of 4-fluorobenzyl methyl ketone) (a) as the starting material.[18]



E. Chemical description.

4-FA is a ring-substituted analog of amphetamine. Amphetamine is listed in Schedule II of the United Nations 1971 Convention on Psychotropic Substances. The *N*-methyl derivative methamphetamine is listed in the same Schedule.

F. Chemical properties

4-FA hydrochloride is as a crystalline solid and soluble in ethanol, DMSO and dimethyl formamide (DMF). The solubility of 4-FA hydrochloride in ethanol is given as approximately 20 mg/mL and approximately 30 mg/mL in DMSO and DMF, and approximately 10 mg/mL in phosphate-buffered saline (PBS, pH 7.2).[19]

G. Chemical identification

The first melting point was described in the early 1940s followed by several examples in later years (Section B). More detailed analytical were published in 1992 and included thermal investigations into the nature of polymorphism,[20] NMR[21] and crystal structure analysis.[22] The first comprehensive characterization of 4-FA and related isomers and derivatives was reported in 2005.[23] Presumptive test results for 4-FA using the RAL color scheme were as follows. Marquis: RAL 9003 at 0 min and RAL 2012 at 5 min; Mecke: RAL 9003 at 0 min and RAL 1016 at 5 min; Mandelin: RAL 1018 at 0 min and RAL 1020 at 5 min; Simon: RAL 1017 at 0 min; Simon + catalyst: RAL 1017 at 0 min and RAL 8008 at 5 min; Scott: RAL 3014 at 0 min and RAL 3014 at 5 min.[24] 4-FA has been employed for analytical purposes and featured in a range of routine methods of analysis associated with forensic and clinical investigations (Table 1).

Table 1. Representative examples of scientific literature associated with chemical analysis and 4-fluoroamphetamine

Techniques [a]	**Comment**	**Reference**
Thermal methods	Characterization of 4-FA HCl polymorphism.	Marthi *et al.*[20]
^{1}H-NMR	Characterizations of compound including use chiral Eu-shift reagents.	Podányi[21]
XRD	Characterization of crystal structure properties of compound.	Simon *et al.*[22]
GC-MS	Metabolism study in rats following administration of *para*-fluoro-deprenyl.	Lajtha *et al.*[25]
GC-MS, IR, NMR	Characterization of seized compounds.	Rösner *et al.*[23]
GC-MS, LC, LC-MS	Characterization of collected compounds.	Kikura-Hanajiri *et al.*[26]
LC-FL, LC-TOF-MS	Characterization of collected compounds.	Min *et al.*[27, 28]
GC-MS, LC-DAD	Characterization of collected compounds.	Takahashi *et al.*[29]
GC-(EI/CI)-MS(/MS)	Characterization of seized compounds.	Westphal *et al.*[30]
LC-FL, LC-ESI-TOF-MS	Characterization of collected compounds.	Inagaki *et al.*[31]
PS-MS, CE-MS, CZE-UV	Method development.	Jhang *et al.*[32]
LC-TOF-MS	Detection in whole blood samples related to casework.	Johansen and Hansen[33]
Various approaches to ionization and MS	Method development.	Lee *et al.*[34]
^{1}H-NMR and UV	4-FA obtained from synthesis.	Lichtenberger [9]
GC-MS	Employment of chiral derivatization reagent.	Mohr *et al.*[35]
Immunoassays	Evaluation of cross-reactivities to EMIT assays.	Nakanishi *et al.*[36]
GC-MS, LC-Q-TOF-MS, NMR	Characterization of seized compounds.	Reitzel *et al.*[37]
Immunoanalysis, GC-MS	Detection biofluids.	Röhrich *et al.*[38]
LC-Q-trap-MS/MS	Detection in hair samples.	Rust *et al.*[39]
LC-TOF-MS	Characterization of collected compounds.	Shanks *et al.*[40]
UHPLC-QqQ-MS/MS	Detection in oral fluid.	Strano-Rossi *et al.*[41]
PTR-MS	Method development.	Sulzer *et al.*[42]
LC-QqQ-MS/MS	Detection in authentic urine samples.	Al-Saffar *et al.*[43]
CE-LIF, CE-UV, MEKC-UV, LC-Q-TOF-MS	Method development for saliva analysis.	Chen *et al.*[44]
LC-QqQ-MS/MS	Analyses of biofluids.	Helander *et al.*[45]
GC-MS	Method development and application to waste water analysis.	Mwenesongole *et al.*[46]
GC-MS, LC-IT-MS, NMR	Synthesis and characterization of isomers.	Nakazono *et al.*[47]
LC-Q-TOF-MS	Method development in whole blood and application to casework.	Pedersen *et al.*[48]
Immunoanalysis	Cross-reactivity studies.	Petrie *et al.*[49]
Colour spot test	Method development using a spectrophotometric reagent.	Philp *et al.*[50]
LC-TOF-MS	Method development and application to postmortem blood samples.	Roman *et al.*[51]
UPLC-QqQ-MS, LC-Q-TOF-MS	Method development in blood matrix for application to casework.	Rosano *et al.*[52]
LC-DAD, LC-Q-MS	Method development and application to collected samples combined with *in vitro* pharmacology assays.	Rosenauer *et al.*[53]
GC-MS, LC-DAD, LC-Q-TOF-MS, NMR	Detection of seized compounds.	Zuba *et al.*[54]
HS-SRI-TOF-MS	Method development.	Acton *et al.*[55]
LC-Q-TOF-MS/MS, LC-Q-ion trap-MS/MS	Detection in serum and urine.	Al-Abri *et al.*[56]
LC-DAD	Method development for chiral separation.	Geryk *et al.*[57]
Immunoanalysis, GC-MS	Method development and chemical derivatizations.	Holler *et al.*[58]
LC-Q-TOF-MS	Method development for urine analysis.	Paul *et al.*[59]
LC-QqQ-MS/MS	Method development for hair analysis and application to authentic specimens.	Strano-Rossi *et al.*[60]
LC-QqQ-MS/MS	Method development for urine analysis and application to authentic specimens.	Tang *et al.*[61]
LC-UV	Chiral analysis of products obtained from Internet retailers.	Taschwer *et al.*[62]
LC-DAD	Method development for chiral separation.	Geryk *et al.*[63]

TLC, GC-NPD, GC-MS	Identification of submitted samples.	Hondebrink *et al.*[64]
LC-DAD	Method development for chiral separation.	Kalíková *et al.*[65]
EMIT, LC-QqQ-MS/MS	Detection in serum and urine.	Laskowski *et al.*[66]
GC-MS, LC-QqQ-MS/MS	Detection in serum.	Maas *et al.*[67]
LC-QqQ-MS/MS	Method development in whole blood.	Odoardi *et al.*[68]
LC-TOF-MS	Application to analyses of authentic urine samples.	Sundström *et al.*[69]

