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# Methoxyacetylfentanyl

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

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

## About this series

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

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

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## 1. Introduction

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

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

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

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

## 2. Information collection process

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

### Information collected by Europol

Europol asked the Europol national units to provide information on:

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

Europol received responses from 19 Member States <sup>(2)</sup> and Canada.

### Information collected by the EMA

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

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

Twenty five countries provided a response to the EMA's request regarding human and/or veterinary medicinal products <sup>(3)</sup>. The EMA also provided information as relevant to the centralised procedure for authorising human and veterinary medicinal products.

<sup>(2)</sup> In alphabetical order: Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Slovenia, Spain.

<sup>(3)</sup> Austria, Belgium, Croatia, Estonia, Finland, Germany, Greece, Ireland, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden provided a response in relation to human and veterinary medicinal products. Cyprus, the Czech Republic, Denmark and Hungary provided a response in relation to human medicinal products. France, Romania and the United Kingdom provided a response in relation to veterinary medicinal products.

<sup>(1)</sup> OJ L 127, 20.5.2005, p. 32.

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

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

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

### Information collected by the EMCDDA

The EMCDDA collected information through:

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

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

## 3. Information required by Article 5.2 of the Council Decision

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

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

#### Chemical description and names

Methoxyacetylfentanyl belongs to the 4-anilidopiperidine class of synthetic opioids. This class also includes fentanyl <sup>(5)</sup>, which is internationally controlled, and a number of other fentanils.

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

Methoxyacetylfentanyl differs from fentanyl due to the replacement of the propionamide group with a 2-methoxyacetamide group. Methoxyacetylfentanyl is also structurally related to ofentanil <sup>(7)</sup>, which was critically reviewed at the 39<sup>th</sup> meeting of the Expert Committee on Drug Dependence (ECDD) in November 2017 (World Health Organisation, 2017). Methoxyacetylfentanyl differs from ofentanil due to the absence of the fluorine in the 2-position on the phenyl ring.

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

The synthesis of methoxyacetylfentanyl has been described in the scientific and patent literature (Huang, 1985; Jílek 1990; Jílek 1992).

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

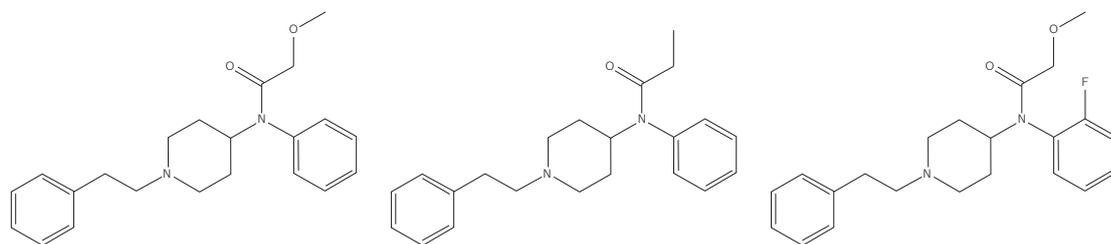
<sup>(5)</sup> *N*-Phenyl-*N*-[1-(2-phenylethyl)piperidin-4-yl]propanamide

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

<sup>(7)</sup> *N*-(2-Fluorophenyl)-2-methoxy-*N*-[1-(2-phenylethyl)piperidin-4-yl]acetamide

FIGURE 1

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



	methoxyacetylfentanyl	fentanyl	ocfentanil
Molecular formula	C <sub>22</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub>	C <sub>22</sub> H <sub>28</sub> N <sub>2</sub> O	C <sub>22</sub> H <sub>27</sub> FN <sub>2</sub> O <sub>2</sub>
Molecular mass	352.48	336.48	370.47

*Commonly used names:*

methoxyacetylfentanyl

*Systematic (IUPAC) name:*

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

*Other chemical names:*

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

2-methoxy-*N*-(1-phenethylpiperidin-4-yl)-*N*-phenylacetamide;

2-methoxy-*N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidiny]-acetamide

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

*N*-[1-(2-phenylethyl)-4-piperidiny]-2-methoxyacetanilide

*Other names and code names:*

methoxyacetyl fentanyl, methoxyacetyl-F, methoxy-AcF, methoxyacetyl fentanyl, desfluoro ocfentanil (Sweden)

