



European Monitoring Centre
for Drugs and Drug Addiction

DRAFT

**Technical report on *N*-(4-fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide
(4-fluoroisobutyrylfentanyl; 4F-iBF)**

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The *Risk assessment report on a new psychoactive substance: N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide (4-fluoroisobutyrylfentanyl; 4F-iBF)* to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

3 November 2017

Annex 1 to the *Risk Assessment Report on N-(4-fluorophenyl)-N-(1-phenethylpiperidin-4-yl)isobutyramide (4-fluoroisobutyrylfentanyl; 4F-iBF)*

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Introduction

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ⁽¹⁾ on 25 April 2017, the EMCDDA and Europol launched the Joint Report procedure for *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl) on the basis of data reported by the Member States to the European Union Early Warning System in accordance with Article 4 of the Council Decision. The information collection process for the Joint Report was completed in June 2017. The report was submitted to the Institutions of the European Union in July 2017 (EMCDDA, 2017a). In accordance with Article 6 of the Council Decision, on 14 September 2017, the Council of the European Union requested that a risk assessment on 4-fluoroisobutyrylfentanyl should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for a risk assessment, and, to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as well as drafting a technical report. This technical report has been prepared for the risk assessment of 4-fluoroisobutyrylfentanyl that will be held at the EMCDDA premises in Lisbon on Wednesday 8 November 2017.

Some of the sections in this report were prepared under EMCDDA contracts (ref. CT.17.SAT.0084.1.0 and CT.17.SAT.0110.1.0).

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with the Council Decision (EMCDDA, 2017a); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, Internet drug discussion forums and related websites, and online vendors selling 4-fluoroisobutyrylfentanyl.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in October 2017. The retrieved publications were then reviewed for additional relevant references (snowballing technique).

Chemical structure-based searches were done in SciFinder[®] (American Chemical Society, Chemical Abstract Service) and Reaxys[®] (Elsevier) databases using both the exact structure of 4-

⁽¹⁾ OJ L 127, 20.5.2005, p. 32.

fluoroisobutyrylfentanyl and a similarity search. Structural and text-based searches in the SureChEMBL patent database retrieved only one, though irrelevant, hit ⁽²⁾.

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), Web of Science™ (Thomson Reuters), and in popular English-language drug forums. The search terms used were: '4-fluoroisobutyrylfentanyl', '4-fluoro-isobutyrylfentanyl', '4-fluoro-isobutyrfentanyl', '4-fluoro-isobutyrylfentanyl', '*para*-fluoroisobutyrylfentanyl', 4-F-iBF, 4-FiBF, 4-FIBF, FIBF, p-FIBF and p-FiBF.

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry numbers listed below. The searches returned no hits.

Cursory, though repeated, inspections of English-language Internet forums covered Bluelight, Drugs-forum, ecstasydata.org, Erowid, Eve&Rave, Reddit and The Vespiary.

Additionally, the scientific networks of the authors were contacted to obtain information.

Note

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, the actual composition of the substance/product may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of 4F-iBF and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Reported prepared by

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Acknowledgements

The EMCDDA would like to extend their sincere thanks and appreciation to: the Early Warning System (EWS) correspondents of the Reitox national focal points and experts from their national early warning system networks; the Europol national units and Europol Project Synergy; and, Dr István Ujváry, iKem BT, Budapest, Hungary for reviewing some of the sections of this report.

⁽²⁾ A recent US patent mentions '*p*-fluoroisobutyrylfentanyl' as one of the opioids against which a novel nasal naloxone spray formulation can be applied (Keegan et al., 2017).

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Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

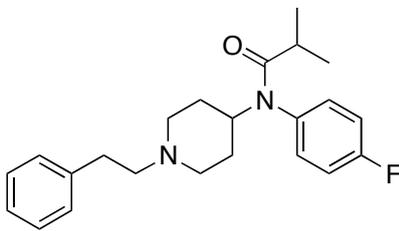
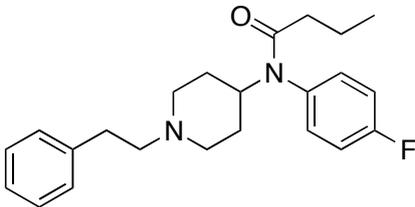
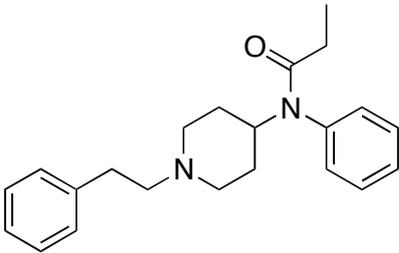
Chemical description and names

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (4-fluoroisobutyrylfentanyl) is structurally related to fentanyl, which is a fast and short-acting synthetic opioid that has been widely used in clinical practice as an adjunct to general anaesthesia during surgery and for postoperative pain management. 4-Fluoroisobutyrylfentanyl contains one basic nitrogen atom in the piperidine ring readily forming salts with organic or inorganic acids.

4-Fluoroisobutyrylfentanyl is also structurally related to acetylfentanyl, acrylylfentanyl, and furanylfentanyl, which were the subjects of EMCDDA–Europol Joint Reports submitted in December 2015, November 2016 and January 2017, respectively, following reports of deaths in Europe (EMCDDA, 2016a; EMCDDA, 2017b; EMCDDA, 2017c). In February 2017 and May 2017, risk assessment meetings on acrylylfentanyl (EMCDDA, 2017d) and furanylfentanyl (EMCDDA, 2017e) were convened under the auspices of the Scientific Committee of the EMCDDA following the request by the Council of the European Union. On 25 September 2017, the Council of the European Union decided that acrylylfentanyl should be subjected to control measures across the European Union (CEU, 2017).

4-Fluoroisobutyrylfentanyl differs from fentanyl by the presence of a fluorine atom on the anilido phenyl ring and the presence of an isobutyramide group in place of the propanamide group. 4-Fluoroisobutyrylfentanyl is the positional isomer of 4-fluorobutyrylfentanyl (4F-BF) and thus both substances are structurally very closely related, which results in the same molecular formula and molecular mass. The molecular structure, molecular formula, and molecular mass of 4-fluoroisobutyrylfentanyl are provided in Figure 1.

The first reference to 4-fluoroisobutyrylfentanyl in the scientific literature appears to have been in a paper published in 1999, wherein the synthesis of the substance and analytical discrimination from fentanyl was reported (Ohta, 1999).

4-fluoroisobutyrylfentanyl	4-fluorobutyrylfentanyl	Fentanyl
		
C ₂₃ H ₂₉ FN ₂ O	C ₂₃ H ₂₉ FN ₂ O	C ₂₂ H ₂₈ N ₂ O
368.50 g/mol	368.50 g/mol	336.48 g/mol
Figure 1. The molecular structure, molecular formula and molecular mass of 4-fluoroisobutyrylfentanyl (left), 4-fluorobutyrylfentanyl (middle) and fentanyl (right).		

Fifteen fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol: 3-methylfentanyl, 3-methylthiofentanyl, acetyl-alpha-methylfentanyl, acetylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl and thiofentanyl, are controlled under Schedule I and IV; alfentanil, butyrfentanyl, fentanyl, remifentanil and sufentanil are controlled under Schedule I. The controls on acetylfentanyl and butyrfentanyl entered into force in 2016 and 2017, respectively.