[a] XRD: X-ray diffraction; GC: gas chromatography; MS: mass spectrometry; IR: infrared; NMR: nuclear magnetic resonance spectroscopy; LC: liquid chromatography (various forms); FL: fluorescence; TOF: time-of-flight; EI: electron ionization; CI: chemical ionization; DAD: diode array detector; ESI: electrospray ionization; PS: paper spray; CE: capillary electrophoresis; CZE: capillary zone electrophoresis; Q: quadrupole; QqQ: triple quadrupole; PTR: proton-transfer-reaction; LIF: laser induced fluorescence; MEKC: micellar electrokinetic capillary chromatography; IT: linear ion trap; HS: head space; SRI: selective reagent ionization; TLC: thin-layer chromatography; NPD: nitrogen-phosphorus detector; EMIT: enzyme multiplied immunoassay technique.

3. Ease of convertibility into controlled substances

No information available.

4. General pharmacology

4-FA is a ring-substituted amphetamine with properties that are also encountered with cocaine and other amphetamine-like psychostimulants and a key feature includes the ability to increase extracellular levels of dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT), respectively. From a contextual perspective, earlier research involving 4-FA is related to work on substances with pressor effects (e.g. ephedrine derivatives), in addition to research on potential appetite suppressants (e.g. fenfluramine or phenmetrazine) and other substances known to interact with the monoaminergic system, such as *L*-deprenyl or 4-chloroamphetamine.

A. Pharmacodynamics

As summarized in Tables 2 and 3, earlier work pointed toward interactions with the monoaminergic system and data obtained from studies in more recent years supports the suggestion that 4-FA functions as a substrate-type releasing agent of DA, NE and 5-HT and that it displays amphetamine-like features in a number of *in vivo* and *in vitro* assays. 4-FA induces locomotor activity in mice and is associated with DA release in rat striatum and rat nucleus accumbens.[70, 71] Drug discrimination studies performed in rats showed that 4-FA substituted for the 5-HT releaser fenfluramine[72] although this was not confirmed in rats trained to discriminate between the 5-HT releasing agents (+)-MBDB, 5-methoxy-6-methyl-2-aminoindan (MMAI) and saline. In this case, 4-FA fully mimicked (+)-amphetamine instead.[70] It has recently been shown that 4-FA differed from (+)-amphetamine in its ability to result in higher 5-HT dialysate concentrations. These levels were obtained from rat nucleus accumbens and correlated with diminished motor stimulant activity, which provided support for the hypothesis that 5-HT release might be able to dampen the stimulant effects of amphetamine-type substances that are mediated by DA.[71] Some user reports indicate that 4-FA might show pro-social effects in humans that might share some overlap with MDMA.[73, 74]

Table 2. 4-FA *in-vitro* uptake and release data

Uptake [a]			**Release** [b]			**Affinity** [c]			**Ref**
DAT IC_{50}/µM	NET IC_{50}/µM	SERT IC_{50}/µM	DAT	NET	SERT	DAT K_i/µM	NET K_i/µM	SERT K_i/µM	
--	--	ID_{50} = 10 [d]	4.10% [d]	1.16% [d]	2.98% [d]	--	--	--	Magyar and Knoll[75]
ID_{50} = 48.7 [d]	--	ID_{50} = 10 [d]	--	--	--	--	--	--	Magyar *et al.*[76]
0.270	0.356	2.352	--	--	--	--	--	--	Marona-Lewicka *et al.*[70]
--	--	--	EC_{50}/nM 51.5	EC_{50}/nM 28.0	EC_{50}/nM 939	--	--	--	Wee *et al.*[7]
0.77	0.42	6.8	EC_{50}/nM 200	EC_{50}/nM 37	EC_{50}/nM 730	--	--	--	Nagai *et al.*[77]
9.5	10.3	94.83	--	--	--	--	--	--	Rosenauer *et al.*[53]
3.7	0.2	19	Yes [e]	Yes [e]	Yes [e]	11.0	13.5	32.1	Rickli *et al.*[78]
Additional *in-vitro* data									
Receptor binding profiles [c]: K_i (µM): 5-HT_{1A} = 4.4; 5-HT_{2A} = 11.3; 5-HT_{2C} = 7.8; α_{1A} > 4.9; α_{2A} = 4.4; D_1 > 12; D_2 > 20; D_3 > 17; H_1 > 13; TA_{1rat} = 0.08; TA_{1mouse} = 0.32; TA_{1human} > 20; 5-HT_{2B} receptor activation: EC_{50}/µM = 11.4; activation efficacy = 49%. Comparison with MDMA: K_i (µM): 5-HT_{1A} = 12.2; 5-HT_{2A} = 5.9; 5-HT_{2C} > 13; α_{1A} > 6; α_{2A} = 15; D_1 > 12; D_2 = 25; D_3 > 17; H_1 > 13; TA_{1rat} = 0.37; TA_{1mouse} = 2.4; TA_{1human} = 14.6. [78] Cytotoxicity: None detected under conditions used. [f]									Rickli *et al.*[78]
Release studies in mice using radiolabeled cardiac norepinephrine showed that 4-FA cause dose-dependent release. At the 10 mg/kg level, observed release following amphetamine and *d*-methamphetamine administration was comparable. [g]									Benington and Morin [6]
Inhibition of monoamine oxidase (MAO): 40% inhibition at 1 mM. [h]									Beregi *et al.*[79]
Inhibition of phenethanolamine *N*-methyltransferase studied with pI_{50} = 3.01; comparison with tranylcypromine: pI_{50} = 4.05 [i]									Fuller *et al.*[80]
Binding to phenylalanyl-tRNA synthetase isolated from E. coli with K_i = 0.48 mM.									Santi *et al.*[81]
Investigation of MAO inhibition (MAOI) using rat brain mitochondria. I_{50} value for 4-FA = 16 µM compared to 1.9 µM for 4-chloroamphetamine. [j]									Fuller *et al.*[82]
Study with homologous initiating and non-initiating protein synthesis systems using rabbit reticulocyte lysates. 4-FA and amphetamine were observed to inhibit protein synthesis and aminoacylation under the conditions studied.									Nowak and Munro [83]
Investigation of MAOI using mitochondrial MAO obtained from whole rat brain homogenates. Fixed concentrations of 100 µM ^{14}C-5-HT (MAO-A) and ^{14}C-phenethylamine (MAO-B) were used as substrates. K_i/µM (4-FA) = 28 (MAO-A) and 240 (MAO-B), competitive inhibition. Comparison: K_i/µM (amphetamine) = 8.0 (MAO-A) and 475 (MAO-B).									Fuller *et al.*[84]
G-protein activation was not observed with 4-FA when using a [^{35}S]GTPγS binding assay.									Nonaka *et al.*[85]
In contrast to number cathinone derivatives, 4-FA and some other amphetamines, did not react with the tetrazolium-based WST-1 reagent when tested in the absence of SH-SY5Y neuroblastoma cells.									den Hollander *et al*[86]

