Butyrfentanyl (Butyrylfentanyl)
Critical Review Report
Agenda item 4.2

Expert Committee on Drug Dependence
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Summary

Butyrfentanyl is a potent, short-acting mu opioid receptor agonist, and an analogue of fentanyl, differing by only one methyl group. It has no approved medical indications, but is being used for recreational purposes, with cases of fatal overdoses reported in Europe and the United States. In the United States, butyrfentanyl has been temporarily scheduled as a Schedule 1 controlled substance under the Controlled Substances Act, and the DEA has confirmed at least 40 fatalities as of May 2016. It is sold over the Internet, often as a “research chemical”, and a number of online drug forums contain information on common routes of administration, dosing, and reported effects. The actual extent of abuse and mortality associated with butyrfentanyl is not known because it is not tested for in routine toxicological analyses.

Case studies and drug forums have suggested that butyrfentanyl is typically used as a nasal spray, snorted as a white powder, or injected intravenously, and doses range from 0.5 to 3 mg. Clinical studies of the pharmacological effects of butyrfentanyl in humans are not available, but the effects appear to be similar to the effects of fentanyl, including euphoria, altered mood states, drowsiness, and respiratory depression. Studies in non-human primates have found that butyrfentanyl is associated with body and jaw sag, ataxia, slowed movement, and scratching.

Pre-clinical studies of butyrfentanyl are scarce; however, the few available studies suggest that butyrfentanyl is about 30 times less potent than fentanyl itself, and has significant antinociceptive properties, as demonstrated by the acetic acid writhing test in rodents.

Butyrfentanyl is being abused for its opioid effects. As with other mu opioid agonists, it can induce respiratory depression which may lead to death and numerous deaths have been reported. No accepted medical purpose has been identified.
1. Substance identification

A. International Nonproprietary Name (INN)
   Not applicable

B. Chemical Abstract Service (CAS) Registry Number
   1169-70-6 (base); 1443-52-3 (hydrochloride)

C. Other Chemical Names
   N-[(1-phenethylpiperidin-4-yl)]-N-phenylbutyramide, N-(1-phenethylpiperidin-4-yl)-N-phenylbutanamide, butyryl fentanyl, NIH 10486

D. Trade Names
   None

E. Street Names
   bf or b-f

F. Physical Appearance
   White/yellow powder

G. WHO Review History
   Not previously reviewed

2. Chemistry

A. Chemical Name

   IUPAC Name: N-(1-phenethylpiperidin-4-yl)-N-phenylbutyramide
   CA Index Name: not available

B. Chemical Structure

   Free base:

   ![Chemical Structure Image]

   Molecular Formula: \( \text{C}_{23}\text{H}_{30}\text{N}_2\text{O} \); \( \text{C}_{23}\text{H}_{30}\text{N}_2\text{O} \cdot \text{HCl} \) (for HCl salt)
   Molecular Weight: 350.503 g/mol (base); 386.9639 (HCl)
C. **Stereoisomers**

None

D. **Methods and Ease of Illicit Manufacturing**

The synthesis of butyrfentanyl was first described by Janssen in 1961 in a US Patent.¹

E. **Chemical Properties**

Melting point: no data identified
Boiling point: no data identified
Solubility: no data identified

F. **Identification and Analysis**

Butyrfentanyl is not included in regular screening tests for drugs of abuse and may go undetected in many cases. Immunoassays (e.g., ELISA) for fentanyl do not distinguish between fentanyl and butyrfentanyl.²³ Additional confirmatory testing such as gas chromatography/mass spectrometry (GC/MS) is needed to identify butyrfentanyl.

3. **Ease of Convertibility Into Controlled Substances**

Butyrfentanyl contains a carboxamide group which can be easily hydrolysed in strong acid or strong base when heated. The product can then be converted by condensation into another carboxamide. Therefore butyrfentanyl can be relatively easily converted into another fentanyl (including fentanyl itself). Fentanyl is a Schedule I drug under the UN 1961 Single Convention on Narcotic Drugs.

