



# Critical Review Report: *p*-Methoxy-butrylfentanyl

Expert Committee on Drug Dependence

Forty-first Meeting

Geneva, 12-16 November 2018

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## Acknowledgements

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This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a critical review for the 41st Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge Simon Brandt for drafting the report and Jurgen Rehm, Jakob Manthey, and Astrid Otto for the questionnaire analysis and writeup.

The WHO Secretariat would also like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA) for providing data on p-methoxy-butyrylfentanyl collected through the European Union Early Warning System, which includes data provided by Reitox National Focal Points in the EU Member States, Turkey and Norway, as well as the Europol National Units.

## Executive Summary

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### Substance identification

*p*-Methoxy-butyrylfentanyl (IUPAC name: *N*-(4-methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide) is a synthetic analog of the opioid analgesic fentanyl. In Europe, it was first reported in 2015 followed by the United States of America later on. Samples obtained from seizures and collections suggest that *p*-methoxy-butyrylfentanyl occurs in powder, tablet, and nasal spray form.

### WHO Review History

*p*-Methoxy-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*-methoxy-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*-Methoxy-butyrylfentanyl could be converted into various other fentanils but retaining the 4-methoxyphenyl group would also render them uncontrolled at this time.

### 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*-methoxy-butyrylfentanyl are also shared by other synthetic opioids such as fentanyl and heroin.

### General pharmacology

Pharmacological studies have shown that *p*-methoxy-butyrylfentanyl is qualitatively similar to fentanyl and heroin. *p*-Methoxy-butyrylfentanyl binds to  $\mu$ -opioid receptors (MOR) with high selectivity over the  $\kappa$ - and  $\delta$ -opioid receptors and has been shown to act as a partial agonist at MOR in a [<sup>35</sup>S]GTP $\gamma$ S binding assay. Similar to both fentanyl and morphine, *p*-methoxy-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*-methoxy-butyrylfentanyl could not be identified.

### Adverse reactions in humans

*p*-Methoxy-butyrylfentanyl has been detected in biological samples obtained from acute intoxication cases. Reported clinical features included reduced level of consciousness, respiratory depression, miosis, tachycardia, renal insufficiency, suspected aspiration, and apnea. Naloxone treatments were required in some cases to reverse drug-induced respiratory depression.

### **Dependence potential**

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

### **Abuse potential**

Whilst no formal studies exist, the limited available information indicates that *p*-methoxy-butyrylfentanyl is used by experimental users (psychonauts) including people who have a history of abusing other synthetic opioids and opiates. It seems likely that *p*-methoxy-butyrylfentanyl might be associated with abuse liability.

### **Therapeutic applications / usefulness**

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

### **Listing on WHO Model List of Essential Medicines**

*p*-Methoxy-butyrylfentanyl is not listed.

### **Marketing authorizations**

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

### **Industrial use**

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

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### **Illicit manufacture and traffic**

So far the total number of reports describing the identification of *p*-methoxy-butyrylfentanyl is very limited. *p*-Methoxy-butyrylfentanyl can be purchased from Internet retailers.

### **Current international controls and their impact**

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

### **Current and past national controls**

*See Annex A*



## 1. Substance identification

### A. International Nonproprietary Name (INN)

Not applicable.

### B. Chemical Abstract Service (CAS) Registry Number

2088842-68-4 (free base)

### C. Other Chemical Names

*N*-(4-Methoxyphenyl)-*N*-(1-phenethylpiperidin-4-yl)butyramide  
*N*-(4-Methoxyphenyl)-*N*-(1-phenethyl-4-piperidinyl)butanamide  
*p*-Methoxy-butyrylfentanyl  
*para*-Methoxy-butyrylfentanyl  
4-Methoxy-butyrylfentanyl  
4'-Methoxy-butyrylfentanyl  
*p*-Methoxy-butanoylfentanyl  
*para*-Methoxy-butanoylfentanyl  
4-Methoxy-butanoylfentanyl  
4'-Methoxy-butanoylfentanyl  
*p*-Methoxy-butyrfentanyl  
*para*-Methoxy-butyrfentanyl  
4-Methoxy-butyrfentanyl  
4'-Methoxy-butyrfentanyl

### D. Trade Names

Not applicable.