*Street names*

'MAF' (Belgium),

'methoxy' (Belgium),

'synthetic heroin' (Belgium)

*Chemical Abstracts Service (CAS) registry numbers* <sup>(8)</sup>:

101345-67-9 base

101365-54-2 hydrochloride salt

*IUPAC International Chemical Identifier Key (InChI Key)* <sup>(9)</sup>:

SADNVKRDSWWFTK-UHFFFAOYSA-N

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

**Physical description**

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

Limited solubility data available on methoxyacetylfentanyl in the hydrochloride and citrate salt forms indicates that it is soluble in dichloromethane, methanol, and water (Slovenian National Forensic Laboratory, 2016; Slovenian National Forensic Laboratory, 2017). Due to its similarity to fentanyl, the free base could be expected to be sparingly soluble in water.

Methoxyacetylfentanyl is expected to be lipophilic.

The measured melting point of methoxyacetylfentanyl was reported as 96–97°C (Jílek, 1990).

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

<sup>(8)</sup> 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.

<sup>(9)</sup> InChI Key is a unique, non-proprietary structural identifier of chemical substances useful in electronic sources.

## Detection and analysis

Methods documented in the literature for the detection of methoxyacetylfentanyl include: gas chromatography–mass spectrometry (GC-MS), high performance liquid chromatography time-of-flight (HPLC-TOF), Fourier transform infrared spectroscopy attenuated total reflectance (FTIR-ATR), gas chromatography–mass spectrometry–infrared spectroscopy (GC-(MS)-IR) condensed phase (Slovenian National Forensic Laboratory, 2016; Slovenian National Forensic Laboratory, 2017), and nuclear magnetic resonance (Slovenian National Forensic Laboratory, 2016).

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

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

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

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

#### 3.2.1 Information provided to Europol

Europol received replies from 19 Member States (Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Lithuania, Luxembourg, the Netherlands, Poland, Portugal, Slovenia, and Spain) and Canada.

##### The level of production

No information was received in relation to the production of methoxyacetylfentanyl <sup>(10)</sup>.

<sup>(10)</sup> Canada reported that there have been no clandestine laboratories seized by the Royal Canadian Mounted Police and no confirmed cases of trafficking related to methoxyacetylfentanyl. They also reported that although the level of distribution is unknown, Canadian-based darknet vendors offer methoxyacetylfentanyl for sale.

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

##### The level of distribution

Limited information was received in relation to the distribution (seizures) of methoxyacetylfentanyl <sup>(11)</sup> <sup>(12)</sup>.

Finland reported that the level of distribution and seizures of methoxyacetylfentanyl in the country is considered to be minimal.

Slovenia reported a case of a customer who suffered severe poisoning following the purchase of a substance, believed to be methoxyacetylfentanyl. The substance was purchased from eurochemicalsco.com, on 2 October 2017. The analysis of a sample seized in relation to this case, a blue bag labelled as 'CHING', confirmed the presence of methoxyacetylfentanyl.

Sweden reported that 21 seizures of methoxyacetylfentanyl have been made since the substance was introduced on to the market. They also reported that the substance is ordered from Swedish websites on the surface web and sent directly to the end user, or, in some cases, to relatives of the user.

There is no information to indicate that Swedish customers use methoxyacetylfentanyl purchased from international websites.

##### The level of trafficking

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

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

#### 3.2.2 Information provided to the EMCDDA

The EMCDDA received responses from the 28 Member States, Turkey, and Norway. Of these, 9 Member States (Austria, Belgium, Denmark, France, Hungary, Latvia, Sweden, Slovenia, and the United Kingdom) and Norway reported

<sup>(11)</sup> Canada reported that there has been one confirmed seizure of 10 g of methoxyacetylfentanyl as a white powder. The country of origin was reported as China and no concealment method was used.

<sup>(12)</sup> Austria provided information on a collected sample, analysed through the anonymous drug checking service 'ChEck iT!' (section 3.2.2).

detections of methoxyacetylfentanyl<sup>(13)</sup>. Images of seizures and collected samples reported to the EMCDDA are provided in Annex 1.

