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Cyclopropylfentanyl

EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] cyclopropanecarboxamide (cyclopropylfentanyl)

In accordance with Article 5 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

About this series

EMCDDA–Europol Joint Report publications examine the detailed information provided by the EU Member States on individual new psychoactive substances. Information is collected from the Reitox network, the Europol national units and the national competent authorities of the European Medicines Agency.

Each Joint Report serves as the basis upon which the decision to conduct a risk assessment of the new psychoactive substance is taken. It is part of the three-step procedure involving information exchange, risk assessment and decision-making in the framework of Council Decision 2005/387/JHA.

EUROPOL

EMCDDA–Europol
joint publication

Contents

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1. Introduction

Article 5.1 of Council Decision 2005/387/JHA [1] (hereinafter the 'Council Decision') stipulates that 'Where Europol and the EMCDDA, or the Council, acting by a majority of its members, consider that the information provided by the Member State on a new psychoactive substance merits the collection of further information, this information shall be collated and presented by Europol and the EMCDDA in the form of a Joint Report.' The Joint Report shall be submitted to the Council of the European Union, the European Medicines Agency (EMA), and the European Commission.

In September 2017, the EMCDDA and Europol examined the available information on the new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide, commonly known as cyclopropylfentanyl, through a joint assessment based upon the following criteria:

1. the amount of the material seized;
2. evidence of organised crime involvement;
3. evidence of international trafficking;
4. analogy with better-studied compounds;
5. evidence of the potential for further (rapid) spread; and,
6. evidence of cases of serious intoxication or fatalities.

The EMCDDA and Europol agreed that the information collected on cyclopropylfentanyl satisfied criteria 4 and 6. The two agencies therefore concluded that sufficient information had been accumulated to merit the production of a Joint Report on cyclopropylfentanyl as stipulated by Article 5.1 of the Council Decision.

2. Information collection process

In compliance with the provisions of the Council Decision, on 12 October 2017 the EMCDDA and Europol launched a procedure for the collection of information on cyclopropylfentanyl, in order to prepare the Joint Report. The information was collected mainly through the Reitox national focal points in the Member States, Turkey, Norway, as well as the Europol national units. In addition, the EMA collected information through the national competent authorities responsible for human and veterinary medicinal products in the Member States as well as in Norway, Iceland, and Liechtenstein. The EMA also provided information as relevant to the centralised procedure for authorising medicinal products. The information collection process was largely concluded by 23 November 2017.

[1] OJ L 127, 20.5.2005, p. 32.

Information collected by Europol

Europol asked the Europol national units to provide information on:

- the level of production of cyclopropylfentanyl in their country;
- the level of distribution of cyclopropylfentanyl in their country;
- the level of trafficking of cyclopropylfentanyl in their country, both for internal, transit, or export purposes;
- the number of seizures of cyclopropylfentanyl in their country, the total amount of the seizures, country of origin, and details on the physical forms (including photos);
- the role of organised crime, or criminal groups, in the production, distribution, and trafficking of cyclopropylfentanyl in their country; and,
- any known aspect of violence and/or money laundering relating to the production and trafficking of cyclopropylfentanyl.

Europol received responses from 20 Member States [2], the Republic of Serbia, and Canada.

Information collected by the EMA

According to Article 5.3 of the Council Decision, the EMA requested that the national competent authorities responsible for human and veterinary medicinal products in the Member States, Norway, Iceland, and Liechtenstein provide information on whether:

- the new psychoactive substance cyclopropylfentanyl has obtained a marketing authorisation;
- the new psychoactive substance cyclopropylfentanyl is the subject of an application for a marketing authorisation; and,
- a marketing authorisation that had been granted in respect to the new psychoactive substance cyclopropylfentanyl has been suspended.

Twenty six countries provided a response to the EMA's request regarding human and/or veterinary medicinal products [3]. The EMA also provided information as relevant to the centralised procedure for authorising human and veterinary medicinal products.

[2] In alphabetical order: Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Slovenia, Spain, Sweden.
[3] Austria, Belgium, Croatia, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, and Sweden provided a response in relation to human and veterinary medicinal products. Cyprus, the Czech Republic, Denmark, and Hungary provided a response in relation to human medicinal products. France, Romania and the United Kingdom provided a response in relation to veterinary medicinal products.

