Critical Review Report:

p-Fluoro-butyrylfentanyl

Expert Committee on Drug Dependence

Forty-first Meeting

Geneva, 12-16 November 2018

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

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Executive Summary

Substance identification

p-Fluoro-butyrylfentanyl (IUPAC name: *N*-(4-fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analog of the opioid analgesic fentanyl. In Europe, it was first reported in 2014 followed by the Untied States of America in 2015. Samples obtained from seizures and collections suggest that *p*-fluoro-butyrylfentanyl appears in powder, tablet, nasal spray and e-liquid form. Examples exist where it might be found in samples mixed with heroin.

WHO Review History

p-Fluoro-butyrylfentanyl has not been previously pre-reviewed or critically reviewed.

Chemistry

There is no specific information available about the routes of synthesis employed for the *p*-fluoro-butyrylfentanyl products circulating on the drug market but straightforward methods for its preparation exist without requiring access to precursors that are controlled internationally. Routes of synthesis also exist that might require the use of a controlled precursor.

Ease of convertibility into controlled substances

p-Fluoro-butyrylfentanyl could be converted to its isomer *p*-fluoro-isobutyrylfentanyl (IUPAC name: *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide), which is listed in Schedule I of the Single Convention on Narcotic Drugs of 1961, as amended by the 1972 Protocol.

Similarity to known substances / Effects on the central nervous system

Data from human studies are not available but the information available so far suggests that the effects induced by *p*-fluoro-butyrylfentanyl are also shared by other synthetic opioids such as fentanyl and heroin.

General pharmacology

Pharmacological studies have shown that *p*-fluoro-butyrylfentanyl is qualitatively similar to fentanyl and heroin. *p*-Fluoro-butyrylfentanyl binds to μ-opioid receptors (MOR) with high selectivity over the κ- and δ-opioid receptors and has been shown to act as a partial agonist at MOR in a [^{35}S]GTPγS binding assay. Similar to both fentanyl and morphine, *p*-fluoro-butyrylfentanyl was also shown to induce locomotor activity and antinociceptive effects in mice. Antinociceptive effects were attenuated by pre-treatment with naltrexone.

Toxicology

Data on the toxicology of *p*-fluoro-butyrylfentanyl could not be identified.

Adverse reactions in humans

p-Fluoro-butyrylfentanyl has been detected in biological samples obtained from fatal intoxication cases although unambiguous differentiation from the *p*-fluoro-isobutyrylfentanyl isomer was not

always possible. A report detailing an acute intoxication revealed that clinical features included disorientation, slurred speech and hypotension.

Dependence potential

No studies available. Experience with fentanyl and other synthetic opioids suggest that the dependence potential might extend to *p*-fluoro-butyrylfentanyl but further studies are warranted to explore this.

Abuse potential

Whilst no formal studies exist, the limited available information indicates that *p*-fluoro-butyrylfentanyl is used by experimental users (psychonauts) and people who also use synthetic opioids and opiates. It is likely that *p*-fluoro-butyrylfentanyl will be associated with abuse liability.

Therapeutic applications / usefulness

p-Fluoro-butyrylfentanyl is not known to have any therapeutic uses.

Listing on WHO Model List of Essential Medicines

p-Fluoro-butyrylfentanyl is not listed.

Marketing authorizations

p-Fluoro-butyrylfentanyl is not known to have any marketing authorizations.

Industrial use

p-Fluoro-butyrylfentanyl is not known to have any agricultural, industrial or cosmetic uses even though it is available for purchase as a 'research chemical'.

Non-medical use

The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Similar to other fentanils, *p*-fluoro-butyrylfentanyl may be administered as a solution (e.g. using nasal sprays), orally as a powder (including in capsules or tablets), or by insufflation of a powder; it can also be administered sublingually or intranasally via a spray; administered by injection (intramuscular or intravenous) or inhaled by vaporizing.

Nature and magnitude of public health problems

Use of *p*-fluoro-butyrylfentanyl appears to be limited to recreational substance users rather than the general population. Marginalized and vulnerable opioid users including those who inject such substances also use fentanyl analogs. However, users may not be aware of using them and the high potency associated with fentanyl analogs might result in increased risks of life-threatening overdoses. At the same time, fentanyl and its analogs pose a serious risk of accidental exposure to such products with the potential for subsequent poisoning of the public, law enforcement and emergency personnel, as well as medical/laboratory personnel.

Licit production, consumption, and international trade

p-Fluoro-butyrylfentanyl is not known to have any agricultural, industrial or cosmetic uses even though it is available for purchase as a 'research chemical'.