4. **General Pharmacology**

A. **Routes of administration and dosage**

According to case reports of fatal and non-fatal intoxications, butyrfentanyl is used in a nasal spray⁴ or snorted as a white powder⁴⁵. Butyrfentanyl nasal spray and blotters are available for purchase through chemical retailers in Europe, with reported doses ranging from 0.5 mg to 3 mg.⁴ Drug forums have suggested other routes of administration, including rectal, intravenous, and sublingual use.⁴ In addition, re-dosing is apparently a common phenomenon.⁴

B. **Pharmacokinetics**

Postmortem redistribution of butyrfentanyl and its metabolites was studied using LC-MS/MS in a case of a fatal poisoning.⁵ At t1 (9 hours after death), butyrfentanyl was present at highest concentrations in the lung tissue (3000 ng/g), followed by the spleen (590 ng/g) and adipose tissue (550 ng/g), with lower concentrations in the kidney (160 ng/g), muscle (110 ng/g), liver (57 ng/g), femoral blood (66 ng/g), and heart blood (39 ng/g).⁵ The high concentration in lung tissue was likely due to the nasal administration of butyrfentanyl, which resulted in inhalation of some of the powder.⁵ Carboxybutyrfentanyl and hydroxybutyrfentanyl were the two most abundant metabolites detected (mainly in the
kidney and liver), though only a few metabolites were included in the analysis due to the lack of information regarding butyrfentanyl metabolism.\textsuperscript{5}

C. Pharmacodynamics

Receptor binding and \textit{in vitro} functional activity: NIH10486 (butyrfentanyl) displaced \textsuperscript{3}H-etorphine binding in rat cerebral membrane with an EC\textsubscript{50} of 58.7 nM in the presence of NaCl.\textsuperscript{6} NIH10486 (butyrfentanyl) completely inhibited the mouse vas deferens stimulated twitch with an EC\textsubscript{50} of 1.11 x 10\textsuperscript{-7} M.\textsuperscript{6} The inhibitory effects were unaffected by the delta-opioid antagonist, ICI-17864, but were reduced by the mu-opioid receptor antagonist, beta-funaltrexamine, and reversed by naltrexone.\textsuperscript{6} Based on these findings, it was concluded that NIH10486 (butyrfentanyl) is a mu-opioid receptor agonist similar to morphine.\textsuperscript{6} Using \textsuperscript{[3]}H fentanyl as the radioligand in a rat brain receptor preparation, the affinity K\textsubscript{i} value for butyrfentanyl was determined to be 32 nM.\textsuperscript{7} More recent data also found that butyrfentanyl showed mu opioid receptor agonist effects in an \textit{in vitro} functional assay, similar to morphine (EC\textsubscript{50}=37 nM for butyrfentanyl, compared to 42 nM for morphine).\textsuperscript{8} Binding affinities of butyrfentanyl were evaluated using an \textit{in vitro} preparation of Chinese hamster ovary cells expressing human delta and kappa opioid receptors and rat mu opioid receptors. Butyrfentanyl was found to selectively bind to mu opioid receptors with an IC\textsubscript{50} of 2.34 nM, compared to 469 nM for the delta opioid receptor and 429 nM for the kappa opioid receptor.\textsuperscript{8}

Analgesia: n-butyrfentanyl was evaluated for antinociceptive activity in ddy-mice using the acetic acid writhing test, and was found to have and ED\textsubscript{50} of 0.220 mg/kg when injected intraperitoneally.\textsuperscript{9} n-butyrfentanyl was 1.5 times more potent in this test than morphine, but about 30 times less potent than fentanyl.\textsuperscript{9} The LD\textsubscript{50} of n-butyrfentanyl was not estimated in this study. A previous study in mice found similar results; NIH10486 (butyrfentanyl) was estimated to have an ED\textsubscript{50} of 0.2 mg/kg in a tail flick test, and an ED\textsubscript{50} of 0.04 mg/kg in a phenylquinone writhing test, when administered subcutaneously.\textsuperscript{10}

5. Toxicology

No published studies on the toxicity of butyrfentanyl in animals could be identified.