Names and other identifiers

Systematic International Union of Pure and Applied Chemistry (IUPAC) name:

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide

Chemical Abstract name:

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide

Other names:

N-(4-Fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide;

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]propanamide;

N-(4-Fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidyl]propanamide;

N-(4-Fluorophenyl)-*N*-(1-phenethyl-4-piperidinyl)isobutyramide;

N-(4-Fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl) isobutyramide

Chemical Abstract Service Registry Numbers (CAS RNs) ⁽⁶⁾

244195-32-2.

PubChem SID:

Could not be identified ⁽⁷⁾.

IUPAC International Chemical Identifier Key (InChI Key)⁽⁸⁾: OZDOSQNUJIXEOR-UHFFFAOYSA-N

SMILES ⁽⁹⁾: CC(C)C(=O)N(C1CCN(CC1)CCC2=CC=CC=C2)C3=CC=C(F)C=C3

⁽⁶⁾ The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.

⁽⁷⁾ As of 21.10.2017

⁽⁸⁾ InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

Common names:

4-fluoroisobutyrylfentanyl, 4-fluoro-isobutyrylfentanyl, 4-fluoro-isobutyrfentanyl, para-fluoroisobutyrylfentanyl, 4-F-iBF, 4-FiBF, 4-FIBF, FIBF, p-FIBF, p-FiBF.

Street names:

The street names for 4-fluoroisobutyrylfentanyl may include the common names.

Identification and analytical profile

Physical description

4-Fluoroisobutyrylfentanyl hydrochloride has been described as a neat solid (Cayman Chemical Company, 2017) and as a white powder (base) (SWGDRUG, 2016). Due to its similarity to fentanyl, the free base could be expected to be sparingly soluble in water; the hydrochloride and citrate salt could be expected to have greater aqueous solubility. 4-Fluoroisobutyrylfentanyl is expected to be lipophilic. This substance has been seized as a powder, in tablet form, and as a liquid. A more detailed description of seizures and collected samples can be found in Section C.

Chemical stability and typical reactions

Specific information about 4-fluoroisobutyrylfentanyl could not be identified. For long-term storage it is recommended that 4-fluoroisobutyrylfentanyl, supplied as a solid, is stored at -20 °C (Cayman Chemical Company, 2017)

Analytical profile

As summarized in Table 1, some analytical data have been published.

It is possible that immunoassays for fentanyl may not distinguish between 4-fluoroisobutyrylfentanyl and fentanyl due to the structural similarity between the two substances. Identification of 4-fluoroisobutyrylfentanyl therefore would require further confirmatory analysis using more suitable detection techniques based on, for example, (tandem) mass spectrometry (Helander et al., 2017). Similarly, 4-fluoroisobutyrylfentanyl is not expected to give a positive response to tests developed for morphine-type opioids. An analytical challenge might arise from the number of potential positional isomers that could exist as a result of the presence of the fluorine atom. For example, three fluorophenyl and three fluorophenylethyl isomers (2F-, 3F-, 4F-) can exist when just considering the two phenyl rings present in the molecule. These six isomers could also apply to the 4-fluorobutyrylfentanyl counterparts, thus, potentially giving rise to twelve isomers. Information about the detection of isomers other than 4-fluoroisobutyrylfentanyl could not be identified. The availability of standard reference material is recommended in order to facilitate their differentiation.

Analytical difficulty arises due to the isobaric nature and very similar fragmentation patterns of 4-fluoroisobutyrylfentanyl and 4-fluorobutyrylfentanyl. Forensic laboratories, being aware of this, often

⁽⁹⁾ The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

report results as '4-fluoroisobutyrylfentanyl/4-fluorobutyrylfentanyl' for samples where the isobaric substances were not, or could not be, separated.

Table 1. Information associated with the detection and chemical analysis of 4-fluoroisobutyrylfentanyl (amongst other substances). ^a		
Techniques ^b	Comment	Reference
TLC, GC-FID, direct inlet EI-MS, IR	Synthesis and analytical characterisation.	Ohta et al. (1999)
¹ H-NMR, GC-MS, FTIR-ATR	Analytical characterisation of reference material.	SWGDRUG (2016)
GC-MS	Analytical characterisation of reference material.	Cayman Chemical Company (2017)
GC-MS, LC-MS/MS	Blood analysis of 'overdose' cases.	DeRienz et al. (2017)
LC-MS(/MS)	Analysis of serum and urine sample obtained from an intoxication case in September 2016.	Helander et al. (2017)
LC-MS/MS	Method validation and application to analysis of postmortem biological sample material.	Kahl et al. (2017)
GC-MS	Retrospective analysis of GC-MS results obtained from blood samples.	Newmeyer et al. (2017)
GC-MS, GC-NPD	Detection in blood sample.	Poston et al. (2017)
GC-MS, GC-FTIR (condensed phase)	Analytical characterisation of reference material.	Slovenian National Forensic Laboratory (2017)
GC-MS	Analysis of drug paraphernalia (spoon residue) found at the site of fatal intoxication. ^c	Swanson et al. (2017)
LC-MS/MS	Analysis of postmortem and human performance toxicology casework	Turri et al. (2017)
LC-MS(/MS)	In vitro metabolism using pooled human hepatocytes and analysis of authentic human urine samples.	Watanabe et al. (2017)
GC-MS, LC-MS	Analysis of drug paraphernalia (spoon residue) and analysis of postmortem blood specimen.	Zaney et al. (2017)
^a As of 21 October 2017. ^b TLC: Thin-layer chromatography; GC: gas chromatography; FID: flame ionization detection; EI: electron ionization; MS: mass spectrometry; IR: infrared spectroscopy; NMR: nuclear magnetic resonance spectroscopy; FT: Fourier transform; ATR: attenuated total reflectance; LC: liquid chromatography; MS/MS: tandem MS; NPD: nitrogen phosphorus detector;		

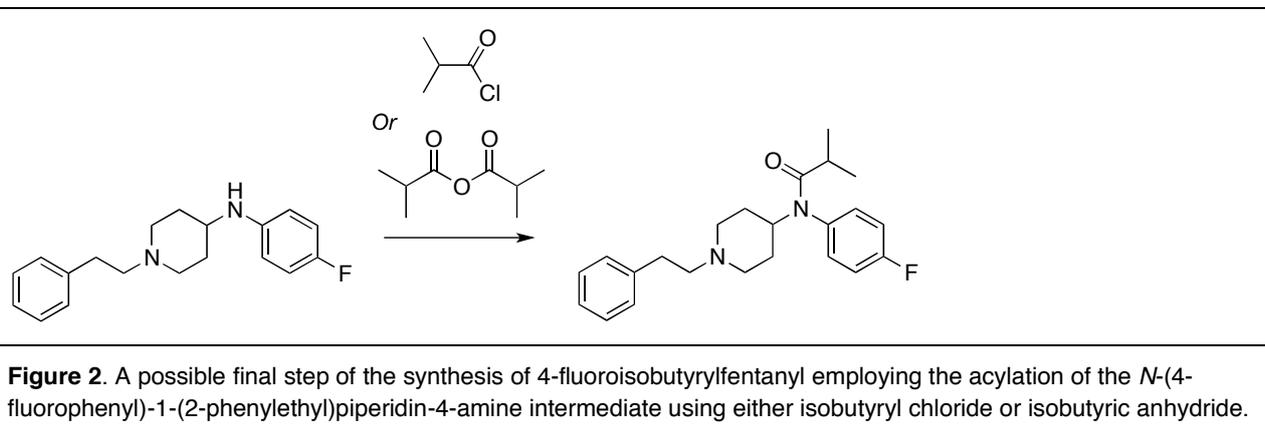
^c Identification based on mass spectral library comparison only.