Illicit manufacture and traffic

So far the total number of reports describing the identification of *p*-fluoro-butyrylfentanyl seems comparatively low but it an increase in detections has been reported in the US. *p*-Fluoro-butyrylfentanyl can be purchased from Internet retailers.

Current international controls and their impact

p-Fluoro-butyrylfentanyl is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

Current and past national controls

p-Fluoro-butyrylfentanyl is controlled in some UN Member States.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

244195-31-1 (free base)

C. Other Chemical Names

N-(4-Fluorophenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide
N-(4-Fluorophenyl)-*N*-(1-phenethyl-4-piperidinyl)butanamide
p-Fluoro-butyrylfentanyl
para-Fluoro-butyrylfentanyl
4-Fluoro-butyrylfentanyl
4′-Fluoro-butyryfentanyl
p-Fluoro-butanoylfentanyl
para-Fluoro-butanoylfentanyl
4-Fluoro-butanoylfentanyl
4′-Fluoro-butanoylfentanyl
p-Fluoro-butyrfentanyl
para-Fluoro-butyrfentanyl
4-Fluoro-butyrfentanyl
4′-Fluoro-butyrfentanyl

D. Trade Names

Not applicable.

E. Street Names

4-FBF; 4PBF; PFBF; *p*-FBF; street names also include chemical names.

F. Physical Appearance

The hydrochloride salt of *p*-fluoro-butyrylfentanyl has been described as an off-white powder[1] 1 and a neat[2] and crystalline solid.[3] In its pure form, *p*-fluoro-butyrylfentanyl hydrochloride is expected to be odorless.

G. WHO Review History

p-Fluoro-butyrylfentanyl has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that *p*-fluoro-butyrylfentanyl 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.

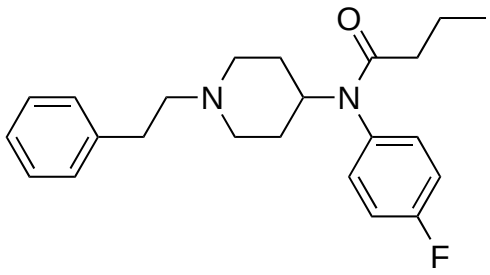
2. Chemistry

A. Chemical Name

IUPAC Name:
N-(4-Fluorophenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide
CA Index Name:
N-(4-Fluorophenyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]butanamide

B. Chemical Structure

Free base:



Molecular Formula: $C_{23}H_{29}FN_2O$
Molecular Weight: 368.50 g/mol

C. Stereoisomers

Not applicable.

D. *Methods and Ease of Illicit Manufacturing*

Information on the synthesis of *p*-fluoro-butyrylfentanyl products encountered on the market could not be identified. It is expected that the methods used for the synthesis of fentanyl[e.g.4-8] are equally applicable to *p*-fluoro-butyrylfentanyl by changing the widely available reagents accordingly. One procedure describing the preparation of fentanyl has also been published on the Internet.[9] The methods used for the synthesis of such fentanyl analogs are straightforward. In the analytical characterization study published by Ohta and Suzuki,[10] *p*-fluoro-butyrylfentanyl and other analogs have been prepared. The methodology was not included in the investigation but the authors commented on the adaptation of a procedure published by Van Bever and co-workers from Janssen Pharmaceutica in 1974.[5] The reaction scheme arising from this (assuming that the procedure was followed verbatim) is summarized in Figure 1A. The carbamate starting material (a) undergoes reductive amination with 4-fluoroaniline via the imine intermediate (b) to form methyl 4-[(4-fluorophenyl)amino]piperidine-1-carboxylate (c). Acylation with butanoic anhydride (or butanoyl chloride) yields (d), which converts under reflux with acid to *N*-(4-fluorophenyl)piperidin-4-amine (e). Substitution with (2-chloroethyl)benzene (or (2-bromoethyl)benzene) gives *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine (f) with the final product (g) being formed by

acylation with butanoic anhydride (or butanoyl chloride). Intermediate (f) represents the fluorinated analog of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP), which is a controlled precursor[11] used for the preparation of fentanyl[9] and other analogs. The fluorinated 4-F-ANPP (f) could also be prepared from 1-(2-phenylethyl)piperidin-4-one (also known as *N*-phenethyl-4-piperidone, NPP) and 4-fluoroaniline. However, NPP is also listed in Table 1 of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.[11]