### E. Street Names

*p*-MeO-BF; 4-MeO-BF; street names also include chemical names.

### F. Physical Appearance

The hydrochloride salt of *p*-methoxy-butyrylfentanyl has been described as a white powder<sup>1</sup> and a neat solid.<sup>2</sup> In its pure form, *p*-methoxy-butyrylfentanyl hydrochloride is expected to be odorless.

### G. WHO Review History

*p*-Methoxy-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*-methoxy-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:**

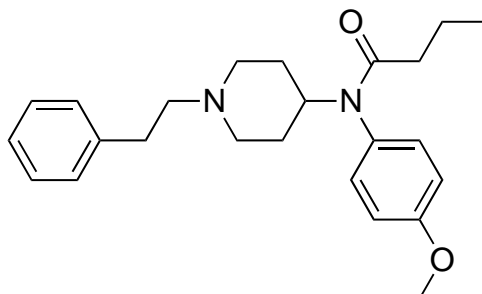
*N*-(4-Methoxyphenyl)-*N*-[1-(2-phenylethyl)piperidin-4-yl]butanamide

**CA Index Name:**

*N*-(4-Methoxyphenyl)-*N*-[1-(2-phenylethyl)-4-piperidinyl]butanamide

### B. Chemical Structure

**Free base:**



**Molecular Formula:** C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>

**Molecular Weight:** 380.53 g/mol

### C. Stereoisomers

Not applicable.

### D. Methods and Ease of Illicit Manufacturing

Information on the synthesis of *p*-methoxy-butrylylfentanyl products encountered on the market could not be identified. It is expected that the methods used for the synthesis of fentanyl<sup>e.g.3-7</sup> are equally applicable to *p*-methoxy-butrylylfentanyl by changing the widely available reagents accordingly. One common procedure is shown in Figure 1A and is based on the published synthesis of *p*-methoxy-fentanyl,<sup>e.g.8</sup> which is comparable to one process describing the preparation of fentanyl available on the Internet.<sup>9</sup> 1-(2-Phenylethyl)piperidin-4-one (a) (also known as *N*-phenethyl-4-piperidone, NPP) is condensed with *p*-methoxyaniline (*p*-anisidine) followed by reduction of the imine (b) to afford *N*-(4-methoxyphenyl)-1-(2-phenylethyl)piperidin-4-amine as intermediate (c). Acylation with butanoic anhydride (or butanoyl chloride) yields the product *p*-methoxy-butrylylfentanyl (d). However, NPP is listed in Table 1 of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.<sup>10</sup> Intermediate (c) represents the methoxylated analog of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP), which is a controlled precursor<sup>10</sup> used for the preparation of fentanyl and other analogs. 4-MeO-ANPP is however currently not controlled.