[a] Ref [75]: Rat brain homogenates obtained from CFY Sprague-Dawley rats following synaptosomal preparation procedure published by Snyder and Coyle for uptake inhibition studies.[87] Concentrations of [^{3}H]5-HT, [^{3}H]DA and [^{3}H]NE were 0.1 nmol/mL. Ref [78]: HEK293-hDAT, HEK293-hNET, HEK293-hSERT; *N*-methyl-[^{3}H]-nisoxetine and indatraline (NET), [^{3}H]citalopram and indatraline (SERT), [^{3}H]WIN35,428 and indatraline (DAT). Ref [70]: whole brain minus cerebellum (male Sprague-Dawley rats) used for synaptosomal preparations; [^{3}H]5-HT, [^{3}H]DA and [^{3}H]NE (10 nM). Ref [53]: HEK293-hSERT, HEK293-hNET and HEK293-hDAT. Cells incubated with test compounds for 5 min before the tritiated substrates were added to incubation buffer: 0.03 µM [^{3}H]5 HT and 0.05 µM [^{3}H]MPP^+.

[b] Ref [7]: Synaptosomal preparations: rat caudate (for DA release) or whole brain minus cerebellum and caudate (for NE and 5-HT release); [^{3}H]MPP^+ as radioligand for DA and NE release, [^{3}H]5-HT for 5-HT release measurements. Ref [78]: 100 µM of test compound used. HEK293-hDAT, HEK293-hNET, HEK293-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT). Ref [77]: Synaptosomal preparations from male Sprague-Dawley rats: striatum for DA and cortex for 5-HT and NE; re-uptake assay initiated by addition of [^{3}H]DA (63 nM), [^{3}H]5-HT (125 nM), and [^{3}H]NE (125 nM); reaction mixture was incubated at 37 °C for 5 min; for release assays: synaptosomes pre-loaded with [^{3}H]DA, [^{3}H]5-HT, and [^{3}H]NE; release terminated after 5

min ([^{3}H]DA) and 30 min ([^{3}H]5-HT, and [^{3}H]NE).
[c] Ref [78]: [^{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 adrenergic receptor), [^{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). 5-HT_{2B} activation: HEK293-h5-HT_{2B} and FLIPR assay.
[d] Ref [75]: release from synaptosomes (rat cerebral cortex, hypothalamus and striatum) determined as a percentage value relative to control following the approach published by Ferris *et al.*[88] Methamphetamine values: [^{3}H]5-HT (5.23%), [^{3}H]DA (8.85%) and [^{3}H]NE (4.75%).
[e] Ref [78]: Monoamine release expressed as percent reduction of monoamine cell content compared with vehicle (0% = no release; 100% release all monoamines released from the cells). DAT: ~45%, NET: ~40%; SERT: ~50%. Essentially comparable with releasing activity of MDMA.
[f] ToxiLight BioAssay (4 h, 37 °C, incubation with 100 µM test drug).
[g] Ref [6]: Injected DL-norepinephrine-7-^{3}H retained by the heart tissue after drug treatment (tail vein injection of the male Swiss white mice); drugs administered subcutaneously after 1 h and mice were sacrificed after 3 h. At 10 mg/kg levels: 4-FA = 50%, amphetamine = 58% and *d*-methamphetamine = 57%.
[h] Ref [79]: Warburg's technique was employed using tyramine as the substrate. Incubation was for 1 h at pH 7 and 37 °C.
[i] Ref [80]: Enzyme source: homogenate of whole rabbit adrenals; norepinephrine (40 µM) as substrate and measurement of epinephrine formation; enzyme transfer of methyl group using *S*-adenosyl-L-methionine (SAM) as co-factor.
[j] Ref [82]: [^{14}C]Serotonin as substrate (100 µM); incubation with enzyme) for 20 min at 37 °C.

Table 3. 4-FA *in-vivo* assays

Behaviour	**Neurochemistry / physiological responses / etc.**	**Ref**
--	Toxicity studies in mice; see Section 5. In dogs and guinea pigs pressor activities were noted whereas depressing effects were observed in rabbits.	Suter and Weston[1]
	Toxicity data in mice, see Section 5; hypertensive effects equivalent to amphetamine; anorectic effects investigated in the rat at 5 mg/kg; locomotor effects in mice investigated at 10 mg/kg. [a]	Beregi *et al.*[4]
--	Anorectic dose (mg/kg): rat = 3.5; dog = 2.[b] Analgesia (mg/kg): mice = 10. [b] Anticonvulsant action (mg/kg): mice > 20. [b] Vasopressive action. Rat: increase at 0.25 and 0.5 mg/kg. [b]	Beregi *et al.*[79]
--	No significant impact on whole rat brain serotonin levels compared to saline. [c]	Fuller *et al.*[89]
Intraperitoneal administration of 5 mg/kg and 10 mg/kg 4-FA in rats trained by the Sidman avoidance conditioning procedure. At the 10 mg/kg dose, bar pressing was disrupted resulted in death within 6–20 h.	--	Beaton *et al.*[90]
--	Temporary reduction of whole rat brain serotonin and 5-hydroxyindoleacetic acid levels and tryptophan hydroxylase activity (up to 24 h) whereas 4-chloro and 4-bromoamphetamine caused reductions for up to a week. [d]	Fuller *et al.*[82] and Gál [91]
--	4-FA administration resulted in reduction of serotonin levels in brainstem and telencephalon when pre-treated with iprindole. No changes observed 24 h without pre-treatment. Two weeks later, reductions were observed in both tissue	Sherman *et al.*[92]