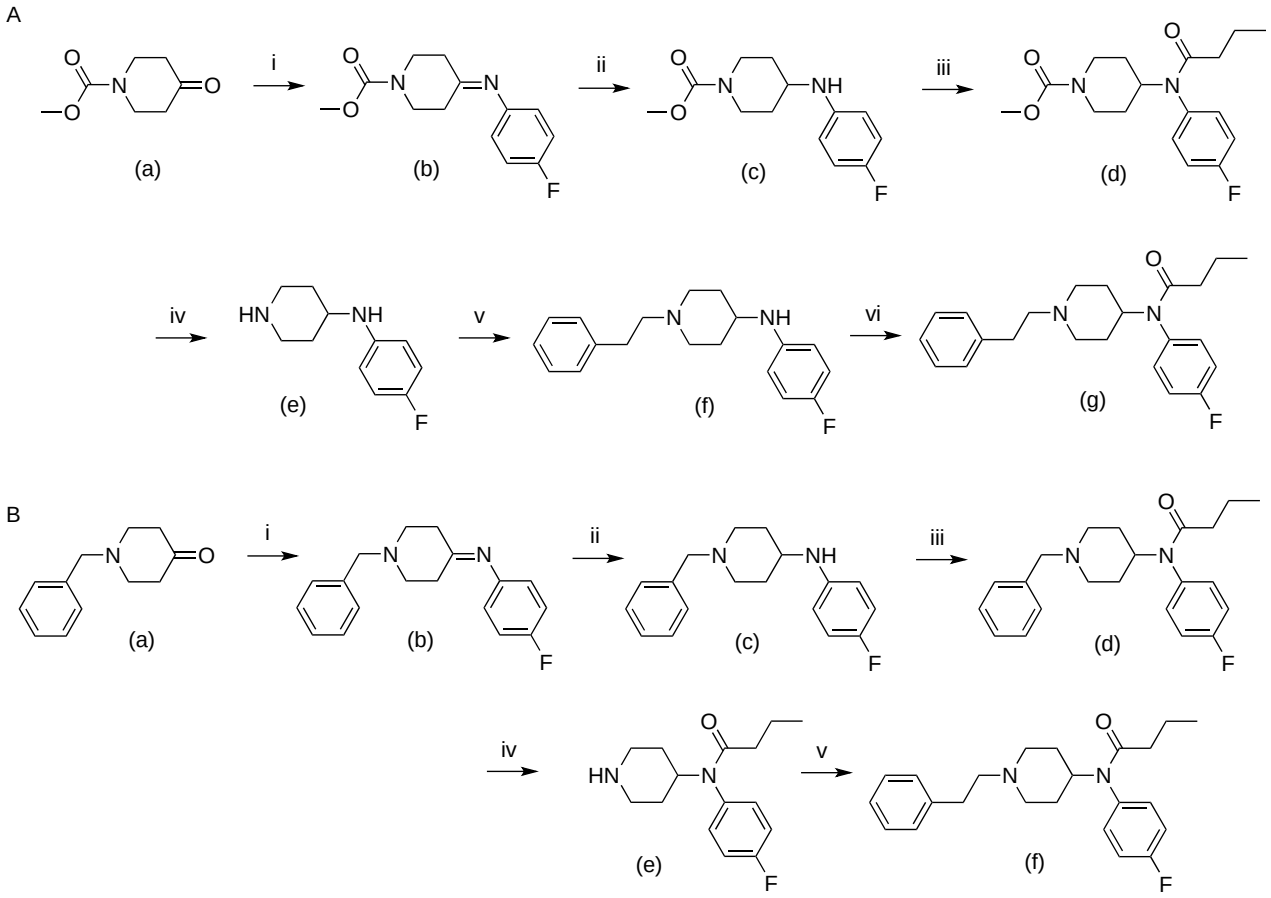


Figure 1. Examples of potential procedures. A. Synthesis of *p*-fluoro-butyrylfentanyl (g) according to Ohta and Suzuki[10] adapting the procedure published by Van Bever et al.[5] i) 4-F(C_6H_4)NH_2; ii) $NaBH_4$; iii) $(CH_3CH_2CH_2CO)_2O$; iv) 48% HBr; v) $PhCH_2CH_2X$ (X = Cl or Br); vi) $(CH_3CH_2CH_2CO)_2O$. B: Potential synthesis of *p*-fluoro-butyrylfentanyl (f) following one of the earliest procedures employed by Janssen.[4] i) 4-F(C_6H_4)NH_2; ii) acid catalyst (e.g. *p*TsOH); ii: $LiAlH_4$; iii) $(CH_3CH_2CH_2CO)_2O$; iv) H_2, Pd-C; v) $PhCH_2CH_2Cl$, KI, Na_2CO_3.

