Critical Review Report:

CYCLOPROPYLFENTANYL

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.
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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 Sandra Comer for the literature review and drafting and Jurgen Rehm, Astrid Otto, and Jakob Manthey for questionnaire analysis and report drafting.

WHO would like to thank the US Drug Enforcement Agency (DEA) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for providing information.
Executive Summary

Cyclopropylfentanyl was synthesized by Paul Janssen as described in the patent literature in 1965 (U.S.) and 1968 (France). It has a chemical structure that is similar to fentanyl and receptor binding data show that it binds selectively to the μ subtype of opioid receptors with subnanomolar affinity relative to δ and κ opioid receptors (DEA-VA, 2017). However, no pharmacokinetic or pharmacodynamic studies of cyclopropylfentanyl are reported in the preclinical or clinical scientific literature. It first appeared in toxicological assays in the U.S. and Europe in 2017.

Based primarily on reports of overdoses attributed to cyclopropylfentanyl describing naloxone-reversible loss of consciousness, depressed respiration, and miosis, it appears to be a potent mu opioid receptor agonist. As such, its pharmacology and toxic effects are likely to be similar to fentanyl. It currently has no legitimate medical or veterinary uses and is relatively easy to manufacture. Cyclopropylfentanyl is being sold as heroin, an adulterant in heroin, or as counterfeit oxycodone pills. Since 2017, a number of fatalities have been attributed to this substance (60 in Europe and 115 in the U.S.) The authors of one report from the U.S. assessing cyclopropylfentanyl in post-mortem blood suggested that most of the deaths associated with the fentanyl analogs are due to cyclopropylfentanyl and, to a lesser extent, methoxyacetylfentanyl (Fogarty et al., 2018).

The totality of data currently available on cyclopropylfentanyl suggests that it has high abuse potential and poses a serious public health threat.

1. Substance identification

   A. **International Nonproprietary Name (INN)**
      
      Cyclopropylfentanyl

   B. **Chemical Abstract Service (CAS) Registry Number**
      
      1169-68-2 free base

   C. **Other Chemical Names**
      
      N-phenyl-N-[1-(2-phenylethyl)-4-piperidyl] cyclopropanecarboxamide;
      N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-
      cyclopropanecarboxamide;
      N-(1-phenethylpiperidin-4-yl)-Nphenylcyclopropanecarboxamide;
      N-fenyl-N-[1-(2-fenylethyl)-4-piperidinyl]
      cyclopropankarboxamid (Swedish);
      N-(1-fenetylpirperidin-4-yl)-N-fenylcyklopropankarboxamid
      (Swedish)

   D. **Trade Names**
      
      None
E. Street Names

‘cyclopropyl’ (Belgium),
‘synthetic heroin’ (Belgium),
‘4-me-MAF’ (Sweden),
‘MAF’ (Poland)

Other names and code names: cyclopropyl fentanyl, cyclopropyl-fentanyl, cyclopropylfent

F. Physical Appearance

Cyclopropylfentanyl has been detected in white or off-white powders and, to a lesser extent, in liquids and in tablets. See below for seizures and collected samples of cyclopropylfentanyl from Poland and the United Kingdom (from the EMCDDA-Europol Joint Report on cyclopropylfentanyl (2018)).

Annex 1
Images from seizures and collected samples provided to the EMCDDA

G. WHO Review History

Cyclopropylfentanyl has not been reviewed previously by the WHO.

2. Chemistry

A. Chemical Name

IUPAC Name: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl] cyclopropanecarboxamide
CA Index Name: Not found
41st ECDD (2018): Cyclopropylfentanyl

B. Chemical Structure

Free base:

![Chemical structure diagram]

**Molecular Formula:** C_{23}H_{28}N_{2}O  
**Molecular Mass:** 348.49

C. Stereoisomers

Cyclopropylfentanyl (A) and crotonylfentanyl (B) are structural isomers (see figure below excerpted from Maher et al., 2018). The propioamide group of fentanyl (C) is replaced by a cyclopropane-carboxamide group for cyclopropylfentanyl and a 2-butenamide group for crotonylfentanyl.

