European Monitoring Centre
for Drugs and Drug Addiction

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Risk assessment report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl)

In accordance with Article 6 of Council Decision 2005/387/JHA on the information exchange, risk assessment and control of new psychoactive substances

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Contents

1. Introduction

This risk assessment report presents the summary findings and the conclusion of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (commonly known as cyclopropylfentanyl). The report is intended for policy makers and decision makers in the institutions of the European Union.

The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the risk assessment operating guidelines ([1]). It is written as a stand-alone document, which presents a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed technical report on cyclopropylfentanyl, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]) (hereafter 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'EU Early Warning System' ([3])) that may pose public health and social threats, including those related to the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances ([4]) that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances ([5]).

Cyclopropylfentanyl was formally notified on 4 August 2017 by the EMCDDA on behalf of Latvia, in accordance with Article 4 of the Council Decision. The notification related to the seizure of 34.5 mg of white powder, seized by the police in Riga on 25 July 2017. Following an assessment of the available information on cyclopropylfentanyl, and in accordance with Article 5 of the Council Decision, on 19 December 2017, the EMCDDA and Europol submitted a *Joint Report* on cyclopropylfentanyl ([6]) to the

([1]) EMCDDA (2010), *Risk assessment of new psychoactive substances: Operating guidelines*, Publications Office of the European Union, Luxembourg. Available at: http://www.emcdda.europa.eu/html.cfm/index100978EN.html

([2]) OJ L 127, 20.5.2005, p. 32.

([3]) The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New Psychoactive Substances ('EU Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Reitox National Focal Points and Europol National Units in the Member States, the European Commission, and the European Medicines Agency.

([4]) According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

([5]) In compliance with the provisions of the United Nations Single Convention on Narcotic Drugs, 1961, and the United Nations Convention on Psychotropic Substances, 1971.

([6]) EMCDDA (2017), EMCDDA–Europol Joint Report on a new psychoactive substance *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl), EMCDDA, Lisbon. Available at: http://www.emcdda.europa.eu/publications/joint-reports/cyclopropylfentanyl_en

Council of the European Union, the European Commission, and the European Medicines Agency (EMA). Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision on 29 January 2018, the Council formally requested that 'the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification'.

In accordance with Article 6.2, the meeting to assess the risks of cyclopropylfentanyl was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of four additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of cyclopropylfentanyl, including health and social risks. A further four experts participated in the risk assessment: two experts from the Commission, one expert from Europol, and one expert from the European Medicines Agency (EMA). The meeting took place on 21 March 2018 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol, and the EMA. A list of the extended Scientific Committee, as well as the list of other participants attending the risk assessment meeting, is annexed to this report (Annex 2).

For the risk assessment, the extended Scientific Committee considered the following information resources:

- Technical report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) (Annex 1);
- EMCDDA–Europol Joint Report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) ([6]);
- Open source information, including: scientific articles, official reports, grey literature, internet drug discussion forums and related websites (hereafter 'user websites');
- Additional information provided during the course of the risk assessment meeting by the participants;
- The EMCDDA operating guidelines for the risk assessment of new psychoactive substances ([1]); and,
- Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances ([2]).

Finally, it is important to note that this risk assessment report contains a discussion of the available information on serious adverse events such as acute intoxications (typically presenting to hospital emergency departments) and deaths associated with cyclopropylfentanyl. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify, and report these events differ both within and between Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. The EMCDDA's toxicovigilance system, which is a central component of the EU Early Warning System, has also been strengthened resulting in more information being available regarding serious adverse events associated with new psychoactive substances. Nonetheless, it is likely that these events remain under-detected and under-reported.

2. Background

During the 1960s, attempts to develop better and safer analgesic medicines led to the synthesis and testing of a series of new opioid narcotic analgesic drugs by the pharmaceutical company *Janssen Pharmaceutica*. Fentanyl was the first substance in this highly potent family to be invented and was followed by a series of related substances that together are commonly known as the fentanils. Since then, dozens more of these substances have been synthesised and tested by scientists, including cyclopropylfentanyl that was invented in 1965.

A small number of the fentanils—fentanyl, alfentanil, sufentanil and remifentanil—have become widely used in human medicine in anaesthesia and for pain management; while some are used in veterinary medicine in anaesthesia and for pain management, and, in the case of carfentanil and thiafentanil, to immobilise large animals. Some of the fentanils are also used to study how the body works, provide insights into disease, and to help develop new medicines.

Alongside these legitimate uses, the fentanils also have a long history of illicit use as replacements for heroin and other controlled opioids. Between 1979 and 1988, more than 10 fentanils that had been made in illicit laboratories were identified on the drug market in the United States. Typically, they were sold as heroin or 'synthetic heroin' and were involved in more than one hundred deaths. Later, in the mid-2000s, illicitly produced fentanyl was sold as heroin or in mixtures with heroin, and was responsible for outbreaks of overdoses that involved hundreds of deaths in the United States. It appears, however, that, with the exception of Estonia, these substances caused limited problems in Europe during this time.

Over the past few years, there has been a large increase in the availability of fentanils in the United States, Canada, and Europe. This has been driven by the opioid epidemics in North America, sale of these substances in Europe, as well as broader changes in the illicit drug market including those related to the growth in the market in new psychoactive substances. Currently, the EMCDDA is monitoring 30 fentanils that are defined as new psychoactive substances under the Council Decision. All of these have been detected on the EU drug market since 2012.

Since late 2015, the EMCDDA has conducted eight Joint Reports with Europol on fentanils that have caused serious concern at European level. This includes acetylfentanyl in 2015, acryloylfentanyl and furanylfentanyl in 2016, and 4-fluoroisobutyrylfentanyl, tetrahydrofuranylfentanyl, carfentanil, methoxyacetylfentanyl, and cyclopropylfentanyl during 2017. Together, these substances have been involved in more than two hundred deaths, many of which were attributed directly to these substances. Five of these substances were formally risk assessed by the EMCDDA during 2017; while cyclopropylfentanyl and methoxyacetylfentanyl are currently the subjects of risk assessments.

Similar to other types of opioid analgesics such as morphine, the fentanils produce most of their effects by activating the μ-opioid receptors in the central nervous system. The acute effects of this include: euphoria, relaxation, analgesia (a reduced ability to feel pain), sedation (inducing a state of calm or sleep), bradycardia (slowing of the heart), hypothermia (dangerously low body temperature), and respiratory depression (slowing down of breathing). It is this latter effect that poses the greatest danger to users, as, due to the high potency of these substances, small amounts can cause life-threatening poisoning from respiratory depression. Left untreated, this can lead to respiratory arrest (stopping breathing) and death. Fentanils also have an abuse liability and dependence potential.

Recognising their potential to cause serious harms, fifteen fentanils (including fentanyl) and two of the main precursors used to make the substances are controlled by the United Nations international drug control system.

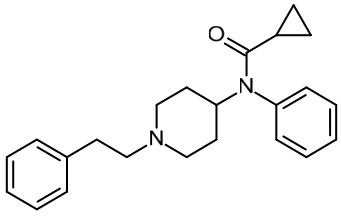
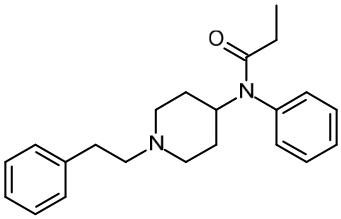
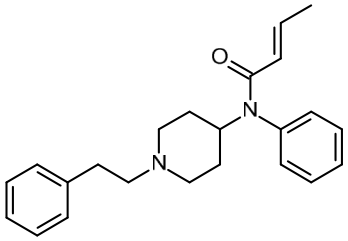
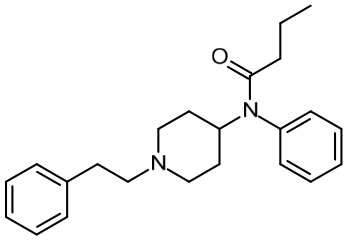
3. Physical, chemical and pharmacological description

Physical and chemical description

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) is structurally related to fentanyl, which is a 4-anilidopiperidine and a controlled substance widely used in medicine in anaesthesia and for pain management. The fentanils have in common an aralkyl group attached to a 4-*N*-acylanilinopiperidine. Cyclopropylfentanyl is also structurally related to butyrfentanyl and to crotonylfentanyl (Figure 1).

Cyclopropylfentanyl contains a basic nitrogen atom in the piperidine ring and therefore can readily form salts with organic or inorganic acids. Cyclopropylfentanyl as free base and as its hydrochloride salt occur as solids. Cyclopropylfentanyl is stable and does not undergo polymerization.

Figure 1. Molecular structure of cyclopropylfentanyl. Information on fentanyl, crotonylfentanyl and butyrfentanyl is provided for comparison.

	
cyclopropylfentanyl	fentanyl
	
crotonylfentanyl	butyrfentanyl

Cyclopropylfentanyl is available as a certified reference standard. The availability of analytical reference material is important for correct identification and for facilitating the quantification of cyclopropylfentanyl in physical and biological samples.

The analytical identification of cyclopropylfentanyl in physical and biological samples is possible using several analytical techniques. These include chromatographic and mass-spectrometric techniques.

Cyclopropylfentanyl and crotonylfentanyl are isomers and they have the same mass spectral properties. Therefore, discrimination between cyclopropylfentanyl and crotonylfentanyl requires analytical reference standards and appropriate analytical techniques.

Cyclopropylfentanyl is not expected to give a positive response to immunoassays developed for morphine-type opioids. Cyclopropylfentanyl may be detected by immunoassays developed for fentanyl and possibly those developed for LSD.

As cyclopropylfentanyl has only been on the drug market for a short period of time it may not be part of most drug screenings in forensic and toxicology laboratories and therefore may be under-detected and under-reported.

Pharmaceutical form

Cyclopropylfentanyl has been detected in powders ranging from white to off-white in colour, and, to a lesser extent, in liquid solutions. In the latter case, this includes nasal spray solutions and in syringes found at the scene of deaths. It has also been detected in tablets, including as falsified (fake) benzodiazepines (Xanax®) and opioid analgesics (OxyContin®).

Pharmacological description

Pharmacologically, cyclopropylfentanyl is an opioid receptor agonist.

The data on the pharmacodynamics of cyclopropylfentanyl are mostly limited to studies investigating its binding and functional activity at opioid receptors *in vitro*. These data show that cyclopropylfentanyl is a highly selective μ-opioid receptor agonist and that its potency is similar to morphine and fentanyl.

Limited data from animal studies suggests that cyclopropylfentanyl also has analgesic properties.

No studies were identified that investigated the pharmacokinetics of cyclopropylfentanyl. Due to its lipophilicity, cyclopropylfentanyl should be rapidly absorbed and readily cross the blood-brain barrier. It is likely that the metabolic pathway of cyclopropylfentanyl shares some similarities with other fentanils. Drug-drug interactions observed with fentanyl might equally apply.

The concomitant use of other central nervous system (CNS) depressants, including other opioids, sedatives/hypnotics, ethanol, pregabalin, gabapentin, tranquillisers, and sedating anti-histamines, may produce additive depressant effects.

From the available data, the psychological and behavioural effects of cyclopropylfentanyl may share some similarities with fentanyl and other opioid analgesics. These would include relaxation and euphoria; at higher doses, sedation and profound intoxication may occur.

Route of administration and dosage

As with other fentanils, cyclopropylfentanyl can be administered orally as a powder (including in capsules), as tablets, or as a solution (using nasal sprays), or by insufflation of a powder; it can also be administered intranasally or sublingually via a spray; inhaled by smoking or vaporizing; and, administered by injection (intravenous and intramuscular). Blotters containing fentanils have also been described.

It is not possible to currently discern the ‘typical’ dosages administered by users and these appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects.

Legitimate uses

Cyclopropylfentanyl is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests cyclopropylfentanyl is used for other legitimate purposes.