Figure 1B outlines another potential approach based on one of the earliest procedures used for the preparation of fentanyl[4] The starting material 1-benzylpiperidin-4-one (a) undergoes reductive amination with 4-fluoroaniline (via imine (b)) to form 1-benzyl-*N*-(4-fluorophenyl)piperidin-4-amine (c), which undergoes acylation with either butanoic anhydride or butanoyl chloride to afford *N*-(1-benzylpiperidin-4-yl)-*N*-(4-fluorophenyl)butanamide (d). Debenzylation by

hydrogenation provides access to *N*-(4-fluorophenyl)-*N*-(piperidin-4-yl)butanamide (e). Alkylation of the piperidine nitrogen with either (2-chloroethyl)benzene or (2-bromoethyl)benzene yields *p*-fluoro-butyrylfentanyl (f).

E. Chemical Properties

Melting point
114–115 °C[12]
Boiling point
Information could not be identified.
Solubility
Hydrochloride salt: ~0.25 mg/mL in a 1:3 solution of dimethyl sulfoxide:phosphate buffered saline (pH 7.2); ~5 mg/mL in ethanol; ~10 mg/mL in dimethyl sulfoxide and dimethylformamide.[3] The free base is expected to be only sparingly soluble in water. A collected hydrochloride salt sample identified as *p*-fluoro-butyrylfentanyl was noted as being "soluble" in dichloromethane, methanol and water.[13]

F. Identification and Analysis

Identification, especially when available in larger quantities than normally encountered in forensic toxicological work, is straightforward. Presumptive color test results performed on submitted samples determined to contain *p*-fluoro-butyrylfentanyl have been published in the public domain.[14] Results from analytical studies have been published and include data on thin layer chromatography,[10] gas chromatography electron ionization mass spectrometry (MS),[1, 10, 12, 13, 15] electrospray ionization tandem MS,[12, 16-20] nuclear magnetic resonance spectroscopy,[12 1, 13], immunoassays,[21] ultraviolet–visible spectrophotometry,[12] and Fourier transform infrared spectroscopy.[13]

Analytical challenges may arise, for example when dealing with closely related isomers such as *N*-(4-fluorophenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (*p*-fluoro-isobutyrylfentanyl)[22] that underwent critical review by the World Health Organization in 2017.[23] In addition, both of these fentanils can also exist in the *ortho*- (2-fluorophenyl) or *meta*-fluoro (3-fluorophenyl) forms, which adds to the complexity. The implementation of adequate separation techniques might be needed to reduce the potential for misidentification, especially when dealing with samples (e.g. biological) that may only contain trace quantities. A case of mislabeling has been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) where a seized, powdered sample labeled as "4-F-BF" was determined to contain an *N*-benzyl analog instead.[24] In this case, the unambiguous identity could not be established as the possibility existed that the seized compound might have represented up to six different isomers, that is, *N*-(1-benzylpiperidin-4-yl)-*N*-(4-fluorophenyl)butanamide (three different fluorophenyl isomers) and *N*-(1-benzylpiperidin-4-yl)-*N*-(4-fluorophenyl)-2-methylpropanamide (three different fluorophenyl isomers). It is noteworthy that the *N*-benzyl analog

could be considered an intermediate formed during the synthesis of the corresponding fentanyl analog (Figure 1B, structure (d)).

3. Ease of Convertibility Into Controlled Substances

No information available. However, since *p*-fluoro-isobutyrylfentanyl is a controlled substance (Schedule I of the Single Convention on Narcotic Drugs of 1961, as amended by the 1972 Protocol), it appears conceivable that *p*-fluoro-butyrylfentanyl could be converted by hydrolysis of the 4-*N*-butanoyl group with an acid (e.g. HCl) to *N*-(4-fluorophenyl)-1-(2-phenylethyl)piperidin-4-amine (4-F-ANPP), which in turn could be acylated again with 2-methylpropanoyl chloride or 2-methylpropanoic anhydride. Examples for acid-induced hydrolysis exist, for example, for fentanyl[25] and ohmefentanyl (*N*-[1-(2-hydroxy-2-phenylethyl)-3-methylpiperidin-4-yl]-*N*-phenylpropanamide).[26]