![Stereoisomers diagram]

D. Methods and Ease of Illicit Manufacturing

The synthesis of cyclopropylfentanyl was described in the patent literature in the U.S. (Janssen, 1965) and France (Janssen, 1968), including the use of “β-phenylethyl” and “N-(4-piperidyl)-N-phenyl-cyclopropanecarboxamide” (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018). As reported by the EMCDDA, the manufacture of cyclopropylfentanyl can also rely on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl” although “use of a different acylating agent in the final acylation step, such as cyclopropanecarbonyl chloride would produce cyclopropylfentanyl” and “a one-step method uses ANPP and cyclopropanecarbonyl chloride for the manufacture of the substance.” In short, “most of the synthetic procedures that could be used for the synthesis of cyclopropylfentanyl are straightforward and use common laboratory equipment and precursors.”

E. Chemical Properties

**Melting point**  
119.5−120.4 °C (Janssen, 1968)

**Boiling point**  
Not found
Solubility

“Limited solubility data available on cyclopropylfentanyl indicates that it is soluble in methanol; 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.” (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018)

F. Identification and Analysis

“Methods documented in the literature for the detection of cyclopropylfentanyl include: gas chromatography–mass spectrometry (GC-MS) (Slovenian National Forensic Laboratory, 2017; SWGDRUG, 2017), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR) (Slovenian National Forensic Laboratory, 2017; SWGDRUG, 2017), gas chromatography–mass spectrometry–infrared spectroscopy (GC-(MS)-IR) condensed phase (Slovenian National Forensic Laboratory, 2017), and nuclear magnetic resonance (NMR) (SWGDRUG, 2017).” (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018)

It is unlikely that cyclopropylfentanyl will cross-react with immunoassays developed for morphine-type opioids, but it is detected by enzyme-linked immunosorbent assay (ELISA) for fentanyl (Guerrieri et al., 2018). However, specific identification of cyclopropylfentanyl requires confirmatory analysis. Because the structure and chromatographic behavior of cyclopropylfentanyl and crotonylfentanyl are so similar, additional analytical techniques are required to differentiate these substances. Specifically, high performance liquid chromatography with diode array UV detection (HPLC-DAD), high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS), and liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QToF-MS) can be used to differentiate the two compounds, as described by Maher et al. (2018). Specifically, evaluation of both chromatographic retention time and UV spectral analysis are needed to differentiate these isomers.

3. Ease of Convertibility into Controlled Substances

No reports of conversion of cyclopropylfentanyl into other controlled substances were found.

4. General Pharmacology

A. Routes of Administration and Dosage

Because powder, liquid, and counterfeit capsules containing cyclopropylfentanyl have been obtained by regulatory agencies throughout the world, it is likely that cyclopropylfentanyl can be used by the intranasal, oral, and intravenous routes. Information from cases submitted for toxicological analyses support the view that cyclopropylfentanyl is being used by the intranasal and intravenous routes (Fogarty et al., 2018).

B. Pharmacokinetics

No controlled pharmacokinetic studies of cyclopropylfentanyl have been reported.
C. Pharmacodynamics

No controlled pharmacodynamic studies of cyclopropylfentanyl have been reported.

5. Toxicology

No formal toxicology studies have been performed with cyclopropylfentanyl.

6. Adverse Reactions in Humans

No controlled clinical studies have been conducted with cyclopropylfentanyl, so adverse reactions in humans are based on reports of fatal and non-fatal overdoses attributed to it. Cyclopropylfentanyl and fentanyl have similar chemical structures, so adverse reactions associated with the compound are expected to be similar to fentanyl. Of 27 overdoses in the U.S. that were linked to a combination of U-47700 and cyclopropylfentanyl, adverse symptoms included loss of consciousness, respiratory depression, and miosis (Edison et al., 2017; Fogarty et al., 2018). While definitive attribution of cyclopropylfentanyl-related toxicity to its activity at mu opioid receptors is currently not possible, the profile of effects described above and reversal of these effects by naloxone suggest activity at mu receptors.