There are no reported uses of cyclopropylfentanyl as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database hosted by the European Chemicals Agency (ECHA) using the available CAS Registry Numbers returned no hits.

There is no marketing authorisation (existing, on-going or suspended) for cyclopropylfentanyl neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process ([6]).

There is no information to suggest that cyclopropylfentanyl is currently used in the manufacture of a medicinal product in the European Union ([6]).

4. Chemical precursors that are used for the manufacture

There is no information on the chemical precursors and the synthetic methods employed to manufacture cyclopropylfentanyl detected on the drug market within the European Union.

The synthesis of cyclopropylfentanyl using (2-chloroethyl)benzene and *N*-phenyl-*N*-(piperidin-4-yl)cyclopropanecarboxamide has been described in the literature in a patent from 1965.

In addition to this synthetic route and precursors, and similar to other fentanils, other methods used to manufacture pharmaceutical fentanyl are generally applicable to the synthesis of cyclopropylfentanyl. For example, the use of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (4-ANPP) and an appropriate acylating agent (in this case cyclopropanecarbonyl chloride) is a viable pathway to produce cyclopropylfentanyl. Most of the synthetic procedures to manufacture fentanyl are relatively straightforward, make use of common laboratory equipment and precursors, and require only basic knowledge of chemistry.

Two potential precursors of cyclopropylfentanyl and other fentanils, 4-ANPP as well as the pre-precursor *N*-phenethyl-4-piperidone (NPP), were scheduled in 2017 ([7]).

There are no data available on the impurities detected in seized and collected samples reported to the EMCDDA. Expected impurities may include chemical reagents such as unconverted precursors and pre-precursors, acylating agents, and hydrolysed reagents used in the acylation step, as well as synthesis by-products.

Cyclopropylfentanyl poses a risk of poisoning if accidental exposure occurs during its manufacture. Extreme care must be taken when carrying out the final synthetic step as well as when purifying and handling the substance.

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

5. Health risks

Individual health risks

The assessment of individual health risks includes consideration of the acute and chronic toxicity of cyclopropylfentanyl, as well as its dependence potential, and its similarities to and differences from other chemically or pharmacologically related substances.

It is important to note that when interpreting the information from deaths reported to the EMCDDA as well as information from user websites, that individuals may have used other substances in addition to cyclopropylfentanyl. The presence of and/or interaction with other substances or pre-existing health conditions may account for some of the reported effects.

While specific information for cyclopropylfentanyl is limited, of note is the apparent popularity of selling ready-to-use or using homemade nasal sprays containing solutions for the administration of fentanils. These typically contain milligram amounts of dissolved substance. The preparation of such solutions is inherently prone to mistakes in weighing and dilution which may lead to solutions with higher (or lower) concentrations. This may constitute an increased risk of acute toxicity to the individuals, who are unlikely to be able to control the dose of fentanil being consumed.

In addition, recent seizures in Europe of nasal sprays containing fentanils found that these have been sold in some cases as unlabelled bottles. In other cases, users have also filled nasal sprays previously containing medicines (such as nasal decongestants) with fentanils. The lack of labelling increases the potential for accidental use by others and therefore poses a risk of poisoning.

Cyclopropylfentanyl appears to be used in combination with other drugs (intentionally or unintentionally) as part of polydrug use. Limited data shows that the substance has been used to make falsified (fake) tablets of benzodiazepine and opioid analgesic medicines that have been sold on the illicit market. In addition, cyclopropylfentanyl might be supplied through the illicit opioid market, including in mixtures with other opioids such as heroin.

Acute toxicity

The acute toxicity of cyclopropylfentanyl has not been studied. Despite this, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl. The acute effects of these types of opioids include sedation, bradycardia, hypothermia, and respiratory depression. They also have an abuse liability and dependence potential.

While there is limited data on the clinical features of poisoning caused by cyclopropylfentanyl, they are likely to include miosis, reduced level of consciousness or unconsciousness, and respiratory depression and arrest. Similar to other opioid analgesics, the most serious acute risk arising from the use of cyclopropylfentanyl is likely to be from respiratory depression, which can lead to apnoea, respiratory arrest, and death.

The timely administration of the antidote naloxone should reverse respiratory depression and other features of acute poisoning caused by cyclopropylfentanyl. 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.

In general for fentanils, the risk of life-threatening poisoning may be exacerbated by: the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used; the apparent rapid onset of severe poisoning following use; using routes of administration that allow large amounts of the substance to rapidly reach the central nervous system (such as injecting, insufflation, and inhalation); availability of easy to use dosage forms (such as nasal sprays and e-liquids); lack of awareness and experience of users with these new substances (effects and dosage); use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol); reduced or no tolerance to opioids in opioid-naïve persons (such as new or former users); use in environments where it may be difficult to summon help in the event of poisoning (e.g. alone in a home environment); and, limited availability of the antidote naloxone in community settings.

In addition, and, often unknown to users, fentanils can be sold as heroin or mixed with heroin and/or other illicit opioids. They are also used to make falsified (fake) versions of highly sought-after analgesic and benzodiazepines medicines. They have also been sold in or as drugs such as cocaine. Due to this, users may not be aware that they are using a fentanil; in some cases these individuals will have no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Acute intoxications

No acute intoxications with confirmed exposure to cyclopropylfentanyl were reported to the EMCDDA.

Deaths

A total of 78 deaths were reported by Sweden (74), the United Kingdom (3 cases), and Norway (1). Exposure to cyclopropylfentanyl was analytically confirmed from post-mortem samples in all 78 deaths.

The deaths occurred within a short time period of between June 2017 and December 2017. Of the 78 deaths, 71 were male (91%) and 7 were female (9%). The mean age of the males was 33 years (median 31) and ranged from 17 to 59 years. The mean age of the females was 34 years (median 31) and ranged from 25 to 54 years.

Cause of death and toxicological significance

The cause of death was available in 74 of the 78 cases. In the 74 deaths, cyclopropylfentanyl was cited (either by name or as an opioid or narcotic) in the cause of death even in presence of other substances. Other substances were detected in 74 cases, with cyclopropylfentanyl being the only drug present in the remaining 4 cases.

Cyclopropylfentanyl was quantified in 77 cases. In the 73 of the 74 cases from Sweden, post-mortem femoral blood concentrations between 1.1 and 270 ng/g blood were recorded (median 8.2 ng/g blood) ([8]). In the 3 cases from the United Kingdom, post-mortem femoral blood concentrations of 20.9, 26.4 and 28.9 ng/mL were found, and in the remaining case from Norway a post-mortem femoral concentration of 82 nmol/L was reported (equivalent to 28.6 ng/mL). Due to the toxicity of potent opioids and variability in user tolerance, a post-mortem blood concentration cannot necessarily be used to determine a ‘fatal’ concentration. In the majority of circumstances involving fentanils, the mere presence of the drug is of

([8]) With ng/g being somewhat but not exactly equivalent to ng/mL.

significance whether the concentration has been determined or not, especially in situations of poly-drug use.

A range of other substances were detected in the deaths, including: cannabinoids, benzodiazepines, cocaine, amphetamine, MDMA, zopiclone, zolpidem, lamotrigine, methylphenidate, β-blockers, gabapentinoids (pregabalin and gabapentin), antidepressants, antipsychotics, antihistamines, synthetic cathinones (alpha-PHP, mephedrone and 4-fluoro-N-ethylpentedrone), synthetic cannabinoids (5Cl-AB-PINACA and AB-PINACA) and ethanol. Other opioids were detected in 22 of the deaths; buprenorphine (7 deaths), morphine (7), oxycodone (4), mitragynine (2), noscapine (2), tramadol (4), methadone (2), codeine (2), acetylfentanyl (1), papaverine (2), and U-47700 (1). 6-Monoacetylmorphine (heroin metabolite) was found in 2 of the 3 deaths reported by the United Kingdom.

Overall, while other substances may have contributed some toxicity, a synergistic effect with cyclopropylfentanyl would have been likely with other central nervous system depressants in particular ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of cyclopropylfentanyl means the primary toxic contribution could be attributed to the drug, and death may not have occurred if cyclopropylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) ([9]) incorporating the above considerations, shows that cyclopropylfentanyl had a TSS value of 3 (high) in 77 out of 78 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining death involving decomposition, toxicological evidence was only available in muscle so the significance is unascertainable.

Circumstances of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the majority of cases, but, where described, in some cases, the deceased was found or had become unconscious. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

Deaths from other sources

In addition to deaths reported by the EMCDDA, during 2017 more than 100 deaths with confirmed exposure to cyclopropylfentanyl were reported in the United States.

Ability to operate machinery and drive

There have been no studies of the effects of cyclopropylfentanyl on the ability to drive and operate machines. However, it is well established that opioid narcotic analgesics, such as fentanyl, impair the mental and physical ability required to drive and operate machines. This effect is likely to extend to cyclopropylfentanyl.

Chronic toxicity

No studies were identified that investigated the chronic health effects of cyclopropylfentanyl.

([9]) Elliott, S., Sedefov, R. and Evans-Brown, M. (2017), 'Assessing the toxicological significance of new psychoactive substances in fatalities', Drug Testing and Analysis. https://doi.org/10.1002/dta.2225

Abuse liability and dependence potential

There have been no studies that have investigated the abuse liability and dependence potential of cyclopropylfentanyl. Given what is currently known about its pharmacology, including some similarities to fentanyl and opioid narcotic analgesics, it may have a potential for abuse and dependence. Further research will be required in order to determine such effects.

Public health risks

The public health risks associated with cyclopropylfentanyl may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences. Detailed information, including data on sporadic versus chronic use, that allow for a determination of public health risks associated with cyclopropylfentanyl are not available. In addition, risk of accidental/occupational exposure needs to be considered.

Extent, frequency, and patterns of use

No studies were identified that have investigated the prevalence of use of cyclopropylfentanyl in the general population. Given its pharmacology, and, that it is sold openly as a 'legal' replacement to illicit opioids, it could be expected that individuals looking for substitutes for opioids, such as heroin and/or prescription opioids, may be interested in cyclopropylfentanyl and other fentanils. This group could include high risk drug users, including individuals who inject opioids. Similar to other new psychoactive substances, it also appears that there is interest in cyclopropylfentanyl by some psychonauts. Overall, the available information does not suggest widespread use of the substance.

Cyclopropylfentanyl appears to be sold online as powders in wholesale and small amounts. It is also sold as ready-to-use nasal sprays. Sometimes it is advertised under the guise of being a 'research chemical'. Cyclopropylfentanyl may be sold on the illicit opioid market, as suggested by a seizure where it was found in a mixture with heroin. Limited data for seizures have shown that cyclopropylfentanyl may also be sold as falsified (fake) tablets of popular benzodiazepine and analgesic medicines; the source of these tablets and their general availability within Europe is unknown. In these cases, it is reasonable to assume that these individuals will not be aware that they are consuming cyclopropylfentanyl.

Availability and quality on the market

Overall, cyclopropylfentanyl has been detected in 6 Member States (Austria, Latvia, Poland, Slovenia, Sweden, and the United Kingdom) and Norway.

A total of 144 seizures made by law enforcement agencies have been reported by 5 Member States (Latvia, Poland, Slovenia, Sweden, and the United Kingdom) and Norway. The seizures took place from June 2017 to January 2018. Cyclopropylfentanyl has been typically seized as a powder (52 seizures; total of 1.76 kg), as a liquid (64 seizures; total of 772 ml), and in tablet form (28 seizures; 329 tablets).

As cyclopropylfentanyl has only been on the drug market for a short period of time it may not be part of most drug screenings in forensic and toxicology laboratories. Therefore the detection of cyclopropylfentanyl may be under-detected and under-reported. In addition, the exact composition or purity of the seized substance, including presence of any adulterants/cutting agents, is rarely reported by laboratories.

Powders and ready-to-use nasal sprays claiming to contain cyclopropylfentanyl have been offered by online vendors. Some of these vendors are apparently based within the European Union. Bulk quantities of powder (amounting to approximately 1 kg) have been seized by customs agencies.