4. General Pharmacology

A. Routes of administration and dosage

Similar to other fentanils,[27, 28] *p*-fluoro-butyrylfentanyl may be administered as a solution (e.g. using nasal sprays), orally as a powder (including in capsules or tablets), or by insufflation of a powder; it can also be administered sublingually or intranasally via a spray; administered by injection (intramuscular or intravenous) or inhaled by vaporizing. Information received by the EMCDDA based on analyses of seized and collected material and published literature involving adverse events suggests the existence of *p*-fluoro-butyrylfentanyl-containing powders, tablets, electronic cigarette liquid,[12] and nasal spray formulations.[16, 29, 30] User reports suggesting intravenous, sublingual (spray) and intranasal (spray) routes of administration of *p*-fluoro-butyrylfentanyl have been published on the Internet.[e.g.31-33] Case report literature suggests that *p*-fluoro-butyrylfentanyl was orally administered in pill form.[16] It has been estimated that oral doses may range from 300 µg ("low") and "common" doses of 600–900 µg to "strong" doses of 900–1200 µg.[34] However, estimating the doses administered by users may not be possible as this appears to depend on factors such as the tolerance of the users, the use of other drugs, desired effects, and the route of administration.[e.g.31-33, 35, 36]

B. Pharmacokinetics

Detailed information specifically on *p*-fluoro-butyrylfentanyl could not be identified but it appears likely that the formation metabolic transformation products (e.g. *N*-(4-fluorophenyl)-*N*-(piperidin-4-yl)butanamide, "nor-*p*-fluoro-butyrylfentanyl"[16]) follows similar mechanisms that were seen with the isomeric *p*-fluoro-isobutyrylfentanyl[23, 37] and other fentanils.[27] "Insufflated" routes of administration have been suggested to induce effects in the 30–60 min range,[34] which suggests that the desired effects may be short-lasting. For the reasons mentioned above however, such estimations should be viewed with caution.

C. *Pharmacodynamics*

In vitro data:

Current available data suggest that *p*-fluoro-butyrylfentanyl, similar to morphine and fentanyl, binds to μ-opioid receptors (MOR) with high selectivity over the κ- and δ-opioid receptors (KOR and DOR) (Table 1).[38] Functional studies using the [^{35}S]GTPγS binding assay also demonstrated that *p*-fluoro-butyrylfentanyl acted as a partial agonist at MOR and KOR, which meant that the test drug showed a reduced efficacy for receptor activation compared with morphine and fentanyl (Table 1). Compared to the recently controlled isomer *p*-fluoro-isobutyrylfentanyl (Ki = 0.451 nM), determined under identical conditions, *p*-fluoro-butyrylfentanyl was found to show a comparable binding affinity at MOR. At the same time, *p*-fluoro-isobutyrylfentanyl was ~6-times less potent (EC_{50} = 115 nM) than *p*-fluoro-butyrylfentanyl although it acted as a full agonist with a maximum efficacy of 91.6%[23, 37] compared to 49.4% observed with *p*-fluoro-butyrylfentanyl.

Table 1. Receptor binding and functional activity data for *p*-fluoro-butyrylfentanyl (modified from[38]).[a]

MOR	***p*FBF** [b]	**Morphine**	**Fentanyl**	**DAMGO**	**Naltrexone**
[^{3}H]DAMGO binding Ki (nM)	0.516 ± 0.073	0.213 ± 0.019	0.150 ± 0.030	0.1313 ± 0.0050	0.0793 ± 0.0042
IC_{50} (nM)	3.58 ± 0.53	1.432	1.00	0.883	0.532
Hill coefficient	-0.73 ± 0.07	-0.95 ± 0.02	-0.72 ± 0.07	-0.89 ± 0.06	-0.81 ± 0.36
[^{35}S]GTPγS binding	***p*FBF** [b]	**Morphine**	**Fentanyl**	**DAMGO**	–
Stimulation EC_{50} (nM)	17.9 ± 1.8	31.0 ± 8.2	17.9 ± 4.3	21.4 ± 4.2	–
Maximal stimulation (%) [c]	49.4 ± 4.3	83.3 ± 5.5	81.2 ± 7.4	96.8 ± 1.9	–
DOR	***p*FBF** [b]	**Morphine**	**Fentanyl**	**DPDPE-OH**	**Naltrexone**
[^{3}H]DPDPE binding K_i (nM)	351 ± 63	111 ± 14	242 ± 20	2.96 ± 0.57	14.2 ± 3.1
IC_{50} (nM)	566 ± 92	182	391	5.0	23.8
Hill coefficient	-0.74 ± 0.10	-0.96 ± 0.02	-0.93 ± 0.09	-0.94 ± 0.10	-1.03 ± 0.12
[^{35}S]GTPγS binding	***p*FBF** [b]	**Morphine**	**Fentanyl**	**DPDPE-OH**	–
Stimulation EC_{50} (nM)	>10 μM	870 ± 140	1,190 ± 140	7.22 ± 0.38	–
Maximal stimulation (%) [c]	6.7 ± 2.2	77.3 ± 2.3	58.0 ± 4.2	100.97 ± 0.97	–
KOR	***p*FBF** [b]	**Morphine**	**Fentanyl**	**U-50,488H**	**Nor-BNI**
[^{3}H]U-69,593 binding K_i (nM)	501 ± 81	27.9 ± 2.7	194 ± 20	0.155 ± 0.048	0.42 ± 0.16
IC_{50} (nM)	1,130 ± 190	63.4	436	0.35	0.86
Hill coefficient	-1.06 ± 0.08	-0.98 ± 0.06	-1.19 ± 0.17	-0.70 ± 0.03	-1.11 ± 0.23
[^{35}S]GTPγS binding	***p*FBF** [b]	**Morphine**	**Fentanyl**	**U-50,488H**	–