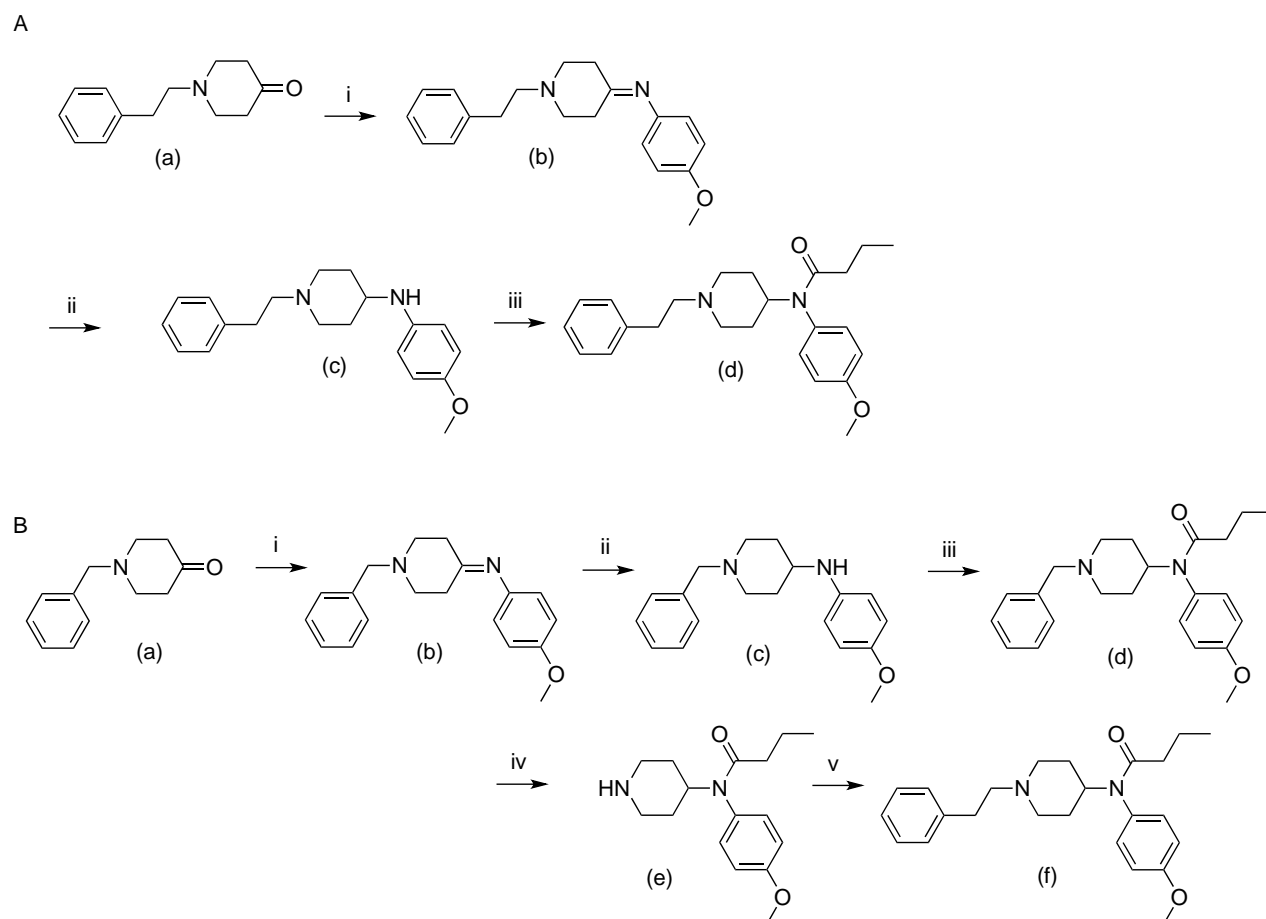


Figure 1. Examples of potential procedures used for the preparation of *p*-methoxy-butrylylfentanyl. A. Adapting the procedure described for the preparation of *p*-methoxy-fentanyl.<sup>e,g,8</sup> i) 4-MeO(C<sub>6</sub>H<sub>4</sub>)NH<sub>2</sub>; ii) NaBH<sub>4</sub>; iii) (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CO)<sub>2</sub>O. B. Potential synthesis of *p*-methoxy-butrylylfentanyl (f) following one of the earliest procedures employed by Janssen.<sup>3</sup> i) 4-MeO(C<sub>6</sub>H<sub>4</sub>)NH<sub>2</sub>; ii) acid catalyst (e.g. pTsOH); ii) LiAlH<sub>4</sub>; iii) (CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>CO)<sub>2</sub>O; iv) H<sub>2</sub>, Pd-C; v) PhCH<sub>2</sub>CH<sub>2</sub>Cl, KI, Na<sub>2</sub>CO<sub>3</sub>.

Figure 1B outlines another potential approach based on one of the earliest procedures used for the preparation of fentanyl.<sup>3</sup> *p*-Methoxy-butrylylfentanyl was captured by the Janssen patent but not explicitly described. The starting material 1-benzylpiperidin-4-one (a) undergoes reductive amination with 4-methoxyaniline (via (b)) to form 1-benzyl-*N*-(4-methoxyphenyl)piperidin-4-amine (c), which undergoes acylation with either butanoic anhydride or butanoyl chloride to afford *N*-(1-benzylpiperidin-4-yl)-*N*-(4-methoxyphenyl)butanamide (d). Debenzylation by hydrogenation provides access to *N*-(4-methoxyphenyl)-*N*-(piperidin-4-yl)butanamide (e). Alkylation of the piperidine nitrogen with either (2-chloroethyl)benzene or (2-bromoethyl)benzene yields *p*-methoxy-butrylylfentanyl (f).