Methods and chemical precursors used for the manufacture

No information was reported by the Member States, Turkey, or Norway, about the chemical precursors or manufacturing methods used to make the 4-fluoroisobutyrylfentanyl that has been detected within Europe.

Synthesis

A synthesis procedure for 4-fluoroisobutyrylfentanyl could not be identified in the published literature but it seems likely that its synthesis relies on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl and other fentanyl analogues. Accordingly, methods adapted for the multistep synthesis of fentanyl are applicable to 4-fluoroisobutyrylfentanyl whereby the final reaction step is expected to apply the acylation of the *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine intermediate, a precursor analogous to the *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) intermediate involved in the preparation of fentanyl and many of its analogues (Figure 2) ⁽¹⁰⁾.



Most of these synthetic procedures are relatively straightforward. Due to the typical high potency of fentanils there is a risk of severe poisoning following accidental exposure during their manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substances. Likewise, accidental exposure to the fentanils could pose a risk of poisoning to the public, law enforcement, emergency personnel, as well as medical and forensic laboratory personnel. In addition to exercising extreme caution when handling materials suspected to contain fentanils, personnel should be equipped with appropriate protective equipment. The antidote naloxone should be readily available to personnel in sufficient quantities; training in resuscitation, including the administration of naloxone, should also be available (IAB, 2017 US CDC, 2013; US CDC, 2016; US DEA, 2017a). Any required responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

⁽¹⁰⁾ Methods not relying on the controlled precursor NPP for the synthesis of 4-fluoroisobutyrylfentanyl are possible. For example, alkylation of *N*-(4-fluorophenyl)-2-methyl-*N*-(piperidin-4-yl)propanamide by phenethyl chloride would afford the title product.

In contrast to the 4-ANPP and its precursor *N*-phenethyl-4-piperidone (NPP), which were scheduled in 2017 and are listed in Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (CND, 2017; INCB, 2017), the fluorinated analogue of 4-ANPP used for the preparation of 4-fluoroisobutyrylfentanyl is not an internationally controlled substance.

Typical impurities encountered in seized and collected samples

There are no quantitative data available on the impurities detected in seized and collected samples reported to the EMCDDA (Section C). A potentially detectable impurity might be predicted to include the *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine intermediate .

A1.2. Physical/pharmaceutical form

Data from seizures and collected samples reported to the EMCDDA have noted that 4-fluoroisobutyrylfentanyl has typically been detected in powders, tablets and liquids (Section C).

A1.3. Route of administration and dosage

As with other fentanils, 4-fluoroisobutyrylfentanyl can be administered orally as a powder (including in capsules), as tablets, or as a solution (using nasal sprays) or by insufflation of a powder; it can also be administered intranasally or sublingually via a spray; inhaled by smoking or vaporizing; and, administered by injection (intravenous and intramuscular). There are also instances where 4-fluoroisobutyrylfentanyl is advertised for sale in the form of blotters by Internet vendors. Users have also described rectal administrations (¹¹).

Of note is the apparent popularity of selling ready-to-use or homemade nasal sprays containing solutions for the administration of fentanils. It is worth noting that some of these products are not always labelled and/or sold as another substance, a phenomenon that extends to the use of other fentanils that have appeared in Europe in the past few years, including acryloylfentanyl (EMCDDA 2017b; EMCDDA 2017d; Ujváry et al., 2017) and furanylfentanyl (EMCDDA, 2017c; EMCDDA, 2017e).

Dosage

Limited information is available regarding the dose and the dose regimens of 4-fluoroisobutyrylfentanyl. Reports available on user discussion forums included single intravenous administrations up to 5 mg followed by nasal spray administrations reportedly amounting to 3 mg over a six-hour period (¹²). Other examples included nasal administrations of 5 mg per day (¹³); “dosing every 2-3 hours (0.7 mg/mL)... up to about 0.35 mg IV” (¹¹); 0.1–0.5 ml intravenous injections of 0.69 mg/mL solutions and 2 mL rectal administrations using the same concentration (¹¹); self-prepared nasal spray concentrations of 10–15 mg/mL have also been mentioned (¹⁴).

(¹¹) [http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-\(4-FiBF-p-FiBF\)/page2](http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-(4-FiBF-p-FiBF)/page2) (last accessed: 22.10.2017).

(¹²) https://erowid.org/experiences/exp_pdf.php?ID=106906&format=pdf (last accessed 21.10.2017).

(¹³) [http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-\(4-FiBF-p-FiBF\)](http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-(4-FiBF-p-FiBF)) (last accessed 21.10.2017).

(¹⁴) https://www.reddit.com/r/opiates/comments/3ved25/anybody_try_furanylfentanyl_fuf_or/ (last accessed 21.10.2017).

From this, however, it is not possible to discern the 'typical' dosages administered by users. Doses appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Pharmacologically, 4-fluoroisobutyrylfentanyl is an opioid receptor agonist.

Pharmacodynamics

In vitro studies

The currently available data suggests that 4-fluoroisobutyrylfentanyl binds to the μ -opioid receptor (MOR) with high selectivity over the κ - and δ -opioid receptors (KOR and DOR) (Table 2) ⁽¹⁵⁾ (US DEA, 2017b).

Table 2 provides a summary of binding and functional activity data that illustrate that 4-fluoroisobutyrylfentanyl ($EC_{50} = 115$ nM, [³⁵S]GTP γ S binding assay, $E_{max} = 91.6\%$) functioned as a MOR agonist ⁽¹⁶⁾. In comparison, morphine ($EC_{50} = 17.2$ nM, [³⁵S]GTP γ S binding assay, $E_{max} = 86.1\%$) and fentanyl ($EC_{50} = 28.8$ nM, $E_{max} = 94.0\%$) were several times more potent than 4-fluoroisobutyrylfentanyl and all three test drugs exhibited comparable efficacy (E_{max}) using this particular *in vitro* assay.

4-Fluoroisobutyrylfentanyl showed relatively low affinity toward KOR ($K_i = 2,700$ nM) with moderate to low potency and moderate relative efficacy ($EC_{50} = 1,330$ nM, [³⁵S]GTP γ S binding assay, $E_{max} = 49.3\%$). As far as DOR was concerned, binding affinity and potency were relatively low, whereas efficacy was moderate ($K_i = 1,670$ nM, $EC_{50} = 2,490$ nM, [³⁵S]GTP γ S binding assay, $E_{max} = 64\%$), which suggested a MOR selective profile, at least under these *in vitro* conditions. All test drugs used as positive control were shown to be efficacious agonists (Table 2).

Table 2. Binding and functional activity data for 4-fluoroisobutyrylfentanyl (4F-iBF) generated via the Drug Enforcement Administration–Veterans Affairs (DEA-VA) Interagency Agreement (modified from US DEA, 2017b).					
MOR	4F-iBF^b	DAMGO	Morphine	Fentanyl	Naltrexone
[³ H]DAMGO binding K_i (nM)	0.451 ± 0.046	0.277 ± 0.027	0.322 ± 0.048	0.144 ± 0.024	0.082 ± 0.011
IC ₅₀ (nM)	2.16 ± 0.20	–	–	–	–
[³⁵S]GTPγS binding	4F-iBF^b	DAMGO	Morphine	Fentanyl	
Stimulation EC_{50} (nM)	115 ± 33	22.4 ± 7.0	17.2 ± 4.5	28.8 ± 6.9	–
Maximal stimulation (%) [*]	91.6 ± 4.1	96.1 ± 2.2	86.1 ± 5.0	94.0 ± 6.0	–

⁽¹⁵⁾ K_i represents the equilibrium inhibition constant for the test drug displacing the radioligand.