6. Adverse Reactions in Humans

The United States Drug Enforcement Agency reported 40 confirmed fatalities associated with butyrfentanyl from 3 states: Maryland (1), New York (38) and Oregon (1) in 2015.

In May 2014 the Swedish National Focal Point reported 1 serious non-fatal intoxication associated with butyrfentanyl. This is believed to be the first such case to be reported to the EU Early Warning System. From May 2014 to January 2015, the Swedish STRIDA project analyzed blood and urine samples from four intoxications involving butyrfentanyl and one involving 4-flurobutyrfentanyl from May 2014 to January 2015 (men, aged 19-30 who presented to the ER or ICU). Clinical features included typical opioid symptoms such as respiratory depression, apnea and loss of consciousness. Butyrfentanyl was found in two serum (0.6 and 0.9ng/mL) and three urine (2.0-65.6.ng/mL) samples from 3 of the 4 cases and in three of the cases fentanyl was also found. In four cases other new psychoactive substances (NPS) and or other drugs were also found. When the ‘butyrfentanyl’ products
(one nasal spray and one powder) brought in to the hospital by the patients were analysed, the more potent fentanyl was the main active ingredient found.\(^4\)

One documented case of butyrfentanyl overdose reported in Minnesota, USA involved an 18 year old male with a past history of heroin abuse. He was found unconscious with labored breathing and taken to the ER. After responding to naloxone, the patient claimed that he had snorted what he believed to be acetylfentanyl which he had purchased over the internet. He then developed pulmonary edema, acute lung injury and diffuse alveolar hemorrhage.\(^{11}\)

Two fatal intoxications (one from Florida and one from Virginia, USA) involving butyrfentanyl have been reported. One case involved a 53 year old female with a history of prescription drug abuse. Butyrfentanyl was the only drug detected in post mortem fluids and tissues and the cause of death was ruled fatal intoxication by butyrfentanyl. The second case involved a 45 year old female with a history of prescription drug and alcohol abuse as well as a history of anxiety, bipolar disorder and two previous suicide attempts. Prescribed medications included alprazolam, diazepam, promethazine, zonisamide, trazodone and topiramate. Post mortem analysis of body fluids and tissues detected butyrfentanyl, acetylfentanyl, alprazolam and ethanol. The cause of death was ruled as a mixed drug intoxication. In both of these cases death was ruled as accidental.\(^{12}\)

A case of an acute butyr-fentanyl fatality was reported in a 44 year old man with a history of heroin abuse in California. He was found unresponsive in his home and drug paraphernalia including a syringe was present at the scene. Toxicological testing confirmed the presence of butyr-fentanyl acetylfentanyl and a relatively low concentration of benzoylecgonine. The cause of death was ruled as acute butyr-fentanyl , acetylfentanyl and cocaine intoxication and death was accidental.\(^{13}\)

### 7. Dependence Potential

#### A. Animal Studies

In 1987, Aceto and colleagues tested NIH10486 (butyrfentanyl) in morphine-dependent rhesus monkeys.\(^{10}\) Rhesus monkeys had been injected with subcutaneous morphine at a dose of 3.0 mg/kg every six hours for 90 days prior to testing. In the single-dose suppression (SDS) test, NIH10486 (butyrfentanyl) at a dose of 0.1 or 0.5 mg/kg substituted almost completely for morphine (i.e., attenuated withdrawal symptoms as well as morphine at 3.0 mg/kg).\(^{10}\) Effects lasted for about 2 ½ hours, and at peak effects, NIH10486 (butyrfentanyl) was reported to be 10-20 times more potent than the reference morphine.\(^{10}\) These results suggest cross-dependency between morphine and butyrfentanyl.

#### B. Human Studies

No studies of butyrfentanyl dependence or cross-dependence conducted in humans could be identified.
8. Abuse Potential

A. Animal Studies
Drug discrimination or self-administration studies of butyrfentanyl conducted in animals could not be found.