Characteristics and behaviour of users

While no specific examples are available on the possible appeal of cyclopropylfentanyl to user groups (aside from psychonauts), it is reasonable to assume that the substance may be sought by those looking for ‘legal’ substitutes for illicit opioids (such as heroin) and/or prescription opioids. This includes high risk drug users, including those who inject opioids.

The available information, including deaths reported by the Member States, suggests that cyclopropylfentanyl is used in the home environment. In fact, in the many of the deaths the individuals were found dead in a home environment. It appears that in at least some of these cases the poisoning with cyclopropylfentanyl was so severe that they were unable to call for help. Polydrug use, including the use of other central nervous system depressants such as opioids and benzodiazepines, was common in the deaths.

Nature and extent of health consequences

In addition to the individual health risks that are discussed above, there are some further considerations related to the fentanils as a group that should be considered in respect to potential risks to public health.

Mirroring the increased availability of fentanils on the drug market over the past few years, there has also been an increase in the number of outbreaks of mass poisoning caused by fentanils, particularly in the United States and Canada. These types of outbreaks have had the potential to overwhelm emergency responders and other local healthcare systems, as well as deplete stocks of naloxone. Stocks and availability of the naloxone, as well as adequacy of training in how to resuscitate poisoned patients both in clinical and community settings may need to be assessed. This might also include a review of the availability of naloxone to users through take-home naloxone programmes.

As noted, new dosage forms—such as ready-to-use nasal sprays and e-liquids for vaping—along with open sales on the surface web and darknet marketplaces add to the complexity of the problem caused by the fentanils. They have become easier to get hold of and easier to use. The Committee is concerned about whether the availability of ‘novel’ dosage forms has the potential to make the use of fentanils more socially acceptable.

An additional challenge in respect to reducing risk in users and potential users is the balance between providing information to prevent harm and the unintended consequences of communicating the risks of opioids. There is evidence that using terms to describe them as 'potent', 'strong', 'deadly', and 'toxic' can lead some individuals to specifically seek out these substances. Such unintended promotion of the substances may also extend to former users and other groups.

Adding to these challenges is evidence that fentanils are sold to unsuspecting users in/as heroin, falsified medicines (particularly commonly used opioid analgesics and benzodiazepines), cocaine, and other illicit drugs. As users will be unaware of this, it increases the risk of severe and fatal poisoning in both opioid users and especially other groups who may have no existing tolerance to opioids. Non-opioid users are unlikely to be aware of these risks and are unlikely to have access to community opioid overdose prevention programmes, including take-home naloxone programmes.

Accidental/occupational exposure to fentanils may also pose a risk of poisoning to those who may come into contact with the substances. This includes 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 necessary, specific risks should be identified and assessed, and, appropriate measures to reduce these risks should be implemented. This may include protective equipment, training in resuscitation, and making naloxone readily available to relevant personnel in sufficient quantities in the event of poisonings. Any required measures should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose.

Long-term consequences of use

There is no information on the long-term consequences of use of cyclopropylfentanyl.

Conditions under which the substance is obtained and used

There is limited information on the conditions which cyclopropylfentanyl is obtained and used. The substance is offered for sale on the surface web as a powder and ready-to-use nasal sprays.

Cyclopropylfentanyl has also been seized as tablets, including falsified (fake) benzodiazepine and analgesic medicines.

Information from a seizure case in the United Kingdom suggests that cyclopropylfentanyl has been sold on the illicit opioid market in mixtures with heroin.

Overall, cyclopropylfentanyl may be deliberately sought after by some users; others, such as those that purchase it at street-level, may be unaware that they are using the substance which presents an inherent risk to the individuals.

6. Social risks

While there have been no studies on the social risks of cyclopropylfentanyl, it is likely that some of the risks are similar to those seen with opioids such as fentanyl and heroin.

Individual social risks

There is no information on whether the use of cyclopropylfentanyl causes individual social risks; however, any such risks may have some similarities with those associated with the illicit use of opioids, including fentanyl. These may impact on education or career, family or other personal and social relationships and may result in marginalisation.

Possible effects on direct social environment (e.g. neglect of family, violence)

There is no information on the possible effects of cyclopropylfentanyl on the direct social environment; however, any such risks may have some similarities with those associated with the use of illicit opioids.

Possible effects on society as a whole (public order and safety, acquisitive crime)

There is no specific information on the possible effects of cyclopropylfentanyl on society as a whole.

As discussed above, accidental exposure of fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes 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.

Economic costs

There are no data on the effects of cyclopropylfentanyl in respect to its health and social costs.

Possible appeal to specific population groups

Whilst no specific examples are available on the possible appeal of cyclopropylfentanyl to user groups, it is reasonable to assume that the substance may be sought by those looking for substitutes for illicit opioids, such as heroin and/or prescription opioids. This includes high risk drug users, including those who inject opioids.

As highlighted, concerns exist over the use of fentanils with novel dosage forms—such as ready-to-use and homemade nasal sprays and e-liquids for vaping—which have the potential to make the use of these substances easier (with similar effects to injecting) and more socially acceptable. Further research is required on this topic to better understand the risks.

7. Information on manufacturing, trafficking, distribution, and the level of involvement of organised crime

There is no direct evidence showing the involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. However, given the fact that it has been detected in a heroin sample and in falsified (fake) medicines, the involvement of organised crime cannot be excluded.

No production sites manufacturing cyclopropylfentanyl have been reported in Europe. Nonetheless, the seizure of illicit laboratories producing fentanils in Europe suggests that the capability to manufacture fentanils may exist within the European Union.

Information from seizures suggests that some cyclopropylfentanyl on the market in Europe has been produced by chemical companies based in China. In a case reported by Poland, two packages amounting to approximately 1 kg in total were seized. In this case, the substance was seized by Polish customs in parcels sent by post from China via Belgium.

8. Information on any assessment in the United Nations system

The World Health Organization (WHO) 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. At the time that the Joint Report was prepared ([6]), the World Health Organization informed the EMCDDA that cyclopropylfentanyl was not currently under assessment nor had it been under assessment by the United Nations system.

9. Description of the control measures that are applicable in the Member States

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.

- In Cyprus, cyclopropylfentanyl is controlled under drug control legislation.
- In Estonia, cyclopropylfentanyl is covered by the fentanyl generic definition.
- In Finland, the substance is controlled under the 'Government decree on substances, preparations and plants considered as narcotics (543/2008)', since 19 October 2017.
- In Ireland, cyclopropylfentanyl is covered by the fentanyl generic definition within the Misuse of Drugs (Amendment) Act 2015.
- In Latvia, cyclopropylfentanyl is included in the Cabinet Regulation N 847 'Regulations regarding Narcotic Substances, Psychotropic Substances and Precursors to be Controlled in Latvia' and the law 'On the Procedures for the Coming into force and Application of the Criminal Law', by way of generic definition.
- In Lithuania, cyclopropylfentanyl is subjected to control measures by The Republic of Lithuania Minister of Health Order No V-1079 (12/09/2017) 'On the amendment of the Ministry of Health of the Republic of Lithuania Order No. 5 of 6 January 2000'.
- In Sweden, cyclopropylfentanyl is regulated as a narcotic, as of 12 December 2017.
- In the United Kingdom, cyclopropylfentanyl is controlled under the Misuse of Drugs Act 1971 by way of a generic definition.
- In Norway, cyclopropylfentanyl is controlled by way of a generic definition.

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

- In Austria, cyclopropylfentanyl is covered by the phenethylamine generic definition within the Austrian Act on New Psychoactive substances.
- In Belgium, cyclopropylfentanyl is controlled by way of generic definition as of 6 September 2017.
- In Germany, cyclopropylfentanyl is controlled by way of generic definition within the new psychoactive substances act (NpSG).
- In Hungary, cyclopropylfentanyl is controlled as a 'new psychoactive substance' by chemical description under 'Point 4.a of Annex 1 of Decree no 55/2014. (XII. 30.) of Ministry of Human Capacities on new psychoactive substances' as of 5 May 2017.
- In Poland, cyclopropylfentanyl is controlled according to the general definition of the 'substitute drug' (Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection, Journal of Laws "Dz.U." No. 213, item 1396). Pursuant to Article 44b of

the Act on counteracting drug addiction, it is prohibited to manufacture and introduce substitute drugs to trade.

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.

10. Options for control and the possible consequences of the control measures

Under Article 9.1 of the Council Decision, the option for control that is available at European Union level is for the Member States to submit the new psychoactive substance cyclopropylfentanyl to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the Single Convention on Narcotic Drugs of 1961.

There are no studies on the possible consequences of such control measures on cyclopropylfentanyl. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- This control option could be expected to limit the availability of cyclopropylfentanyl and hence the further expansion of the current open trade in this substance.

- A health consequence that might result from this control option is the benefit brought about by the presumed reduction in availability and use.

- This control option could facilitate the detection, seizure and monitoring of cyclopropylfentanyl related to its unlawful manufacture, trafficking and use. In so doing, it could facilitate cooperation between the judicial authorities and law enforcement agencies across the European Union.

- This control option would imply additional costs for the criminal justice system, including forensic services, law enforcement, and the courts.

- This control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences and social risks.

- This control option could create an illicit market in cyclopropylfentanyl with the increased risk of associated criminal activity, including the involvement of organised crime.

- This control option could impact on both the quality/purity and price of any cyclopropylfentanyl still available on the illicit market. The extent to which this will impact on public health, criminality, or levels of use, is difficult to predict.

- It is difficult to predict the impact of this control option on current or future research by the pharmaceutical or chemical industries.

- In order to examine the consequences of control, the Committee wishes to note that it will be important to monitor for the presence of cyclopropylfentanyl on the market post-control, should this control option be pursued.

- Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include restricting the importation and supply of the substance as some Member States have already done.

11. Conclusion

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) is a synthetic opioid and is structurally related to fentanyl, a controlled substance widely used in medicine in anaesthesia and for pain management. Currently available information suggests that cyclopropylfentanyl is a narcotic opioid analgesic similar to fentanyl.

Similar to other opioid analgesics, the most serious acute risk arising from the use of cyclopropylfentanyl is likely to be from respiratory depression, which can lead to apnoea, respiratory arrest, and death.

Naloxone is expected to work as an antidote to poisoning caused by cyclopropylfentanyl.

Cyclopropylfentanyl has been available in Europe since at least June 2017 and has been detected in 6 Member States (Austria, Latvia, Poland, Slovenia, Sweden, and the United Kingdom) and Norway. Law enforcement seizures have been reported in 5 Member States (Latvia, Poland, Slovenia, Sweden, and the United Kingdom) and Norway.

A total of 78 deaths with confirmed exposure to cyclopropylfentanyl have been reported by 2 Member States (Sweden and the United Kingdom) and Norway. In many of cases, other drugs were also detected with cyclopropylfentanyl. In at least 74 of the deaths, cyclopropylfentanyl was reported to be either the cause of death or to have contributed to death. There have also been deaths in the United States.

It is important to note that detections of cyclopropylfentanyl may be under-reported since the substance is not routinely screened for in laboratories.

Cyclopropylfentanyl is sold online as a powder in small and wholesale amounts. It is also sold as ready-to-use nasal sprays. Limited information from seizures suggests that cyclopropylfentanyl is used to make falsified (fake) tablets of highly sought-after analgesic and benzodiazepines medicines; the source of these tablets and their general availability within Europe is unknown. Cyclopropylfentanyl may have also been sold on the illicit opioid market.

As with other fentanils, cyclopropylfentanyl can be administered in a range of ways. These include orally, intranasally, by smoking or vaporizing, and by injection. Particular concerns exist over novel ways of administering fentanils, especially the use of nasal sprays as well as e-liquids for vaping. These may have the potential to make the use of fentanils easier and more socially acceptable.