Stimulation EC_{50} (nM) Maximal stimulation (%) [c]	370 ± 120 51.3 ± 2.3	83 ± 23 86.8 ± 6.0	362 ± 47 72.9 ± 3.2	1.15 ± 0.22 93.6 ± 2.2	– –

[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. DOR: delta opioid receptor; KOR: kappa opioid receptor; MOR: mu opioid receptor; DAMGO: Tyr-Ala-Gly-*N*-Me-Phe-Gly-ol, DPDPE-OH: Tyr-Pen-Gly-Phe-Pen-OH [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 were the agonists DPDPE (delta), U50,488H (kappa) and DAMGO (mu) and the antagonists naltrexone (delta and mu) and nor-BNI (kappa).

[c] Maximal stimulation by test compound is normalized to the maximal stimulation by DPDPE (delta), U50,488H (kappa) or DAMGO (mu) above basal. Negative values indicate inhibition of basal [^{35}S]GTPγS binding.

[b] *p*FBF: *p*-Fluoro-butyrylfentanyl.

In vivo data:

Locomotor activity studies (adult male CFW mice; subcutaneous administration; distances traveled during 120 min test sessions recorded in 10 min intervals) have been carried out comparing *p*-fluoro-butyrylfentanyl (tested 0.1, 1, 10, and 100 mg/kg with fentanyl (0.1, 1 and 10 mg/kg) and morphine (1, 10, 100 and 180 mg/kg).[39]

p-Fluoro-butyrylfentanyl significantly increased distance traveled during several time intervals including at 10 mg/kg (10–80 min) and 100 mg/kg (10, 30–120 min). Fentanyl increased locomotion at 1 mg/kg (10–120 min), and 10 mg/kg (30–120 min), and morphine increased distances traveled at 10 mg/kg (40–90 min), 100 mg/kg (20–120 min), and 180 mg/kg (20–120 min). The dose-dependent activation of locomotor activity was confirmed to be qualitatively similar to fentanyl and morphine. As far as the total distances traveled were concerned, fentanyl induced the largest increase at 1 mg/kg followed by morphine at 180 mg/kg and 100 mg/kg, fentanyl at 10 mg/kg and *p*-fluoro-butyrylfentanyl at 10 mg/kg and 100 mg/kg. [39]

Antinociceptive effects (warm water tail-withdrawal test, 50°C, adult male CFW mice; subcutaneous administration) have been investigated and it was confirmed that *p*-fluoro-butyrylfentanyl increased the withdrawal latency consistent with delayed withdrawal times also observed with fentanyl and morphine used for comparison. Significant dose-dependent increases in tail withdrawal latencies were observed for all test drugs, which were attenuated by pre-treatment with naltrexone (Table 2). In this assay, *p*-fluoro-butyrylfentanyl showed 8.8% of the potency of fentanyl although it was 8.6-times more potent than morphine (Table 2).

p-Fluoro-butyrylfentanyl showed a higher potency in eliciting antinociception compared to locomotor stimulation. Straub tail was observed after administering all three drugs during tail-withdrawal tests and it was stated that other obvious and unusual signs were not observed.[40]

Table 2. Antinociceptive effects using the warm-water tail-withdrawal procedure.[40]

Test drug	ED_{50} (mg/kg)
p-Fluoro-butyrylfentanyl	0.9081
p-Fluoro-butyrylfentanyl + naltrexone (1 mg/kg)	9.8740
Fentanyl	0.0801
Fentanyl + naltrexone (1 mg/kg)	0.3162
Morphine	7.8210
Morphine + naltrexone (1 mg/kg)	11.5900

5. Toxicology

No information could be identified.