	extracts under both treatment conditions. [e]	
Unpublished data were mentioned that 4-FA did not show effects on the central nervous system. Details not reported.	Administration of 14 mg/kg (i.p.) resulted in a 11.1% increase of tryptophan levels in rat brain whereas serotonin and 5-hydroxyindoleacetic acid levels did not change significantly. In comparison, a 10 mg/kg dose of amphetamine led to an increase of 96% with respect to tryptophan. Similarly, serotonin and 5-hydroxyindoleacetic acid levels remained unchanged. [f]	Vial *et al*.[93]
--	Anorectic properties of 4-FA comparable to *d*-amphetamine (ED_{50} = 2.5 vs. 1.8 mg/kg) [g]	Beregi and Duhault[94]
--	4-FA administration (100 µmol/kg) failed to produce serotonin depletion in rat brain sections 3 days after administration. [h]	Harvey *et al*.[95]
--	Intracerebroventricular injection of 4-FA (200 µg) resulted in increased levels of serum corticosterone, which pointed toward a mechanism without serotonin involvement since serotonergic neurotoxin administration did not impact on elevation. Dexamethasone pre-treatment (4 mg/kg) 4 h before measurement prevented corticosterone elevation. [i]	McElroy *et al*.[96]
Drug discrimination: [j] Rats trained to discriminate fenfluramine (3 mg/kg) and saline. 4-FA (1.0–4.0 mg/kg) was found to substitute; 100% lever selection at 4 mg/kg.	--	McElroy and Feldman[72]
--	Tissue distribution following 4-[^{18}F]A administration (i.v.) in mice was detected after 5 min (% does/organ: liver > kidneys > lungs > small intestines > brain > spleen) followed by a rapid decline at the 30 min and 60 min mark. [k]	Shiue *et al*.[97]
Drug discrimination: [l] 4-FA displayed (+)-amphetamine-like discriminative stimulus effects; ED50: 0.23 mg/kg, 1.25 µmol/kg for training drug; 0.43 mg/kg, 2.11 µmol/kg for 4-FA; no substitution observed for (+)-MBDB and MMAI.	Microdialysis (rat striatum): [l] At 7 mg/kg (i.p.) of 4-FA, increase of extracellular DA levels (849%) 1 h after administration and non-significant decrease in DOPAC; when DA returned to baseline 3 h later, DOPAC and HVA concentrations still decreased. No effects of the 1.75 mg/kg dose. DA levels increases ~250% at 3.5 mg/kg (at 90 and 120 min post-injection). (+)-Amphetamine (2.0 mg/kg, i.p.) significantly increased dialysate DA levels from 30 to 120 min. DOPAC concentration not altered but HVA significantly decreased in DA dialysates at 1.5 h and 2 h following amphetamine injection.	Marona-Lewicka *et al*.[70]
Self-administration: [m] In rhesus monkeys, 4-FA functioned as a positive reinforcer under fixed-ratio (FR) 25 schedule (biphasic dose-response) and progressive-ratio (PR) conditions; reinforcing efficacy (PR schedule) lower than that of *d*-amphetamine. Potency (FR): 0.3 mg/kg; potency (PR): ED_{50} = 0.26 µmol/kg/injection; *d*-	--	Wee *et al*.[7]

amphetamine: ED_{50} = 0.04 µmol/kg/injection.		
Evaluation of anti-Parkinson effects: [n] 4-FA reported to significantly reduce haloperidol-induced catalepsy in rats. Conditioned place preference: [n] 4-FA did not induce behaviour associated with drug dependence.	--	Nagel and Schmidt[98, 99]
--	Cortical EEG and EMG: [o] 5 mg/kg (i.p.); wakefulness period: power spectral patterns revealed an increase in frequency range of 7.0−8.5 Hz and a decrease in that of 11.5−19.0 Hz for the first 7 h and decreased power spectra in the range 6.5−30.5 Hz for 8 h during non-REM sleep. 4-FA led to increased wakefulness for 7 h after administration; REM and non-REM sleep not detected in 2 h to 6 h following administration.	Uchiyama *et al.*[100]
Locomotor activity: [p] Dialysate DA correlated positively with ambulation and stereotypy whereas dialysate 5-HT correlated positively with stereotypy but not ambulation.	Microdialysis (rat nucleus accumbens): [p] Intravenous administration of 4-FA led to dose-related increases in dialysate: DA ~ 12-fold and 5-HT ~15-fold.	Baumann *et al.*[71]

[a] Ref [4]: male Sprague-Dawley rats; female NMRI mice.
[b] Ref [79]: Anorexia test. Rats: dose at which food intake was reduced by 50% for 2 h when drug administered orally one hour previously; dogs: oral minimum dose delaying food ingestion for 2 h. Analgesia (Haffner's method in mice): intraperitoneal dose which inhibits reflex of biting the artery clip placed on tail by 50%. Anticonvulsant action: oral dose, which protects 50% of mice from tonic extension; bucco-occipital electroshocks were given (7.5 to 30 V lasting 1 s). Vasopressive action: blood pressure variation in pithed rat in mm Hg following intravenous administration.
[c] Ref [89]: Total radioactivity in the brain of male white Harlan rats was measured 20 min after i.p. injection of 5 µmol DL-5-hydroxytryptophan-3-^{14}C/kg.
[d] Ref [82]: male albino Wistar-derived rats; drugs administered intraperitoneally; drug levels in whole brain determined by methyl orange assay; tryptophan hydroxylase activity in whole brain homogenates assayed spectrofluorometrically; monoamine oxidase inhibition also determined, see Table 2. Serotonin and 5-hydroxyindoleacetic acid levels in whole brain assayed spectrofluorometrically following derivatization.
[e] Ref [92]: Sprague-Dawley rats; intraventricular injection (600 µg) with and without iprindole (10 mg/kg, i.p. one hour before drug administration) treatment; cerebellum was removed to dissect into brainstem and telencephalon-cortical sections.
[f] Ref [93]: female Wistar rats; brain levels of tryptophan, serotonin and 5-hydroxyindoleacetic acid were determined following sacrifice after 60 min (amphetamine) and 90 min (4-FA), respectively.
[g] Ref [94]: male Long-Evans rats; inhibition of food consumption determined 2 h after oral administration of test drug. Values expressed as percentage of food consumed the preceding day.
[h] Ref [95]: Male albino rats (i.p. drug administration); brain sections B-7, B- and B-9 were isolated three days following administration and stained to determine abnormal staining and extent of neurotoxicity.
[i] Ref [96]: Male albino rats; trunk blood collected one hour after injection (i.c.v.); dexamethasone treatment (inhibition of pituitary ACTH secretion): 4-FA given 1 h before rats were sacrificed (i.p.) and either after dexamethasone (1 mg/kg i.p.) or 4 h after dexamethasone (4 mg/kg i.p.); chronic depletion of brain 5-HT induced by pre-treatment with *p*-chlorophenylalanine or 5,7-dihydroxytryptamine.
[j] Ref [72]: male albino rats.
[k] Ref [97]: Female CF-1 mice; lateral tail vein injection (0.3-1.5 mCi); tissues removed after 5, 30 and 60 min.
[l] Ref [70]: Male Sprague-Dawley rats; trained with (+)-amphetamine (1 mg/kg, 5.4 µmol/kg (i.p.), (+)-MBDB (1.75 mg/kg, 7.18 µmol/kg (i.p.), MMAI (1.71 mg/kg, µmol/kg (i.p.). Microdialysis: dialysate collected every 30 min (striatum); i.p. injections of 4-FA HCI at 1.75, 3.5, and 7.0 mg/kg followed by determination of dopamine, DOPAC, and HVA; dialysates collected 1.5 h before and extended 3 h after injection of 4-FA or (+)-amphetamine.
[m] Ref [7]: Seven male rhesus monkeys; FR schedule: baseline dose of cocaine = 0.03 mg/kg/injection; test drugs 0.003–1.0 mg/kg; PR schedule: baseline dose of cocaine maintaining maximum injections = 0.1 or 0.3 mg/kg/injection; test drug available at doses of 0.003–1.0 mg/kg. For FR schedule, mean dose that maintained responding at the peak of the biphasic curve was calculated for potency. For PR schedule, ED_{50} dose of dose-response function obtained in individual monkey and