B. Human Studies
Controlled studies of abuse liability of butyrfentanyl conducted in humans could not be found.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use
Butyrfentanyl has no recognized medical use.

10. Listing on the WHO Model List of Essential Medicines
Butyrfentanyl is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)
None.

12. Industrial Use
None.

13. Non-Medical Use, Abuse and Dependence
Butyrfentanyl has been associated with both fatal and non-fatal intoxications. It has been identified in confiscated materials in both the United States of America and Europe. It is being abused and discussions of butyrfentanyl use are mentioned on user websites.

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

The extent to which butyrfentanyl is abused at the population level is not known. Several cases of fatal and non-fatal intoxications in both Europe and in the United States of America have been reported. These are likely underestimations because butyrfentanyl is not included detected in most drug screens. There are reports of seizures where butyrfentanyl has been identified (see section 16).

In February 2016, the US Dept. of Justice reviewed the actual and potential risks of butyrfentanyl to public health and concluded that… “butyryl fentanyl and beta-
hydroxythiofentanyl exhibit pharmacological profiles similar to that of fentanyl and other mu-opioid receptor antagonists. Due to limited scientific data, their potency and toxicity are not known; however, the toxic effects of both butyryl fentanyl and beta-hydroxythiofentanyl in humans are demonstrated by overdose fatalities involving these substances. Abusers of these fentanyl analogues may not know the origin, identity, or purity of these substances, thus posing significant adverse health risks when compared to abuse of pharmaceutical preparations of opioid analgesics, such as morphine or oxycodone.

Based on the documented case reports of overdose fatalities, the abuse of butyryl fentanyl and beta-hydroxythiofentanyl leads to the same qualitative public health risks as heroin, fentanyl and other opioid analgesic substances. The public health risks attendant to the abuse of heroin and opioid analgesics are well established and have resulted in large numbers of drug treatment admissions, emergency room visits, and fatal overdoses. This indicates that both butyryl fentanyl and beta-hydroxythiofentanyl pose an imminent threat to the public safety.”

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

15. Licit Production, Consumption and International Trade

The only licit production of butyrfentanyl is for research purposes (analytic reference standard).

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

16. Illicit Manufacture and Traffic and Related Information

According to the United States National Forensic Laboratory Information System (NFLIS), the first laboratory submission of butyrfentanyl was recorded in Kansas in March 2014. The System to Retrieve Information from Drug Evidence (STRIDE), STARLiMS (a web-based, commercial laboratory information management system) and NFLIS documented seven reports of butyrfentanyl in 2014 and 81 reports in 2015.14

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) database:

Germany: On 4 May 2016 the German Focal Point (FP) reported a seizure of 1.11 grams of cream white powder seized in December 2014 by the customs service in Cologne. The substance was declared as Zinc Dimethylacrylat.15

Finland: On 12 October 2015 the Finnish FP reported several seizures from the Customs at Helsinki-Vantaa Airport:
- 0.6g of powder on June 15, 2015 at incoming mail from China;
- 0.1 + 0.1 +0.1 g powder containing also caffeine on 30.7.2015 at incoming mail from Greece.15

Sweden: On 4 July 2014 the Swedish FP reported a seizure of 9.59 grams of pale yellow
powder seized on 13 April 2014.  

**Poland:** On 12 March 2014 the Polish FP reported 3 seizures of powder by Polish Police during the investigation of a case of illicit drug production at Krakow on July 31, 2013:  
- 5g of a white/yellow powder  
- 200g of white powder in a 1:100 mixture with lactose  
- 290g of white powder in a 1:100 mixture with lactose  

The substance was identified by the National Medicines Institute based on LC-MS/MS-TOF and NMR (the structure was confirmed by 1H- and 13C-NMR).

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

17. **Current International Controls and Their Impact**

Butyrfentanyl is currently not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. **Current and Past National Controls**

United States: butyrfentanyl is a Schedule I substance under the federal Controlled Substances Act (temporary scheduling).

