

4-Fluoroisobutyrfentanyl (4-FIBF)
Critical Review Report
Agenda Item 4.9

Expert Committee on Drug Dependence
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Summary

Potent synthetic analogs of fentanyl continue to emerge on the illicit market, one of the more recent compounds appearing is 4-fluoroisobutyrfentanyl (4-FIBF). 4-Fluoroisobutyrfentanyl belongs to the 4-anilidopiperidine class of synthetic opioids which is the same class of opioids as internationally controlled fentanyl and its derivatives. As other fentanyl derivatives were being scheduled in 2015-16, 4-fluoroisobutyrfentanyl appeared on the illicit market for purchase as powders, tablets, or liquids. The few reports that are available examining the pharmacodynamics, patterns of use, toxicology, adverse events, or abuse liability of this compound indicate that 4-fluoroisobutyrfentanyl is an opioid with abuse liability and dependence potential similar to fentanyl, prescription opioids, and illicit opioids. The most serious acute health risk posed by 4-fluoroisobutyrfentanyl appears to be respiratory depression and death; reported overdose with 4-fluoroisobutyrfentanyl can be reversed with naloxone. The population likely to abuse 4-fluoroisobutyrfentanyl, either knowingly or unknowingly, intersects with the population using heroin, fentanyl, prescription opioid analgesics, and other fentanyl-related substances as evidenced by the routes of drug administration, the drug use history, and the paraphernalia found at fatal overdose cases. In summary, 4-fluoroisobutyrfentanyl is one of the latest fentanyl derivatives to be sold and used in a similar manner as other licit and illicit opioids. At the current time, there is evidence that 4-fluoroisobutyrfentanyl poses similar public health risks as the fentanyl derivatives that preceded it.

1. Substance identification

A. International Nonproprietary Name (INN)

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

B. Chemical Abstract Service (CAS) Registry Number

244195-32-2

C. Other Chemical Names

N-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide;
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;
N-[1-(2-fenyletyl)piperidin-4-yl]-*N*-(4-fluorofenyl)-2-metylpropanamid
(Swedish); 4-fluoroisobutyryl fentanyl; para-fluoroisobutyryl fentanyl; 4-fluoro-
isobutyrylfentanyl, 4-fluoro-isobutyrfentanyl, 4-fluoro-isobutyrylfentanyl

D. Trade Names

No trade names.

E. Street Names

4-F-iBF, 4-FiBF, 4F-iBF, FIBF, p-FIBF, p-FiBF

F. Physical Appearance

White, crystalline solid.

G. WHO Review History

4-Fluoroisobutyrfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that 4-FIBF is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

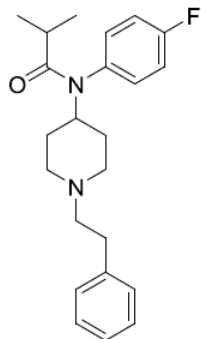
A. Chemical Name

IUPAC Name:

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

CA Index Name:

Propanamide, *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-

B. Chemical Structure**Free base:****4-fluoroisobutyryl fentanyl****Molecular Formula:** C₂₃H₂₉FN₂O; C₂₃H₂₉FN₂O • HCl**Molecular Weight:** 368.50; 405.0**C. Stereoisomers**

4-Fluoroisobutyrylfentanyl is the positional iso isomer of 4-fluoro-butyrylfentanyl (4-FIBF).

D. Methods and Ease of Illicit Manufacturing

4-Fluoroisobutyrylfentanyl differs from fentanyl due to the presence of an isobutyramide group in place of the propanamide group and the presence of a fluorine atom on the anilido phenyl ring. 4-Fluoroisobutyrylfentanyl and 23 other fentanyl-related compounds were first synthesized in 1974 (Van Bever et al., 1974) and the synthesis of 4-fluoroisobutyrylfentanyl was then further described in 1999 (Ohta et al., 1999).

The manufacture of 4-fluoroisobutyrylfentanyl uses precursors and synthetic methods similar to those used to manufacture the pharmaceutical fentanyl (Casy and Huckstep, 1988; Gupta et al., 2013; Zee and Wang, 1980). Therefore, the methods developed for the synthesis of fentanyl are applicable to the synthesis of 4-fluoroisobutyrylfentanyl. Use of a different acylating agent in the final acylation step, such as isobutyryl chloride would produce 4-fluoroisobutyrylfentanyl. A one-step method uses N-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and isobutyryl chloride for the manufacture of the substance (UNODC World Report, 2017). Other routes developed for the production of fentanyl may also be used for the manufacture of 4-fluoroisobutyrylfentanyl. There is no information on the actual method(s) used for the production of 4-fluoroisobutyrylfentanyl that has been detected in Europe or the USA to date. Theoretically, most of the synthetic procedures that could be used would only require common laboratory equipment, a basic knowledge of synthetic chemistry, and the detailed recipes published or available on the internet to facilitate small-scale manufacturing by minor drug trafficking organizations.