⁽¹⁶⁾ EC_{50} represents the concentration that causes a half-maximal response of the agonist.

DOR	4F-iBF^b	DPDPE-OH	Morphine	Fentanyl	Naltrexone
[³ H]DPDPE binding K _i (nM)	1,670 ± 410	1.93 ± 0.14	79.1 ± 5.1	164 ± 13	8.7 ± 1.0
IC ₅₀ (nM)	2,790 ± 630	–	–	–	–
[³⁵S]GTPγS binding	4F-iBF^b	DPDPE-OH	Morphine	Fentanyl	
Stimulation EC ₅₀ (nM)	2,490 ± 390	7.4 ± 1.6	750 ± 160	996 ± 99	–
Maximal stimulation (%)*	64 ± 15	98.90 ± 0.76	64.0 ± 9.7	42.5 ± 3.6	–
KOR	4F-iBF^b	U-50,488H	Morphine	Fentanyl	Nor-BNI
[³ H]U-69,593 binding K _i (nM)	2,700 ± 490	0.143 ± 0.043	34.9 ± 7.0	224 ± 36	0.53 ± 0.17
IC ₅₀ (nM)	4,830 ± 790	–	–	–	–
[³⁵S]GTPγS binding	4F-iBF^b	U-50,488H	Morphine	Fentanyl	–
Stimulation EC ₅₀ (nM)	1,330 ± 290	1.89 ± 0.30	81 ± 10	347 ± 65	–
Maximal stimulation (%)*	49.3 ± 5.8	98.1 ± 1.2	87.3 ± 6.7	74.9 ± 9.0	–

^a In receptor binding experiments, transfected Chinese hamster ovary (CHO) cells expressing human δ- and κ-opioid receptors and rat μ-opioid receptors were used. Experimental details for functional activity studies are not reported. DOR: delta opioid receptor; KOR: kappa opioid receptor; MOR: mu opioid receptor; DAMGO: Tyr-Ala-Gly-*N*-Me-Phe-Gly-ol, DPDPE: Tyr-Pen-Gly-Phe-Pen [disulfide bridge: 2-5]; U-69,593: (+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide; U-50,488H: *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate salt; Nor-BNI: norbinaltorphimine; U-69,593: (+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide. SEM: standard error of the mean.

Numbers represent the means ± SEM from at least three independent experiments, each conducted with duplicate determinations. Standard compounds are the agonists DPDPE (delta), U-50,488H (kappa) and DAMGO (mu) and the antagonists naltrexone (delta and mu) and nor-BNI (kappa).

* Maximal stimulation by test compound is normalized to the maximal stimulation by DPDPE (delta), U50,488H (kappa) or DAMGO (mu) above basal.

^b 4F-iBF: 4-fluoroisobutyrylfentanyl.

Animal studies

It has recently been reported that 4-fluoroisobutyrylfentanyl showed analgesic effects in mice (subcutaneous administration) in the tail-flick test (55°C). The ED₅₀ value for 4-fluoroisobutyrylfentanyl was determined at 1.61 mg/kg, compared to 0.122 mg/kg for fentanyl, and 12 mg/kg for morphine. It was furthermore reported that naltrexone administration (10 mg/kg, s.c.) affected nociceptive effects as demonstrated by a corresponding shift of the dose-response curve to the right (WHO, 2017) ⁽¹⁷⁾.

Pharmacokinetics

A recent *in vitro* investigation using human hepatocytes (10 µM test drug, up to 5 h incubation time) identified 17 metabolites (Figure 3). The identified biotransformations included *N*-dealkylation (C3), hydroxylation (C7, C8, C10, C11, C15, C17) followed by glucuronidation (C5), dihydroxylation (C9), dihydrodiol formation (C4), dihydroxylation with methylation (C12, C13) followed by glucuronidation (C6), amide hydrolysis (C14), oxidative *N*-dealkylation, and further reduction of the keto group (C1), carboxylation (C2), and carbonylation (C16) (Figure 3) (Watanabe et al., 2017).

The parent drug was prevalent in both the hepatocyte incubate and authentic human urine samples. Nine metabolites were observed in hepatocytes (C3, C8, C10, C12, C14–C17) with the desphenethyl (“nor”) metabolite C3 ⁽¹⁸⁾ being the major metabolite in the 5 h sample followed by the monohydroxylated metabolites C15 and C10. Eleven metabolites were detected in hydrolysed urine (C1, C2, C3, C4, C7, C9–C13, C15), which suggested that major metabolites were comparable. The C12 metabolite, a potential target for confirming consumption of 4-fluoroisobutyrylfentanyl, was also identified (Watanabe et al., 2017).

⁽¹⁷⁾ Data provided by the US Drug Enforcement Administration, Food and Drug Administration, National Center for Toxicological Research (2017b). Report: 4-Fluoroisobutyryl fentanyl (FIBF), Evaluation of analgesic effects using the warm water tail withdrawal assay. 28 June 2017.

⁽¹⁸⁾ Systematic name: *N*-(4-Fluorophenyl)-2-methyl-*N*-(piperidin-4-yl)propanamide.