averaged across monkeys for mean.
[n] Refs [98, 99]: Sprague-Dawley rats; several fluorinated amphetamines and MDMA were included in these investigations. 1-(3,4-Difluorophenyl)-*N*-ethylpropan-2-amine was chosen as a representative example and it was claimed that 4-FA, amongst others, gave similar results. Haloperidol (i.p.) was administered at 0.5 mg/kg; quantitative assessment of descent latencies (in seconds) included comparisons between haloperidol and test drug. Conditioned place preference: daily dose of test drug was 5 mg/kg following FDA protocols; further details were not provided.
[o] Ref [100]: Male Sprague-Dawley rats (10 weeks old); electromyogram (EMG) and electroencephalogram (EEG) recorded for 48 h (24 h after saline treatment and 24 h following i.p. drug administration of 5 mg/kg); Cortical EEG and EMG signals were amplified, filtered (EEG, 0.5−35 Hz; EMG, 16–128 Hz) and recorded using 'SleepSign' software.
[p] Ref [71]: Male Sprague-Dawley rats; microdialysis probe tips implanted in nucleus accumbens; locomotor activity: sensor ring lined with photobeams spaced 2.54 cm apart positioned in horizontal plane; activity monitored in 20 min bins, starting 60 min before intravenous drug injections and continuing for 120 min; ambulation and stereotypy quantified separately; ambulation is defined as the total distance travelled in the horizontal plane (measured in cm); rats received intravenous injection of 1 mg/kg of drug at time 0, followed by 3 mg/kg at 60 min and dialysate samples were analysed for 5-HT and DA.

B. Routes of administration and dosage

4-FA appears to be most commonly administered orally or by nasal insufflation (snorting) although the latter has also been associated with intense intranasal burning sensations and pain.[74, 101, 102] A recent survey of 4-FA users in the Netherlands revealed a range of dosage levels that may be encountered: 50–100 mg (44 participants, 17.6%), 100–150 mg (105 participants, 42.2%), more than 150 mg (48 participants, 19.2%, the remainder did not know).[74] Some anecdotal reports indicate that higher doses might also be used.[101, 103] Examples can be found in the patent literature where 4-FA was captured as a potential ingredient in pharmaceutical formulations.[98, 99, 104, 105]

C. Pharmacokinetics

Information collected from systematic studies in humans is lacking. 4-FA has been identified as one of several metabolites formed in male Sprague-Dawley rat brain in following subcutaneous and intracerebral of *para*-fluoro-deprenyl.[25] A transient, i.e. short-lasting, reduction of serotonin levels was observed in male albino Wistar rat brain homogenates after administration of a 0.1 mmol/kg dose. Based on the analysis of drug concentration levels within the first four hours, a half-life of 3.7 h was calculated for 4-FA which compared to about 1 h in the case of amphetamine in the rat brain.[82] Intravenous injection of 4-[^{18}F]A into female CF-1 mice revealed that uptake into brain tissue was detected after 5 minutes (% does/organ: liver > kidneys > lungs > small intestines > brain > spleen) followed by a rapid decline at the 30 min and 60 min mark.[97] Duration of effects obtained from self-reports of 4-FA users: less than 4 hours (57 participants, 22.9%), 4–6 hours (110 participants, 44.2%); 6–8 hours (54 participants, 21.7%) and more than 8 hours (28 participants, 11.2%).[74]

5. Toxicology

Oral administration (white female Cartworth mice): LD_0 = 15 mg/kg, LD_{50} = 25 mg/kg, LD_{100} = 50 mg/kg.[1] Intraperitoneal administration in mice: LD_{50} = 46.4 mg/kg[4, 106] and 46 mg/kg, respectively.[79] Oral administration (male CD Servier mice): LD_{50} = 150 mg/kg (comparison to *d*-amphetamine under identical conditions: 120 mg/kg).[94] A recently carried out cytolysis test that employed 4-FA did not lead to observations of cytotoxic

effects under the conditions studied (4 h incubation at 37°C, drug concentration 100 μM).[78] Data on the effects of 4-FA metabolites are not available.

6. Adverse reactions in humans

Tables 4 and 5 provide an overview of fatal and non-fatal intoxications obtained from the scientific literature and from reports received by EMCDDA. Case report data reported in the scientific literature that unambiguously confirm a causal relationship between adverse 4-FA and presence in biofluids are limited to a relatively low number of cases. In cases where this information is available (e.g.[38]), sympathomimetic features, typically encountered with some amphetamine-type stimulants, have been observed. A recent study carried out in the Netherlands,[74] which included a systematic survey of 4-FA users, who identified the main positive effect and the three most frequent adverse effects, confirmed that adverse effects of 4-FA were consistent psychomotor/entactogen stimulant profile (Table 6).

Table 4. Fatal case reports associated with α-PVP published in scientific literature.