Furthermore, in anticipation of Article 7.3 of the Council Decision in relation to the manufacturing of medicinal products in the European Union, the EMA also requested information on whether the new psychoactive substance cyclopropylfentanyl is used to manufacture a medicinal product:

- which has been granted a marketing authorisation;
- for which an application has been made for a marketing authorisation; and,
- for which a marketing authorisation has been suspended by a competent authority.

Twenty six countries ([4]) provided a response to the EMA's request in this regard. The EMA also provided information as relevant to the centralised procedure for authorising human and veterinary medicinal products.

Information collected by the EMCDDA

The EMCDDA collected information through:

- a structured questionnaire to the Reitox national focal points. The EMCDDA received replies from the 28 Member States, Turkey, and Norway;
- reports previously submitted to the European Union Early Warning System, including EMCDDA–Europol Reporting Forms, Progress Reports, and Final Reports;
- routine monitoring of open source information;
- a specific information request to the World Health Organization on whether or not cyclopropylfentanyl has been assessed or is under assessment by the United Nations system; and,
- a search of open source information conducted specifically for the production of the Joint Report which included: scientific and medical literature, official reports, grey literature, internet drug discussion forums and related websites (hereafter, 'user websites').

Thus, the information included in sections 3.2.1 and 3.3 of the Joint Report was provided by Europol, while the EMCDDA provided information included in sections 3.1, 3.2.2, 3.4, 3.5, 3.6, 3.7, 3.8.1, 3.8.2, and 3.8.3 (in part). The information included in section 3.8.3 (in part) and section 4 was provided by the EMA.

3. Information required by Article 5.2 of the Council Decision

The order and titles of subsections 3.1 to 3.8 and section 4, below, are as they appear in Article 5.2(a) to (h) and Article 5.3(a) to (c) of the Council Decision; sections are cross-referenced with those set down in the Council Decision.

3.1 Chemical and physical description, including the names under which the new psychoactive substance is known (Article 5.2(a) of the Council Decision)

Chemical description and names

Cyclopropylfentanyl belongs to the 4-anilidopiperidine class of synthetic opioids. This class also includes fentanyl ([5]), which is internationally controlled, and a number of other fentanils.

A total of 15 fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol ([6]).

Cyclopropylfentanyl differs from fentanyl by replacement of the propionamide group of fentanyl with a cyclopropanecarboxamide group. Cyclopropylfentanyl is also structurally related to butyrfentanyl ([7]), which is internationally controlled, and differs from butyrfentanyl by replacement of the butyramide group with a cyclopropanecarboxamide group.

The synthesis of cyclopropylfentanyl has been described in the patent literature (Janssen, 1968).

The molecular structure, molecular formula, and molecular mass of cyclopropylfentanyl are provided in in Figure 1.

([4]) Austria, Belgium, Croatia, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden provided a response in relation to human and veterinary medicinal products. Cyprus, the Czech Republic, Denmark and Hungary provided a response in relation to human medicinal products. France, Romania and the United Kingdom provided a response in relation to veterinary medicinal products.

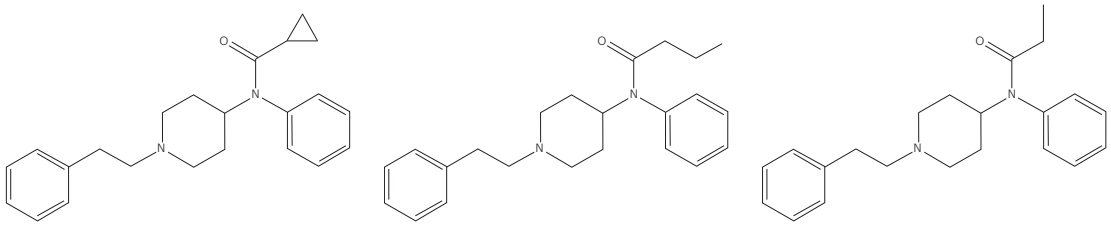
([5]) *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidinyl-4-yl]propanamide

([6]) 3-Methylfentanyl, 3-methylthiofentanyl, acetyl-alpha-methylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl, thiofentanyl and acetylfentanyl are controlled under Schedule I and IV; alfentanil, fentanyl, sufentanil, remifentanil and butyrfentanyl are controlled under Schedule I.