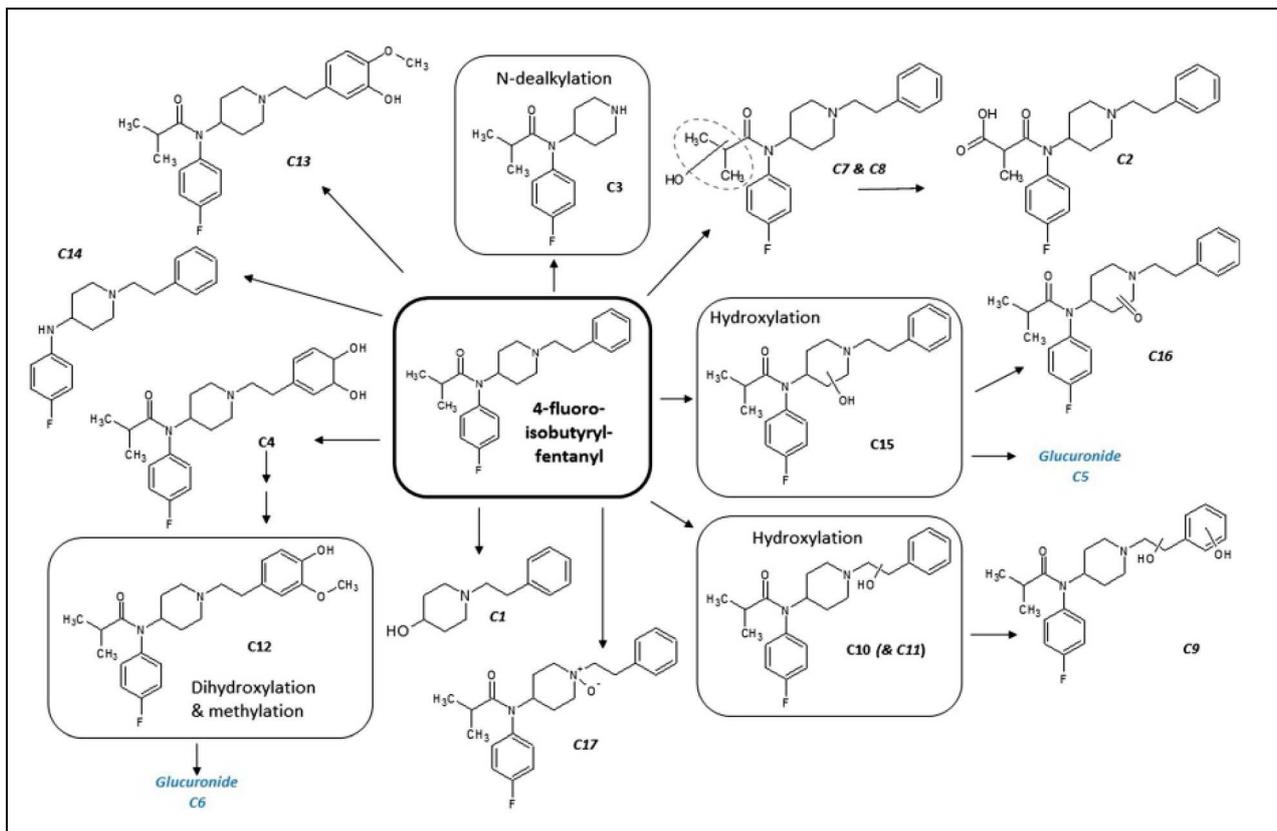


Figure 3. Proposed metabolic pathway of 4-fluoroisobutyrylfentanyl suggested by Watanabe et al. (2017), which summarize the results obtained from *in vitro* incubations with 10-donor pooled human hepatocytes and authentic human urine samples. Enclosed metabolites: major metabolites detected in hydrolysed human urine specimen; metabolites in italics only found in either the *in vitro* or *in vivo* experiment.

A limited number of self-reported user experiences have noted that the duration of effects induced by 4-fluoroisobutyrylfentanyl could be greater than 12 hours^(19,20). If correct, then this would indicate a longer lasting activity compared to fentanyl and other fentanyl analogues available on the market. As noted in the introduction, given the difficulties of collecting such data, these reports should be viewed with caution.

Inter-individual genetic variability in metabolising enzymes

For fentanyl, oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes to norfentanyl has been demonstrated (Guitton et al., 1997, Jin et al., 2005, Labroo et al., 1997). The variation of the expression of the genes coding for these CYP3A isoenzymes among populations might be of clinical significance (Meyer and Maurer, 2011) but further studies are needed to address the toxicological consequences of such polymorphisms.

⁽¹⁹⁾ <https://forum.drugs-and-users.org/index.php?topic=3373.0> (last accessed 22.10.2017).

⁽²⁰⁾ [http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-\(4-FiBF-p-FiBF\)](http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-(4-FiBF-p-FiBF)) (last accessed 22.10.2017).

Interactions with other substances and other interactions

Specific information about 4-fluoroisobutyrylfentanyl could not be identified although it seems conceivable that interactions observed with fentanyl might equally apply (Preston, 2016). For example, should 4-fluoroisobutyrylfentanyl undergo oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes then the use of this substance with inhibitors of these isoenzymes, such as clarithromycin, erythromycin, fluconazole, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, ritonavir, saquinavir, suboxone, verapamil) ⁽²¹⁾ may result in increased plasma concentration of 4-fluoroisobutyrylfentanyl. This could increase the risk of poisoning, including potentially fatal respiratory depression.

The concomitant use of other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol, pregabalin, gabapentin, tranquilisers, and sedating anti-histamines, may produce additive depressant effects.

The use of fentanyl with serotonergic agents, such as selective serotonin re-uptake Inhibitors (SSRIs) (the most commonly prescribed antidepressants) or serotonin norepinephrine re-uptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs) has been associated with a serotonin syndrome, a potentially life-threatening condition. This association is likely to extend to illicit drugs, which act on the serotonergic system. It is not known if this association is also seen with 4-fluoroisobutyrylfentanyl.

Effects on ability to drive and operate machines

No studies of the effects of 4-fluoroisobutyrylfentanyl on the ability to drive and operate machines have been performed. However, it is well established that opioid analgesics, such as fentanyl, impair the mental and physical ability required to drive and operate machines. This effect is likely to extend to 4-fluoroisobutyrylfentanyl.

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of 4-fluoroisobutyrylfentanyl is limited. It appears that the psychoactive profile of 4-fluoroisobutyrylfentanyl might share at least some similarities with other opioid analgesics such as fentanyl and heroin. These would include relaxation and euphoria; at higher doses, sedation and profound intoxication may occur.

A limited number of self-reported user experiences have noted that 4-fluoroisobutyrylfentanyl is 'long lasting' and is less euphorogenic when compared to other opioids ^(22,23,24). As noted in the introduction, given the difficulties of collecting such data, these reports should be viewed with caution. In addition, it should be noted that if 4-fluoroisobutyrylfentanyl was indeed less euphorogenic, this might lead to users increasing the dose, which could increase the risk of opioid toxicity and particularly life-threatening respiratory depression.

⁽²¹⁾ For a more comprehensive list of drug interactions with fentanyl, see, for example, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&source=homeMedSearch&keyword=fentanyl&category=human&isNewQuery=true

⁽²²⁾ <https://forum.drugs-and-users.org/index.php?topic=3373.0> (last accessed 22.10.2017).

⁽²³⁾ [http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-\(4-FiBF-p-FiBF\)](http://www.bluelight.org/vb/threads/774831-Novel-opioid-4-Fluoroisobutyrylfentanyl-(4-FiBF-p-FiBF)) (last accessed 22.10.2017).

⁽²⁴⁾ https://www.reddit.com/r/opiates/comments/3ved25/anybody_try_furanylfentanyl_fuf_or/ (last accessed 22.10.2017).

A4. Legitimate uses of the product

4-Fluoroisobutyrylfentanyl is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests 4-fluoroisobutyrylfentanyl is used for other legitimate purposes.

There are no reported uses of 4-fluoroisobutyrylfentanyl as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the CAS Registry Number returned no results.

There is no marketing authorisation (existing, on-going or suspended) for 4-fluoroisobutyrylfentanyl neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process (EMCDDA, 2017a)

There is no information to suggest that 4-fluoroisobutyrylfentanyl is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not 4-fluoroisobutyrylfentanyl is currently used in the manufacture of a medicinal product.

Section B. Dependence and abuse potential

B1. Animal data

No studies were identified that have investigated the dependence and/or abuse potential of 4-fluoroisobutyrylfentanyl in animal models.

The related des-fluoro analogue, isobutyrylfentanyl (NIH 10487) (Aceto et al., 1988) was studied in rhesus monkeys that received 3.0 mg/kg s.c. of morphine sulfate every 6 h for at least 90 days. In the single dose substitution test in rhesus monkeys, NIH 10487 (evaluated at 0.025 mg/kg and 0.1 mg/kg) “substituted completely for morphine. Potency estimate is 30 times [that of] morphine. Rapid onset and 2.5h duration of action were observed. Sagging, ataxia, slowing and scratching were noted at the highest dose during the first hour”.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of 4-fluoroisobutyrylfentanyl in humans.

Whereas no specific data exist for 4-fluoroisobutyrylfentanyl, it is well established that opioid analgesics such as fentanyl have an abuse liability and can induce tolerance and dependence. Research is required in order to examine these effects with 4-fluoroisobutyrylfentanyl.

Section C. Prevalence of use

Information from seizures, collected and biological samples

4-Fluoroisobutyrylfentanyl was formally notified on 26 August 2016 by the EMCDDA on behalf of the Slovenia, in accordance with Article 4 of the Council Decision. The Reporting Form details a collected sample of 5 grams of white powder that was test-purchased as part of the EU co-funded RESPONSE project, and analysed on 25 May 2016 in Ljubljana. 4-Fluoroisobutyrylfentanyl was analytically confirmed

by GC-MS, HPLC-TOF, FTIR-ATR, GC-MS-IR, ion chromatography and NMR by the Slovenian National Forensic Laboratory and the Faculty of Chemistry and Chemical technology of the University of Ljubljana (EMCDDA, 2017a).