6. Adverse Reactions in Humans

The US Centers for Disease Control and Prevention estimated that drug overdose deaths involving synthetic opioids (excluding methadone) for the 12-month period ending in January of 2017 (20,145 deaths) increased significantly compared to the cases counted for the period ending in January of 2016 (9,945 deaths).[41] However, specific information related to a causal relationship of *p*-fluoro-butyrylfentanyl with adverse reactions is limited. One potential reason includes the challenges that might arise from the analytical differentiation from the *p*-fluoro-isobutyrylfentanyl isomer. For example, in 17 death cases reported to the US Drug Enforcement Administration, the analyses of postmortem blood samples included the identification of "*p*-fluoro-butyrylfentanyl/*p*-fluoro-isobutyrylfentanyl" presumably as a reflection of this challenge. *p*-Fluoro-butyrylfentanyl/*p*-fluoro-isobutyrylfentanyl was the constituent detected at the highest concentrations and thus might have been the main contributor to these deaths. Other drugs of abuse (including fentanyl analogs) have also been detected.

A case of acute intoxication occurring in January 2015 in Sweden and associated with the detection of *p*-fluoro-butyrylfentanyl involved a 25-year old male who presented with disorientation, unsteady, slurred speech and hypotension (90/60 mmHg) (poisoning severity score = 1). The patient was awake and displayed miotic pupils. He also reported the intake of "one pill" ~9 h prior to blood and urine sampling in the emergency department. The analysis of biofluids taken ~ 1h after admission revealed estimated *p*-fluoro-butyrylfentanyl concentrations of 15.0 ng/mL (serum), 9.5 µg/mL (urine), and 1.4 µg/mmol creatinine (urine). Pregabalin, tramadol, *O*-desmethyltramadol, 4-hydroxyalprazolam, and oxazepam were also detected.[16] *p*-Fluoro-butyrylfentanyl (not quantified), together other fentanyl

analogs and prescription medicines were detected in two cases associated with an acute intoxication involving *p*-methoxy-butyrylfentanyl.[30]

Two death cases associated with *p*-fluoro-butyrylfentanyl were reported from Poland (Table 3).[12]

Table 3. Death cases involving the detection of *p*-fluoro-butyrylfentanyl in Poland

Year [a]	Patent, age	Comments	Ref
2017	M, 26	Found dead at home. An electronic cigarette and e-liquid were found near the deceased. *p*-Fluoro-butyrylfentanyl was identified in e-liquid (35 mg/mL); glycerol was the main matrix and nicotine was also detected. *p*-Fluoro-butyrylfentanyl detections in biological samples: 91 ng/mL (blood); 200 ng/mL (urine); 902 ng/g (liver); 411 ng/g (kidney); 248 ng/g (brain), 8450 ng/g (stomach).	12
2017	F, 26	Found dead at home; known as occasional user of new psychoactive substances and "drugs". A plastic bag with a light-yellow powder was found near the deceased. Powder was identified as *p*-fluoro-butyrylfentanyl. *p*-Fluoro-butyrylfentanyl detections in biological samples: 112 ng/mL (blood); 414 ng/mL (urine); 136 ng/g (liver); 197 ng/g (kidney).	12

[a] Year of publication. Cases occurred in 2015.

The detection of other substances has not been reported. A 2017 case series (22 male, 3 female, January to May) from the United Kingdom revealed the detection of *p*-fluoro-butyrylfentanyl in biological samples obtained from acute intoxication and death cases (12/22 cases). Carfentanil concentrations were predominant but a range of other fentanyl analogs (including *p*-fluoro-butyrylfentanyl but not quantified), benzodiazepines, markers for street heroin use, and other substances were also detected.[20]

7. Dependence Potential

A. Animal Studies

Studies that have investigated the dependence potential of *p*-fluoro-butyrylfentanyl in animals could not be identified.

B. Human Studies

Studies that have investigated the dependence potential of *p*-fluoro-butyrylfentanyl in humans could not be identified. However, it is well established that opioid analgesics such as fentanyl can induce tolerance and dependence. Further research

might be required in order to investigate these effects with *p*-fluoro-butyrylfentanyl.