## E. Chemical Properties

### Melting point

Information could not be identified.

### Boiling point

Information could not be identified.

### Solubility

The free base is expected to be only sparingly soluble in water. A collected hydrochloride salt sample identified as *p*-methoxy-butyrylfentanyl was noted as being soluble in methanol and water and partially soluble in dichloromethane.<sup>11</sup>

## F. Identification and Analysis

Identification, especially when available in larger quantities than normally encountered in forensic toxicological work, is straightforward. Results from analytical studies have been published and include data on gas chromatography electron ionization mass spectrometry (MS),<sup>1, 11, 12</sup> electrospray ionization MS,<sup>13, 14</sup> nuclear magnetic resonance spectroscopy,<sup>1, 11</sup> immunoassays,<sup>15</sup> and Fourier transform infrared spectroscopy.<sup>1, 11</sup>

Analytical challenges may arise, for example when dealing with closely related isomers such as *N*-(4-methoxyphenyl)-2-methyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide (*p*-methoxy-isobutyrylfentanyl). In addition, both of these fentanils can also exist in the *ortho*- (2-methoxyphenyl) or *meta*-methoxy (3-methoxyphenyl) 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.

## 3. Ease of Convertibility Into Controlled Substances

No information available. A conversion of *p*-methoxy-butyrylfentanyl to a range of other fentanyl analogs is feasible but the retention of the 4-methoxyphenyl group would lead to substances that are also currently not controlled under the UN system.

## 4. General Pharmacology

### A. Routes of administration and dosage

Similar to other fentanils,<sup>16, 17</sup> *p*-methoxy-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 suggests the existence of *p*-methoxy-butyrylfentanyl-containing powders, tablets and nasal

spray formulations.<sup>13, 18</sup> Information on *p*-methoxy-butyrylfentanyl shared in the form of user reports is limited, which means that reliable information on doses could not be identified. In addition, 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. Case report literature suggests that *p*-methoxy-butyrylfentanyl-containing pills and nasal sprays were ingested.<sup>13</sup>

## B. Pharmacokinetics

Detailed information specifically on *p*-methoxy-butyrylfentanyl could not be identified but it appears likely that at least some of the metabolic transformation products follows similar mechanisms of formation that were seen with other fentanils.<sup>e.g.13, 16, 19</sup> Regarding the duration of effects, some estimations exist online. “Insufflated” routes of administration: onset 1–2 min; duration 30–75 min; after effects 1–2 h. Oral administration: onset 5–15 min; duration 45–120 min; after effects 1–2 h.<sup>20</sup> For the reasons mentioned above however, such estimations should be viewed with caution.

## C. Pharmacodynamics

### In vitro data:

Current available data suggest that *p*-methoxy-butyrylfentanyl, similar to morphine and fentanyl, binds to  $\mu$ -opioid receptors (MOR) with high selectivity over the  $\kappa$ - and  $\delta$ -opioid receptors (KOR and DOR) (Table 1).<sup>21</sup> Functional studies using the [<sup>35</sup>S]GTP $\gamma$ S binding assay also demonstrated that *p*-methoxy-butyrylfentanyl acted as a partial agonist at MOR with a far reduced efficacy at DOR and agonist properties at KOR. Its potency for binding and MOR activation was significantly lower compared to morphine and fentanyl (Table 1).