Since then, a total of 5 Member States (Belgium, Germany, Slovenia, Sweden and the United Kingdom) have reported detections ⁽²⁵⁾ of 4-fluoroisobutyrylfentanyl (EMCDDA, 2017a).

It is important to note that detections of 4-fluoroisobutyrylfentanyl may be under-reported since the substance is not routinely screened for. Three Member States (Austria, Slovenia and Sweden) and Norway reported that 4-fluoroisobutyrylfentanyl is part of routine screening in some (but not all) laboratories.

Information from seizures

Information reported to the EMCDDA and Europol indicates that 24 seizures of 4-fluoroisobutyrylfentanyl have been reported by 4 Member States: Sweden (20 seizures), Belgium (1), Germany (1), and the United Kingdom (2). The majority of the seizures took place in 2016, while the most recent events took place in 2017.

Additionally, Finland reported a seizure of 0.05 g of a powder which was reported as '2F-, 3F- or 4F-BF; 2F-, 3F- or 4F-iBF', as the exact isomer was not determined. This case is not discussed further in this report.

No information regarding the purity of the samples was provided.

Powders

A total of 9 seizures of powders were reported by: Belgium, Germany, Sweden, and the United Kingdom, amounting to a total of 378.6 g.

The powder seizure reported by Germany also contained furanylfentanyl. In one case reported by the United Kingdom, the powder also contained furanylfentanyl and an unspecified isomer of 'fluorofentanyl'.

In the other seizure reported by the United Kingdom, a number of different items were seized, and different substances identified, including heroin, cocaine, steroids and synthetic cannabinoids (5F-MDMB-PINACA and MMB-FUBINACA). Nine of the items were found to contain 4-fluoroisobutyrylfentanyl, as follows:

- 0.436 grams of crystalline powder which appeared to be pure 4-fluoroisobutyrylfentanyl (no other compounds detected in the crystals);
- 0.425 grams of brown powder, found to contain mainly 4-fluoroisobutyrylfentanyl mixed with smaller amounts of paracetamol and caffeine;

⁽²⁵⁾ 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

- 7 items, consisting of heroin containing paracetamol, caffeine and 4-fluoroisobutyrylfentanyl. These were of various strengths of heroin and 4-fluoroisobutyrylfentanyl which were not determined. The total weight of these powders was 105.8 g.

Other physical forms

Sweden reported seizures of 4-fluoroisobutyrylfentanyl in tablets and liquids, as follows:

- 12 seizures of tablets, amounting to a total of 6727 tablets;
- 3 seizures of liquids, amounting to a total of 208 millilitres.

Information from collected samples

Slovenia reported a sample of 5 g of 4-fluoroisobutyrylfentanyl base in powder form which was purchased from an Internet vendor. The sample was apparently shipped from China and was received in May 2016. No other substances were detected in the sample

Information from biological samples

Serious adverse events (deaths and acute intoxications) with confirmed exposure to 4-fluoroisobutyrylfentanyl from biological samples are discussed in Section D.

Availability, supply, price

Information on production

No information was received in relation to the production of 4-fluoroisobutyrylfentanyl.

Information on trafficking

No information was reported to the EMCDDA in relation to the trafficking of 4-fluoroisobutyrylfentanyl. Information on the source of 4-fluoroisobutyrylfentanyl is limited to one report regarding collected sample of the substance. Here, the substance was ordered from an online vendor apparently based in China (see above). In addition, Belgium reported a seizure of 4-fluoroisobutyrylfentanyl to the EMCDDA where the final destination was Germany.

Availability from Internet vendors

A structured search of online vendors on the surface web by the EMCDDA ⁽²⁶⁾ found that the substance is offered for sale online in small and wholesale amounts, typically as a 'research chemical' and as powders, liquids, and blotters.

On the websites identified, 4-fluoroisobutyrylfentanyl was available in powder, liquid and blotter form. For powders, amounts on sale ranged from 0.5 grams to 10 kg, for liquids 5 to 50 mL and for blotters 1 to 500

⁽²⁶⁾ The search for online vendors of 4-fluoroisobutyrylfentanyl on the surface web was performed on 06/06/2017 using previously established methodology (EMCDDA, 2017c). The search identified 31 vendors that appeared to be based in, and/or claim to have presence in China (n=18), India (n=3), USA (n=2), Hong Kong (n=2), Hungary (n=1), Sweden (n=1), Turkey (n=1) and European Union (not specified) (n=1); the remaining 2 websites did not list a location. Nineteen websites listed quantities and prices for 4-fluoroisobutyrylfentanyl. The remaining websites only provided prices on request.

units. Prices varied according to the amounts on sale. Powders ranged from EUR 0.7 per gram to EUR 238 per gram. Liquids and blotters were only sold in one internet retailer. The price of the liquids varied from EUR 1 to EUR 5 per mL; for blotters a price of EUR 1 per unit was indicated.

The availability of 4-fluoroisobutyrylfentanyl on the darknet is not currently known.

Prevalence of use

No studies were identified that have investigated the prevalence of use of 4-fluoroisobutyrylfentanyl in the general population. Given its pharmacology and that it is sold openly as a 'legal' replacement to illicit opioids, it would be expected that users looking for substitutes for opioids, which would include individuals who use illicit opioids, such as heroin and/or prescription opioids, may seek out 4-fluoroisobutyrylfentanyl and other fentanils. It also appears that there is interest in this substance by some psychonauts. Overall, the available information does not suggest widespread use of the substance.

Of additional note is that, in the past few years, fentanils have been sold in Europe as ready-to-use nasal sprays. In some cases they have also been sold as e-liquids for vaping. In general, these novel products could make it easier to use such substances (with similar effects to injecting) and make them more socially acceptable, potentially expanding their use in new user groups. These are new developments that will require careful monitoring.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

Data on the acute toxicity, abuse liability, and dependence producing potential of 4-fluoroisobutyrylfentanyl could not be identified.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of 4-fluoroisobutyrylfentanyl and/or its metabolites in humans. Although the pharmacology and toxicology of 4-fluoroisobutyrylfentanyl remains largely unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl. The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, miosis, and respiratory depression or arrest. They also have an abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute health risk associated with 4-fluoroisobutyrylfentanyl use is probably respiratory depression, which can lead to apnoea, respiratory arrest and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White & Irvine, 1999). This risk may be greater due to: the difficulty in diluting the substance; a lack of experience with its effects and dosing; the use of other central nervous system depressants at the same time (such as other opioids, benzodiazepines, gabapentanoids, and alcohol); a lack of tolerance to opioids; and, using the substance alone (such as at home) which would make it more difficult for users to call for help in the case of poisoning.

The antidote naloxone should reverse acute poisoning caused by 4-fluoroisobutyrylfentanyl (Kim and Nelson, 2015).

Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required (Klar et al., 2016; Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017).

There is a lack of information on the clinical features of poisoning caused by 4-fluoroisobutyrylfentanyl. Nonetheless, the available data suggests that the nature of the effects of 4-fluoroisobutyrylfentanyl share some similarities with opioid analgesics such as morphine and fentanyl. As a result, features of poisoning are likely to include reduced level of consciousness or unconsciousness, respiratory depression and arrest, and miosis ⁽²⁷⁾.

Acute intoxications reported by the Member States

No acute intoxications with confirmed exposure to 4-fluoroisobutyrylfentanyl were reported ^(27,28).