E. Chemical Properties

Melting point: 75.21±3.0 kJ/mol (flash point predicted; melting point not found)

Boiling point: 486.4±45.0 °C (predicted)

Solubility: There are no definitive solubility data on 4-fluoroisobutyrfentanyl or its hydrochloride salt at the time of this report. Based on Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2017 ACD/Labs), 4-fluoroisobutyrfentanyl is predicted to be sparingly soluble (0.74 g/L) at a temperature of 25 °C and pH 7. In addition, 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. As with fentanyl, 4-fluoroisobutyrfentanyl would be expected to be stable for at least 2 years; polymerization will not occur if properly stored.

F. Identification and Analysis

At the current time, commonly used opioid drug screening methods including the enzyme-linked immunosorbent assay (ELISA) are unable to differentiate between 4-fluoroisobutyrfentanyl and fentanyl due to the structural similarity between the two substances (Ruangyuttikarn, 1990; Alburges, 1992; US DEA, 2017a). Further confirmatory testing (i.e., mass spectrometry) is required to identify 4-fluoroisobutyrfentanyl. Similarly, 4-fluoroisobutyrfentanyl is not expected to give a positive response to tests developed for morphine-type opioids.

There is no information on the reaction of 4-fluoroisobutyrfentanyl to presumptive color tests.

In the literature, chromatographic and spectrometric discrimination by thin-layer chromatography (TLC), gas chromatography (GC), GC-MS, and FTIR for a number of fentanyls are presented, including 4-fluoroisobutyrfentanyl. In this study, the condensed-phase infrared spectrometry was able to differentiate structurally similar fentanyl compounds, but vapor-phase infrared spectra were not useful for discrimination of fentanyls (Ohta et al., 1999). To positively identify 4-fluoroisobutyrfentanyl and/or its metabolites, additional testing is required including high performance liquid chromatography time-of-flight (HPLC-TOF) (Watanabe et al., 2017), liquid chromatography high-resolution mass spectrometry (LC-HRMS) (Watanabe et al., 2017; Helander et al., 2017), gas chromatography – mass spectrometry (GC-MS), HPLC-TOF, Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR), gas chromatography–mass spectrometry–infrared (GC-MS-IR) condensed phase, and nuclear magnetic resonance spectrometry (NMR) (Slovenian National Forensic Laboratory, 2016). Similar mass spectrometry fragmentation patterns are observed for 4-fluoroisobutyrfentanyl (4-FIBF) and 4-fluoro-butyrfentanyl (4F-BF) when using GC-MS analysis so that distinguishing between the two isomers requires the use of analytical reference standards or access to reference spectra for both substances (EMCDDA-Europol, 2017; USA DEA, 2017a).

A deuterated form, 4-fluoroisobutyrylfentanyl-d7, is available for use as an internal standard for the quantification of 4-fluoroisobutyrylfentanyl via GC- or LC-MS

3. Ease of Convertibility Into Controlled Substances

At the time of the report, no information was found on whether 4-fluoroisobutyrylfentanyl is converted into controlled substances.

4. General Pharmacology

A. *Routes of administration and dosage*

4-Fluoroisobutyrylfentanyl has been seized as a liquid, in powder form, and as tablets. Based on forensic reports and paraphernalia found at overdose sites, routes of administration appear to be intravenous, oral, and as a nasal spray (EMCDDA-Europol, 2017; USA DEA, 2016a, USA DEA, 2017a). In the STRIDA project study, with analytically confirmed existence of 4-fluoroisobutyrylfentanyl, the authors observed higher serum concentrations of 4-fluoroisobutyrylfentanyl compared with acrylfentanyl in the intoxication cases suggesting 4-fluoroisobutyrylfentanyl may be a less potent opioid receptor agonist (Helander et al., 2017). Similarly, self-reports posted on Swedish Internet drug discussion forums in June 2016 and the claimed contents of 4-fluoroisobutyrylfentanyl on the novel psychoactive substances vendor websites (60–100 mg/10 mL for nasal sprays, and 4–10 mg for tablets) suggests that 4-fluoroisobutyrylfentanyl might be less potent than acrylfentanyl. However, these estimates should be viewed with caution as verified potency comparisons are not currently available.