Table 1. Receptor binding and functional activity data for *p*-methoxy-butyrylfentanyl (modified from<sup>21</sup>).<sup>a</sup>

MOR	<i>p</i> MBF <sup>b</sup>	Morphine	Fentanyl	DAMGO	Naltrexone
[ <sup>3</sup> H]DAMGO binding K <sub>i</sub> (nM)	1.485 ± 0.097	0.213 ± 0.019	0.150 ± 0.030	0.1313 ± 0.0050	0.0793 ± 0.0042
IC <sub>50</sub> (nM)	9.91 ± 0.40	1.432	1.00	0.883	0.532
Hill coefficient	-0.87 ± 0.03	-0.95 ± 0.02	-0.72 ± 0.07	-0.89 ± 0.06	-0.81 ± 0.36
[ <sup>35</sup> S]GTP $\gamma$ S binding	<i>p</i> MBF <sup>b</sup>	Morphine	Fentanyl	DAMGO	–
Stimulation EC <sub>50</sub> (nM)	72 ± 11	31.0 ± 8.2	17.9 ± 4.3	21.4 ± 4.2	–
Maximal stimulation (%) <sup>c</sup>	55.2 ± 3.7	83.3 ± 5.5	81.2 ± 7.4	96.8 ± 1.9	–
DOR	<i>p</i> MBF <sup>b</sup>	Morphine	Fentanyl	DPDPE-OH	Naltrexone
[ <sup>3</sup> H]DPDPE binding K <sub>i</sub> (nM)	593 ± 51	111 ± 14	242 ± 20	2.96 ± 0.57	14.2 ± 3.1
IC <sub>50</sub> (nM)	988 ± 96	182	391	5.0	23.8

Hill coefficient	$-0.98 \pm 0.07$	$-0.96 \pm 0.02$	$-0.93 \pm 0.09$	$-0.94 \pm 0.10$	$-1.03 \pm 0.12$
<b>[<sup>35</sup>S]GTPγS binding</b>	<b><i>p</i>MBF<sup>b</sup></b>	<b>Morphine</b>	<b>Fentanyl</b>	<b>DPDPE-OH</b>	–
Stimulation EC <sub>50</sub> (nM)	$2,850 \pm 920$	$870 \pm 140$	$1,190 \pm 140$	$7.22 \pm 0.38$	–
Maximal stimulation (%) <sup>c</sup>	$13.07 \pm 0.58$	$77.3 \pm 2.3$	$58.0 \pm 4.2$	$100.97 \pm 0.97$	–
<b>KOR</b>	<b><i>p</i>MBF<sup>b</sup></b>	<b>Morphine</b>	<b>Fentanyl</b>	<b>U-50,488H</b>	<b>Nor-BNI</b>
[ <sup>3</sup> H]U-69,593 binding K <sub>i</sub> (nM)	$136 \pm 27$	$27.9 \pm 2.7$	$194 \pm 20$	$0.155 \pm 0.048$	$0.42 \pm 0.16$
IC <sub>50</sub> (nM)	$308 \pm 63$	63.4	436	0.35	0.86
Hill coefficient	$-0.97 \pm 0.09$	$-0.98 \pm 0.06$	$-1.19 \pm 0.17$	$-0.70 \pm 0.03$	$-1.11 \pm 0.23$
<b>[<sup>35</sup>S]GTPγS binding</b>	<b><i>p</i>MBF<sup>b</sup></b>	<b>Morphine</b>	<b>Fentanyl</b>	<b>U-50,488H</b>	–
Stimulation EC <sub>50</sub> (nM)	$193 \pm 31$	$83 \pm 23$	$362 \pm 47$	$1.15 \pm 0.22$	–
Maximal stimulation (%) <sup>c</sup>	$80.5 \pm 3.3$	$86.8 \pm 6.0$	$72.9 \pm 3.2$	$93.6 \pm 2.2$	–

<sup>a</sup> 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-pyrrolidiny)]-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide; U-50,488H: *trans*-(±)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidiny)]cyclohexyl]benzeneacetamide methanesulfonate salt; Nor-BNI: norbinaltorphimine; U-69,593: (+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidiny)]-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).

<sup>c</sup> 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 [<sup>35</sup>S]GTPγS binding.

<sup>b</sup> *p*MBF: *p*-methoxy-butrylylfentanyl.