([7]) *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidinyl-4-yl]butanamide

FIGURE 1

Molecular structure, molecular formula, and molecular mass of cyclopropylfentanyl. Information on butyrfentanyl and fentanyl is provided for comparison.



	cyclopropylfentanyl	butyrfentanyl	fentanyl
Molecular formula	$C_{23}H_{28}N_2O$	$C_{23}H_{30}N_2O$	$C_{22}H_{28}N_2O$
Molecular mass	348.49	350.51	336.48

Commonly used names:
cyclopropylfentanyl

Systematic (IUPAC) name:
N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl] cyclopropanecarboxamide

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)-*N*-phenylcyclopropanecarboxamide;

N-fenyl-*N*-[1-(2-fenyletyl)-4-piperidinyl] cyklopropankarboxamid (Swedish);

N-(1-fenetylpiperidin-4-yl)-*N*-fenylcyklopropankarboxamid (Swedish)

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

Street names
'cyclopropyl' (Belgium),
'synthetic heroin' (Belgium),
'4-me-MAF' (Sweden),
'MAF' (Poland)

Chemical Abstracts Service (CAS) registry numbers ([8]):
1169-68-2 free base

IUPAC International Chemical Identifier Key (InCHI Key) ([9]):
OIQSKDSKROTEMN-UHFFFAOYSA-N

The REACH registered substances database hosted by the European Chemicals Agency (ECHA) was searched using the CAS registry number listed above. The searches returned no hits.

Physical description

Cyclopropylfentanyl contains one basic nitrogen atom in the piperidine ring which can readily form salts with organic or inorganic acids.

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.

Cyclopropylfentanyl is expected to be lipophilic.

The measured melting point of cyclopropylfentanyl was reported as 119.5–120.4 °C (Janssen, 1968).

Cyclopropylfentanyl has been detected in powders and, to a lesser extent, in liquids and in tablets. A more detailed description of seizures and collected samples can be found in section 3.2.1 and section 3.2.2.

([8]) The Chemical Abstract Service Registry Number (CAS RN) is a unique numeric identifier assigned by the Chemical Abstract Service Division of the American Chemical Society to a specific, single chemical substance.

([9]) InChI Key is a unique, non-proprietary stuctural identifier of chemical substances useful in electronic sources.

Detection 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).

There is no information on the reaction of cyclopropylfentanyl to presumptive colour tests.

Cyclopropylfentanyl is not expected to give a positive response to immunoassays developed for morphine-type opioids. It is unknown if immunoassays for fentanyl will detect cyclopropylfentanyl. In addition, it is unknown whether such assays can distinguish between cyclopropylfentanyl and fentanyl (US DEA, 2017b). Identification of cyclopropylfentanyl requires confirmatory analysis (US DEA, 2017b).

3.2 Information on the frequency, circumstances and/or quantities in which a new psychoactive substance is encountered, and information on the means and methods of manufacture of the new psychoactive substance (Article 5.2(b) of the Council Decision)

The data reported to Europol discussed in section 3.2.1 may overlap with the data reported to the EMCDDA discussed in section 3.2.2.

3.2.1 Information provided to Europol

Europol received replies from 20 Member States (Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Slovenia, Spain and Sweden), the Republic of Serbia, and Canada.

The level of production

No information was received in relation to the production of cyclopropylfentanyl.

Sweden reported that there is no known production of cyclopropylfentanyl in the country. Vendors mix the substance in powder form with water and then they package the resulting solution into nasal spray bottles, ordered from China. This approach has been reported as characteristic for marketing fentanils in Sweden.

The level of distribution

Limited information was received in relation to the distribution (seizures) of cyclopropylfentanyl ([10]).

Sweden reported 26 seizures of cyclopropylfentanyl since the substance was introduced on to the market. They reported two 'large seizures' distributed via a postal-hub in Belgium.

Sweden reported that the substance is ordered from Swedish websites on the surface web and sent directly to the end user, or, in some cases, to relatives of the user. They also reported that there is no information to indicate that Swedish customers use cyclopropylfentanyl purchased from international websites.

As part of an ongoing investigation, it is estimated that 600 people have purchased cyclopropylfentanyl from a specific webpage. However, it is not possible to confirm that all the purchases involved cyclopropylfentanyl. Cyclopropylfentanyl was reported to be available in Sweden as of 13 June 2017; a death associated with cyclopropylfentanyl was also reported on the same day.