Year	Cases	Patient/Age	Context/clinically related comments	Notes	Ref
2012	1	F/44	HIV-positive, 18 years history of drug dependence undergoing methadone treatment. Death considered due to high level of methadone in combination with 4-FA and amphetamine.	Whole blood analysis: 4-FA 0.58 mg/kg; amphetamine 0.30 mg/kg; diazepam 0.029 mg/kg; oxazepam 0.043 mg/kg, methadone 0.65 mg/kg.	Johansen *et al*.[33]
2013	1	Not reported	Not reported.	Detection of 4-FA in one post-mortem blood sample.	Rosano *et al*.[52]

Table 5. Non-fatal case reports associated with detection of 4-FA reported in the scientific literature.[a]

Year	Cases	Patient/ Age	Context/clinically related comments (examples)	Notes	Ref
2012	14	12 x M, 19-38; 2 x F, 17 and 21	Case history details not reported. Amphetamine also detected in most cases; whole blood 0.049 mg/kg – 0.70 mg/kg; in nine cases, additional drugs were detected, such as several benzodiazepines, tetrahydrocannabinol (THC), ketamine, 4-methylamphetamine and lidocaine.	One rape case and 13 DUID cases observed between 2009 – 2011. Whole 4-FA blood concentrations in DUID cases between 0.006 – 0.43 mg/kg (mean 0.087 mg/kg, median 0.021 mg/kg).	Johansen *et al*.[33]
2012	2	Not reported	Case 1: police traffic check and medical examination indicative of sympathomimetic drug use: pupils dilated and delayed contraction in response to light; fingertips trembling; Romberg test showed tremor and swaying; restless behavior. Case 2: symptoms associated with psychostimulants, such as slow pupil light reflex, tremor and restlessness.	DUID cases. 4-FA serum concentrations 350 ng/mL and 475 ng/mL.	Röhrich *et al*.[38]
2012	14	Not reported	Not reported.	4-FA was detected in 12 cases subjected to hair analysis.	Rust *et al*.[39]
2013	14	Not reported	Not reported. Urine drug screening of authentic samples obtained from 'addiction treatment clinics' during one year in Sweden.	In combination with 4-FMC (3), 3-FMC (1) and MDPV (1). Total number of urine samples: 1335.	Al-Saffar *et al*.[43]
2013	2	Not reported	Not reported. In 2010, 103 cases received from patients presenting at emergency departments across Sweden.	4-FA detection reported in 2 cases.	Helander *et al*.[45]
2013	5	Not reported	Not reported. Analysis of 1335 DUID cases.	4-FA detected in whole blood and considered below the legal limit.	Pedersen *et al*.[48]
2014	1	M, 18	Abrupt onset of nausea, vomiting, shortness of breath and chest tightness 5 h after drug consumption; received intramuscular naltrexone two days prior to admission as part of opioid addiction treatment program; fluoxetine and trazodone were also taken. 'Reverse takotsubo cardiomyopathy': cardiogenic shock developed requiring invasive management and life support. Acute cardiomyopathy caused by 4-FA catecholamine- induced myocarditis and/or small vessel myocardial ischemia was suggested. It has been suggested that the medication used during treatment might have contributed to triggering the Takotsubo syndrome.[107]	4-FA urine and serum levels 64,000 ng/mL and 118 ng/mL. Also detected in urine: naproxen, fluoxetine, trazodone, naltrexone, nicotine, and cotinine in urine; in serum: 4-FA, naproxen, trazodone, and cotinine.	Al-Abri *et al*.[56]
2015	1	M, 27	Patient with history of polysubstance dependence; agitated with non-sensible speech, diaphoresis, dilated pupils, and hyperreflexia without clonus. Vital signs included: heart rate 156 beats/min and rectal temperature 41.4 °C; treatment: dextrose (50 g, i.v.), midazolam (multiple boluses, i.v., 28 mg in total), and submerged in ice water.	Urine tests with EMIT positive for amphetamines and PCP; qualitative serum and urine analysis confirmed presence of 4-FA.	Laskowski *et al*.[66]

2015	1	M, 35	Routine traffic control; slow coordination, deficiency in concentration, washed-out pronunciation, agitation, restlessness, dry mouth, eyes reddened, and glassy, and pupil abnormalities (slow reaction to light, enlarged pupils). Orders had to be repeated multiple times and the man could not follow long sentences.	Blood sample taken 1 h and 55 min afterwards: THC 0.9 ng/mL; 11-OH-THC < 0.8 ng/mL; THC-COOH 6.8 ng/mL; 4-FA 90.0 ng mL.	Maas *et al.*[67]
2015	1	Not reported	Details not reported. 4-FA detected in one out of 34 irregular attendees of drug treatment centre.	4-FA detected.	Sundström *et al.*[69]
2015	4	Not reported	Tachycardia, headache, dizziness, restlessness, visual disturbances, tremors, agitation, tachypnea, confusion, nausea, vomiting, abdominal pain, dysphagia, neck pain, feeling of fainting.	Reported to the Dutch Poisons Information Centre in 2013.	Hondebrink *et al.*[64]
[a] The EMCDDA also received reports about positive identifications of 4-FA in biofluids although case level data are not reported, see Table 7.					

Table 6. Reported positive and adverse effects of 4-FA, adapted from Linsen *et al.*[a,74]

Effects	***n***	**%**	***95% CI***
Positive			
Stimulatory	145	58.2	51.4–64.3
Euphoria	69	27.9	22.1–33.3
Empathic	24	9.6	6.0–13.3
Sedative	11	4.3	1.1–5.6
Adverse			
Difficulty falling asleep	133	53.4	47.4–59.0
Dry mouth	109	43.8	37.4–50.2
Jaw tension/cramp	106	42.6	36.2–49.0
Elevated heartbeat	92	36.9	30.9–43.4
Sweating/high body temperature	83	33.3	27.7–39.4
Lowered mood in the days after use	49	19.7	14.9–24.5
Muscle weakness in days after use	46	18.5	13.7–23.3
Nausea	17	4.8	3.6–10.0
The drug had no effect	16	6.4	3.6–9.6
Tachycardia	29	11.6	8.0–15.7
Headache	21	8.4	5.2–12.4
Loss of memory (while intoxicated)	17	6.8	4.0–10.4
Unpleasant hallucinations	3	1.2	0.0–2.8
Difficulty breathing	2	0.8	0.0–2.0
Tolerance (higher dose needed after first use)	16	6.4	3.6–9.6
Other	6	2.4	1.0–4.6
[a] Multiple answers were possible for adverse effects; CI = confidence interval. Users of 4-FA have identified pro-social effects similar to MDMA, which was not associated with effects induced by amphetamine.			