### 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*-methoxy-butrylylfentanyl (tested 0.1, 1, and 10 mg/kg) with fentanyl (0.1, 1 and 10 mg/kg) and morphine (1, 10, 100 and 180 mg/kg).<sup>22</sup>

*p*-Methoxy-butrylylfentanyl significantly increased distance traveled during all time intervals at 10 mg/kg (10–120 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. The total distances traveled following administration of *p*-methoxy-butyrylfentanyl (10 mg/kg) and morphine (100 and 180 mg/kg) were comparable.<sup>22</sup>

Antinociceptive effects (warm water tail-withdrawal test, 50°C, adult male CFW mice; subcutaneous administration) have been investigated and it was confirmed that *p*-methoxy-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).<sup>23</sup> In this assay, *p*-methoxy-butyrylfentanyl was almost equipotent to fentanyl and 74-times more potent than morphine (Table 2). *p*-Methoxy-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.<sup>23</sup>

Test drug	ED <sub>50</sub> (mg/kg)
<i>p</i> -Methoxy-butyrylfentanyl	0.1057
<i>p</i> -Methoxy-butyrylfentanyl + naltrexone (1 mg/kg)	3.9860
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).<sup>24</sup> However, specific information related to a causal relationship of *p*-methoxy-butyrylfentanyl with adverse reactions is currently very limited.

Three cases of acute intoxications associated with *p*-methoxy-butyrylfentanyl and one case involving *p*-methoxy-butyrylfentanyl and furanylfentanyl (*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]furan-2-carboxamide)<sup>25, 26</sup> occurring between April and November 2015 in Sweden have been published (Table 3). Clinical features included reduced level of consciousness, respiratory depression, miosis,

tachycardia, renal insufficiency, suspected aspiration, and apnea.<sup>13</sup> In three of the four cases, naloxone treatment was needed to reverse respiratory depression.

Year <sup>a</sup>	Patient, age	Comments <sup>b</sup>	Ref
2016	F, 29	<p>Patient reported intake of unknown new psychoactive substance and tramadol. Detection of <i>p</i>-methoxy-butyrylfentanyl (1 h after admission): 1.3 ng/mL (serum), 5.1 ng/mmol creatinine (urine).</p> <p>GCS 15, miotic pupils, HR 134/min, BP 143/93 mmHg on ambulance arrival. Two days of hospital care.</p> <p>Naloxone treatment: no</p> <p>Other substances detected (including some that may have been treatment-related): butyrylfentanyl, 4F-butyrylfentanyl, phytocannabinoids, tramadol, <i>O</i>-desmethyltramadol, and desmethyldiazepam.</p>	13
2016	M, 28	<p>Patient reported intake of unknown opioids and benzodiazepines. Detection of <i>p</i>-methoxy-butyrylfentanyl (promptly after admission): 3.1 ng/mL (serum).</p> <p>RLS 8, RR 7/min, SpO<sub>2</sub> 83%, miotic pupils, pH 7.24, pCO<sub>2</sub> 6.4 kPa, pO<sub>2</sub> 10.3 kPa, lactate 4.7 mmol/L, standard-bicarbonate 19.0 mmol/L, base excess -6 mmol/L, S-creatinine 163 mg/L, HR 117/min on ambulance arrival. P-troponin I 1.2 µg/L, S-ALT 10.4 µkat/L, S-AST 9.0 µkat/L. Two days of hospital care.</p> <p>Naloxone treatment: 0.4 mg iv and 0.2 mg iv.</p> <p>Other substances detected (including some that may have been treatment-related): 4F-butyrylfentanyl, alprazolam, OH-alprazolam, 7-amino-clonazepam, benzoylecgonine, clonazepam, cocaine, <i>O</i>-desmethyltramadol, diazepam, and oxazepam.</p>	13
2016	M, 34	<p>Patient reported intake of unknown drug tablet and fentanyl. Detection of <i>p</i>-methoxy-butyrylfentanyl (1 h after admission): 11.9 ng/mmol creatinine (urine).</p> <p>RLS 8, temporary apnoea, miotic pupils, HR 100/min. Two days of hospital care.</p>	13