Beginning in May 2017, 115 confirmed fatalities associated with cyclopropylfentanyl were reported in Georgia (1), Maryland (24), Mississippi (1), North Carolina (75), and Wisconsin (14), based on post-mortem toxicology and medical examiner reports. As noted above, additional confirmatory testing is required to definitively identify cyclopropylfentanyl, so the prevalence of this substance in opioid-related emergency room admissions and deaths is most likely underreported (DEA report on cyclopropyl fentanyl, 2017).

7. Dependence Potential

A. Animal Studies

No preclinical dependence potential studies were found in the published literature.

B. Human Studies

No clinical dependence potential studies were found in the published scientific literature.

8. Abuse Potential

A. Animal Studies

No preclinical abuse potential studies were found in the published scientific literature.

B. Human Studies

No clinical abuse potential studies were found in the published scientific literature.

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

Cyclopropylfentanyl is not approved in any country for therapeutic use.
10. **Listing on the WHO Model List of Essential Medicines**
Cyclopropylfentanyl is not included in the WHO Model List of Essential Medicines.

11. **Marketing Authorizations (as a Medicinal Product)**
Cyclopropylfentanyl is not approved in any country as a medicinal product.

12. **Industrial Use**
Cyclopropylfentanyl is available commercially for research and forensic purposes and as an analytical reference standard.

13. **Non-Medical Use, Abuse and Dependence**
Because of the difficulties associated with positively identifying cyclopropylfentanyl in standard assays, the magnitude of misuse and abuse of the drug is likely to be underreported. Given the structural similarity between cyclopropylfentanyl and fentanyl, it is expected that cyclopropylfentanyl has high potential for non-medical use, abuse, and dependence.

14. **Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence**
Cyclopropylfentanyl-related deaths were first reported in the U.S. in May 2017: A total of 115 fatalities have been confirmed thus far (DEA report on cyclopropyl fentanyl, 2017). The authors of one report from the U.S. assessing cyclopropylfentanyl in post-mortem blood suggested that most of the deaths associated with the fentanyl analogs are due to cyclopropylfentanyl and methoxyacetylfentanyl (Fogarty et al., 2018).

A total of 60 deaths associated with cyclopropylfentanyl were reported in Europe (59 in Sweden and 1 in Norway; EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018). These fatalities occurred between June and October 2017.

15. **Licit Production, Consumption and International Trade**
Cyclopropylfentanyl does not appear to have licit medicinal or veterinary use in any country.

16. **Illicit Manufacture and Traffic and Related Information**
In recent years, the U.S. Drug Enforcement Agency has identified cyclopropylfentanyl in STARLiMS, a web-based, commercial laboratory information management system that is used as its laboratory drug evidence data system of record. Between October 1, 2014 and August 25, 2017, 3 reports containing cyclopropylfentanyl were obtained from California, Connecticut, and New York. Of the 3 exhibits, one had a net weight of ~1 kg. The first report was obtained in Connecticut in June 2017 (DEA report on cyclopropyl fentanyl, 2017).

In addition to STARLiMS, reports of cyclopropylfentanyl have appeared in other DEA databases. The National Forensic Laboratory Information System (NFLIS) is a program within the DEA that systematically collects results from drug chemistry analyses conducted by other federal, state and local forensic laboratories across the U.S. These laboratories analyze substances obtained by U.S.
law enforcement operations. As of August 29, 2017, NFLIS had 10 reports containing cyclopropylfentanyl from state or local forensic laboratories in Oklahoma in July 2017 (DEA report on cyclopropylfentanyl, 2017).

Cyclopropylfentanyl also was identified in drug evidence submitted to forensic laboratories in the U.S. states of Georgia and Pennsylvania. It was combined with U-47700 in counterfeit oxycodone tablets in Georgia and with U-47700 in 24 glassine paper packets in Pennsylvania (DEA report on cyclopropylfentanyl, 2017).

Based on the above evidence, the DEA concluded that the pattern of cyclopropylfentanyl abuse parallels that of heroin and prescription opioid analgesics and is used either knowingly or unknowingly.