7. Dependence potential

A. Animal Studies

As shown in Table 3, self-administration studies in rhesus monkeys indicated that 4-FA functioned as a positive reinforcer under fixed-ratio (FR) 25 schedule (biphasic dose-response) and progressive-ratio (PR) conditions. The reinforcing efficacy (PR schedule) was lower than that of *d*-amphetamine and it was hypothesized that the 5-HT releasing effects of 4-FA might have negatively

impacted on the potency as a reinforcer compared to *d*-amphetamine. Correspondingly, it was suggested that a DA/5-HT ratio might serve as a potential predictor. Taking into account the EC_{50} values obtained from rat brain synaptosome release assays, the DA/5-HT ratio obtained for 4-FA was 0.05 compared to 0.004 for *d*-amphetamine, which reflected the higher 5-HT releasing potency of 4-FA.[7] An example was found in the patent literature where it was claimed that 4-FA did not display signs of dependence potential based on experiments that assessed conditioned place preference (Sprague-Dawley rats).[98, 99] Further work seems warranted to determine the extend of dependence potential in animals.

B. Human Studies

Data from clinical studies in humans are not available.

8. Abuse potential

A. Animal Studies

As shown in Table 3 and Section 4A, limited information is available. From the available data it appears that 4-FA shows classic features associated with psychomotor stimulants such as amphetamine. Further studies seem warranted to clarify the similarities and differences that exist between 4-FA and amphetamine and other amphetamine-type substances.

B. Human Studies

Data from clinical studies in humans are not available.

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

Not applicable.

10. Listing on the WHO Model List of Essential Medicines

4-FA is not listed.

11. Marketing authorizations (as a medicinal product)

4-FA was never marketed as a medicinal product.

12. Industrial use

4-FA has no recorded industrial use.

13. Non-medical use, abuse and dependence

Use of 4-FA appears to be limited to recreational substance users rather than the general population. The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Dependence-producing properties in humans have not been studied. The appearance of 4-FA in Europe has been observed since at least 2007.

Over the years, it has been found in products sold as 'ecstasy'/MDMA tablets, amphetamine powder but also as adulterants present in other illicit controlled substances.[64, 73, 74, 102, 108-110]

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

Surveys that systematically assess the prevalence of use 4-FA within the general population are not available. Research carried out in the Netherlands suggest that 4-FA, which originally appeared as one of many new psychoactive substances (NPS) (e.g. as an adulterant or as an alternative to reduced availability of substances such as MDMA) has established itself as a substance of choice in a subpopulation of recreational substance users, especially those who might prefer using this substance in a social context.[64, 74] However, further studies seem indicated to investigate the prevalence of use in more detail.

15. Licit production, consumption and international trade

In countries where 4-FA is not subject to legislative control, marketing efforts might include advertisement and sale as a 'research chemical'. Information about agricultural, cosmetic or industrial use of 4-FA is not available.

16. Illicit manufacture and traffic and related information

Information provided to Europol and EMCDDA by European Member States, Turkey and Norway is summarized in Table 7.

Table 7. Information available on the EMCDDA's European database on new drugs (EDND). 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, provided data. [a]

Information provided to EMCDDA

Seizures 2008:

- Belgium – 2 seizures of powder.
- Denmark – 2 seizures; 1 sample seized (4 g) containing 1% amphetamine.
- Netherlands – 4 collected samples of powder; 1 collected sample of capsule; 1 collected sample of liquid; 3 seizures totalizing 212 g of powder and 1 seizure of liquid containing also 2C-B and BZP.

Seizures 2009 (January – June) plus update from 9th Annual EWS meeting, 4-5 June 2009, Lisbon (A. Gallegos and R. Sedefov):

- Austria – 2 seizures of powder totaling 707 g and 4 collected samples of powder.
- Belgium – 6 seizures of 33.9 g powder; 1 seizure of 49.79 g of paste/sticky powder and 1 seizure of tablets.
- Croatia: 4 seizure of white powder also containing amphetamine traces, caffeine, mannitol and creatine.
- Denmark – 5 seizures; one seizure of 4 g white powder that also contained 1% amphetamine.
- Estonia – 1 seizure of 0.32 g powder.
- Finland – 1 seizure of 12 tablets (Forensic Laboratory) and 2 seizures of powder/capsule, 5g/3units (Customs)
- France – 8 seizures of powder, 3115 g
- Germany – seizure between November 2008 and June 2009: in one case, 60 kg of amphetamine were seized, 14 of which were a mixture of amphetamine and 4-FA; two seizures of a 'few grams' of powder and one seizure of 1 kg.
- Hungary – 2 seizures of powder, 2.5 g (powder in 36 capsules); 1 collected sample of 638.2 g powder; 4 seizures of 211 tablets (from 2008), one seizure of 700 g homogenous powder.
- Netherlands – From DIMS: 60 collected samples of powder, 6 collected samples of tablets and 1 collected sample of liquid; from NFI: 1 seizure of powder > 340 kg; 98 seizures of powder, > 100 kg, 98 seizures of powder > 100 kg in combination with amphetamine.
- Slovakia – 1 seizure of 16 mg powder.
- Sweden – 105 seizures of 6174 g powder; 7 seizures of 21 mL liquid; 24 biological samples of urine; 71

biological samples of blood and 57 seizures of 1460.4 g powder.

- United Kingdom – 2 seizures of 0.9 mL liquid; 102 seizures (93 kg powder); 4 seizures (6.67 kg powder); 6 seizures of paste (6.355 kg); 1 seizure of 300 g powder; 1 seizure of 7.627 kg paste containing also amphetamine. UK National Focal Point also reported a seizure of 371 mg of a pale pink powder in Guernsey.

Seizures 2010:

- Belgium – 1 seizure of 112.5 tablets containing also caffeine and piperonal; 1 seizure of 3.18 g powder containing also caffeine and amphetamine; 3 biological samples of urine.
- Denmark – 13 seizures.
- Finland – 3 seizures of 5g powder; 1 biological sample of blood; 13 seizures of 46 g powder and 1 seizure of 2 tablets (last two, both reported as 3-FA or 4-FA).
- France – 4 seizures of 340 g liquid; 7 seizures of tablets.
- Hungary –10 seizures of 35 g powder and 7 seizures of 14 tablets (reported as fluoramphetamine).
- Netherlands – 13 seizures: 2775 tablets and 65 g powder (from NFI).
- Norway – 8 seizures of 106 g powder.
- Poland – 1 seizure of 10 capsules; 1 seizure of 550 tablets containing piperonal and caffeine.
- Slovenia – 5 seizures of 9.21 g white powder, most of the samples containing caffeine.
- United Kingdom – From a variety of forensic providers. Key Forensics: 3 seizures of powder, 157.7 g; 1 seizure of powder, 23.5 g in an amphetamine sample. From LGC Forensics: 6 seizures of powder, 136.3 g; 13 seizures of powder, 520 g. From FSNI: 1 seizure of 16.76 g powder containing traces of mephedrone; 1 seizure of 102 g white powder. From FSS: 3 seizures of liquid, 1.6 mL; 152 seizures of powder, 46.4 kg; 1 seizure of 5 tablets. From Scotland: 9 seizures of powder, 529.5 g.From Key Scientifics: 3 seizures of powder, 14.46 g; 1 seizure of 2 tablets, 0.46 g; 3 seizures of powder, 5.73 g.