Acute intoxications identified from other sources

No cases of acute intoxications were identified from other sources ⁽²⁷⁾.

Deaths reported by the Member States

A total of 20 deaths were reported by 2 Member States: Sweden (16) and the United Kingdom (4). Exposure to 4-fluoroisobutyrylfentanyl was analytically confirmed in post-mortem samples in all cases from Sweden; no reference standard was available to distinguish between 4-fluoroisobutyrylfentanyl and 4-fluorobutyrylfentanyl in cases from the United Kingdom.

The deaths occurred between July 2016 and March 2017, with 17 occurring in 2016 and 3 in 2017.

Of the 18 deaths where demographic data were available, 16 were male (80%) and 2 were female (20%). The mean age of the males was 35 years (median 34) and ranged from 20 to 52 years; the age of the females was 24 and 36 years.

Circumstances and cause of death

In the majority of cases there was a lack of information regarding any symptoms experienced by the deceased prior to death, but, where described in a few cases, the deceased had become unconscious

⁽²⁷⁾ Information on the clinical features of intoxication caused by 4-fluoroisobutyrylfentanyl is limited to a single report involving a death published by Helander et al., (2017). In this case, a male user had apparently injected intravenously 250 mg of 4-fluoroisobutyrylfentanyl and was 'discovered lifeless'. The main features reported were unconsciousness, apnoea, and asystole. The patient 'was discovered lifeless with a syringe reportedly containing "4-iBF" next to him. Cardiopulmonary resuscitation (CPR) was initiated by relatives. On ambulance arrival, the first recorded rhythm was asystole and CPR was maintained with an automated device. He was given 0.4mg of naloxone and repeated 1mg doses of adrenaline intravenously. Palpable pulses appeared only transiently and CPR was maintained during transport to hospital. Return of spontaneous circulation occurred after 90 min of CPR. The patient was unconscious (RLS 8), had dilated pupils unresponsive to light, and was normothermic. He was intubated, put on ventilator, and mildly therapeutically cooled to the target 36 (C (96.8 (F) body temperature, according to hospital guidelines. An early computed tomography (CT) showed brain edema. His neurological condition did not improve during the following 24 h and he was declared dead 43 h after arriving to hospital' (Helander et al., 2017). This case is included in the deaths reported by the Member States.

⁽²⁸⁾ Sweden reported 2 acute intoxications with suspected exposure to 4-fluoroisobutyrylfentanyl. These cases are not discussed further in this report.

and in one case the deceased was found convulsing. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

The cause of death was reported in 16 out of 20 cases. In at least 13 deaths, intoxication with 4-fluoroisobutyrylfentanyl was reported either as the primary cause of death or as likely to have contributed to death (even in presence of other substances); other substances were detected in 19 cases (with creatinine detected in the remaining case).

4-Fluoroisobutyrylfentanyl was quantified in 16 cases. Post-mortem femoral blood concentrations ranged from 0.76 to 370 ng/g blood (median 41 ng/g blood). In 2 cases, although the concentration was measured (44 and 85 ng/mL), it was not possible to determine if it related to 4-fluoroisobutyrylfentanyl or 4-fluorobutyrylfentanyl. Due to the toxicity of potent opioids and variability in user tolerance, determination of a 'fatal' concentration based on a post-mortem blood concentration is not reliable. In the majority of circumstances involving fentanils, the mere presence of the drug is of significance whether concentration has been determined or not, especially in situations of poly-drug use.

A range of other substances were detected in the deaths, including: cannabinoids, benzodiazepines, amphetamine, zopiclone, zolpidem, gabapentinoids (pregabalin and gabapentin), antidepressants, antipsychotics, antihistamines, a synthetic cathinone (alpha-PHP), ketamine and ethanol. Other opiates/opioids were detected in 9 of the deaths; codeine, buprenorphine, tramadol, methadone, oxycodone, fentanyl, despropionylfentanyl, tetrahydrofuranlylfentanyl, and acryloylfentanyl.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with 4-fluoroisobutyrylfentanyl would have been likely with other central nervous system depressants such as ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of 4-fluoroisobutyrylfentanyl means that the primary toxic contribution could be attributed to 4-fluoroisobutyrylfentanyl and death may not have occurred if 4-fluoroisobutyrylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) (Elliott, Sedefov, & Evans-Brown, 2017) incorporating the above considerations shows that 4-fluoroisobutyrylfentanyl had a TSS value of 3 (high) in 15 out of 16 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining death, an alternative cause of death (drowning) was cited (TSS value of 1, low). The 4 cases where 4-fluoroisobutyrylfentanyl could not be unequivocally confirmed were not part of the assessment.

Deaths identified from other sources

Since August 2016, more than 60 deaths associated with 4-fluoroisobutyrylfentanyl have been reported in the United States (US DEA, 2017b).

D2. Chronic health effects

D2.1. Animal data

No studies were identified that have investigated the chronic health effects of 4-fluoroisobutyrylfentanyl in animals.

D2.2. Human data

No studies were identified that have investigated the chronic health effects of 4-fluoroisobutyrylfentanyl in humans.

D3. Factors affecting public health risks

D3.1. Availability and quantity of the new psychoactive substance on the market

4-Fluoroisobutyrylfentanyl is being sold on the surface web as a drug in its own right. It is sold in both retail and wholesale quantities. It has been sold as a 'research chemical' in powder form, liquids, and blotters.

4-Fluoroisobutyrylfentanyl is also used to make tablets, as evidenced by the 12 seizures by Swedish Police of 6727 tablets. No further details are available on these cases.

Information from a seizure case in the United Kingdom suggests that 4-fluoroisobutyrylfentanyl has been sold on the illicit opioid market in mixtures with heroin.

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

Due to its relatively recent availability on the drug market, the availability of information, degree of knowledge and perceptions amongst users concerning 4-fluoroisobutyrylfentanyl and its effects are limited.

D3.3. Characteristics and behaviour of users

No studies were identified that have examined the characteristics and behaviours of users of 4-fluoroisobutyrylfentanyl. Section C (above) and Section E6 (below) provides additional information on the likely user groups of 4-fluoroisobutyrylfentanyl.

D3.4. Nature and extent of health consequences

Acute health risks

Although the pharmacology and toxicology of 4-fluoroisobutyrylfentanyl remains largely unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl.

The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression. They also have an abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute risk arising from the use of 4-fluoroisobutyrylfentanyl is probably from respiratory depression, which can lead to apnoea, respiratory arrest, and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White & Irvine, 1999).

In general, this risk may be exacerbated by:

- the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used (de Boer et al., 2003; Sutter et al., 2017);
- the apparent rapid onset of severe poisoning following use (Somerville et al., 2017);
- central nervous system (such as injecting, insufflation, and inhalation) (Macleod et al., 2012);
- availability of easy to use dosage forms (such as nasal sprays and e-liquids);

- use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol) (e.g. van der Schrier et al., 2017) ;
- lack of tolerance to opioids in opioid-naïve persons (such as new or former users);
- use in environments where it may be difficult to summon help in the event of poisoning (e.g. alone in a home environment) (Somerville et al., 2017);
- limited availability of the antidote naloxone in community settings (EMCDDA, 2015; EMCDDA, 2016b; Somerville et al., 2017).

In addition, and, often unknown to users, the fentanils are sold as heroin or mixed with heroin. They are also used to make counterfeits of highly sought-after analgesics and benzodiazepines. They have also been sold in or as drugs such as cocaine (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017). Due to this, users may not be aware that they are using a fentanyl; in some cases these individuals will have no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Given the above risks, poisonings by fentanils may manifest as outbreaks which have the potential to overwhelm emergency responders and other local healthcare systems (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017).