Also 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**

Butyrfentanyl is in the phenylpiperidine class of opioids which includes fentanyl and it is convertible into fentanyl. It has a similar pharmacological profile to fentanyl and other opioid analgesics. Fentanyl is currently scheduled under the 1961 Single Convention on Narcotic Drugs (Schedule I).
References


Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 46 Member States (4 AFR, 2 EMR, 25 EUR, 7 PAH, 1 SEAR and 7 WPR) answered the questionnaire for butyrfentanyl. Of these, 13 respondents (9 EUR, 2 PAH and 2 WPR) had information on the substance.

LEGITIMATE USE

There were 12 countries that reported no approved medical products containing butyrfentanyl for human or veterinarian indications. There was no reported industrial use for butyrfentanyl in 9 countries.

Butyrfentanyl is currently being used in medical or scientific research in two countries, with one country specifying that is being researched for metabolism and abuse potential.

Butyrfentanyl was not reported to be used for any cultural, religious or ceremonial purposes in 12 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 9 countries that reported butyrfentanyl as being misused for its psychoactive properties (as a recreational drug). Common routes of administration are oral (6 countries), injection (3 countries), inhalation (2 countries), sniffing (4 countries) and smoking (2 countries). Another route of administration mentioned was sublingually (1 country). The main route of administration for butyrfentanyl was specified as oral (4 countries) followed by smoking (2 countries) and insufflation (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (6 countries), followed by tablets (3 countries), injectable formulations (2 countries) and liquid or solution for oral administration/use (1 country). Other formulations mentioned were nasal spray (1 country) and plant material impregnated with the substance (1 country).

There were 7 countries which reported that the source of butyrfentanyl for non-medical/non-scientific use was smuggling.

One country specified users of prescription opioid analgesics and heroin as a subpopulation known to misuse butyrfentanyl.

The level of negative health-impact originating from this substance's non-medical consumption was reported as serious (5 countries). Countries indicated the serious level of negative health-impact was chosen due to the butyrfentanyl being an opioid that may cause respiratory depression and the life threatening risk as a result of overdose. One country stated that it has been implicated in several fatalities.
Three countries reported a total of 7 emergency room or hospital visits related to the non-medical use of butyrfentanyl. The adverse effects which presented for butyrfentanyl at the emergency room/department included respiratory depression, tachycardia, cardiac arrest, somnolence, miosis, elevated body temperature, alveolar hemorrhaging and seizures.

In regards to the mortality rate, data was provided by two countries. The total combined rate which included involvement of other substances was reported to be 41 cases in 2015 to 2016. The rate, where it was unknown if other substances were involved was 1 case in 2016. Another country commented that there is no reporting obligation by hospitals, poison centers etc. so there may be more cases.

**STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL**

There were 9 countries reported that butyrfentanyl was under national control. The legislation that the control is based upon included the Controlled Substances Act (7 countries), Criminal Law Act (1 country) and other specific legislation (1 country stated that it was specific legislation for new psychoactive substances). Two countries reported that the control is a temporary provision. There were no challenges to implementing controls for butyrfentanyl reported.

The scope of the controls includes production (7 countries), manufacturing (8 countries), exporting (8 countries), importing (9 countries), distribution (8 countries), use (7 countries) and possession (8 countries).

Reported illicit activities involving butyrfentanyl include manufacture of the substance by chemical synthesis (1 country), trafficking (6 countries), smuggling (1 country), diversion (1 country), domestic internet sales (1 country), internet sales from abroad (4 countries), internet sales from unknown locations (1 countries) and finally sales to people who use this substance (2 countries).

There were 5 countries which completed the section on the number of seizures. The combined number of seizures was 10 (2014), 217 (2015) and 41 (2016 to date).

If butyrfentanyl was placed under international control, 12 countries responded that they would have the capacity to enforce the control at the national level. There were 13 countries which responded that they would have the forensic laboratory capacity to analyse the substance.