There may be a risk of accidental exposure in the family and friends of those who use fentanils. In addition, in some settings, occupational exposure to cyclopropylfentanyl, as well as to other fentanils, may pose a risk to law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as to those working in custodial settings and the postal services. Where necessary, specific risks and appropriate measures to reduce these risks should be identified and implemented. Any required measures should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose, including the availability and use of naloxone.

There is no direct evidence showing the involvement of organised crime in the manufacture, distribution (trafficking) and supply within the European Union. However, given the fact that it has been detected in a heroin sample and in falsified medicines, the involvement of organised crime cannot be excluded.

There is limited information on the chemical precursors and the synthetic routes used to manufacture the cyclopropylfentanyl detected within the European Union. Most of the synthetic routes are straightforward, make use of common laboratory equipment and readily available precursors, and require only basic knowledge of chemistry. Information from seizures suggests that some cyclopropylfentanyl on the market in Europe has been produced by chemical companies based in China.

Cyclopropylfentanyl has no recognised human or veterinary medical use in the European Union, nor, it appears, elsewhere. There are no indications that cyclopropylfentanyl may be used for any other purpose aside from as an analytical reference standard and in scientific research.

Cyclopropylfentanyl is not listed for control in the Single Convention on Narcotic Drugs, 1961, nor in the Convention on Psychotropic Substances, 1971. Cyclopropylfentanyl is not currently under assessment by the United Nations system.

The available information would suggest that cyclopropylfentanyl is liable to similar abuse and produce similar ill-effects, including dependence, that are comparable to fentanyl.

Eight Member States (Cyprus, Estonia, Finland, Ireland, Latvia, Lithuania, Sweden, and the United Kingdom) and Norway control cyclopropylfentanyl under drug control legislation. Five Member States (Austria, Belgium, Germany, Hungary, and Poland) control cyclopropylfentanyl under other legislation.

As for any new psychoactive substance, many of the questions related to cyclopropylfentanyl that are posed by the lack of data on the risks to individual health, risks to public health, and social risks, could be answered through further research. Areas where additional information would be important include studies on: rationale for use, prevalence and patterns of use (including studies that examine user groups and risk behaviours); the market; chemical profiling; complete pharmacological profiling; metabolic pathways; behavioural effects; acute and chronic toxicity; the potential interaction between cyclopropylfentanyl and other substances; the dependence and abuse potential; and the public health risks associated with its use.

The Committee notes that a decision to control cyclopropylfentanyl has the potential to bring with it both intended and unintended consequences. Potential intended consequences include reduced levels of availability and ultimately use. This may reduce the health and social risks and consequences arising from the use of cyclopropylfentanyl. It is important to recognise that a potential unintended consequence of control may be the manufacture and availability of other substances. Indeed, since cyclopropylfentanyl was first detected at least six new fentanils and a number of other new opioids that may replace it are already being sold on the drug market. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation.

Finally, the Committee notes that it is important to continue to collect and disseminate accurate information on cyclopropylfentanyl to users, those who may be at risk of occupational exposure, practitioners, policy makers, and decision makers.

12. List of annexes

Annex 1: Technical report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl).

Annex 2: List of participants at the risk assessment meeting of *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl).

European Monitoring Centre
for Drugs and Drug Addiction

DRAFT

Technical report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl)

Parts of this technical report were prepared under contract from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Given the time frame stipulated in the Council Decision, additional data presented and discussed during the preparatory meeting for the risk assessment and the risk assessment meeting have not yet been incorporated into the technical report. In addition, this technical report has not been formally edited by the EMCDDA. As such, this report should be regarded as a draft document until such time that the final version is produced by the EMCDDA which will incorporate the additional data and which will be formally edited. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The Risk assessment report on a new psychoactive substance: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) to which this report is annexed, was produced by the extended Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.

Annex 1 to the *Risk Assessment Report on N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl)*

Table of contents

Introduction

In accordance with Article 5 of the *Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances* ([1]), on 12 October 2017, the EMCDDA and Europol launched the Joint Report procedure for *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) on the basis of data reported by the Member States to the European Union Early Warning System in accordance with Article 4 of the Council Decision. The information collection process for the Joint Report was largely concluded by 23 November 2017. The report was submitted to the EU Institutions on 19 December 2017 (EMCDDA, 2017a). In accordance with Article 6 of the Council Decision, on 29 January 2018, the Council of the European Union requested that a risk assessment on cyclopropylfentanyl should be carried out by the extended Scientific Committee of the EMCDDA.

In order to prepare for the risk assessment, and, to facilitate the risk assessment process, the EMCDDA is responsible for the collection and analysis of data on the substance to be assessed as well as drafting a technical report. This technical report has been prepared for the risk assessment of cyclopropylfentanyl that will be held at the EMCDDA premises in Lisbon on Wednesday 21 March 2017.

Part of Section D in this report was prepared under EMCDDA contract (ref. CT.18.SAS.0017.1.0).

Data sources

The information in this technical report is derived from:

- data reported by the Member States, Turkey, and Norway to the EMCDDA and Europol in accordance with Council Decision 2005/387/JHA (EMCDDA, 2017a); and,
- data collected through systematic searches of open source information, including the scientific and medical literature, patents, official reports, grey literature, online drug discussion forums and related websites, and online vendors selling cyclopropylfentanyl.

Search strategy

Literature searches used both chemical structure and text queries in online databases; searches were conducted in January 2018. The retrieved publications were then scanned for additional relevant references (snowballing technique).

Chemical structure-based searches were done in SciFinder® (American Chemical Society, Chemical Abstract Service) using the exact structure and substructure of cyclopropylfentanyl as well as a similarity search. Structural and text-based searches in SureChEMBL patent database retrieved no hits.

Textual searches were conducted online in *PubMed* (National Center for Biotechnology Information), , and in English-language online drug forums. The search terms used were: ‘cyclopropylfentanyl’; ‘cyclopropyl fentanyl’; ‘cyclopropyl-fentanyl’; and ‘cyclopropanoylfentanyl’.

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

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

Note

It is important to note that when interpreting the information on self-reported user experiences in this report, it is not possible to confirm the specific substance(s) that have been claimed to be used; similarly it is also not possible to confirm the strength, purity, dose/amount, etc., used. Moreover, chemical analysis of substances and products that are claimed by vendors to contain specific substances has shown that the composition of these may differ over time and different geographical areas. In addition, the information provided on user websites may not necessarily be representative of other users of cyclopropylfentanyl and should be regarded as illustrative only. In general, given the difficulties of collecting accurate self-reported data, it should be interpreted with caution.

Technical report prepared by

Simon Elliott ([2]), Rachel Christie ([3]), Joanna de Morais ([3]), Rita Jorge ([3]), Anabela Almeida ([3]), Sofía Sola ([3]), Ana Gallegos ([3]), Michael Evans-Brown ([3]), and Roumen Sedefov ([3]).

Acknowledgements

The EMCDDA would like to extend their sincere thanks and appreciation to: the Early Warning System (EWS) correspondents of the Reitox national focal points and experts from their national early warning system networks; the Europol national units and Europol Project Synergy; and, Dr István Ujváry, iKem BT, Budapest, Hungary for reviewing some of the sections of this report.

([2]) Alere Forensics, Malvern, Worcestershire, United Kingdom.

([3]) European Monitoring Centre for Drugs and Drug Addiction.

Section A. Physical, chemical, pharmaceutical and pharmacological information

A1. Physical, chemical, and pharmaceutical information

A1.1. Physical and chemical description

Chemical description and names

N-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl) is structurally related to fentanyl ([4]), which is a 4-anilidopiperidine. Fentanyl and fentanyl derivatives ('fentanils') have in common an aralkyl group attached to a 4-*N*-acylanilinopiperidine. Fentanyl is an internationally controlled substance that is widely used in medicine in anaesthesia and for pain management.

Cyclopropylfentanyl differs from fentanyl due to the presence of a cyclopropane moiety in place of the ethyl linked to the carboxamide (Figure 1). Cyclopropylfentanyl is also structurally related to butyrfentanyl, which has been recently controlled internationally ([5]) (Figure 1). The main difference between the two compounds is the replacement of the butyramide group in butyrfentanyl with a cyclopropanecarboxamide group.

Tetramethylcyclopropanefentanyl ([6]), a close structural derivative of cyclopropylfentanyl, where the cyclopropane ring is fully substituted with four methyl groups at positions 2 and 3, was formally notified as a new psychoactive substance by the EMCDDA on behalf of Sweden in June 2017. Cyclopropyl derivatives of 3-methylfentanyl ([7]) (Zhu et al., 1983) and carfentanil ([8]) (Lu et al., 1990) have also been described.

Cyclopropylfentanyl and crotonylfentanyl ([9]) are constitutional isomers and therefore they are isobaric, i.e. they have different molecular structures but the same molecular mass (Figure 1). The identification of isobaric substances presents an analytical challenge (Section A1.1.). At the time of writing this report, the detection of crotonylfentanyl on the drug market in Europe has not been reported to the EMCDDA.

A total of fifteen fentanils are controlled under the United Nations Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol ([10]).

([4]) Systematic chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidinyl-4-yl]propanamide.

([5]) Systematic chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidinyl-4-yl]butanamide.

([6]) Systematic chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]-2,2,3,3-tetramethylcyclopropane-1-carboxamide.

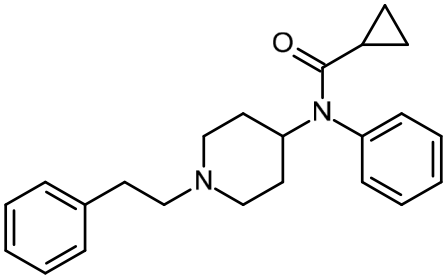
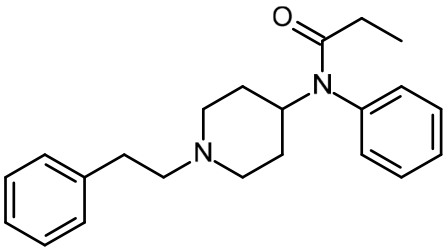
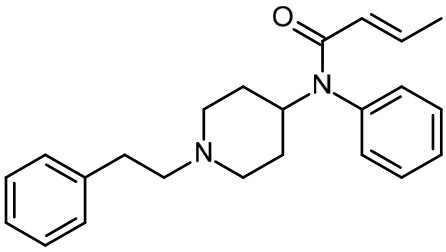
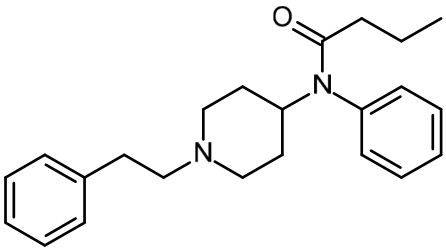
([7]) Systematic chemical name: *N*-(3-methyl-1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide, internationally controlled.

([8]) Systematic name: methyl 1-phenethyl-4-(*N*-phenylpropionamido)piperidine-4-carboxylate.

([9]) Systematic chemical name: *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-2-butenamide.

([10]) 3-Methylfentanyl, 3-methylthiofentanyl, acetyl-alpha-methylfentanyl, acetylfentanyl, alpha-methylfentanyl, alpha-methylthiofentanyl, beta-hydroxy-3-methylfentanyl, beta-hydroxyfentanyl, para-fluorofentanyl, and thiofentanyl are controlled under Schedule I and IV; alfentanil, butyrfentanyl, fentanyl, sufentanil and remifentanil are controlled under Schedule I.

Figure 1. Molecular structure, molecular formula, and molecular mass of cyclopropylfentanyl. Information on fentanyl, crotonylfentanyl, and butyrfentanyl is provided for comparison.