The level of trafficking

Limited information was received in relation to the trafficking of cyclopropylfentanyl.

Sweden reported that the domestic postal service is used for the distribution of the substance which is ordered from China in powder form and then distributed to buyers via domestic postal services. There is no information to indicate that the substance is exported from Sweden.

3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States, Turkey, and Norway. Of these, 5 Member States (Austria, Latvia, Poland, Sweden, and the United Kingdom) and Norway reported detections of cyclopropylfentanyl ([11]).

([10]) Canada reported two seizures of cyclopropylfentanyl. One seizure of 11 grams of white powder originated in China and was concealed in bags of dog food/treats. The analysis confirmed the citrate salt of cyclopropylfentanyl (*N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide). The second seizure was 268 grams of white powder, which originated in Hong Kong and, unlike the previous seizure, was not concealed. The analysis confirmed furanylfentanyl and cyclopropylfentanyl..

([11]) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples that are analytically confirmed. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.).

Images of seizures and collected samples reported to the EMCDDA are provided in Annex 1.

It is important to note that cyclopropylfentanyl may be under-detected since the substance is not routinely screened for. Three Member States (Belgium, Slovenia, and Sweden) and Norway reported that cyclopropylfentanyl is part of routine screening in some (but not all) laboratories.

Seizures

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.

Cyclopropylfentanyl was detected in powders, and, to a lesser extent, in liquids and in tablets. Aside from cyclopropylfentanyl, no other substances were reported to have been detected in the seizures.

Powders

A total of 1.6 kg of powder containing cyclopropylfentanyl was seized in 26 cases that were reported by Latvia (18 cases), Poland (2), Sweden (4), and the United Kingdom (2). Where known, the powders were reported to be white or off-white in colour.

In 23 cases, the quantities seized were less than 5 g. However, in a case reported by Poland, two samples amounting to approximately 500 g each were seized. In this case, the substance was seized by Polish customs in parcels sent by post from China (via Belgium) to a private address in Poland in September 2017 (Annex 1); while in a case reported by Sweden, approximately 600 g was seized by customs (no additional details are available).

Liquids

A total of 240 mL of liquid containing cyclopropylfentanyl was seized in 27 cases that were reported by Latvia (7 cases), Sweden (19), and the United Kingdom (1).

The quantity seized ranged from 0.1 to 49 mL. In the cases reported by Latvia the liquids were recovered from syringes. In the case reported by the United Kingdom, a nasal spray containing 3.8 mL of a liquid containing cyclopropylfentanyl was seized.

Tablets

A total of 87 tablets containing cyclopropylfentanyl were seized in 4 cases that were reported by Sweden.

Collected samples

A total of 4 collected samples containing cyclopropylfentanyl were reported by 3 Member States (Austria, Poland, and the United Kingdom) and Norway. All the samples were collected between June and October 2017.

In the two cases reported by Austria and the United Kingdom, the samples were purchased as a powder from the internet. In the case reported by the United Kingdom, acetylfentanyl was also detected in the powder.

In the case reported by Poland, the sample was collected from a user and was sold as 'MAF'.

In the case reported by Norway, cyclopropylfentanyl was detected in a liquid in a nasal spray that was recovered from the scene of a death. Both cyclopropylfentanyl and acetylfentanyl were detected in the liquid as well as in a biological sample from the deceased (see section 3.4.1). It was reported that the user had used a 'methoxyacetylfentanyl nasal spray'.

Biological samples

Serious adverse events with confirmed exposure to cyclopropylfentanyl from biological samples are discussed in section 3.4.2.

In addition to these, Sweden reported a suspected petty drug offence where cyclopropylfentanyl was analytically confirmed in a biological sample; the case occurred in September 2017.

3.3 Information on the involvement of organised crime in the manufacture or trafficking of the new psychoactive substance (Article 5.2(c) of the Council Decision)

No information concerning the involvement of organised crime in the manufacture and/or trafficking of the cyclopropylfentanyl was provided.

Sweden reported that the availability of cyclopropylfentanyl can be linked to two known vendors who sell substances on several domestic websites on the surface web. These vendors are both known to police and have been previously convicted of serious drug offences. It is thought that the vendors have contacts in China but it is unknown whether they use the same source for their products.