8. Abuse Potential

A. Animal Studies

Studies that have investigated the abuse potential of *p*-fluoro-butyrylfentanyl in animals could not be identified.

B. Human Studies

Studies that have investigated the abuse potential of *p*-fluoro-butyrylfentanyl in humans could not be identified although cases of analytically confirmed ingestions have been reported (Section 6).

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

Information about therapeutic use could not be identified.

10. Listing on the WHO Model List of Essential Medicines

p-Fluoro-butyrylfentanyl is not listed.

11. Marketing Authorizations (as a Medicinal Product)

p-Fluoro-butyrylfentanyl was never marketed as a medicinal product.

12. Industrial Use

Information about recorded industrial use could not be identified.

13. Non-Medical Use, Abuse and Dependence

Surveys that systematically assess the prevalence of *p*-fluoro-butyrylfentanyl use within the general population are not available. The detection of *p*-fluoro-butyrylfentanyl in biological fluids confirms that this substance is used recreationally (Sections 4 and 6). The available information suggests that the use of this substance is associated with individuals who might be abusing/misusing heroin and prescription opioid analgesics and heroin. *p*-Fluoro-butyrylfentanyl might also have attracted the attention of experimental substance users (psychonauts) (Section 4).

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

Data on the effects of *p*-fluoro-butyrylfentanyl on the ability to drive and operate machines could not be identified. Since it is well established that opioid analgesics, such as fentanyl, impact on the mental and physical ability required for driving and operating machinery, it is likely that this might also extend to *p*-fluoro-butyrylfentanyl. Some of these substances

may be sold as another substance and/or are not always labeled, a phenomenon that has been observed with the use of other fentanyl analogs. Examples exist where *p*-fluoro-butyrylfentanyl was detected as an adulterant in samples of heroin obtained from the cryptomarket.[42] The US Drug Enforcement Administration reported the detection of cocaine samples adulterated with fentanyl and fentanyl analogs. The detections occurred in seized samples obtained in the period from 2016–2017 in Florida (USA).[43] Marginalized and vulnerable opioid users including those who inject such substances also use fentanyl analogs. However, users may not be aware of using them and the high potency associated with fentanyl analogs might result in increased risks of life-threatening overdoses.

The observation that *p*-fluoro-butyrylfentanyl and other analogs are also available in the form of nasal sprays (a case of a *p*-fluoro-butyrylfentanyl containing e-liquid has also been reported) raises questions as to whether these dosage forms might render the use of fentanils more attractive and/or socially acceptable.[28] Further studies are warranted to assess whether this might be associated with the attraction of new user groups.

The high potency of fentanyl and its analogs pose a serious risk of accidental exposure to products with the potential for subsequent poisoning of the public, law enforcement and emergency personnel, as well as medical/laboratory personnel.[27, 28]

15. Licit Production, Consumption and International Trade

It is used as a reference material for scientific research. It is not known to have any agricultural, industrial or cosmetic uses even though it is available for purchase as a 'research chemical'. Please refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit Manufacture and Traffic and Related Information

Reports have been received from the European Early-Warning System on new psychoactive substances that *p*-fluoro-butyrylfentanyl (first notified to EMCDDA in March 2014[44]) was encountered in seizures and collected specimen (powder and tablets) in Latvia, Slovenia, Sweden and Poland.[29]

The background information and evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for temporary scheduling document[45] states that the identification of *p*-fluoro-butyrylfentanyl was featured in five reports since September 2014 (STRIDE and STARLiMS queries). The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the USA, has recorded 220 reports when queried on November 3, 2017.[46] According to the Drug Enforcement Administration's (DEA) Special Testing and Research Laboratory's Emerging Trends Program, *p*-fluoro-butyrylfentanyl was identified in 3 out of 1299 identifications of fentanyl and fentanyl related substances (and other new opioids).[47]

Detections of *p*-fluoro-butyrylfentanyl have also been reported to the United Nations Office on Drugs and Crime's (UNODC) Early Warning Advisory on New Psychoactive

Substances. Detections of *p*-fluoro-butyrylfentanyl were reported by three countries in 2015, five countries in 2016, and one country in 2017 (as of 25 August 2018).[48]

Please also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

p-Fluoro-butyrylfentanyl is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

Detections of *p*-fluoro-butyrylfentanyl may be under-reported given that the substance might not be routinely screened for in all laboratories receiving samples for analysis.

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