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

Names and other identifiers

Systematic International Union of Pure and Applied Chemistry (IUPAC) name:

N-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide

Chemical Abstract name:

cyclopropanecarboxamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-

Other names:

N-phenyl-*N*-[1-(2-phenylethyl)-4-piperidyl]cyclopropanecarboxamide;

N-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-cyclopropanecarboxamide;

N-[(1-phenethyl)-4-piperidyl]cyclopropanecarboxanilide;

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)

Chemical Abstract Service Registry Numbers (CAS RNs) ([11]):

1169-68-2 (free base)

PubChem CID ([12])*:*

Not available

IUPAC International Chemical Identifier Key (InCHI Key) ([13]):

OIQSKDSKROTEMN-UHFFFAOYSA-N

SMILES ([14]):

O=C(C1CC1)N(C2=CC=CC=C2)C3CCN(CCC4=CC=CC=C4)CC3

O=C(C1CC1)N(C3CCN(CCc2ccccc2)CC3)c4ccccc4

Common names:

cyclopropylfentanyl, cyclopropyl fentanyl, cyclopropyl-fentanyl

Street/user names and/or sold as:

'cyclopropylfent', 'Cp-FEN', cyclopropyl (Belgium), 'synthetic heroin' (Belgium), '4-me-MAF' (Sweden), 'MAF' (Poland) ([15])

Identification and analytical profile

Physical description

Cyclopropylfentanyl contains a basic nitrogen atom in the piperidine ring and therefore can readily form salts with organic or inorganic acids. Its hydrochloride salt has been described as a crystalline solid (Cayman Chemical Company, 2018) and as a white powder (Slovenian National Forensic

([11]) 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.

([12]) National Center for Biotechnology Information. PubChem Compound Database; https://pubchem.ncbi.nlm.nih.gov/ (accessed Jan. 25, 2018).

([13]) InChI Key is a unique, non-proprietary structural identifier of chemical substances used in electronic sources.

([14]) The simplified molecular-input line-entry system (SMILES) is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

([15]) 'MAF' is also a street name for methoxyacetylfentanyl. The available information suggests that cyclopropylfentanyl has been mis-sold as methoxyacetylfentanyl.

Laboratory, 2017; SWGDRUG, 2017). The melting point of the free base of cyclopropylfentanyl is 119.5–120.4 °C (Janssen, 1965).

The hydrochloride salt of cyclopropylfentanyl is soluble in methanol (Slovenian National Forensic Laboratory, 2017). No solubility data are available regarding the free base of cyclopropylfentanyl but given its similarity to fentanyl, it is expected to be lipophilic ([16]) and sparingly soluble in water.

Cyclopropylfentanyl has been detected in powders ranging from white to off-white, and, to a lesser extent, in liquids and tablets. A more detailed description of seizures and collected samples can be found in Section C.

Chemical stability and typical reactions

The material safety data sheet for cyclopropylfentanyl from the Cayman Chemical Company specifies that the compound is stable and does not undergo polymerization (Cayman Chemical Company, 2017). No other information is available regarding the stability of the substance.

Recent information, however, suggests that under certain conditions, such as gas chromatographic analysis using high temperature in the injection port, cyclopropylfentanyl may rearrange into crotonylfentanyl, and these isobaric fentanils could be difficult to distinguish (Figure 1).

Analytical profile

Analytical data for cyclopropylfentanyl are available in the literature. Cyclopropylfentanyl is commercially available as a certified reference standard ([17]). Methods documented in the literature for the detection of cyclopropylfentanyl include: gas chromatography–mass spectrometry (GC-MS) (Cayman Chemical Company, 2018; 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), liquid chromatography–mass spectrometry–mass spectrometry (LC/MS/MS), high resolution liquid chromatography–mass spectrometry (HR–LC/MS/MS) (Palaty et al., 2018) and proton nuclear magnetic resonance (^{1}H-NMR) (SWGDRUG, 2017).

An analytical challenge arises due to the isobaric nature of cyclopropylfentanyl and its isomer crotonylfentanyl, which have the same mass spectral properties. Recent work on the analytical identification of cyclopropylfentanyl has been limited by the challenges in distinguishing the two isomers (Simons and Juhascik, 2017; Palaty et al., 2018). GC-MS and LC-MS/MS analyses for both substances yielded virtually identical retention times, spectra and transition responses (Simons and Juhascik, 2017). Identification of cyclopropylfentanyl therefore requires analytical methodologies that account for these challenges, such as Raman, FTIR, or NMR.

One author suggests that the compounds should be reported as cyclopropyl/crotonyl fentanyl unless they are separated or identified by independent methodologies (Simons and Juhascik, 2017).

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

([16]) logP provides a measure of lipophilicity of a compound. The respective predicted logP values for cyclopropylfentanyl and fentanyl are 4.59 and 3.68 (calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 ©1994-2018 ACD/Labs). The measured logP value for fentanyl is 4.05 (Hansch et al., 1995).

([17]) The Cayman Chemical Company lists cyclopropylfentanyl hydrochloride as a certified reference material in its catalogue (https://www.caymanchem.com/product/23603).

Cyclopropylfentanyl is not expected to give a positive response to immunoassays developed for morphine-type opioids. Cyclopropylfentanyl may be detected by immunoassays developed for fentanyl (Kronstrand, 2018) and possibly those developed for LSD (Gagajewski et al., 2002).

Methods and chemical precursors used for the manufacture

The synthesis of cyclopropylfentanyl has been described in the literature (Janssen, 1965) and the method included the use (2-chloroethyl)benzene and *N*-phenyl-*N*-(piperidin-4-yl)cyclopropanecarboxamide.

In addition to this synthetic route and precursors, other methods used to manufacture pharmaceutical fentanyl are generally applicable to the synthesis of cyclopropylfentanyl (Casy and Huckstep, 1988; Gupta et al., 2013; Zee and Wang, 1980). For example, the use of ANPP ([18]) and an appropriate acylating agent (in this case cyclopropanecarbonyl chloride) is a viable pathway to produce cyclopropylfentanyl.

The synthesis of fentanyl has been extensively reviewed (Soine, 1986; Carroll and Brine, 1989; Hsu and Banks, 1992; Fritschi and Klein, 1995; Yadav et al., 2010; Vardanyan and Hruby, 2014). Most of these synthetic procedures are relatively straightforward and use common laboratory equipment. Detailed methods are available on the internet ([19]).

Due to the typical high potency of fentanils there is a risk of severe poisoning following accidental exposure during their manufacture, particularly in the final step of the synthetic routes. The accidental/occupational exposure to fentanils may also pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in working in custodial settings and in the postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in managing poisoning, including in resuscitation and adequate provision of naloxone to reverse poisoning (IAB, 2017; US CDC, 2013; US CDC, 2016). Any such responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole and Nelson, 2017; Lynch, Suyama, and Guyette, 2017).

The precursor ANPP, as well as the pre-precursor NPP ([20]), were scheduled in 2017 and are listed in Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (CND, 2017). The scheduling came into force on 18 October 2017 (INCB, 2017). In 2010, the U.S. Drug Enforcement Administration placed ANPP into Schedule II of the Controlled Substances Act in 2010 following its use as a precursor to make fentanyl in illicit laboratories (US DEA, 2010). To date, there is no information on the actual method(s) used for the production of cyclopropylfentanyl that has been detected on the European drug market.

([18]) The systematic name for ANPP, a common precursor to fentanyl and several fentanyl derivatives, is *N*-phenyl-1-(2-phenylethyl)piperidin 4-amine.

([19]) 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).

([20]) The systematic name for NPP, a common pre-precursor to fentanyl and several fentanyl derivatives, is *N*-phenylethyl-4-piperidinone.

Typical impurities encountered in seized and collected samples

There are no data available on the impurities detected in seized and collected samples reported to the EMCDDA.

A1.2. Physical/pharmaceutical form

In Europe, cyclopropylfentanyl has been typically found as a powder. Seizures and collected samples of the substance in liquid and in tablet form have also been reported to the EMCDDA. Some of the liquids have been detected in nasal sprays and in syringes found at the scene of deaths.

Forensic laboratories usually do not report whether cyclopropylfentanyl present in seizures/collected samples is in its free base or salt form.

A1.3. Route of administration and dosage

As with other fentanils, cyclopropylfentanyl can be administered orally as a powder (including in capsules), as tablets, or as a solution, or by insufflation of a powder; it can also be administered intranasally or sublingually via a spray; inhaled by smoking or vaporizing; and, administered by injection. Blotters containing fentanils have also been described.

Of note is the apparent popularity of selling ready-to-use or making homemade nasal sprays containing solutions for the administration of fentanils. Some of these products are not always labelled and/or they may be sold as another substance (EMCDDA, 2017b; EMCDDA, 2017c; Ujváry et al., 2017).

Data reported to the EMCDDA regarding deaths with confirmed exposure to cyclopropylfentanyl noted that in some cases nasal sprays were found close to the decedents. In addition, syringes containing cyclopropylfentanyl have also been found at the scene of deaths.

Dosage

Limited information is available regarding the dose and the dose regimens of cyclopropylfentanyl. It is not possible to currently discern the ‘typical’ dosages administered by users. Doses appear to differ depending on factors such as the route of administration, the tolerance of the users, the use of other drugs, and the desired effects. Given the difficulties of collecting such data, it should be used with caution.

A2. Pharmacology, including pharmacodynamics and pharmacokinetics

Published data on the pharmacology of cyclopropylfentanyl are limited to non-clinical studies. These data suggest that cyclopropylfentanyl is a selective μ-opioid receptor agonist that shares some similarities with opioid analgesics such as morphine and fentanyl. Additional research is required in order to have a more detailed understanding of the mode and mechanism of action of cyclopropylfentanyl and its metabolites.

Pharmacodynamics

In vitro studies

In vitro pharmacological data on cyclopropylfentanyl have been published recently by the United States Drug Enforcement Administration (US DEA, 2017a).

The binding affinity (K_i) ([21]) of cyclopropylfentanyl to opioid receptors was evaluated using an *in vitro* preparation of transfected Chinese hamster ovary (CHO) cells expressing rat μ-opioid receptors and transfected CHO cells expressing human δ- and κ- opioid receptors (US DEA, 2017a).

These data show that cyclopropylfentanyl binds to the μ-opioid receptor (MOR) with high selectivity (Ki = 0.088 ± 0.027 nM; [^{3}H]-DAMGO used as a radioligand) over the δ- and κ-opioid receptors (DOR and KOR) with Ki values of 59.4 ± 3.0 nM ([^{3}H]DPDPE used as radioligand) and 36 ± 10 nM ([^{3}H]U69,593 used as radioligand), respectively.

An *in vitro* functional assay found that cyclopropylfentanyl (EC_{50} = 10.8 ± 2.7 nM) ([22]) has μ-opioid receptor agonist activity similar to morphine (EC_{50} = 16.5 ± 3.1 nM) and fentanyl (EC_{50} = 32 ± 11 nM).

Together, these studies suggest that cyclopropylfentanyl is a μ-opioid receptor agonist. It is not known to what extent this agonist effect would translate to high toxicity *in vivo*.

The effect of cyclopropylfentanyl on pharmacological targets other than the three opioid receptor subtypes is not known.

Animal studies

Data on the pharmacology of cyclopropylfentanyl from animal studies is limited to a single mention of its ability to reduce sensitivity in mice to noxious stimulation (Janssen et al., 1968). Here, the tabulated activity of cyclopropylfentanyl was reported to be 280 times greater than pethidine ([23]) (the reference substance); the activity of acetylfentanyl ([24]) and butyrfentanyl were reported to be 50 and 90 times greater than pethidine, respectively. The authors caution that these data should only be interpreted as indicating no more than an order of magnitude.

Pharmacokinetics

No non-clinical or clinical studies were identified that have investigated the pharmacokinetics, including metabolism, of cyclopropylfentanyl. Due to its high lipophilicity (Section A1.1.), cyclopropylfentanyl, like fentanyl, is expected to readily cross the blood–brain barrier and also diffuse into fat and other tissues (i.e., it is likely to have a large volume of distribution).

The extent to which the biotransformation products of cyclopropylfentanyl are comparable to closely related fentanils remains to be investigated. It seems likely that some overlap might exist, including *N*-dealkylation to nor-cyclopropylfentanyl, hydroxylations on the phenyl rings, and amide hydrolysis producing 4-ANPP (Palaty et al., 2018; Watanabe et al., 2017).