([12]) Many 'seizures' relate to individual cases, however, some data provided to the EMCDDA are aggregated at the country level. Data is drawn from the Joint Report Questionnaires and data provided in the bi-annual data gathering (EU EWS Progress Reports and Final Reports) and from individual EMCDDA–Europol Reporting forms submitted to the EMCDDA on an ad hoc basis.

Money laundering aspects
Limited information was received in relation to the money laundering in connection with the production and/or trafficking of cyclopropylfentanyl.

Sweden reported that the known vendors for fentanils in the Swedish domestic market sell the substances through established companies and that payment is through bank transfer, cash on delivery, bitcoin, or Swish ([13]). They reported that money laundering is considered an element in those cases. In addition, the sale of fentanils in Sweden is considered to be very profitable due to the relatively low cost of purchasing and distributing the substances compared to the financial gains.

Violence in connection with production, wholesale and distribution
No information was received on incidents of violence in connection with the production, wholesale, and/or trafficking of cyclopropylfentanyl.

3.4 A first indication of the risks associated with the new psychoactive substance, including the health and social risks, and of the characteristics of users — Article 5.2(d) of the Council Decision

3.4.1 Health risks

Limited data suggests that cyclopropylfentanyl is a μ-opioid receptor agonist that shares some similarities with opioid analgesics such as morphine and fentanyl (Janssen and Van der Eycken, 1968; US DEA, 2017a; US DEA, 2017b).

The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, and respiratory depression. They also have an abuse liability and dependence potential (Herz, 1993; Kieffer, 1999, Pasternak and Pan, 2013; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute health risk from using cyclopropylfentanyl is probably respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death (EMCDDA, 2017; Pattinson, 2008; White and Irvine, 1999). This risk may be greater due to: the difficulty in diluting the substance; a lack of experience with its effects and dosing; the use of other central nervous system depressants at the same time (such as other opioids, benzodiazepines, gabapentanoids, and alcohol); a lack of tolerance to opioids; and, using the substance alone (such as at home) which would make it more difficult for users to call for help in the case of poisoning.

Available information shows that fentanils are being sold to users in or as heroin or other illicit opioids, as well as used to make counterfeit (fake) medicines (such as fake opioid analgesics ('pain killers') and benzodiazepines). They may also be sold as or in other illicit drugs such as cocaine. As users will be unaware of this, it could increase the risk of life-threatening poisoning in opioid users and especially other user groups (such as cocaine users) who may have no existing tolerance to opioids

The antidote naloxone should reverse the respiratory depression and other features of acute poisoning caused by cyclopropylfentanyl (Kim and Nelson, 2015; Ujváry et al., 2017). Recent clinical and community experience in treating poisonings caused by fentanils suggests that larger than normal doses and repeated doses of naloxone may be required to manage the poisoning in some cases; longer periods of observation may also be required (EMCDDA, 2017).

While there is limited data for cyclopropylfentanyl, the chronic health risks might share some similarities to opioids such as heroin and other fentanils. This may include dependence.

3.4.2 Serious adverse events

Acute intoxications reported to the EMCDDA
No acute intoxications with confirmed exposure to cyclopropylfentanyl were reported to the EMCDDA ([14]).

Deaths reported to the EMCDDA
In total, 60 deaths with confirmed exposure to cyclopropylfentanyl were reported to the EMCDDA by Sweden (59 cases) and Norway (1 case). In addition, Latvia reported 4 deaths with possible exposure to cyclopropylfentanyl ([15]); these 4 cases are not discussed further in this report.

The 60 deaths occurred between June and October 2017. Of these, 55 (92 %) were male and 5 (8 %) were female. The males were aged between 21 and 59 years (mean 33.2; median: 32); the females were aged between 25 and 32 years (mean: 29; median: 30). A range of other substances were detected in the deaths, including other central nervous system depressants. Other opioids were detected in 16 cases;

([13]) Swish is a mobile app payment system which allows users to send money using a mobile phone connected to an online banking service. Swish is a payment system used between bank accounts in Sweden.

([14]) Sweden reported 2 acute intoxications with suspected exposure to cyclopropylfentanyl. These cases are not discussed further in this report.
([15]) Latvia reported 4 deaths where syringes containing cyclopropylfentanyl where found next to the deceased. Analytical confirmation of exposure from biological samples is not available.

in only one of these cases was another fentanil detected (acetylfentanyl). In all of the cases the decedents were either found dead or unconscious, predominantly in a home environment.