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

### Seizures

In total, 33 seizure cases<sup>(14)</sup> were reported to the EMCDDA by 7 Member States: Belgium (1 case), Denmark (1), Hungary (1), Latvia (7), Sweden (20), Slovenia (1), the United Kingdom (1), and Norway (1). Where known, the seizures took place between July and October 2017 and were made by police or customs agencies.

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

#### Powders

A total of 65.3 g of powder containing methoxyacetylfentanyl was seized in 13 cases that were reported by Belgium (1 case), Denmark (1), Hungary (1), Latvia (6), Sweden (2), Slovenia (1), and the United Kingdom (1). Where known, the powders were reported to be white or off-white in colour. In one case, the powders were reported to be brown.

In 8 of the cases, the quantities seized were below 1 g. The largest seizure of powder was reported by Swedish customs and consisted of 48.9 g of substance. The seizure reported by Danish customs consisted of 12.7 g of powder which was sent from China.

In the seizure reported by Slovenia, methoxyacetylfentanyl was detected in a 'legal high' type product containing 110 mg of powder that was labelled as 'Ching' (see Annex 1). The substance was found as its citrate salt and was purchased by a user from the internet.

<sup>(13)</sup> '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.).

<sup>(14)</sup> 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.

#### Liquids

A total of 271 mL of liquid containing methoxyacetylfentanyl was seized in 18 cases that were reported by Latvia (1 case), Sweden (16), and Norway (1).

Sweden reported a total of 270 mL. In the case reported by Latvia, the liquid was recovered from a syringe. In the case reported by Norway, the liquid was found in a nasal spray.

#### Tablets

A total of 74.5 tablets containing methoxyacetylfentanyl were seized in 2 cases that were reported by Sweden.

### Collected samples

A total of 4 collected samples containing methoxyacetylfentanyl were reported by 4 Member States (Austria, France, Slovenia, and the United Kingdom). In all the cases the sample was purchased as a powder on the internet.

In 2 cases, methoxyacetylfentanyl was bought online as another substance. In one of these cases, reported by France, the user purchased the substance on the darknet as 'fentanyl' and submitted the sample for testing apparently because the 'low' price of sale elicited suspicion (EUR 17/100 mg). In a second case, reported by Austria, the user intended to purchase '4-HO-MET' and received a powder containing 4-HO-MET and methoxyacetylfentanyl.

### Biological samples

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

No other types of biological detections were reported.

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

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

Sweden reported that the availability of methoxyacetylfentanyl can be linked to two known vendors who sell substances on several domestic websites on the surface web. These vendors are both known to police and have been previously convicted of serious drug offences. It is reported that the vendors have contacts in China.

### Money laundering aspects

Limited information was received on money laundering in connection with the production and/or trafficking of methoxyacetylfentanyl.

Sweden reported that the known vendors for fentanils in the Swedish domestic market sell the substances through established companies and that payment is through bank transfer, cash on delivery, bitcoin, or Swish<sup>(15)</sup>. They reported that money laundering is considered an element in those cases. In addition, the sale of fentanils in Sweden is considered to be very profitable due to the relatively low cost of purchasing and distributing the substances compared to the financial gains.

### Violence in connection with production, wholesale and distribution

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

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

### 3.4.1 Health risks

Limited data suggests that methoxyacetylfentanyl is a  $\mu$ -opioid receptor agonist that shares some similarities with opioid analgesics such as morphine and fentanyl (US DEA, 2017a; US DEA, 2017b).

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

Similar to other opioid analgesics, the most serious acute health risk from using methoxyacetylfentanyl is probably respiratory depression, which in overdose could lead to apnoea, respiratory arrest, and death (EMCDDA, 2017; Pattinson, 2008; White and Irvine, 1999). This risk may be greater due to: the difficulty in diluting the substance; a lack of experience with its effects and dosing; the use of other central nervous system depressants at the same time (such as other

opioids, benzodiazepines, gabapentanoids, and alcohol); a lack of tolerance to opioids; and, using the substance alone (such as at home) which would make it more difficult for users to call for help in the case of poisoning.

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

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

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

### 3.4.2 Serious adverse events

#### Acute intoxications reported to the EMCDDA

No acute intoxications with confirmed exposure to methoxyacetylfentanyl were reported to the EMCDDA<sup>(16)</sup>.