B. *Pharmacokinetics*

4-Fluoroisobutyrylfentanyl is expected to be lipophilic; however no pharmacokinetic studies have been performed at the time of this report. From online drug forums, self-report users mention a “12+ hour duration of effects,” “high may not be the most euphoric,” or “requires a higher dose than normal fentanyl analogues” (for example, <https://forum.drugs-and-users.org/index.php?topic=3373.0>). The reliability of these reports are uncertain, however, as the substance is not verified.

C. *Pharmacodynamics*

In radioligand binding assays, K_i values for 4-fluoroisobutyrylfentanyl were: 0.451 ± 0.046 nM for MOR using [3H]DAMGO; $2,700 \pm 490$ nM for KOR using [3H]U69,593; and $1,670 \pm 410$ nM for DOR using [3H]DPDPE. Therefore, 4-fluoroisobutyrylfentanyl selectively bound to μ -opioid receptors when [3H]-DAMGO was used as the radioligand (USA DEA, 2017b).

When 4-fluoroisobutyrylfentanyl was evaluated in a [35S]GTP γ S functional assay using preparations of transfected Chinese hamster ovary cells expressing human δ - and κ -opioid receptors and rat μ -opioid receptors, 4-fluoroisobutyrylfentanyl produced $64 \pm 15\%$, $49.3 \pm 5.8\%$, and $91.6 \pm 4.1\%$ maximum stimulation with EC_{50}

potencies of $2,490 \pm 390$ nM, $1,330 \pm 290$ nM, and 115 ± 33 nM, respectively (DEA-VA, 2017a, b, c). In summary, 4-fluoroisobutyrylfentanyl was most effective and most potent at μ -opioid receptors (USA DEA, 2017b).

4-Fluoroisobutyrylfentanyl, fentanyl, and morphine administered s.c. to mice produced dose-dependent increases in tail-flick latency in a 55°C tail withdrawal assay with ED₅₀ values of 1.61 mg/kg, 0.122 mg/kg, and 12 mg/kg, respectively. A dose of 10 mg/kg naltrexone, s.c., shifted each opioid dose-response curve to the right. Therefore, similar to fentanyl and morphine, 4-fluoroisobutyrylfentanyl had an analgesic effect and functioned as a μ opioid receptor agonist *in vivo* (USA DEA 2017b).

5. Toxicology

At the time of the report, there were no acute or chronic preclinical toxicology studies found.

6. Adverse Reactions in Humans

As discussed in the EMCDDA-Europol Joint Report (2017), 4- fluoroisobutyrylfentanyl is similar to other opioids and the most serious acute health risk is respiratory depression, which could lead to apnea, respiratory arrest, and death ((EMCDDA-Europol, 2017; Pattinson, 2008; White and Irvine, 1999). The antidote naloxone should reverse acute poisoning caused by 4-fluoroisobutyrylfentanyl (Kim and Nelson, 2015; Ujváry *et al.*, 2017). For 4-fluoroisobutyrylfentanyl, the risk may be increased due to a number of factors which include: difficulty in diluting the substance, unknown dosage amounts, the concurrent use of other central nervous system depressants along with a lack of tolerance to opioids. The effects caused by the substance may make it more difficult for users to call for help if they are in an isolated environment (e.g. at home alone) in the case of overdose.

To date, Sweden has reported 16 deaths with confirmed exposure to 4-fluoroisobutyrylfentanyl were reported occurring between 2016 and 2017. In at least 11 cases, 4-fluoroisobutyrylfentanyl was the cause of death or contributed to the death. Most of the individuals were found deceased in their homes; 14 were male (88%) aged between 24 and 42 years (mean 36, median 36) and 2 were female (12%) aged 24 and 36 years. Other substances were detected in the deaths, including other central nervous system depressants, while other opioids were only detected in 5 cases (EMCDDA-Europol, 2017; USA DEA, 2017c).