The cause of death was reported for 24 cases. In 23 cases, cyclopropylfentanyl was the cause of death or contributed to the death.

Serious adverse events identified in open source information

During 2017, more than 100 deaths associated with cyclopropylfentanyl were reported in the United States (US DEA, 2017b; Smith and Kinkaid, 2017) ([16]).

3.4.3 Characteristics of users

Similar to other new fentanils, cyclopropylfentanyl is sold and used as a 'legal' substitute for illicit opioids and prescription opioids medicines; this may include for self-medication, such as the alleviation of pain and/or opioid withdrawal. Users may include high-risk drug users as well as others (such as psychonauts) who may be experimenting with the substance.

3.4.4 Social risks

While there is limited data for cyclopropylfentanyl, the social risks might share some similarities with opioids such as heroin and other fentanils.

Of additional note is that in the past few years fentanils have been sold in Europe as ready-to-use nasal sprays and e-liquids for vaping. In general, these novel products could make it easier to use such substances (with similar effects to injecting) and make them more socially acceptable. Further research is required on this topic to better understand the risks.

Similar to other fentanils, accidental exposure to cyclopropylfentanyl may also pose a risk of poisoning. Those at risk may include the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in custodial settings and postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in resuscitation and adequate provision of the antidote naloxone (IAB, 2017; White House National Security Council, 2017).

([16]) In addition, an outbreak of poisonings that involved 26 non-fatal intoxications and 1 death was associated with counterfeit Percocet tablets that contained cyclopropylfentanyl and U-47,700 in Georgia during June 2017 (Edison et al., 2017).

3.5 Information on whether or not the new substance is currently under assessment, or has been under assessment, by the UN system (Article 5.2(e) of the Council Decision)

The World Health Organization is the specialised United Nations agency designated for the evaluation of the medical, scientific, and public health aspects of psychoactive substances under the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances, 1971.

On 22 October 2017, the World Health Organization informed the EMCDDA that cyclopropylfentanyl is currently not under assessment and has not been under assessment by the UN system.

3.6 The date of notification on the Reporting Form of the new psychoactive substance to the EMCDDA or to Europol (Article 5.2(f) of the Council Decision)

The first official EMCDDA–Europol notification of cyclopropylfentanyl dates from 4 August 2017 from the Latvian national focal point. The Reporting Form details the seizure of cyclopropylfentanyl in 34.5 mg of white powder, seized by the police in Riga on 25 July 2017. The substance was analytically confirmed by the Forensic Service Department of the State Police by GC-MS, and a library match with the Cayman Spectral Library.

Cyclopropylfentanyl was added to the list of new psychoactive substances monitored by the EMCDDA and Europol through the European Union Early Warning System. A profile of the substance was created on the European Database on New Drugs (EDND). Since then, analytical details and other information, including a public health alert, have been exchanged between the EMCDDA, Europol, and the Member States, Turkey, and Norway, on an ad hoc basis; the European Commission and the EMA have been kept duly informed.

Of note is that data from biological samples related to death cases reported to the EMCDDA shows that cyclopropylfentanyl has been on the market in Europe since at least June 2017.

3.7 Information on whether or not the new psychoactive substance is already subject to control measures at national level in a Member State (Article 5.2(g) of the Council Decision)

Eight Member States (Cyprus, Estonia, Finland, Ireland, Latvia, Lithuania, Sweden, and the United Kingdom) and Norway reported that cyclopropylfentanyl is controlled under drug control legislation.

Five Member States (Austria, Belgium, Germany, Hungary, and Poland) reported that cyclopropylfentanyl is controlled under specific new psychoactive substances control legislation.

Fifteen Member States (Bulgaria, Croatia, Czech Republic, Denmark, France, Greece, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia, and Spain) and Turkey reported that cyclopropylfentanyl is not subject to control measures at the national level.

3.8 Further information (Article 5.2(h) of the Council Decision)

3.8.1 The chemical precursors that are known to have been used for the manufacture of the substance

No information was reported by the Member States, Turkey, or Norway about the chemical precursors or manufacturing methods used to make the cyclopropylfentanyl which has been detected within Europe.