Seizures 2011:

- Austria –1 seizure of 9.4 g of powder.
- Bulgaria – 3 seizures of 5.60 g of powder
- Denmark – 5 (19)* seizures of 442.2 g of powder (*The number in brackets is the total number of individual exhibits in all seizures).
- Finland – 38 seizures of 198 g of powder; 4 seizures of 20 tablets/blotters; 7 seizures of 82 g of powder; 2 biological samples of blood (all reported as 2-, 3- or 4-FA).
- France – 17 seizures of tablets.
- Hungary – 18 seizures of 15 g of powder, 60 seizures of 3235 tablets; 27 seizures of 26 g powder also containing amphetamine; 1 seizure of 3 tablets also containing 2C-D; 462 biological samples.
- Italy – 1 seizure of 1.18 g of tablets; 2 seizures of powder (one seizure also contained MDPV, 4-MEC, lidocaine or procaine and the other also contained mephedrone and MDPV, lidocaine and propanamide were also identified).
- Netherlands – 7 seizures of 279 tablets and 16 g powder (from NFI); 61 collected samples of powder (from DIMS); 9 collected samples of tablets (from DIMS); 3 collected samples of liquid (from DIMS); 1 collected sample of capsules (from DIMS).
- Norway – 3 seizures of 517 g of powder.
- Spain – 1 seizure of powder.
- United Kingdom – From FSNI: 1 seizure of 2.05g of powder; from FSS: 13 seizures of 400.1 g powder.

Seizures 2012:

- Austria – 1 seized powder sample.
- Belgium – 1 kg white powder seized by customs at airport, package sent from China.
- Denmark – 3 cases of seized powder, 9.5 g.
- Spain – Seizure of 7760 tablets and 15 tablets where 4-FA was present in combination with other substances; seizure of 210 g powder.
- Finland – Customs seizures of 243.8 g powder (53 cases), 18 tablets/blotter and 28.8 g 'other'. Police seizure of 28 g powder and 10 cases of biological analyses with positive identification. Note: not clear what positional isomer might have been identified.
- France – seizures of tablets (5 cases) and two liquids (customs); police seizure of 100 tablets.

- Hungary – seizures of 421 tablets (13 cases), 2 g powder (2 cases); presence of additional substances: 7 g of powder (4-FA + amphetamine, 4 cases), 38 g of powder (4-FA + MDPV, 1 case), 33 tablets (4-FA + methoxetamine, 1 case), 30 tablets (4-FA + 4-MEC + methylone, 1 case); 43 samples of biological origin tested positive for 4-FA but details not reported.
- Netherlands – seizure of 1060.2 g (27 cases), 7 tablets and 11 tablets (4-FA + PMMA + 3,4-dimethoxymethamphetamine).
- Norway – seizure of materials in three cases and positive identification in one biofluids sample.
- Poland: 1 g powder and 2.99 g powder also containing amphetamine and caffeine.
- Slovakia – seizure of 367 g powder (see also Reitox National Focal Point Slovakia, below).
- Slovenia – 1 powdered sample (1.3 g).
- United Kingdom – Seizures of 1010 g powder (18 cases), 1488.57 mL liquid (3 cases), 1 tablet and 1 'other' (6.34 g).

Seizures 2013:

- Denmark – 2 cases of collected powder (1.9 g)
- Finland – Powder (141.6 g, 34 cases); positional isomer not specified.
- France – seizure of tablets (6378 g, 37 cases), liquid (9312 g, 40 cases), and 97 g powder (8 cases).
- Greece – seizure of 2.4 g powder
- Italy – seizure of 1.69 g powder containing 4-FA + 4-MEC + methedrone (bk-PMMA) + methylone + 5-MeO-MIPT + 5-MeO-DALT.
- Latvia – seizure of 49.42 g powder
- Poland – seizure of 796.66 g powder (64 cases)
- Spain – 50 g powder (12 cases) and 11 g powder (18 cases) containing additional substances.

Information provided to Europol

Seizures 2009 (January – June) plus update from 9th Annual EWS meeting, 4-5 June 2009, Lisbon (A. Gallegos and R. Sedefov) and newsletter related to Europol's SYNERGY project[111]

- Sweden: Two seizures of 700 g and 340 g.
- Netherlands: found at two illegal amphetamine laboratories.
- From SYNERGY newsletter: 'A total of 19 member states had replied to Europol's request for information, with four member states (Finland, Germany, the Netherlands and the United Kingdom) reporting seizures of the substance, both in powder and tablet form. Additionally, insofar not yet officially provided, the Slovak Republic has also forensically identified this substance amongst submitted seizures. Equally, reports submitted to the EMCDDA from the NFP's reveal that seizures of this substance have taken place in Belgium, Croatia, Denmark, Estonia, France and Hungary.'

  'In fact, the Dutch National Crime Squad reported that this substance was increasingly emerging on the national users market. Also, two production sites had been dismantled, with one in January 2009 where both this substance and its precursor chemical were seized; the other took place in February 2009, where traces of both this substance and amphetamine were found. Besides, one additional seizure totalling 169 kg of the substance was made in January 2009.'

Reitox National Focal Point Slovakia

- Rented premises were used for 4-FA manufacturing, packing and distribution. Mixing equipment and facilities for pills processing were encountered, including 367 g powdered 4-FA.

[a] Some of the data reported to Europol and EMCDDA may overlap. Data were drawn from bi-annual data gathering (EU EWS progress and final reports) and from individual Reporting forms submitted on an *ad hoc* basis to EMCCDA. Positive identifications of 4-FA in various biofluids have also been reported but further are not available.

17. Current international controls and their impact

Not applicable in terms of medical use.

18. Current and past national controls

The EMCDDA's European database on new drugs (EDND) lists that the following countries have taken legislative measures to control 4-FA: Belgium, Czech Republic,

Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden, Turkey, United Kingdom. 4-FA is not a controlled Substance in Greece. Confirmation from all Reitox National Focal Points, however, might be needed to obtain an update.

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

Not applicable.

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