		<p>Naloxone treatment: 0.4 mg iv</p> <p>Other substances detected (including some that may have been treatment-related): 4F-butyrylfentanyl, clonazepam, GHB, fentanyl.</p>	
2016	M, 22	<p>Patient reported intake of unknown new psychoactive substance (nasal spray; nasal insufflation and intramuscular administration) and clonazepam. Detection of <i>p</i>-methoxy-butyrylfentanyl and furanylfentanyl (promptly after admission): 11.0/4.4 ng/mL (serum); 51.3/9.2 ng/mmol creatinine (urine). Two days of hospital care.</p> <p>Naloxone treatment: 0.4 mg iv</p> <p>RLS 8, apnea and cyanosis on ambulance arrival. Initial VBG: pH 7.27, pCO<sub>2</sub> 8.0 kPa, pO<sub>2</sub> 4.8 kPa, SpO<sub>2</sub> 58%. BT 36 °C, P-creatinine 113 µg/ L, P-ALT 1.2 µkat/L, P-AST 0.8 µkat/ L. HR 120/min.</p> <p>Other substances detected (including some that may have been treatment-related): EtG/EtS, MDPHP, pregabalin, and clonazepam.</p>	13
<p><sup>a</sup> Year of publication. Cases occurred in 2015.</p> <p><sup>b</sup> RLS: Reaction Level Scale; GCS: Glasgow Coma Scale; BT: body temperature; HR: heart rate; BP: blood pressure; RR: respiratory rate; SaO<sub>2</sub>/SpO<sub>2</sub>: oxygen saturation; S: serum; P: plasma; ALT: alanine aminotransferase; AST: aspartate aminotransferase; VBG: venous blood gas; EtG/EtS: ethanol metabolites ethyl glucuronide and ethyl sulfate;; MDPHP: α-pyrrolidinoheptanophenone.</p>			

## 7. Dependence Potential

### A. Animal Studies

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

### B. Human Studies

Studies that have investigated the dependence potential of *p*-methoxy-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*-methoxy-butyrylfentanyl.

## 8. Abuse Potential

### A. Animal Studies

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

### B. Human Studies

Studies that have investigated the abuse potential of *p*-methoxy-butyrylfentanyl in humans could not be identified although cases of analytically confirmed recreational use 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*-Methoxy-butyrylfentanyl is not listed.

## 11. Marketing Authorizations (as a Medicinal Product)

*p*-Methoxy-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*-methoxy-butyrylfentanyl use within the general population are not available. The detection of *p*-methoxy-butyrylfentanyl in biological fluids confirms that this substance is used recreationally (Section 6). Experience with fentanyl and other analogs has shown that the use of such substances is often associated with individuals who might be abusing/misusing heroin and prescription opioid analgesics and heroin.

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

Data on the effects of *p*-methoxy-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*-methoxy-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 fentanyl analogs were detected as an adulterant in samples of heroin obtained from the cryptomarket.<sup>27</sup> The US Drug Enforcement Administration reported the detection of cocaine samples adulterated with fentanyl and fentanyl analogs, which occurred in

seized samples obtained in the period from 2016–2017 in Florida (USA).<sup>28</sup> 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*-methoxy-butyrylfentanyl and other analogs are also available in the form of nasal sprays raises questions as to whether these dosage forms might render the use of fentanils more attractive and/or socially acceptable.<sup>17</sup> 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.<sup>16, 17</sup>

## 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*-methoxy-butyrylfentanyl (first notified to EMCDDA in August 2015<sup>29</sup>) was encountered in seizures and collected specimen (powder and tablets) in Slovenia and Sweden.<sup>18</sup>

The background information and evaluation of ‘Three Factor Analysis’ (Factors 4, 5 and 6) for temporary scheduling document<sup>30</sup> states that the identification of *p*-methoxy-butyrylfentanyl was featured once based on queries (November 3, 2017) of 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.

Detections of *p*-methoxy-butyrylfentanyl have also been reported to the United Nations Office on Drugs and Crime’s (UNODC) Early Warning Advisory on New Psychoactive Substances by Slovenia and Sweden in 2015 (as of 25 August 2018).<sup>31</sup>

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

## 17. Current International Controls and Their Impact

*p*-Methoxy-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*-methoxy-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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