Two potential precursors of fentanyl and other fentanils — 4-anilino-*N*-phenethylpiperidine (ANPP) as well as *N*-phenethyl-4-piperidone (NPP, a pre-precursor) — have been recently scheduled under the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 ([17]).

The synthesis of cyclopropylfentanyl has been described in the literature (Janssen, 1968) and the method included the use of 'β-phenyl-ethyl' and '*N*-(4-piperidyl)-*N*-phenyl-cyclopropanecarboxamide'.

The manufacture of cyclopropylfentanyl can also rely on precursors and synthetic methods similar to those used for the manufacture of pharmaceutical fentanyl (Casy and Huckstep, 1988; Gupta *et al.*, 2013; Zee and Wang, 1980). Therefore, the methods developed for the synthesis of fentanyl are applicable to the synthesis of cyclopropylfentanyl. Use of a different acylating agent in the final acylation step, such as cyclopropanecarbonyl chloride would produce cyclopropylfentanyl. A one-step method uses ANPP and cyclopropanecarbonyl chloride for the manufacture of the substance.

France reported that aniline, NPP, ANPP, and cyclopropanecarbonyl chloride could be used as potential precursors for the synthesis of cyclopropylfentanyl.

Most of the synthetic procedures that could be used for the synthesis of cyclopropylfentanyl are straightforward and use common laboratory equipment and precursors. Detailed methods are available on the internet ([18]). While only basic knowledge of synthetic chemistry is required, due to the potency of fentanils extreme caution is required when carrying out the final synthetic step as well as when purifying and handling the substance. Exposure of the skin and mucous membranes to fentanils as well as their inhalation pose a serious risk of accidental poisoning. In addition to exercising extreme caution, suitable personal protective equipment as well as sufficient stocks of naloxone as an antidote to poisoning following accidental exposure should be available when handling materials suspected to contain these substances (IAB, 2017; White House National Security Council, 2017).

In summary, the synthesis of cyclopropylfentanyl has been described in the literature. In addition, other routes developed for the manufacture of fentanyl may also be used. There is no information on the actual method(s) used for the production of cyclopropylfentanyl that has been detected in Europe to date.

3.8.2 The mode and scope of the established or expected use of the new substance

No studies were identified that have examined the mode and scope of established or expected use of cyclopropylfentanyl. Given the limited information currently available, the relevant information has been included in the previous sections.

([17]) Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

([18]) The detailed description of the most common procedure, referred to as the 'Siegfried method', is readily available on the internet (see, for example, http://opioids.com/fentanyl/synthesis.html).

3.8.3 Other use of the new psychoactive substance and the extent of such use, the risks associated with this use of the new psychoactive substance, including the health and social risks

No information was provided by the Member States, Turkey, or Norway that indicated that cyclopropylfentanyl had any other use apart from in analytical reference materials and scientific research.

From the available information, it does not appear that cyclopropylfentanyl is used in the manufacture of a medicinal product in the European Union. However, the data collection is incomplete and some countries indicated that this information is not known. It is understood that the collection of such information is a challenge in the absence of a database on the synthetic route of all medicinal products.

Ten countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, Germany, Greece, Latvia, and the Netherlands) reported that cyclopropylfentanyl is not used to manufacture a medicinal product for human use. Thirteen countries (Cyprus, Estonia, Hungary, Iceland, Ireland, Italy, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, and Sweden) reported that it was unknown if cyclopropylfentanyl is used to manufacture a medicinal product for human use.

In addition, the EMA reported that it is not known if cyclopropylfentanyl is used in the manufacture of medicinal products for human use and which are centrally authorised within the European Union.

Ten countries (Austria, Belgium, Croatia, Finland, France, Greece, Latvia, Poland, Romania, and the United Kingdom) provided information that cyclopropylfentanyl is not used to manufacture a medicinal product for veterinary use. Twelve countries (Estonia, Germany, Iceland, Ireland, Italy, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, and Sweden) reported that it was unknown if cyclopropylfentanyl is used to manufacture a medicinal product for veterinary use.

In addition, the EMA reported that it is not known if cyclopropylfentanyl is used in the manufacture of medicinal products for veterinary use and which are centrally authorised within the European Union.