The Swedish STRIDA project monitors the occurrence and health hazards of novel psychoactive substances in their country, through evaluation of analytically confirmed serious adverse events presenting in the emergency department and intensive care units. Consistent with previous cases involving fentanyl analogues and derivatives (Bäckberg *et al.*, 2015, Helander *et al.* 2016), typical opioid overdose symptoms of CNS and respiratory depression and miotic pupils were observed but tachycardia and hypertension were also common. In this report, 4-fluoroisobutyrylfentanyl was analytically confirmed in biological samples obtained from an intoxication case where respiratory depression and

decreased consciousness were noted. In this paper, one patient tested positive for 4-FIBF and did not survive. The patient abused various types of drugs and was discovered unconscious at home with a syringe report to contain 4-fluoroisobutyrfentanyl next to him. In the ambulance, asystole was recorded. The patient was administered 0.4 mg of naloxone and repeated 1 mg doses of adrenaline intravenously. Palpable pulses appeared only transiently and return of spontaneous circulation occurred after 90 min of cardiopulmonary resuscitation. The patient was unconscious, had dilated pupils unresponsive to light, and was normothermic. He was intubated, put on ventilator, and therapeutically cooled to the target 36 C (96.8 F) body temperature, according to hospital guidelines. An early computed tomography 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).

Reports collected by the United States DEA indicate that 4-fluoroisobutyrfentanyl is being abused for its opioid properties and has resulted in mortality. Authorities reported that 62 overdose deaths involving 4-fluoroisobutyrfentanyl abuse occurred in Maryland in 2016. The DEA collected post-mortem toxicology and medical examiner reports on two confirmed fatalities associated with 4-fluoroisobutyrfentanyl which occurred in New Jersey and Wisconsin. However, the DEA states that it is likely that the prevalence of the 4-fluoroisobutyrfentanyl in opioid-related emergency room admissions and deaths is underreported as standard immunoassays may not differentiate 4-fluoroisobutyrfentanyl from fentanyl (US-DEA, 2017a,c).

In addition to the adverse effects related to respiratory depression, material safety sheets from online chemical companies (for example, Cayman Chemical, Ann Arbor, MI USA), report that 4-fluoroisobutyrfentanyl may be irritating to the mucous membranes and upper respiratory tract and caution should be taken when handling. 4-Fluoroisobutyrfentanyl may be harmful if inhaled, ingested, or absorbed through the skin to cause eye, skin, or respiratory system irritation.

7. Dependence Potential

A. *Animal Studies*

At the time of the report, there are no physical dependence studies available.

B. *Human Studies*

From the limited data that exist from adverse effects reports in humans, dependence potential for 4-fluoroisobutyrfentanyl is likely high as 4-fluoroisobutyrfentanyl is a μ -opioid receptor agonist that shares some similarities with opioid analgesics such as morphine, fentanyl, and heroin.

8. Abuse Potential

A. *Animal Studies*

The USA DEA is currently working on testing 4-fluoroisobutyrfentanyl in rats trained to discriminate morphine; however, the results of these studies are not available at the time of the report (personal communication).

B. *Human Studies*

At the time of the report, no human abuse potential studies are available.

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

There is currently no therapeutic applications or recorded medical use at this time.

10. Listing on the WHO Model List of Essential Medicines

4-Fluoroisobutyrfentanyl is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing Authorizations (as a Medicinal Product)

To date, Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom reported that 4-fluoroisobutyrfentanyl: 1) has not been granted a marketing authorization as a medicinal product for human use; 2) has not been the subject of an application for marketing authorization as a medicinal product for human use; or, 3) has not had a case of suspended marketing authorization as a human medicine.

In addition, Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Latvia, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom reported that 4-fluoroisobutyrfentanyl: 1) has not been granted a marketing authorization as a veterinary medicinal product; 2) has not been not the subject of an application for a marketing authorization as a veterinary medicinal product for use; or 3) has not had a case of suspended marketing authorization as a veterinary medicine.

Finally, the European Medicines Agency reported that 4-fluoroisobutyrfentanyl has not been granted a marketing authorization, been the subject of a suspended marketing authorization, or been the subject of a marketing authorization as a medicinal product for neither human nor veterinary use through the centralized procedure. The EMA reports that to date, 4-Fluoroisobutyrfentanyl only reported use is as an analytical reference material for scientific research (EMCDDA-Europol, 2017).

There are currently no investigational new drug applications or approved new drug applications for 4-fluoroisobutyrfentanyl based on a review by the United States Food and Drug Administration. Taken together from the available information, 4-

fluoroisobutyrfentanyl does not appear to be used in the manufacture of a medicinal product in the European Union or the United States. However, the data collection is incomplete and some countries indicated that this information is not known. There is a ‘Nasal Drug Product and Methods of their Use’ patent for opioid antagonist delivery in which for 4-fluoroisobutyrfentanyl is specifically mentioned as a potential opioid that would cause overdose and the potential need for this delivery system (Keegan et al., March 16, 2017; US Patent Application US 20170071851A1).