There is some information on the biological activity of 4-ANPP using intact guinea pig ileum preparations. Compared to fentanyl (IC_{50} = 4 nM), 4-ANPP was significantly less potent in inhibiting contractions of ileum segments induced by coaxial electrical stimulation (IC_{50} = 12,000 nM). The IC_{50} value determined for morphine was 50 nM (Schneider and Brune, 1986). Two metabolites showed activity in this study: the phenolic derivative hydroxylated at the 4-position of the phenylethyl moiety of

([21]) K_i in a binding assay is defined as the affinity constant of a displacer compound for the receptor.

([22]) EC_{50} is the effective concentration at 50% maximal response.

([23]) The United States Adopted Name (USAN) for pethidine is meperidine.

([24]) Acetylfentanyl is included in Schedule I of the 1961 United Nations Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol.

fentanyl, the activity (IC_{50} = 240 nM) of which was found to lie between morphine and pethidine (IC_{50} = 1,300 nM), and the benzylic alcohol type derivative hydroxylated at the alpha-position, i.e. benzylic methylene, of the phenylethyl moiety of fentanyl which had an IC_{50} value of 50 nM.

Inter-individual genetic variability in metabolising enzymes

Specific information about cyclopropylfentanyl could not be identified. For fentanyl, oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes to norfentanyl has been demonstrated (Guitton et al., 1997; Jin et al., 2005; Labroo et al., 1997). The variation of the expression of the genes coding for these CYP3A isoenzymes among populations might be of clinical significance (Meyer and Maurer, 2011) but further studies are needed to examine the toxicological significance, if any, of such polymorphisms.

Interactions with other substances and other interactions

Specific information about cyclopropylfentanyl could not be identified, although it seems conceivable that interactions observed with fentanyl might equally apply (Preston, 2016). For example, should cyclopropylfentanyl undergo oxidative dealkylation by hepatic CYP3A4 and by CYP3A5 isoenzymes then the use of this substance with inhibitors of these isoenzymes, such as clarithromycin, erythromycin, fluconazole, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, ritonavir, saquinavir, suboxone, verapamil ([25]) may result in increased plasma concentration of cyclopropylfentanyl. This could increase the risk of poisoning, including potentially fatal respiratory depression.

The concomitant use of other central nervous system (CNS) depressants with cyclopropylfentanyl, such as other opioids, sedatives/hypnotics (such as the benzodiazepines and the z-drugs), ethanol, pregabalin, gabapentin, tranquillisers, and sedating anti-histamines, may produce additive depressant effects.

The use of fentanyl with serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs) (the most commonly prescribed antidepressants), serotonin norepinephrine re-uptake inhibitors (SNRIs), or monoamine oxidase inhibitors (MAOIs) has been associated with a serotonin syndrome, a potentially life-threatening condition. This association is likely to extend to illicit drugs that act on the serotonergic system. It is not known if this association with serotonin syndrome is also seen with cyclopropylfentanyl.

Effects on ability to drive and operate machines

No studies of the effects of cyclopropylfentanyl on the ability to drive and operate machines have been performed. However, it is well established that opioid analgesics, such as fentanyl, impair the mental and physical ability required to drive and operate machines. This effect is likely to extend to cyclopropylfentanyl.

A3. Psychological and behavioural effects

Information on the psychological and behavioural effects of cyclopropylfentanyl is limited. From the data available, it appears that the psychoactive profile of cyclopropylfentanyl might share at least

([25]) For a more comprehensive list of drug interactions with fentanyl, see, for example, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&source=homeMedSearch&keyword=fentanyl&category=human&isNewQuery=true

some similarities with other opioid analgesics such as fentanyl and heroin. These would include relaxation and euphoria; at higher doses, sedation and profound intoxication may occur.

A4. Legitimate uses of the product

Cyclopropylfentanyl is used as an analytical reference material in clinical and forensic case work/investigations as well as scientific research. There is currently no information that suggests cyclopropylfentanyl is used for other legitimate purposes.

There are no reported uses of cyclopropylfentanyl as a component in industrial, cosmetic or agricultural products. In addition, a search of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registered substances database (ECHA, 2018) using the CAS Registry Number for cyclopropylfentanyl returned no results.

There is no marketing authorisation (existing, on-going or suspended) for cyclopropylfentanyl neither in the European Union nor in the Member States that responded to the request for information from the European Medicines Agency, which was undertaken as part of the Joint Report process (EMCDDA, 2017a).

There is no information to suggest that cyclopropylfentanyl is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a database on the synthetic routes of all medicinal products it is not possible to confirm whether or not cyclopropylfentanyl is currently used in the manufacture of a medicinal product.

Section B. Dependence and abuse potential

B1. Animal data

No studies were identified that have investigated the dependence and/or abuse potential of cyclopropylfentanyl in animal models.

B2. Human data

No studies were identified that have investigated the dependence and/or abuse potential of cyclopropylfentanyl in humans.

While no specific data exist for cyclopropylfentanyl, it is well established that opioid analgesics such as fentanyl have an abuse liability and can induce tolerance and dependence. Research is required in order to examine these effects with cyclopropylfentanyl.

Section C. Prevalence of use

Information from seizures, collected and biological samples

Cyclopropylfentanyl was formally notified on 4 August 2017 by the EMCDDA on behalf of Latvia, in accordance with Article 4 of the Council Decision. The Reporting Form details the detection 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.

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.

In total, 6 Member States (Austria, Latvia, Poland, Slovenia, Sweden, and the United Kingdom) and Norway reported detections of cyclopropylfentanyl ([26]) (EMCDDA, 2017a).

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

In addition, some laboratories may not be able to distinguish cyclopropylfentanyl from its constitutional isomer crotonylfentanyl.

Information from seizures

In total, 144 seizures of cyclopropylfentanyl ([27]) were reported to the EMCDDA by 5 Member States and Norway: Latvia (47 cases), Poland (2), Slovenia (1), Sweden (85), the United Kingdom (5), and Norway (4). Where known, the seizures took place from June 2017 to January 2018 and were made by police or customs agencies.

Cyclopropylfentanyl was detected in powders, and, to a lesser extent, in liquids and in tablets. The exact composition or purity of the seized substance, including presence of any adulterants or cutting agent, were not reported.

Powders

A total of 1.76 kg of powder containing cyclopropylfentanyl was seized in 52 cases. The cases were reported by: Latvia (38), Poland (2), Slovenia (1), Sweden (7), and the United Kingdom (4). Where known, the powders were reported to be white or off-white in colour. Briefly:

- In about 90% of the cases, the quantities seized were under 1 g.
- In 1 case, reported by Poland, two parcels were seized by customs that each contained approximately 500 g of cyclopropylfentanyl in powder form. The parcels were sent by post from China, via Belgium, to a private address in Poland in September 2017 (Annex 1).
- In 3 cases reported by Swedish customs, a total of approximately 600 g were seized (no additional details are available).
- Three small seizures were made in prisons in Latvia.

([26]) '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.).

([27]) 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.

- In the large majority of seizures, cyclopropylfentanyl was the only substance reported as detected in the powders.

- In 2 cases, cyclopropylfentanyl was detected along with other substances: in 1 case, reported by the United Kingdom, heroin was detected alongside cyclopropylfentanyl in 36 g of powder; in 1 case reported by Latvia, the substance was detected with methadone.

Liquids

A total of 772 mL of liquid containing cyclopropylfentanyl were seized in 64 cases. The cases were reported by: Latvia (9 cases), Sweden (53), the United Kingdom (1), and Norway (1). Sweden accounted for over 98% of the total quantity seized (760 mL).

- In 6 of the cases, all reported by Latvia, the liquids were recovered from syringes.

- The United Kingdom reported a seizure of a nasal spray that was found at a scene of death and contained cyclopropylfentanyl only.

- Norway reported a seizure of two nasal sprays found at the scene of a death. Both of the sprays contained a colourless liquid in which cyclopropylfentanyl and traces of acetylfentanyl were detected. At least one of the nasal sprays was reported to be labelled as 'methoxyacetylfentanyl'.

Tablets

At least 329 tablets containing cyclopropylfentanyl were seized in 28 cases. The cases were reported by Sweden (25 cases) and Norway (3).

Between mid-November 2017 and mid-January 2018, Swedish police made 10 seizures of falsified (fake) Xanax tablets ('2 mg Xanax bars') (quantity seized not reported) (Annex 1). The tablets were found to contain approximately 0.5 mg of cyclopropylfentanyl per tablet and no alprazolam (the benzodiazepine that is present in legitimate Xanax tablets). Additionally, 18 falsified Xanax tablets that contained cyclopropylfentanyl were found at a scene of a death in Norway.

During December 2017, Swedish Police made a seizure of falsified OxyContin tablets ('OP 80') (quantity seized not reported) (Annex 1). The tablets contained approximately 2 mg of cyclopropylfentanyl per tablet and no oxycodone (the opioid that is present in legitimate OxyContin tablets).

Swedish Police also reported one seizure of white round tablets with a cross-cut which contained approximately 2 mg of cyclopropylfentanyl (quantity seized not reported). No further details regarding this seizure are available.

Information from collected samples

Three collected samples containing cyclopropylfentanyl were reported by 3 Member States: Austria, Poland, and the United Kingdom. All the samples were collected between August 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', which is actually a street name for methoxyacetylfentanyl.

Information from biological samples

Serious adverse events (deaths and acute intoxications) with confirmed exposure to cyclopropylfentanyl from the analysis of biological samples are discussed in Section D.

In addition, Sweden reported 5 detections of cyclopropylfentanyl from biological samples not related to serious adverse events. In one of these cases, the detection was related to a suspected petty drug offense. No further details are available on the remaining 4 cases.

Availability, supply, price

The available information suggests that cyclopropylfentanyl is typically sold online in powder form and as a solution in ready-to-use nasal sprays. Sometimes it is advertised under the guise of being a 'research chemical'. Seizures reported by Sweden and Norway show that cyclopropylfentanyl has been used to make falsified (fake) Xanax tablets. Falsified OxyContin tablets have also been seized in Sweden. The source of these tablets and their general availability within Europe is unknown. In one case, cyclopropylfentanyl has also been detected in a powder containing heroin.

Availability from Internet vendors

Cyclopropylfentanyl is sold on the surface web, typically as a powder and as a solution in ready-to-use nasal sprays.

Austria and the United Kingdom reported collected samples of cyclopropylfentanyl in powder form that were purchased from vendors on the surface web.

The availability of cyclopropylfentanyl on the darknet is currently unknown.

Prevalence of use

No studies were identified that have investigated the prevalence of use of cyclopropylfentanyl in the general population. Given its pharmacology, and, that it is sold openly as a 'legal' replacement to illicit opioids, it could be expected that individuals looking for substitutes for opioids, such as heroin and/or prescription opioids, may be interested in cyclopropylfentanyl and other fentanils. This group could include high risk drug users, including individuals who inject opioids. Similar to other new psychoactive substances, it also appears that there is interest in cyclopropylfentanyl by some psychonauts. Overall, the available information does not suggest widespread use of the substance.

Seizures reported by Sweden and Norway show that cyclopropylfentanyl has been used to make falsified (fake) Xanax tablets. Falsified OxyContin tablets have also been seized in Sweden. The source of these tablets and their general availability within Europe is unknown. Such benzodiazepines and opioid analgesics are typically highly sought after products on the illicit drug market. People who use such fakes will not be aware that they are using cyclopropylfentanyl.

Of additional note is that, in the past few years, fentanils have been sold in Europe as ready-to-use nasal sprays. In some cases, they have also been sold as 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, potentially expanding their use in new user groups. These are new developments that will require careful monitoring. Nasal sprays claiming to contain cyclopropylfentanyl have been offered by online vendors within the European Union. Analysis of seized nasal sprays confirms that such products have been used in Europe.