4. Information from the EMA (Article 5.3 of the Council Decision)

Twenty-three countries (Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, and Sweden) reported that:

- cyclopropylfentanyl has not been granted a marketing authorisation as a medicinal product for human use;
- cyclopropylfentanyl is not the subject of an application for a marketing authorisation as a medicinal product for human use;
- there had been no cases of suspended marketing authorisation in respect to cyclopropylfentanyl as a human medicine.

Twenty-two countries (Austria, Belgium, Croatia, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom) reported that:

- cyclopropylfentanyl has not been granted a marketing authorisation as a medicinal product for veterinary use;
- cyclopropylfentanyl is not the subject of an application for a marketing authorisation as a medicinal product for veterinary use;
- there had been no cases of suspended marketing authorisation in respect to cyclopropylfentanyl as a veterinary medicine.

The EMA also reported that cyclopropylfentanyl:

- has not been granted a marketing authorisation as a medicinal product for neither human nor veterinary use through the centralised procedure;
- is not the subject of an application for a marketing authorisation for neither human nor veterinary use through the centralised procedure;
- is not the subject of a suspended marketing authorisation for neither human nor veterinary use through the centralised procedure.

5. Conclusion

Cyclopropylfentanyl belongs to a group of synthetic opioids known as the fentanils. It is closely related to fentanyl, which is controlled under the United Nations Single Convention on Narcotic Drugs, 1961. Data suggests that cyclopropylfentanyl may be an opioid narcotic analgesic in humans, and, as such, may have an abuse liability and dependence potential; overall, these effects may be broadly comparable to fentanyl. The most serious acute health risk posed by cyclopropylfentanyl is likely to be respiratory depression, which in overdose is life-threatening. The antidote naloxone should reverse this respiratory depression.

Cyclopropylfentanyl has been available in the European Union since at least June 2017. It has been detected in 5 Member States and Norway where it has been seized as a powder, liquids, and tablets. While the detected quantities are relatively small, they include 3 seizures of bulk quantities of powder weighing approximately between 500 and 600 g each. Overall, the quantities detected should be seen within the context of the high potency that is typical of the fentanils.

There are indications that the cyclopropylfentanyl currently available on the market is synthesised by chemical companies based in China. Cyclopropylfentanyl is sold online often under the guise of a 'research chemical'. It is available, and, has been seized, in wholesale amounts and in consumer amounts.

A total of 60 deaths with confirmed exposure to cyclopropylfentanyl have been reported to the EMCDDA by Sweden (59 cases) and Norway (1). In at least 23 of the deaths, cyclopropylfentanyl was the cause of death or contributed to the death.

Cyclopropylfentanyl is sold and used as a substitute for illicit opioids and prescription opioids. Similar to other fentanils, serious concerns exist that the substance could be supplied surreptitiously to a range of drug users.

Cyclopropylfentanyl has not been assessed within the United Nations system nor is it currently under assessment. Cyclopropylfentanyl is not subject to control measures in 15 Member States and Turkey.

Cyclopropylfentanyl does not appear to have any recognised human or veterinary medical use in the European Union.

We conclude that the health and social risks caused by the manufacture, trafficking, and use of cyclopropylfentanyl, as well as the involvement of organised crime and possible consequences of control measures, could be thoroughly assessed through a risk assessment procedure in accordance with Article 6 of Council Decision 2005/387/JHA.

The EMCDDA and Europol will continue to intensively monitor cyclopropylfentanyl in order to ensure that new information is provided to the Member States, the EMA, and the Commission via the information exchange of the European Union Early Warning System.

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Annex 1

Images from seizures and collected samples provided to the EMCDDA

Country	Image	Description
Poland	 	**Seizure** Date: 5 September 2017 Seizing authority: Customs Services at the Polish Post White powder; 1 package containing 495.4 grams and 1 package containing 499 grams. The package was shipped from China and had transited through Belgium before it was seized in Poland.
United Kingdom		**Collected sample** Date: 22 August 2017 Collecting authority: TICTAC Communications Ltd.

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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For over 20 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

The EMCDDA's publications are a prime source of information for a wide range of audiences including: policymakers and their advisors; professionals and researchers working in the drugs field; and, more broadly, the media and general public. Based in Lisbon, the EMCDDA is one of the decentralised agencies of the European Union.

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EMCDDA and Europol

- *EMCDDA–Europol 2016 Annual Report on the implementation of Council Decision 2005/387/JHA*, Implementation reports, 2017

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