12. Industrial Use

No potential industrial use was detected for 4-fluoroisobutyrfentanyl besides as an analytical reference standard for scientific research and forensic applications. 4-Fluoroisobutyrfentanyl-d7 is also available for use as an internal standard for the quantification of 4-fluoroisobutyrfentanyl using GC- or LC-MS methods for research and forensic purposes. 4-Fluoroisobutyrfentanyl currently is available for purchase synthesized by various chemical companies available in wholesale amounts and in consumer amounts.

13. Non-Medical Use, Abuse and Dependence

In different countries of countries in East Asia, Europe, and North America between 2012 and 2016, multiple fentanyl analogues were reported to the UNODC early warning advisory on new psychoactive substances. These synthetic opioids, such as 4-fluoroisobutyrfentanyl, are most commonly sold as adulterated/substituted heroin or counterfeit prescription pills in North America whereas in Estonia, illicitly produced fentanyl analogues are sold as the drug of choice (UNODC, World Drug Report 2017). 4-Fluoroisobutyrfentanyl is currently sold online and through illicit markets as a nonscheduled substitute for illicit opioids and/or prescription opioids. On drug forums, users report using the novel fentanyl-like derivatives for exploration of new opioid experiences, self-medication, such as the alleviation of pain, and/or to prevent opioid withdrawal (Zawilska, 2017). Novel psychoactive fentanyl analogs have appeared on the illicit market since 2013 with a typical turnover times of 0.5–1 year (Helander and Backberg, 2017).

Users may include high-risk drug users as well as others (such as psychonauts) who may be experimenting with the substance (e.g., [http:// forum.drugs-and-users.org/index.php?topic=3373.0](http://forum.drugs-and-users.org/index.php?topic=3373.0)). The population likely to abuse 4-fluoroisobutyrfentanyl would be assumed to overlap with the population abusing prescription opioid analgesics, heroin, fentanyl, and other fentanyl-related substances (Zawilska, 2017). This statement is supported by the routes of drug administration and drug use history documented in 4-fluoroisobutyrfentanyl overdose cases.

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

It is likely the abuse of 4-fluoroisobutyryfentanyl is as a replacement for heroin or other synthetic opioids, either known or unknown, as 4-fluoroisobutyryfentanyl seizures are predominantly powder form and contained within glassine bags,. 4-

Fluoroisobutyrylfentanyl has been encountered as a single substance or in a mixture with heroin, fentanyl, furanyl fentanyl, methamphetamine, and cocaine. 4-Fluoroisobutyrylfentanyl has been connected to fatal overdoses in which intravenous and insufflation routes of administration are authenticated. In individuals who may initiate or use a drug for the first time, 4-fluoroisobutyrylfentanyl use is likely to be at risk for overdose, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). As 4-fluoroisobutyrylfentanyl is available in liquid form it could be used as a nasal sprays or e-liquid for vaping, a formulation which may make it more acceptable to use (Zawilska, 2017). Similar to other fentanyls, accidental exposure to 4-fluoroisobutyrylfentanyl may also pose a risk of severe poisoning. Those at risk may include law enforcement, emergency personnel, medical and forensic laboratory personnel, postal workers and the friends and family of users (EMCDDA-Europol, 2017; USA DEA, 2016a, 2017c). If possible, these risks should be assessed and mitigated by appropriate training and protective measures such as training in resuscitation and adequate use of naloxone (Kim and Nelson, 2015; Ujváry *et al.*, 2017).

The chronic health risks for 4-fluoroisobutyrylfentanyl likely share similarities to opioids such as heroin and other fentanyls including the potential for dependence.

15. Licit Production, Consumption and International Trade

There is currently no licit production, consumption, or trade for 4-fluoroisobutyrylfentanyl.

16. Illicit Manufacture and Traffic and Related Information

4-Fluoroisobutyrylfentanyl can be found in trace amounts in illicitly manufactured material or mixed with heroin or other opioids making the detection very challenging for forensic laboratories and likely lead to the underreporting of the extent to which it appears on the market (UNODC, World Drug Report 2017). Europol received reports from Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Finland, Greece, Latvia, Lithuania, Luxembourg, Romania, Slovakia, and Spain that they have no available information on 4-fluoroisobutyrylfentanyl. Slovenia provided information on a collected sample, however, they reported no information on production, distribution, or trafficking (EMCDDA-Europol, 2017). However, there have been reports of seizures and illicit traffic as listed below.