Section D. Health risks

D1. Acute health effects

D1.1. Animal data

Data on the acute toxicity, abuse liability, and dependence producing potential of cyclopropylfentanyl could not be identified.

D1.2. Human data

No clinical studies were identified that have examined the acute health effects of cyclopropylfentanyl and/or its metabolites in humans. Although the pharmacology and toxicology of cyclopropylfentanyl remains largely unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl. The acute effects of these types of opioids include: euphoria, relaxation, analgesia, sedation, bradycardia, hypothermia, miosis, respiratory depression, and respiratory arrest. They also have an abuse liability and dependence potential (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; Romberg et al., 2003).

Similar to other opioid analgesics, the most serious acute health risk associated with cyclopropylfentanyl use is probably respiratory depression, which can lead to apnoea, respiratory arrest and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White and Irvine, 1999).

In addition, it has recently been suggested that another possible serious acute risk associated with the fentanils is from sudden onset rigidity of the chest wall musculature that leads to apnoea and respiratory arrest (Burns et al., 2016) ([28]).

There is lack of information on the clinical features of poisoning caused by cyclopropylfentanyl. Nonetheless, the available data suggests that the nature of the effects of cyclopropylfentanyl share some similarities with opioid analgesics such as morphine and fentanyl. As a result, features of poisoning are likely to include miosis, reduced level of consciousness or unconsciousness, and respiratory depression and arrest.

Data from serious adverse events associated with cyclopropylfentanyl are discussed below.

Acute intoxications reported by the Member States

No acute intoxications with confirmed exposure to cyclopropylfentanyl were reported to the EMCDDA ([29]).

Acute intoxications identified from other sources

Edison et al., reported a cluster of 27 overdose cases associated with the use of the falsified (fake) Percocet tablets ([30]) that occurred during 4-13 June 2017 in Georgia, United States. Of the 27 cases,

([28]) This phenomenon appears to be linked to the use of routes of administration that rapidly deliver the substances to the systemic circulation, such as intravenous administration. Further study of this phenomenon would appear to be warranted. Similar to respiratory depression, chest wall rigidity is rapidly reversed by administration of the antidote naloxone.

([29]) Sweden reported 2 acute intoxications with suspected exposure to cyclopropylfentanyl. These cases are not discussed further in this report.

16 (59%) were male; median age was 34 years (range = 19–69 years). Symptoms included loss of consciousness (25 patients [93%]) and respiratory distress (22 [81%]). Twenty-five (93%) patients received naloxone, and 11 (41%) required intubation and mechanical ventilation. One of the patients died ([31]). Routine urine drug screens were positive for multiple drugs in 16 (59%) patients; synthetic opioids are not detected by these screens. Chemical analysis of tablets believed to be linked to the outbreak identified cyclopropylfentanyl and U-47,700 (Edison et al., 2017).

Deaths reported by the Member States

A total of 78 deaths were reported to the EMCDDA by Sweden (74), the United Kingdom (3 cases), and Norway (1). Exposure to cyclopropylfentanyl was analytically confirmed from post-mortem biological samples in all 78 deaths.

In two of the deaths, nasal sprays were found at the scene. In one case, analysis of the content of the spray detected cyclopropylfentanyl only. In the other case, analysis of the contents of two sprays detected cyclopropylfentanyl and acetylfentanyl; at least one of the sprays was labelled with 'methoxyacetylfentanyl' (Section C).

The deaths occurred within a short time period of between June 2017 and December 2017.

Of the 78 deaths, 71 were male (91%) and 7 were female (9%). The mean age of the males was 33 years (median 31) and ranged from 17 to 59 years. The mean age of the females was 34 years (median 31) and ranged from 25 to 54 years.

In addition, Latvia reported 4 deaths with possible exposure to cyclopropylfentanyl, where syringes containing cyclopropylfentanyl where found next to the deceased. Analytical confirmation of exposure from biological samples is not available. These cases are not considered further in this report.

Circumstances and cause of death

There was a lack of information regarding any symptoms experienced by the deceased prior to death in the majority of cases, but, where described, in some cases, the deceased was found or had become unconscious. Where information was known, in the majority of instances the individuals were found dead, predominantly in a home environment (either their own or a friend's). Consequently, it was not possible to identify or evaluate ante-mortem symptoms (especially in relation to acute intoxication) in these cases.

The cause of death was available in 74 of the 78 cases. In the 74 deaths, cyclopropylfentanyl was cited (either by name or as an opioid or narcotic) in the cause of death even in presence of other substances. Other substances were detected in 74 cases with cyclopropylfentanyl being the only drug present in the remaining 4 cases.

Cyclopropylfentanyl was quantified in 77 of the 78 cases. In 73 of the 74 cases from Sweden, post-mortem femoral blood concentrations between 1.1 and 270 ng/g blood were recorded (median 8.2 ng/g blood) (with ng/g being somewhat but not exactly equivalent to ng/mL). In the 3 cases from the United Kingdom, post-mortem femoral blood concentrations of 20.9, 26.4 and 28.9 ng/mL were found. In the remaining case from Norway, a post-mortem femoral concentration of 82 nmol/L was reported

([30]) Percocet tablets are prescription-only opioid analgesics that contain oxycodone and paracetamol and are authorised in the United States.

([31]) The fatal case may be a duplicate of case from Georgia reported by the United States Drug Enforcement Administration (US DEA, 2017a).

(equivalent to 28.6 ng/mL). Due to the toxicity of potent opioids and variability in user tolerance, a post-mortem blood concentration cannot necessarily be used to determine a 'fatal' concentration. In the majority of circumstances involving fentanils, the mere presence of the drug is of significance whether the concentration has been determined or not, especially in situations of polydrug use.

A range of other substances were detected in the deaths, including: cannabinoids, benzodiazepines, cocaine, amphetamine, MDMA, zopiclone, zolpidem, lamotrigine, methylphenidate, β-blockers, gabapentinoids (pregabalin and gabapentin), antidepressants, antipsychotics, antihistamines, synthetic cathinones (alpha-PHP, mephedrone and 4-fluoro-N-ethylpentedrone), synthetic cannabinoids (5Cl-AB-PINACA and AB-PINACA), and ethanol. Other opioids were detected in 22 of the deaths; buprenorphine (7 deaths), morphine (7), oxycodone (4), mitragynine (2), noscapine (2), tramadol (4), methadone (2), codeine (2), acetylfentanyl (1), papaverine (2), and U-47700 (1). 6-Monoacetylmorphine (heroin metabolite) was found in 2 of the deaths.

Overall, whilst other substances may have contributed some toxicity, a synergistic effect with cyclopropylfentanyl would have been likely with other central nervous system depressants in particular ethanol, benzodiazepines, opioids, etc. Nevertheless, the potent opioid nature of cyclopropylfentanyl means the primary toxic contribution could be attributed to the drug and death may not have occurred if cyclopropylfentanyl had not been used. An assessment of the Toxicological Significance Score (TSS) (Elliott, Sedefov, and Evans-Brown, 2018) incorporating the above considerations, shows that cyclopropylfentanyl had a TSS value of 3 (high) in 77 out of 78 of the deaths (where it was cited as the cause of death or is likely to have contributed to death). In the remaining death involving decomposition, toxicological evidence was only available in muscle so the significance is unascertainable.

Deaths identified from other sources

The United States Drug Enforcement Administration reported 115 confirmed deaths associated with cyclopropylfentanyl that occurred as early as May 2017. The deaths occurred in Georgia (1), Maryland (24), Mississippi (1), North Carolina (75), and Wisconsin (14) (US DEA, 2017a; US DEA, 2017b).

Smith and Kinkaid reported identification of cyclopropylfentanyl in 3 post mortem cases in Allegheny County, Pennsylvania, United States (Smith and Kinkaid, 2017).

Simons and Juhascik reported the identification of nine suspected cases of cyclopropylfentanyl in biological matrices (including one death) by the Miami Valley Regional Crime Laboratory / Montgomery County Coroner's Office, Ohio, United States. The reported death case involved a 36 year old white male found deceased with an unknown white powder on his clothing. The sample of the powder was submitted to the laboratory in late May 2017. Initial ELISA screening was positive for fentanyl. After inclusion of cyclopropylfentanyl as part of the LC-MS/MS confirmation assay the sample was re-extracted. The authors also reported that the analysis of crotonyl fentanyl by GC/MS and LC-MS/MS yielded identical retention time, MS spectrum, and transition responses to those of cyclopropylfentanyl and that their laboratory recommends reporting as cyclopropyl / crotonyl fentanyl unless the compounds can be separated or identified by different methodology (such as Raman and FTIR) (Simons and Juhascik, 2017).

D2. Chronic health effects

D2.1. Animal data

No studies were identified that have investigated the chronic health effects of cyclopropylfentanyl in animals.

D2.2. Human data

No studies were identified that have investigated the chronic health effects of cyclopropylfentanyl in humans.

D3. Factors affecting public health risks

D3.1. Availability and quantity of the new psychoactive substance on the market

Cyclopropylfentanyl is sold on the surface web as a drug in its own right. Typically, it is offered as a powder and as a solution in ready-to-use nasal sprays. Sometimes it is advertised under the guise of being a 'research chemical'. Bulk quantities of powder (~500 g) that originated from China have been seized by customs agencies (Section C).

Cyclopropylfentanyl is also used to make tablets. This includes falsified (fake) Xanax and OxyContin tablets. The source of these tablets and their general availability within Europe is unknown.

Limited information suggests that it might also be sold by street-level dealers. Information from a single seizure case in the United Kingdom suggests that cyclopropylfentanyl may be sold on the illicit opioid market in mixtures with heroin.

The available information also suggests that cyclopropylfentanyl has also been mis-sold as methoxyacetylfentanyl.

D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects

Due to its relatively recent availability on the drug market, the availability of information, degree of knowledge and perceptions amongst users concerning cyclopropylfentanyl and its effects are limited.

D3.3. Characteristics and behaviour of users

While no specific examples are available on the possible appeal of cyclopropylfentanyl to user groups (aside from psychonauts), it is reasonable to assume that the substance may be sought by those looking for 'legal' substitutes for illicit opioids (such as heroin) and/or prescription opioids. This includes high risk drug users, including those who inject opioids.

The available information, including deaths reported by the Member States, suggests that cyclopropylfentanyl is used in the home environment. In fact, in the majority of the deaths the individuals were found dead. It appears that in at least some of these cases the poisoning with cyclopropylfentanyl was so severe that they were unable to call for help. Polydrug use, including the use of other central nervous system depressants such as opioids and benzodiazepines, was common in the deaths.

D3.4. Nature and extent of health consequences

Acute health risks

Although the pharmacology and toxicology of cyclopropylfentanyl remains largely unstudied, the available data suggests that the nature of its effects share some similarities with opioid analgesics such as morphine and fentanyl.

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 (Cox, 2011; Dahan et al., 2001; Pattinson, 2008).

Similar to other opioid analgesics, the most serious acute risk arising from the use of cyclopropylfentanyl is probably from respiratory depression, which can lead to apnoea, respiratory arrest, and death (Cox, 2011; Dahan et al., 2001; Pattinson, 2008; White and Irvine, 1999).

In general, this risk may be exacerbated by:

- the difficulty in diluting/using fentanils (as they are typically highly potent), which can lead to a toxic dose being accidentally used (de Boer et al., 2003; Sutter et al., 2017);
- the apparent rapid onset of severe poisoning following use (Somerville et al., 2017);
- using routes of administration that allow large amounts of the substance to rapidly reach the central nervous system (such as injecting, insufflation, and inhalation) (Macleod et al., 2012);
- availability of easy to use dosage forms (such as nasal sprays and e-liquids);
- lack of awareness and experience of users with these new substances (effects and dosage);
- use of other central nervous system depressants (such as other opioids, benzodiazepines, and alcohol) (e.g. van der Schrier et al., 2017);
- lack of tolerance to opioids in opioid-naïve persons (such as new or former users);
- use in environments where it may be difficult to summon help in the event of poisoning (e.g. alone in a home environment) (Somerville et al., 2017);
- limited availability of the antidote naloxone in community settings (EMCDDA, 2015; EMCDDA, 2016; Somerville et al., 2017).