#### Deaths reported to the EMCDDA

In total, 6 deaths with confirmed exposure to methoxyacetylfentanyl were reported to the EMCDDA by Sweden. The cases occurred between December 2016 and June 2017.

Of the deaths, 5 were male and 1 was female. The males were aged between 28 and 41 years (mean 34.8, median 34); the age of female was 28 years. A range of other substances were detected in the deaths, including other central nervous system depressants. Other opioids were only detected in 1 case. In 5 cases, the individuals were found dead (two in a home environment).

<sup>(15)</sup> Swish is a mobile app payment system which allows users to send money using a mobile phone connected to an online banking service. Swish is a payment system used between bank accounts in Sweden.

<sup>(16)</sup> Sweden reported 3 acute intoxications with suspected exposure to methoxyacetylfentanyl. These cases are not discussed further in this report.

In 5 cases, methoxyacetylfentanyl was the cause of death or contributed to the death.

#### **Serious adverse events identified in open source information**

During 2017, more than 15 deaths associated with methoxyacetylfentanyl were reported in the United States (Beck et al., 2017; Smith and Kinkaid, 2017; US DEA, 2017b; Yong et al., 2017).

#### **3.4.3 Characteristics of users**

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

#### **3.4.4 Social risks**

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

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

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

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

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

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

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

The first official EMCDDA–Europol notification of methoxyacetylfentanyl dates from 9 December 2016 from the Slovenian national focal point. The Reporting Form details a collected sample of 5 g of brown powder purchased from the Internet as part of the EU-funded project *Response* on 14 November 2016. The sample was shipped from China. Methoxyacetylfentanyl was analytically confirmed by GC-MS, HPLC-TOF, FTIR-ATR, FTIR-condensed phase and Ion Chromatography at the Slovenian National Forensic Laboratory in Ljubljana and by NMR at the Faculty of Chemistry and Chemical technology, University of Ljubljana (Slovenian National Forensic Laboratory, 2016).

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

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

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

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

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

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

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

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

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

The synthesis of methoxyacetylfentanyl has been described in the scientific and patent literature (Huang, 1985; Jílek 1990; Jílek 1992). Synthesis of methoxyacetylfentanyl using ANPP and 2-methoxyacetic anhydride (Jílek 1990; Jílek 1992), as well as using NPP and aniline have been documented (Huang, 1985).

The manufacture of methoxyacetylfentanyl can also rely on precursors and synthetic methods similar to those

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

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

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

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

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

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

<sup>(17)</sup> Table I of the United Nations Convention against Traffic in Narcotic Drugs and Psychotropic Substances, 1988.

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

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

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

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

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

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

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

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

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

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

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

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

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

The EMA also reported that methoxyacetylfentanyl:

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

## 5. Conclusion

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

Methoxyacetylfentanyl has been available in the European Union since at least November 2016. It has been detected in 9 Member States and Norway where it has been seized as a powder, liquids, and tablets. The detected quantities are relatively small; however, they should be seen within the context of the high potency that is typical of the fentanils.

There are indications that the methoxyacetylfentanyl currently available on the market is synthesised by chemical companies based in China. Methoxyacetylfentanyl is sold online often under the guise of a 'research chemical'. It is offered in wholesale amounts and in consumer amounts.

Six deaths with confirmed exposure to methoxyacetylfentanyl have been reported by Sweden. In at least 5 of the deaths, methoxyacetylfentanyl was the cause of death or contributed to the death.

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

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

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

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

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

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## Annex 1

Images from seizures and collected samples provided to the EMCDDA

Country	Image	Description
Slovenia		<b>Seizure</b> Date: 10 November 2017 Seizing authority: Police Ordered from a website for 'personal use'
United Kingdom		<b>Collected sample</b> Date: 29 March 2017 Collecting authority: TICTAC Communications Ltd.

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The Joint Report represents a legal document, prepared in cooperation with the Council, EMA, and Commission and is published in the original version that has not been edited.

**About the EMCDDA**

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

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

**Related publications and websites****EMCDDA and Europol**

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

These and all other EMCDDA publications are available from [www.emcdda.europa.eu/publications](http://www.emcdda.europa.eu/publications)

| EMCDDA Action on new drugs:  
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