Accidental exposure to the fentanils may also pose a risk to non-users, including family and friends, law enforcement and emergency responders. Such risks may need to be assessed so that, where required, appropriate procedures, training and environmental and personal protective measures can be provided for handling materials suspected to contain these substances (US CDC, 2016; Moss et al., 2017; US DEA, 2017a). Any required responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

Managing poisoning

The antidote naloxone should reverse acute poisoning caused by 4-fluoroisobutyrylfentanyl (Kim and Nelson, 2015; Ujváry et al., 2017). Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required (Klar et al., 2016; Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017). This may reflect, among other factors, the high potency of the fentanils, their half-lives, the dose an individual is exposed to, and, the relatively short half-life of naloxone.

Chronic health risks

While there is limited data, the chronic health risks of carfentanyl might share some similarities to opioids such as heroin and other fentanils. This may include dependence.

D3.5. Long-term consequences of use

While there is limited data, the chronic health risks of 4-fluoroisobutyrylfentanyl might share some similarities to opioids such as heroin and other fentanils. This may include dependence.

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

There is limited data on the conditions under which 4-fluoroisobutyrylfentanyl is obtained and used. 4-Fluoroisobutyrylfentanyl is offered for sale on the surface web as a powder, liquids, and blotters.

It has also been seized as tablets. Information from a seizure case in the United Kingdom suggests that 4-fluoroisobutyrylfentanyl has been sold on the illicit opioid market in mixtures with heroin.

Section E. Social Risks

While there have been no studies on the social risks of 4-fluoroisobutyrylfentanyl, it is likely that some of the risks are similar to those associated with illicit opioids, including fentanyl and heroin.

E1. Individual social risks

There is no information on the individual social risks that may be associated with the use of 4-fluoroisobutyrylfentanyl. Given that 4-fluoroisobutyrylfentanyl appears to act as an opioid analgesic, any such risks may have some similarities with those associated with illicit opioids. These may negatively impact on education or career, family or other personal and social relationships and may result in marginalisation.

E2. Possible effects on direct social environment

There is no information on the possible effects of 4-fluoroisobutyrylfentanyl on the direct social environment. Given that 4-fluoroisobutyrylfentanyl appears to act as an opioid analgesic, any such effects may have some similarities with those associated with the use of illicit opioids.

E3. Possible effects on society as a whole

There is no specific information on the possible effects of 4-fluoroisobutyrylfentanyl on society as a whole.

As discussed above, accidental exposure to the fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel as well as custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in managing poisoning, including in resuscitation and adequate provision of naloxone to reverse poisoning. Any required responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole & Nelson, 2017; Lynch, Suyama, & Guyette, 2017).

E4. Economic costs

There are no data on the health and social costs related to 4-fluoroisobutyrylfentanyl.

E5. Possible effects related to the cultural context, for example marginalization

There are no data on the possible effects of 4-fluoroisobutyrylfentanyl related to the cultural context.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

While no specific examples are available on the possible appeal of 4-fluoroisobutyrylfentanyl to specific user groups (aside from psychonauts), it is reasonable to assume 4-fluoroisobutyrylfentanyl may be sought by those looking for 'legal' substitutes for illicit opioids, such as heroin and/or prescription opioids.

As discussed above, the open sale of fentanils in novel dosage forms—such as ready-to-use nasal sprays and e-liquids for vaping—poses additional concerns. These novel forms have the potential to make the use of fentanils easier (with similar effects to injecting) and more socially acceptable.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

There is no specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution and supply of 4-fluoroisobutyrylfentanyl.

Slovenia reported a collected sample of 4-fluoroisobutyrylfentanyl to both Europol and the EMCDDA where the country of origin was indicated as China.

Belgium reported a seizure of 4-fluoroisobutyrylfentanyl to the EMCDDA where the final destination was Germany.

The seizure of an illicit laboratory producing fentanils in Europe in 2013 (EMCDDA, 2017e) suggests that the capability to manufacture fentanils may exist within the European Union.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

No information was reported nor identified concerning the impact of 4-fluoroisobutyrylfentanyl on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances.

F3. Evidence of the same groups of people being involved in different types of crime

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of 4-fluoroisobutyrylfentanyl.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

No information was reported nor identified concerning incidents of violence related to the availability of 4-fluoroisobutyrylfentanyl.

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of 4-fluoroisobutyrylfentanyl.

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

No information was reported nor identified concerning the economic costs and consequences related to the availability of 4-fluoroisobutyrylfentanyl.

F7. Use of violence between or within criminal groups

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of 4-fluoroisobutyrylfentanyl.

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of 4-fluoroisobutyrylfentanyl.

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Annex 2. List of participants at the risk assessment meetings of *N*-(4-Fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)isobutyramide (4-fluoroisobutyrylfentanyl)

7-8 November 2017

A. Extended Scientific Committee

Dr Anne Line BRETTEVILLE-JENSEN

Norwegian Institute for Alcohol and Drug Research, Oslo
Chair of the Scientific Committee

Professor Dr Gerhard BUEHRINGER

Addiction Research Unit, Department of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich

Professor Dr Paul DARGAN

Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Dr Marina DAVOLI

Department of Epidemiology, Lazio Regional Health Service, Rome

Professor Dr Gabriele FISCHER

Medical University Vienna, Center of Public Health, Vienna

Professor Dr Henk GARRETSEN

Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg

Professor Dr Krzysztof KRAJEWSKI

Department of Criminology, Jagiellonian University, Krakow

Dr Fernando RODRÍGUEZ de FONSECA

Fundación IMABIS, Hospital Universitario Carlos Haya de Málaga, Málaga

Professor Dr Rainer SPANAGEL

Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Dr Wim BEST

Utrecht University, Faculty of Science, Freudenthal Institute, Utrecht

Dr Simon BRANDT

School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Professor Dr Gaetano Di CHIARA

Biomedical Sciences Department, University of Cagliari, Cagliari

Professor Dr Éva KELLER

Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

Dr Claude GUILLOU

Directorate F – Health, Consumers and Reference Materials, DG Joint Research Centre, European Commission

Edith HOFER

Organised Crime and Drugs Policy Unit, DG HOME, European Commission

Dr Leon Van Aerts

Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht, on behalf of European Medicines Agency

Werner VERBRUGGEN

Europol's Drug Unit, Europol

Paul GRIFFITHS

Scientific Director, EMCDDA

Dr Roumen SEDEFOV

Head of Unit, Supply reduction and new drugs unit, EMCDDA

B. Invited Experts

Professor Dr Volker AUWÄRTER

Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Robert KRONSTRAND

Dep. Forensic Genetics and Toxicology, Swedish National Board of Forensic Medicine, Linköping

Professor Dr Bela SZABO

Institute of Experimental and Clinical Pharmacology and Toxicology, Freiburg

Dr István UJVÁRY

Budapest University of Technology and Economics, Budapest

C. EMCDDA Staff

Anabela ALMEIDA

Action on new drugs sector, Supply reduction and new drugs unit

Rachel CHRISTIE

Action on new drugs sector, Supply reduction and new drugs unit

Michael EVANS-BROWN

Action on new drugs sector, Supply reduction and new drugs unit

Ana GALLEGOS

Action on new drugs sector, Supply reduction and new drugs unit

Rita JORGE

Action on new drugs sector, Supply reduction and new drugs unit

Joanna DE MORAIS

Action on new drugs sector, Supply reduction and new drugs unit

Sofía SOLA

Action on new drugs sector, Supply reduction and new drugs unit