In addition, and, often unknown to users, the fentanils are sold as heroin or mixed with heroin and other illicit opioids. They are also used to make falsified (fake) versions of highly sought-after analgesics and benzodiazepines. They have also been sold in or as drugs such as cocaine (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017). Due to this, users may not be aware that they are using a fentanil; in some cases these individuals will have reduced or no tolerance to opioids nor access to community naloxone programmes. Overall, these factors may increase the risk of life-threatening poisoning.

Given the above risks, poisonings by fentanils may manifest as outbreaks which have the potential to overwhelm emergency responders and other local healthcare systems (Klar et al., 2016; SFDPH, 2015; Sutter et al., 2017; Tomassoni et al., 2017).

Accidental/occupational exposure to the fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in working in custodial settings and in the postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in managing poisoning, including in resuscitation and adequate provision of naloxone to reverse poisoning (IAB, 2017; US CDC, 2013; US CDC, 2016). Any such responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole and Nelson, 2017; Lynch, Suyama, and Guyette, 2017).

Managing poisoning

The antidote naloxone should reverse 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 (Klar et al., 2016; Klebacher et al., 2017, Moss et al., 2017; Somerville et al., 2017; Sutter et al., 2017). This may reflect, among other factors, the high potency of the fentanils, their half-lives, the dose an individual is exposed to, and, the relatively short half-life of naloxone.

Chronic health risks

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

D3.5. Long-term consequences of use

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

D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks

There is limited data on the conditions in which cyclopropylfentanyl is obtained and used. Cyclopropylfentanyl is offered for sale on the surface web, typically as powders and ready-to-use nasal sprays. It has also been seized as tablets, including as falsified (fake) Xanax and OxyContin tablets. Information from a single seizure case in the United Kingdom may suggest that cyclopropylfentanyl may have also been sold on the illicit opioid market in mixtures with heroin.

Section E. Social Risks

While there have been no studies on the social risks of cyclopropylfentanyl, it is likely that some of the risks are similar to those associated with illicit opioids, including fentanyl and heroin.

E1. Individual social risks

There is no information on the individual social risks that may be associated with the use of cyclopropylfentanyl. Given that cyclopropylfentanyl appears to act as an opioid analgesic, any such risks may have some similarities with those associated with illicit opioids. These may negatively impact on education or career, family or other personal and social relationships and may result in marginalisation.

E2. Possible effects on direct social environment

There is no information on the possible effects of cyclopropylfentanyl on the direct social environment. Given that cyclopropylfentanyl appears to act as an opioid analgesic, any such effects may have some similarities with those associated with the use of illicit opioids.

E3. Possible effects on society as a whole

There is no specific information on the possible effects of cyclopropylfentanyl on society as a whole.

As discussed above, accidental/occupational exposure to the fentanils may pose a risk of poisoning to those who may come into contact with the substances. This includes the family and friends of users, law enforcement, emergency personnel, medical and forensic laboratory personnel, as well as those in working in custodial settings and in the postal services. Where required, these risks should be assessed and appropriate procedures, training, and protective measures should be implemented. This may include training in managing poisoning, including in resuscitation and adequate provision of naloxone to reverse poisoning (IAB, 2017; US CDC, 2013; US CDC, 2016). Any such responses should continue to ensure the delivery of prompt and appropriate care to patients with suspected overdose (Cole and Nelson, 2017; Lynch, Suyama, and Guyette, 2017).

E4. Economic costs

There are no data on the health and social costs related to cyclopropylfentanyl.

E5. Possible effects related to the cultural context, for example marginalization

There are no data on the possible effects of cyclopropylfentanyl related to the cultural context.

E6. Possible appeal of the new psychoactive substance to specific population groups within the general population

While no specific examples are available on the possible appeal of cyclopropylfentanyl to specific user groups (aside from psychonauts), it is reasonable to assume cyclopropylfentanyl may be sought by those looking for ‘legal’ substitutes for illicit opioids, such as heroin and/or prescription opioids. This may include high risk drug users, including those who inject.

As discussed above, the open sale of solutions of cyclopropylfentanyl, as well as other fentanils, in novel dosage forms (such as ready-to-use nasal sprays and e-liquids for vaping) poses additional concerns. These novel forms have the potential to make the use of fentanils easier (with similar effects to injecting) and more socially acceptable.

Section F. Involvement of organised crime

F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain

There is no specific information to suggest the involvement of organised crime or established criminal groups in the manufacture, distribution, and supply of cyclopropylfentanyl.

There are indications that production of fentanils such as cyclopropylfentanyl may occur in legitimate chemical companies in China, which ship the products typically as powders to retailers and persons in Europe. Bulk powders may be processed and packaged into novel dosage forms such as nasal sprays, and, less commonly, as e-liquids for vaping or plant material that is intended to be smoked.

These are typically sold on the internet by retailers. Fentanils may also be distributed directly in the illicit drug supply chain as drugs in their own right, or by passing them off as heroin and other illicit opioids, as well as falsified (fake) medicines, and, less commonly, as cocaine.

Information on production

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

Sweden reported that there is no known production in the country. They also reported, that, similar to the supply of other fentanils, the cyclopropylfentanyl sold in Sweden is obtained in powder form, dissolved in an appropriate solvent by vendors, and packaged into nasal sprays which are ordered from China.

The seizure of an illicit laboratory producing fentanils in Europe in 2013 (EMCDDA, 2017b) suggests that the capability to manufacture fentanils may exist within the European Union.

Information on trafficking

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

Sweden reported that cyclopropylfentanyl 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.

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.

F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances

No information was reported nor identified concerning the impact of cyclopropylfentanyl on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances. However, it appears that cyclopropylfentanyl has been sold as methoxyacetylfentanyl in some circumstances.

F3. Evidence of the same groups of people being involved in different types of crime

No information was reported nor identified concerning evidence of the same groups of people being involved in different types of crime related to the availability of cyclopropylfentanyl.

F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)

No information was reported nor identified concerning incidents of violence related to the availability of cyclopropylfentanyl.

F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society

No information was reported nor identified concerning evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society related to the availability of cyclopropylfentanyl.

F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)

No information was reported nor identified concerning the economic costs and consequences related to the availability of cyclopropylfentanyl.

F7. Use of violence between or within criminal groups

No information was reported nor identified concerning the use of violence between or within criminal groups related to the availability of cyclopropylfentanyl.

F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation

No information was reported nor identified concerning evidence of strategies to prevent prosecution related to the availability of cyclopropylfentanyl.

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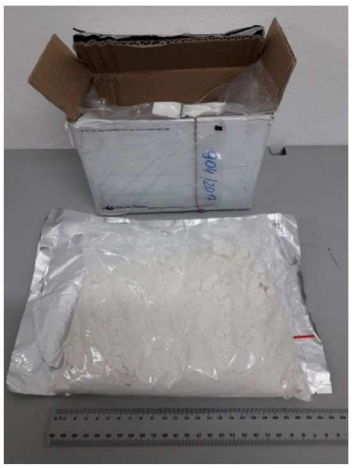
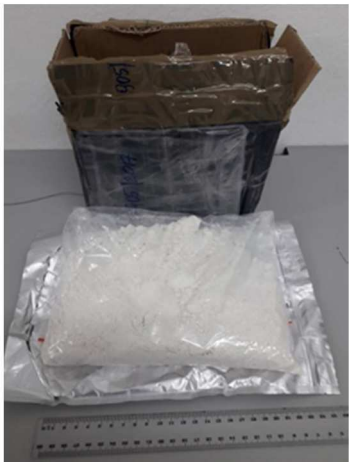
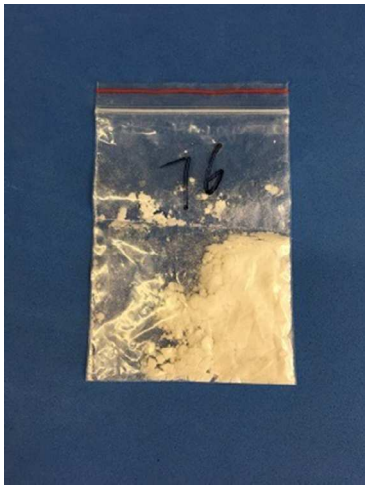
Annex 1

Technical Report on *N*-phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl)

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.

Country	Image	Description
Sweden		**Seizure** Date: November 2017 – January 2018 Seizing authority: Swedish Police Falsified Xanax tablets; white elongated, marked ‘XANAX’/’2’
Sweden		**Seizure** Date: December 2017 Seizing authority: Swedish Police Falsified OxyContin tablets; green round, marked ‘OP’/‘80’
United Kingdom		**Collected sample** Date: 22 August 2017 Collecting authority: TICTAC Communications Ltd.

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for Drugs and Drug Addiction

Annex 2. List of participants at the risk assessment meetings of cyclopropylfentanyl and methoxyacetylfentanyl

21 March 2018

A. Extended Scientific Committee

Dr Anne Line BRETTEVILLE-JENSEN
Norwegian Institute for Alcohol and Drug Research, Oslo
Chair of the Scientific Committee

Professor Dr Gerhard BUEHRINGER
Addiction Research Unit, Department of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Institut für Therapieforschung (IFT), Munich

Professor Dr Catherine COMISKEY
Director, Centre for Practice and Healthcare Innovation, Trinity College Dublin, Dublin
Vice-Chair of the Scientific Committee

Professor Dr Paul DARGAN
Clinical Toxicology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London

Professor Dr Fabrizio FAGGIANO
Department of Translational Medicine of Università del Piemonte Orientale and Epidemiologic Observatory of the Local Health Unit of Vercelli, Novara

Professor Dr Gabriele FISCHER
Medical University Vienna, Center of Public Health, Vienna

Professor Dr Henk GARRETSEN
Faculty of Social and Behavioural Sciences, Tilburg University, Tilburg

Professor Dr Krzysztof KRAJEWSKI
Department of Criminology, Jagiellonian University, Krakow

Dr Fernando RODRÍGUEZ de FONSECA
Fundación IMABIS, Hospital Universitario Carlos Haya de Málaga, Málaga

Professor Dr Rainer SPANAGEL
Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim

Dr Wim BEST
Utrecht University, Faculty of Science, Freudenthal Institute, Utrecht

Dr Simon BRANDT
School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool

Professor Dr Gaetano di CHIARA
Biomedical Sciences Department, University of Cagliari, Cagliari

Professor Dr Éva KELLER
Semmelweis University, Department of Forensic and Insurance Medicine, Budapest

Dr Claude GUILLOU
Directorate F – Health, Consumers and Reference Materials, DG Joint Research Centre, European Commission

Edith HOFER
Organised Crime and Drugs Policy Unit, DG HOME, European Commission

Dr Jean-Marc VIDAL
Human Medicines Research and Development Support Division, European Medicines Agency

Marike Brenda WEBER
O2 European Serious Organised Crime Centre (ESOCC), O21 – Drugs, Europol

Dr Roumen SEDEFOV
Head of Unit, Risks to public safety and security unit, EMCDDA

Michael EVANS-BROWN
Action on new drugs sector, Risks to public safety and security unit

B. Invited Experts

Dr Leon van AERTS
Section Pharmacology, Toxicology and Biotechnology, College ter Beoordeling van Geneesmiddelen, Medicines Evaluation Board, Utrecht

Professor Dr Volker AUWÄRTER
Freiburg University, Institute of Forensic Medicine, Freiburg

Dr Simon ELLIOTT
Alere Forensics, Worcestershire

Dr Robert KRONSTRAND
Dep. Forensic Genetics and Toxicology, Swedish National Board of Forensic Medicine, Linköping

Dr István UJVÁRY
Budapest University of Technology and Economics, Budapest

C. EMCDDA

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