In September 2017, a newspaper reported that cyclopropylfentanyl was seized by authorities in Sault Ste. Marie, Canada (https://www.cbc.ca/news/canada/sudbury/new-opioid-sault-streets-1.4284512 accessed 23 September 2018). A subsequent study conducted in Canada using a novel urinalysis technique reported that approximately 5-7% of urine samples testing positive for fentanyl also tested positive for cyclopropylfentanyl and its dealkylated nor metabolite, cyclopropylnorfentanyl [8 of 104 samples in November 2017 (7.7%), 4 of 79 samples from February to October 2017 (5.1%), and 56 of 1048 samples collected over an 8-day period in 2017 (5.3%)] (Palaty et al., 2018). The authors acknowledged, however, that their assay does not differentiate cyclopropylfentanyl from crotonylfentanyl. The authors concluded that the high levels of cyclopropylfentanyl in the urine samples (median 24 ng/ml; range 1-3200 ng/ml) support the view that it is deliberately being added to illicit opioids, as opposed to being a synthetic byproduct or accidental contaminant.

Another study reported that the mean blood level of cyclopropylfentanyl measured in 32 post-mortem cases from the U.S. was 15.3 (± 11.9 ng/ml) [median = 12.3 ng/ml; range = 1.4 – 43.3 ng/ml] (Fogarty et al., 2018). These authors noted that “In late 2017, NMS Labs observed increases in rates of detection of methoxyacetylfentanyl and cyclopropylfentanyl and there are indications that they are among the most prominent of the fentanyl analogs contributing to fatalities.” (Fogarty et al., 2018).

Limited information is available about trafficking of cyclopropylfentanyl in Europe (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018). In Sweden, cyclopropylfentanyl is purchased from China in powder form by drug sellers, ordered by buyers through a surface website, and then distributed through the domestic postal service. Swedish authorities reported 26 seizures of cyclopropylfentanyl and 2 large seizures via a postal hub in Belgium. The drug is sometimes mixed with water and then packaged into nasal spray bottles purchased in China (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018).

“In total, 57 seizure cases (12) were reported to the EMCDDA by 4 Member States: Latvia (25 cases), Poland (2), Sweden (27), and the United Kingdom (3). Where known, the seizures took place between July and November 2017 and were made by police or customs agencies.” (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018)
The quantities of cyclopropylfentanyl powder that have been seized in Europe range between less than 5 g to 1.6 kg (EMCDDA-Europol Joint Report on cyclopropylfentanyl, 2018). Liquid quantities range between 0.1 to 49 ml and a total of 87 tablets containing cyclopropylfentanyl have been confiscated.

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

   Cyclopropylfentanyl was temporarily placed into Schedule 1 by the DEA on January 4, 2018 [21 CFR Part 1308, Docket No. DEA-474]. Although the impact of cyclopropylfentanyl scheduling is difficult to determine at present, the fact that it appeared on the illicit market soon after the scheduling of acrylfentanyl in June 2017 suggests that scheduling actions may influence the availability of new substances (Fogarty et al., 2018).

18. **Current and Past National Controls**

   CA: Schedule I  
   UK: Class A  
   US: Schedule I (temporary)

   According to the EMCDDA, cyclopropylfentanyl is controlled in 8 member states (Cyprus, Estonia, Finland, Ireland, Lithuania, Sweden, and the United Kingdom) and Norway. In 5 member states (Austria, Belgium, Germany, Hungary, and Poland), cyclopropylfentanyl is controlled under specific new psychoactive substances control legislation. But in 15 member states (Bulgaria, Croatia, Czech Republic, Denmark, France, Greece, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) and Turkey, it is not subject to control measures at the national level (EMCDDA-Europol Joint Report on cyclopropyl fentanyl, 2018).

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

   None.
References

Cyclopropyl Fentanyl: Background Information and Evaluation of ‘Three Factor Analysis’ (Factors 4, 5 and 6) for Temporary Scheduling. Drug Enforcement Agency report, October 2017.