In total, the EMCDDA reported 23 seizures of 4-fluoroisobutyrylfentanyl: 12 seizures of 6727 tablets, all reported by Sweden; 8 seizures of 272 g of powders by Belgium, Germany, Sweden and the United Kingdom; 3 seizures of liquids totaling 208 mL by Sweden. Finland reported a seizure of 0.05 g of a powder although the exact isomer was not resolved and reported as '2F-, 3F- or 4F-BF; 2F-, 3F- or 4-FIBF.' For most of the seizures, there is no information on whether additional substances were also detected and no information on purity was shared. However, furanylfentanyl was found in the powder seizure in Germany, and fluorofentanyl and furanylfentanyl were found in the powder seizure from the United Kingdom.

The commercial, web-based laboratory information management system STARLiMS used by the United States DEA, registered 22 drug exhibits beginning in March 2016 containing

4-fluoroisobutyrfentanyl from Florida, Maryland, Mississippi, New Jersey, New York, Pennsylvania, Texas, and the District of Columbia. The first US laboratory submissions of 4-fluoroisobutyrfentanyl occurred in March 2016 according to STARLiMS. In January 2017, The National Forensic Laboratory Information System (NFLIS) registered one report of 4-fluoroisobutyryl fentanyl in August 2016 in Pennsylvania from state or local forensic laboratories. The DEA is not aware of any laboratory identifications 4-fluoroisobutyrfentanyl prior to 2016. Together, STARLiMS and NFLIS recorded 22 drug reports in which 4-fluoroisobutyrfentanyl was identified in drug exhibits submitted to forensic laboratories in 2017 from law enforcement encounters in Florida, Maryland, Mississippi, New Jersey, New York, Pennsylvania, Texas, and the District of Columbia.

Slovenia reported a collected sample which consisted of 5 grams of powder test-purchased from the internet from a site based in China. No additional substances were detected in the sample.

17. Current International Controls and Their Impact

4-fluoroisobutyrfentanyl is not controlled under the 1961, 1971 or 1988 United Nations Conventions. Two possible precursors of fentanyl and potentially 4-fluoroisobutyrfentanyl, 4-aminophenyl-1-phenethylpiperidine (4-ANPP) and N-phenethyl-4-piperidone (NPP, a pre-precursor) have been scheduled under the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

18. Current and Past National Controls

The USA DEA temporarily placed 4-fluoroisobutyrfentanyl into Schedule I on May 3, 2017 citing high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. This temporary scheduling includes the isomers, esters, ethers, salts and salts of isomers, esters and ethers of 4-fluoroisobutyrfentanyl (US-DEA, 2017c).

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol added 4-fluoroisobutyrfentanyl to the list of new psychoactive substances to be monitored through the European Union Early Warning System and a profile of the substance was created on the European Database on New Drugs (EDND). Analytical details and other information, including a public health alert, have been exchanged between the EMCDDA, Europol, and the Member States, Turkey, and Norway.

Cyprus, Estonia, Latvia, Lithuania, Sweden and the United Kingdom reported that 4-fluoroisobutyrfentanyl is controlled under drug control legislation. Austria and Poland reported that 4-fluoroisobutyrfentanyl is controlled under specific new psychoactive substances control legislation. Norway reported that 4-fluoroisobutyrfentanyl is currently not covered by any of the generic groups defined in drug control legislation but may eventually be covered under medicines legislation. However, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovenia and Spain and Turkey reported that 4-fluoroisobutyrfentanyl is not subject to control measures at the national

level. Slovakia did not provide information on 4-fluoroisobutyrfentanyl controls. The EMCDDA and Europol continues to monitor 4-fluoroisobutyrfentanyl to confirm that new information is provided to the Member States, the European Medicines Agency, and the Commission through information exchange of the European Union Early Warning System.

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

Because abusers of 4-fluoroisobutyrfentanyl are likely to obtain these substances through unregulated sources and in uncontrolled clandestine laboratories, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user (Baron et al., 2011; Davies et al., 2010). Limited pharmacological information is available for 4-fluoroisobutyrfentanyl, increasing the risk for harmful adverse events.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 39th ECDD: Evaluation of 4-FIBF

Please refer to separate Annex 1 document published on ECDD website